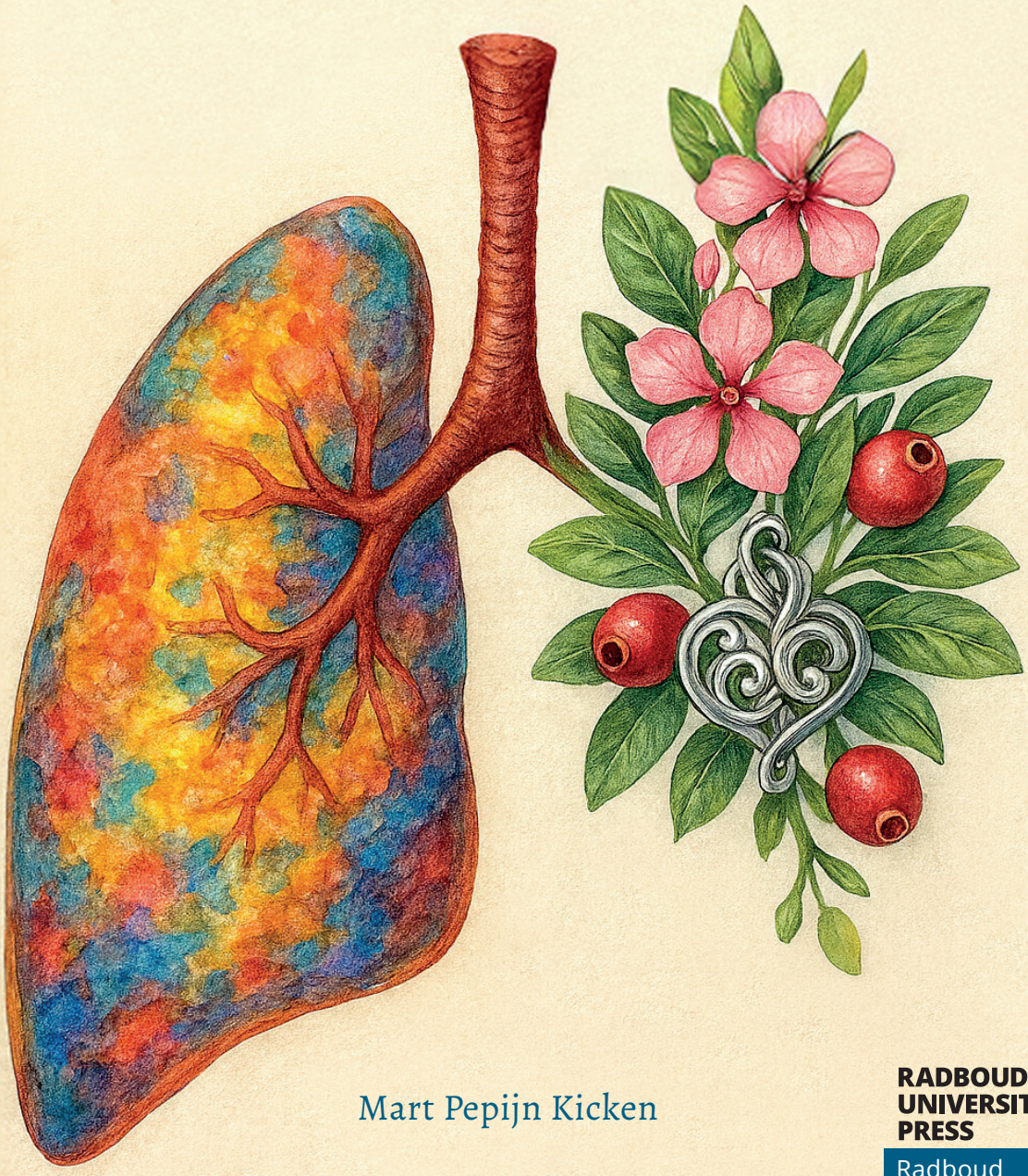
Opportunities in optimizing cytotoxic treatment of lung cancer in the era of immunotherapy



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The research presented in this thesis was performed at Radboud University Medical Center, Nijmegen, the Netherlands and at Catharina Hospital, Eindhoven, the Netherlands.

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General introduction

Lung cancer is the most common cancer in the world. In 2022, an estimated 2.5 million new cases were reported globally (12.4% of all cancer cases), along with 1.8 million deaths (18.7% of all cancer-related fatalities) [1]. Moreover, the World Health Organization (WHO) projects a 59% increase in lung cancer incidence and a 64% rise in mortality from 2020 to 2040 [2]. These alarming trends highlights the urgent need for advancements in lung cancer treatment to improve outcomes for patients.

Lung cancer is categorized into two histological categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC accounting for 80-85% of all lung cancer cases [3]. NSCLC is further classified into three main subtypes: adenocarcinoma (50%; arising from mucus gland cells), squamous cell carcinoma (20-30%; originating from the airway squamous epithelium), and large cell carcinoma (a heterogeneous group of undifferentiated epithelial tumors). Rare subtypes, such as adenosquamous and sarcomatoid carcinomas, are also observed [4]. The stage of the disease, ranging from stage I (localized tumor ≤3 cm without lymph node involvement) to stage IV (where distant metastases are present), determines the type of treatment that is given [4, 5]. This thesis will focus specifically on the systemic treatment of advanced NSCLC (stage IV), which currently accounts for approximately half of all diagnosed NSCLC cases [4].

CURRENT TREATMENT OF STAGE IV NSCLC

Treatment of stage IV NSCLC depends on the presence of actionable driver mutations, tumor histology (squamous versus non-squamous), immunohistochemistry (e.g., programmed cell death ligand-1 (PD-L1) expression), and performance score (Eastern Cooperative Oncology Group performance score (ECOG-PS)). When actionable driver mutations are identified, targeted therapy is the preferred option. For patients with PD-L1 expression ≥50%, immune checkpoint blockers (ICBs) have shown to improve survival outcomes as monotherapy [4]. Additionally, combination regimens of ICBs and chemotherapy have demonstrated a synergistic effect, further enhancing survival outcomes. As a result, ICB-chemotherapy combinations are frequently administered, guided by PD-L1 expression levels, ECOG performance status, and tumor histology [6]. See Figure I for an overview of advanced stage IV NSCLC treatment strategies.

Although immunotherapy and targeted therapies play an increasingly important role in the treatment of advanced NSCLC, classical cytotoxic chemotherapy remains

an important cornerstone. Depending on the patient and tumor characteristics and stage of disease, classical cytotoxic agents may be indicated and it can often be combined with immunotherapy or targeted therapy.

A significant limitation of classical cytotoxic chemotherapy, however, is that these older agents are still not dosed optimally. Moreover, while advances in targeted therapies and immunotherapies have revolutionized the treatment of advanced NSCLC for specific patient populations [7], improvements and developments in optimizing treatment with classical chemotherapeutic agents are seriously lagging behind.

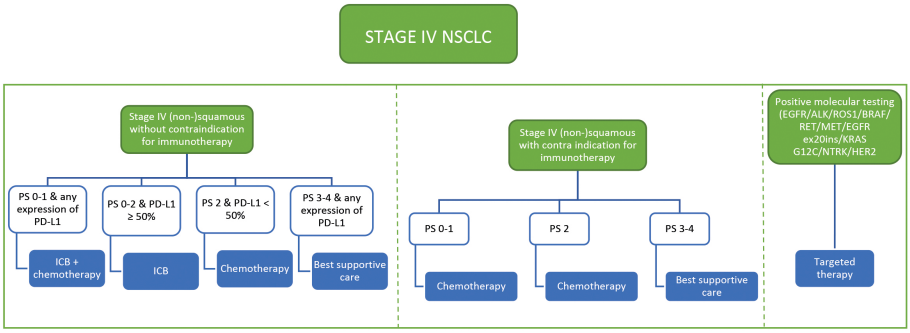

Figure I: Overview of the treatment of advanced stage IV NSCLC with or without contraindication for immunotherapy based on recent ESMO (European Society for Medical Oncology) guidelines [6]. Orange: general categories or stratification; white: other aspects of patient and tumor differentiation; blue: systematic anticancer therapy.

Contra-indication for immunotherapy determines the specific systematic treatment. In this figure, chemotherapy is taken as a collection of all classical cytotoxic drugs (i.e., cisplatin, carboplatin, pemetrexed, docetaxel, (nab-)paclitaxel, gemcitabine, and vinorelbine) and ICB a collection of all immunotherapy agents (e.g., pembrolizumab, atezolizumab, nivolumab)

Abbreviations: PS = performance score, PD-L1 = programmed cell death ligand-1 expression, ICB = immune checkpoint blockers

DOSING OF CLASSIC CYTOTOXIC AGENTS

An important parameter for appropriate drug dosing, is the rate at which the body eliminates the drug and the amount of dose required to achieve its therapeutic effect. Drug elimination or clearance involves metabolism and excretion. Metabolism typically entails the chemical or enzymatic conversion of the parent compound into one or more, often water-soluble metabolites, primarily in the liver. Excretion consists of removing the parent drug and its metabolites from the body, predominantly

facilitated by the kidneys through renal clearance and, to a lesser extent, by the liver through biliary clearance [8]. The required drug dose is determined by estimating its clearance (CL) and the desired level of drug exposure, expressed as the Area Under the Concentration-Time Curve (AUC) [8]:

$$DOSE = AUC * CL$$

*Dose as mass (e.g., mg); AUC as mass/volume multiplied with time (e.g., mg/mL*min); CL in mass/volume (e.g., mg/mL*

The dosing of classical cytotoxic drugs is particularly unique, as the goal is to achieve maximum cytotoxicity while minimizing harm to the patient. This requires a delicate balance between underdosing (which can lead to treatment ineffectiveness) and overdosing (which can lead to treatment toxicity). In this thesis, I will explore the dosing strategies for key cytotoxic agents in the treatment of advanced NSCLC: carboplatin, pemetrexed, docetaxel—and the immune checkpoint inhibitor atezolizumab.

DOSING CHALLENGES AND KNOWLEDGE GAPS

In the early 20th century, a relationship between a species' basal metabolic rate and body surface area (BSA) was identified. In 1916, the brothers Dubois and Dubois introduced a formula for the estimation of BSA based on the data of only nine participants [9]. When tested further in a large sample of 237 individuals, the Dubois formula systematically underestimated the BSA, particularly in individuals with a BSA below 1.3 m^2, limiting its use in children [10]. The following widespread adoption of BSA-based dosing gained traction after early studies by Pinkel *et al.* (1958) and Freireich *et al.* (1966) reporting a relationship between BSA and pharmacokinetics (clearance and exposure) across different animal species [11]. These findings led to BSA-based dosing becoming the cornerstone of chemotherapy drug administration. At the time, the general assumption was that physiologic parameters relevant to drug metabolism and elimination (i.e., metabolic rate, renal and hepatic function) would scale between species and individuals according to BSA [11]. This assumption is incorrect and was mistakenly inferred from the original papers as renal and hepatic function do only weakly or do not correlate with BSA [12]. Furthermore, the validity of BSA as a mechanistic determinant for drug elimination is highly questionable, as no cytotoxic drug is completely eliminated through the body surface (i.e., the skin).

At present, the dosing of cytotoxic agents—except for carboplatin—for advanced NSCLC treatment is BSA-based. However, two patients with identical BSA may respond differently to the same drugs due to variations in individual patient characteristics, such as hepatic or renal function, age, or genetic polymorphisms. Consequently, high interindividual variability in clearance and exposure has been observed for many cytotoxic agents, demonstrating that dosing based on BSA leads to over- or underexposure for the individual patient [13].

In the current era of precision medicine, in which treatments are increasingly tailored to patients' genetic and individual characteristics, the precision dosing of classical cytotoxic drugs remains underdeveloped and insufficiently individualized [14]. Regulatory agencies, such as the USA Food and Drug Administration (FDA), have also realized that the current paradigm for the dose selection of new oncology drugs is inadequate and needs improvement [15]. Through initiatives like Project Optimus (2024), the FDA aims to drive a paradigm shift to individualized dosing by identifying better dosing strategies for new oncology drugs [16]. However, this initiative does not extend to older oncology drugs, which remain largely unexamined under the current shifting framework, thereby creating a significant knowledge gap.

In this thesis, I investigate the dosing of various cytotoxic agents used in the treatment of NSCLC and explore strategies to optimize their administration based on individual patient characteristics. Given the large population of NSCLC patients, even modest improvements in dosing could have a profound impact on treatment outcomes, reducing toxicity, enhancing quality of life, and benefiting a significant number of individuals both currently and in the future.

CARBOPLATIN

Carboplatin, a platinum-based chemotherapy drug, was approved in 1986 using BSA-based dosing at 300 mg/m² every three weeks [17]. However, subsequent studies demonstrated that carboplatin clearance is linearly correlated with renal function (i.e., glomerular filtration rate, GFR) [18]. And since carboplatin systemic drug exposure correlates strongly with toxicity, Calvert *et al.* developed the following dosing formula for dosing based on AUC [18]:

$$\text{Calvert formula} \mid \text{DOSE} = \text{AUC}_{\text{target}} * (\text{GFR} + 25)$$

*Dose as mass (e.g., mg); AUC as mass/volume multiplied with time (e.g., mg/mL*min); GFR in mass/volume (e.g., mg/mL)*

The target AUC depends on the performance score of the patient, treatment regimen, and dose interval [18]. In the original Calvert formula, the GFR is based on the clearance of the 100% glomerular filtrated chromium 51-ethylene-diaminetetra-acetic acid (^{51}Cr-EDTA). In clinical practice, the GFR is typically estimated using the 1976 Cockcroft-Gault formula, which accounts for weight, gender, age, and serum creatinine levels [19]:

$$\text{Cockcroft} - \text{Gault formula} \mid \text{estimated CrCL} = \frac{(140 - \text{AGE}) * \text{WEIGHT}}{0.815 * \text{Cr}_{\text{SERUM}}} * 0.85 \text{ [IF FEMALE]}$$

Creatinine clearance (CrCL) in volume/time (e.g., mL/min); age in time (e.g., years); weight as mass (e.g., kg); serum creatinine in mass/volume (e.g., mg/dL)

Creatinine is a breakdown product of creatine phosphate found in skeletal muscle, making its production dependent on and associated with muscle mass [20]. The Cockcroft-Gault formula indirectly estimates the muscle mass using weight, gender, age. The difference between creatinine production (i.e., muscle mass estimation) and serum creatinine is the creatinine clearance.

However, the Cockcroft-Gault formula is known to overestimate the CrCL in overweight and obese patients [21, 22]. Overestimation of CrCL will lead to either overdosing of carboplatin in overweight and obese patients, or underdosing in underweight patients with low creatinine values (e.g., cachectic patients) [23, 24].

PEMETREXED

Pemetrexed, a folate antimetabolite, was approved in 2004 with BSA-based dosing at 500 mg/m² every three weeks [25]. Despite that pemetrexed is almost completely cleared and excreted by the kidneys (70–90% within 24 hours), dosing remains based on BSA [26]. Hence, patients with impaired renal function exhibit reduced clearance of pemetrexed, increasing the risk of overdosing and toxicity [27]. This poses a dilemma for clinicians, as approximately 30% of lung cancer patients have an impaired renal function [28].

DOCETAXEL

Docetaxel, a taxoid antineoplastic agent, was approved in 1996 for NSCLC treatment at a dose of 75 mg/m^2 [29]. However, studies have shown that BSA-based dosing only minimally reduces interindividual variability in the pharmacokinetics of docetaxel [30]. Despite the identification of numerous covariates influencing docetaxel pharmacokinetics, much of the variability in drug exposure remains unexplained.

Total systemic exposure to docetaxel is closely correlated with both treatment efficacy and toxicity, particularly hematological toxicity [31], with docetaxel-induced neutropenia serving as a predictive marker for treatment outcomes [32, 33]. Given this, dosing docetaxel based on the degree of (hematological) toxicity could potentially optimize treatment. However, these studies were all conducted for first- or second-line treatment of docetaxel, prior to the widespread adoption of immunotherapy in 2015, which has relegated docetaxel to a last-line treatment option for NSCLC [34]. Patients receiving later-line treatments often present with greater frailty, poorer performance scores, and extensive metastases [35], which complicates dosing decisions, especially when the dosing strategy is based on toxicity levels.

ATEZOLIZUMAB

Immunotherapy often consists of antibodies targeting different immune checkpoints, including programmed cell death protein-1/programmed cell death ligand-1 (PD-1/PD-L1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) pathways [36]. Atezolizumab, an immune checkpoint inhibitor targeting PD-L1, is a key agent in NSCLC immunotherapy. Recently, the subcutaneous formulation of atezolizumab received approval from the European Medicines Agency (EMA) and the FDA as a fixed dose of 1875 mg administered every three weeks [37, 38]. However, treatment with atezolizumab is expensive [39]. Furthermore, the financial burden of cancer care continues to rise globally due to an increasing number of cancer patients, driven by advancements in effective screening, early detection, and an aging population [40, 41]. Consequently, the growing economic strain of cancer treatment places substantial pressure on both personal and national healthcare budgets. Given the expanding list of indications for atezolizumab and its considerable cost, there is an urgent need to implement cost-saving strategies wherever possible. A potential approach to reducing the costs associated with SC atezolizumab treatment is through dose optimization, leveraging PK modeling, and simulation of different patient populations.

DRUG	DOSING METHOD	KEY CHALLENGES
Carboplatin	AUC and GFR based using the Calvert formula	GFR estimation via the Cockcroft-Gault formula is prone to inaccuracies, particularly in overweight and obese patients.
Pemetrexed	BSA-based	Pemetrexed is primarily cleared by the kidneys. Hence, patients with impaired renal function are at higher risk of pemetrexed-associated toxicity.
Docetaxel	BSA-based	There is a limited correlation between BSA and drug exposure. Early research suggests a link between docetaxel-associated toxicity and survival outcomes. Hence, docetaxel-associated toxicity could be a predictor of drug exposure. However, the role of docetaxel-associated toxicity as a predictive marker for treatment outcomes remains under-explored, particularly in the post-immunotherapy era.
Atezolizumab	Fixed dose - subcutaneous	High costs for SC atezolizumab treatment are straining healthcare budgets globally. However, there exists a potential for improved dosing strategies based on PK modeling of different patient populations.

AIM AND OUTLINE OF THIS THESIS

The aim of this thesis is to investigate the dosing strategies of cytotoxic agents used in the treatment of NSCLC and to explore approaches for optimizing dosing based on individual patient characteristics. By doing so, the thesis seeks to improve treatment outcomes, reduce toxicity, and enhance the quality of life for patients.

In **Chapter I**, I provide a comprehensive review of precision dosing opportunities for classical cytotoxic drugs commonly used in stage IV NSCLC treatment, including platinum compounds (cisplatin, carboplatin), taxanes (docetaxel, paclitaxel, nab-paclitaxel), pemetrexed, gemcitabine, and vinorelbine.

Next, I focus on improvement in dosing strategies for carboplatin, docetaxel, and pemetrexed. In **Chapter II,** I investigate the potential overestimation in carboplatin dosing in overweight and obese patients, what the implications are for overdosing these patients, and the subsequent effects on survival and toxicity outcomes. In **Chapter III**, I explore adjustments to the Cockcroft-Gault formula, especially for overweight and obese patients, and evaluate, through a pharmacokinetic study, whether the adjusted formula improves reaching target drug exposure (AUC_{target}) for carboplatin.

Chapter IV focuses on the toxicity profile of pemetrexed in stage IV NSCLC patients with renal impairment (creatinine clearance <45 mL/min). Using real-world data, I provide insights to guide clinical decision-making for this vulnerable population.

Chapter V examines the relationship between docetaxel-induced hematological toxicity and survival outcomes in the current era of immunotherapy, and addresses the potential shifts in predictive significance of docetaxel-associated toxicity and treatment paradigms.

In **Chapter VI**, I explore ways of optimizing the dosing regimen of atezolizumab based on modeling and simulation, aimed at reducing drug expenses without compromising effective systemic drug exposure.

Lastly, I provide a comprehensive **General summary and discussion** of the findings presented in this thesis, emphasizing their implications for individualized dosing strategies in NSCLC. I summarize key insights and propose recommendations for future research and clinical applications to enhance therapeutic efficacy and safety in stage IV NSCLC treatment.

CHAPTER		AIM OF THE CHAPTER
I	*Opportunities for precision dosing of cytotoxic drugs in non-small cell lung cancer - bridging the gap in precision medicine*	To describe opportunities for precision dosing of classical cytotoxic drugs for improved safety and efficacy of chemotherapeutic treatment of NSCLC.
II	*The association of body mass index with safety and effectiveness of first-line carboplatin-based chemotherapy in patients with metastatic non-small cell lung cancer*	To investigate the association of body mass index (BMI) on overall survival (OS) and progression-free survival (PFS) in stage-IV NSCLC patients treated with first-line carboplatin-based chemotherapy.
III	*Pharmacokinetic study of carboplatin using various overweight-correcting dosing algorithms and biomarkers in patients with varying BMI categories*	To evaluated the use of an adjusted Cockcroft-Gault formula correcting for overweight, high renal function and low creatinine
IV	*The toxicity profile of pemetrexed in non-small cell lung cancer patients with moderate renal impairment - a retrospective cohort study*	To describe the toxicity profile of pemetrexed in NSCLC patients with renal impairment (creatinine clearance < 45 mL/min)
V	*Early-onset hematological toxicity of docetaxel and survival in non-small cell lung cancer patients in the immune checkpoint inhibition era*	To determine to which extent the association between docetaxel-associated hematological toxicity and overall survival still holds in the immunotherapy era in NSCLC patients
VI	*An Evidence-Based Rationale for Dose De-escalation of Subcutaneous Atezolizumab*	To develop an optimized dosing regimen of subcutaneous atezolizumab based on modeling and simulation, resulting in reduced drug expenses without compromising effective systemic drug exposure.

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CHAPTER I

Opportunities for precision dosing of cytotoxic drugs in non-small cell lung cancer - bridging the gap in precision medicine

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ABSTRACT

Precision dosing of classical cytotoxic drugs in oncology remains underdeveloped, especially in treating non-small cell lung cancer (NSCLC). Despite advancements in targeted and immunotherapy, classical cytotoxic agents continue to play a critical role in NSCLC treatment. However, the current body surface area (BSA-)based dosing of these agents fails to adequately address interindividual variability in pharmacokinetics. By better considering patient characteristics, treatment outcomes can be improved, reducing risks of underexposure and overexposure. This narrative review explores opportunities for precision dosing for key cytotoxic agents used in NSCLC treatment: cisplatin, carboplatin, pemetrexed, docetaxel, (nab-)paclitaxel, gemcitabine, and vinorelbine. A comprehensive review of regulatory reports and an extensive literature search were conducted to evaluate current dosing practices, pharmacokinetics, pharmacodynamics, and exposure-response relationships.

Our findings highlight promising developments in precision dosing, though the number of directly implementable strategies remains limited. The most compelling evidence supports using the biomarker cystatin C for more precise carboplatin dosing and adopting weekly dosing schedules for docetaxel, paclitaxel, and nab-paclitaxel. Additionally, we recommend direct implementation of therapeutic drug monitoring (TDM-)guided dosing for paclitaxel.

This review stresses the urgent need to reassess conventional dosing paradigms for classical cytotoxic agents to better align with the principles of the precision dosing framework. Our recommendations show the potential of precision dosing to improve NSCLC treatment, addressing gaps in the current dosing of classical cytotoxic drugs. Given the large NSCLC patient population, optimizing the dosing of these agents could significantly improve treatment outcomes and reduce toxicity for many patients.

INTRODUCTION

Lung cancer is the second most common cancer in the world. In 2022, a total of 2.5 million people worldwide were diagnosed with lung cancer, followed by an estimated 1.8 million deaths that year, indicating much need for treatment improvement [1]. Lung cancer is categorized based on histological categories: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Around 80-85% of lung cancers are NSCLC, divided mainly into adenocarcinoma (40-45%) of the small airway epithelium and type II alveolar cells, squamous cell lung carcinoma (25-30%) of the epithelial cells of the bronchial tubes and large cell carcinoma (5-10%) targeting the central parts of the lungs [2].

The type of treatment for NSCLC depends on the tumor stage. In the treatment of stage I-III NSCLC, surgery is preferred and often combined with (neo)adjuvant treatment using classic cytotoxic agents, immune checkpoint inhibitors, or targeted therapy [3]. Treatment of stage IV NSCLC is based on patient and tumor characteristics like performance score (i.e., Eastern Cooperative Oncology Group (ECOG) – performance score), molecular profiling of the tumor, and immunohistochemistry (i.e., Programmed Death Ligand 1 (PD-L1) expression). Its treatment includes targeted therapy, immunotherapy, and chemotherapy [4]. However, while recent developments in targeted therapy have shown promising results in specific patient populations, classical cytotoxic therapy will remain an important pillar of the treatment of stage IV NSCLC for the upcoming decade.

For cytotoxic drugs, there is always a complex balance between subtherapeutic therapy (i.e., underexposure) and toxicity (i.e., overexposure) to find the individual optimal therapeutic effective dose. Since systemic exposure to the drug largely determines its effect and toxicity, prediction of individual pharmacokinetics can be used to tailor the dose. Historically, the dosing of cytotoxic drugs has been adapted to body size, for example, by using the estimated body surface area (BSA). This approach is based on early studies by Pinkel (1958) and Freireich (1966) showing a "reasonable" relationship between BSA and the pharmacokinetics of various chemotherapeutic drugs [5]. However, since body size only modestly correlates with the metabolic capacity of the liver and the glomerular filtration rate - the two main organ systems responsible for drug elimination - BSA is a poor predictor for individual pharmacokinetics [6]. Moreover, using BSA for dosing is only based on correlation (which disappears in the pharmacokinetic interindividual variability) and not on a causal physiological relationship with the clearance of cytotoxic drugs [7].

Nonetheless, the current dosing of cytotoxic agents for NSCLC treatment is still primarily BSA-based. This may lead to unwanted interindividual variability, as two patients with the same BSA may experience different drug exposures (and consequently, different treatment responses) due to variances in individual patient characteristics, such as hepatic or renal function, age, and genetic polymorphisms. High interindividual variability in clearance and exposure for many anticancer drugs has been observed, showing that dosing based on BSA leads to over- or underexposure for the individual patient [7]. Overexposure is unwanted since it may lead to severe toxicity, early treatment discontinuation, and reduced quality of life. Underexposure is unwanted since it may negatively impact the efficacy of anticancer treatment. Precision dosing is adjusting the dose based on the patient's characteristics known already before the start of treatment (e.g., hepatic and renal function, genetic factors) or during treatment through assessment of the drug's exposure, i.e., pharmacokinetically-guided dosing using therapeutic drug monitoring (TDM-) guided or toxicity-guided dosing [8]. In the era of advancing precision medicine, the tailoring of dosing of classical cytotoxic drugs to individual patients' characteristics is lagging and remains insufficient [8]. Regulatory agencies, such as the Food and Drug Administration (FDA), have also realized that the current paradigm for the dose selection of new oncology drugs is inadequate and needs improvement [9]. Through project Optimus, the FDA aims for a paradigm shift to identify optimal doses of new oncology drugs [10]. However, this initiative does not extend to older oncology drugs, which remain largely unexamined under the current shifting framework, creating a significant knowledge gap. We postulate that existing oncological drugs, especially classical cytotoxic drugs, should not be neglected and should undergo the same re-evaluation to optimize their dosing strategies. As the population of patients with NSCLC is large, an even slight improvement in dosing can affect and improve the treatment of many patients. Therefore, the aim of this narrative review is to describe opportunities for precision dosing of classical cytotoxic drugs for improved safety and efficacy of chemotherapeutic treatment of NSCLC.

METHODS

The scope of this narrative review was limited to the treatment of NSCLC with classical cytotoxic agents, including platinum (cis- or carboplatin) and taxane (docetaxel, paclitaxel, or nab-paclitaxel) compounds, pemetrexed, gemcitabine, and vinorelbine [3, 4]. First, we assessed the European Public Assessments Reports (EPARs) from the European Medicines Agency (EMA) and pharmacology and pharmacokinetic reviews of the FDA gather regulatory insights on approved indications, dosing

recommendations, and available pharmacokinetic/pharmacodynamic (PK/PD) data. From these regulatory documents, we extracted relevant information on each drug. Next, we examined the pharmacokinetics, pharmacodynamics, exposure-response relationships, and dose-treatment optimization strategies for each cytotoxic agent. After that, we queried PubMed to identify additional relevant literature on personalized medicine of these cytotoxic agents. For example, when a PK relationship was found between BSA and exposure for a specific agent, we searched for "BSA" AND "exposure" AND "[drug-name]" (e.g., cisplatin, carboplatin). Filters were applied to include only English-language publications, with a priority given to studies in NSCLC populations, clinical trials, meta-analyses, and reviews, in that order. Lastly, we employed citation snowballing, specifically backward snowballing, by examining the reference lists of key studies to identify other potentially relevant publications.

The general approach for dose individualization of selected cytotoxic agents starts with the current state of dosing and general pharmacokinetic and pharmacodynamic characteristics ("Pharmacokinetics, pharmacodynamics and current practice in dosing"), followed by "Promising developments" of opportunities and research already performed for optimizing and personalizing of dosing, followed by our recommendation to improve precision dosing of these cytotoxic agents. All directly implementable opportunities and proposed PK/PD relationships of these cytotoxic agents in treating NSCLC were summarized in Table 2.

PLATINUM-BASED COMPOUNDS (CISPLATIN, CARBOPLATIN)

After intravenous administration, cis- and carboplatin are hydrolyzed to active platinum metabolites, which bind to proteins through sulfide bonds of albumin and globulins. Hence, only a small part of elimination depends on protein turnover [11]. Compared to cisplatin, carboplatin is chemically more stable and less reactive, hydrolyzed at a lower constant rate, and forms fewer complexes with plasma proteins. Both cisplatin and carboplatin are cleared by the kidneys as free platinum, with carboplatin being excreted up to 65-77% within 24 hours versus 28% for cisplatin [11]. Hence, the dosing of carboplatin is adjusted for renal function, while adjustment of the dosing of cisplatin in patients with renal impairment is only advised [12].

Both drugs are considered interchangeable for the treatment of NSCLC, as a large meta-analysis (n=2048) including twelve randomized controlled trials (RCTs) did not show any significant differences in survival outcomes between first-line cisplatin- and carboplatin-based chemotherapy. Nevertheless, differences in toxicity profiles exist, with a higher incidence of thrombocytopenia and anemia for carboplatin and

an increased risk of nausea and vomiting for cisplatin [13]. Furthermore, cisplatin shows higher incidences of ototoxicity and neurotoxicity compared to carboplatin. The specific mechanism underlying this difference in sensitivity is still poorly understood. However, studies have found a higher accumulation of cisplatin in the cochlea, resulting in reactive oxygen species (ROS) overload and an impaired antioxidant system [14].

The cytotoxic mode of action of platinum drugs has been linked to forming DNA-crosslinks, causing DNA damage, and inducing apoptosis of tumor cells, but as a side effect also in healthy cells [11]. Most chemotherapy-induced toxicity encompasses rapidly dividing cells, including in the bone marrow. Neutropenia is the most common form of bone marrow toxicity, as neutrophils are especially vulnerable to cell-diving toxicity due to their extremely short circulating half-life (6-8 hours) and the need for continuous replenishment by the bone marrow [15]. The nadir neutrophil count occurs 8-10 days after administration and is associated, among others, with systemic exposure to the specific cytotoxic drug [16]. An exception to this rule is carboplatin, where carboplatin-associated hematological toxicity mainly manifests as thrombocytopenia. This difference in hematological toxicity might be explained by the downregulation of the JAK2/STAT2 pathway critical for megakaryocyte proliferation and differentiation by carboplatin [17].

Platinum-based drugs not only function as cytotoxic drugs but may also exert immunomodulatory effects that contribute to their efficacy and synergetic effect in chemoimmunotherapy. For example, cisplatin *in vitro* increases the number of effector cells (i.e., NK-cells, cytotoxic T-cells, antigen presenting cells (APCs), and macrophages) while decreasing the number of myeloid-derived suppressor cells (MDSCs) and regulatory T-cells [18]. Moreover, cisplatin seems to enhance the effect of immunotherapy by remodeling the tumor microenvironment (by ferroptosis and neutrophil polarization) and enhancing T-cell infiltration and Th1 differentiation [19]. The same synergistic effect was found for carboplatin and PD-1 inhibitors (i.e., pembrolizumab and nivolumab) in NSCLC cell lines [20].

CISPLATIN

PHARMACOKINETICS, PHARMACODYNAMICS AND CURRENT PRACTICE IN DOSING

Cisplatin entered the market in 1978 as an anticancer drug for the first-line treatment of several malignant tumors, including lung, ovarian, and colorectal cancers [21]. The cumulative exposure to unbound cisplatin (expressed as Area Under the Curve (AUC)) is strongly correlated with the formation of DNA-adducts in tumor cells and tumor response [22] as well as toxicity [23]. The main cisplatin-induced toxicities are nephrotoxicity, ototoxicity, myelotoxicity, nausea, and peripheral neuropathy [23]. Specifically, an increased systemic drug exposure (AUC) and maximal plasma concentration (C_{max}) of unbound platinum are correlated with an increased risk of cisplatin-induced nephrotoxicity [24]. Slow infusion rates may prevent nephrotoxicity and myelotoxicity in addition to hyperhydration and diuresis [25]. Incidences of neuropathy and ototoxicity are only preventable by dose reduction or cessation of cisplatin [26]. Although BSA only weakly correlates with cisplatin systemic exposure [27], cisplatin is still dosed based on BSA 75-100 mg/m^2 3-weekly dosing in NSCLC treatment [12].

PROMISING DEVELOPMENTS

Since cisplatin is eliminated by the kidneys, dosing in patients with renal impairment should be adjusted. At the moment, dose adjustment in patients with impaired renal function is only advised by the label and not mandatory [12]. However, recent guidelines, including the International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD), recommend avoiding the administration of cisplatin in patients with renal impairment (eGFR <45 mL/min/1.73 m^2) [28]. Limited prospective data in NSCLC are available, and the best approach for adjusting cisplatin dosage in patients with impaired renal function has yet to be determined [29]. Interestingly enough, a study investigating dose reduction of cisplatin for patients (n=151) with metastatic urothelial carcinoma and renal dysfunction 30-60 mL/min found no negative impact or significant differences in severe toxicity or survival outcomes compared to standard dosing in patients with renal function >60 mL/min [30]. Since cisplatin and carboplatin are considered interchangeable in treating NSCLC [13], changing treatment to carboplatin may also be an option to adjust treatment to individual renal function more easily (see chapter Carboplatin).

An increasing number of pharmacogenomic (PGx) studies of cisplatin-induced toxicity have been published, especially regarding cisplatin-induced ototoxicity [31] and nephrotoxicity [32]. For example, a large genome-wide study (GWAS) of 608

European patients found an association between a predisposition of the BACH2 gene and an increased risk of cisplatin-induced nephrotoxicity [33]. At the moment, there is no place for PGx for cisplatin-induced toxicity due to the lack of consistency in study results. Nevertheless, PGx remains highly relevant and important for future research.

Neutrophil-guided dosing of cisplatin could be a potential opportunity for treatment optimization. A large retrospective study by Di Maio *et al.* based on three RCTs (n=1265) found the degree of cisplatin-induced neutropenia to be associated with increased overall survival (OS) [34]. Unfortunately, to our knowledge, no prospective studies have confirmed this relationship between the incidence of neutropenia and survival outcomes in cisplatin treatment.

As cisplatin exposure is related to its efficacy and toxicity, TDM-guided dosing of cisplatin based on reaching a specific AUC or C_{max} would be possible, especially in specific populations (e.g., pediatric, high-dose treatment) and for treatment that is administered over several days [35]. To this day, no studies have yet investigated the added value of TDM-guided dosing of cisplatin in NSCLC patients. In patients with other types of solid tumors, TDM-guided dosing of cisplatin (n=58) as a 5-day continuous infusion successfully reached the target C_{max} and reduced interindividual variability of PK parameters [36]. Another PK study in 19 patients of different solid tumors also successfully achieved targeted C_{max}, with little grade III-IV toxicities (10% leukocytopenia, 6% anemia, and thrombocytopenia) and no nephrotoxicity and neurotoxicity, and all patients still alive and disease-free after a follow-up of 15 years [37].

RECOMMENDATIONS AND OPPORTUNITIES FOR TREATMENT OPTIMIZATION

Currently, dosing is still based on BSA, and there is not enough evidence to adjust cisplatin dosing based on renal function or to use cisplatin-induced hematological toxicity, a potential opportunity for neutrophil-guided dosing. For specific NSCLC patient populations like pediatric patients or 5-day continuous infusion of cisplatin, we recommend further exploring TDM-guided dosing based on the limited promising results in other tumors.

CARBOPLATIN

PHARMACOKINETICS, PHARMACODYNAMICS AND CURRENT PRACTICE IN DOSING

Carboplatin entered the market roughly ten years after cisplatin in 1986 as a potential substitution for cisplatin [38]. Carboplatin was initially approved on BSA-based dosing [39]. However, studies showed carboplatin clearance to be linearly correlated with glomerular filtration rate (GFR) [40]. The toxicity of carboplatin treatment showed high variability and higher incidences of (hematological) toxicity with decreasing renal function [41]. Since carboplatin systemic drug exposure correlates well with toxicity, Calvert *et al.* developed the following dosing formula for dosing based on AUC: Dose (mg) = AUC_{target} * (GFR +25) [40]. In this formula, the GFR is based on the measured glomerular filtration rate using chromium 51-ethylenediaminetetra-acetic acid (^{51}Cr-EDTA). In daily practice, directly measuring the GFR using exogenous markers is complex, expensive, and inconvenient [42], and the GFR is frequently substituted by the estimated creatine clearance (CrCL) [43]. However, creatinine is not 100% cleared by the glomerulus but undergoes active tubular secretion as well, resulting in a 10-20% systematic overestimation of GFR [42]. Moreover, besides biased estimation, serum creatinine-based estimations of renal function have proven to be imprecise. A study by Ekhart *et al.* showed that adjusting carboplatin dose using estimated renal function based on serum creatinine provided similar drug exposure levels as administering a flat dose to patients with normal renal function [44]. This finding can be explained by the fact that serum creatinine correlates with muscle mass and that in advanced cancer patients, muscle mass deviates from the population where equations for estimation of renal function were developed [45]. For example, cachectic patients, often seen in oncological populations, have an abnormally low creatinine production, and assessing the creatinine clearance in this population will provide an overestimation of GFR [46, 47]. Directly measuring (24-hour) creatinine clearance as a proxy for GFR might be more accurate than relying on estimated GFR for carboplatin dosing. Still, this has been proved inaccurate for carboplatin dose individualization [48].

PROMISING DEVELOPMENTS

Since carboplatin is dosed to a specific target AUC, TDM-guided dosing may aid in dosing carboplatin to improve target attainment. An extensive review by Maillard *et al.* [35] found multiple small studies demonstrating that TDM-guided carboplatin dosing in children with retinoblastoma successfully achieved target AUC, leading to remission without reported renal toxicity [49, 50]. Similarly, high-dose carboplatin has been shown to reach target AUC in adults with advanced germ cell tumors [51].

Looking at carboplatin toxicity and treatment outcomes, the association between (hematological) toxicity and survival outcomes of carboplatin treatment has not been established [52]. However, there is still potential for improvement in carboplatin dosing by adjusting for baseline hematological status (i.e., low platelets or absolute neutrophil counts at baseline), concomitant therapy, and better estimation of renal function [53].

As stated earlier, estimating renal function based on the creatinine clearance (i.e., carboplatin clearance) in patients with an abnormal body composition gives an under- or overestimation of the estimated GFR (eGFR). However, developments in deep learning and medical imaging allow accurate assessment of an individual's body composition, including muscle mass, using X-ray computed tomography (CT-) scans [54]. As muscle mass correlates with creatinine production, creatinine clearance might be accurately estimated using a CT-scan assessment of body composition and serum creatinine to improve carboplatin dosing [55]. Other biomarkers, cystatin C and pro-enkephalin (PENK), are more effective in estimating the GFR than creatinine clearance [56, 57]. Using cystatin C for dosing of carboplatin better attains target AUC compared to serum creatinine-based assessments of renal function in individualizing the dose [58, 59]. White-Koning *et al.* combined three previously published clinical studies of 491 patients receiving carboplatin and compared various formulas for estimating carboplatin clearance to actual clearance. They found that cystatin C (used in the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)) was the best predictor (i.e., least bias, highest precision) of carboplatin clearance, independent of other patient characteristics such as sex, body mass index (BMI) (only significant at the 1% level), and age [60]. See Table 1 for different cystatin C formulae tested for estimating carboplatin clearance.

RECOMMENDATIONS AND OPPORTUNITIES FOR TREATMENT OPTIMIZATION

Dosing of carboplatin is already adjusted for exposure (AUC) and clearance (GFR) using the Calvert formula. We recommend implementing and using cystatin C as a marker for renal clearance and adjusting dosage for baseline hematological status and concomitant therapy. Cystatin C has the most evidence as an ideal estimator of carboplatin clearance independent of patient characteristics (see Table 2). Moreover, prospective studies in cystatin C have already shown that it is a better approximation of carboplatin clearance compared to conventional creatinine clearance formulae. However, its impact on clinical outcomes has yet to be evaluated. Finally, TDM-guided dosing could be an option in specific patient groups, such as pediatrics or high-dose protocols.

Table 1: Different cystatin c formulas for estimating carboplatin clearance

Schmitt *et al.* [58]	$\mathrm{CL\ [mL/min]} = 117.8 * \left(\frac{\mathrm{Cr_{SERUM}}}{75}\right)^{-0.450} * \left(\frac{\mathrm{cystatin\ C_{SERUM}}}{1.0}\right)^{-0.385} * \left(\frac{\mathrm{WEIGHT}}{65}\right)^{+0.504} * \left(\frac{\mathrm{AGE}}{56}\right)^{-0.366} * 0.847\ \mathrm{[IF\ FEMALE]}$
Thomas *et al.* [59]	$\mathrm{CL\ [mL/min]} = 110.0 * \left(\frac{\mathrm{Cr_{SERUM}}}{75}\right)^{-0.512} * \left(\frac{\mathrm{cystatin\ C_{SERUM}}}{1.0}\right)^{-0.327} * \left(\frac{\mathrm{WEIGHT}}{65}\right)^{+0.474} * \left(\frac{\mathrm{AGE}}{56}\right)^{-0.387} * 0.854\ \mathrm{[IF\ FEMALE]}$
CKD-EPI (creatinine + cystatin C) [57]	$\mathrm{eGFR\ [mL/min/1.73m^2]} = 135 * \left(\frac{\mathrm{Cr_{SERUM}}}{\mathrm{A}}\right)^{\mathrm{B}} * \left(\frac{\mathrm{cystatin\ C_{SERUM}}}{\mathrm{C}}\right)^{\mathrm{D}} * 0.9961^{\mathrm{AGE}} * 0.963\ \mathrm{[IF\ FEMALE]}$
	If *male* and: • Serum creatinine ≤ 0.9 and serum cystatin C ≤ 0.8: • A = 0.9, B = -0.144, C = 0.8, and D = -0.323 • Serum creatinine ≤ 0.9 and serum cystatin C > 0.8: • A = 0.9, B = -0.144, C = 0.8, and D = -0.778 • Serum creatinine > 0.9 and serum cystatin C ≤ 0.8: • A = 0.9, B = -0.544, C = 0.8, and D = -0.323 • Serum creatinine > 0.9 and serum cystatin C > 0.8: • A = 0.9, B = -0.544, C = 0.8, and D = -0.778
	If *female* and: • Serum creatinine ≤ 0.7 and serum cystatin C ≤ 0.8: A = 0.7, B = -0.219, C = 0.8, and D = -0.323 • Serum creatinine ≤ 0.7 and serum cystatin C > 0.8: A = 0.7, B = -0.219, C = 0.8, and D = -0.778 • Serum creatinine > 0.7 and serum cystatin C ≤ 0.8: A = 0.7, B = -0.544, C = 0.8, and D = -0.323 • Serum creatinine > 0.7 and serum cystatin C > 0.8: A = 0.7, B = -0.544, C = 0.8, and D = -0.778

PEMETREXED

PHARMACOKINETICS, PHARMACODYNAMICS AND CURRENT PRACTICE IN DOSING

Pemetrexed is a folate antimetabolite, moderately protein bound (81%), and is almost entirely eliminated as unchanged drug by the kidneys (70-90% within 24 hours in patients with adequate renal function) [61]. After uptake in the (tumor) cell, a polyglutamate chain is added by folylpolyglutamate synthetase (FPGS) increasing the affinity and inhibition by pemetrexed of enzymes used in purine and pyrimidine synthesis, including thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT). Inhibiting these enzymes disrupts DNA and RNA synthesis, thus blocking cell replications and growth [62]. TS inhibition and consequential cell death of tumor and healthy cells are the most important factors for both pemetrexed's efficacy and toxicity effects (mainly nephrotoxicity and hematological toxicity) [62]. Furthermore, pemetrexed acts synergetic when combined with immunotherapy. By inactivating TS in tumor cells, pemetrexed stimulates the upregulation of PD-L1 by activating CD274 through upregulating NF-κB signaling [63], and the addition of pemetrexed to platinum-pembrolizumab doublet chemotherapy significantly improves OS in patients with stage IV NSCLC [64], as well as for platinum-atezolizumab [65].

Since pemetrexed is mainly excreted by the kidneys by both tubular secretion and glomerular filtration, clearance of pemetrexed correlates linearly with renal function [66]. Hence, a decrease in renal function will lead to an increase in pemetrexed exposure and risk of (hematological) toxicity [67, 68]. Even though pemetrexed exposure primarily depends on renal function, dosing is individualized based on BSA, with an approved dose of 500 mg/m^2 3-weekly dosing [69].

The primary hematological toxicity for pemetrexed is neutropenia, as observed in early trials with a 39-42% incidence for grade III-IV neutropenia for pemetrexed monotherapy (500-600 mg/m^2 without vitamin supplementation) [70, 71]. Pemetrexed-induced neutropenia is caused by the inhibition of proliferation of progenitor cells to fully differentiated leukocytes [72] and follows the maturation and life cycle of neutrophils with the nadir absolute neutrophil count at 8-10 days after administration [69]. An extensive study by Niyikiza *et al.* showed that vitamin B12 deficiency is associated with increased myelotoxicity [73]. These findings resulted in adding folic acid (vitamin B9) and vitamin B12 as standard supplementation in pemetrexed treatment. After introducing vitamin supplementation, a phase III study showed a decrease in hematological toxicity to 5.8% grade III-IV neutropenia and

1.9% febrile neutropenia [74]. However, real-world data shows a higher incidence of 26% for grade III-IV neutropenia [75]. Hematological toxicity of pemetrexed is driven by a "time above a toxicity concentration threshold" [76], comparable to methotrexate [77]. Consequently, patients with decreased pemetrexed elimination (i.e., impaired renal function) are prone to hematological toxicity. Moreover, cumulative exposure to pemetrexed was found to be a risk factor for the development of renal injury, consequently associated with increased incidence of treatment discontinuation related to renal events of 4 to 33% increasing with age, pre-existing condition, and use of nephrotoxic drugs [78, 79]. Hence, patients with impaired renal function (<45 mL/min) cannot be administered an effective dose without risk for severe toxicity [80], and dosing in patients with renal function <45 mL/min is contraindicated [69]. Other non-hematological toxicities for pemetrexed, besides nephrotoxicity, include gastro-intestinal and skin toxicities [69]. Cells in the gastro-intestinal tracts and skin contain both highly proliferating cells and are therefore more prone to cytotoxic effects of pemetrexed. For skin toxicities, it is still unclear if these reactions are immunologically mediated or arise from the direct cytotoxic effect on keratinocytes [81].

PROMISING DEVELOPMENTS

For efficacy, higher dosing of pemetrexed up to 900 or 1000 mg/m^2 3-weekly dosing did not improve survival outcomes compared to 500 mg/m^2 but came with greater toxicity [82, 83]. While pemetrexed exposure largely depends on renal function, dosing based on BSA proves to be effective and generally safe in patients with adequate renal function (CrCL ≥45 mL/min) [84]. However, a recent study applying dose individualization for pemetrexed based on renal function (dose = 109 × (weight/70)$^{0.75}$ + 561 × (eGFR/75)) showed the potential to reduce the incidence of toxicity (i.e., neutropenia) and decrease the costs of pemetrexed-associated neutropenia without compromising effective exposure [85]. It was recently found that the CKD-EPI equation to estimate the GFR using serum creatinine and cystatin C could best predict the pemetrexed pharmacokinetics, showing opportunities for better dose individualization [86].

Large interindividual variability in pemetrexed plasma concentration is observed, and TDM-guided dosing could be used to reduce variability in specific cases (e.g., high risk of toxicity, interaction with concomitant medication) [87]. A proposed target AUC for effective and safe treatment has already been determined for pemetrexed at 164 mg/L*h [66, 68]. However, the target AUC is not a reliable predictor of toxicity in patients with impaired renal function. Instead, time above the threshold concentration is a more accurate measure for predicting pemetrexed toxicity in these

patients. Boosman *et al.* (2021) identified pemetrexed threshold concentrations of 0.030 mg/L for not-supplemented patients and 0.110 mg/L for vitamin-supplemented patients for daily dosing of pemetrexed [76].

Finally, the timing of pemetrexed administration may be an important factor in optimizing pemetrexed efficacy, especially since NSCLC expresses various circadian genes that play key roles in DNA synthesis and nucleotide metabolism [88]. A retrospective study in 78 advanced NSCLC patients showed that patients who received pemetrexed and platinum in the morning (n=26) had a higher PFS as compared to patients receiving chemotherapy after 2:00 pm (n=52; 13 versus 43 months, respectively) [89].

RECOMMENDATIONS AND OPPORTUNITIES FOR TREATMENT OPTIMIZATION

For patients with adequate renal function (CrCL ≥45 ml/min), dose individualization based on renal function to target an AUC of 164 mg/L*h could already be implemented in clinical practice, similar to carboplatin dosing based on target AUC. Preferably, the CKD-EPI equation using serum creatinine and cystatin C should be used. However, caution is warranted for patients with impaired renal function, as data in this population remain limited. We align with regulatory guidelines contra-indicating administering pemetrexed to patients with CrCL <45 mL/min.

TAXANES (DOCETAXEL, PACLITAXEL, NAB-PACLITAXEL)

Taxanes are plant isolates used as anticancer drugs for NSCLC. It started with the discovery of paclitaxel in 1971 from the yew tree: *Taxus brevifolia*. At that time, the direct extraction of the highly lipophilic paclitaxel from the *Taxus brevifolia* proved not economically viable, needing at least 2-3 full-grown yew trees to treat one patient [90]. Only 20 years later, the preparation of economically viable quantities of paclitaxel was possible by a semisynthetic approach of modification of the precursor 10-deacetyl-baccatin III naturally and in high quantities available from the extraction of the needles of the European *Taxus Baccata*. From 1996 onwards, another semisynthetic derivative of 10-deacetyl-baccatin III was developed: docetaxel [91].

Both docetaxel and paclitaxel are highly lipophilic and extensively bound to plasma proteins [92, 93]. They are metabolized in the liver by cytochrome P450 (CYP) enzymes and excreted through the bile. Additionally, both drugs are substrates for ATP-binding cassette (ABC) transporters, which facilitate their efflux from cells, a process that affects treatment efficacy (e.g., tumor resistance due to the efflux of taxanes by

cancer cells) and toxicity (e.g., reduced efflux of taxanes by healthy cells) [91]. Solvents are added to their formulations to improve the solubility of docetaxel and paclitaxel. Docetaxel is made soluble by adding polysorbate 80 [92]. Paclitaxel uses the micelle-forming cremophor EL to increase its water solubility [93]. Both compounds are associated with high rates of hypersensitivity and infusion reactions and require the addition of prophylactic antihistamines and dexamethasone [94, 95]. Moreover, polysorbate 80 and cremophor EL can hinder circulating taxane molecules from crossing the endothelial barrier of blood vessels or penetrating tumor tissue [96]. To tackle these problems and reduce toxicity while increasing efficacy, nanoformulation of albumin-bound paclitaxel (nab-paclitaxel) was developed [91]. A large phase III trial compared docetaxel (60 mg/m^2 3-weekly dosing) with nab-paclitaxel (100 mg/m^2 weekly) in 503 patients with advanced NSCLC and found no significant differences in OS (adjusted hazard ratio (aHR) = 0.85 (95%-confidence interval (CI): 0.68-1.07). However, nab-paclitaxel did show an increased progression-free survival (PFS; aHR = 0.76; 95%-CI: 0.63-0.92, p=0.0042)) compared to docetaxel and lower incidence of grade III-IV febrile neutropenia (2% vs. 22%), although with a higher incidence of grade III-IV peripheral sensory neuropathy (10% vs. 1%) [97]. The same trend was seen in 1052 patients with advanced NSCLC treated with paclitaxel (200 mg/m^2 3-weekly dosing) or nab-paclitaxel (100 mg/m^2 weekly), finding no significant differences in OS and PFS, but significantly less neutropenia grade III (32% vs. 26%) and grade IV (33% vs. 14%) and neuropathy grade III (11% vs. <1%) and grade IV (3% vs. 0%) for nab-paclitaxel. Nab-paclitaxel was associated with a significantly increased incidence of thrombocytopenia grade III (13% vs. 5%) and IV (7% vs. 2%) and anemia grade III (22% vs. 5%) and IV (6% vs. <1%) [98]. Due to the lack of improved survival outcomes with nab-paclitaxel and its higher incidence of severe peripheral sensory neuropathy, paclitaxel and docetaxel are typically preferred. In this chapter, paclitaxel and nab-paclitaxel are discussed together since the active compound of nab-paclitaxel in tumor cells is still paclitaxel.

Taxanes bind to the binding site for GTP on microtubules (β-tubulin) and stabilize the peeling off and polymerization of the protofilaments of microtubules, leading to G2-M arrest, resulting in cell apoptosis [91]. Different effects are observed depending on taxane concentration, with docetaxel having a higher binding site affinity than paclitaxel. At high concentrations, taxanes induce cell apoptosis. However, at low concentrations (or high concentrations after adaptation to taxane treatment), taxanes alter mitosis and disturb the formation of micronuclei and aggregation of chromosomes, leading to DNA damage and the activation of the cGAS/STING pathway [91]. The cGAS/STING pathway activates the innate immune system and stimulates macrophage activity, providing a synergetic effect with immune

checkpoint inhibitors [99]. Additionally, paclitaxel binds toll-like receptor 4 (TLR-4), leading to the secretion of pro-inflammatory cytokines and enhancing inflammation response by activating dendritic, NK- and cytotoxic T-cells [100]. Moreover, paclitaxel and docetaxel inhibit the accumulation of endothelial progenitor cells (EPC) and induce the expression of thrombospondin-1 (TSP-1) in the tumor microenvironment, leading to the inhibition of angiogenesis [101].

DOCETAXEL

PHARMACOKINETICS, PHARMACODYNAMICS AND CURRENT PRACTICE IN DOSING

Docetaxel is hydrophobic, and more than 90% is bound in plasma to albumin, α1-acid glycoprotein (AAG), and lipoprotein (mainly high-density and low-density lipoprotein) [102]. Docetaxel is primarily eliminated by CYP3A4 enzymes and excreted through biliary excretion into the feces with less than 5% renal excretion [92]. The pharmacokinetics of docetaxel appear to be linear over the clinically relevant range of doses, with exposure to docetaxel increasing proportionately with the dose [92]. Covariates that influence docetaxel clearance are age, BSA, albumin and AAG concentrations, and hepatic function [103]. Although many covariates for docetaxel pharmacokinetics have been identified, most variability in exposure remains unexplained. In clinical practice, docetaxel is dosed based on BSA at 75 mg/m^2 3-weekly dosing [95]. Nevertheless, solely dosing docetaxel on BSA results in a negligible reduction in interindividual variability of the pharmacokinetics of docetaxel [104].

Systemic docetaxel drug exposure significantly correlates with the risk of toxicity, specifically with neutropenia, but also with better survival outcomes [105]. Moreover, the degree of neutropenia is associated with the efficacy of docetaxel [106]. A large study involving 885 patients with advanced or metastatic NSCLC identified grade I-II and grade III-IV docetaxel-induced neutropenia as independent factors associated with improved time to progression (TTP) and OS compared to patients without neutropenia [107].

PROMISING DEVELOPMENTS

As docetaxel is mainly metabolized by CYP3A enzymes in the liver, genotyping and phenotyping of the metabolic activity of the liver could be an option. However, evidence for genotyping is limited. A study of 92 patients with solid tumors could not find any association between CYP3A polymorphisms and docetaxel's pharmacokinetics [108]. Another candidate for genotyping could be ABC-transporters.

Studies found an association between carriers of ABCB1 gene polymorphisms and increased exposure [108] and risk of docetaxel-associated neutropenia [109].

Regarding metabolic phenotyping, an erythromycin breath test (ERMBT; ^{14}C-labelled erythromycin is administered and exhaled ^{14}C-labelled CO_2 is measured as an indicator for CYP3A activity) was found to explain 67% of interindividual variability of docetaxel exposure [110]. Other studies showed no correlation between CYP3A(4) probes like midazolam and docetaxel clearance [111, 112]. A study by Yamamoto *et al.* found the renal excretion of 6-β-hydroxy cortisol (6-β-OHF) to be significantly and highly correlated with docetaxel clearance ($r=0.867$; $p<0.001$) [113]. A subsequent prospective randomized study found the use of 6-β-OHF to reduce docetaxel interindividual variability by 46.2% compared to BSA-based dosing [114]. Similar results were found for other non-invasive methods to determine the patient individual CYP3A4 phenotyping using 6-β-OHF to cortisol ratio or other endogenous markers [115]. Clearance of a microdose of docetaxel before treatment could potentially be linearly extrapolated to therapeutically relevant doses. However, docetaxel clearance did not show a linear increase from 0.1 and 1 mg microdoses to a therapeutic dose, presumable because of plasma protein binding to AAG and other lipoproteins, which might be saturated at therapeutic doses [116, 117].

Another promising development is the change of 3-weekly to weekly dosing for docetaxel. A meta-analysis including 6 RCTs in 1018 advanced NSCLC patients investigating weekly versus 3- weekly dosing of docetaxel showed a significant decrease in grade III-IV neutropenia, while OS (relative risk (RR)=1.01; 95%-CI: 0.76-1.42, p=0.785) and objective response rate (RR=0.81; 95%-CI: 0.47-1.40, p=0.465) remained unaffected [118].

Evidence on the effectiveness of TDM-guided dosing for docetaxel in NSCLC patients is still limited. A small study (n=30) across multiple tumor types showed that TDM-guided dosing, compared to standard BSA-based dosing, reduced interindividual variability in docetaxel exposure by 39% and variability of neutropenia by 50% when targeting at a docetaxel exposure (AUC) of 4.9 mg/L*h [119]. Lastly, TDM-guided dosing could potentially be utilized for subsequent cycles in specific patient populations, such as metastatic castration-resistant prostate cancer (mCRPC) patients. A large meta-analysis of 26 RCTs (n=1150) identified a 1.8-fold lower docetaxel exposure and 2.2-fold lower odds of developing grade III-IV neutropenia for mCRPC patients compared to patients with other solid tumors [120].

Research data suggest a link between patient survival and neutrophil count in the first cycle, showing a potential benefit for dose reduction after the first cycle of docetaxel [106]. In clinical practice, neutrophil counts are measured as part of the standard of care one day before the next cycle. Yet, the most accurate estimate of the neutrophil nadir would be obtained by measuring it approximately 8-10 days after docetaxel administration. Interestingly, a simulation study showed that one extra neutrophil measurement is sufficient to limit severe neutropenia while increasing dose intensity [121]. However, to our knowledge, this has not yet been prospectively tested in clinical practice. Although promising, we are still hesitant at the moment to recommend docetaxel dosing based on neutrophil counts. The available evidence is based on older studies conducted when docetaxel was given as an earlier line of treatment. Currently, however, docetaxel is generally used as a third- or fourth-line therapy, where any added toxicity could be especially risky and potentially life-threatening. Moreover, an extra neutrophil measurement during treatment comes with additional logistic consequences.

RECOMMENDATIONS AND OPPORTUNITIES FOR TREATMENT OPTIMIZATION

We recommend weekly dosing of docetaxel, as it decreases the incidence of severe neutropenia while similar efficacy is maintained. However, this will impact hospital infusion care and patient visits. With regard to other promising developments, including neutrophil-guided dosing, metabolic genotyping and phenotyping, and TDM-guided dosing, more clinical evidence is needed before further recommendations can be made.

PACLITAXEL AND NAB-PACLITAXEL

PHARMACOKINETICS, PHARMACODYNAMICS AND CURRENT PRACTICE IN DOSING

Paclitaxel clearance is non-linear, which is especially apparent in up to 3-hour infusion. Its non-linear clearance is attributed to the saturation of paclitaxel transport, binding (albumin and AAG), CYP2C8-mediated metabolism, and by the formulation of paclitaxel using the solvent cremophor EL mixed 1:1 with ethanol [96, 122]. Different PK parameters have been tested for association with clinical outcome parameters of paclitaxel treatment: AUC, C_{max}, and time above threshold concentration ($T_{>concentration}$). Time above paclitaxel plasma concentration of 0.05 μmol/L ($T_{>0.05}$) appeared to be the best predictor of paclitaxel-associated neutropenia, paclitaxel-induced polyneuropathy (cumulative chemotherapy-induced peripheral neuropathy (CIPN)), and clinical outcomes [123]. Some studies even suggest a higher time above the threshold ($T_{>0.10}$) [124]. Like docetaxel, paclitaxel

is primarily cleared by the liver and eliminated through biliary excretion. Hence, patients with impaired liver function or liver metastases have a decreased paclitaxel clearance, leading to increased exposure and an increased risk of paclitaxel-induced toxicity [125].

Nab-paclitaxel is albumin-bound paclitaxel. The albumin part binds to albondin (gp60) receptors on endothelial cells. and paclitaxel-albumin complexes are carried across the endothelial membrane (transcytosis) into surrounding tissues, including tumor tissue. Accumulation of albumin-paclitaxel complexes is increased by a high amount of leaky tumor vasculature and by the albumin binding activity of secreted protein acidic and rich in cysteine (SPARC) in tumor tissue [96]. The albumin-paclitaxel formulation rarely shows infusion or hypersensitivity reactions. Therefore, nab-paclitaxel does not require prophylactic medication and can be administered by intravenous infusion 30 minutes faster compared to 1- or 3-hour paclitaxel and 1-hour docetaxel infusions [126]. Nab-paclitaxel pharmacokinetics show linear elimination with a higher free fraction of paclitaxel (6.2%) [127] compared to paclitaxel cremophor EL (2.3%) [128]. Still, since albumin has multiple times higher molecular weight compared to paclitaxel, nab-paclitaxel is dosed at a higher dose of 300 mg/m^2 versus 175 mg/m^2 for paclitaxel cremophor EL 3-weekly dosing [96]. At high dosages of nab-paclitaxel, elimination is non-linear, indicating a possible saturation of metabolism at high paclitaxel concentrations [122]. Clearance of nab-paclitaxel is equal to clearance of its active component paclitaxel. Hence, clearance is mainly by the liver, and dose reduction is recommended for patients with impaired liver function [126].

Exposure to nab-paclitaxel is associated with toxicity, including (febrile) neutropenia and alopecia, but without acute or infusion-related hypersensitivity systemic reactions [129]. Moreover, nab-paclitaxel is still associated with cumulative CIPN, even though the formulation of nab-paclitaxel was developed to reduce peripheral neuropathy compared to paclitaxel and docetaxel. However, studies have been conflicting. The latest meta-analysis, including 24 studies, found a significantly higher incidence of peripheral neuropathy for nab-paclitaxel versus paclitaxel (16% vs. 5%) [130].

PROMISING DEVELOPMENTS

Paclitaxel's time above plasma concentration of 0.05 μmol/L ($T_{>0.05}$) is associated with both efficacy and toxicity outcomes, suggesting the potential for TDM-guided dosing. Several prospective RCTs in patients with advanced NSCLC have been conducted, aiming for a target time above 0.05 μmol/L paclitaxel plasma concentration between 26 and 31 hours or ≥15 hours without a clearly defined upper limit for 0.10 μmol/L ($T_{>0.10}$) [123]. All studies demonstrated reduced paclitaxel-associated toxicity,

primarily neuropathy, while efficacy was not significantly different compared to BSA-based dosing. For nab-paclitaxel, literature concerning TDM-guided dosing in NSCLC patients based on a specific plasma concentration is limited. A study by Chen *et al.* in 150 patients with various tumors receiving either 100 mg/m^2 weekly or 300 mg/m^2 3-weekly dosing nab-paclitaxel found time above the $C_{threshold}$ of 720 μg/L (respectively 0.86 and 3.75 hours) to be associated with a ≥50% decrease in neutrophils and that the development of neutropenia to be positively associated with age (but not with hepatic function, tumor type, gender, or dosing schedule) [127].

Genotyping and metabolic phenotyping for paclitaxel, and thus nab-paclitaxel, may also be an opportunity, though to a lesser extent. Ovarian cancer patients (n=93) carrying the *CYP2C8*3* allele showed a significantly increased paclitaxel AUC and 11% lower clearance than non-carriers [131]. Unsurprisingly, patients carrying the *CYP2C8*3* allele were associated with an increased risk of paclitaxel-associated neurotoxicity and higher incidences of complete response compared to non-carriers (55% vs. 23%) [132]. Lastly, having an *ABCB1* dysfunctional allele was associated with an increase in paclitaxel-associated hematological and neuropathy [133], gastro-intestinal toxicity, and possibly increased survival outcomes relative to non-carriers [134].

Weekly dosing of paclitaxel instead of 3-weekly dosing has shown favorable results. A meta-analysis including 10 RCTs in 3504 advanced solid tumor patients showed that weekly paclitaxel treatment reduces severe neutropenia and sensor neuropathy (10 RCTs; odds ratio (OR)=0.49; 95%-CI: 0.30-0.82)) and improves response rates (5 NSCLC RCTs; OR=1.24; 95%-CI: 1.01-1.53) compared to 3-weekly dosing [135]. For nab-paclitaxel, multiple studies show that reducing the dosing interval of nab-paclitaxel to 100 mg/m^2 weekly resulted in improved efficacy and less toxicity compared to 300 mg/m^2 3-weekly dosing [136, 137].

In pancreas cancer studies, the grade of nab-paclitaxel-induced neutropenia of weekly dosing seems to be an independent predictive for grade III-IV versus grade I-II neutropenia (19.2 vs. 11.3 months, p<0.001) and prognostic factor (HR=0.79; 95%-CI: 0.69-0.91, p=0.001) associated with increased OS [138]. A prospective study by Scheithauer *et al.* in 421 patients with metastatic pancreas cancer receiving nab-paclitaxel 125 mg/m^2 weekly found 172 (41%) patients to receive a dose reduction and 300 (71%) a dose delay. Patients who had a dose reduction and dose delay completed more cycles and received higher cumulative dosing compared to patients not receiving a dose reduction. Furthermore, patients receiving no dose reduction and dose delay were significantly associated with decreased OS compared to patients

receiving dose reduction (6.9 vs. 11.4 months, HR=1.93; 95%-CI: 1.53-2.44, p<0.0001) and dose delay (6.2 vs. 10.1 months, HR=2.05; 95%-CI: 1.60-2.63, p<0.0001) [139].

RECOMMENDATIONS AND OPPORTUNITIES FOR TREATMENT OPTIMIZATION

For paclitaxel, we recommend starting the first cycle using BSA-based dosing for 3-weekly dosing of paclitaxel, followed by blood sampling around 24 hours after the start of infusion and a TDM-guided dose aiming at the time above plasma concentration of 0.05 μmol/L ($T_{>0.05}$) of 26-31 hours based on the recommendation by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) [123]. A validated commercial assay is readily available including a decision support tool for routine paclitaxel TDM [140]. If neutropenia grade III-IV occurred in the previous cycle, the dose of paclitaxel is reduced. Moreover, weekly dosing of paclitaxel may ameliorate the toxicity profile of paclitaxel without compromising efficacy (see Table 2). We recommend weekly dosing of nab-paclitaxel, as it offers similar opportunities to reduce toxicity while enhancing efficacy as paclitaxel does.

GEMCITABINE

PHARMACOKINETICS, PHARMACODYNAMICS AND CURRENT PRACTICE IN DOSING

Gemcitabine (dFdC) is an analog of cytidine with the addition of two fluorine substituents on the 2' position of the furanose ring [141]. As dFdC is a hydrophilic prodrug, it must first be transported into the cell by membrane nucleoside transporters (mainly human equilibrative nucleoside transporters (hENTs)). Once inside the cell, dFdC is activated through intracellular phosphorylation to gemcitabine monophosphate (dFdCMP) primarily by the rate-limiting enzyme deoxycytidine kinase (dCK) [141, 142]. Additional phosphorylation creates the active metabolites gemcitabine di-(dFdCDP) and triphosphate (dFdCTP) and prevents them from being excreted from the cell [143].

Gemcitabine clearance from plasma is linear and independent of dosing up to 3650 mg/m^2 [144]. However, the phosphorylation of gemcitabine intracellular to dFdCDP and dfdCTP is saturated at high concentrations of gemcitabine [145]. Gemcitabine is inactivated mainly by deoxycytidine deaminase (dCDA) to di-fluoro-deoxyuridine (dFdU) or phosphorylated gemcitabine by deoxycytidylate deaminase to phosphorylated uridine (e.g., dFdCMP to dFdUMP) and subsequently to dFdU [141]. Gemcitabine and dFdU are excreted from the cell since they are not a substrate for

pyrimidine nucleoside phosphorylases [144]. dCDA is expressed at high levels in the plasma and the liver [142]. Hence, clearance of gemcitabine is fast ($t_{1/2}$ = 2-15 min), with 50-95% of gemcitabine metabolized into dFdU and excreted via the urine within 24 hours (>90% within one week as either gemcitabine (1%) or dFdU (99%)) [143]. Since dCK is the rate-limiting enzyme for activation of gemcitabine, saturation or deficiency of dCK decreases the effectiveness of gemcitabine [142]. Moreover, phosphorylated dFdU still present in the (tumor)cell can again be incorporated in DNA (and RNA) and is associated with cytotoxicity, increasing with prolonged exposure [146]. Covariates that influence gemcitabine clearance, and thus exposure, are creatinine clearance, sex, *dCDA* polymorphisms, and BSA [147], while age seems not [148]. Currently, gemcitabine is dosed based on BSA 1000-1250 mg/m^2 weekly and administrated in 30 minutes (40 mg/m^2/min), resulting in dFdC plasma concentration of 20-60 μM, whereas saturation of dCK is already reached at 15-20 μM [145].

The phosphorylated gemcitabine anabolites have multiple intracellular targets influencing DNA synthesis. dFdCDP inhibits ribonucleotide reductase (RNR) needed for producing deoxynucleotides, further stimulating the incorporation of gemcitabine anabolites into DNA [149]. dFdCTP inhibits DNA polymerase and is incorporated into DNA, leading to direct termination of chain elongation, preventing DNA repair enzymes from detecting DNA chain termination and inducing apoptosis [141, 142].

PROMISING DEVELOPMENTS

To avoid dCK saturation and to increase intracellular accumulation of dFdCTP, prolonged gemcitabine infusion times at 10 mg/m2/min have been proposed. Indeed, dosing at 10 mg/m2/min increased the accumulation of dFdCTP. However, at the same time, gemcitabine-induced toxicity was increased compared to conventional 30-minute infusion without affecting survival outcomes [150]. Literature on this topic is conflicting. A study by Lee *et al.* (n=48) examining the toxicity and efficacy of prolonged gemcitabine infusion (1000 mg/m^2) combined with cisplatin (25 mg/m^2) in elderly or poor performance status patients with NSCLC found comparable response rates and toxicity levels to those in patients with good performance status [151]. Similarly, an observational study (n=39) by Locher *et al.* reported similar outcomes for elderly patients (≥70 years) with pancreatic cancer [152]. As survival outcomes remain unaffected, but toxicity increases, this suggests that the intracellular concentrations of gemcitabine achieved with the current dosage are within the therapeutic range. Therefore, administering a reduced dose of gemcitabine over an extended period could maintain similar efficacy (being within the therapeutic exposure range) while reducing toxicity. Hence, another proposed treatment regimen for gemcitabine is the prolonged infusion of weekly low-dose gemcitabine (PLDG) for 250 mg/m^2 over

6 hours (=0.7 mg/m²/min). Compared to the standard dosing of gemcitabine, an extensive study by Patil *et al.* in 308 advanced SCLC patients showed no significant difference in median OS, PFS, and adverse event rate for PLDG compared to standard weekly gemcitabine dosing of 1000 mg/m² in 30 minutes [153].

Likewise, for gemcitabine, dosing based on neutropenia as a prognostic factor for treatment outcome is possible [34, 138]. A large study by Pallis *et al.* looked at docetaxel-gemcitabine treatment in advanced NSCLC patients (n=885) and found a significantly increased median OS of 12.5 (95%-CI: 11.3-13.7) and 11.2 months (95%-CI: 9.2-13.2) for mild (grade I-II) and severe (grade III-IV) neutropenia compared to 7.9 months (95%-CI: 6.9-8.8) for absence (grade 0) of neutropenia [107]. However, to our knowledge, only one large RCT (phase III) has been conducted, describing 402 metastatic pancreas cancer patients receiving gemcitabine monotherapy and showed a significant association between decreased OS and gemcitabine-induced toxicity [139].

Genotyping for *dCK* [154] and tumor expression analysis of *hENT* [155] show promising results as a predictor of gemcitabine treatment outcomes. A meta-analysis including 29 studies of 253 patients with advanced pancreatic carcinoma found an association between higher *hENT1* tumor expression and increased OS (HR=0.674; 95%-CI: 0.509-0.893, p=0.006), without an increase in PFS (HR=0.740; 95%-CI: 0.517-1.059, p=0.100) [156]. To further reduce interpatient variability, TDM-guided dosing for gemcitabine could be possible with a target concentration of 20 μM (~5 μg/mL) corresponding with saturation levels of dCK [157] or C_{max} correlated with gemcitabine-induced toxicity [158]. However, gemcitabine's standard of care is administrated in 30 minutes, making the blood sampling needed hours after administration difficult. Moreover, immunoassays for gemcitabine are still being developed and optimized [157].

RECOMMENDATIONS AND OPPORTUNITIES FOR TREATMENT OPTIMIZATION

At the moment, we cannot recommend prolonging the gemcitabine infusion time, as more research is needed to determine whether a prolonged infusion of low-dose gemcitabine can maintain efficacy while reducing toxicity. Moreover, whether extended hospital stays due to longer infusion times outweigh the costs has yet to be investigated.

VINORELBINE

PHARMACOKINETICS, PHARMACODYNAMICS AND CURRENT PRACTICE IN DOSING

Vinorelbine is a semisynthetic vinca alkaloid that reversibly binds to microtubules' positive end, destabilizing its function. The primary binding site of vinorelbine is β-tubulin, which induces a conformational change that increases the affinity of tubulin for itself and influences microtubules' dynamics of lengthening and shortening and increases. At high concentrations, vinorelbine stimulates microtubule depolymerization and mitotic spindle destruction, and at low concentrations, it blocks mitotic progression [159]. Vinorelbine is highly lipophilic and primarily metabolized in the liver (<20% through urinary excretion) and excreted unchanged in bile to vinorelbine N-oxide and desacetyl-vinorelbine [160]. Vinorelbine clearance is shown to be correlated with creatinine clearance but not with age and BSA [161]. However, currently, vinorelbine is still dosed based on BSA. Due to a relatively low oral bioavailability of 40%, a higher dose is given per os compared to intravenous administration (60 mg/m^2 vs. 25-30 mg/m^2, respectively) [162].

The hepatic clearance of vinorelbine is shown to be associated with *ABCB1* [161] and partly with *CYP3A* genotypes [163]. Nevertheless, clearance of vinorelbine in plasma is high and approaches hepatic blood flow, indicating that the overall capacity of the liver in removing vinorelbine is high (i.e., maximized to hepatic blood flow) [160]. Only small prospective studies have investigated the relationship between vinorelbine clearance and hepatic function and found no effect of liver impairment on the pharmacokinetics of vinorelbine [161, 164]. The primary vinorelbine-induced toxicity is neutropenia, anemia, and thrombocytopenia, with the maximum dose of vinorelbine intravenously set at 35 mg/m^2 due to the dose-limiting toxicity of neutropenia [162].

PROMISING DEVELOPMENTS

BSA is associated with the degree of myelosuppression (i.e., neutropenia) in vinorelbine treatment [161]. A study in metastatic breast cancer patients (n=25) showed fixed dose vinorelbine (+ capecitabine) to be more effective and safer compared to dosing based on BSA and found no association between vinorelbine clearance and BSA [165]. Gusella *et al.* (n=82) found high blood concentrations of vinorelbine and its metabolites associated with increased toxicity but not efficacy in NSCLC patients [166]. Another study (n=201) found high BMI to be associated with increased vinorelbine-induced toxicity but found no association for the covariates sex, chemotherapeutic regimen (monotherapy vs. combination therapy), prior chemotherapy, and dose of vinorelbine

(<40 vs. ≥40 mg) [167]. In contrast, Nobili *et al.* (n=83) did find an association between vinorelbine toxicity and covariates age and sex [168].

The clearance of technetium labeled sestamibi (^{99m}Tc-MIBI) and midazolam could be used for phenotyping of *ABCB1* and *CYP3A*, and clearance of both substances significantly correlated to vinorelbine clearance. However, as vinorelbine clearance is associated with creatinine clearance, the partial correlation between vinorelbine clearance and hepatic ^{99m}TC-MIBI clearance was 0.44 after adjusting for creatinine clearance [161].

Metronomic dosing of vinorelbine has also been investigated with promising results. A meta-analysis including 509 stage IIIb/IV NSCLC (11 RCTs) identified a similar efficacy compared to monotherapy vinorelbine, with a median PFS of 3.5 months (95%-CI: 2.5-4.4) and OS of 8.2 months (95%-CI: 7.2-9.2), and less and lighter adverse events with an only 16% incidence of grade III-IV adverse events (95%-CI: 10-22) with 9% neutropenia (95%-CI: 2-20) [169]. Furthermore, adding granulocyte colony-stimulating factor (G-CSF) could increase the dose intensity of vinorelbine for both daily and weekly dosing without a corresponding increase in toxicity [170].

The limited and conflicting data, particularly in NSCLC patients, prevent a definitive conclusion regarding the relationship between PK parameters and PD efficacy and toxicity endpoints of vinorelbine treatment. In addition, while prolonged infusion of vinorelbine over 96 hours in a dose of 8 mg/m^2 has demonstrated considerable therapeutic activity, it is associated with severe toxicities, affecting half of the patients treated [171]. These results do not indicate an advantage of prolonged infusion compared to conventional weekly administration.

RECOMMENDATIONS AND OPPORTUNITIES FOR TREATMENT OPTIMIZATION

Currently, we still recommend dosing at BSA. There is not enough evidence to suggest dosing differently, especially since BSA seems to correlate with toxicity. However, a clear PK/PD relationship between plasma exposure and response to vinorelbine has yet to be found (see Table 2), and TDM-guided dosing is not advised.

CONCLUDING REMARKS

Currently, all classical cytotoxic drugs, except for carboplatin, in NSCLC are dosed based on BSA. In this review, we showed many opportunities for precision dosing

of classical anticancer drugs to improve NSCLC treatment outcomes in which the incidence of severe toxicity can be reduced, and efficacy can be improved (see Table 2). An important point to note is that while the type of cancer may not necessarily alter pharmacokinetics, it could impact efficacy (pharmacodynamics), making extrapolation to NSCLC patients potentially unfeasible. To address this concern, we have added footnotes to highlight which recommendations were not investigated in NSCLC populations.

While multiple promising developments exist for cisplatin, pemetrexed, and vinorelbine, these opportunities are not yet for direct implementation and require further research. In the case of carboplatin, we recommend immediately adopting cystatin C to individualize the dose of carboplatin. We suggest weekly dosing for docetaxel, paclitaxel, and nab-paclitaxel to minimize toxicity while maintaining treatment efficacy. Specifically, for paclitaxel, when administered in a 21-day cycle, we recommend the use of TDM-guided dosing following the international IATDMCT guidelines. Finally, we advise investigating prolonging infusion times for gemcitabine to reduce toxicity without compromising effectiveness.

Although dose individualization strategies have been shown to significantly improve health outcomes and reduce side effects, implementing precision dosing opportunities may also pose challenges. For example, individualized dosing based on TDM requires extra time and sampling, clear PK/PD relationships (often tumor-specific), logistical planning, dosing decision support, and facilities [172, 173]. Therefore, further research is needed to ensure that these strategies are both cost-effective and feasible for routine clinical settings without overstraining existing healthcare systems.

Currently, much of the effort toward dose optimization remains within the academic sphere. A major barrier to the implementation of precision dosing recommendations, based on readily available evidence, is that academic research is often not integrated or adopted by regulatory agencies or license holders. The findings of this review, alongside other academic dose optimization studies, should reach governments, regulatory agencies, license holders, and key healthcare professionals. These recommendations should not be confined to stay an academic exercise but should be actively considered by all stakeholders. However, there is limited commercial incentive for license holders to adjust their labeling. This is why initiatives by regulatory agents like the FDA's Project Renewal, which aims to update prescribing information (i.e., labeling) for older oncology drugs, are so critical [174]. Such initiatives help ensure that information remains clinically meaningful and scientifically up-to-date.

In conclusion, this narrative review provided a comprehensive overview of studies focused on individualized dosing opportunities of classical cytotoxic drugs in patients with NSCLC and outlined the most promising, readily implementable dose optimization strategies. Some of these approaches have already been proven in multiple prospective studies and can be directly implemented into clinical practice, requiring minimal further research. Finally, even though there is still a lot to be done to optimize classical cytotoxic therapy dosing strategies to individual patients' characteristics in the era of precision medicine, promising developments and opportunities are numerous and encouraging.

Table 2: Characteristics, proposed pk/pd relationships and opportunities for precision dosing strategies for classical cytotoxic drugs in treatment of nsclc

Cytotoxic drug	Target	Approved dose
Cisplatin	Bind to DNA-adducts in cells	75 mg/m² IV Q3W
Carboplatin		400 mg/m² IV Q3W Dose = AUC_{target} * (GFR +25)
Pemetrexed	Folate antimetabolite needed for DNA and RNA synthesis	500 mg/m² IV Q3W
Docetaxel	Binding site GTP on microtubules	75 mg/m² IV Q3W
Paclitaxel		175 mg/m² IV Q3W
Nab-paclitaxel		100 mg/m² IV Q1W
Gemcitabine	Pyrimidine antagonist	1250 mg/m² IV Q3W
Vinorelbine	Binding site β-tubulin on microtubules	25-30 mg/m² IV 60 mg/m² PO

[a] No prospective studies available

[b] Not investigated in NSCLC population

Abbreviations: PK/PD = pharmacokinetic/pharmacodynamic, NSCLC = non-small cell lung cancer, IV = intravenously, Q1W = weekly dosing, Q3W = 3-weekly dosing, AUC = area under the curve, Cmax = maximum concentration, TDM = therapeutic drug monitoring, GFR = glomerular filtration rate, CrCL = creatinine clearance, mCRPC = metastatic castration-resistant prostate cancer, dCK = deoxycytidine kinase, hENT = human equilibrative nucleoside transporters, PO = per os

Proposed PK/PD relationships		Precision dosing	
Efficacy	**Toxicity**	**Opportunities for treatment optimization to be directly implemented**	**Promising developments**
AUC	AUC C_{max}	-	- Dosing based on renal function[a] - Neutrophil-guided dosing[a] - TDM-guided dosing in pediatric patients and 5-day continuous infusion[b]
AUC	AUC	Dosing based on cystatin C as novel biomarker for estimating carboplatin clearance For example Schmitt *et al.* carboplatin clearance = $117.8*(Cr_{serum}/75)^{-0.450}*$cystatin $C^{-0.385}*$(body weight/65)$^{+0.504}*$ (age/56)$^{-0.366}*$ 0.847^{sex} with sex = 0 for male [58]	- TDM-guided dosing in pediatric and high-dose carboplatin protocols Improved estimation of carboplatin clearance using: 1. CT derived body composition and serum creatinine[a] P2. ro-enkephalin
AUC	AUC Time above threshold	Dose individualization (for patients with CrCL ≥45 ml/min) based on renal function to target an AUC of 164 mg/L*h	- TDM-guided dosing for normal renal function based on proposed target AUC of 164 mg/L*h [66, 68][a] - Dosing adjustment in patients with impaired renal function (<45 mL/min) and potentially adding folinic acid prophylaxis therapy[a]
AUC	AUC	Weekly dosing	- Neutrophil-guided dosing[a] - TDM-guided dosing in specific populations such as patients with mCRPC - Genotyping and metabolic phenotyping (e.g., *CYP3A* and *ABCB1*)
Time above threshold	Time above threshold	- TDM-guided dosing at time-above-threshold of 0.05 μmol/L ($T_{>0.05}$) - Weekly dosing	- Genotyping and metabolic phenotyping (e.g., *CYP2C8*3* and *ABCB1)*
		Weekly dosing	- Neutrophil-guided dosing[b] - TDM-guided dosing - Genotyping and metabolic phenotyping (e.g., *CYP2C8*3* and *ABCB1)*
Inconclusive		-	- Prolonged infusion times - Genotyping (e.g., *dCK* and *hENT*[a,b]) - Neutrophil-guided dosing
Inconclusive		-	- Neutrophil-guided dosing[a]

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CHAPTER II

The association of body mass index with safety and effectiveness of first-line carboplatin-based chemotherapy in patients with metastatic non-small cell lung cancer

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ABSTRACT

INTRODUCTION

Carboplatin is an anticancer drug used for treatment of various types of cancer including non-small cell lung cancer (NSCLC). Dosing is based on estimated glomerular filtration rate (GFR) using the Cockcroft-Gault formula. In overweight patients, the GFR is more likely overestimated, resulting in a potentially overdose of carboplatin affecting treatment response. This study investigated the effect of body mass index (BMI) on overall survival (OS) and progression-free survival (PFS) in patients with stage IV NSCLC treated with first-line carboplatin-based chemotherapy. Secondary safety endpoints were thrombocytopenia and toxicity-related hospitalizations.

PATIENTS AND METHODS

This was a retrospective multicenter cohort study. Patients were categorized according to BMI <25.0 kg/m^2 (normal weight and reference), 25.0-29.9 kg/m^2 (overweight) or ≥30.0 kg/m^2 (obese). For survival analyses adjusted hazard ratios [aHR] were calculated using multivariate Cox regression analysis. Secondary outcomes were analyzed using multivariate logistic regression providing adjusted odd ratios [aOR].

RESULTS

Overweight patients (n=174) had a significantly better OS (aHR=0.72, 95%-CI:0.59-0.89) and PFS (aHR=0.74, 95%-CI:0.61-0.90) compared to normal weight patients (n=268). OS nor PFS were different in obese patients (n=51) compared to normal weight patients. However, obesity was associated with a significantly higher incidence of thrombocytopenia grade ≥3 (aOR=3.47, 95%-CI:1.75-6.90).

CONCLUSION

This study shows a significantly longer survival for overweight patients compared to normal weight patients. Obese patients have an increased risk for grade ≥3 thrombocytopenia without an increase in survival from carboplatin-based chemotherapy. This suggest that a lower carboplatin starting dose in obese patients followed by thrombocytopenia-guided dosing may enable safer therapy without negatively affecting treatment effectiveness.

INTRODUCTION

Carboplatin is an alkylating anticancer drug that is registered for the treatment of various types of cancer, including non-small cell lung cancer (NSCLC). It can be given as single agent, although it is typically given in combination with other chemotherapeutic drugs with or without the addition of biological agents [1]. Despite the emerging role of immunotherapy, classical anticancer drugs including carboplatin are the cornerstone of first-line treatment of NSCLC.

Carboplatin is largely renally excreted for up to 75% as unchanged drug. Thereby, clearance and hence systemic exposure of carboplatin is linearly associated with the glomerular filtration rate (GFR) [2-4]. Furthermore, there is a clear correlation between the area under the concentration-time curve (AUC) and hematological toxicity, as well as response rate in patients receiving carboplatin [5-6]. Therefore, dosing of carboplatin is adjusted for renal function and target AUC using the Calvert formula:

$$\text{Dose} = \text{AUC}_{\text{target}} * (\text{GFR} + 25)$$

The target AUC generally ranges between 2-7 [mg*min/mL] depending on type of treatment regimen and dosing interval [7]. Internationally, the GFR is typically calculated using the Cockcroft-Gault formula, based on the weight, sex, age and serum creatinine of the patient [7-9].

$$\text{GFR} = \frac{(140 - \text{age}) * \text{weight}}{0.815 * \text{Cr}_{\text{serum}}} * [\text{IF FEMALE} * 0.85]$$

In the Cockcroft-Gault formula serum creatinine and weight are strong determinants. Using the Cockcroft-Gault formula in patients with normal weight and normal creatinine values provides an adequately estimated GFR. However, it is known that in overweight and obese patients the GFR is more likely to be overestimated using the Cockcroft-Gault formula [10-12]. Consequently, using an overestimated GFR value in the Calvert equation may then result in a potential overdose of carboplatin. This has indeed been demonstrated in a pharmacokinetic study by Herrington JD *et al.* who showed an average overestimation of carboplatin target AUC of 24.0% (95% confidence interval (CI): 12.9-35.2) in patients with a Body Mass Index (BMI) of ≥ 27.0 kg/m^2 [13]. Thereby, an overestimated clearance of carboplatin may directly affect risk of toxicity, affecting dose adjustment and thereby potentially also effectiveness

of treatment. Indeed, the relationship between higher incidences of toxicity in patients with higher BMI is confirmed in literature, and several studies have demonstrated a significant relationship between higher BMI and higher risk of severe carboplatin-induced toxicity [14-17]. However, with regard to effectiveness, there is a knowledge gap about the BMI- effectiveness relationship. On the one hand, one could argue that a higher than targeted carboplatin dose due to overweight may indeed increase effectiveness of treatment, however, on the other hand it may also negatively affect effectiveness, due to more frequent treatment complications, treatment delays and early treatment withdrawals as a result of higher risk of severe toxicity. A study by Lam *et al.* found an association between increased BMI and long-term improved survival in patients with NSCLC with a reduction of 31-58% in mortality for obese patients (BMI ≥ 30.0 kg/m^2) relative to normal weight patients [18]. However, although this patient population was well defined, consisting of only locally advanced NSCLC patients, treatment regimens largely varied in this study population and not all patients were treated with carboplatin-based chemotherapy. In addition, a significant part of patients received concurrent chemoradiotherapy, and in 30% of patients' resection of residual tumor was performed followed by consolidative chemotherapy. Another smaller study by Cuesta *et al.* did not find a significant difference in effectiveness between overweight and obese patients versus normal-weight patients treated with carboplatin, however, this was a very heterogeneous patient population with regard to the primary tumor [19]. Thereby, the effect of BMI on the effectiveness of carboplatin-based chemotherapy in clearly defined patient populations, and whether BMI is prognostic or predictive for treatment efficacy of carboplatin remains rather unestablished. Hence, more studies are needed for a conclusive answer.

The hypothesis of this study was that the calculated GFR is more likely to be overestimated in overweight and obese patients using the standard Cockcroft-Gault formula compared to normal weight patients, thereby resulting in increased risk of carboplatin-induced severe toxicity, but, with an unknown effect on survival outcomes. Therefore, the primary objective of the study was to determine the effect of BMI on overall survival (OS) and progression-free survival (PFS) in patients with stage IV NSCLC treated with first-line carboplatin-based chemotherapy. Secondary objectives were to determine the effect of BMI on toxicity-associated hospitalization and thrombocytopenia.

PATIENTS AND METHODS

STUDY DESIGN AND PATIENT POPULATION

This was a retrospective, multi-center cohort study to determine the effect of BMI on treatment outcome of first-line carboplatin-based chemotherapy in patients with metastatic NSCLC in terms of toxicity and survival. The study population consisted of patients diagnosed with metastatic stage IV NSCLC between 2008 and 2014, and treated with first-line carboplatin-based chemotherapy in 3-weekly cycles with a carboplatin target AUC of 5 or 6 [mg*min/mL]. The patient population was selected from a larger NSCLC cohort of patients as previously described by Cramer-van der Welle CM *et al.* [20]. All patients were treated in one of the six participating hospitals within the Santeon hospital network. This network consists of a total of seven large (non-university) teaching hospitals dispersed over the Netherlands, compromising >11% of the Dutch population [21].

For this study purpose patients were categorized by BMI following the standard WHO classification index, i.e. patients with BMI <18.5 kg/m^2 were defined as underweight, BMI 18.5-24.9 kg/m^2 as normal weight, BMI 25.0-29.9 kg/m^2 as overweight and BMI ≥30.0 kg/m^2 as obese.[22] Given the relatively low number of patients with underweight, this category was combined with the patients with normal weight.

STUDY VARIABLES

Patient baseline characteristics that were collected at time of first carboplatin administration were age, sex, weight, length, GFR, target AUC, Charlson comorbidity index (CCI), Eastern Cooperative Oncology Group - Performance status (ECOG-PS), and tumor histology (squamous, adenocarcinoma, large cell, other or not otherwise specified (NOS)). Treatment characteristics that were obtained included dose of carboplatin, use of other concomitant anticancer drugs, start date of chemotherapy, serum creatinine, lowest platelet count between cycles, toxicity-related hospitalization and duration of toxicity-related hospitalization, all during the first 3 cycles of treatment.

STUDY ENDPOINTS

Primary endpoints of this study were progression free and overall survival for the three BMI categories. Secondary endpoints were toxicity-associated hospitalization and thrombocytopenia. Overall survival was defined as the time interval in days from start with carboplatin-based treatment until death from any cause or last date of follow-up (November 2019). Progression-free survival was defined as the time interval in months from start with carboplatin-based treatment until documented

progression or death, whichever occurred first. Documented progression was either obtained from the reports of the radiologist's assessment of radiological scans used to determine response to treatment; otherwise, this was obtained from correspondence of the evaluation by the treating oncologist.

Thrombocytopenia was graded according to common terminology criteria for adverse events (CTCAE) v4.0 of the National Cancer Institute (NCI) [23]. Hospitalization was defined as hospitalization due to side-effects or complications of chemotherapy. All data were retrieved from the electronic health records (EHR) of the participating hospitals.

A potential carboplatin overdose in the first cycle, due to overestimation in GFR, may be adjusted in subsequent cycles based on thrombocyte counts and clinical tolerance. Possible dose reduction and/or treatment delay can be expressed as relative dose intensity (RDI). In this study, the RDI for each cycle was calculated as an additional indicator for carboplatin-induced toxicity. A reduction of more than 20% (RDI below 80%) was considered as reduced dose intensity due to treatment related toxicity.

$$\mathrm{RDI} = \left(\frac{\mathrm{Dosage(actual\ given)_n}}{\mathrm{Duration_n}}\right) \Big/ \left(\frac{\mathrm{Dosage(calculated\ using\ Calvert\ formula)_n}}{21}\right)$$

In this formula, n represents cycles 1-3, dosage [mg] is calculated using the Calvert formula for each cycle and duration is in days. The RDI was calculated for each individual cycle of treatment as well as the average RDI (aRDI) of all three cycles.

Given the fact that target AUC was not always specified in the patients' record file, target AUCs were uniformly set and based on general treatment guidelines: the carboplatin target AUC of patients treated with concomitant gemcitabine or pemetrexed was set at 5 mg*min/mL; for patients treated with concomitant etoposide, paclitaxel (± bevacizumab) and docetaxel the carboplatin target AUC was set at 6 mg*min/mL [24].

STATISTICAL ANALYSIS

Categorical data were expressed in numbers and percentages and continuous data as mean and standard deviation or median and interquartile range, depending on normality. Differences in continuous data between BMI groups were analyzed using ANOVA one-way (normal distribution) analysis or the Kruskal-Wallis test (not-normal distribution). Differences in categorical data were analyzed using Chi-square or Fisher's Exact, where applicable.

Concerning clinical outcomes, the time-to-event distributions of the effect of BMI on survival was analyzed. Kaplan-Meier curves and a log-rank test were determined to assess differences in survival outcomes between BMI groups.

Hereafter, a bivariate Cox regression model was used to investigate if age, sex, ECOG-PS, Charlson Comorbidity index (CCI), histology (adenocarcinoma vs squamous + large cell + other + NOS), and concomitant chemotherapy (paclitaxel/bevacizumab vs gemcitabine + paclitaxel + docetaxel + etoposide + pemetrexed) were confounding factors for BMI expressed in hazard ratios (HRs) with 95% confidence intervals (CIs). The two different histology categories were based on the differences in histologic subtypes on the survival of stage IV NSCLC patients using Cetin K *et al*. [25]. Likewise, the subdivision in concomitant chemotherapy was based on differences in survival for triplet treatment with bevacizumab against doublet therapies with carboplatin [26-30]. Next, variables from bivariate analyses with a p-value below <0.10 were further analyzed in multivariate Cox's proportional hazards analysis providing adjusted hazard ratios (aHR).

Similarly, for toxicity parameters, first univariate logistic regression with BMI as independent variable was performed, followed by bivariate logistic regression analyses with the above described covariates. Values with p <0.10 were used in multivariate logistic regression analysis expressed as an adjusted OR (aOR) for BMI.

In multivariate analysis, interaction tests with a p-value <0.05 were considered statistically significant. All statistical tests were performed with IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp, released 2017).

RESULTS

PATIENTS AND BASELINE CHARACTERISTICS

A total of 520 patients with metastatic NSCLC diagnosed within the years 2008 – 2014 and treated with first-line carboplatin-based chemotherapy were included. Of these 520 patients, 27 patients were excluded due to insufficient information for BMI calculation, resulting in 493 patients eligible for analysis. The median follow-up was 7 (0.03 - 127) months.

Table 1: Baseline characteristics of stage iv nsclc patients treated with carboplatin-based chemotherapy by bmi

Characteristics	TOTAL (n=493)	Normal weight (<25.0 kg/m²) (n=268)	Overweight (25.0-29.9 kg/m²) (n=174)	Obese (≥30.0 kg/m²) (n=51)	p-value
Sex, n (%)					
Male	312 (63%)	154 (58%)	128 (74%)	30 (59%)	
Female	181 (38%)	114 (43%)	46 (26%)	21 (41%)	<0.001
Age [years], mean (SD)	65 (9)	63 (9)	67 (9)	66 (7)	<0.001
Weight [kg], mean (SD)	75 (15)	66 (9)	82 (9)	97 (14)	<0.001
BMI [kg/m²], mean (SD)	25.1 (4.5)	22.0 (2.0)	27.4 (1.3)	34.0 (4.3)	
GFR baseline[1] [mL/min], mean (SD)	84 (27)	81 (24)	84 (28)	102 (32)	<0.001
Target AUC [mg*min/mL], n (%)					
5	361 (73%)	185 (69%)	134 (77%)	42 (82%)	
6	132 (27%)	83 (31%)	40 (23%)	9 (18%)	0.05
Charlson Comorbidity Index, n (%)					
0	230 (47)	136 (51%)	80 (46%)	14 (28%)	
1	140 (28%)	74 (28%)	47 (27%)	19 (37%)	
2	117 (24%)	55 (21%)	44 (25%)	18 (35%)	
3-4	6 (1%)	3 (1%)	3 (2%)	0 (0%)	0.06
ECOG performance status, n (%)					
0	202 (41%)	107 (40%)	73 (42%)	22 (43%)	
1	212 (43%)	119 (44%)	71 (41%)	22 (43%)	
2	49 (10%)	26 (10%)	19 (11%)	4 (8%)	
3	17 (3%)	9 (3%)	5 (3%)	3 (6%)	
4	3 (1%)	3 (1%)	0 (0%)	0 (0%)	
Missing	10 (2%)	4 (2%)	6 (3%)	0 (0%)	0.88
Primary tumor, n (%)					
Adenocarcinoma	299 (61%)	169 (63%)	103 (59%)	27 (53%)	
Squamous	75 (15%)	32 (12%)	33 (19%)	10 (20%)	
Large cell	67 (14%)	35 (13%)	22 (13%)	10 (20%)	
Other or NOS	52 (11%)	32 (12%)	16 (9%)	4 (8%)	0.27
Concomitant chemotherapy, n (%)					
Etoposide					
Gemcitabine	7 (1%)	4 (2%)	1 (1%)	2 (4%)	
Paclitaxel	160 (32%)	79 (30%)	58 (33%)	23 (45%)	
Pemetrexed	13 (3%)	6 (2%)	7 (4%)	0 (0%)	
Docetaxel	201 (41%)	106 40%)	76 (44%)	19 (37%)	
Paclitaxel + bevacizumab	38 (8%)	26 (10%)	10 (6%)	2 (4%)	
	74 (15%)	47 (18%)	22 (13%)	5 (10%)	<0.001

[1] according to the Cockcroft-Gault formula

Abbreviations: NSCLC = non-small cell lung cancer, SD = standard deviation, GFR = glomerular filtration rate, ECOG = eastern cooperative oncology group, NOS = not otherwise specified

Table 1 shows the baseline characteristics according to BMI. The average BMI was 25.1 ± 4.5 kg/m^2 and ranged from 15.8-52.7 kg/m^2. A total of 268 patients (54%) had a BMI <25.0 kg/m^2, 174 patients (35%) had a BMI between 25.0-29.9 kg/m^2 and 51 patients (10%) a BMI greater than or equal to 30.0 kg/m^2. There were statistically significant differences in baseline characteristics, including amongst others gender and age, though corrected for in the multivariate analyses (Table 1).

SURVIVAL OUTCOMES RELATIVE TO BMI

Overall, BMI was significantly associated with OS ($p < 0.049$) and with PFS ($p = 0.042$); Figure 1 provides the survival curves. In univariate analysis, both PFS and OS were better in overweight patients versus normal weight patients (HR 0.78; 95%-CI: 0.65-0.95; $p = 0.01$, and HR=0.74; 95%-CI: 0.61-0.90; $p < 0.013$, respectively). There was no difference in PFS and OS between obese patients and patients with normal weight.

The effects of longer PFS and OS for overweight patients with reference to normal weight patients persisted in the bivariate and multivariate analyses (Table 2). Overweight patients had both a longer PFS (aHR=0.74 (95%-CI: 0.61-0.90)) as well as OS (aHR=0.72 (95%-CI: 0.59-0.89)) relative to BMI < 25.0 kg/m^2. Besides BMI, the only other variable that was significantly associated with PFS and OS in multivariate analyses was ECOG performance score.

SAFETY OUTCOMES RELATIVE TO BMI

Table 3 shows the results of the toxicity outcomes thrombocytopenia, treatment-related hospitalization and relative dose intensity of carboplatin by BMI category. Dose intensity expressed as RDI was significantly lower and more prevalent for patients with higher BMI. Furthermore, a RDI below 80% occurred more frequently in patients with BMI ≥ 30.0 kg/m^2.

With regard to toxicity, higher BMI was significantly associated with both more severe as well as more frequent grade ≥3 thrombocytopenia. Moreover, higher BMI was significantly associated with a lower nadir in cycles 1-3. This is visually represented in Figure 2, where the percentual change in thrombocytes count relative to baseline is greater and more prevalent with higher BMI. These findings were confirmed by logistic regression analysis (table 4). After adjustment for possible confounders in multivariate logistic regression, obese patients had a significantly higher incidence of thrombocytopenia with an aOR of 3.47 (95%-CI: 1.75-6.90) relative to normal weight patients; in overweight patients the association did not reach statistical significance. With regard to hospitalization, higher BMI was not significantly associated with incidence of toxicity-associated hospitalization.

Table 2: Bivariate and multivariate analysis of overall survival and progression free survival in stage iv nsclc patients

			Progression free survival	
			Bivariate analysis	
Characteristics	**No**	**%**	**HR (95% CI)**	**p-value**
BMI [kg/m²]				
< 25.0	268	54%	1.00 (ref)	
25.0-29.9	174	35%	0.78 (0.65-0.95)	0.01
≥ 30.0	51	10%	0.95 (0.70-1.28)	0.72
Sex				
< 25.0	154/114	58/43%	1.00 (ref)	
25.0-29.9	128/46	74/26%	0.76 (0.62-0.92)	0.01
≥ 30.0	30/21	59/41%	0.96 (0.71-1.29)	0.77
male (ref) vs female			0.82 (0.68-0.99)	0.04
Age	[mean (SD)]			
< 25.0	63 (9)		1.00 (ref)	
25.0-29.9	67 (9)		0.78 (0.64-0.95)	0.01
≥ 30.0	66 (7)		0.94 (0.70-1.27)	0.70
Age [year]			1.00 (0.99-1.01)	0.75
CCI				
< 25.0	210/58	78/22%	1.00 (ref)	
25.0-29.9	127/47	73/27%	0.78 (0.64-0.95)	0.01
≥ 30.0	33/18	65/35%	0.94 (0.69-1.27)	0.44
<2 (ref) vs ≥ 2			1.08 (0.88-1.33)	0.74
ECOG PS				
< 25.0	226/38	83/14%	1.00 (ref)	
25.0-29.9	144/24	83/14%	0.77 (0.64-0.94)	0.01
≥ 30.0	44/7	86/14%	0.93 (0.69-1.26)	0.63
<2 (ref) vs ≥ 2			1.35 (1.05-1.75)	0.02
Primary tumor				
< 25.0	169/99	63/37%	1.00 (ref)	
25.0-29.9	103/71	59/41%	0.78 (0.64-0.94)	0.01
≥ 30.0	27/24	53/47%	0.92 (0.68-1.25)	0.61
Adenocarcinoma (ref) vs Large cell + squamous + other			1.18 (0.98-1.41)	0.08

Overall survival					
Multivariate analysis		**Bivariate analysis**		**Multivariate analysis**	
aHR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
1.00 (ref)		1.00 (ref)		1.00 (ref)	
0.74 (0.61-0.90)	0.003	0.78 (0.65-0.95)	0.01	0.72 (0.59-0.89)	0.002
0.90 (0.66-1.22)	0.49	0.91 (0.67-1.23)	0.54	0.84 (0.62-1.14)	0.26
		1.00 (ref)			
		0.76 (0.62-0.93)	0.01		
		0.91 (0.68-1.23)	0.56		
0.84 (0.70-1.02)	0.09	0.84 (0.69-1.01)	0.06	0.88 (0.72-1.06)	0.18
		1.00 (ref)			
		0.75 (0.61-0.91)	0.004		
		0.88 (0.65-1.19)	0.42		
		1.01 (1.00-1.02)	0.03	1.01 (1.00-1.02)	0.15
		1.00 (ref)			
		0.77 (0.64-0.94)	0.01		
		0.89 (0.66-1.20)	0.44		
		1.21 (0.98-1.49)	0.07	1.13 (0.91-1.40)	0.27
		1.00 (ref)			
		0.78 (0.64-0.95)	0.01		
		0.89 (0.66-1.20)	0.43		
1.35 (1.04-1.75)	0.02	1.43 (1.11-1.85)	0.01	1.39 (1.07-1.80)	0.01
		1.00 (ref)			
		0.78 (0.64-0.95)	0.01		
		0.89 (0.66-1.21)	0.46		
1.15 (0.95-1.38)	0.16	1.14 (0.95-1.37)	0.17		

Table 2: Continued

			Progression free survival	
			Bivariate analysis	
Characteristics	**No**	**%**	**HR (95% CI)**	**p-value**
Concomitant chemotherapy				
< 25.0	47/221	18/83%	1.00 (ref)	
25.0-29.9	22/152	13/87	0.77 (0.64-0.94)	0.01
≥ 30.0	5/46	10/90%	0.92 (0.69-1.24)	0.56
Paclitaxel/bevacizumab (ref) vs				
Gemcitabine + pemetrexed + paclitaxel + etoposide + docetaxel			1.29 (1.01-1.66)	0.04

Abbreviations: No = number of patients, P = p-value, HR = hazard ratio, aHR = adjusted hazard ratio, CI = confidence interval, BMI = body mass index, CCI = Charlson comorbidity index, ECOG PS= eastern cooperative oncology group performance status

	Overall survival					
	Multivariate analysis		Bivariate analysis		Multivariate analysis	
	aHR (95% CI)	p-value	HR (95% CI)	p-value	aHR (95% CI)	p-value
			1.00 (ref)			
			0.78 (0.64-0.94)	0.01		
			0.88 (0.65-1.20)	0.42		
	1.21 (0.93-1.56)	0.15	1.25 (0.97-1.60)	0.09	1.14 (0.89-1.48)	0.32

Table 3: Carboplatin dose intensity, thrombocytopenia, and hospitalization by bmi of carboplatin in stage iv nsclc patients

Characteristics	Normal weight (<25.0 kg/m²) (n=268)	Overweight (25.0-30.0 kg/m²) (n=174)	Obese (≥ 30.0 kg/m²) (n=51)	p-value
Number of treatment cycles, median (IQR)	4 (2 – 4)	4 (2 – 4)	4 (2 – 4)	0.97
Treatment delay 1 week or more, n (%)				
Yes	82 (31%)	54 (31%)	20 (39%)	
No	147 (55%)	94 (54%)	22 (43%)	
1 cycle	39 (15%)	26 (15%)	9 (18%)	0.34
Dose reduction in cycles 1-3, n (%)	102 (38%)	71 (41%)	28 (55%)	0.08
RDI cycle 1, [%] mean (SD)	94% (16%)	92% (19%)	84% (18%)	
RDI cycle 1 < 0.80, n (%)				
Yes	45 (17%)	32 (18%)	18 (35%)	0.01
No	179 (67%)	114 (66%)	23 (45%)	0.004
RDI cycle 2, [%] mean (SD)	93% (17%)	90% (18%)	85% (19%)	
RDI cycle 2 < 0.80, n (%)				
Yes	27 (10%)	28 (16%)	9 (18%)	0.13
No	104 (39%)	72 (41%)	14 (28%)	0.12
RDI cycle 3, [%] mean (SD)	91% (18%)	90% (20%)	91% (33%)	
RDI cycle 3 < 0.80, n (%)				
Yes	28 (10%)	24 (14%)	7 (14%)	0.93
No	81 (30%)	56 (32%)	16 (31%)	0.77
aRDI (1-3), [%] mean (SD)	92% (15%)	89% (17%)	85% (19%)	
RDI cycles 1-3 < 0.80, n (%)				
Yes	78 (29%)	59 (34%)	24 (47%)	0.02
No	146 (55%)	87 (50%)	17 (33%)	0.02
Treatment-related hospitalization in cycles 1-3, n (%)	83 (31%)	61 (35%)	20 (39%)	0.43
Average duration hospitalization cycles 1-3, [days] median (IQR)	5 (2 – 8)	3.5 (1 – 10)	2 (2 – 7)	0.43
Lowest thrombocytes cycles 1-3, [x 10^9/L] median (IQR)	121 (60 – 184)	95 (46 – 150)	50 (18 – 124)	<0.001
Thrombocytopenia (grade 3-4) in cycles 1-3, n (%)	54 (20%)	48 (28%)	25 (49%)	<0.001

Abbreviations: NSCLC = non-small cell lung cancer, SD = standard deviation, AUC = area under the curve, RDI = relative dose intensity, aRDI = average relative dose intensity IQR = interquartile range (25-75%)

Table 4: Results of bivariate and multivariate logistic regression of thrombocytopenia and hospitalization

			Grade ≥3 Thrombocytopenia	
			Bivariate analysis	
Characteristics	**No**	**%**	**OR (95% CI)**	**p-value**
BMI [kg/m²]				
< 25.0	268	54%	1.00 (ref)	
25.0-29.9	174	35%	1.51 (0.97-2.36)	0.07
≥ 30.0	51	10%	3.81 (2.04-7.12)	<0.001
Sex				
< 25.0	154/114	58/43%	1.00 (ref)	
25.0-29.9	128/46	74/26%	1.39 (0.88-2.19)	0.15
≥ 30.0	30/21	59/41%	3.86 (2.06-7.26)	<0.001
male (ref) vs female			0.57 (0.36-0.90)	0.02
Age				
< 25.0	63 (9)		1.00 (ref)	
25.0-29.9	67 (9)		1.20 (0.75-1.91)	0.44
≥ 30.0	66 (7)		3.35 (1.77-6.34)	<0.001
Age [years]			1.06 (1.03-1.09)	<0.001
CCI				
< 25.0	210/58	78/22%	1.00 (ref)	
25.0-29.9	127/47	73/27%	1.46 (0.93-2.29)	0.11
≥ 30.0	33/18	65/35%	3.53 (1.87-6.67)	<0.001
<2 (ref) vs ≥ 2			2.21 (1.41-3.47)	0.001
ECOG PS				
< 25.0	226/38	83/14%	1.00 (ref)	
25.0-29.9	144/24	83/14%	1.54 (0.98-2.42)	0.06
≥ 30.0	44/7	86/14%	3.92 (2.09-7.35)	<0.001
<2 (ref) vs ≥ 2			1.27 (0.68-2.38)	0.45
Concomitant chemotherapy				
< 25.0	47/221	18/83%	1.00 (ref)	
25-29.9	22/152	13/87%	1.55 (0.97-2.48)	0.07
≥ 30.0	5/46	10/90%	4.09 (2.10-7.99)	<0.001
Gemcitabine + paclitaxel + paclitaxel/ bevacizumab (ref) vs				
pemetrexed + etoposide+ docetaxel			4.54 (2.85-7.24)	<0.001

Abbreviations: No = number of patients, OR = odds ratio, CI = confidence interval, BMI = body mass index, CCI = Charlson comorbidity index, ECOG PS= eastern cooperative oncology group performance status

			Hospitalization			
	Multivariate analysis		Bivariate analysis		Multivariate analysis	
	aOR (95% CI)	p-value	OR (95% CI)	p-value	aOR (95% CI)	p-value
	1.00 (ref)		1.00 (ref)		1.00 (ref)	
	1.20 (0.73-1.97)	0.47	1.20 (0.80-1.80)	0.37	1.18 (0.78-1.77)	0.44
	3.47 (1.75-6.90)	<0.001	1.44 (0.77-2.67)	0.25	1.34 (0.72-2.51)	0.36
			1.00 (ref)			
			1.21 (0.81-1.83)	0.35		
			1.44 (0.78-2.67)	0.25		
	0.74 (0.45-1.21)	0.22	1.06 (0.71-1.57)	0.79		
			1.00 (ref)			
			1.16 (0.77-1.77)	0.47		
			1.40 (0.75-2.61)	0.29		
	1.04 (1.01-1.07)	0.01	1.01 (0.99-1.03)	0.50		
			1.00 (ref)			
			1.18 (0.79-1.77)	0.42		
			1.37 (0.74-2.56)	0.32		
	2.09 (1.27-3.42)	0.003	1.43 (0.94-2.19)	0.10	1.45 (0.94-2.22)	0.09
			1.00 (ref)			
			1.18 (0.78-1.78)	0.43		
			1.41 (0.76-2.63)	0.28		
			1.43 (0.85-2.42)	0.18		
			1.00 (ref)			
			1.20 (0.80-1.81)	0.38		
			1.41 (0.76-2.63)	0.28		
	4.51 (2.78-7.29)	<0.001	1.54 (1.05-2.24)	0.03	1.54 (1.06-2.26)	0.03

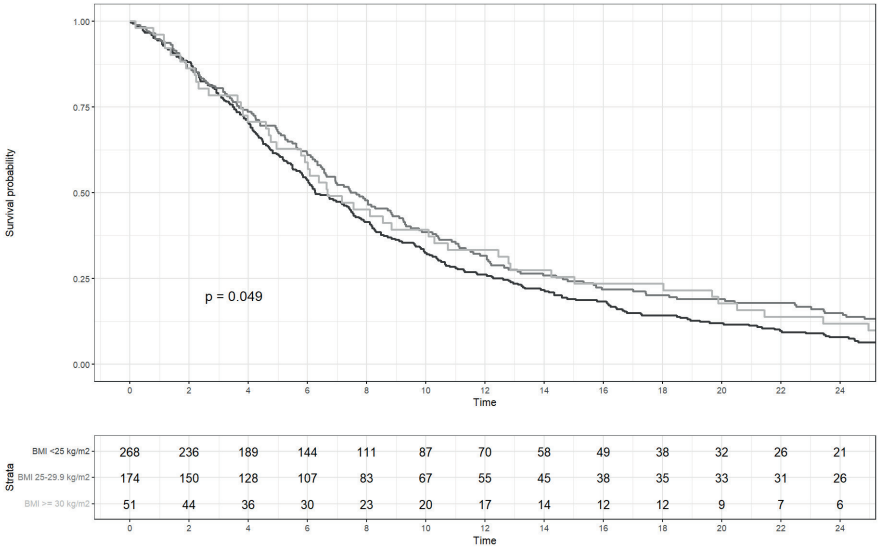

Figure 1a: Overall survival from start chemotherapy to 24 months. Black lines represent normal weight (BMI<25 kg/m²) patients, dark grey overweight (25.0-30.0 kg/m²) and light gray obese (≥30.0 kg/m²).

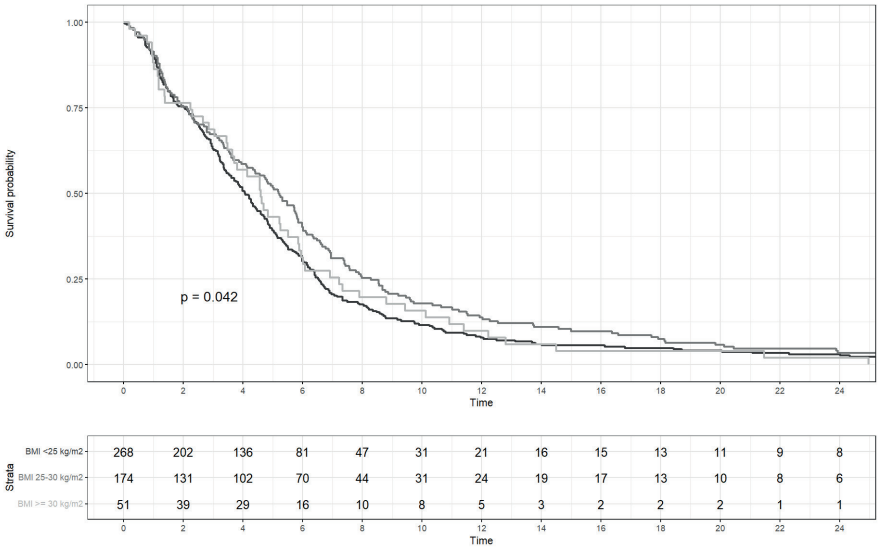

Figure 1b: Progression free survival from start chemotherapy to 24 months. Black lines represent normal weight (BMI<25 kg/m2) patients, dark grey overweight (25.0-30.0 kg/m2) and light gray obese (≥30.0 kg/m2).

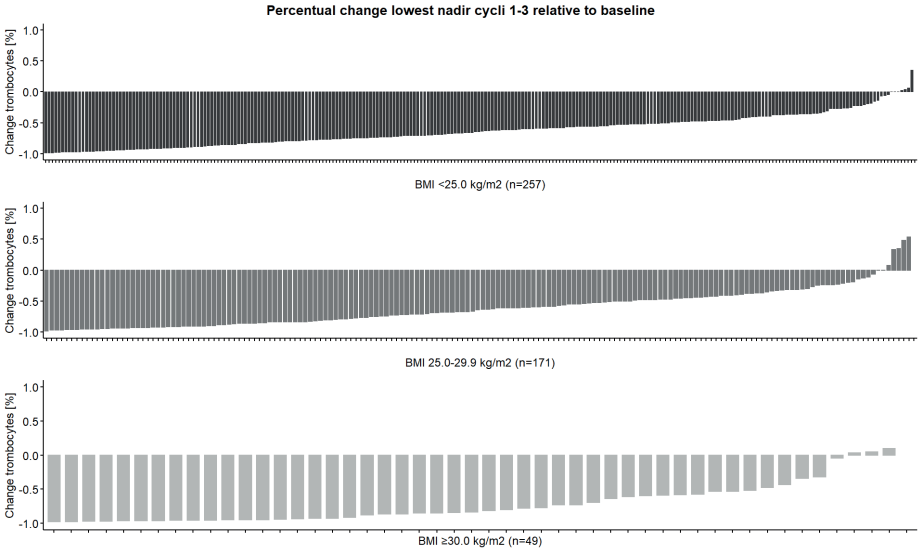

Figure 2: Change in percentage (-1 = -100% to 1 = 100%) of lowest nadir in cycles 1-3 relative to baseline thrombocyte count

DISCUSSION

Under the hypothesis that patients with higher BMI would be more likely at risk for overdosing of carboplatin, this study investigated the effect of BMI on survival and safety outcomes in patients with NSCLC treated with first-line carboplatin-based chemotherapy. Overweight patients had a significantly longer OS and PFS relative to normal weight patients, whereas obese patients had an increased risk for grade ≥3 thrombocytopenia without an additional increase in survival from carboplatin-based chemotherapy.

These findings support the hypothesis that BMI has a predictive effect following carboplatin-based chemotherapy, at least when calculated using the Cockcroft-Gault formula. The results indicate that the Cockcroft-Gault formula should be used with caution in obese patients and that potentially other dose descriptors should be used to derive a more safe dose of carboplatin. This need is further supported by the fact that relative dose intensity was significantly lower in the obese patients and more frequently <80%. Since systemic exposure is directly related to the administered dose of carboplatin [25], the higher dosing in obese patients as a consequence of overestimated GFR, directly will lead to higher incidences of thrombocytopenia, as has been demonstrated by multiple studies [14-17, 31]. This is further confirmed by our study where obese patients had a more than double risk of severe thrombocytopenia compared to normal weight patients.

Despite the fact that severe thrombocytopenia occurred more frequently in patients with higher BMI, this did not translate into increased hospitalization or duration of hospitalization. The effect of BMI on hospitalization was also not significant after adjustment for potential confounders. This is in contrast to our previous findings. In a smaller retrospective study we found BMI to be significantly associated with toxicity-related hospitalization (aOR=1.07, 95%-CI: 1.00-1.14) [31]. It needs to be recognized however that not much is known about potential predictors for hospitalization in patients with NSCLC, especially not for BMI as a predictor of hospitalization. A study by Fessele KL et al. investigating predictors of hospitalization in patients with lung cancer during chemotherapy included sex, age, race, education, income, urbanization, radiation therapy, marital status and comorbidities. They found urbanization, radiotherapy, and comorbidity to be significantly associated with hospitalization [32]. The effect of BMI was not investigated. For further research, additional adjustment for the confounders urbanization and radiotherapy could possibly give a more profound insight in the association of BMI with risk of hospitalization.

Our study shows a potential beneficial effect of BMI on treatment outcome in overweight patients. It remains however rather elusive thus far whether this is a predictive effect as a result of a slightly overestimated GFR, or whether it is prognostic. It must be noted that the first 3-4 months following start of therapy the survival lines rather overlap, and start to split afterwards. Whether this is either a preventive effect of the chemotherapy for progression, or otherwise a prognostic factor of a higher BMI, remains inconclusive based on these data. Other literature indicates BMI as a prognostic value for survival and (hematological) toxicity. Survival studies have shown a paradoxal relationship between higher BMI and lower lung cancer mortality in general, irrespective of carboplatin-based chemotherapy. A recent large study by the International Lung Cancer Consortium including 25,430 patients with NSCLC found patients being overweight or obese had higher survival rates with decrease in hazards of 11% (aHR=0.89, 95%-CI: 0.85–0.95) and 14% (aHR=0.86, 95%-CI: 0.82–0.91), respectively [20]. Notwithstanding, given the obvious clear predictive effect of BMI on toxicity, altogether the effect on survival is likely to be a mix of predictive and prognostic effect. Overall, it shows that BMI is a relevant covariate for NSCLC treatment outcomes.

A strength of this study is its relatively homogeneous population of all patients with NSCLC stage IV treated with first-line carboplatin-based chemotherapy. In addition, patients were included from multiple hospitals, across a time period of 6 years, reducing potential bias of regional treatment therapies. This is one of the few cohort studies specific for a large group of patients with NSCLC all treated with first-line carboplatin-based chemotherapy, providing a special insight in the effect of BMI on the outcomes in this patients group.

Being a retrospective study, there may be a small chance of information bias as data were not prospectively obtained. Nonetheless, all data were derived from individual patients' electronic health records. All data was digitally entered at the time of treatment so all possible testing and documenting was available, resulting in hardly any missing data.

Lastly, the dosing of carboplatin differs from dosing of most other chemotherapeutics by the fact that it is not dosed on body surface area (BSA), but on estimated renal function. Whereas dose capping of chemotherapeutics in case of a BSA >2.0 m^2 or 2.2 m^2 is regularly performed [33]. This contrasts to the dosing of carboplatin, which is mostly not capped, or only capped in patients with GFR > 125 mL/min [7]. To gain more insight in administered dose intensity, we calculated the RDI in all patients, as the RDI is a direct indicator for dose capping, but also for overdosing.

Patients with obesity had a significantly lower RDI. Specifically, in cycle 1 obese patients had more often a RDI below 80% compared to normal weight patients (35.3% vs 16.8%), indicating that dose capping was more frequently applied in obese patients; nonetheless, obese patients had still more frequently severe thrombocytopenia. When overall analyzed throughout cycles 1-3, obese patients had significantly more often (47.1%) a RDI under 80% compared to normal and overweight patients (29.1% and 33.9%, respectively, $p<0.016$), suggesting that additional dose reductions were indicated due to toxicity, besides the initial dose capping. This is in accordance with literature. A study by Au-Yeung *et al.* in patients with advance stage serous ovarian cancer treated with carboplatin, found obese (BMI >30.0 kg/m^2 patients to receive significantly more often a dose reduction of RDI <85% compared with non-obese patients [34]. Furthermore, a study by Hanna *et al.* in patients with epithelial ovarian cancer treated with carboplatin found that a BMI >30.0 kg/m^2 was a strong and significant predictor for a lower RDI (OR = 2.35, 95%-CI: 1.25 -4.41) [35]. A study by Bandera *et al.* investigating the effect of BMI on carboplatin chemotherapy dosing in ovarian cancer found high BMI being the strongest predictor for dose reduction [36]. Even though there were significant differences to be found in RDI between BMI groups, this can be deceptive. That is to say, the carboplatin dosage is calculated based on the Calvert formula using standard AUCs depending on guidelines for concomitant therapy given. Therefore, pragmatic adjustments of target AUC by the physician were not taken into account, including specific situations of the patient. Additionally, the target AUC is seen as a constant through each cycle. Whereas in practice the physician most often lowers the target AUC (and thus dosage) when toxicity occurs. There is a potential risk of bias here. Physicians could be more easily lower dosage of carboplatin in patients with higher BMI. Despite the fact that patients in ≥30.0 kg/m^2 more often received a dose reduction, the patients still experienced more hematological toxicity.

Finally, it is of importance to note that our observations are only true for patients treated with carboplatin at a target AUC of 5 or 6; the findings may not necessarily hold true for patients treated with the weekly administered regimens at a target AUC of 2. Generally, carboplatin treatment regimens at lower target AUCs are known to result less frequently and less pronounced toxicity.

CONCLUSION

This study showed a significantly better progression free survival and overall survival for overweight versus normal weight patients, whereas obese patients had an increased risk for grade ≥3 thrombocytopenia without an additional increase in survival from carboplatin-based chemotherapy. Moreover, the effect of BMI on survival and toxicity was significant even after adjusting for possible confounders, indicating a large and potent effect of BMI specifically for obese patients. The implications for clinical practice are that the Cockcroft-Gault formula should be used with caution in patients with BMI ≥30.0 kg/m^2, and the calculated dose should be properly verified for appropriateness. This study results suggest that potentially a lower carboplatin starting dose in obese patients followed by thrombocytopenia-guided dose adjustment may enable safer therapy without negatively affecting treatment effectiveness.

CLINICAL PRACTICE POINTS

Despite emerging immunotherapy for treatment of NSCLC, carboplatin remains part of first-line cornerstone treatment. Its dosing is internationally based on estimated glomerular filtration rate (GFR) using the Cockcroft-Gault (CG) formula. In overweight patients the CG formula is likely to overestimate GFR potentially resulting in overdosing of carboplatin and multiple studies have shown an increased risk of severe (hematological) toxicity in patients with higher BMI [14-17]. Concerning its relationship with survival, data are scarce. This is among the first and largest study in a rather homogeneous NSCLC patient population treated with first-line carboplatin-based chemotherapy. We showed that overweight patients had a significantly higher OS and PFS relative to normal weight patients. Obese patients had an increased risk for grade ≥3 thrombocytopenia and required more often dose reductions, without an additional increase in survival from carboplatin-based chemotherapy relative to normal weight. Following these study results, the implications for clinical practice are that the Cockcroft-Gault formula should be used with caution in patients with BMI ≥30.0 kg/m^2, and in these cases the calculated dose should be properly verified for appropriateness. We suggest a potentially lower carboplatin starting dose in obese patients followed by thrombocytopenia-guided dose adjustment may enable safer therapy without negatively affecting treatment effectiveness.

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CHAPTER III

Pharmacokinetic study of carboplatin using various overweight-correcting dosing algorithms and biomarkers in patients with varying BMI categories

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ABSTRACT

BACKGROUND

In overweight patients, the Cockcroft-Gault (CG) formula is more likely to overestimate renal function and carboplatin dosing. In this prospective pharmacokinetic study, we evaluated the use of an adjusted Cockcroft-Gault formula (aCG) correcting, amongst other things, for overweight.

METHODS

aCG adjusted in patients with BMI>25 kg/m^2 using adjusted ideal body weight, capping low serum creatinine values at 60 µmol/L, and high creatinine clearance values at 125 mL/min. Patients were categorized: BMI<25.0 (normal weight), 25.0-29.9 (overweight), and ≥30.0 kg/m^2 (obese). To assess pharmacokinetics, blood samples were taken and carboplatin ultrafiltrate concentrations were analyzed. Exposure was estimated using a population pharmacokinetic model and compared to the target AUC regarding bias (Mean Prediction Error, MPE%) and imprecision (Mean Absolute Prediction Error, MAPE%). Additionally, substitutes for renal function, including weight descriptors, cystatin C, 24-hour creatinine clearance, and GFR estimators were compared.

RESULTS

Eighteen patients were included. aCG slightly underestimated individual carboplatin clearance across all weight groups, with the highest deviation in obese patients (MPE%: -10.5%) versus +8.8% using CG. aCG underestimated -5.7% in normal weight and overestimated +1.1% on overweight patients compared to -4.2% and +2.8%, respectively, using CG. The most accurate predictor of target AUC for all weight categories was cystatin C (MPE%: +0.2%, -2.0 and -0.1% for normal, overweight, and obese patients respectively) with low imprecision (MAPE%: 9.8%, 9.5%, and 13.3%).

CONCLUSION

This study could not find evidence to support using our aCG to better predict carboplatin clearance compared to CG. Cystatin C showed to be the most precise and accurate biomarker for carboplatin clearance.

INTRODUCTION

Carboplatin is mainly excreted by the kidneys, where up to 50-75% of total platinum is excreted within 24 hours after administration [1-3]. Dosing of carboplatin is adjusted for renal function as it is linearly correlated to the glomerular filtration rate (GFR) [4-7]. In addition, several studies have found an association between systemic carboplatin exposure and efficacy and toxicity. Hence, carboplatin dosing is based on a targeted systemic carboplatin exposure expressed as the Area Under the concentration-time Curve (AUC) [1, 8-13]. The target AUC values typically range between 4 and 7 mg*min/mL and depend on the type of treatment regimen and dose interval frequency [4].

Several formulas exist to calculate the individual carboplatin dosage. The Calvert formula is internationally the most widely used [1, 2, 4, 5, 14-16]. In this formula, the GFR is generally substituted by the estimated creatinine clearance (CrCL) using the Cockcroft-Gault (CG) formula [14]. For different formulas, see Supplementary S1. The CG formula is well-suited for estimating the CrCL in patients with normal weight and normal creatinine serum values. However, since creatinine is primarily produced by skeletal muscle (i.e., muscle mass), the CG estimation of creatinine clearance is not directly biased by body weight itself but rather by discrepancies between absolute body weight and lean body mass. Hence, the estimated CrCL is more likely to be overestimated in overweight patients (as an increase in absolute body weight does not necessarily correspond to a proportional increase in muscle mass) and patients with low serum creatinine values, typically cachectic patients. Indeed, multiple studies have shown that having a high Body Mass Index (BMI) or low serum creatinine is independently associated with overestimating creatinine clearance and, thereby, increased risk of carboplatin toxicity [10, 11, 15-21].

We hypothesized that the potential overestimation and increased risk of carboplatin-associated severe toxicity could be prevented by adjusting for high BMI and low serum creatinine values. Hence, we designed an adjusted Cockcroft-Gault (aCG) dosing algorithm based on available evidence and guidelines regarding carboplatin dosing in overweight and cachectic patients (see Figure 1), with the ultimate aim of improving safe dosing of carboplatin in overweight and cachectic patients. The aCG adjusted for overweight by using adjusted ideal body weight (AIBW) instead of absolute body weight (ABW) in patients with BMI ≥25 kg/m^2 and for cachexia by substituting serum creatinine values <60 µmol/L with 60 µmol/L [2, 22, 23]. Indeed, studies have shown that using AIBW instead of actual body weight better approximates the target AUC in overweight and obese patients [2, 22, 24, 25]. Moreover, multiple guidelines proposed

using an alternative weight descriptor such as AIBW in patients with a BMI ≥25 kg/m^2 and affirm the minimum cut-off value of 60 μmol/L for serum creatinine [26, 27]. Lastly, we adjust for overestimating CrCL by capping the maximum estimated CrCL at 125 mL/min [26-29].

In this prospective pharmacokinetic study, we evaluated the performance of the adjusted dosing algorithm in which the measured carboplatin AUCs were compared to the target AUCs. The secondary objective was to investigate and compare the performance of aCG to other substitutes for renal function based on the measured carboplatin exposure, including other weight descriptors, cystatin C, and 24-hour creatinine clearance and estimated GFR by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

MATERIALS AND METHODS

STUDY DESIGN

We conducted a prospective study at the Rijnstate Hospital in Arnhem, the Netherlands. The primary objective was to evaluate the pharmacokinetics and safety of our adjusted carboplatin dosing algorithm that adjusted for overweight, defined as BMI ≥25 kg/m^2, low serum creatinine, defined as serum creatinine <60 μmol/L, and maximal estimated creatinine clearance, defined as a maximum estimated CrCL of 125 mL/min. See Figure 1. The secondary objective was to investigate and compare the performance of aCG to other substitutes for renal function based on the measured carboplatin clearance, including other weight descriptors, cystatin C using formula of Schmitt *et al.* [16], 24-hour creatinine clearance, and CKD-EPI estimating the GFR (eGFR). The administered dose of carboplatin was calculated using the aCG. Blood sampling was conducted for pharmacokinetic measurements on day 1 of the first treatment cycle. Further treatment was provided according to standard treatment protocols and routine clinical care. The study was approved by the local medical ethics committee and followed the principles of the Declaration of Helsinki. All patients signed written informed consent.

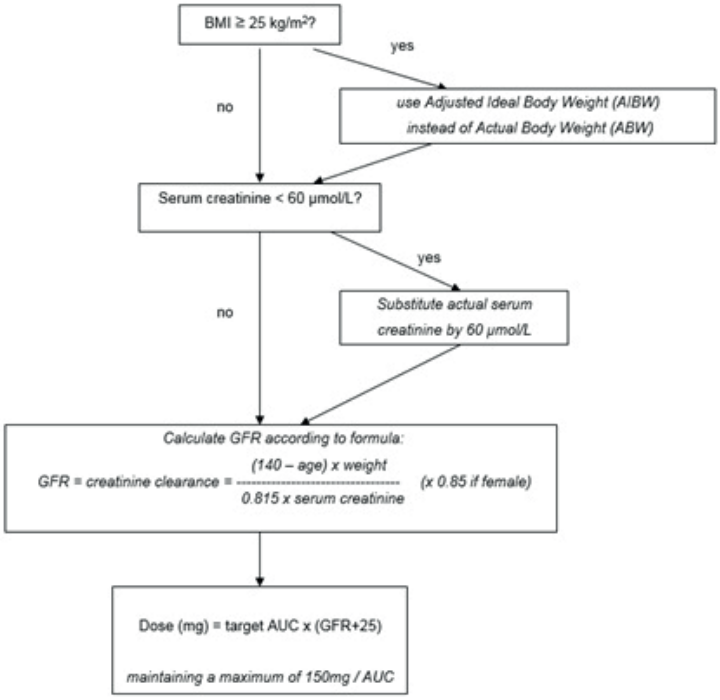

Figure 1: Proposed adjusted dosing algorithm of carboplatin

Abbreviations: aCG = adjusted Cockcroft-Gault, BMI = body mass index, GFR = glomerular filtration rate, AUC = area under the curve

PATIENT POPULATION

Patients were included if they were aged 18 years or older; had a histologically or cytologically proven non-small-cell lung carcinoma (NSCLC), small-cell lung carcinoma (SCLC), ovarian or endometrial cancer for which they were treated with carboplatin at a target AUC of 4, 5 or 6 mg*min/mL; had an estimated life expectancy of at least 12 weeks; had a WHO performance status of 0-2. Furthermore, patients had to have adequate baseline liver function and bone marrow defined as hemoglobin ≥6.0 mmol/L, white blood cell count ≥3.0 * 10^9/L, absolute neutrophil count (ANC) ≥1.5 * 10^9/L, platelet count ≥100 * 10^9/L, bilirubin ≤1.5 times the upper limit of normal (ULN), and ALAT and ASAT ≤2.5 times ULN (in case of liver metastases ≤5.0 times ULN). Patients were included and categorized into three different BMI categories: <25.0, 25.0-29.9, or ≥30.0 kg/m^2. Patients were excluded if they were treated with carboplatin at a target AUC below 4 mg*min/mL; had an active clinically serious infection or a history of a kidney allograft; were pregnant or breastfeeding; were unsuitable for follow-up. The study was completed four weeks after the last participant received their last cycle of carboplatin.

BLOOD AND MATERIAL SAMPLING

The pharmacokinetics of carboplatin was determined by obtaining a total of five blood samples of 4 mL heparinized collection tubes on day 1 of the first cycle of treatment: one sample was taken before the start of the carboplatin infusion, one sample at the end of the infusion (t=0), and one at t=1 h, 2.5 h, and 5 h after the end of the infusion. In addition, a 24-hour creatinine clearance and cystatin C samples were taken from patients the day before the start of treatment to estimate renal clearance. Immediately after blood drawing to obtain plasma, the blood samples were centrifuged at 4˚C at 3000 rpm for 10 minutes. Next, plasma ultrafiltrate was obtained by centrifuging 1 mL of plasma for 15 minutes through an ultrafiltrate filter (Merck Millipore Ltd., Tullagreen, Carrigtwohill, Co. Cork, Ireland). Plasma ultrafiltrate was stored at -70˚C until analysis.

BIOANALYSIS

The concentrations of carboplatin in human plasma ultrafiltrate were determined using a validated graphite-furnace atomic-absorption spectrometry assay with slight modifications in optimization settings as previously described [30,31].

PHARMACOKINETIC ANALYSIS

The AUCs of patients' ultrafilterable carboplatin concentrations, when dosed according to aCG, were estimated using a post hoc estimation in NONMEM (FOCE+I) using the 2-compartment nonlinear mixed effects model for carboplatin described by Ekhart *et al.* [2]. All estimations and simulations were performed using the nonlinear mixed-effects modeling software package NONMEM V7.4.4 (Development Solutions, Ellicott City, MD, USA). Perl Speaks NONMEM (v.5.0.0). Pirana (v.2.9.8) and R statistics (v.4.2.3) were used for interpretation and visualization. Next, we accounted for dose rounding when estimating the AUC. For example, if the calculated carboplatin dosage at the target AUC of 5 for a typical patient was 620 mg, the actual dosage administered would have been 600 mg due to dose rounding.

Next, different weight descriptors for estimating creatinine clearance were converted into an estimated AUC by dividing the administered dose by the calculated carboplatin clearance: estimated CrCL+25. See Supplementary S1 for all different carboplatin dosing formula. For example, the conventional CG formula using ABW could provide an estimated CrCL of 80 mL/min for the patient receiving 600 mg, resulting in an estimated AUC of 5.7 mg*min/mL. In this way, the estimated AUCs of different weight descriptors ABW and AIBW using the conventional CG formula were estimated, either with or without substituting serum creatinine values <60 µmol/L with 60 µmol/L and capping estimated CrCL at 125 mL/min. Moreover, the weight descriptor of Bénézet *et*

al. using ideal body weight (IBW) and absolute body weight were compared [32]. For an overview of the equations of different weight descriptors, see Supplementary S2.

Lastly, the AUC was estimated for 24-hours creatinine clearance, for cystatin C the formula by Schmitt *et al.* [16], for flat dosing based on the mean carboplatin population clearance [2, 15], and for the GFR estimators: the 2021 CKD-EPI creatinine, and CKD-EPI creatinine-cystatin C equations [33].

SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS

A total of 7 patients per BMI category (<25.0, 25.0-29.9, and ≥30.0 kg/m^2) were required to detect an anticipated difference of 30% between the actual versus the target AUC of carboplatin, with a standard deviation of 1.2 mg/mL*min, an alpha of 0.05%, and a power of 80%. We anticipated based on previous data that at least one in four patients would have a serum creatinine concentration below 60 µmol /L. Data were analyzed per protocol analysis. The patient characteristics and pharmacokinetic data were analyzed using descriptive statistics. Continuous variables were analyzed using the Kruskal-Wallis test. All statistical tests were performed with IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, released 2017. Armonk, NY).

STUDY ENDPOINTS

The primary endpoints of the study were the mean prediction error (MPE%) and mean absolute prediction error (MAPE%) of the aCG algorithm, which were expressed by the measured plasma concentration-time curve (actual AUC) of the carboplatin ultrafiltrate. Acceptance criteria for MPE% and MAPE% were within 85% and 115% of the actual and estimated AUC versus the target AUC.

The secondary endpoints were the MPE% and MAPE% of other substitutes for renal function based on the measured clearance, including other weight descriptors (Bénézet [32], AIBW in CG), capping CG, cystatin C-based estimates using the Schmitt *et al.* [16] formula (which besides cystatin C also incorporates additional patient characteristics), 24-hour creatinine clearance, and eGFR formulas of the CKD-EPI creatinine, and CKD-EPI creatinine-cystatin C [33].

Safety parameters were the incidence of hematological and non-hematological toxicity, toxicity-related hospitalization, carboplatin dosage reduction, and treatment delay. Toxicity was assessed using the common terminology criteria for adverse events (CTCAE) v5.0 [34].

Table 1: Population characteristics of different bmi subgroups

Characteristics	**Normal and underweight (BMI < 25.0 kg/m²)**	**Overweight (BMI 25.0 – 29.9 kg/m²)**	**Obese (BMI ≥ 30.0 kg/m²)**
N (%)	7 (37%)	5 (32%)	6 (32%)
Age [years], median (range)	68 (50 – 78)	60 (54 – 77)	66 (56 – 78)
Sex, n (%)			
Male	6 (86%)	1 (20%)	3 (50%)
Female	1 (14%)	4 (80%)	3 (50%)
Weight [kg], median (range)	68 (48 – 80)	76 (72 – 81)	99 (87 – 115)
Length [cm], median (range)	179 (171 – 185)	170 (166 – 173)	170 (160 – 180)
BSA [m²], median (range)	1.8 (1.5 – 2.0)	1.9 (1.8 – 2.0)	2.2 (2.0 – 2.4)
Baseline serum creatinine [µmol/L], median (range)	69 (49 – 95)	82 (67 – 130)	77 (57 – 114)
24 hours creatinine [mmol/L/24hours], median (range)	9.8 (3.8 – 11.8)	8.6 (7.7 – 10.5)	14.5 (7.7 – 16.3)
24 hours creatinine clearance [mL/min/24 hours], median (range)	105.1 (98.4 – 110.4)	69.6 (46.5 – 108.5)	122.8 (71.6 – 139.4)
Cystatin C [mg/L], median (range)	0.9 (0.8 – 1.6)	1.5 (0.8 – 1.9)	1.3 (0.8 – 1.5)
Target AUC [mg*min/mL], median (range)	6.0 (6.0 – 6.0)	6.0 (5.0 – 6.0)	6.0 (5.0 – 6.0)
Primary tumor, n (%)			
NSCLC	6 (86%)	1 (20%)	3 (50%)
SCLC	1 (14%)	3 (60%)	2(33%)
Other	0 (0%)	1 (20%)	1 (17%)
Concurrent therapies, n (%)			
Paclitaxel	4 (57%)	2 (40%)	2 (33%)
Gemcitabine	2 (29%)	0 (0%)	1 (17%)
Pemetrexed	0 (0%)	0 (0%)	1 (17%)
Etoposide	1 (14%)	3 (60%)	4 (67%)
Bevacizumab	1 (14%)	0 (0%)	2 (25%)
Radiotherapy	0 (0%)	1 (20%)	1 (13%)

Abbreviations: BMI = body mass index, NSCLC = non-small-cell lung carcinoma, SCLC = small-cell lung carcinoma, AUC = area under the curve, BSA = body surface area

RESULTS

STUDY POPULATION

A total of 21 patients were included. General patient and treatment characteristics are provided in Table 1. Pharmacokinetic sampling was completed successfully in 18 of the 21 included patients, and failed for 2 patients (plasma was taken instead of ultrafiltrate), and for 1 patient, only 1 blood sample was taken. There were 7 patients with a BMI <25.0 kg/m^2, 5 with 25.0-29.9 kg/m^2, and 6 with ≥30.0 kg/m^2.

PHARMACOKINETIC ANALYSIS

Table 2 shows the MPE% and MAPE% of the estimated AUCs of the various weight descriptors. The actual $AUC_{0-\infty}$ following dosing according to the aCG formula across all BMI subgroups was slightly lower compared to the target AUC with the highest MPE% deviation of -10.5% (95% confidence interval [CI]: -21.9 – 1.0%) in patients with BMI ≥30.0 kg/m^2 compared to +8.8% (95% CI: -4.5 – 22.1%) when the conventional CG was used. Patients with a BMI <25.0 kg/m^2 or 25.0-29.9 kg/m^2 had an underestimation of -5.7% and +1.1% using aCG, while the conventional CG formula gave an under- and overestimation of -4.2% and +2.8%, respectively (see Figure 2). Furthermore, a higher BMI was associated with an increase of MPE% for conventional CG, either uncapped or capped, ranging from an underestimation of -6.6% in BMI <25.0 kg/m^2 to an overestimation of +8.8% in ≥30.0 kg/m^2. See Supplementary S3 for the concentration curves and exposure of each patient.

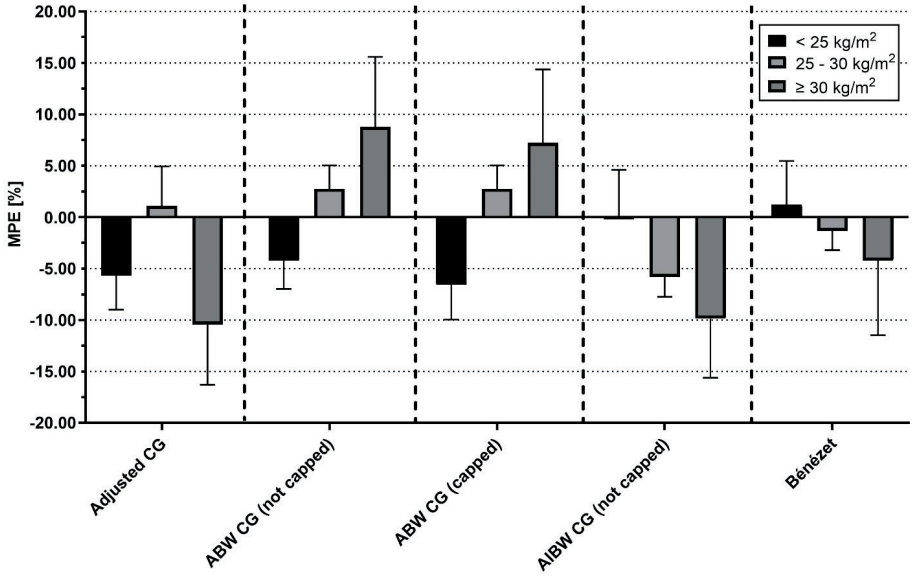

Figure 2: AUC (expressed as mpe%) of different weight descriptors relative to the target auc

Abbreviations: AUC = area under the curve, MPE% = mean percentage error, (a)CG = (adjusted) Cockcroft-Gault, ABW = absolute body weight, AIBW = adjusted ideal body weight. The margins of error are equal to the standard error (SE) of the mean of the particular weight descriptor

Table 2: Primary outcomes of different weight descriptors and estimators of gfr

	BMI < 25.0 kg/m² (n = 7)			BMI 25.0 – 29.9 kg/m² (n = 5)			BMI ≥ 30.0 kg/m² (n = 6)		
	AUC[mg* min/mL]	MPE% [95% CI]	MAPE% [95% CI]	AUC [mg* min/mL]	MPE% [95% CI]	MAPE% [95% CI]	AUC [mg* min/mL]	MPE% [95% CI]	MAPE% [95% CI]
Target AUC (reference)	5.9 (5.7 – 6.1)			5.8 (5.4 – 6.1)			5.7 (5.4 – 6.1)		
Adjusted Cockcroft-Gault	5.6 (5.2 – 6.0)	−5.7 (-12.2 – 0.8)	7.9 (3.0 – 12.7)	5.7 (5.6 – 5.9)	1.1 (-6.4 – 8.6)	5.4 (0.0 – 10.9)	5.1 (4.4 – 5.8)	−10.5 (−21.9 – 1.0)	13.6 (5.0 – 22.2)
WEIGHT DESCRIPTORS									
Conventional Cockcroft-Gault									
ABW (not capped)	5.7 (5.4 – 6.0)	-4.2 (-9.6 – 1.1)	7.1 (4.3 – 10.0)	5.9 (5.3 – 6.4)	2.8 (-1.7 – 7.2)	4.5 (1.7 – 7.3)	6.2 (5.4 – 7.0)	8.8 (-4.5 – 22.1)	15.7 (8.7 – 22.6)
ABW (capped)*	5.5 (5.2 – 5.9)	-6.6 (-13.2 – 0.1)	8.7 (3.9 – 13.5)	5.9 (5.3 – 6.4)	2.8 (-1.7 – 7.2)	4.5 (1.7 – 7.3)	6.1 (5.3 – 7.0)	7.2 (-6.7 – 21.2)	15.5 (8.3 – 22.7)
AIBW (not capped)	5.9 (5.4 – 6.4)	0.1 (-8.8 – 9.0)	10.7 (8.4 – 13.0)	5.4 (4.9 – 5.9)	-5.8 (-9.6 – (-2.0)	5.8 (2.0 – 9.6)	5.2 (4.5 – 5.8)	-9.9 (-21.1 – 1.4)	13.0 (4.5 – 21.5)
Bénézet equation32	6.0 (5.5 – 6.5)	1.2 (-7.1 – 9.5)	9.8 (6.9 – 12.8)	5.8 (5.5 – 6.1)	-1.3 (-5.0 – 2.3)	2.5 (-0.3 – 5.2)	5.6 (4.9 – 6.3)	-4.2 (−18.4 – 10.0)	12.8 (4.9 – 20.7)
ESTIMATORS OF GFR									
24 hours creatinine clearance†	6.0 (4.9 – 7.0)	2.2 (-16.3 – 20.7)	17.7 (7.6 – 27.9)	6.0 (5.1 – 7.0)	7.0 (-4.5 – 18.6)	8.6 (-1.6 – 18.7)	4.7 (3.1 – 6.3)	-17.6 (-45.8 – 10.6)	19.7 (-7.1 – 46.5)
Cystatin C‡16	5.9 (5.4 – 6.4)	0.2 (-8.9 – 9.2)	9.8 (5.1 – 14.4)	5.8 (5.2 – 6.3)	-2.0 (-12.9 – 8.8)	9.5 (6.4 – 12.5)	5.8 (5.0 – 6.7)	-0.1 (−17.7 – 17.5)	13.3 (1.5 – 25.1)
CKD-EPI (creatinine)33	6.3 (5.7 – 6.7)	5.5 (-3.6 – 14.7)	11.1 (6.1 – 16.1)	5.9 (5.5 – 6.3)	-0.2 (-8.4 – 8.1)	6.5 (2.9 – 10.2)	5.3 (4.4 – 6.2)	-9.5 (-26.4 – 7.3)	15.2 (3.1 – 27.4)
CKD-EPI (creatinine-cystatin C)33	5.9 (5.2 – 6.7)	0.4 (-13.3 – 14.1)	14.9 (8.2 – 21.6)	5.5 (4.5 – 6.4)	-7.0 (-24.2 – 10.2)	14.4 (4.9 – 24.0)	4.8 (4.0 – 5.6)	-17.8 (-33.1 – (-2.4))	21.0 (-33.1 – 31.7)
Flat dosing¬2,15	5.8 (5.3 – 6.4)	-1.6 (-10.2 – 6.9)	8.6 (3.4 – 13.8)	7.1 (5.9 – 8.3)	23.9 (7.1 – 40.7)	23.9 (7.1 – 40.7)	5.6 (4.1 – 7.1)	-2.2 (-28.6 – 24.2)	26.3 (13.4 – 39.3)

* Estimated creatinine clearance capped at the upper limit of 125 mL/min, serum creatinine capped at the lower limit of 60 µmol/L

† Four patients were excluded for having insufficient measurements to determine 24 hours creatinine clearance

‡ Two patients were excluded for having insufficient measurements

¬ Based on the mean carboplatin population clearance of 112.4 mL/min

Abbreviations: GFR = glomerular filtration rate, BMI = body mass index, AUC = area under the curve, MPE% = mean percentage error, MAPE% = mean absolute percentage error, 95% CI = 95% confidence interval, ABW = absolute body weight, AIBW = adjusted ideal body weight, GFR = glomerular filtration rate, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

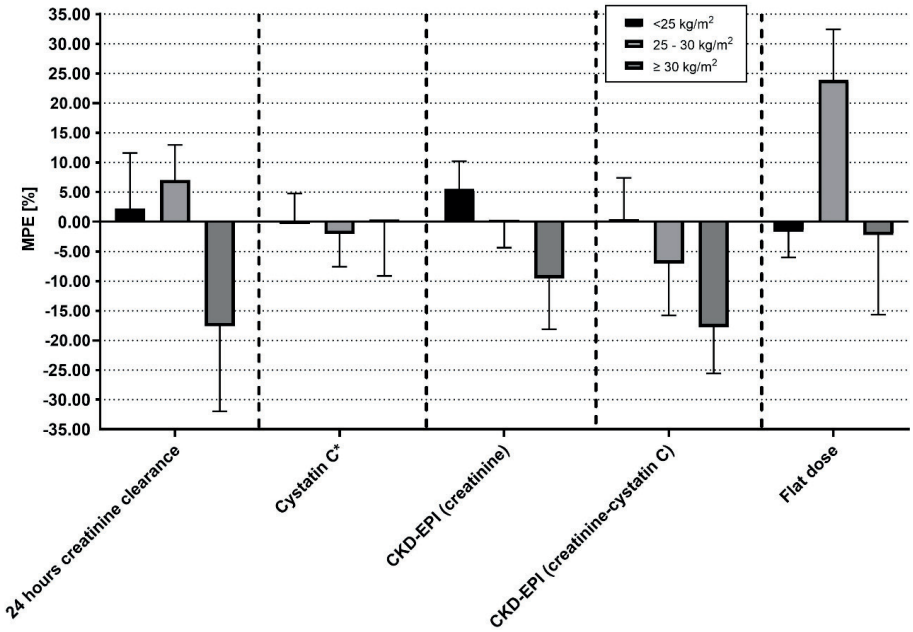

figure 3: AUC (expressed as mpe%) of different estimators of gfr relative to target auc

* Following the cystatin C formula of Schmitt *et al.* [16]

Abbreviations: AUC = area under the curve, MPE = mean percentage error, GFR = glomerular filtration rate, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration. Margins of error are equal to the standard error (SE) of the mean of the particular GFR estimator. The mean carboplatin population clearance for flat dosing was 112.4 mL/min

The most accurate predictor of target AUC across all BMI categories was cystatin C, with a minimal deviation in MPE% between -2.0% and +0.2%, followed by the Bénézet equation with +1.2% for BMI <25.0 kg/m², -1.3% for BMI 25.0-29.9 kg/m², and -4.2% for BMI ≥30.0 kg/m². All MPE% remained between 85-115% of the actual AUC irrespective of weight descriptor or formula for renal function used, except for 24-hour creatinine clearance (MPE% = -17.6% (95% CI: -45.8 – 10.6)) and CKD-EPI (creatinine-cystatin C) in patients with BMI ≥30.0 kg/m² (MPE% = -17.8% (95% CI: -33.1 – (-2.4))), and flat dose in patients 25.0-29.9 kg/m² (MPE% = 23.9% (95% CI: 7.1 – 40.7)). See Table 2. All MAPE% ranged between 2.5% and 26.3% and were the highest for flat dose, 24-hour creatinine clearance, and CKD-EPI (creatinine and creatinine-cystatin C), and in the BMI ≥30.0 kg/m² group compared to the other BMI groups.

The mean carboplatin population clearance was 112.4 mL/min. Flat dosing resulted in an overestimation of +23.9% (95% CI: 7.1 – 40.7%) for BMI 25.0-29.9 kg/m² and an underestimation of -1.6% (95% CI: -10.2 – 6.9) for <25.0 kg/m² and -2.2% (95% CI: -28.6 – 24.2%) for ≥30.0 kg/m². CKD-EPI (creatinine) showed a 5.5% overestimation in patients with BMI <25.0 kg/m², near perfect approximation for patients with BMI 25.0-29.9 kg/m² (MPE% = -0.2%) and -9.5% underestimation in BMI ≥30.0 kg/m². The same trend was seen for CKD-EPI (creatinine-cystatin C) with respectively overestimation of 0.4% in BMI < 25.0 kg/m², and underestimation in 25.0-29.9 kg/m² -7.0% and -17.8% in ≥30.0 kg/m² (see Figure 3).

TREATMENT AND TOXICITY OUTCOMES

Patients were treated with a median of 3 cycles. Table 3 shows the treatment and toxicity outcomes of dosing according to the aCG across the different BMI subgroups.

3: Patient treatment characteristics of different bmi subgroups

Parameter		**General (n=18)**	**Normal and underweight (BMI < 25.0 kg/m²) (n=7)**	**Overweight (BMI 25.0 – 29.9 kg/m²) (n=5)**	**Obese (BMI ≥ 30.0 kg/m²) (n=6)**
End of treatment, n [%]		9 (50%)	2 (29%)	4 (80%)	3 (50%)
Number of cycles of treatment planned, median (range)		4 (3 – 6)	4 (4 – 5)	4 (3 – 6)	4 (4 – 6)
Number of cycles of treatment performed, median (range)		3 (1 – 6)	2 (1 – 5)	4 (3 – 6)	3 (1 – 5)
Hematological toxicity (any CTCAE grade), n [%]		15 (83%)	5* (83%)	5 (100%)	5 (83%)
Non-hematological toxicity, n [%]		4 (22%)	2 (29%)	0 (0%)	1 (17%)
Toxicity-related hospitalization, n [%]		4 (22%)	1 (14%)	1 (20%)	1 (17%)
Toxicity related to dosage reduction, n [%]		1 (6%)	0 (0%)	0 (0%)	1 (17%)
Toxicity-related delay treatment, n [%]		6 (33%)	2 (29%)	3 (60%)	1 (17%)
Delay treatment [day], median (range)		0 (0 – 14)	0 (0 – 7)	6 (0 – 14)	0 (0 – 8)
Hematological toxicity					
Hemoglobin	CTCAE grade 1-2, n [%]	12 (71%)	3*	4	5
	CTCAE grade 3-4, n [%]	4 (24%)	3*	1	0
Leukocytes	CTCAE grade 1-2, n [%]	7 (42%)	3*	3	1
	CTCAE grade 3-4, n [%]	4 (24%)	0*	2	2
Thrombocytes	CTCAE grade 1-2, n [%]	2 (12%)	1*	1	0
	CTCAE grade 3-4, n [%]	4 (24%)	1*	2	1
Neutrophils†	CTCAE grade 1-2, n [%]	2 (33%)	1	1	0
	CTCAE grade 3-4, n [%]	2 (33%)	0	0	2

* 1 patient had no hemoglobin, leukocytes, or thrombocytes measured

† Only 6 patients (respectively 1, 2, and 3 patients) had their neutrophils determined

Abbreviations: BMI = body mass index, CTCAE = Common Terminology Criteria for Adverse Events version 5.0 [34]

DISCUSSION

We conducted a pharmacokinetic study to prospectively investigate the performance of an alternative dosing algorithm (aCG) for carboplatin in patients with varying BMI categories. Our study did not confirm that dosing with aCG resulted in improved exposure compared to the conventional CG formula. In addition, other formulas previously describing the pharmacokinetics of carboplatin were assessed for performance, of which cystatin C (based on the formula of Schmitt *et al.* [16]) provided the best approximation of the target AUC independent of weight expressed as BMI.

Even though our aCG did not approximate the target AUC better than the use of conventional CG, it did show a slight underdosing in overweight patients (BMI ≥30 kg/m^2). The underestimation of carboplatin dosing in overweight patients could be explained by the increased bias in using IBW to calculate AIBW. A similar trend of underestimation in our study was also seen in the weight descriptor of Bénézet. AIBW instead of absolute body weight considers muscle mass better by adjusting for both gender and fat mass. The possible use of AIBW instead of ABW is in line with other studies that show the use of AIBW to better predict the target AUC in overweight and obese patients, whereas the use of ABW provided an overestimation of the carboplatin AUC [2, 22, 24, 25]. In addition to body weight adjustment using AIBW, another adjustment in our formula was capping serum creatinine at 60 µmol/L, which is especially important in patients with sarcopenic obesity (loss of muscle mass combined with increased fat mass) [36]. Indeed, multiple studies have shown a benefit for capping low creatinine values, typically seen in cachectic patients [22, 23] Guidelines of the Gynaecologic Oncology Group [26] and the National Comprehensive Cancer Network [27] recommend the use of a minimum cut-off of serum creatinine of 0.7 mg/dL (~60 µmol/L) for all weight classes and capping estimated CrCL at 125 mL/min [26-29]. Moreover, these guidelines recommend using an alternative weight descriptor, such as AIBW, for patients with a BMI ≥25.0 kg/m^2 [26, 27]. In our study, only two patients had a serum creatinine below 60 µmol/L. Therefore, it was not possible to reach a conclusion regarding the minimalization of serum creatinine and the maximizing of renal function for carboplatin dosing. Furthermore, only one patient in the ≥30 kg/m^2 group had their estimated CrCL capped to 125 mL/min (from 139.54 mL/min), making it impossible to evaluate to what extent capping estimated creatinine clearance increases the risk of carboplatin underdosing across different weight classes.

Carboplatin's clearance is determined by the GFR, as Calvert initially using the 100% glomerular filtered ^{51}Cr-EDTA as an ideal predictor of GFR [4]. Creatinine, however, is

not solely cleared by the GFR but as well undergoes active secretion by the peritubular capillaries in the kidneys resulting in an 10-20% overestimation of GFR [37]. In our study, the different weight descriptors provided an adequate approximation of target exposure in underweight and normal weight patients (-5.7% to +2.8%). However, other estimators of GFR and carboplatin clearance performed better at each BMI group, especially the biomarker cystatin C. Cystatin C is a direct biomarker for glomerular filtration rate since it is produced at a constant rate and is 100% freely filtered at the glomerulus, and neither secreted nor reabsorbed at the proximal or distal renal tubule [38]. In our study, cystatin C provided the best approximation of the target AUC independent of BMI. This aligns with the original Calvert formula that initially used the 100% glomerular filtered ^{51}Cr-EDTA as an ideal predictor of GFR [4]. However, the formula of Schmitt *et al.* uses, besides cystatin C also body composition parameters ABW, age, sex, and serum creatinine [16]. Therefore, it is impossible to identify cystatin C as a sole predictor of carboplatin clearance. The same goes for CKD-EPI (creatinine-cystatin C), that uses serum creatinine, cystatin C, gender, and age of the patient [33]. Nonetheless, in our study, CKD-EPI (creatinine-cystatin C) provided an underestimation of carboplatin exposure dependent on BMI going from +0.4% for normal weight patients to -7.0% for overweight and -17.8% for obese patients. Possibly indicating that using only cystatin C without adjusting for weight is insufficient in estimating carboplatin exposure. Indeed, multiple prospective studies have shown cystatin C in addition to other covariates serum creatinine, bodyweight, age and sex to accurately predict carboplatin clearance [17, 39].

The dosing of carboplatin based on body weight has been a topic of discussion for a while. A large study by Ekhart *et al.* in NSCLC patients receiving carboplatin compared different weight descriptors, including AIBW, IBW, FFM (fat-free mass), LBM (lean body mass), and Bénézet, and found flat dosing to be the best weight descriptor in patients with a BMI ≥25.0 kg/m^2, questioning if weight altogether is even correlated with carboplatin exposure [15]. In our study, flat dosing, as with cystatin C, showed perfect estimation of carboplatin exposure in underweight and overweight groups and only provided an overestimation in the BMI 25.0-29.9 kg/m^2 group (see Figure 3). This result, together with the results of cystatin C, suggests that weight is not strongly correlated to carboplatin exposure, as already proposed by some other studies [2, 15] Moreover, a large study (n=491) by White-Koning *et al.* comparing different formulas to actual carboplatin clearance found CKD-EPI with cystatin C to be best predictor of carboplatin clearance, independent by any patient characteristics as sex, BMI (only significant at the 1% level), age and eGFR [40]. Lastly, besides weight not being correlated strongly to carboplatin clearance, hydrophilic compounds such as carboplatin can also be directly affected by obesity [41]. Since

adipose tissue consists of relatively more fat than water molecules, hydrophilic drugs such as carboplatin will not easily penetrate adipose tissue. Consequently, it could be assumed that weight descriptors accounting for the excess of fatty tissue (e.g., using AIBW) would be a more accurate indicator of carboplatin clearance than actual body weight.

Some studies suggest using CKD-EPI for improved carboplatin dosing [35, 42]. However, in our study, CKD-EPI based on creatinine or creatinine + cystatin C showed an underestimation of carboplatin exposure with increasing BMI (see Figure 3). Moreover, using the conventional CG resulted in a better approximation of carboplatin clearance than using the CKD-EPI creatinine across all BMI groups. Hence, our study suggests, in contrast with the literature, that CKD-EPI does not improve dosing compared to conventional CG.

This study's sample size (and thus statistical power) was determined based on different pharmacokinetic parameters expected in each BMI subgroup. Previous studies showed an average overestimation of carboplatin exposure (AUC) in obese patients of 30-35%, and hence the study was powered on these observations [2]. Consequently, based on a maximum difference of AUC of 30% between BMI categories, seven patients for each BMI subgroup should have been enlisted for sufficient power to make a significant conclusion concerning primary outcomes. Unfortunately, none of the BMI subgroups reached the anticipated patients included due to time and resource limitations, and due to the exclusion of patients based on insufficient pharmacokinetic data due to sampling issues. Additionally, we initially anticipated based on previous data that at least one in four patients would have a serum creatinine concentration below 60 μmol/L; however, only two such patients (out of 18) were identified. Therefore, it was impossible to perform statistical testing and draw an unambiguous conclusion, which should be considered an important study limitation. Moreover, in our study, the differences in carboplatin exposure between BMI categories were nowhere near the >30% overestimation as previously reported, indicating that even more patients would be needed to prove a significant difference [2].

For future development, advances in deep learning and medical imaging could provide an opportunity for the complete evaluation of body composition and thus creatinine clearance in oncology patients. Studies have shown the possibility of using CT-scans to acquire body composition estimates as muscle and fat volumes [43]. More specifically, the cross-sectional muscle area at the L3 level is strongly associated with total muscle volume and, thus, creatinine excretion [44, 45]. Indeed, recent studies

using deep learning body-composition analyses of clinically acquired CT-scans have shown the possibility of estimating creatinine excretion with high accuracy using the L3 cross-sectional muscle area [46, 47]. Consequently, creatinine clearance estimated by CT-scans can potentially be used to predict creatinine clearance and, thus, carboplatin exposure. Additionally, other 100% glomerular filtrated biomarkers, besides cystatin C, are being investigated: pro-encephalin [48] and iohexol [49]. However, the method of assessing GFR based on these biomarkers is often still complex, expensive and time-consuming [37], and prospective evaluation is needed before implementation in clinical practice.

In conclusion, our study did not find a preference for using AIBW, substituting low creatinine concentrations with a value of 60 µmol/L and capping estimated creatinine clearance at a maximum of 125 mL/min for patients with a BMI >25.0 kg/m^2 over the conventional Cockcroft-Gault formula. However, biomarker cystatin C using the formula of Schmitt *et al.* [16] approximated the target AUC almost perfectly over all BMI groups. Hence, our study suggests the use of cystatin C for dosing of carboplatin should be considered as an improved dosing strategy for the safe dosing of carboplatin.

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SUPPLEMENTARY MATERIAL

Supplementary table S1: CARBOPLATIN DOSING FORMULAS

Calvert formula [1]

$$\text{DOSE [mg]} = \text{AUC}_{\text{target}} * (\text{GFR} + 25)$$

International System (SI) units: AUC in mg/mL*min, GFR in mL/min

The Cockcroft Gault formula [2][1]

$$\text{estimated CrCL [mL/min]} = \frac{(140 - \text{AGE}) * \text{WEIGHT}}{0.815 * \text{Cr}_{\text{SERUM}}} * 0.85 \text{ [IF FEMALE]}$$

SI units: age in years, weight in kg, serum creatinine in mg/dL

Schmitt *et al.* cystatin C formula [3][1]

$$\text{CL [mL/min]} = 117.8 * \left(\frac{\text{Cr}_{\text{SERUM}}}{75}\right)^{-0.450} * \left(\frac{\text{cystatin C}_{\text{SERUM}}}{1.0}\right)^{-0.385} * \left(\frac{\text{WEIGHT}}{65}\right)^{+0.504} * \left(\frac{\text{AGE}}{56}\right)^{-0.366} * 0.847 \text{ [IF FEMALE]}$$

SI units: serum creatinine in µmol/L, cystatin C in mg/L, weight in kg, age in years

Flat dosing [4,5]

$$\text{Flat dosing [mg]} = \text{carboplatin population clearance} * \text{AUC}_{\text{target}}$$

SI units: carboplatin population clearance in mL/min, AUC in mg/mL*min

CKD-EPI creatinine formula [6][2]

$$\text{eGFR [mL/min/1.73m}^2\text{]} = 142 * \left(\frac{\text{Cr}_{\text{SERUM}}}{A}\right)^{B} * 0.9938^{\text{AGE}} * 1.012 \text{ [IF FEMALE]}$$

If *female* and:	If *male* and:
Serum creatinine ≤ 0.7: use A = 0.7 and B = -0.241	Serum creatinine ≤ 0.9: use A = 0.9 and B = -0.302
Serum creatinine > 0.7: use A = 0.7 and B = -1.200	Serum creatinine > 0.9: use A = 0.9 and B = -1.200

SI units: serum creatinine in mg/dL, age in years

CKD-EPI creatinine + cystatin C formula [6][2]	
$\text{eGFR [mL/min/1.73m}^2\text{]} = 135 * \left(\frac{\text{Cr}_{\text{SERUM}}}{\text{A}}\right)^{\text{B}} * \left(\frac{\text{cystatin C}_{\text{SERUM}}}{\text{C}}\right)^{\text{D}} * 0.9961^{\text{AGE}} * 0.963 \text{ [IF FEMALE]}$	
If *female* and:	If *male* and:
Serum creatinine ≤ 0.7 and serum cystatin C ≤ 0.8: A = 0.7, B = -0.219, C = 0.8, and D = -0.323	Serum creatinine ≤ 0.9 and serum cystatin C ≤ 0.8: A = 0.9, B = -0.144, C = 0.8, and D = -0.323
Serum creatinine ≤ 0.7 and serum cystatin C > 0.8: A = 0.7, B = -0.219, C = 0.8, and D = -0.778	Serum creatinine ≤ 0.9 and serum cystatin C > 0.8: A = 0.9, B = -0.144, C = 0.8, and D = -0.778
Serum creatinine > 0.7 and serum cystatin C ≤ 0.8: A = 0.7, B = -0.544, C = 0.8, and D = -0.323	Serum creatinine > 0.9 and serum cystatin C ≤ 0.8: A = 0.9, B = -0.544, C = 0.8, and D = -0.323
Serum creatinine > 0.7 and serum cystatin C > 0.8: A = 0.7, B = -0.544, C = 0.8, and D = -0.778	Serum creatinine > 0.9 and serum cystatin C > 0.8: A = 0.9, B = -0.544, C = 0.8, and D = -0.778

SI units: serum creatinine in mg/dL, cystatin C in mg/L, age in years

[1] Estimated clearance [mL/min] is used as substitute of the GFR in the Calvert formula

[2] Estimated clearance [mL/min/1.73m^2] is adjusted for body surface area (BSA) and then used as substitute of GFR in the Calvert formula

Supplementary table s2: Weight descriptors used in the cockcroft-gault formula

Weight descriptor	**Equation**
Ideal Body Weight (IBW)	IBW [kg] = 49.9 + 0.89 x (HEIGHT [cm] - 152.4) for men IBW [kg] = 45.4 + 0.89 x (HEIGHT [cm] - 152.4) for women
Adjusted Ideal Body Weight (AIBW)	AIBW [kg] = IBW + 0.4 x (ABW − IBW)
Bénézet formula [7]	Bénézet [kg] = (IBW + ABW) x 0.512

Abbreviations: ABW = absolute body weight

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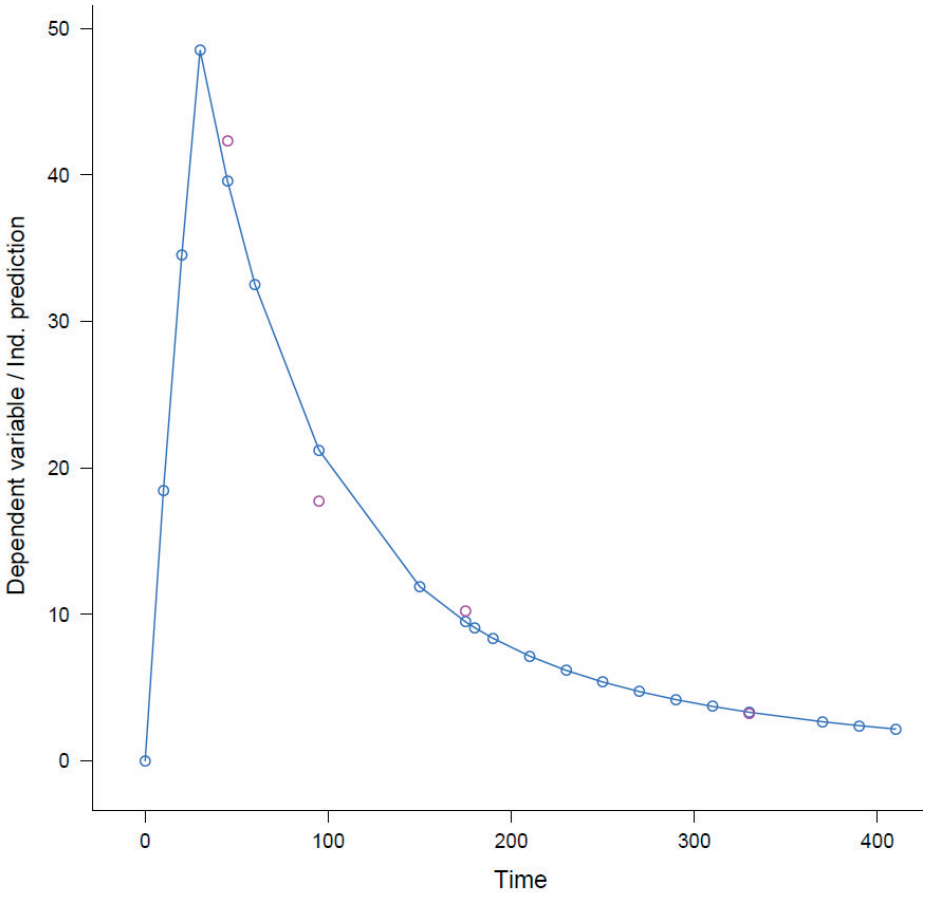
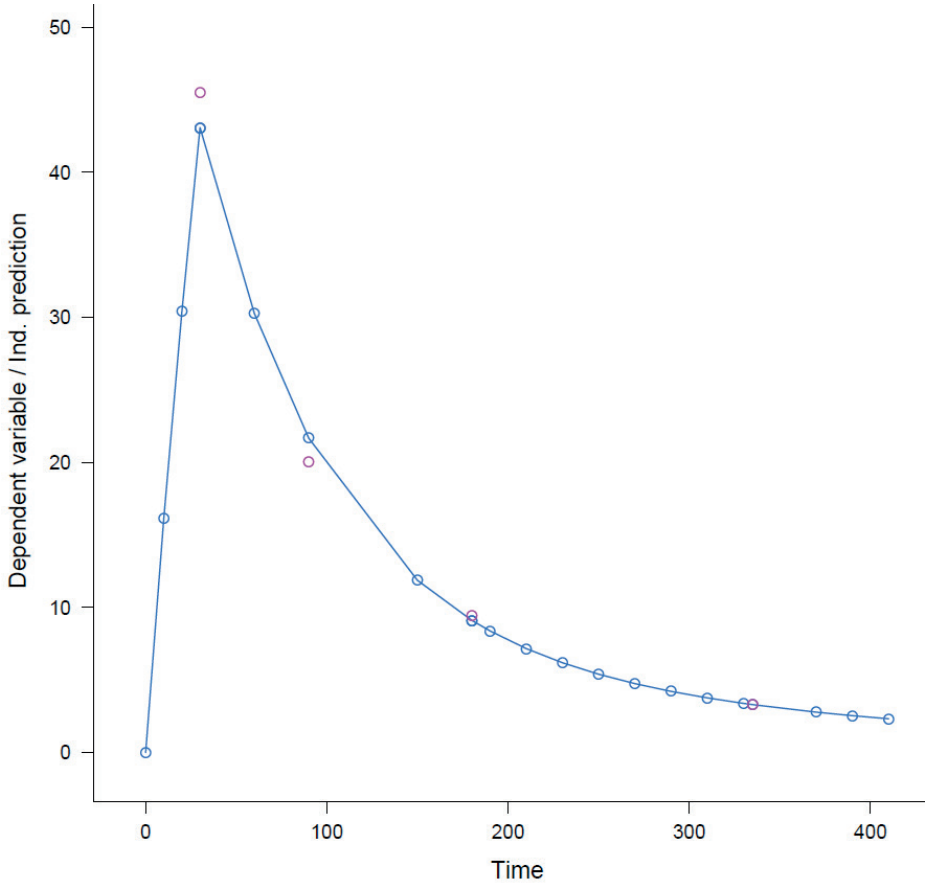
Supplementary table s3: Different concentration curves of each patient

The pink dots represent measured carboplatin concentrations over time, while the blue dots represent predicted carboplatin concentrations over time based on the NONMEM model by Ekhart *et al.* [4].

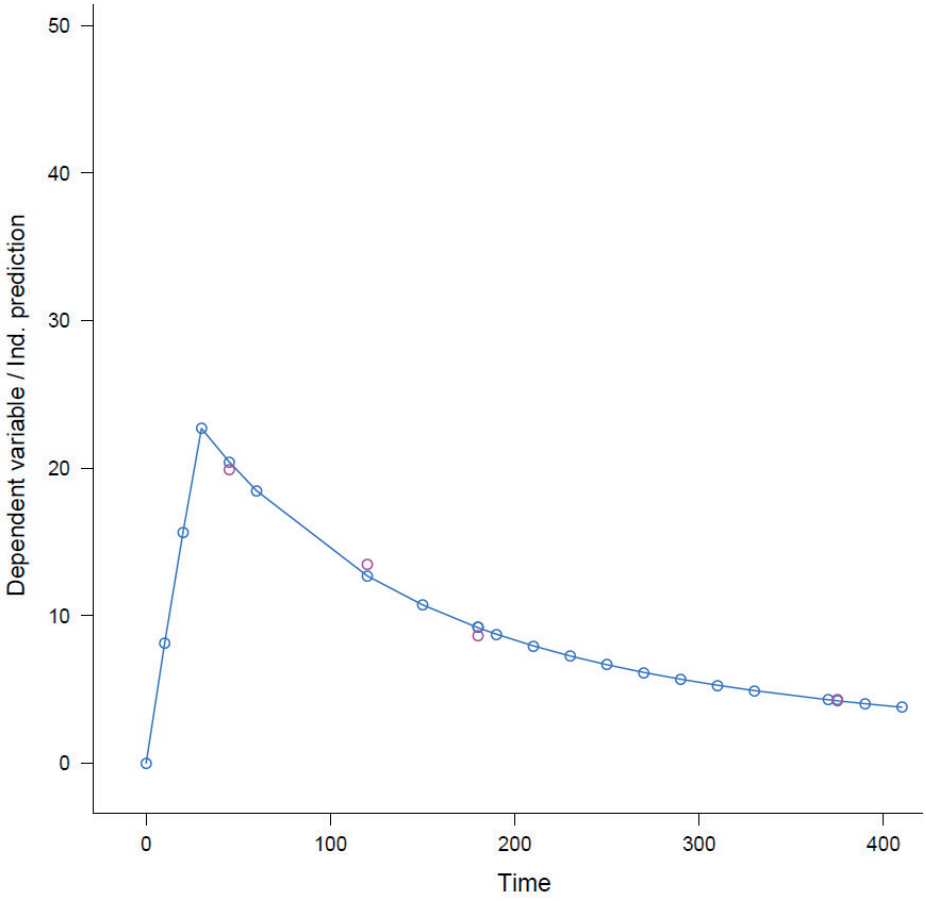
PATIENT 1 (BMI <25 kg/m²): AUC = 5.57 mg/mL*min



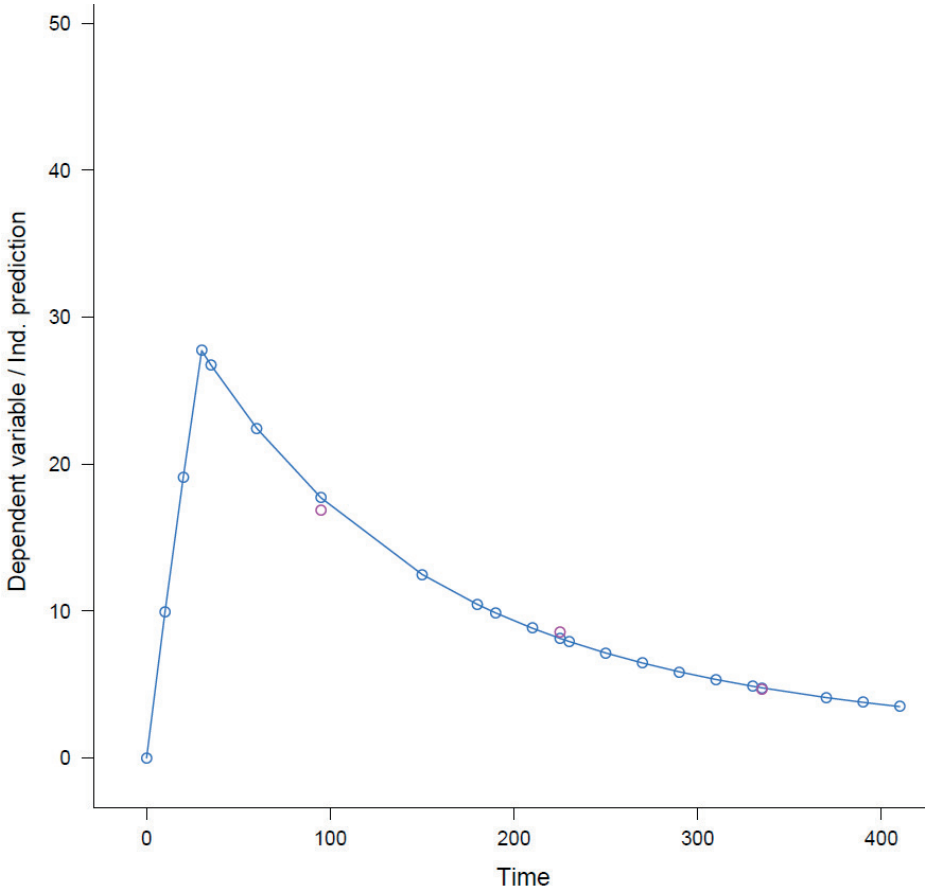
PATIENT 2 (BMI <25 kg/m²): AUC = 5.49 mg/mL*min



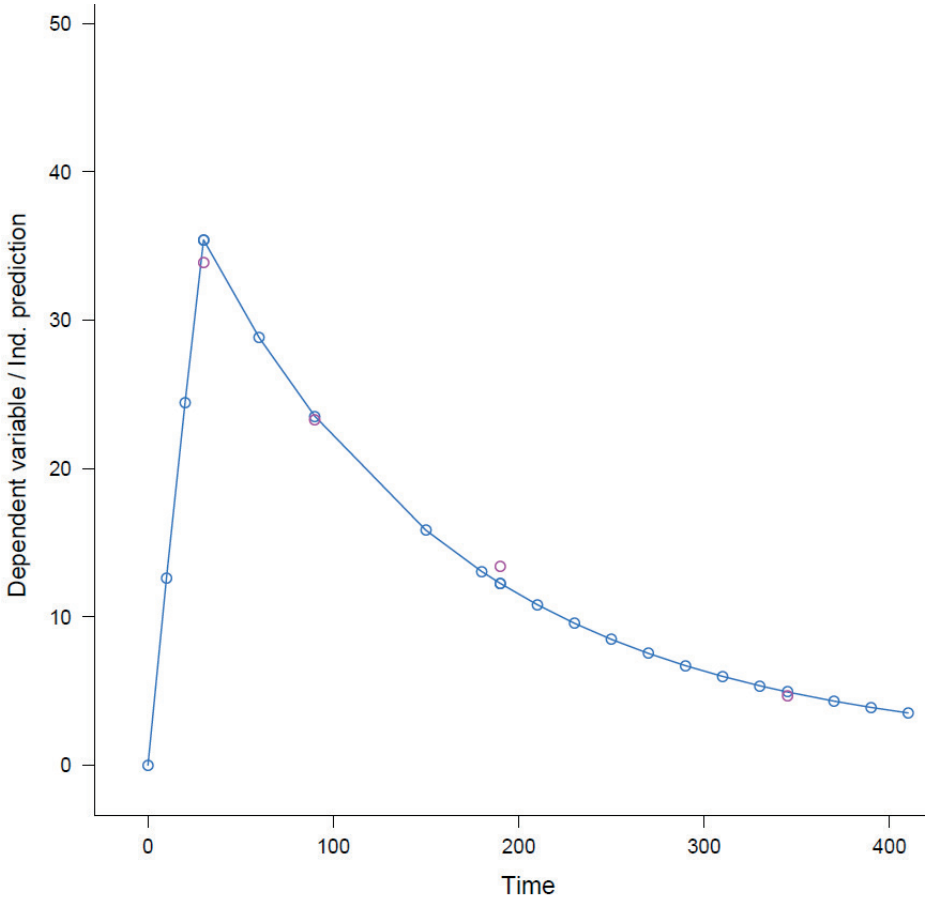
PATIENT 3 (BMI 25 – 30 kg/m²): AUC = 5.35 mg/mL*min



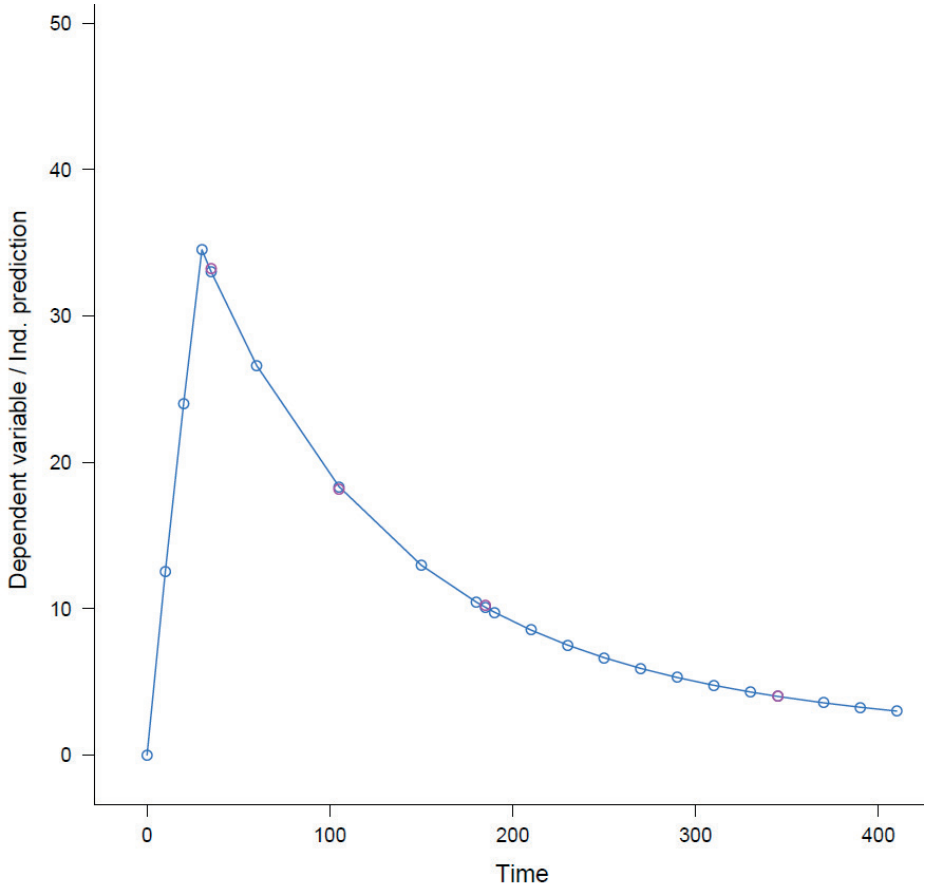
PATIENT 4 (BMI ≥30 kg/m²): AUC = 5.54 mg/mL*min



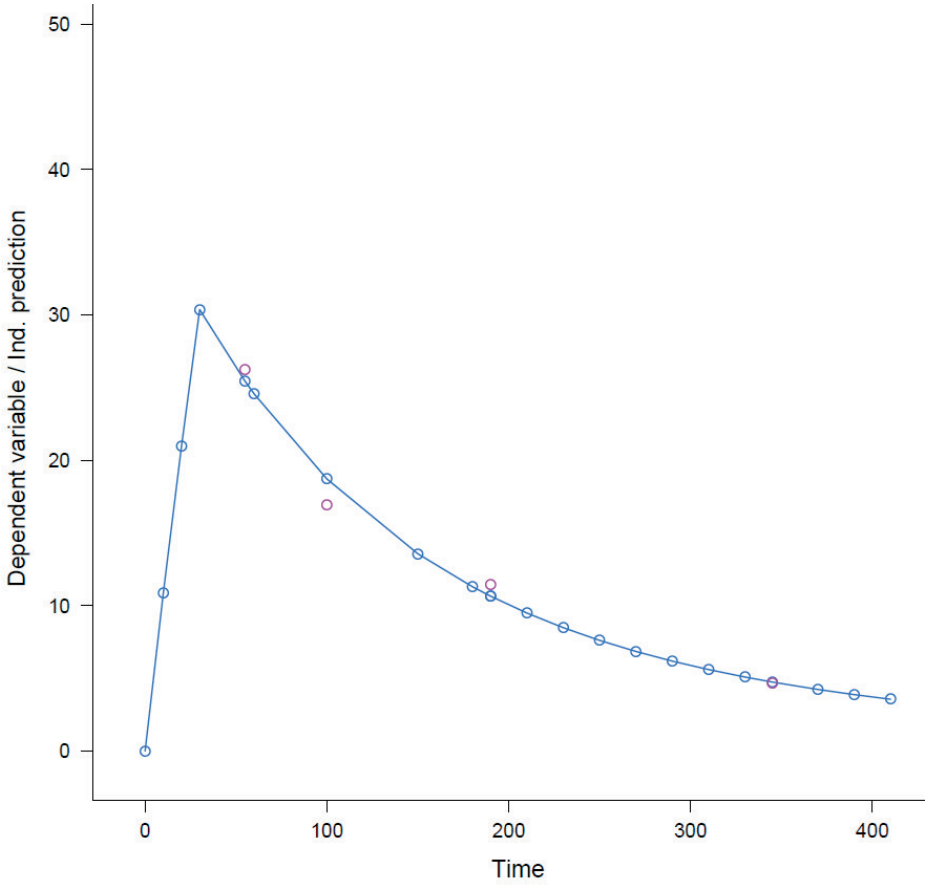
PATIENT 5 (BMI <25 kg/m²): AUC = 6.49 mg/mL*min



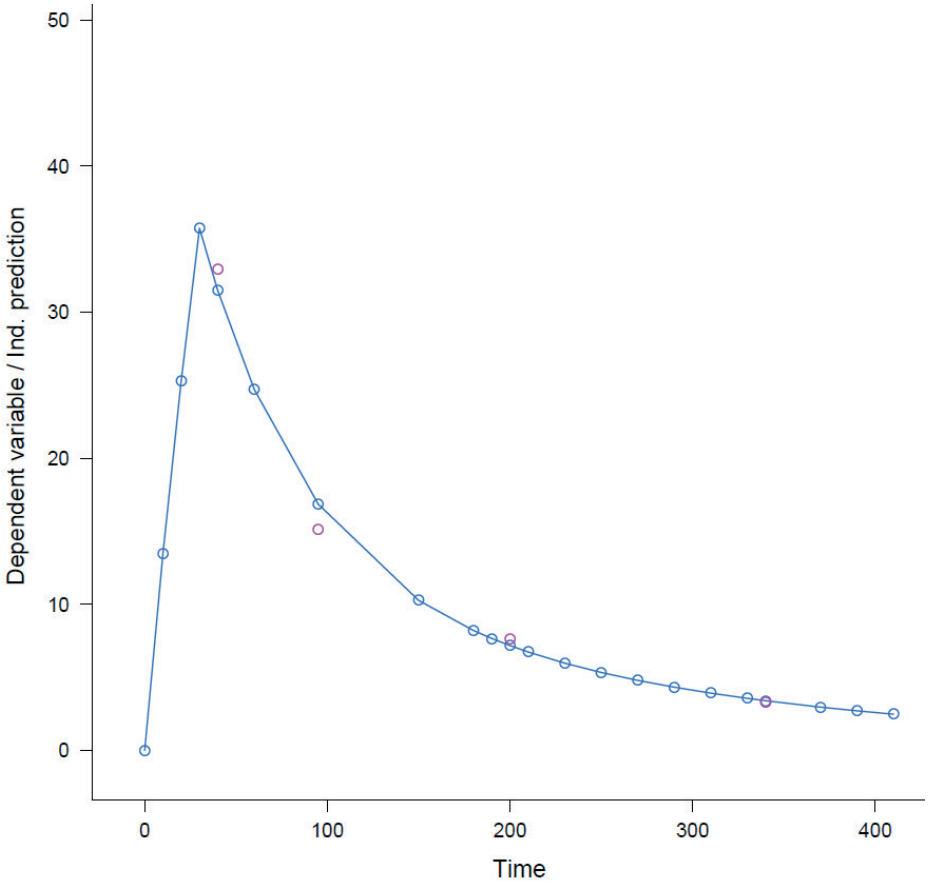
PATIENT 6 (BMI <25 kg/m²): AUC = 5.72 mg/mL*min



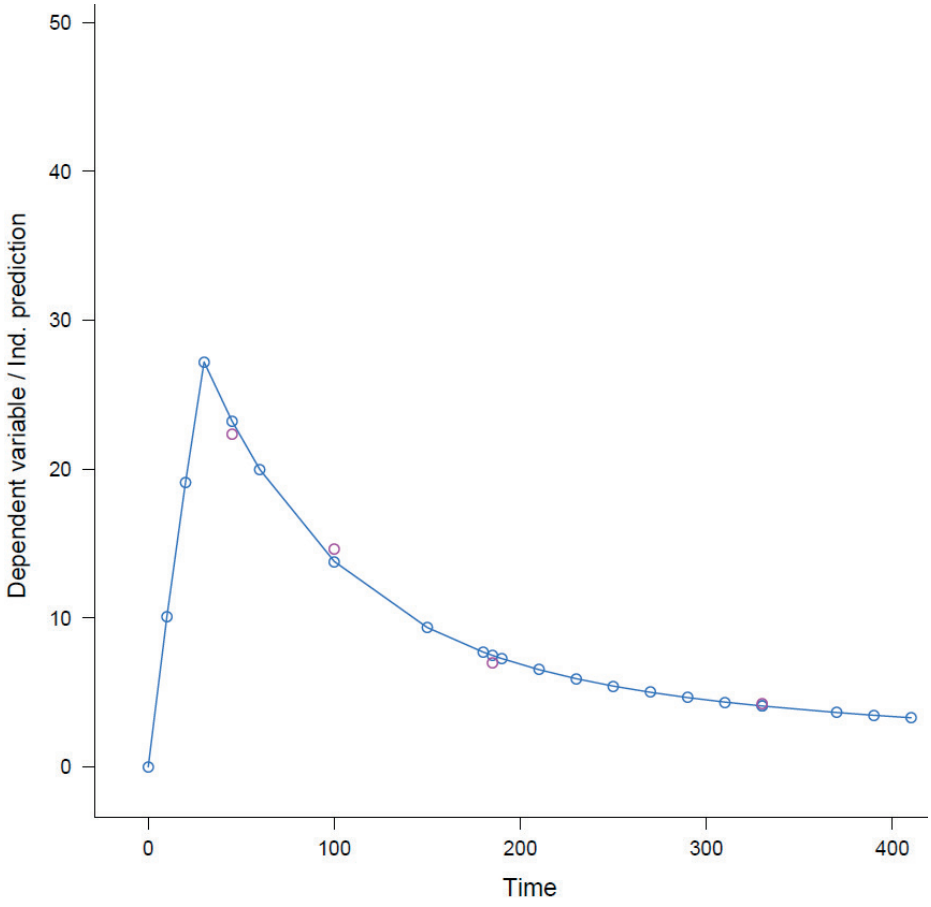
PATIENT 7 (BMI 25 – 30 kg/m²): AUC = 5.84 mg/mL*min



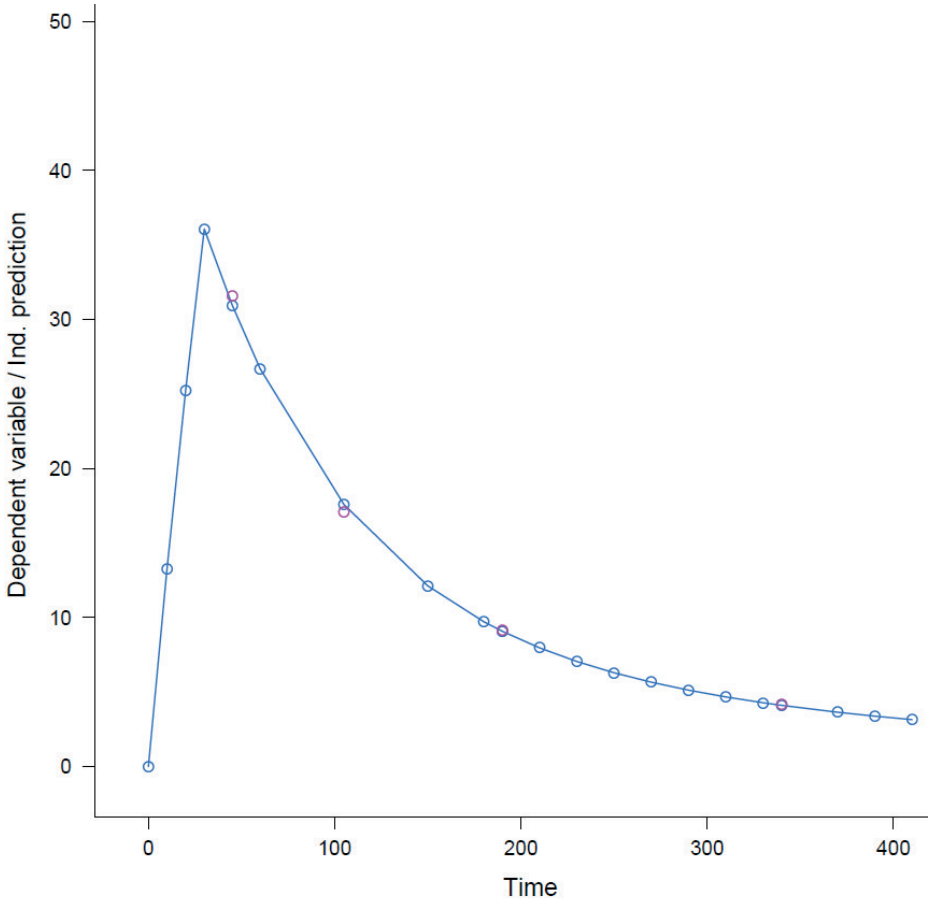
PATIENT 8 (BMI <25 kg/m²): AUC = 4.81 mg/mL*min



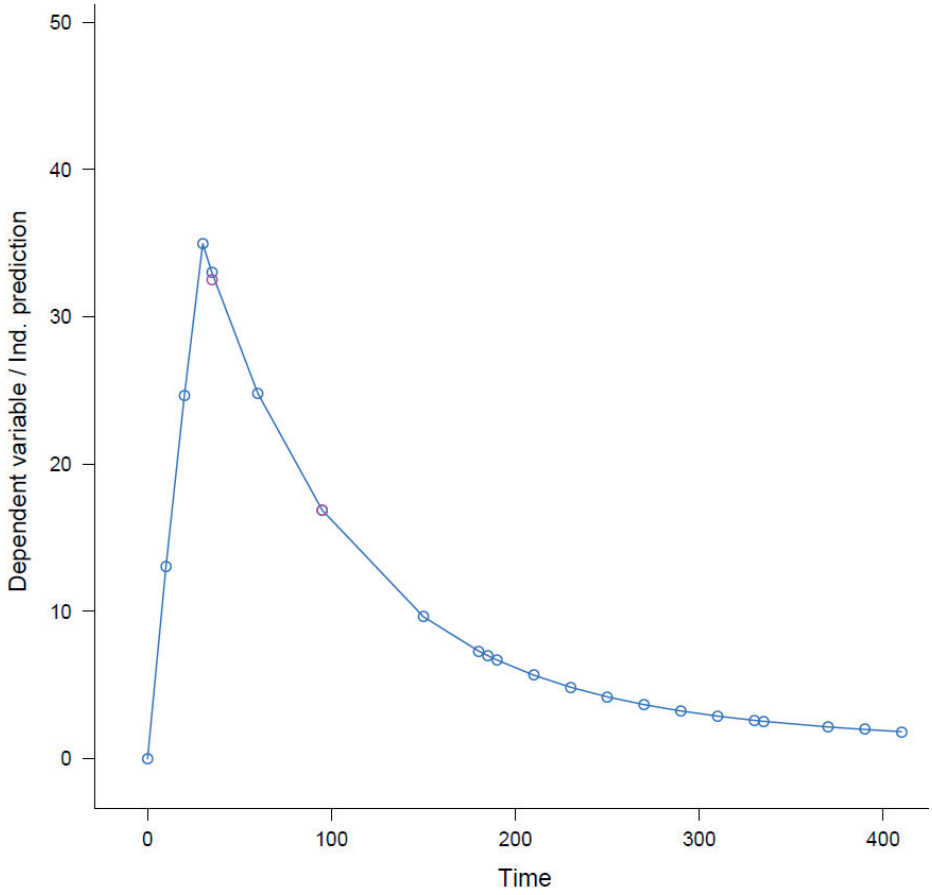
PATIENT 9 (BMI <25 kg/m²): AUC = 5.29 mg/mL*min



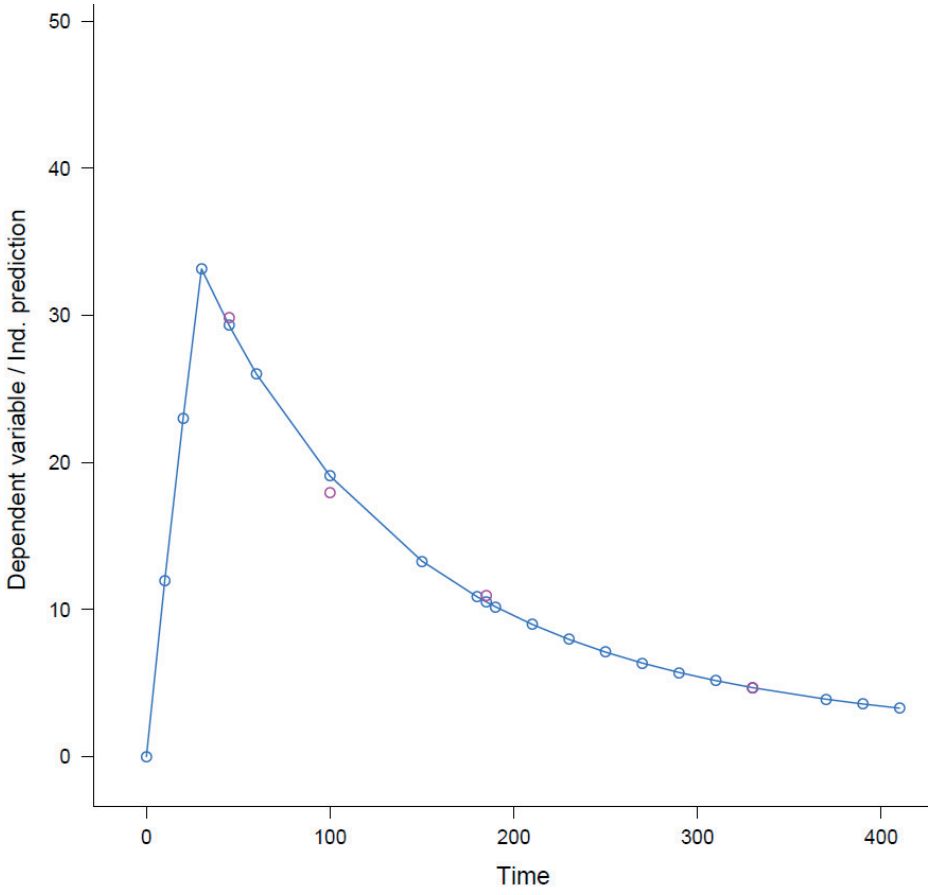
PATIENT 10 (BMI <25 kg/m²): AUC = 5.77 mg/mL*min



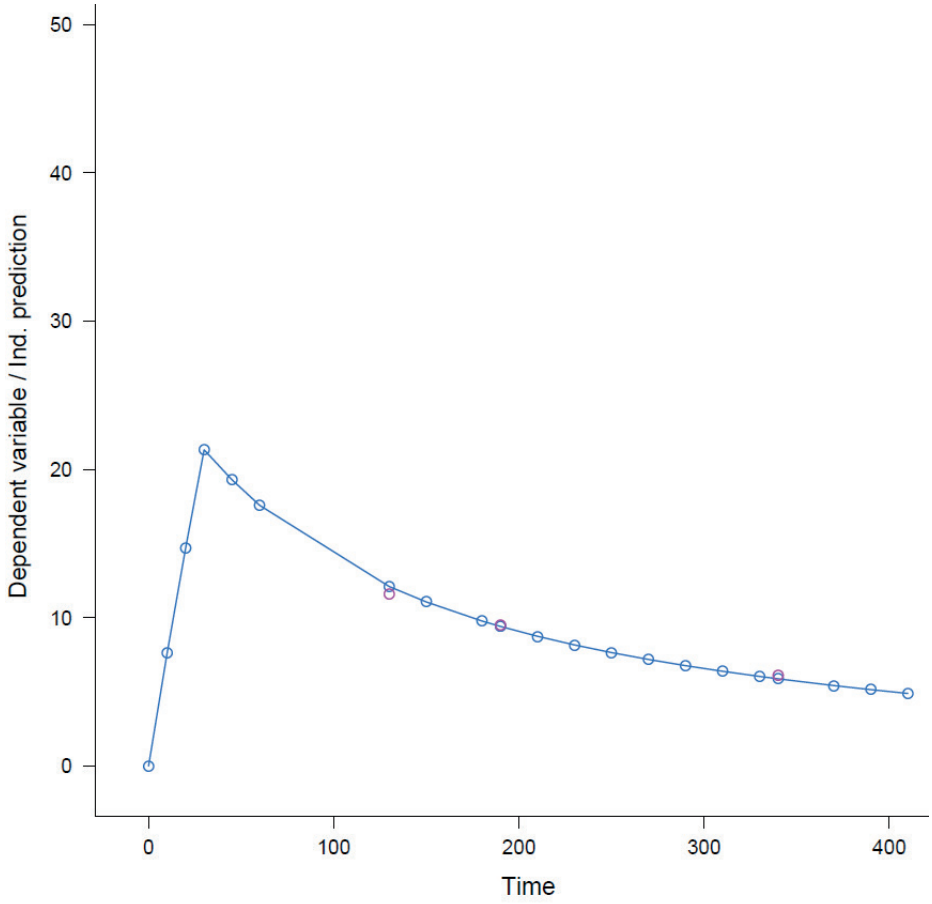
PATIENT 11 (BMI ≥30 kg/m²): AUC = 4.61 mg/mL*min



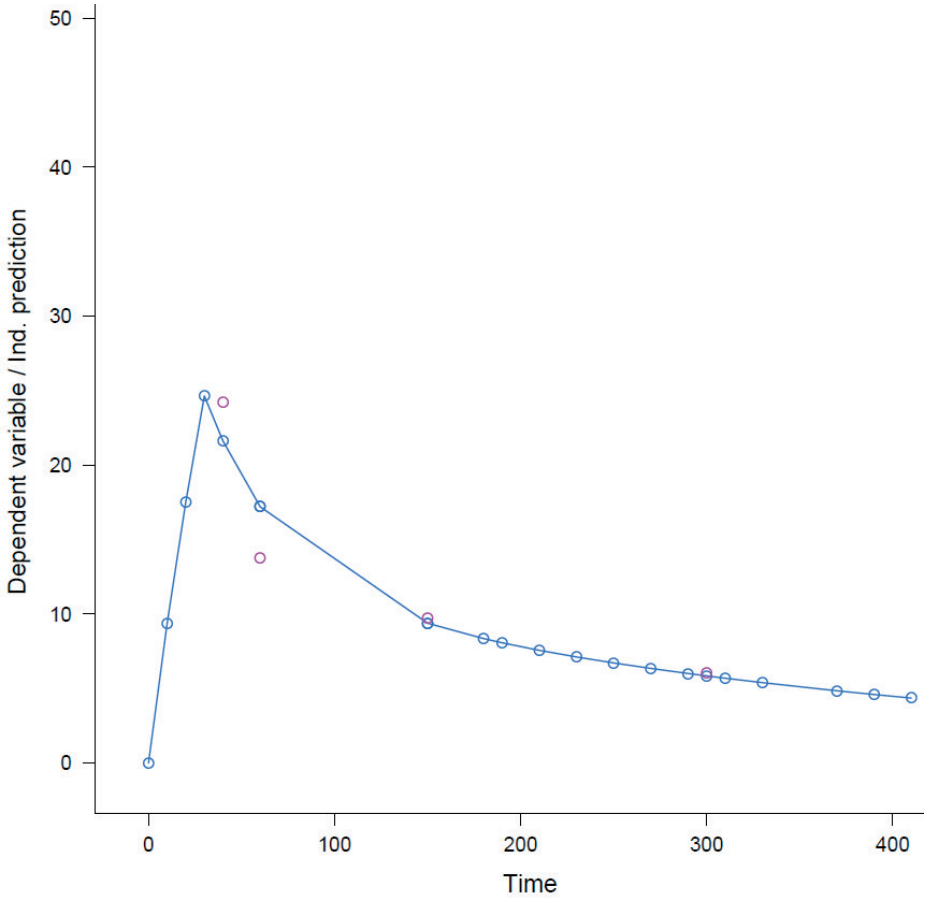
PATIENT 12 (BMI 25 – 30 kg/m²): AUC = 5.84 mg/mL*min



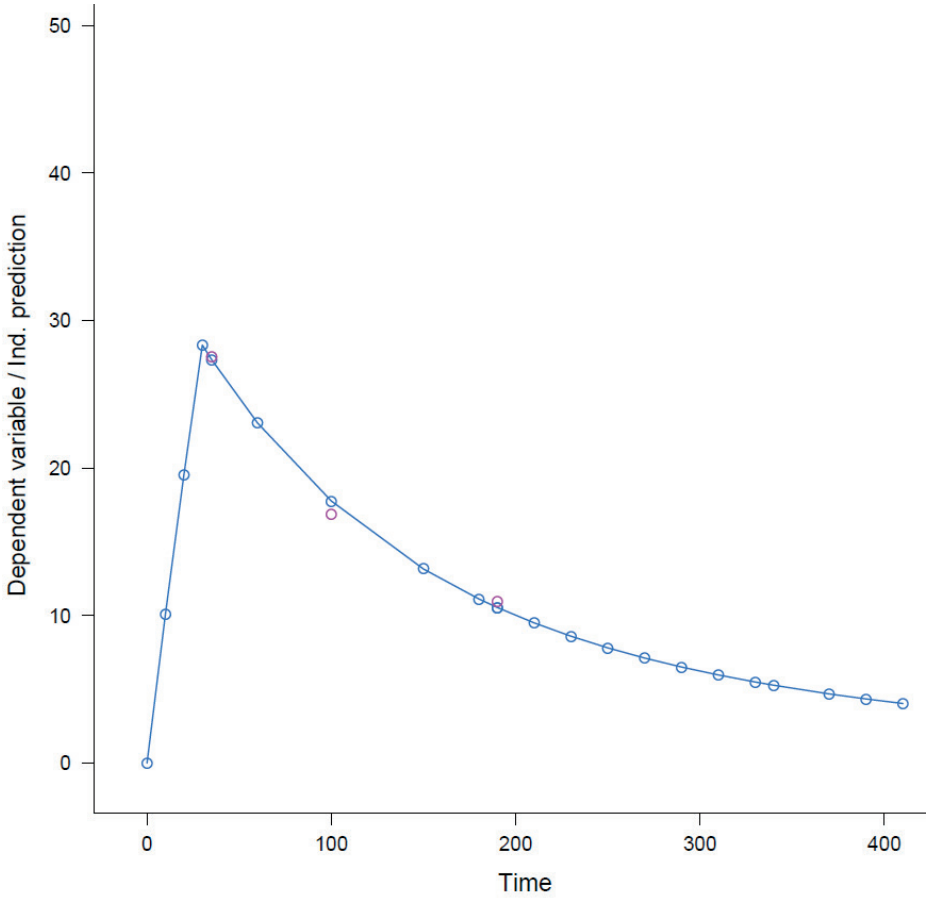
PATIENT 13 (BMI ≥30 kg/m²): AUC = 6.10 mg/mL*min



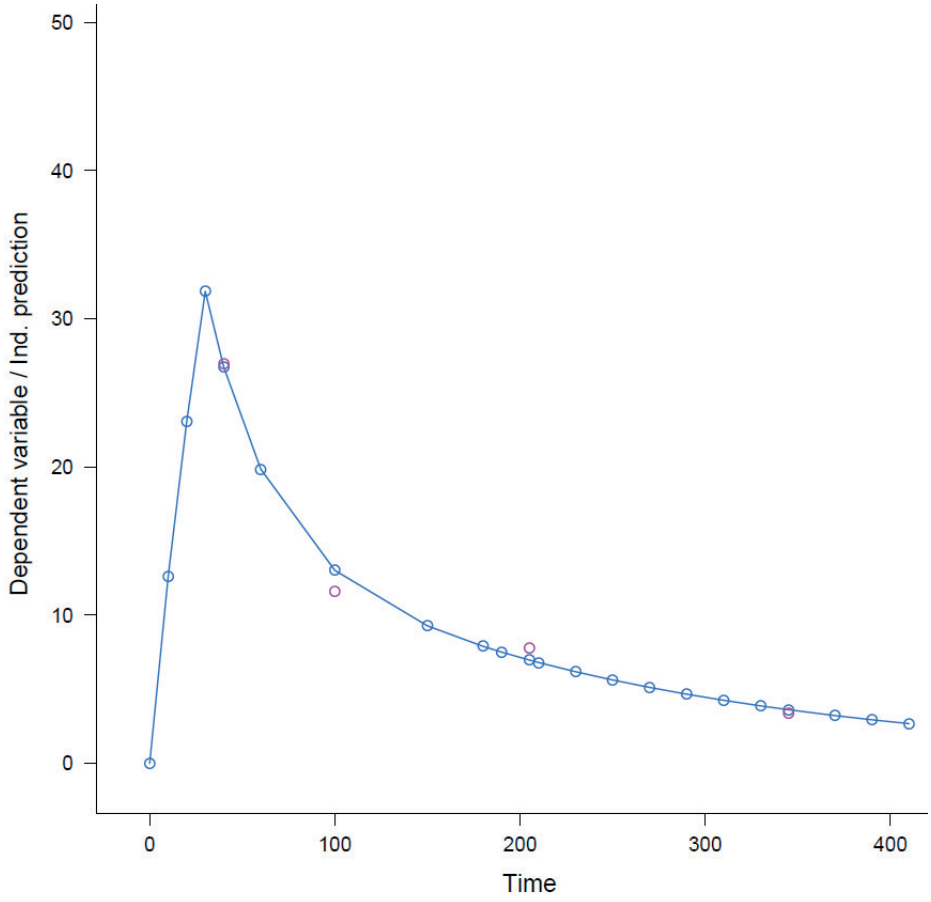
PATIENT 14 (BMI 25 – 30 kg/m²): AUC = 5.84 mg/mL*min



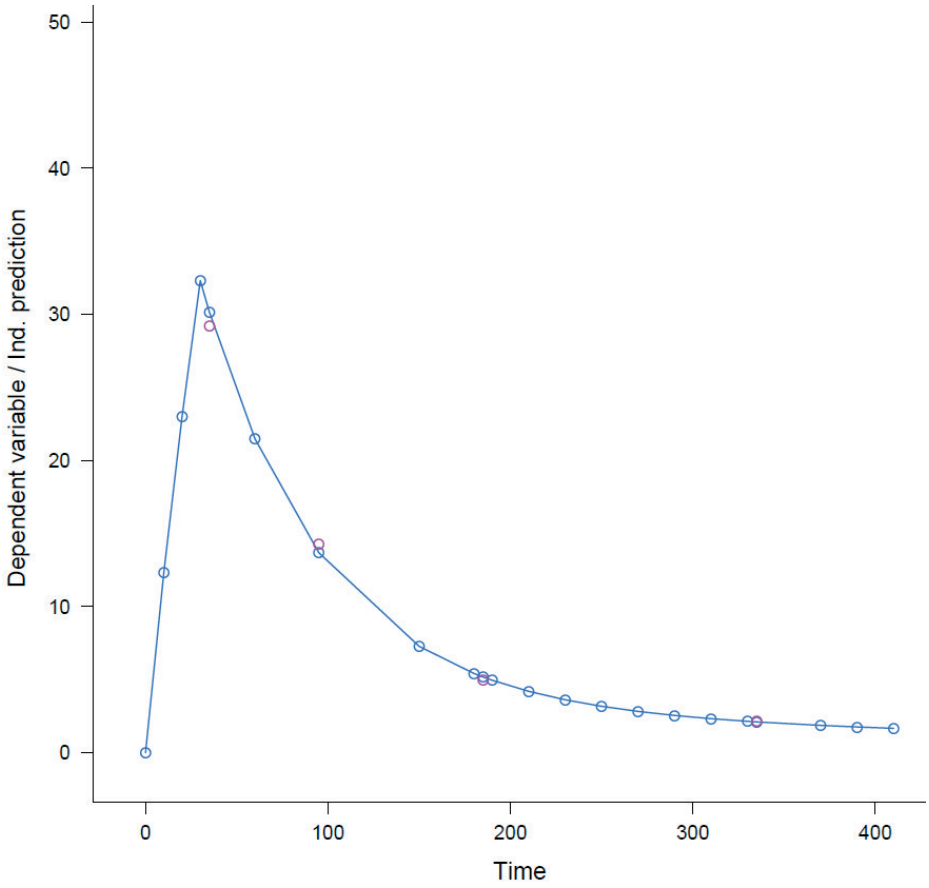
PATIENT 15 (BMI ≥30 kg/m²): AUC = 6.00 mg/mL*min



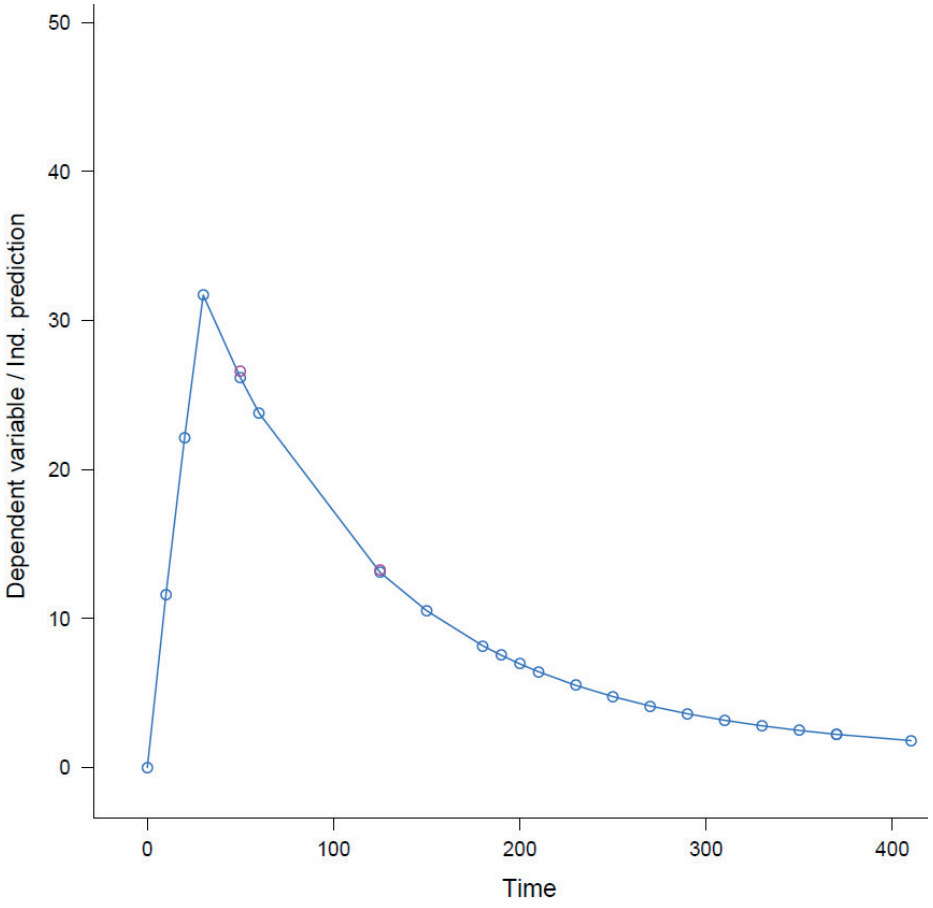
PATIENT 16 (BMI ≥30 kg/m²): AUC = 4.39 mg/mL*min



PATIENT 17 (BMI ≥30 kg/m²): AUC = 4.10 mg/mL*min



PATIENT 18 (BMI 25 – 30 kg/m²): AUC = 5.84 mg/mL*min



III

CHAPTER IV

The toxicity profile of pemetrexed in non-small cell lung cancer patients with moderate renal impairment - a retrospective cohort study

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ABSTRACT

PURPOSE

Pemetrexed is a key drug in the immunochemotherapy of non-small cell lung cancer (NSCLC). However, its use is contraindicated in patients with renal impairment due to severe toxicity risks. As renal impairment is common in lung cancer patients, healthcare professionals face a dilemma between withholding effective treatment and risking toxicity. Real-world data on pemetrexed toxicity may aid in this decision. The primary objective of this study was to describe the toxicity profile of pemetrexed treatment in NSCLC patients with renal impairment.

PATIENTS AND METHODS

This multicenter, descriptive, retrospective study was conducted across nine hospitals in the Netherlands between 2015-2024. Patients included had a diagnosis of NSCLC, received ≥1 cycle of standard dose pemetrexed, and had a baseline creatinine clearance (CrCL)<45 mL/min. Data were collected on patient and treatment characteristics, hematological and non-hematological toxicity incidences, treatment discontinuation, dose reduction, and treatment-related hospitalization.

RESULTS

Forty-four patients were included, with median CrCL 41.1 mL/min (interquartile range: 35.0-43.9). Thirty-one patients (70%) did not finish four cycles of pemetrexed treatment, with fourteen patients (45%) discontinuing due to pemetrexed-associated toxicity. More than half of patients (n=28; 64%) were hospitalized due to treatment-related toxicity. Seventeen patients (39%) developed grade 3-4 neutropenia and leukopenia. Gastro-intestinal toxicity grade 3-4 occurred in fifteen (34%) patients.

CONCLUSION

Pemetrexed treatment of NSCLC patients with moderate renal impairment was associated with high incidence of hematological toxicity, hospitalization, dose reduction, and treatment discontinuation. These results highlight the necessity of developing new treatment regimens to enable safe pemetrexed-based immunochemotherapy in NSCLC patients with renal impairment.

INTRODUCTION

Pemetrexed is a multi-targeted cytostatic anti-folate antagonist used to treat non-squamous non-small cell lung cancer (NSCLC) and mesothelioma [1-3]. Treatment usually consists of four cycles of pemetrexed plus a platinum agent. Moreover, from 2015 onwards, NSCLC treatment has been increasingly combined with programmed death ligand 1 (PD-L1) interfering agents like the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab [4, 5]. Pemetrexed is for 70-90% eliminated by the kidneys within 24 hours as unchanged drug via tubular secretion and glomerular filtration in patients with normal renal function [3, 6]. Hence, besides dose, renal function primarily determines pemetrexed exposure [7, 8]. However, in daily practice, pemetrexed dosing is based on body surface area (BSA), which only poorly correlates with renal clearance and thus exposure [7-9].

Pemetrexed dosing based on BSA has been proven to be effective and generally safe in patients with adequate renal function (creatinine clearance (CrCL) ≥45 mL/min) [10-12]. However, dosing in patients with impaired renal function increases systemic pemetrexed exposure, resulting in an increased risk of hematological and non-hematological toxicity that may even be fatal [7, 13-18]. A renal impairment study by the license holder of pemetrexed examined the toxicity and pharmacokinetics of pemetrexed in patients with varying renal function [19]. This study was terminated early when one patient with a CrCL <20 mL/min died shortly after the start of treatment due to severe pemetrexed-induced toxicity. Based on this observation, administration of pemetrexed in patients with a CrCL <45 mL/min is prohibited according to the label [2, 3]. A new study recently showed that the exposure-toxicity relationship of pemetrexed is driven by a time over a plasma concentration threshold, which is prolonged in patients with impaired renal function. As a result, when administering the approved dose of 500 mg/m^2, the probability of grade ≥3 neutropenia increases to 50-90% in patients with CrCL <45 mL/min [20].

As previously stated, pemetrexed is the preferred chemotherapeutic agent as part of the platinum doublet immunochemotherapy of non-squamous NSCLC patients with low PD-L1 expression (<50%) [2, 9]. The majority of NSCLC patients have a non-squamous histology and PD-L1 expression of <50% [21]. In addition, around 30% of lung cancer patients have impaired renal function [22]. As a result, many clinicians are confronted with the dilemma of administering effective treatment with major concerns for life-threatening toxicity or withholding the patient from a proven effective line of treatment. Real-world data on the toxicity profile of pemetrexed in this vulnerable population are of added value in guiding clinical decision-making but

are scarcely available [19]. Therefore, this study aimed to describe the toxicity profile of pemetrexed in NSCLC patients with renal impairment.

MATERIALS AND METHODS

STUDY DESIGN AND PATIENT POPULATION

We conducted a retrospective, multi-center, cohort study in patients with non-squamous NSCLC receiving standard-dose treatment of pemetrexed (500 mg/m^2) between January 2015 and April 2024 with an estimated glomerular filtration rate (eGFR) or creatinine clearance of <45 mL/min at baseline in nine hospitals across the Netherlands. All patients were treated at Radboud University Medical Center in Nijmegen, Amphia Hospital in Breda, or one of the seven hospitals within the Santeon hospital network. The Santeon network comprises seven non-university teaching hospitals (Catharina, OLVG, St. Antonius, Medisch Spectrum Twente, Canisius-Wilhelmina, Martini, and Maasstad Hospitals), representing more than 12% of the Dutch population [23].

Patients were retrospectively selected from participating hospitals if they met all of the following inclusion criteria: age ≥18 years; diagnosis of NSCLC; being treated with at least one cycle of standard dose pemetrexed (500 mg/m2); and having an impaired renal function of <45 mL/min at baseline. An impaired renal function was determined by using estimators of Glomerular Filtration Rate (eGFR) calculated using 1) the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [24] or 2) the Modification of Diet in Renal Disease (MDRD) equation [25], both adjusted for BSA, or by using 3) an estimator of creatinine clearance (CrCL) using the Cockcroft-Gault equation (see Supplementary Table S1 for the different formulas) [26]. Patients were included if the eGFR or CrCL was <45 mL/min based on any of the three formulas. Exclusion criteria were pregnancy, lactation, and limb amputation, resulting in incorrect creatinine clearance estimation.

All baseline patient and treatment characteristics, including age, sex, height, weight, BSA, serum creatinine, eGFR (CKD-EPI 2009), Eastern Cooperative Oncology Group - Performance Status (ECOG-PS), medication use, histology (adenocarcinoma, large cell, not otherwise specified), line of treatment, and the total amount of cycles were obtained from electronic health records (EHR) of the individual hospitals. Toxicity outcomes were retrospectively collected from the EHR. For hematological toxicities, the nadir of available results of thrombocytes, erythrocytes, leukocytes, and neutrophils were collected during treatment up until one month after the last treatment cycle.

The grade of anemia was estimated based on the calculated mean hemoglobin. Mean hemoglobin [g/dL] was calculated as the product of the mean corpuscular hemoglobin (MCH) [pg] and erythrocyte count [x109/dL], using the average MCH of 29 pg [27]. Non-hematological toxicities assessed in this study included gastro-intestinal adverse events (i.e., vomiting, nausea, diarrhea, stomatitis), skin reactions (i.e., rash, exfoliation), and cachexia. Hematological and non-hematological toxicities were graded following the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 of the National Cancer Institute (NCI) [28].

The Medical research Ethics Committee United (MEC-U, Nieuwegein, the Netherlands) declared the study not to be subject to the Medical Research Involving Human Subjects Act (ethical approval code MEC W23.130). Furthermore, the Committee provided a waiver for the necessity of written informed consent, given the retrospective character of the study in patients of whom most were already deceased. The study was approved by the individual institutional review boards of all participating hospitals. For personal data protection, all patient data were coded with a research number and processed anonymously in a research database (ResearchManager, Deventer, the Netherlands).

STUDY ENDPOINTS AND DATA ANALYSIS

The primary objective of this study was to describe the toxicity profile of pemetrexed in NSCLC patients with renal impairment. Primary endpoints were hematological and non-hematological toxicity, treatment-related hospitalization, and treatment discontinuation.

The secondary objective was to describe the overall survival (OS) after treatment with pemetrexed in these patients. OS was calculated as the time interval in days from the start of treatment until death or the last follow-up date and expressed as median survival with a 95% confidence interval (95%-CI). Categorical data were expressed in numbers and percentages, and continued data as median and interquartile range (IQR).

RESULTS

STUDY POPULATION

A total of 46 non-squamous NSCLC patients met the inclusion criteria. Two patients were excluded due to not having received a standard dose of pemetrexed and participating in another study, resulting in a total of 44 included patients (see Supplementary Table S2 for the details of data collection for each hospital).

Table 1 describes the patients' baseline characteristics. At baseline, all patients had moderate renal function between 30-45 mL/min with the median creatinine clearance and eGFR (corrected for BSA) being 41.1 mL/min (IQR: 35.0 – 43.9) and 43.7 mL/min (IQR: 36.8 – 47.3), respectively. Treatment with pemetrexed was first-line therapy for most patients (n= 35; 80%). For concomitant therapy, most patients received carboplatin (n=41; 93%) or cisplatin (n=2; 5%), and 20 patients (45%) received immunochemotherapy (pembrolizumab) in combination with pemetrexed treatment.

Table 1: Population characteristics at baseline

	TOTAL (n=44)
Age [years], median (IQR)	74.0 (70.0 – 80.8)
Sex (male/female), n (%)	22/22 (50/50%)
Height [cm], median (IQR)	168.0 (160.3 – 174.0)
Weight [kg], median (IQR)	66.5 (60.0 – 76.8)
BSA [m^2], median (IQR)	1.8 (1.7 – 1.9)
CKD-EPI adjusted for BSA [mL/min], median (IQR)	43.7 (36.8 – 47.3)
Creatinine clearance* [mL/min], median (IQR)	41.1 (35.0 – 43.9)
Histology, n (%)	
• Adenocarcinoma	39 (89%)
• Large cell	1 (2%)
• Not otherwise specified	4 (9%)
ECOG-PS, n (%)	
• 0	10 (23%)
• 1	23 (52%)
• 2	10 (23%)
• 3 – 4	1 (2%)
Line of treatment, n (%)	
• First line	35 (80%)
• Second line	7 (16%)
• Third line	0 (0%)
• More than third line	2 (5%)
Comorbidities	
• Congestive heart failure	6 (14%)
• COPD	13 (30%)
• Diabetes mellitus	11 (25%)
• Liver disease	1** (2%)
Immunochemotherapy (pembrolizumab), n (%)	20 (45%)

* Creatinine clearance calculated using the Cockcroft-Gault formula
** Mild liver disease (chronic hepatitis)
Abbreviations: IQR = interquartile range, BSA = Body Surface Area, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, ECOG-PS = Eastern Cooperative Oncology Group - Performance status, COPD = chronic obstructive pulmonary disease

TREATMENT OUTCOMES

Patients received a median of 2 cycles of pemetrexed (IQR: 1-4), with 21 patients (48%) completing the third and 13 patients (30%) the fourth cycle. Of the 44 patients, 42 patients (95%) received folic acid and vitamin B12. Concomitant therapy included furosemide in five patients (11%) and granulocyte colony-stimulating factor (G-CSF) in one patient (2%). Other concomitant medications that could potentially influence toxicity when given with pemetrexed, such as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or proton pump inhibitors (PPIs), were not used. In total, 31 patients (70%) discontinued treatment with pemetrexed, of which nearly half of the patients (n=14) because of treatment-related toxicity. Of these fourteen patients, nine patients were hospitalized due to pemetrexed-associated toxicity, eight patients were suffering from hematological toxicity and infection (e.g., pancytopenia/anemia, fever, pneumonia, oral candida), and six patients had non-hematological toxicity (e.g., neuropathy, colitis, malaise), including one patient having an allergic reaction to pemetrexed. Hospitalization due to pemetrexed-associated toxicity occurred in 28 (64%) of all patients with a median duration of hospitalization of 3 (IQR: 1-8) days. Treatment delay of at least one week occurred in 15 patients (34%), with two patients (5%) having a treatment delay of more than 21 days. Furthermore, 21 patients (48%) received a dose reduction during treatment due to toxicity. Notably, only one patient (2%) had their pemetrexed dosage increased following a dose reduction, while all other patients maintained their reduced dose, with some requiring further reductions in subsequent cycles.

Grade 3-4 leukopenia and neutropenia occurred in 17 patients (39%). Anemia grade 3-4 was seen in 14 patients (32%). Grade 3-4 thrombocytopenia occurred in 10 patients (23%). Moreover, grade 3-4 hematological toxicities mainly occurred early during the first treatment cycle (see Table 2).

Any grade of gastro-intestinal toxicity was observed in 26 patients (59%), with grade 3-4 toxicity occurring more frequently (n=15; 34%) than grade 1-2 toxicity (n=11; 25%). A complete overview of all treatment-related toxicities is provided in Table 2 and Supplementary S3. Lastly, the median OS of the study population was 8.9 months (95%-CI: 3.7-4.2 months; see Figure 1).

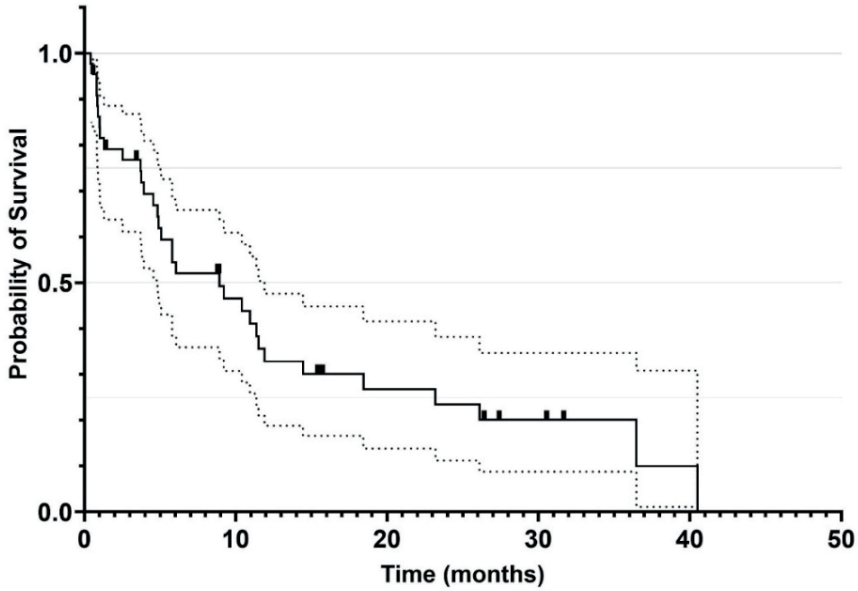

Figure 1: Overall survival from the start of pemetrexed treatment until 40 months

Number at risk	43	24	17	10	8	6	3	2	1
Time [months]	0	5	10	15	20	25	30	35	40

Table 2: Treatment and toxicity outcomes of pemetrexed in patients with impaired renal function

	OVERALL	**DURING EACH CYCLE OF TREATMENT**			
	C1-4 (n=44)	**C1 (n=44)**	**C2 (n=29)**	**C3 (n=21)**	**C4 (n=13)**
Pemetrexed dosage, [mg/m²] median (IQR)	494 (387-506)	493 (420-505)	497 (388-508)	483 (372-508)	412 (374-504)
Treatment delay 1 week or more, n (%)					
• Less than one cycle (< 21 days)	13 (30%)	11 (25%)	9 (31%)	6 (29%)	0 (0%)
• More than one cycle (≥ 21 days)	2 (4%)	1 (2%)	0 (0%)	1 (5%)	0 (0%)
• No	29 (66%)	32 (73%)	20 (69%)	14 (67%)	13 (100%)
Dose reduction, n (%)	21 (48%)	12 (27%)	10 (35%)	9 (43%)	6 (46%)
Hospitalization, n (%)	28 (64%)	17 (39%)	10 (34%)	5 (24%)	2 (15%)
• 1-5 days, n	18	8	9	3	2
• 5-10 days, n	6	7	0	0	0
• >10 days, n	4	2	1	2	0

Table 2: Continued

	OVERALL	**DURING EACH CYCLE OF TREATMENT**			
	C1-4 (n=44)	**C1 (n=44)**	**C2 (n=29)**	**C3 (n=21)**	**C4 (n=13)**
Cause of treatment discontinuation, n (%)	31 (70%)	15 (34%)	8 (28%)	8 (38%)	NA****
• Progression	14	9	4	1	
• Treatment toxicity	14	5	3	6	
• Death during treatment	1	0	1**	0	
• Other	2	1*	0	1***	
Thrombocytopenia, n (%)					
• Grade 1-2	13 (30%)	8 (18%)	6 (21%)	1 (5%)	4 (31%)
• Grade 3-4	10 (23%)	6 (14%)	3 (10%)	2 (10%)	0 (0%)
• Missing	0 (0%)	0 (0%)	2 (7%)	1 (5%)	0 (0%)
Neutropenia, n (%)					
• Grade 1-2,	5 (11%)	5 (11%)	4 (14%)	4 (19%)	1 (8%)
• Grade 3-4	17 (39%)	12 (27%)	4 (14%)	1 (5%)	2 (15%)
• Missing	8 (18%)	11 (25%)	10 (34%)	6 (29%)	3 (23%)
Anemia, n (%)					
• Grade 1-2	22 (50%)	23 (52%)	19 (66%)	11 (52%)	5 (38%)
• Grade 3-4	14 (32%)	5 (11%)	4 (14%)	5 (24%)	7 (54%)
• Missing	6 (14%)	9 (20%)	6 (21%)	5 (24%)	1 (8%)
Leukopenia, n (%)					
• Grade 1-2	15 (34%)	15 (34%)	10 (34%)	10 (48%)	6 (38%)
• Grade 3-4	17 (39%)	10 (23%)	5 (17%)	2 (10%)	1 (8%)
• Missing	0 (0%)	0 (0%)	2 (7%)	1 (5%)	0 (0%)
Gastro-intestinal, n (%)					
• Grade 1-2	11 (25%)	10 (23%)	8 (28%)	3 (14%)	1 (8%)
• Grade 3-4	15 (34%)	10 (23%)	7 (24%)	3 (14%)	0 (0%)
Cachexia, n (%)					
• Grade 1-2	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
• Grade 3-4	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Skin, n (%)					
• Grade 1-2	8 (18%)	8 (18%)	1 (3%)	3 (14%)	2 (15%)
• Grade 3-4	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Other, n (%)					
• Grade 1-2	5 (11%)	3 (7%)	1 (3%)	3 (14%)	0 (0%)
• Grade 3-4	6 (14%)	4 (9%)	0 (0%)	2 (10%)	0 (0%)

* Patient discontinued due to severe thrombolysis (not treatment related)

** Not treatment related

*** Patient still under treatment at time of lost to follow-up (01-04-2024)

**** All 13 patients completed cycle 4

Abbreviations: C1-4 = cycles 1 to 4, IQR = interquartile range, NA: not applicable

DISCUSSION

In this study, we described the toxicity profile of standard-dose pemetrexed in non-squamous NSCLC patients with moderate renal impairment (30-45 mL/min). We found that standard dosing led to a high rate of severe hematological and gastro-intestinal side effects, leading to early treatment discontinuation in the majority of patients. Furthermore, the severe treatment-related toxicity was specifically reflected in the high incidence of hospitalization, as approximately two-thirds of the population had to be hospitalized because of pemetrexed-associated toxicity.

Concerning hematological toxicity, more than a third of the study population developed severe hematological toxicity, including leukopenia (39%), neutropenia (39%), anemia (32%), and thrombocytopenia (23%). For non-hematological toxicity, an incidence of 34% was found for gastro-intestinal toxicity. The highest incidences of toxicity occurred in the first cycle and decreased in subsequent cycles. However, the incidence of toxicity remained elevated, leading to a high incidence of early treatment discontinuation in the majority of all patients (70%). The high incidence of treatment discontinuation and toxicity are unwanted and disadvantageous for patient outcomes. Given the retrospective nature of the analysis, the extent to which patients were informed of these potential risks during the consent process remain unclear. Furthermore, hospitalization and long-lasting recovery from toxicity have a detrimental effect on quality of life. It should be noted that in our population, no severe renal impairment (eGFR <30 mL/min) was observed. Consequently, it can be expected that even more severe toxicity is likely to occur in patients with worse renal function. Lastly, due to the small number of six patients in the 30-35 mL/min CrCL range, meaningful subgroup analysis by narrower CrCL categories (i.e., 40-45, 35-40 and 30-35 mL/min) was not possible.

The observation that the risk of severe pemetrexed-associated toxicity is increased with decreasing renal function is not unexpected. An extensive population pharmacokinetic-pharmacodynamic (PK/PD) analysis study by Boosman *et al.* predicted a high incidence (51-93%) of grade 3-4 neutropenia in individuals with renal impairment (eGFR <45 mL/min) [20]. This result is comparable to what we have found in our population with moderate renal impairment. Furthermore, our results also correlate well with a small, retrospective study by Ando *et al.* that found an incidence of 37.5% for grade 3-4 neutropenia in eight patients with renal impairment (CrCL < 45 mL/min) [13].

As to be expected, we showed a higher incidence of hematological toxicity compared to the incidences reported in phase III studies of pemetrexed conducted in patients with normal renal function. A study by Vogelzang *et al.*, comparing pemetrexed plus cisplatin (n=226) versus cisplatin monotherapy (n=222) in mesothelioma patients, found an incidence of 23.2% grade 3-4 neutropenia, 14.9% leukopenia and 5.4% thrombocytopenia [12]. Another more extensive study by Scagliotti *et al.*, comparing pemetrexed plus cisplatin (n=862) versus cisplatin plus gemcitabine (n=863) in NSCLC patients, found a lower incidence of grade 3-4 hematological toxicity (neutropenia: 15.1%, leukopenia: 4.8%, thrombocytopenia: 4.1%) for pemetrexed plus cisplatin [11]. Regarding non-hematological toxicity, a phase III study by Hanna *et al.* regarding monotherapy pemetrexed in patients with normal renal function showed a considerably lower incidence of hospitalization (6.4%), grade 3-4 gastro-intestinal toxicity (5.6%), and grade 3-4 neutropenia (5.3%) and thrombocytopenia (1.9%) compared to our results [10]. In the era of immunotherapy, pemetrexed treatment is often co-administered with a platinum compound and immune checkpoint inhibitor [29], making it difficult to compare these results directly. However, similar incidences of severe toxicity were found for immunotherapy treatment in NSCLC of pembrolizumab, pemetrexed plus cis-/carboplatin of 15.8% grade ≥3 neutropenia and 7.9% thrombocytopenia as compared to no-immunotherapy regimens [4]. Lastly, our study showed a high percentage of treatment discontinuation (n=31; 70%). In contrast, the same phase-III trail of NSCLC patients receiving pembrolizumab plus pemetrexed plus cis-/carboplatin showed treatment discontinuation of only 14% [4] or 27-37% in a recent real-world data study [30]. Lastly, our study population was older, with a median age of 74.0 years (IQR: 70.0–80.8). Administering treatment to older individuals with renal impairment is particularly risky due to their increased vulnerability. The International Society of Geriatric Oncology (SIOG) contraindicates the use of pemetrexed in patients with a renal function below 45 mL/min [31]. Indeed, 64% of patients required hospitalization due to treatment-related toxicity, further highlighting that the usage of pemetrexed in this population may have been more harmful than beneficial.

Our study is the most extensive real-world population study investigating the toxicity of pemetrexed in patients with impaired renal function. Nonetheless, there are some potential limitations associated with our study. Firstly, since this was a retrospective study, the data for this study depended on reported data and, inevitably, had missing and incomplete values as most measurements were conducted on day 20 in line with the label, whereas the precise neutrophil nadir is often reached around day 10 [16]. Therefore, the observed toxicity is most likely underestimated. Secondly, data collection of non-hematological toxicities is susceptible to information bias,

since these toxicities are not always consistently reported during routine patient visits and may vary by treating physician. Moreover, reporting of adverse non-hematological events may differ by institution. Therefore, it may have led to differences in reported incidences between institutions in this multicenter study among nine hospitals dispersed around the Netherlands. Nonetheless, all information stemmed from electronic health care records, which made all data readily available. Notwithstanding the potential risk of underreporting non-hematological toxicities, we still noticed high incidences, reflecting that standard-dosed pemetrexed results in overdosing in patients with moderate renal impairment. Since our study was conducted exclusively within a Dutch population, limits the generalizability of our findings to other patient populations. Treatment practices, healthcare systems, and patient characteristics in the Netherlands may differ from those in other countries. Nevertheless, renal function remains an important predictor of severe toxicity for pemetrexed, regardless of the healthcare setting.

Most patients received carboplatin and pembrolizumab in combination with pemetrexed, thereby complicating the assessment of the independent association of pemetrexed with toxicity. Nevertheless, current guidelines for non-squamous NSCLC treatment include first line treatment combination of pemetrexed plus platinum plus pembrolizumab. Since our data collection started from the introduction of immunotherapy into NSCLC treatment in 2015, our study population offers an accurate portrayal of today's non-squamous NSCLC population [29]. Moreover, a large group of patients is not eligible for immunotherapy as the real-world prevalence of PD-L1 <50% is around 78% [21].

Due to the expected severe toxicity, the pemetrexed label states not to use pemetrexed in patients with a creatinine clearance of <45 mL/min [2, 3]. Our study results serve as a valuable addition to the currently available information regarding pemetrexed, indicating a higher incidence of hematological toxicity and hospitalization, especially a high incidence of treatment discontinuation, in patients with non-squamous NSCLC and moderately impaired renal function (30-45 mL/min) compared to patients with normal renal function. Our results imply that BSA-based pemetrexed dosing in patients with moderately impaired renal function is not recommended in clinical practice. Of note, only applying pemetrexed dose reductions will likely insufficiently reduce the elevated risk for severe toxicity. Although a case-report described minimal toxicities and stable disease throughout four years of pemetrexed treatment following a 20% dose reduction and interval elongation to four weeks in a patient with impaired renal function [32], the PK/PD simulation study by Boosman *et al.* showed that a 20 mg pemetrexed dose for a patient with an eGFR of 20 mL/min

led to the same neutropenic risk as the approved dose of 1000 mg in a patient with adequate renal function due to the time-above-threshold relationship between exposure and toxicity (eGFR 90 mL/min and BSA of 2.0 m2). Notably, despite its similar risk for neutropenia, this 50-fold reduction of pemetrexed dosing resulted in a 13-fold lower exposure to pemetrexed, potentially decreasing treatment efficacy [20]. Hence, pemetrexed treatment should be avoided in patients with renal impairment unless adequate prophylaxis for its toxicity can be applied.

CONCLUSION

Based on the study results, it can be concluded that standard dosing of pemetrexed in non-squamous NSCLC patients with a moderately impaired renal function (30-45 mL/min) at the start of the treatment is associated with a high incidence of severe toxicity, treatment-related hospitalization, necessity of dose reductions, and early treatment discontinuation. These results highlight the importance of developing new treatment regimens of pemetrexed in patients with renal impairment and encourage further research in this patient population to enable safe treatment with this first-line agent in the era of immunotherapy.

CLINICAL PRACTICE POINTS

- Real-world data from this multicenter study reveal that standard-dose pemetrexed is associated with high incidence of toxicity in patients with moderate renal impairment (30-45 mL/min), including:
  - Hematological toxicities: grade 3-4 neutropenia (39%), leukopenia (39%), and thrombocytopenia (23%)
  - Non-hematological toxicities: grade 3-4 gastrointestinal toxicity (34%), and required hospitalization due to treatment-related complications (64%)
- In addition, the majority of patients (70%) discontinued treatment prematurely, with 45% discontinuing due to pemetrexed-associated toxicity.
- Severe toxicity and related hospitalizations not only impact treatment outcomes but also detrimentally affect patients' quality of life. Moreover, early treatment discontinuation limits the therapeutic potential of pemetrexed, compounding the challenges in managing NSCLC in patients with renal impairment.
- These results highlight the necessity of developing new treatment regimens to enable safe pemetrexed-based immunochemotherapy in NSCLC patients with renal impairment.

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SUPPLEMENTARY MATERIAL

Supplementary s1: Different formulas to estimate renal function

CKD-EPI creatinine formula [1]

$$\text{eGFR [mL/min/1.73m}^2\text{]} = A * \left(\frac{\text{Cr}_{\text{SERUM}}}{B}\right)^{C} * 0.993^{\text{AGE}} * 1.159 \text{ [IF BLACK]}$$

If *female* and:	If *male* and:
Serum creatinine ≤ 0.7: use A = 144,	Serum creatinine ≤ 0.9: use A = 141,
B = 0.7 and C = -0.329	B = 0.9 and C = -0.411
Serum creatinine > 0.7: use A = 144,	Serum creatinine > 0.9: use A = 141,
B = 0.7 and C = -1.209	B = 0.9 and C = -1.209

SI units: serum creatinine in mg/dL, age in years

MDRD formula [2]

$$\text{eGFR [mL/min/1.73m}^2\text{]} = 175 * \text{Cr}_{\text{SERUM}}{}^{-1.154} * age^{-0.203} * 0.742 \text{ [IF FEMALE]} * 1.212 \text{ [IF BLACK]}$$

SI units: serum creatinine in mg/dL, age in years

Cockcroft Gault formula [3]

$$\text{estimated CrCL [mL/min]} = \frac{(140 - \text{AGE}) * \text{WEIGHT}}{0.815 * \text{Cr}_{\text{SERUM}}} * 0.85 \text{ [IF FEMALE]}$$

International System (SI) units: age in years, weight in kg, serum creatinine in mg/dL

Supplementary s2: Overview participating hospitals

Overview of participating hospitals in the Netherlands with the starting year of data collection and the number of included patients per hospital

Hospital	Location in the Netherlands	Data collection from	Number of patients [n]
Santeon group [4]			
Medisch Spectrum Twente	Enschede	2021	4
Martini hospital	Groningen	2017	0
Catharina hospital	Eindhoven	2015	4
Canisius-Wilhelmina hospital	Nijmegen	2017	4
Sint Antonius hospital	Nieuwegein/Utrecht	2015	2
OLVG hospital	Amsterdam	2015	6
Maasstad hospital	Rotterdam	2015	0
Other hospitals			
Amphia hospital	Breda	2015	20
Radboud university medical center	Nijmegen	2015	4

SUPPLEMENTARY S3 – TREATMENT OUTCOMES

Table s3.1: Continuous values of hematological toxicities and renal function during treatment

	OVERALL	DURING EACH CYCLE OF TREATMENT			
	C1-4 (n=44)	**C1 (n=44)**	**C2 (n=29)**	**C3 (n=21)**	**C4 (n=13)**
Lowest value during cycle (nadir):					
• Thrombocytes [x10^9/L], median (IQR)	158 (87-288)	187 (80-297)	148 (87-230)	151 (115-247)	179 (93-303)
• Neutrophiles [x10^9/L], median (IQR)	2.2 (1.0-3.0)	1.9 (0.5-6.2)	2.3 (1.0-2.6)	2.7 (1.6-3.0)	2.2 (1.0-4.5)
• Erythrocytes [x10^{12}/L], median (IQR)	3.2 (2.8-3.6)	3.5 (3.1-4.1)	3.3 (2.8-3.6)	3.0 (2.4-3.2)	2.6 (2.5-3.2)
• Leukocytes [x10^9/L], median (IQR)	3.8 (2.4-5.2)	3.7 (2.2-6.3)	3.9 (2.4-4.5)	3.7 (2.7-4.6)	3.9 (2.2-5.4)
• Lymphocytes [x10^9/L], median (IQR)	1.0 (0.6-1.4)	0.9 (0.5-1.5)	0.9 (0.7-1.4)	1.1 (0.8-1.3)	0.9 (0.8-1.2)
CKD-EPI* [mL/min], median (IQR)	44.4 (37.2-49.7)	43.3 (36.4-46.9)	47.7 (36.6-54.4)	42.7 (38.7-53.1)	46.6 (44.2-52.3)
Cockcroft-Gault [mL/min], median (IQR)	41.6 (37.2-45.6)	41.1 (35.0-43.9)	43.7 (35.8-47.5)	39.6 (38.2-48.4)	42.1 (38.3-47.1)

* Adjusted for body surface area of individual patients

Abbreviations: C1-4 = cycles 1 to 4, IQR = interquartile range, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

Table s3.2: Hepatic function values during treatment

	OVERALL	DURING EACH CYCLE OF TREATMENT			
	C1-4 (n=44)	C1 (n=44)	C2 (n=29)	C3 (n=21)	C4 (n=13)
ALAT, n (%)					
• Grade 0	26 (59%)	27 (61%)	18 (62%)	12 (57%)	9 (69%)
• Grade 1-2	11 (25%)	8 (18%)	3 (10%)	4 (19%)	1 (8%)
• Grade 3-4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
• Missing	7 (16%)	9 (20%)	8 (28%)	5 (24%)	3 (23%)
ASAT, n (%)					
• Grade 0	27 (61%)	29 (66%)	20 (69%)	13 (62%)	8 (62%)
• Grade 1-2	10 (23%)	6 (14%)	1 (3%)	3 (14%)	2 (15%)
• Grade 3-4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
• Missing	7 (16%)	9 (20%)	8 (28%)	5 (24%)	3 (23%)
Total bilirubin, n (%)					
• Grade 0	31 (70%)	27 (61%)	19 (66%)	13 (62%)	7 (54%)
• Grade 1-2	3 (7%)	3 (7%)	0 (0%)	0 (0%)	0 (0%)
• Grade 3-4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
• Missing	10 (23%)	14 (32%)	10 (34%)	8 (38%)	6 (46%)
AP, n (%)					
• Grade 0	18 (41%)	28 (64%)	15 (52%)	0 (0%)	0 (0%)
• Grade 1-2	18 (41%)	7 (16%)	6 (21%)	15 (71%)	10 (77%)
• Grade 3-4	2 (5%)	1 (2%)	0 (0%)	1 (5%)	1 (8%)
• Missing	6 (14%)	8 (18%)	8 (28%)	5 (24%)	2 (15%)
GGT, n (%)					
• Grade 0	13 (30%)	11 (25%)	7 (24%)	6 (29%)	4 (31%)
• Grade 1-2	19 (43%)	19 (43%)	11 (38%)	8 (38%)	5 (38%)
• Grade 3-4	5 (11%)	4 (9%)	2 (7%)	2 (10%)	1 (8%)
• Missing	7 (16%)	10 (23%)	9 (31%)	5 (24%)	3 (23%)
Hypoalbuminemia, n (%)					
• Grade 0	27 (61%)	31 (71%)	11 (38%)	10 (48%)	5 (38%)
• Grade 1-2	15 (34%)	10 (23%)	8 (28%)	4 (19%)	2 (15)
• Grade 3-4	1 (2%)	1 (2%)	1 (3%)	0 (0%)	0 (0%)
• Missing	1 (2%)	2 (5%)	9 (31%)	7 (33%)	6 (46%)

Abbreviations: C1-4 = cycles 1 to 4, ALAT = alanine aminotransferase, ASAT = aspartate aminotransferase, AP = alkaline phosphatase, GGT = gamma-glutamyltransferase

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IV

CHAPTER V

Early-onset hematological toxicity of docetaxel and survival in non-small cell lung cancer patients in the immune checkpoint inhibition era

[to be published]

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ABSTRACT

PURPOSE

Docetaxel remains a next-line treatment option for non-small cell lung cancer (NSCLC) following progression on immunotherapy. Early studies show docetaxel-associated hematological toxicity to be a predictive factor for improved survival outcomes, serving as a surrogate for the degree of systemic exposure and clinical activity. However, it is unclear whether docetaxel is still effective in the immunotherapy era. We investigated the relationship between first-cycle docetaxel-associated hematological toxicity and overall survival (OS) in patients treated during the immunotherapy era as a surrogate for clinical efficacy.

METHODS

We conducted a retrospective, multi-center cohort study across nine Dutch hospitals. Eligible NSCLC patients received at least one cycle of docetaxel 75 mg/m^2 every 21 days between July 2017 and August 2024. Hematological toxicity outcomes were collected from electronic health records. The primary outcome was OS in patients with or without any grade of hematological toxicity in the first-cycle.

RESULTS

Data from 286 patients were available. The median OS was 7.2 months (95%-CI: 5.8–8.3). Any grade and grade III-IV hematological toxicity in the first cycle was observed in 30% (n=85) and 21% (n=61) of patients, respectively. Patients who experienced first-cycle grade III-IV docetaxel-associated hematological toxicity had a longer OS compared to no grade III-IV, with this effect becoming evident 12 months after the first docetaxel administration (log-rank test, p=0.120; Fleming-Harrington weighted log-rank test, p=0.0149).

CONCLUSION

Our findings indicate an association between improved OS later in time and first-cycle grade III-IV docetaxel-associated hematological toxicity in NSCLC post-immunotherapy, suggesting clinical activity of docetaxel in the immune checkpoint inhibition era.

INTRODUCTION

Docetaxel, a taxoid anti-neoplastic agent, received initial approval from the Food and Drug Administration in 1996 as a first- or second-line treatment for advanced non-small cell lung cancer (NSCLC) [1]. Systemic exposure to docetaxel has been strongly associated with survival outcomes and toxicity, particularly hematological toxicity, such as neutropenia, thrombocytopenia and anemia [2]. Docetaxel-associated neutropenia has been shown to be predictive for treatment efficacy [3, 4]. The reported hazard ratios (HRs) for overall survival vary across studies, with values ranging from 0.71 to 0.77 for any grade of neutropenia compared to cases without hematological toxicity, highlighting its potential as an early indicator of survival outcomes [5-7].

The advent of immunotherapy in 2015 relegated docetaxel to a next-line treatment for patients with advanced or metastatic NSCLC, without knowledge of its clinical efficacy in this setting [8, 9]. Patients receiving later-line treatments often exhibit greater frailty, poorer performance scores, and more extensive metastases [10]. Additionally, tumor characteristics may alter after becoming resistant to prior lines of treatment with any systemic treatment including immunotherapy. For example, in advanced prostate cancer, cross-resistance between treatment lines, including resistance to docetaxel, has been attributed to alterations in tumor cell gene expression [11]. Moreover, the adverse effects of docetaxel treatment can significantly impact the quality of life in lung cancer patients at the end of life [12]. These challenges raise the critical question of whether the survival benefits of docetaxel treatment are still present in the post-immunotherapy setting. In addition, it remains unclear whether the survival advantages previously associated with docetaxel-induced hematological toxicities, such as neutropenia, persist in the current NSCLC population.

Directly addressing this question through clinical trials raises ethical concerns, as it would require withholding an established treatment from patients. Therefore, to determine to which extent the association between docetaxel-associated hematological toxicity and overall survival still holds in the immunotherapy era, we retrospectively investigated the efficacy of docetaxel and the relationship between first-cycle docetaxel-associated hematological toxicity and survival outcomes in patients with NSCLC.

MATERIALS AND METHODS

STUDY DESIGN AND PATIENT POPULATION

We conducted a retrospective, multi-center cohort study in patients with NSCLC initiating treatment with standard-dose docetaxel (75 mg/m^2 every 21 days) between July 2017 and August 2024 in nine hospitals across the Netherlands. The introduction of immunotherapy agents in the Netherlands started from July 2017 as the date of market approval and admission by the Dutch National Health Care Institute [13]. Patients were treated either at Amphia Hospital in Breda, Radboud University Medical Center in Nijmegen, or one of the seven non-university teaching hospitals within the Santeon hospital network: Catharina Hospital, OLVG, St. Antonius Hospital, Medisch Spectrum Twente, Canisius-Wilhelmina Hospital, Martini Hospital, and Maasstad Hospital [14].

Patients were retrospectively selected from participating hospitals if they met the following inclusion criteria: age ≥18 years, diagnosis of NSCLC, and treated with at least one cycle of standard dose docetaxel (75 mg/m^2 every 21 days). Data were collected from the electronic health record (EHR). Baseline patient and treatment characteristics included age, sex, height, weight, body surface area (BSA), estimated glomerular filtration rate (eGFR), docetaxel treatment information, and number of cycles. Hematological toxicity outcomes were collected from the EHR and included all leukocytes and neutrophils taken at baseline (seven days prior to treatment initiation) and during treatment cycles (up to a maximum of four treatment cycles) until one month after start of the last treatment cycle. Hematological toxicities were graded following the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 of the National Cancer Institute [15].

Data were manually collected from Amphia, CZE, and Radboud UMC hospitals, while data from the remaining six Santeon hospitals were automatically and pseudo-anonymously retrieved using the Health Intelligence Platform Santeon (HIPS) database [16]. Following data retrieval, only patients meeting the predefined inclusion criteria were retained for analysis, and ineligible records were excluded during post-extraction filtering.

The Medical research Ethics Committee United (MEC-U, Nieuwegein, the Netherlands) declared the study not to be subject to the Medical Research Involving Human Subjects Act (ethical approval code MEC W23.130) and provided a waiver for the necessity of written informed consent, given the retrospective character of the study in patients of whom most were already deceased. The study was approved by

the individual institutional review boards of all participating hospitals. To ensure the protection of personal data, all patient information was coded with a unique research number and processed pseudo-anonymously, with each hospital retaining a local key for patient identification.

STUDY ENDPOINTS

The main objective was to examine the relationship between first-cycle hematological toxicity and overall survival (OS), defined as the time interval (in months) from the start of treatment to death or the last follow-up date, reported as median survival with a 95% confidence interval (95%-CI). Hematological toxicity was evaluated using neutrophil counts or leukocyte counts whenever neutrophil count was not available, and defined as the occurrence of any grade of neutropenia (or leukopenia) during the first cycle, in accordance with CTCAE version 5.0 criteria [15]. Leukocyte counts were included to provide a more comprehensive assessment of hematological toxicity, as leukocytes consist of approximately 70% neutrophils, offering a reliable proxy for neutrophil levels [17].

Two analyses were conducted to evaluate the relationship between first-cycle docetaxel-associated toxicity and OS. The primary analysis examined the association between first cycle grade III-IV hematological toxicity and OS by comparing patients with and without such level of toxicity. The secondary analysis examined the association between any grade of hematological toxicity versus no hematological toxicity during the first cycle on the OS.

STATISTICAL ANALYSIS

Categorical data were summarized in numbers and percentages, while continuous data were presented as mean and standard deviation or median and interquartile range, depending on the type of distribution. Differences in continuous data between groups were analyzed using an independent samples t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. For categorical data, differences between groups were analyzed using Chi-square tests or Fisher's Exact tests where appropriate. Data processing and analysis were conducted using R (version 4.2.2, 2024) [18]. Details on the specific packages and their versions can be found in the Supplementary S3.

The association between docetaxel-associated toxicity and OS was evaluated using time-to-event analysis. Kaplan-Meier curves were generated to visualize survival probabilities over time, stratified by levels of docetaxel-associated toxicity. Survival distributions were compared using the log-rank test when the proportional hazards

assumption was met, as assessed by visual inspection and Schoenfeld residuals. If the proportional hazard assumption was violated, alternative non-parametric tests were applied, adapted to the segment of the survival curve exhibiting non-proportionality. The Wilcoxon (Breslow) test was used for early violations and the Fleming-Harrington test was applied for violations toward the end of the curve [19]. A p-value of <0.05 was considered statistically significant.

RESULTS

STUDY POPULATION

A total of 286 NSCLC treated patients met the inclusion criteria and had available measurements for neutrophils or leukocytes in the first cycle. The average age was 65.7 years and 62% of patients were male. Supplementary Table S1 provides the details of data collection for each hospital. All baseline patient characteristics are summarized in Table 1. For the primary analysis, no significant differences in baseline characteristics were observed between patients with grade III-IV hematological toxicity in the first cycle (n=61) and those without such toxicity (n=225). Similarly, no statistically significant differences in baseline characteristics were observed between patients with any grade of hematological toxicity during the first cycle (n=85) and those without toxicity (n=201) (see Supplementary Table S2). Neutrophil counts were available for 65% of patients (n=185). For the remaining patients (n=101), leukocyte counts were used as a substitute marker. At baseline, five patients presented with grade I neutropenia (neutrophil counts 1.6-1.9 $\times 10^9$/L) and two patients had grade II neutropenia (1.1 and 1.3 $\times 10^9$/L). No patients exhibited any grade of leukopenia at baseline. In 44 patients, neither neutrophil nor leukocyte measurements were available at baseline, i.e., within 7 days prior to treatment initiation.

Table 1: Population characteristics at baseline and docetaxel treatment information

	TOTAL (n=286)	**Grade III-IV hematological toxicity C1 (n=61)**	**No grade III-IV hematological toxicity C1 (n=225)**	**p-value**
Age [years], mean (SD)	65.7 (8.9)	67.4 (8.0)	65.2 (9.2)	0.091
Sex, n (%) Male Female	 177 (62%) 109 (38%)	 43 (70%) 18 (30%)	 134 (60%) 91 (40%)	0.119
Height [cm], mean (SD) Missing, n (%)	173.5 (9.3) 14 (5%)	173.1 (9.2) 3 (5%)	173.6 (9.4) 11 (5%)	0.731
Weight [kg], mean (SD) Missing, n (%)	77.2 (16.3) 25 (9%)	76.7 (16.2) 6 (10%)	77.3 (16.3) 19 (8%)	0.813
BSA [m^2], mean (SD) Missing, n (%)	1.9 (0.2) 38 (13%)	1.9 (0.2) 15 (9%)	1.9 (0.2) 29 (13%)	0.606
CKD-EPI [mL/min/1.73m^2], median (IQR) Missing, n (%)	77.0 (62.0–90.0) 23 (8%)	79.3 (57.5–90.0) 5 (8%)	77.0 (63.0–90.0) 18 (8%)	0.902
Treatment information				
Previously received immunotherapy, n (%) Missing, n (%)	243 (85%) 24 (8%)	51 (84%) 6 (10%)	192 (85%) 20 (9%)	0.794
Docetaxel dosage [mg], median (IQR) Missing, n (%)	140.0 (130.0–155.0) 14 (5%)	140.0 (130.0–152.0) 6 (10%)	140.0 (130.0–155.0) 8 (4%)	0.591
Number of docetaxel treatment cycles, median (IQR)	3 (2-4)	2 (2-4)	3 (2-4)	0.191

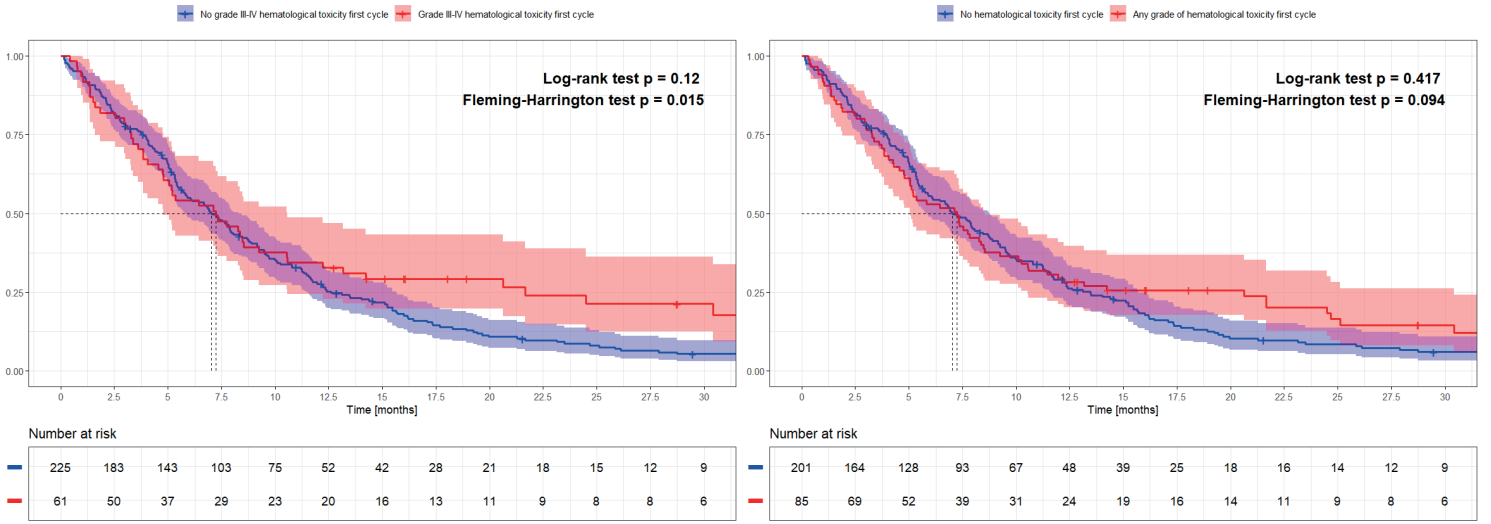
Abbreviations: C1 = first cycle, SD = standard deviation, BSA = Body Surface Area, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, IQR = interquartile range

SURVIVAL ANALYSIS

The median follow-up time was 35.1 months (range: 3.0–51.9). During follow-up, 255 of 286 (89%) NSCLC patients died. The OS median for the whole population was 7.2 months (95%-CI: 5.8–8.3). Patients with grade III-IV hematological toxicity during the first cycle (n=61) had a median OS of 7.3 months (95%-CI: 4.8–10.6), compared to 7.0 months (95%-CI: 5.8–8.3) for patients without grade III-IV hematological toxicity (n=225) (HR=0.78, 95%-CI: 0.57–1.07). The difference between the two groups was not statistically significant using the log-rank test, p=0.120. Visual inspection of the survival curves, along with a significant Schoenfeld residuals test for proportional hazards (p=0.022), indicated a violation of the proportional hazard assumption in the tail of the survival curve, which may compromise the reliability of the log-rank test result. To address this, the non-parametric Fleming-Harrington test was applied, revealing a significant difference in survival (p=0.015). The Kaplan-Meier curves of the different groups are shown in Figure I.

There was no significant difference in OS between patients with any grade of hematological toxicity in the first cycle (n=85) and those without toxicity (n=201): 7.2 months (95%-CI: 5.1–8.5) vs. 7.0 months (95%-CI: 5.9–8.7) (HR=0.89, 95%-CI: 0.68–1.17; log-rank test, p=0.417).

Figure 1: K aplan-meier curves of different analyses of the association between overall survival and docetaxel-associated hematological toxicity in nsclc patients



Left: the overall survival of grade III-IV docetaxel-associated hematological toxicity (Schoenfield residuals, p=0.022) **Right:** the overall survival of any grade docetaxel-associated hematological toxicity first cycle (Schoenfield residuals, p=0.051).

DISCUSSION

Our results show an association between improved OS later in time and first-cycle grade III-IV docetaxel-associated hematological toxicity in NSCLC as next-line treatment. While no significant difference in OS was observed between groups within the first 12 months (log-rank p>0.05), the Fleming–Harrington test indicated a statistically significant divergence in survival curves beyond this period, suggesting a delayed survival benefit associated with early high-grade hematological toxicity. However, the absolute difference in median OS between groups was limited (7.3 vs 7.0 months), indicating that the observed statistical significance may not translate into clinical relevance. To the best of our knowledge, this was the first study to examine the relationship between docetaxel-induced hematological toxicity and survival outcomes in the post-immunotherapy era, suggesting that the clinical activity of docetaxel as a next-line therapy remains evident following the introduction of immunotherapy for NSCLC treatment in 2017.

Previous studies conducted before the advent of immunotherapy reported an association between docetaxel-associated neutropenia and improved treatment efficacy. Most notably, a study by Pallis *et al.* (n=858) found an HR of 0.71 (95%-CI: 0.58–0.86) for OS in patients with grade I-II neutropenia and an HR of 0.70 (95%-CI: 0.58–0.85) for those with grade III-IV neutropenia, both compared to patients without neutropenia [7]. In contrast to Pallis *et al.*, we focused our analysis on the first cycle toxicity based on the hypothesis that patients who experience early toxicity may have a more immediate treatment effect on the tumor, potentially influencing long-term survival. Since cancer growth can be considered an exponential process, patients who develop hematological toxicity early during treatment, due to higher systemic exposure to docetaxel, may have a more profound effect on tumor growth, resulting in longer survival for this group. Finally, the median OS after start of docetaxel in our real-world cohort was 7.2 months (95%-CI: 5.8–8.3), which aligns with the survival outcomes reported in earlier phase I-III studies for first-line docetaxel treatment for advanced NSCLC of ~7 months [20]. In contrast, a more recent phase III trial investigating docetaxel in patients with metastatic NSCLC, who progressed on/after platinum-based chemotherapy and anti-PD-(L)1 therapy, reported a median higher median OS of 9.8 months (95%-CI: 8.1-10.6) [21]. Nevertheless, direct comparisons between real-world data and clinical trial outcomes are inherently limited as discrepancies in survival may reflect differences in study populations, treatment settings (e.g., trial vs. real-world), and patient selection criteria [22].

In our study, hematological measurements were typically performed 1–3 days before the next treatment cycle (i.e., approximately 20 days after previous administration of docetaxel), consistent with routine clinical practice in the Netherlands. However, the neutrophil nadir following docetaxel administration occurs approximately 8–10 days post-treatment [23]. This could lead to an underestimation of the incidence of hematological toxicity, as bone marrow recovery may have already occurred by the time measurements are taken. In our study, the incidence of any-grade hematological toxicity in the first cycle was 30%, while grade III-IV toxicity occurred in 21% of patients. These rates are indeed lower than literature-reported incidences of up to 40% for grade III-IV hematological toxicity in second-line docetaxel treatment for NSCLC [24]. Consequently, the association between hematological toxicity and treatment efficacy may also be underestimated. Furthermore, comparison with other studies is complicated by differences in measurement frequency and timing such as Pallis *et al.*, who reported a complete blood cell count weekly [7].

Systemic docetaxel exposure increases proportionally to the administered dose [25]. Although numerous covariates influencing docetaxel pharmacokinetics have been identified, a substantial proportion of the variability in its exposure remains unexplained [26] and BSA-based dosing of docetaxel only results in a minimal reduction in interindividual variability in its pharmacokinetics [27]. In clinical practice, docetaxel is typically administered every 21 days based on BSA at 75 mg/m^2 [23]. The systemic exposure of docetaxel significantly correlates with both the risk of toxicity, specifically neutropenia, and with increased survival outcomes [28]. This raises the possibility of docetaxel dosing based on docetaxel-induced toxicity as an option for improvement of dosing after a first administration.

Although our analysis suggests clinical activity of docetaxel for NSCLC patients, an important question remains as the survival benefit associated with docetaxel-induced hematological toxicity is worth the significant burden of treatment-related adverse effects. The toxicity of docetaxel, particularly in patients with advanced lung cancer at the end of life, can severely impact their quality of life [12]. Furthermore, while increased hematological toxicity may be linked to better survival, it is also likely to be accompanied by a rise in non-hematological toxicities. Unfortunately, the data for this study were largely collected automatically and anonymously from individual patients' electronic health records. Therefore, not all variables were accessible for analysis, limiting a thorough evaluation of the overall burden and clinical toxicity of next-line docetaxel treatment. Moreover, adjustment for potential confounders affecting survival and hematological toxicity (such as histology, performance status, previous response to treatment, and comorbidities) was not possible for the same

reason. Similarly, factors influencing docetaxel exposure, including hepatic function, were not accounted for, which may have further impacted our findings.

Finally, we observed a stronger association between improved survival and the incidence of higher-grade hematological toxicity. These findings align with Pallis *et al.*, who reported slightly longer OS for grades III-IV docetaxel-induced hematological toxicity compared to grades I-II [7]. This further raises the question of whether dose adjustments based on higher toxicity grades would really improve treatment outcomes or merely reduce the quality of life for patients, or that we should better dose docetaxel and prevent under-treatment. Our study cannot provide a definitive answer to these crucial questions. Following the credo that absence of evidence does not equate to evidence of absence, we recommend further research directed at selecting patients who relevantly benefit from treatment.

Our findings indicate an association between improved OS later in time and first-cycle grade III-IV docetaxel-associated hematological toxicity in NSCLC as next-line treatment and observed a median OS of docetaxel treatment comparable with previous pre-immunotherapy era research. Considering the toxicity profile and sobering survival benefit associated with docetaxel, we advocate studies to better select patients who will have clinical benefit and explore the possibility of neutropenia-guided dosing without notable loss in quality of life.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY S1: OVERVIEW PARTICIPATING HOSPITALS

Table S1.1: Overview of participating hospitals in the Netherlands with the number of patients included and end of follow-up date

Hospital	Location in the Netherlands	End of follow-up	Number of patients
Amphia hospital	Breda	01-10-2024	108
Radboud university medical center	Nijmegen	01-10-2024	28
Catharina hospital	Eindhoven	01-10-2024	41
Canisius-Wilhelmina hospital	Nijmegen	05-11-2024	0*
Medisch Spectrum Twente	Enschede	19-01-2025	14
Maasstad hospital	Rotterdam	17-10-2024	1
Martini hospital	Groningen	09-12-2024	35
OLVG hospital	Amsterdam	03-10-2024	24**
Sint Antonius hospital	Nieuwegein/Utrecht	22-01-2025	35
TOTAL			286

* No hematological toxicity available

** Specific dosing information for docetaxel was unavailable for 14 patients. Nevertheless, all administrated dosing was 75 mg/m² and below 190 mg

SUPPLEMENTARY S2 – ANY GRADE HEMATOLOGICAL TOXICITY DURING FIRST CYCLE

Table S2.1: Population characteristics at baseline and docetaxel treatment information

	TOTAL (n=286)	**Grade III-IV hematological toxicity C1 (n=85)**	**No grade III-IV hematological toxicity C1 (n=201)**	**p-value**
Age [years], mean (SD)	65.7 (8.9)	66.8 (8.7)	65.2 (9.0)	0.160
Sex, n (%)				
• Male	177 (62%)	58 (68%)	119 (59%)	
• Female	109 (38%)	27 (32%)	82 (41%)	0.151
Height [cm], mean (SD)	173.5 (9.3)	173.0 (9.5)	173.7 (9.3)	
• Missing, n (%)	14 (5%)	3 (4%)	11 (5%)	0.553
Weight [kg], mean (SD)	77.2 (16.3)	76.3 (16.1)	77.6 (16.4)	
• Missing, n (%)	25 (9%)	9 (11%)	16 (8%)	0.560
BSA [m^2], mean (SD)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)	
• Missing, n (%)	38 (13%)	12 (14%)	26 (13%)	0.558
CKD-EPI [mL/min/1.73m^2], median (IQR)	77.0 (62.0–90.0)	77.0 (58.0–90.0)	77.0 (63.0–90.0)	
Missing, n (%)	23 (8%)	8 (9%)	15 (7%)	0.925
Treatment information				
Previously received immunotherapy, n (%)	243 (85%)	72 (85%)	171 (85%)	
Missing, n (%)	24 (8%)	7 (8%)	12 (6%)	0.634
Docetaxel dosage [mg], median (IQR)	140.0 (130.0–155.0)	140.0 (130.0–155.0)	140.0 (130.0–151.5)	
Missing, n (%)	14 (5%)	5 (6%)	9 (4%)	0.761
Number of docetaxel treatment cycles, median (IQR)	3 (2-4)	2 (2-4)	3 (2-4)	0.144

* Specific dosing information for docetaxel was unavailable for 14 patients. Nevertheless, all administrated dosing was 75 mg/m^2 and below 190 mg

Abbreviations: C1 = first cycle, SD = standard deviation, BSA = Body Surface Area, CKD-EPI **=** Chronic Kidney Disease Epidemiology Collaboration, IQR = interquartile range

SUPPLEMENTARY S3 – DIFFERENT PACKAGES USED FOR DATA PROCESSING AND ANALYSIS

Data manipulation and reshaping (tidyr, dplyr, lubridate, data.table)

- Wickham H, Vaughan D, Girlich M (2024). *tidyr: Tidy Messy Data*. R package version 1.3.1. https://CRAN.R-project.org/package=tidyr
- Wickham H, François R, Henry L, Müller K, Vaughan D (2023). *dplyr: A Grammar of Data Manipulation*. R package version 1.1.4. https://CRAN.R-project.org/package=dplyr
- Garrett Grolemund, Hadley Wickham (2011). *Dates and Times Made Easy with lubridate*. Journal of Statistical Software, 40(3), 1-25. https://www.jstatsoft.org/v40/i03/.
- Barrett T, Dowle M, Srinivasan A, Gorecki J, Chirico M, Hocking T, Schwendinger B (2024). *data.table: Extension of `data.frame`*. R package version 1.16.4. https://CRAN.R-project.org/package=data.table

Reading and writing files (readxl, writexl, arrow)

- Wickham H, Bryan J (2023). *readxl: Read Excel Files*. R package version 1.4.3. https://CRAN.R-project.org/package=readxl
- Ooms J (2024). *writexl: Export Data Frames to Excel 'xlsx' Format*. R package version 1.5.1. https://CRAN.R-project.org/package=writexl
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Statistical analysis (stats, survival, survminer, nphRCT)

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CHAPTER VI

An Evidence-Based Rationale for Dose De-escalation of Subcutaneous Atezolizumab

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ABSTRACT

BACKGROUND

Atezolizumab is a programmed death-ligand 1 (PD-L1) checkpoint inhibitor for the treatment of different forms of cancer. The subcutaneous formulation of atezolizumab has recently received approval. However, treatment with atezolizumab continues to be expensive, and the number of patients needing treatment with this drug continues to increase.

OBJECTIVE

We propose two alternative dosing regimens for subcutaneous atezolizumab to reduce drug expenses while ensuring effective exposure; one may be directly implemented in the clinic.

PATIENTS AND METHODS

We developed two alternative dose interval prolongation strategies based on pharmacokinetic modelling and simulation. The first dosing regimen was based on patients' weight while maintaining equivalent systemic drug exposure by adhering to Food and Drug Administration (FDA) guidelines for in-silico dose adjustments. The second dosing regimen aimed to have a minimum atezolizumab concentration above the 6 μg/mL threshold, associated with 95% intratumoral PD-L1 receptor saturation for at least 95% of all patients.

RESULTS

We found that for the weight-based dosing regimen, the approved 3-week dosing interval could be extended to 5 weeks for patients <50 kg and 4 weeks for patients weighing 50-65 kg. Besides improving patient convenience, these alternative dosing intervals led to a predicted 7% and 12% cost reduction for either the USA or European population. For the second dosing regimen, we predicted that a 6-week dosing interval would result in 95% of the patients above the 6 μg/mL threshold while reducing costs by 50%.

CONCLUSIONS

We have developed and evaluated two alternative dosing regimens that resulted in a cost reduction. Our weight-based dosing regimen can be directly implemented and comply with FDA guidelines for alternative dosing regimens of PD-L1 inhibitors. For the more progressive alternative dosing regimen aimed at the intratumoral PD-L1 receptor threshold, further evidence on efficacy and safety is needed before implementation.

INTRODUCTION

Atezolizumab (Tecentriq®) is a programmed death-ligand 1 (PD-L1) checkpoint inhibitor approved as a treatment for different forms of cancer, including advanced non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and urothelial carcinoma [1, 2]. It is given as an intravenous (IV) formulation and is usually administered in a hospital setting during a 30-60 minutes infusion as either 840 mg administered once every two weeks, 1200 mg administered once every three weeks, or 1680 mg once every four weeks [2].

Recently, the subcutaneous (SC) formulation of atezolizumab received approval from the European Medicine Agency and it is currently under assessment by the Food and Drug Administration (FDA) [3, 4]. The approved subcutaneous dose is 1875 mg once every three weeks, based on a population pharmacokinetic (POPPK) study and a clinical study that verified the efficacy of this novel formulation in advanced NSCLC [1, 5]. The subcutaneous administration of atezolizumab potentially has several benefits for the patient (e.g., improved quality of life and at-home administration/ less traveling) as well as for the healthcare provider (e.g., lower acquisition costs and lower drug administration burden) [6, 7]. The SC formulation is, therefore, expected to become the preferred treatment of cancer in the near future, as did with SC monoclonal antibodies in other disease areas (i.e., diabetes, rheumatoid arthritis, multiple sclerosis, and primary immunodeficiency) [6].

However, treatment with atezolizumab is still expensive [8]. Moreover, the number of cancer patients and accompanying treatments is increasing due to advances in effective screening and early detection, and to the rise of aging [9, 10]. For example, the United States of America (USA) is projected to see a 34% increase in cancer-attributable costs from 2015 to 2030 for a total of $246 billion [11]. Hence, the increasing economic burden of cancer treatment is putting a severe strain on personal and national health budgets. Moreover, with the ever-growing list of indications and the heft price tag of atezolizumab, there is an urgent need to save costs wherever possible [12, 13].

A potential way of reducing costs for SC atezolizumab treatment is by optimizing the dose using modeling and simulation of different PK populations. The use of POPPK modeling to develop alternative dosing regimens for monoclonal antibodies has already been widely accepted by the medical community, drug corporations, and regulatory agencies [14-17].

The aim of the present study was, therefore, to develop an optimized dosing regimen of subcutaneous atezolizumab based on modeling and simulation, resulting in reduced drug expenses without compromising effective systemic drug exposure.

METHODS

GENERAL APPROACH

We performed an *in-silico* evaluation of alternative dosing regimens for two scenarios. For Scenario I, we aimed to develop a cost-saving dosing regimen for atezolizumab based on the recently published FDA guidance of "Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer" for developing alternative dosing regimens of PD-1 or PD-L1 blocking antibodies [14]. For this scenario, we evaluated dosing interval prolongation based on weight while complying with the criteria as set out in the FDA guidance: the geometric mean (GM) of the average concentration ($C_{average}$) and the trough concentration (C_{trough}) at steady state should not be more than 20% lower than the approved dose, and the GM of the steady-state maximum concentration (C_{max}) should not be more than 25% higher than the approved dose. The endpoints for Scenario I were the GMs of C_{trough}, C_{max}, and $C_{average}$ of the approved and alternative dosing regimens and the arithmetic mean of dose reduction per year per patient. The $C_{average}$ is defined as the area under the concentration time curve during a dosing interval divided by the duration of the dosing interval. This pharmacokinetic endpoint can, therefore, be considered a time-corrected measure for AUC and allows comparison of cumulative exposure for different dosing intervals.

For Scenario II, we evaluated the potential of dose interval prolongation irrespective of body weight to achieve theoretically effective exposure throughout the treatment period. The license holder previously defined the putative threshold for efficacy as a trough concentration (C_{trough}) above 6 μg/mL, associated with 95% intratumoral PD-L1 receptor saturation [18,19]. Since the C_{trough} in the approved IV and SC dose at steady state is approximately 20-fold higher than this predefined threshold of 6 μg/mL [20], we explored extended dosing intervals where at least 95% of patients had an exposure above this threshold. The endpoints for Scenario II were the fraction of patients with a C_{trough} above 6 μg/mL just before the second administration and at the pharmacokinetic steady state of the alternative dosing regimen and the arithmetic mean of dose reduction per year per patient.

PHARMACOKINETIC MODELING AND SIMULATION

For the simulations, we used the population pharmacokinetic model that was previously developed by the license holder as described in the FDA review documents and by Felip *et al.* [5, 19] All simulations were performed using the non-linear mixed effects modeling software package NONMEM V7.5 (Icon, Dublin, Ireland). The NONMEM model code is included in the supplemental material of the manuscript. The covariates for clearance (CL) in this model were serum albumin concentration, anti-therapeutic antibodies (ATAG), tumor burden, and body weight. Covariates for the volume of distribution in the central compartment were albumin concentration, body weight, and gender. Gender was also a covariate for the peripheral compartment. Lastly, this model contained a high inter-individual variability in bioavailability after SC administration.

For our simulation, a European and a USA population of 1000 virtual individuals were generated using PopGen [21]. The European population was based on the ICRP database, and the USA population was based on the NHANES III survey. The European population comprised 46% men with a median weight of 67.3 kg (interquartile range (IQR): 57.0 - 77.6 kg). In the USA population were 47% men with a median weight of 75.4 kg (IQR: 63.5 - 87.7 kg), and probability of ethnicity of 0.673 for being white, 0.136 for being black and 0.191 for being non-black Hispanic [22]. The two different populations were used to account for differences in body size composition between these populations [23]. In these populations, we assumed the following covariate distributions:

1. A serum albumin concentration of 40 g/L with a geometric coefficient of variation of 5%, resulting in a representative distribution of serum albumin concentrations in lung cancer patients, based on the atezolizumab clinical studies [19]
2. ATAG prevalence of 40% [24]
3. The tumor burden was set to 63 mm with a variability of 30%, as observed in the clinical studies of atezolizumab [19]

The reference dosing regimen for our simulations was the approved 1875 mg SC once every three weeks (Q3W). Various alternative dosing regimens were tested at the discretion of the investigators.

For Scenario I, we varied the dosing interval by weeks based on the knowledge that systemic exposure depends on body weight while maintaining predicted exposure for the population within the predefined equivalence criteria. For Scenario II, we varied

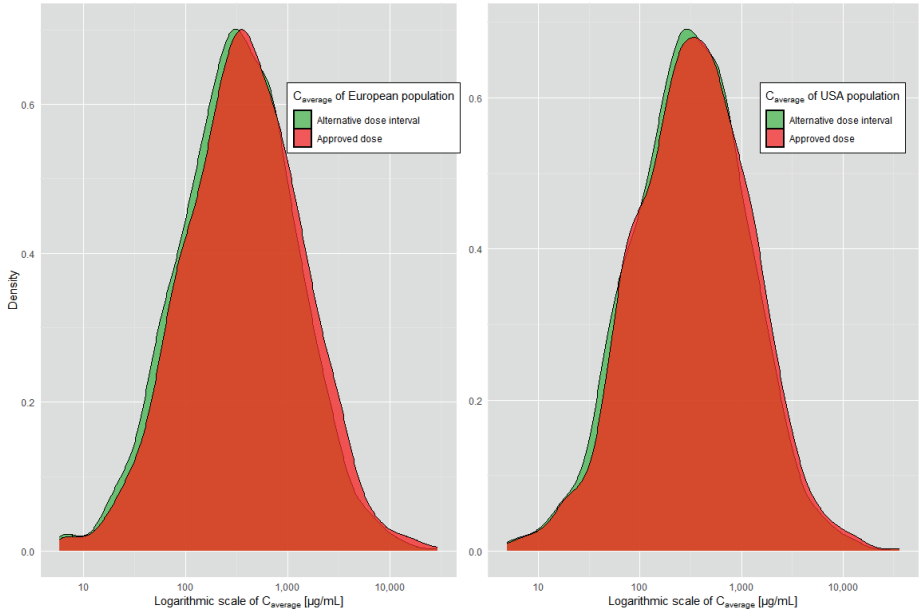
the dosing interval by half a month (multiplicity of 2 weeks) to be more practical while maintaining at least 95% of all individuals above the 6 µg/mL threshold.

RESULTS

SCENARIO I – WEIGHT-BASED DOSING WHILE ADHERING TO THE FDA CRITERIA

We found that the following alternative dosing regimen for 1875 mg SC atezolizumab resulted in equivalent exposure and maximum dose reduction: Q5W (35 days) for patients with body weight under 50 kg, Q4W (28 days) for patients 50-65 kg and Q3W (21 days) for patients with body weight higher than 65 kg. The results of different PK parameters of the approved dosing regimen relative to the alternative dosing regimen all complied with the FDA criteria. This results in nearly completely overlapping density plots of PK parameters between the approved dosing regime and alternative dose interval. The average exposure ($C_{average}$) in the USA population was lower, as seen in Figure 1, than in the European population. The same relationship was observed for C_{trough} and C_{max} (see Supplementary Figures 1 and 2).

Figure 1: $c_{average}$ density plot of alternative dose interval versus approved dose in European and USA population



Additionally, the alternative dosing regimen resulted in a lower average exposure ($C_{average}$) and variability (i.e., confidence interval) in patients with body weights below 65 kg compared to the approved dose in both European (see Figure 2) and USA populations (see Figure 3). As expected, the $C_{average}$ did not change in patients with body weights above 65 kg.

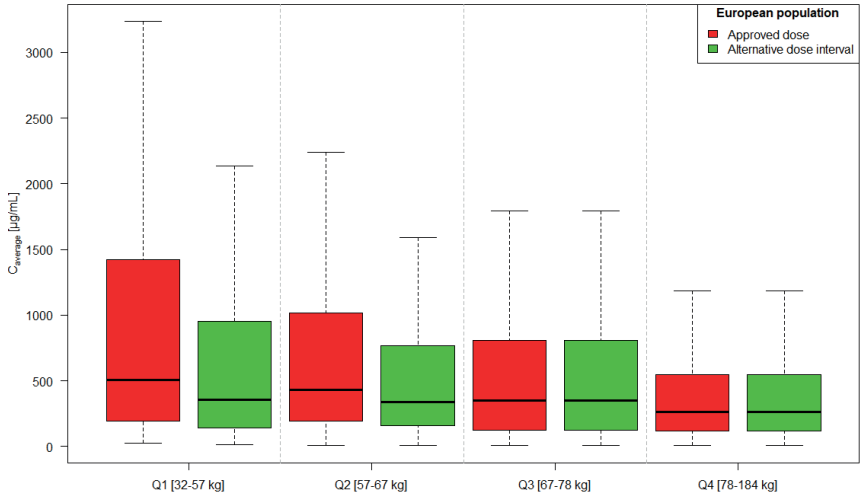


Figure 2: $C_{average}$ of alternative versus approved dose interval in a European population

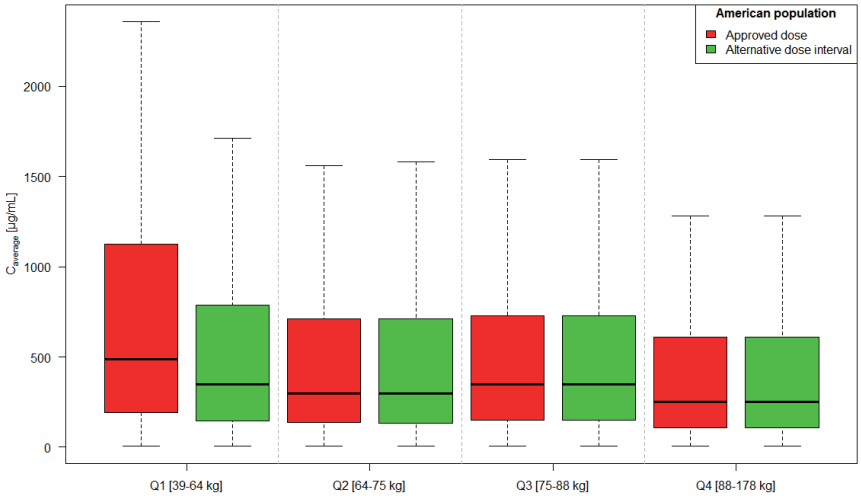


Figure 3: $C_{average}$ of alternative versus approved dose interval in a USA population

Table 1: Results of alternative dosing regimen in european and usa population

	PHARMACOKINETIC PARAMETERS						**COST REDUCTION**	
	GM C_{trough} [µg/mL] (CV%)		**GM C_{max} [µg/mL] (CV%)**		**GM $C_{average}$ [µg/mL] (CV%)**		**Average quantity of drug [mg]* (number of vials [n]**)**	
	EU	**USA**	**EU**	**USA**	**EU**	**USA**	**EU**	**USA**
Approved 1875 mg Q3W	285.6 (230.4%)	253.9 (229.2%)	477.7 (214.7%)	437.0 (212.2%)	369.6 (218.9%)	335.2 (216.6%)	33,750 (18)	33,750 (18)
Alternative dosing regimen < 50 kg 1875 mg Q5W 50-65 kg 1875 mg Q4W > 65 1875 mg Q3W	230.3 (223.2%)	224.2 (223.5%)	430.2 (208.5%)	411.0 (208.5%)	318.5 (211.8%)	307.3 (212.1%)	29,715 (16)	31,322 (17)
Ratio alternative to reference	0.81	0.88	0.90	0.94	0.86	0.91	0.88 (2)	0.93 (2)

* Arithmetic mean of quantity of drug used during 1 year per patient

** Rounded up

Abbreviations: GM = geometric mean, CV% = coefficient of variation, n = numero, EU = European population, USA = United States of America

The GM of the C_{trough} of the European population was the constraining PK parameter at 81%, whereas there was still an opportunity for decreasing the C_{max} and $C_{average}$ PK parameters. Implementing our alternative dosing regimen could lead to a cost reduction of 12.0% for the European population and 7.2% for the USA population (see Table 1).

SCENARIO II - DOSING AT THERAPEUTIC THRESHOLD

Scenario II is based on dosing at least 95% of the population above the putative efficacy threshold of 6 µg/mL, irrespective of the patients' weight. For both the European and the USA population, the maximum dosing interval was approximately 44 days for which at least 95% of patients were above the threshold of 6 µg/mL. For pragmatic reasons, a 6-week dosing interval (Q6W) was used for further simulations for both the European and the USA population to assure adequate exposure throughout the treatment period.

Due to rounding down, the number of patients with a minimum concentration (C_{trough}) above the threshold exceeded 95% at both the first cycle and steady state. At steady state, 98% of patients in the European population and 97% in the USA population had a C_{trough} above 6 µg/mL (see Table 2). Using the Q6W dosing regimen, the dosing interval is doubled compared to the regular 3-week dosing of atezolizumab, resulting in a cost reduction of 50.0% for both the European and the USA population.

Table 2: C_{trough} of dosing at therapeutic threshold

	PHARMACOKINETIC PARAMETERS			
	GM C_{trough} (first cycle) [µg/mL] (CV%)		**GM C_{trough} (steady state) [µg/mL] (CV%)**	
	EU	**USA**	**EU**	**USA**
1875 mg Q6W	68.2 (227.7%)	61.0 (228.1%)	102.3 (254.2%)	88.6 (253.7%)
Fraction of patients above 6 µg/mL [%]	96.1%	95.5%	97.4%	97.2%

Abbreviations: GM = geometric mean, CV% = coefficient of variation, n = numero, EU = European population, USA = United States of America

The doubling of the dosing interval is reflected in the approximating halving of the C_{trough} in both the first cycle and at steady state. Figure 3 shows that almost all patients in both dosing intervals have a C_{trough} above the threshold of 6 µg/mL (red-dotted line is equal to 6 µg/mL). The same was seen in the USA population (see Figure 4).

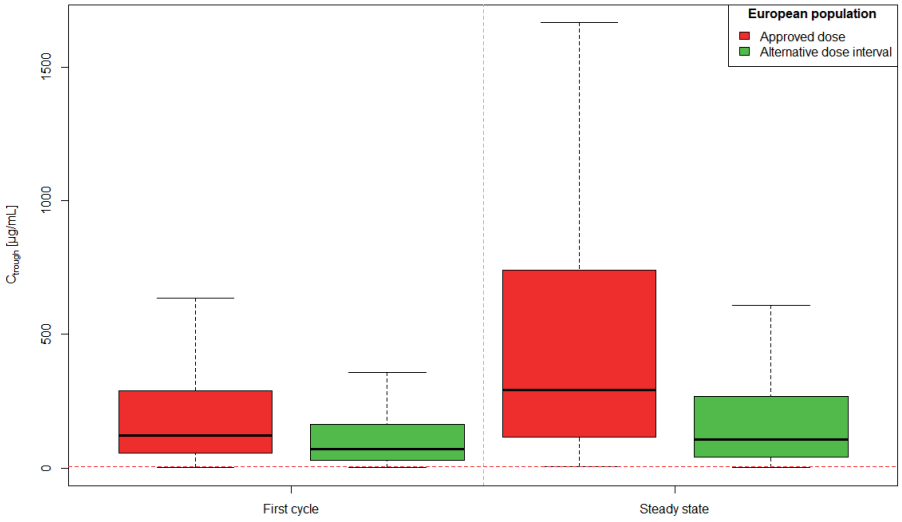


Figure 4: C_{trough} of Q6W dose interval versus approved dose interval in a european population in the first cycle and at steady state

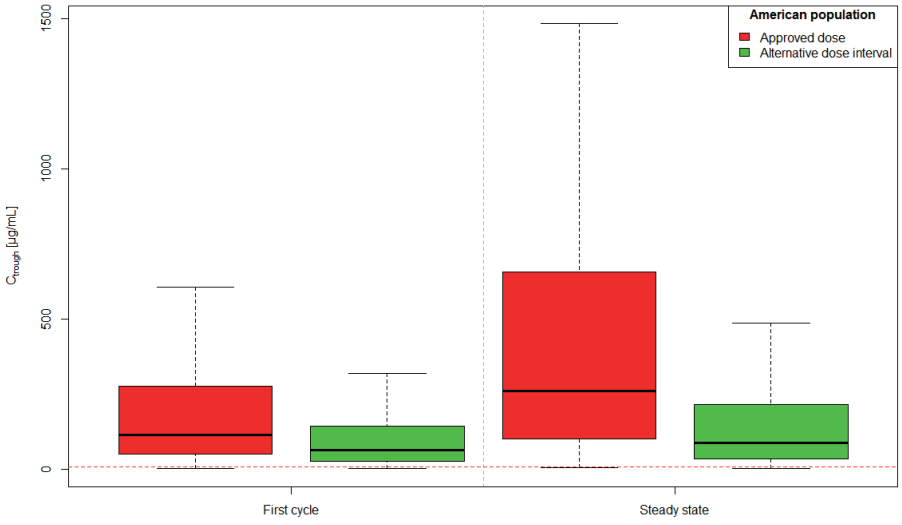


Figure 5: C_{trough} of Q6W dose interval versus approved dose interval in a usa population in the first cycle and at steady state

DISCUSSION

In this study, we aimed to develop two alternative dosing regimens for 1875 mg SC atezolizumab to minimize drug expenses while maintaining effective systemic drug exposure.

For the first alternative dosing regimen (Scenario I), we propose dosing interval prolongation for patients with a body weight below 50 kg to a 5-week interval (Q5W), to a 4-week interval (Q4W) for patients weighting 50-65 kg, while maintaining a 3-week interval (Q3W) for patients with a body weight above 65 kg. This weight-based alternative dosing regimen will reduce drug expenses by 12% in the European and 7% in the USA population while preserving equivalent exposure compared to the approved dose in line with the FDA guidance for developing alternative dosing regimens for PD-L1 blocking antibodies in the treatment of patients with cancer, facilitating direct implementation in clinical practice without the need for a clinical study [14]. Interestingly, a recent study showed that low-dose nivolumab for a specific indication is as effective as approved (high) dose nivolumab [25]. This result encourages further investigation whether this is also the case for atezolizumab, bearing in mind that dose-response relationships for immune checkpoint inhibitors may differ by indication as shown by Agrawal *et al.* [26].

For the second alternative dosing regimen (Scenario II), we propose a 6-week interval (Q6W) for both the European and the USA population, resulting in at least 95% of patients with an exposure above the 6 µg/mL target threshold for intratumoral PD-L1 receptor saturation at both the first cycle and steady state, irrespective of the patients' weight. Consequently, a reduction of 50% in drug expenses was achieved. This is in line with PK data for IV administration of atezolizumab in humans, where anti-tumor activity (i.e., 95% of patients have a minimum concentration above 6 µg/mL) was found across a dosing range of 1-20 mg/kg (Q3W) [27], which evolved to 15 mg/kg (the equivalent fixed dose of 1200 mg) Q3W [28]. In addition, a recent analysis by Chou *et al.* of intravenously administered atezolizumab predicted that when decreasing the cumulative atezolizumab by a two-fold, no changes in the efficacy profile can be expected [29]. These results encourage investigating further tapering strategies to reduce the financial toxicity and improve the patient-friendliness of subcutaneously administered atezolizumab.

The efficacy target concentration of atezolizumab of 6 µg/mL is based on the assumptions that 95% tumor receptor saturation is needed for efficacy, the tumor-interstitial concentration to plasma ratio is 0.3 based on the tissue distribution data

in tumor-bearing mice [30] and that the combination with bevacizumab will reduce tumor penetration by at least ~30% [18]. Although our analysis predicts sufficient target attainment in a Q6W dosing interval, such a dosing regimen should be evaluated for non-inferiority in a clinical study before implementation.

Notably, because of the high variability in subcutaneous bioavailability, lower cumulative doses are likely possible using IV administration. This is due to the absence of variability in bioavailability for the fraction of the dose reaching the systemic circulation, resulting in less variability in C_{trough} concentrations. Lower variability in C_{trough} concentrations means one can further prolong the dosing interval before the threshold is reached. This high variability in the bioavailability of subcutaneously administered monoclonal antibodies may stem from differences in subcutaneous tissue composition and local degradation, affecting the physiochemical properties of the subcutaneous absorption [31]. Regarding IV administration, Peer *et al.* proposed an 840 mg Q6W IV dose to maintain 99% of the population above the proposed therapeutic threshold based on in silico simulation [32]. A recent real-world pharmacokinetic study by Marolleau *et al.* showed relatively long dosing intervals of intravenously administered atezolizumab might be possible based on therapeutic drug monitoring, with an extension of a 1200 mg IV dose to a mean interval of approximately three months, indicating that real-world pharmacokinetics may raise opportunities for further dose interval prolongation [33]. Hence the intravenous dosing regimen could also be an option in order to optimize patient friendliness and cost-efficacy of atezolizumab. However, this option was beyond the scope of our study, which focused on improving the cost-efficacy of the novel SC formulation of atezolizumab.

Besides lower drug expenses, our alternative dosing regimens also pose other benefits. These include lowering direct medical costs (e.g., decrease of the number of drug administrations and use of resources and healthcare staff costs) and indirect medical costs (e.g., less travelling costs). In addition, it may improve patient convenience and quality of life by decreasing the number of hospital visits and used resources, accommodating both patients and healthcare professionals [6, 7].

Our simulations were based on a representative European and USA population, and differences in predicted drug expenses were observed. These differences can be explained by the USA population's higher average weight. Since lower exposure is expected in higher body weight patients, the USA population shows lower C_{trough}, C_{max}, and $C_{average}$ thant the European population. An additional simulation conducted in the USA population found a cost reduction of 11.7% while complying with FDA criteria if

patients were dosed Q5W for body weight under 50 kg, Q4W between 50 and 75 kg, and Q3W for body weight higher than 75 kg (see Supplementary Table 1).

CONCLUSION

Our study shows a maximum 12% cost reduction for body weight-based dosing interval prolongation (Scenario I), which can be implemented directly into practice since it adheres to the FDA guideline for the development of alternative dosing regimens for PD-L1 antibodies. By implementing this alternative strategy, healthcare costs can be reduced without impacting drug efficacy and safety. For a more progressive approach, dosing aimed at maintaining receptor saturation by targeting an efficacy threshold concentration (Scenario II), further evidence on efficacy and safety is needed for implementation. We propose a prospective evaluation of this latter approach using a non-inferiority study.

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SUPPLEMENTARY INFORMATION

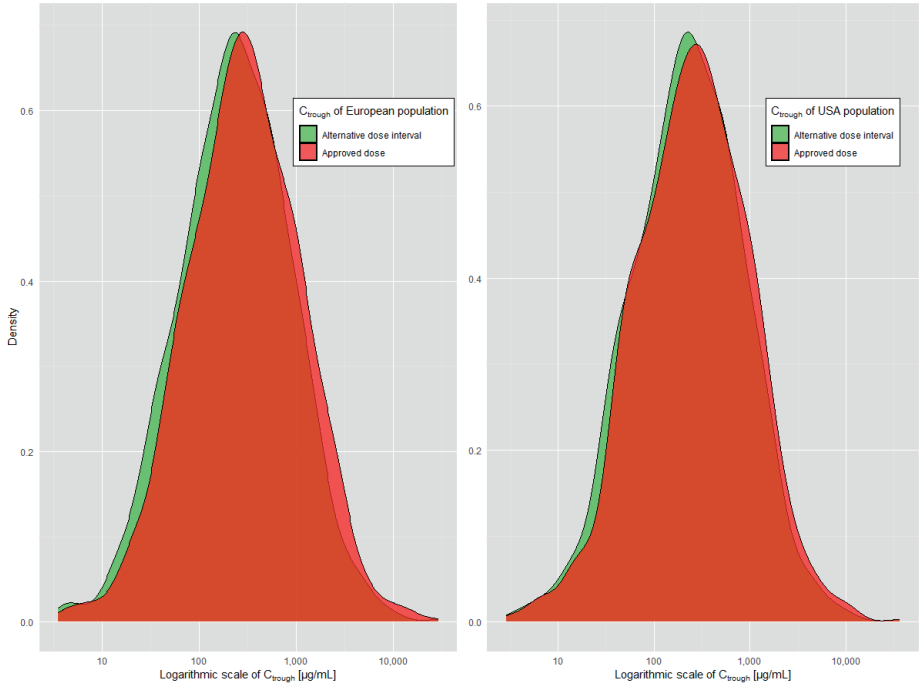

Figure 1: C_{trough} density plot of alternative dose interval versus approved dose in European and USA population

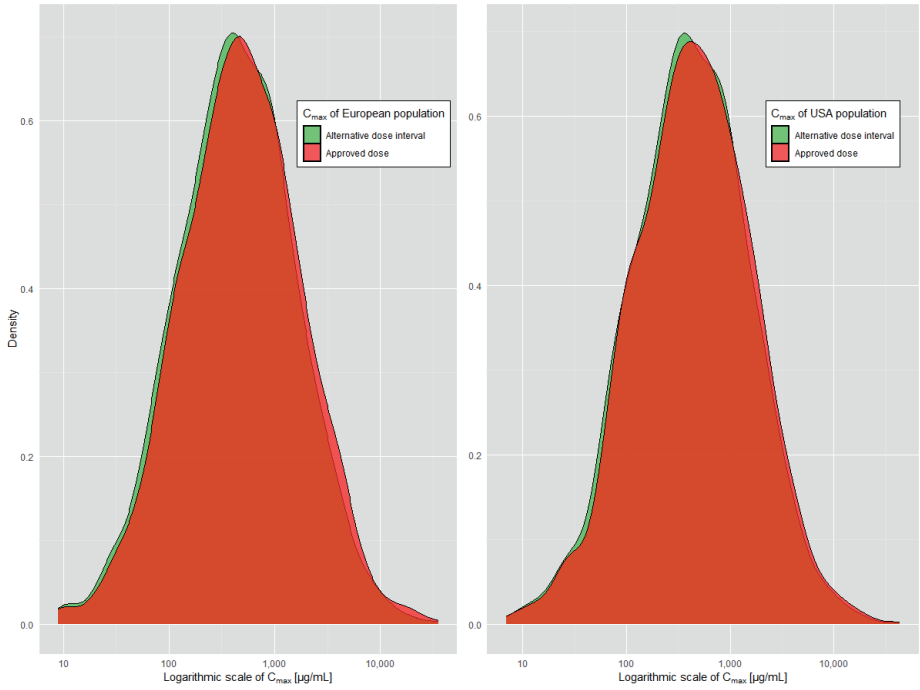

Figure 2: C_{max} density plot of alternative dose interval versus approved dose in European and USA population

Table 1: Results of alternative dosing regimen in a usa population

	PHARMACOKINETIC PARAMETERS			**COST REDUCTION**
	GM C_{trough} [µg/mL] (CV%)	**GM C_{max} [µg/mL] (CV%)**	**GM $C_{average}$ [µg/mL] (CV%)**	**Average quantity of drug [mg]* (number of vials [n]**)**
Approved 1875 mg Q3W	253.9 (229.2%)	437.0 (212.2%)	335.2 (216.6%)	33,750 (18)
Alternative dosing regimen < 50 kg 1875 mg Q5W 50-75 kg 1875 mg Q4W > 75 1875 mg Q3W	205.6 (225.8%)	394.8 (209.3%)	290.0 (213.3%)	29,799 (16)
Ratio alternative to reference	0.81	0.90	0.86	0.88 (2)

Abbreviations: GM = geometric mean, CV% = coefficient of variation, n = numero, USA = United States of America

* Arithmetic mean of quantity of drug used during 1 year per patient

** Rounded up

MODEL CODE

```
$SUBROUTINE ADVAN6 TOL=4
$ABB COMRES=1

$MODEL

COMP=(CENTRAL)
COMP=(PERI)
COMP=(SC)
COMP=(AUC)

$PK

;--- COVARIATES
FLAFEM=0; FEMALE
IF (SEX.EQ.1) FLAFEM=1; MALE

FLATAG=0; ASSUMPTION NO ANTIDRUG ANTIBODIES 0, 0.4 has ATA
IF (ATAG.EQ.1) FLATAG=1; ATAG ON CLEARANCE

TB=63*EXP(ETA(1)); TUMOR BURDEN IIV FROM PERCENTILES IN TABLE 7 OF FDA REVIEW
ALB=40*EXP(ETA(2)); ALBUMIN IN G/L IIV FROM PERCENTILES

CLBWT=((WT/77)**0.808); BODY WEIGHT ON CLEARANCE SCALED 77KG
CLALB=((ALB/40)**(-1.12)); ALBUMINE ON CLEARANCE SCALED TO 40 G/L
CLATAG=1+THETA(1); ATAG ON CLEARANCE
CLTB=((TB/63)**0.125); TUMOR BURDEN ON CLEARANCE SCALED TO 63 MM
V1ALB=((ALB/40)**(-0.35)); ALBUMINE ON VOLUME 1 SCALED TO 40 G/L
V1BWT=((WT/77)**0.559); BODY WEIGHT ON VOLUME 1 SCALED TO 77 KG
V1FEM=1+THETA(2); FEMALE SEX ON VOLUME 1
V2FEM=1+THETA(3); FEMALE SEX ON VOLUME 2

;--- ADMINISTRATION
F1=1200; APPROVED DOSE 1200 MG Q3W
D1=1/24; INFUSION DURATION OF 1H

;--- PK
CL=THETA(4)*CLBWT*CLALB*(CLATAG**FLATAG)*CLTB*EXP(ETA(3))
V1=THETA(5)*V1BWT*(V1FEM**FLAFEM)*V1ALB*EXP(ETA(4))
V2=THETA(6)*(V2FEM**FLAFEM)*EXP(ETA(5))
Q=THETA(7)
KA=THETA(8)*EXP(ETA(6))
F3=THETA(9)*EXP(ETA(7))

S1=V1
K10=CL/V1
K12=Q/V1
K21=Q/V2
K31=KA

$DES
; --- PK
DADT(1)=-K10*A(1)-K12*A(1)+K21*A(2)+K31*A(3)
```

```
DADT(2)=-K21*A(2)+K12*A(1)
DADT(3)=-K31*A(3)

$ERROR
IPRED=F
Y=IPRED+IPRED*ERR(1)

$THETA
0.159; 1 ATAG ON CLEARANCE
-0.129; 2 FEM ON VOLUME 1
-0.272; 3 FEM ON VOLUME 2
0.2; 4 CLEARANCE (CL) L/DAY
3.28; 5 VOLUME 1 (V1) L
3.63; 6 VOLUME 2 (V2) L
0.546; 7 Q L/DAY
0.269; 8 K31=KA IN THIGH
0.829; 9 F IN THIGH

$OMEGA
0.09; IIV TUMOR BURDEN
0.0025; IIV ALB

$OMEGA BLOCK(3)
0.0867; CL
0.0181 0.0328; CL-V1 V1
-0.0235 0.0265 0.114; CL-V2 V1-V2 V2

$OMEGA
0.0818; IIV KA=KA31
1.54; IIV F1

$SIGMA
0 FIX; PROP ERR

$SIM ONLYSIM SUBPROBLEMS=1 (2252) (74292)
```

VI

GENERAL SUMMARY AND DISCUSSION

Lung cancer remains the leading cause of cancer-related deaths worldwide, with around 14.500 new patients diagnosed annually in the Netherlands [1]. Despite rapid innovations in treatment, such as immunotherapy and targeted therapy, classical chemotherapy remains the cornerstone of advanced NSCLC treatment. Moreover, while immunotherapy can be highly effective for some patients, it is expensive and poses significant challenges [2]. Improving the cost-effectiveness of immunotherapy agents could play a crucial role in expanding affordable access to these treatments.

When it comes to classical cytotoxic drugs, dosing presents a unique challenge: achieving the delicate balance of maximizing cytotoxicity while minimizing patient harm. This delicate balance requires careful consideration to avoid both underdosing (risking treatment ineffectiveness) and overdosing (risking severe toxicity). Currently, the dosing of cytotoxic drugs is often based on the outdated paradigm of BSA-based dosing rather than truly tailoring the dose to the individual. This approach risks suboptimal dosing, potentially reducing treatment effectiveness and increasing the likelihood of (severe) toxicity. These challenges particularly concern patients with advanced NSCLC, who are often frail and already face poor survival outcomes. Hence, for vulnerable patients, the treatment-associated toxicity of cytotoxic drugs may pose a greater threat to their overall health than the cancer itself.

The primary objective of this thesis was to investigate the dosing strategies of cytotoxic agents used in the treatment of advanced NSCLC and to explore approaches for optimizing these strategies based on individual patient characteristics leading to improvements in treatment outcomes, cost-effectiveness, reduction of incidence of toxicity, and the enhancement of the quality of life for patients.

This thesis examined the dosing strategies for key agents' carboplatin, pemetrexed, docetaxel, and atezolizumab (immune checkpoint inhibitor) used in the treatment of advanced NSCLC. Based on the knowledge gaps presented in the introduction, several hypotheses were formulated and investigated:

1. The use of the Cockcroft-Gault formula for estimating renal function in overweight and obese advanced NSCLC patients leads to overdosing of carboplatin, resulting in increased treatment toxicity and potentially impacting survival outcomes.
2. By adjusting the Cockcroft-Gault formula, amongst other things, in overweight patients improves the accuracy of carboplatin clearance estimation, enabling more precise dosing of carboplatin in overweight patients.

3. Advanced NSCLC patients with renal impairment (creatinine clearance <45 mL/min) treated with pemetrexed experience increased hematological and non-hematological toxicity, potentially leading to dose reductions and treatment discontinuation.
4. First-cycle docetaxel-associated hematological toxicity remains a predictive marker of survival outcomes in NSCLC patients in the era of immunotherapy.
5. Modeling and simulation can be used to develop an optimized subcutaneous dosing regimen for atezolizumab to reduce cumulative drug consumption and drug costs while maintaining equivalent therapeutic exposure.

EVALUATION OF CARBOPLATIN DOSING PARADIGMS

Carboplatin dosing is traditionally based on the Calvert formula, developed in 1989 using 100% glomerular filtered ^{51}Cr-EDTA as an ideal predictor of GFR [3]. In clinical practice, creatinine clearance is estimated as a surrogate for the GFR using the 1976 Cockcroft-Gault formula (CG formula) [4]. The CG formula estimates creatinine clearance by estimating creatinine production based on variables for muscle mass (i.e., sex, age, and weight) and serum creatinine. See **Introduction** for the CG formula. However, in overweight and obese patients, increased body weight typically reflects a greater increase in fat mass rather than muscle mass. Hence, The CG formula is likely to overestimate GFR in patients with higher body mass index (BMI), potentially leading to carboplatin overdosing and an increased risk of severe (hematological) toxicity [5-8]. Indeed, in **Chapter II**, we show that overweight (BMI 25.0-30.0 kg/m^2) and obese (BMI ≥30 kg/m^2) patients have a lower relative dose intensity compared to normal-weight patients (BMI <25.0 kg/m^2). Moreover, overweight patients had a significantly longer overall survival (OS) and progression-free survival (PFS) compared to normal-weight patients, and obese patients had an increased risk for grade III-IV thrombocytopenia without a difference in survival outcomes. These findings remained consistent even after adjusting for potential confounders.

Whether the observed effects of high BMI are predictive—stemming from an overestimation of GFR—or prognostic remains unclear. Unfortunately, our retrospective study design does not allow for the establishment of the causality of this association. Furthermore, the survival curves appear to overlap during the initial 3–4 months following the start of carboplatin treatment, diverging only thereafter. This raises the question, whether the improved outcomes reflect an anti-tumor effect of chemotherapy on disease progression or a prognostic advantage associated with higher BMI.

Higher carboplatin exposure is linked to increased toxicity, particularly thrombocytopenia, without a corresponding improvement in survival outcomes. As thrombocytopenia is the dose-limiting toxicity of carboplatin, the Calvert formula's target AUC is designed to balance maximizing carboplatin exposure by minimizing the risk of thrombocytopenia [9, 10]. This effect is more likely because of the initial aggressive targeting of the tumor during the first cycle, followed by treatment adaptations such as dose delays and dose reductions. Indeed, these adaptations, as reflected in the relative dose intensity, were significantly higher in the overweight and obese groups compared to the normal-weight group. Considering that cancer growth often follows an exponential trajectory, overweight and obese patients who are overdosed and experience early toxicity from higher carboplatin exposure may achieve a more pronounced suppression of tumor growth. This difference in treatment outcomes for overweight and obese patients may reflect a predictive effect of carboplatin treatment.

In general, increased BMI is associated with heightened inflammation, greater metastatic potential, upregulation of growth factors such as IGF-1, angiogenesis, and evasion of apoptosis [11]. In addition, overweight patients often exhibit a higher incidence of comorbidities, including heart disease, type 2 diabetes, hypertension, asthma, and other cancers, largely attributed to the body's heightened "meta-inflammatory" state [11, 12]. Interestingly, existing literature identifies BMI as a prognostic factor for survival and hematological toxicity in NSCLC. Studies report a paradoxical relationship between higher BMI and lower lung cancer mortality, independent of carboplatin-based chemotherapy [11, 13]. Notably, an extensive study by the International Lung Cancer Consortium, including 25,430 patients with NSCLC, found that overweight or obese patients had higher survival rates with a decrease in hazard ratio of 11% (adjusted hazard ratio (aHR)=0.89, 95%-CI: 0.85–0.95) and 14% (aHR=0.86, 95%-CI: 0.82–0.91), respectively [14].

Given the likely predictive effect of BMI on toxicity (resulting from an overestimation of carboplatin clearance) and its potential prognostic implications, it is likely that the overall impact on survival reflects a combination of both predictive and prognostic factors. These findings confirm the importance of BMI as a key covariate in evaluating both the toxicity and effectiveness of NSCLC treatment, emphasizing the need for personalized dosing strategies for overweight and obese patients in order to optimize treatment outcomes and minimize adverse effects.

It is evident that a more accurate method for estimating carboplatin clearance is required, as the outdated CG formula presents significant limitations. In **Chapter III**,

we proposed an adjusted CG formula that adjusted for overweight (BMI ≥25 kg/m^2), low serum creatinine (<60 µmol/L), and a maximal estimated creatinine clearance at 125 mL/min. Additionally, we evaluated alternative weight descriptors and GFR estimators, including the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. However, creatinine is not exclusively cleared by GFR but is also actively secreted by peritubular capillaries in the kidneys, leading to a 10-20% overestimation of GFR [15]. To address this limitation, we additionally evaluate the use of the biomarker cystatin C. Cystatin C is a direct biomarker for GFR since it is produced at a constant rate and is 100% freely filtered at the glomerulus, and neither secreted nor reabsorbed at the proximal or distal renal tubule [16].

Our adjustments to the CG formula did not improve accuracy in approximating target carboplatin exposure compared to the conventional CG formula. Among the alternative weight descriptors, GFR estimators, and biomarkers evaluated, cystatin C emerged as the most reliable marker for approximating the target AUC, independent of weight expressed as BMI. These findings align with the original Calvert formula, which used the 100% glomerular filtered ^{51}Cr-EDTA as an ideal predictor of GFR [3]. However, the formula of Schmitt *et al.* includes not only cystatin C but also body composition parameters such as absolute body weight, age, sex, and serum creatinine [17]. Moreover, it is important to note that our study included only five patients (28%) with BMI of 25.0-29.9 kg/m^2 and six patients (32%) with a BMI of ≥30.0 kg/m^2, resulting in insufficient statistical power to draw definitive conclusions regarding our primary outcomes.

Similarly, to the formula of Schmitt *et al.*, the CKD-EPI (creatinine-cystatin C) formula incorporates body composition parameters such as gender, age, and serum creatinine alongside cystatin C, but importantly excludes body weight [18]. See **Chapter III - Supplementary** for a detailed overview of different formulas and their parameters. Nonetheless, in our study, CKD-EPI (creatinine-cystatin C) provided an underestimation of carboplatin exposure dependent on BMI, going from +0.4% for normal-weight patients to -7.0% for overweight and -17.8% for obese patients. This may indicate that using only cystatin C without adjusting for body weight is insufficient for estimating carboplatin exposure.

Existing literature presents conflicting evidence on whether cystatin C alone, without considering other patient parameters, is sufficient for carboplatin dosing to achieve target AUC more effectively than traditional serum creatinine-based assessments of renal function. Thomas *et al.* developed a formula similar to that of Schmitt *et al.*, incorporating cystatin C alongside body weight, age, sex, and serum

creatinine [19]. An extensive study by White-Koning *et al.* (n=491) compared various formulas—including Thomas *et al.*, the CG formula, CKD-EPI creatinine, and CKD-EPI creatinine-cystatin C—for estimating carboplatin clearance to actual clearance. They observed that cystatin C (used in CKD-EPI) was the best predictor (with the least bias and highest precision) in estimating carboplatin clearance, largely independent of other patient characteristics, such as sex, BMI (which was only significant at the 1% level), and age [20]. These findings align with our own, supporting cystatin C as a potentially valuable marker for estimating carboplatin clearance and exposure, independent of patient characteristics like body weight (expressed as BMI).

The use of cystatin C for predicting renal clearance was already proposed in 2012, when the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommended cystatin C testing for chronic kidney disease (CKD) diagnosis in cases where serum creatinine values are unreliable. In 2019, KDIGO further emphasized the necessity of using both serum creatinine and cystatin C for the initial diagnosis and staging of CKD [21]. More recently, prominent kidney organizations, such as the National Kidney Foundation and the American Society of Nephrology, have also advocated for the integration of cystatin C testing into routine clinical practice [22]. Furthermore, the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula incorporates cystatin C in combination with creatinine [18], performing better than creatinine or cystatin C alone [23].

Despite the long-recognized predictive value of cystatin C for renal function, its clinical routine implementation and adoption for dosing of renally excreted drugs remain largely absent across healthcare settings [21]. Awareness and utilization of cystatin C testing vary significantly among hospitals, and the prevalence of its use remains low, with many clinicians unfamiliar with the assay [24]. Furthermore, not all clinical chemistry laboratories are equipped to measure cystatin C levels or provide its measurement as a routine service, partly because of the substantially higher costs associated with cystatin C testing compared to serum creatinine [25]. Additionally, cystatin C levels seem to be dependent on individual patient characteristics. For example, elevated levels of cystatin C have been observed in obesity [26], hyperthyroidism [27], inflammatory states [28], and with the use of (glucocorticoid) steroids [29]. The lack of standardization in cystatin C measurement further hinders its widespread adoption in clinical practice [30] and further research is needed to establish its implementation. Meanwhile, creatinine is widely accepted as a reliable (enough) surrogate for the GFR and is routinely tested and well-established in clinical workflows [31]. Hence, enhancing the estimation of creatinine clearance may currently offer greater clinical impact than expanding the use of cystatin C testing.

One interesting potential alternative method of measuring creatinine clearance is by using computed tomography (CT) scans. As described above, estimating renal function based on creatinine clearance in patients with abnormal body composition can lead to inaccurate estimations of either over- or underestimation of creatinine clearance [32]. A more accurate estimation of body composition, particularly muscle mass, could enhance predictions of creatinine production. When combined with serum creatinine, this approach may lead to more precise estimations of creatinine clearance and, consequently, carboplatin clearance. Recent advancements in deep learning and medical imaging have made it possible to assess an individual's body composition, including muscle mass, with high precision using X-ray CT scans [33]. Since muscle mass directly correlates with creatinine production, incorporating CT scan-based body composition data alongside serum creatinine measurements could offer a more accurate method for estimating creatinine clearance [34]. This, in turn, could improve carboplatin dosing, potentially optimizing treatment efficacy and minimizing toxicity in patients, particularly those with abnormal body composition. Now, patient enrollment is ongoing for the **EXAMINE-I study**, which aims to develop a novel dosing algorithm for carboplatin using CT scans (for body composition estimation) and serum creatinine measurements to predict creatinine clearance and, thus, carboplatin exposure better.

DOSING OF PEMETREXED IN PATIENTS WITH RENAL IMPAIRMENT

Pemetrexed is an anti-folate agent mainly excreted by the kidneys through tubular secretion and glomerular filtration, resulting in a linear correlation between its clearance and renal function [35]. Consequently, a decline in renal function leads to an increase in pemetrexed exposure and an increase in the risk of pemetrexed-associated toxicity [36, 37]. Although studies demonstrated that pemetrexed exposure is mostly dependent on renal function, its dosing is currently standardized based on BSA at 500 mg/m^2 [38]. As a result, patients with impaired renal function cannot receive an effective dose without a significant risk of severe toxicity [39]. In fact, the label explicitly contraindicates dosing in patients with renal function below 45 mL/min due to concerns for fatal toxicity [38].

Approximately 30% of lung cancer patients have impaired renal function [40]. As a result, many clinicians are confronted with the dilemma of administering effective treatment with major concerns for life-threatening toxicity or withholding the patient from a proven effective line of treatment. Real-world data on the toxicity profile of

pemetrexed in this high-risk population are crucial for informing clinical decision-making but remain limited [39]. In **Chapter IV**, we addressed this gap by examining the toxicity profile of standard-dose pemetrexed in non-squamous NSCLC patients with moderate renal impairment (30–45 mL/min). Our findings revealed that even in patients with only moderate renal impairment, standard dosing was associated with a high incidence of severe hematological and gastrointestinal side effects, resulting in early treatment discontinuation in approximately one-third of patients due to treatment-related toxicity. Moreover, severe toxicity was evident in the high rate of hospitalization, with nearly two-thirds of patients requiring hospitalization for pemetrexed-associated complications.

Because of the lack of real-world data on patients with renal impairment receiving pemetrexed, comparing our findings to other studies is challenging. For instance, and as to be expected, we observed a higher incidence of hematological toxicity in our study compared to the rates reported in phase III studies of pemetrexed conducted in patients with normal renal function [41, 42]. Moreover, our clinical data support the results from previous simulation studies. An extensive population pharmacokinetic-pharmacodynamic (PK/PD) analysis by Boosman *et al.* predicted a comparable incidence (51-93%) of grade III-IV neutropenia in individuals with renal impairment (eGFR <45 mL/min) [43]. However, it must be noted that, since our study was retrospective, the available data were dependent on reported values, which inevitably included missing or incomplete information. For example, most hematological measurements were conducted on day 20 of the 21-day cycle, although the lowest (nadir) neutrophil value is often reached around day 10 [37]. Despite these limitations, our study observed high incidences of both hematological and non-hematological toxicity, supporting the hypothesis that standard dosing of pemetrexed leads to overdosing and overexposure in patients with moderate renal impairment.

Although our results suggest that BSA-based dosing of pemetrexed is not recommended for patients with moderately impaired renal function, a simple dose reduction alone is likely insufficient to mitigate the elevated risk of severe toxicity. The previously mentioned PK/PD simulation study by Boosman *et al.* demonstrated that a 20 mg dose of pemetrexed in a patient with an eGFR of 20 mL/min resulted in the same neutropenic risk as the approved dose of 1000 mg in a patient with normal renal function (eGFR 90 mL/min and BSA of 2.0 m^2). This outcome was caused by the time-above-threshold relationship between exposure and toxicity. Hence, despite the 50-fold reduction in dose, this adjustment only resulted in a 13-fold lower exposure to pemetrexed (potentially reducing the treatment's efficacy) [43]. Considering these findings, we recommend alternative measures, such as adding standard folinic

acid prophylaxis therapy, as is commonly done with other anti-folate agents like methotrexate [44].

DOCETAXEL-ASSOCIATED TOXICITY AND SURVIVAL OUTCOMES

Docetaxel, a taxoid anti-neoplastic agent, received initial approval from the Food and Drug Administration (FDA) in 1996 for a first- or second-line treatment modality for advanced non-small cell lung cancer (NSCLC) [45]. Docetaxel exposure increases proportionally with its administered dose [46]. While numerous covariates influencing docetaxel pharmacokinetics have been identified, a substantial portion of the variability in drug exposure remains unexplained [47]. In clinical practice, docetaxel is dosed based on BSA at 75 mg/m^2 every 21 days [48]. However, BSA-based dosing only results in a minimal reduction in interindividual variability in docetaxel pharmacokinetics [49], highlighting the need for an improved method of individualized docetaxel dosing.

Systemic exposure to docetaxel has been shown to correlate significantly with both the risk of toxicity, particularly neutropenia, and improved survival outcomes [50]. Furthermore, various studies have revealed docetaxel-associated neutropenia as a prognostic marker for treatment efficacy [51, 52]. This raises the possibility of using docetaxel-induced toxicity as a basis for optimizing dosing a posteriori to improve treatment precision and outcomes.

With the advent of immunotherapy in 2015, docetaxel has been relegated to a last-line treatment for patients with advanced or metastatic NSCLC. Patients undergoing later-line treatments often exhibit greater frailty, poorer performance scores, and more extensive metastases [53]. Moreover, tumor sensitivity can change after resistance develops to previous lines of treatment. For instance, in advanced prostate cancer, cross-resistance between treatment lines, including resistance to docetaxel, has been linked to alterations in tumor cell gene expression [54]. Additionally, the adverse effects of docetaxel treatment can drastically impact the quality of life of lung cancer patients nearing the end of life [55]. This raises the critical question of whether the survival benefits are still relevant in the present-day NSCLC population.

Given the ethical challenges of studying the clinical value of docetaxel by withholding an approved treatment, we conducted a retrospective cohort study. In **Chapter V**, we explored the relationship between first-cycle docetaxel-associated hematological

toxicity and survival outcomes in NSCLC patients. Two analyses were performed to assess this relationship:

- **Grade III-IV docetaxel-associated hematological toxicity** versus the absence of grade III-IV hematological toxicity during the first cycle on overall survival.
- **Any grade docetaxel-associated hematological toxicity** versus no hematological toxicity during the first cycle on overall survival.

We did not find a significantly improved survival for patients with any grade of docetaxel-associated hematological toxicity. Still, our findings suggest a trend toward improved OS in patients (n=61) who experienced grade III-IV hematological toxicity during the first cycle of treatment, compared to those without such toxicity (n=225). Notably, this difference in OS was statistically significant only after 12 months. In contrast, no statistically significant association with OS was observed for OS in patients experiencing any grade of hematological toxicity first cycle (n=85) versus those without (n=201).

These results highlight the potential of docetaxel as an effective last-line treatment option in the post-immunotherapy era, even when dosed according to body surface area. However, the significant difference in OS observed between patients with or without grade III-IV hematological toxicity after 12 months raises an important question: is the survival benefit worth the added burden of treatment-induced adverse effects? The toxicities associated with docetaxel, particularly in patients with advanced lung cancer nearing the end of life, can severely affect quality of life [55]. Unfortunately, the retrospective design of this study, which relied on data extraction from electronic health records, limited our ability to evaluate the overall burden of last-line docetaxel treatment comprehensively. Despite robust digital documentation minimizing missing data and ensuring the availability of relevant laboratory tests, certain variables (such as non-hematological toxicities) were not available for analysis. This limitation prevented a complete assessment of the overall burden of last-line docetaxel treatment. Furthermore, we could not adjust for potential confounding factors affecting survival and hematological toxicity—such as histology, performance status, comorbidities, and hepatic function—because of the same data limitations. These missing factors may have influenced both docetaxel exposure and the observed outcomes.

As often is the case with retrospective studies, prospective studies are needed to further explore this relationship in the post-immunotherapy era. Nevertheless, our results suggest that the occurrence of mild toxicity during docetaxel treatment may

not necessarily warrant immediate intervention and does not appear to have a direct impact on survival outcomes.

OPTIMIZING SUBCUTANEOUS DOSING OF ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to PD-L1 [56]. It exhibits linear pharmacokinetics (PK) within a 1–20 mg/kg dose range, as observed in metastatic urothelial carcinoma [57]. The subcutaneous formulation of atezolizumab includes recombinant human hyaluronidase PH20, to increase absorption from the subcutaneous depot [56]. However, this subcutaneous formulation is administered as a flat fixed dose of 1875 mg every 3 weeks. Consequently, the only means of tailoring atezolizumab dosing to individual patient characteristics is by adjusting the interval between administrations.

The license holder for atezolizumab developed an extensive population PK model to support the application of atezolizumab to the U.S. market in 2016 [58]. In **Chapter VI**, we used this model to explore alternative dosing regimens. Since clearance depends on body weight, as indicated by the population PK (POPPK) model of the license holder, we evaluated dosing interval prolongation in the first scenario based on patient body weight [58]. By adhering to the FDA guidance for bioequivalence analysis of PD-L1 blocking antibodies through simulation, any findings may be implemented immediately [59]. By simulating interval prolongation across different weight groups within European and U.S. populations, we identified opportunities for dose optimization. Specifically, we propose a 5-week dosing interval for patients with a body weight <50 kg, a 4-week dosing interval for those weighing 50–65 kg, and the standard 3-week dosing interval for patients >65 kg. Implementing these weight-based dosing groups would result in a 12% dose reduction for European populations and a 7% dose reduction for U.S. populations (up to 11.7% if the upper weight limit of 65 kg were raised to 75 kg). Our simulated concentrations demonstrated equivalence to exposure of the approved intravenous dose of atezolizumab, aligning with FDA guidance for developing alternative dosing regimens for PD-L1 blocking antibodies in cancer treatment [59], making direct implementation possible.

In the second scenario we evaluated the potential of dose interval prolongation independent of body weight to maintain effective exposure throughout the treatment period, based on a conservative concentration threshold of 6 µg/mL associated with 95% intratumoral PD-L1 receptor saturation [58, 60]. By exploring interval

prolongation to achieve and sustain minimal effective exposure, we propose a 6-week interval for subcutaneous atezolizumab administration for both European and U.S. populations, ensuring that at least 95% of patients maintain exposure above the 6 µg/mL threshold for intratumoral PD-L1 receptor saturation during both the first cycle and at steady state. As a result, this regimen achieves a 50% reduction in drug expenses while preserving therapeutic efficacy.

Our study highlights the effectiveness and convenience of POPPK studies in optimizing dosing strategies for agents used in the treatment of advanced NSCLC. Other stakeholders, such as pharmaceutical companies, regulatory agencies, and the medical community, have all already welcomed the use of modeling and simulation to explore alternate dose regimens for monoclonal antibodies [61]. This approach has the potential to reduce cumulative drug consumption and associated costs while maintaining equivalent therapeutic exposure. Continued application of these methods could significantly improve the cost-effectiveness of cancer treatment, making novel treatment options more accessible and reducing the strain on national healthcare budgets.

RECOMMENDATIONS FOR CURRENT CLINICAL PRACTICE

Based on the results and findings presented in this thesis, we have formulated recommendations for optimized and more personalized dosing of carboplatin, pemetrexed, docetaxel, and atezolizumab (**Table I**).

Table I: recommendations for clinical practice

DRUG		RECOMMENDATION
I	*Carboplatin*	We recommend using cystatin C as a marker for dosing of carboplatin. For example, using the cystatin-C formula of Schmitt *et al.* [17]: Carboplatin clearance = $117.8^{*}(Cr_{serum}/75)^{-0.450}$ *cystatin $C^{-0.385}$*(body weight/65)$^{+0.504}$* (age/56)$^{-0.366}$* 0.847^{sex} with sex = 0 for male Substantial evidence supports the Schmitt formula as a highly accurate and precise estimator of carboplatin clearance and includes additional patient-specific characteristics. Evidence includes prospective studies demonstrating that cystatin C provides a more accurate estimation of carboplatin clearance compared to traditional creatinine clearance formulas.
II	*Pemetrexed*	We recommend developing new treatment regimens for pemetrexed in patients with renal impairment (GFR <45 mL/min) to minimize the risk of severe toxicity associated with standard dosing. We suggest incorporating prophylactic measures, such as folinic acid supplementation (45 mg, four times daily from day 2 to day 15 of a 21-day treatment cycle), in line with established methotrexate prophylaxis protocols.
III	*Docetaxel*	We recommend that docetaxel remains a viable last-line treatment option for advanced NSCLC in the post-immunotherapy era. Currently, we do not recommend using docetaxel-associated hematological toxicity as a means to predict survival outcomes. Furthermore, we emphasize the need for prospective studies to more comprehensively explore this relationship in the context of post-immunotherapy treatment.
IV	*Atezolizumab*	We recommend a 5-week dosing interval for patients with a body weight <50 kg; a 4-week dosing interval for those weighing 50–65 kg; and the standard 3-week dosing interval for patients >65 kg. Direct implementation is possible and will result in a 12% dose reduction for European populations and a 7% dose reduction for U.S. populations (up to 11.7% if the upper weight limit of 65 kg were raised to 75 kg).

FUTURE PERSPECTIVES

The field of research for advanced NSCLC continues to evolve. However, as described in this thesis, the optimized dosing for many classical cytotoxic agents lags behind current advancements. The FDA and other regulatory bodies have recognized the need to improve the current paradigm for dose selection of novel oncology drugs [62]. By discovering better ways of dosing for novel oncology medications, the FDA hopes to accelerate a paradigm shift to more individualized dosing through projects like Project Optimus (2024) [63]. However, there is a substantial knowledge gap because this program does not cover older oncology medications, which are still mainly unexplored under the current evolving paradigm.

In **Chapter I**, we evaluated and described opportunities for precision dosing of various classical cytotoxic drugs to improve the safety and efficacy of chemotherapy in NSCLC treatment. The recommendations and conclusions of this review largely align with the dosing strategies suggested for the classical cytotoxic agents discussed in different chapters of this thesis. Additionally, we propose dose optimization for paclitaxel, nab-paclitaxel, gemcitabine, and vinorelbine, with the most compelling evidence supporting the adoption of weekly dosing schedules for docetaxel, paclitaxel, and nab-paclitaxel, along with the direct implementation of therapeutic drug monitoring (TDM)-guided dosing for paclitaxel.

The research into precision dosing for chemotherapeutic agents, especially in the treatment of advanced NSCLC, holds significant potential for improving patient outcomes. While advancements in monoclonal antibody therapies such as atezolizumab demonstrate the utility of modeling and simulation for optimizing dosing regimens, similar efforts are needed for classical cytotoxic agents. Precision dosing holds the promise of improving efficacy while minimizing toxicity, particularly for patient's individual characteristics, for example, patients with renal impairment receiving pemetrexed.

Future research should focus on refining population PK models and expanding their application to a broader range of drugs used in the treatment of advanced NSCLC. Individual patient characteristics, such as renal function and tumor-specific factors, can be easily simulated, and drug exposure can be modeled when clear PK/PD relationships are established. Even small-scale studies can have a tremendous impact, driving advancements in precision dosing for the largest oncological patient population being lung cancer. Furthermore, real-world data is crucial for validating these simulation models and accounting for variabilities and patient parameters that

may influence drug exposure and patient response. This combined approach will enhance the accuracy and applicability of dosing regimens, ultimately improving treatment outcomes for NSCLC patients.

However, while the benefits of precision dosing are evident, several challenges remain. For example, individualized dosing based on TDM requires additional time and sampling, clear pharmacokinetic/pharmacodynamic (PK/PD) relationships (often tumor-specific), logistical planning (e.g., measurement of cystatin C as routine clinical practice), dosing decision support, and specialized facilities [64, 65]. Moreover, further research is needed to ensure that these strategies are both cost-effective and feasible in routine clinical settings without placing too much burden on healthcare systems.

CONCLUDING REMARKS

Implementing precision dosing to classical cytotoxic chemotherapy is an exciting and promising direction to improve the treatment of advanced NSCLC. By applying population model-informed precision dosing, therapeutic drug monitoring, and other individualization strategies, we have the potential to reduce adverse effects while enhancing the therapeutic efficacy of cytotoxic agents in the treatment of advanced NSCLC. POPPK modeling, in particular, can be used effectively and easily to reduce cumulative drug consumption and associated costs, while maintaining equivalent therapeutic exposure—especially for expensive novel drugs like atezolizumab.

However, for these strategies to be widely implemented, future research must focus on refining these models, addressing logistical challenges, and ensuring their practical applicability in diverse clinical settings. Only through continued collaboration between researchers, clinicians, and regulatory agencies can we fully realize the potential of precision dosing in the treatment of advanced NSCLC and improve treatment for all cytotoxic agents and all patients.

At present, much of the work and effort toward dose optimization remains an academic exercise and is often not integrated or adopted by license holders or regulatory agencies. The findings of this thesis, along with other dose optimization studies conducted within the academic context, should also reach governments, regulatory agencies, license holders, and other key healthcare professionals involved.

These analyses should not remain confined to academia, but should be broadened and considered by all stakeholders.

I recommend aligning academic research more closely with the development of clinical guidelines. These guidelines often identify knowledge gaps that can be addressed through targeted academic research, ensuring that the findings are more directly relevant to the practical needs of the field. Additionally, I recommend that research questions be more actively shaped, not only by clinical guidelines, but also by regulatory agencies and healthcare professionals. These stakeholders, being most directly involved in patient care, are in the best position to identify critical issues and challenges that need to be addressed.

Furthermore, I recommend updating chemotherapy drug labels to include therapeutic ranges rather than relying solely on fixed-dose regimens. Given the variability in patient responses due to factors like renal and hepatic function, including therapeutic ranges for dosing could help optimize efficacy while reducing toxicity. Additionally, pharmaceutical companies should be required to incorporate new clinical evidence and dosing recommendations into their drug labels as research evolves. Ensuring that labels reflect the latest scientific insights is essential for improving patient outcomes and preventing outdated prescribing practices.

It comes down time and again to the fact that it is not just about exploring opportunities for dose optimization, but also about translating these findings into clinical practice. In the end, our compassion for the patient is what unites us, as we all strive for better treatment of (lung) cancer while upholding the highest quality of life. Let's start today!

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Appendices

NEDERLANDSE SAMENVATTING

Longkanker is verantwoordelijk voor de meeste kanker-gerelateerde sterfgevallen, met naar schatting 10.000 dodelijke gevallen in 2023 en jaarlijks 14.500 nieuwe diagnoses in Nederland volgens het Integraal Kankercentrum Nederland (IKNL). Ondanks innovaties in de behandeling van longkanker, zoals immunotherapie en doelgerichte therapieën, blijft klassieke chemotherapie een belangrijk onderdeel van de behandeling. Hoewel immunotherapie bij sommige patiënten zeer effectief kan zijn, gaat deze behandelmethode gepaard met hoge kosten, wat een aanzienlijke druk legt op de financiële middelen van gezondheidszorgsystemen. Het verbeteren van de kosteneffectiviteit van immunotherapie is daarom cruciaal om deze behandelingen betaalbaar te maken én te houden.

Bij chemotherapie is het vinden van de juiste dosering een grote uitdaging. Het draait om het vinden van de optimale balans: enerzijds maximale effectiviteit tegen kankercellen en anderzijds minimale bijwerkingen voor de patiënt. Bij een te lage dosering wordt mogelijk onvoldoende chemotherapie toegediend, waardoor de behandeling ineffectief is. Daarentegen kan een te hoge dosering weliswaar effectief zijn tegen de kanker, maar kan dit leiden tot ernstige schade aan gezonde cellen, met (levens)gevaarlijke bijwerkingen als gevolg.

Momenteel is de dosering van klassieke cytotoxische geneesmiddelen (chemotherapie) vaak gebaseerd op het verouderde paradigma van lichaams-oppervlakte (BSA)-gebaseerde dosering. Echter, zullen twee patiënten met identieke lichaamsoppervlaktes anders reageren op hetzelfde medicijn door variaties in individuele patiënt karakteristieken zoals verschillen in lever- of nierfunctie, leeftijd of genetische polymorfismes. Door o.b.v. lichaamsoppervlakte te doseren, doseer je suboptimaal op individueel patiënt niveau (bijvoorbeeld iemand met een slechte nierfunctie), wat de effectiviteit van de behandeling kan verminderen en de kans op (ernstige) toxiciteit kan vergroten. Deze problematiek is met name gevaarlijk bij patiënten met gevorderd niet-kleincellig longcarcinoom (NSCLC), die vaak al kwetsbaar zijn en te maken hebben met slechte overlevingskansen. Voor deze patiënten kan enige extra toxiciteit als gevolg van de behandeling een grotere bedreiging vormen voor hun algehele gezondheid dan de kanker zelf.

Het doel van dit proefschrift is om de huidige doseringsstrategieën van cytotoxische middelen die worden gebruikt bij de behandeling van gevorderd NSCLC te analyseren en nieuwe benaderingen te ontwikkelen die de dosering beter afstemmen op individuele patiëntkenmerken. Dit zou kunnen leiden tot verbeterde behandelingsresultaten,

een hogere kosteneffectiviteit, een vermindering van de incidentie van toxiciteit en een betere kwaliteit van leven voor patiënten. Het onderzoek zoals beschreven in dit proefschrift richtte zich op de doseringsstrategieën van de belangrijkste middelen die worden gebruikt bij de behandeling van gevorderd NSCLC: carboplatine, pemetrexed, docetaxel en atezolizumab (een immuuncheckpointremmer).

In **Hoofdstuk I** hebben we mogelijkheden geëvalueerd om de dosering van verschillende klassieke cytotoxische geneesmiddelen beter af te stemmen op individuele patiëntkenmerken om daarmee de veiligheid en werkzaamheid van chemotherapie bij de behandeling van NSCLC te verbeteren. Hierbij hebben we gekeken naar alle klassieke cytotoxische middelen die worden gebruikt bij de behandeling van NSCLC: cisplatine, carboplatine, pemetrexed, docetaxel, (nab-) paclitaxel, gemcitabine en vinorelbine. De aanbevelingen en conclusies van deze review sluiten grotendeels aan bij de doseringsstrategieën die in de opvolgende hoofdstukken van dit proefschrift worden besproken:

- Voor carboplatine bevelen we dosisoptimalisatie aan door gebruik te maken van de biomarker cystatine C. Deze methode biedt een nauwkeurigere voorspelling van de carboplatine-klaring dan de conventionele methode die gebaseerd is op creatinineklaring.
- Bij pemetrexed adviseren we voor het ontwikkelen van nieuwe behandelregimes voor patiënten met een verminderde nierfunctie (<45 mL/min) en te starten met folinezuurprofylaxe voor deze patiënten om het risico op ernstige toxiciteit te verminderen.
- Voor paclitaxel, nab-paclitaxel en docetaxel adviseren we wekelijkse doseringsschema's in plaats van de standaard driewekelijkse dosering. Onderzoek toont aan dat wekelijkse dosering de kans op toxiciteit verminderd zonder in te geven op effectiviteit. Daarnaast adviseren we de directe implementatie van therapeutische geneesmiddelmonitoring (TDM) voor paclitaxel o.b.v. time-above-threshold doseren.

Voor gemcitabine en vinorelbine hebben we geen direct implementeerbare adviezen kunnen formuleren.

Vervolgens zijn we dieper ingegaan in het gebruik van carboplatine in NSCLC. In **Hoofdstuk II** hebben we aangetoond dat het conventionele gebruik van de Cockcroft-Gault formule voor het doseren van carboplatine leidt tot overdosering bij patiënten

met overgewicht (BMI 25,0–30,0 kg/m²) en obesitas (BMI ≥30,0 kg/m²). Bij patiënten met overgewicht (n=174) werd een langere overleving (adjusted HR (aHR)=0,72; 95%-BI (betrouwbaarheidsinterval):0,59-0,89; p<0,01) en een langere tijd tot ziekteprogressie (aHR=0,74; 95%-BI: 0,61-0,90; p<0,013) waargenomen in vergelijking met patiënten met een normaal gewicht (n=268; BMI <25,0 kg/m²). Daartegen zagen we bij patiënten met obesitas geen verbeterde overleving of minder progressie, maar wel een significant hoger risico op ernstige toxiciteit (graad III-IV trombocytopenie; adjusted odds ratio (aOR)=3,47, 95%-BI: 1,75-6,90). Deze resultaten benadrukken dat de Cockcroft-Gault formule met zorgvuldigheid moet worden toegepast bij patiënten met overgewicht en extra nog bij patiënten met obesitas door het verhoogd risico op ernstige toxiciteit.

Ons vervolgidee was om het doseren op basis van de Cockcroft-Gault (CG-)formule te verbeteren. In **Hoofdstuk III** hebben we een prospectieve farmacokinetische studie uitgevoerd om een aangepaste Cockcroft-Gault (aCG-)formule te testen, die onder andere aanpast voor patiënten met overgewicht (BMI ≥25,0 kg/m²) en past een maximale afkapwaarde toe voor doseren. De Cockcroft-Gault-formule wordt specifiek gebruikt om de uitscheiding van carboplatine via de nieren te schatten op basis van de creatinineklaring. Creatinine, een afbraakproduct van spieren dat door de nieren wordt uitgescheiden, leidt echter tot een overschatting van de nierfunctie (glomerulaire filtratiesnelheid; GFR) met 10-20% [15]. Daarom hebben we, naast de aangepaste CG-formule, ook de alternatieve biomarker cystatine C geëvalueerd. Cystatine C is een directe marker voor de GFR, wordt met een constante snelheid geproduceerd en volledig vrij gefilterd [16]. In totaal hebben we 18 patiënten in onze studie geïncludeerd, waarvan 7 patiënten met een BMI <25,0 kg/m², 5 patiënten 25,0-29,9 kg/m² (overgewicht) en 6 patiënten met een BMI ≥30.0 kg/m² (obesitas). Onze aCG-formule onderschatte de individuele carboplatineklaring in alle gewichtsgroepen, met de hoogste afwijking van -10,5% bij patiënten met obesitas versus +8,8% bij gebruik van de conventionele CG. De aCG-formule onderschatte -5,7% bij normaal gewicht en overschatte +1,1% bij patiënten met overgewicht, vergeleken met respectievelijk -4,2% en +2,8% bij gebruik van de conventionele CG-formule. De meest nauwkeurige voorspeller van carboplatineklaring over alle gewichtscategorieën was cystatine C (+0,2%, -2,0 en -0,1% voor respectievelijk patiënten met normaal, overgewicht of obesitas). Concluderend konden we in onze studie geen voorkeur vaststellen voor onze aangepaste Cockcroft-Gault-formule, die onder andere rekening houdt met lichaamsgewicht. De biomarker cystatine C benaderde daarentegen de target AUC voor carboplatine vrijwel perfect in alle BMI-groepen. In lijn met de bevindingen uit onze review in **Hoofdstuk I** adviseren we

daarom het gebruik van cystatine C te overwegen voor het doseren van carboplatine in plaats van de Cockcroft-Gault-formule.

Het volgende middel dat we hebben onderzocht voor dosisoptimalisatie is de antimetaboliet pemetrexed. Pemetrexed wordt voornamelijk door de nieren uitgescheiden en vertoont een lineaire correlatie tussen de klaring en de nierfunctie. Een afname van de nierfunctie zal leiden tot een toename van blootstelling aan pemetrexed en een toename van het risico op pemetrexed-geassocieerde toxiciteit. Hoewel studies aantonen dat de blootstelling aan pemetrexed grotendeels afhankelijk is van de nierfunctie, wordt het middel momenteel standaard gedoseerd op basis van lichaamsoppervlak (500 mg/m^2). Hierdoor lopen patiënten met een verminderde nierfunctie een verhoogd risico op overmatige blootstelling aan pemetrexed en ernstige toxiciteit. Dit is bijzonder relevant, aangezien ongeveer 30% van de longkankerpatiënten een verminderde nierfunctie heeft. Dit plaatst artsen voor een lastig dilemma in het behandelen van patiënten met een verminderde nierfunctie met pemetrexed: enerzijds streven naar een effectieve behandeling, anderzijds rekening houden met het risico op potentieel levensbedreigende toxiciteit.

Gegevens uit de praktijk over het toxiciteitsprofiel van pemetrexed bij patiënten met een verminderde nierfunctie zijn essentieel voor het ondersteunen van klinische besluitvorming, maar blijven tot op heden beperkt. Om dit kennisgebrek aan te pakken, hebben we in **Hoofdstuk IV** een retrospectieve studie uitgevoerd om het toxiciteitsprofiel van pemetrexed in standaarddosering te onderzoeken bij NSCLC-patiënten met een matige nierfunctiestoornis (creatinineklaring 30–45 mL/min). In totaal hebben we 44 patiënten geïncludeerd, met een mediane nierfunctie van 41,1 mL/min (interkwartielbereik: 35,0–43,9). Uit onze analyse bleek dat 70% van de patiënten (n=31) de vier geplande behandelingscycli van pemetrexed niet voltooide. Bijna de helft van de patiënten (n=14; 45%) stopte voortijdig vanwege pemetrexed-geassocieerde toxiciteit. Meer dan de helft van de patiënten (n=28; 64%) werd bovendien opgenomen in het ziekenhuis wegens behandeling gerelateerde complicaties. Ernstige (graad III-IV) hematologische toxiciteit neutropenie en leukopenie, kwam voor bij 39% van de patiënten (n=17). Daarnaast ontwikkelde 34% (n=15) graad III-IV gastro-intestinale toxiciteit.

Onze bevindingen toonden aan dat de standaarddosering van pemetrexed zelfs bij patiënten met slechts matige nierfunctiestoornissen gepaard ging met een hoge incidentie van ernstige hematologische en gastro-intestinale bijwerkingen. Deze resultaten onderstrepen de dringende noodzaak om nieuwe behandelstrategieën te

ontwikkelen die de veiligheid van pemetrexed verbeteren voor NSCLC-patiënten met een verminderde nierfunctie, zoals we hebben voorgesteld in **Hoofdstuk I.**

Docetaxel is een ander veelgebruikt chemotherapeutisch middel en werd in 1996 goedgekeurd als eerste- of tweedelijnsbehandeling voor gevorderde NSCLC. De systemische blootstelling aan docetaxel neemt proportioneel toe met de toegediende dosis. Hoewel meerdere covariaten zijn geïdentificeerd die de farmacokinetiek van docetaxel beïnvloeden, blijft een groot deel van de interindividuele variabiliteit in blootstelling onverklaard. In de klinische praktijk wordt docetaxel doorgaans gedoseerd op basis van lichaamsoppervlakte (75 mg/m^2 elke 21 dagen). Studies hebben echter aangetoond dat doseren o.b.v. lichaamsoppervlakte slechts een minimale reductie oplevert in de variabiliteit van de blootstelling aan docetaxel. Dit benadrukt de noodzaak voor het vinden van betere methoden voor het individueel doseren van docetaxel.

Een interessante bevinding bij docetaxel is dat de systemische blootstelling significant correleert met zowel het risico op toxiciteit (voornamelijk neutropenie) als met verbeterde overlevingsresultaten. Dit suggereert dat de mate waarin een patiënt bijwerkingen ervaart, kan dienen als een indirecte maatstaf voor de werkzaamheid van de behandeling. Deze eigenschap opent mogelijkheden om docetaxel-geïnduceerde toxiciteit te gebruiken als basis voor het optimaliseren van doseringen. Echter zijn de studies die deze relatie hebben onderzocht uitgevoerd voor de komst van immunotherapie in 2015, toen docetaxel nog als eerste of tweedelijns middel werd gegeven. Sinds de komst van immunotherapie is de rol van docetaxel verschoven naar een laatstelijnsbehandeling voor gevorderde NSCLC. Dit is een totaal andere populatie patiënten. Patiënten in deze fase van de behandeling zijn vaak kwetsbaarder, zieker en hebben meer uitgebreide metastasen. Bovendien kan de gevoeligheid van tumoren veranderen door resistentie die ontstaat na eerdere behandelingslijnen. Daarbij is het belangrijk om te benadrukken dat de (ernstige) bijwerkingen van een docetaxel behandeling een grote impact kunnen hebben op de kwaliteit van leven van longkankerpatiënten die zich in de laatste fase van hun leven bevinden. Dit roept de vraag op of de overlevingsvoordelen van docetaxel nog steeds relevant zijn voor de huidige NSCLC-populatie.

In **Hoofdstuk V** hebben we de relatie onderzocht tussen docetaxel-geassocieerde hematologische toxiciteit tijdens de eerste behandelingscyclus en de overlevings-uitkomsten bij NSCLC-patiënten in het huidige post-immunotherapie tijdperk. Onze resultaten toonden aan dat patiënten die hematologische toxiciteit van graad III-IV ervoeren tijdens de eerste cyclus een mediane algehele overleving (OS) hadden van 7,28 maanden (95%-BI: 4,80–10,58), in vergelijking met 7,03 maanden

(95%-BI: 5,82–8,31) bij patiënten zonder hematologische toxiciteit van graad III-IV (p=0,120). Opvallend was dat een verbeterde OS bij patiënten met graad III-IV toxiciteit zichtbaar werd na 12 maanden in vergelijking met patiënten zonder hematologische toxiciteit (p=0,0149). Wanneer we keken naar de groep met enige graad (I t/m IV) van hematologische toxiciteit, vonden we een mediane OS van 7,23 maanden (95%-BI: 5,06–8,54), terwijl dit 7,03 maanden (95%-BI: 5,88–8,74) was voor patiënten zonder enige hematologische toxiciteit (p=0,4167). Deze resultaten benadrukken effect voor docetaxel als een effectieve laatstelijnsbehandeling in het post-immunotherapietijdperk, zelfs bij dosering op basis van lichaamsoppervlak. Het significante OS-verschil na 12 maanden tussen patiënten met en zonder graad III-IV hematologische toxiciteit roept echter de vraag op of het overlevingsvoordeel de bijwerkingen rechtvaardigt. Helaas beperkt het retrospectieve studieontwerp onze evaluatie van de totale ziekte last van docetaxel behandeling zoals het evalueren van niet-hematologische toxiciteit. Prospectieve studies zijn nodig om onze bevindingen verder te valideren en te bevestigen. Onze resultaten suggereren echter dat milde toxiciteit tijdens de behandeling niet direct tot aanpassing hoeft te leiden, aangezien het geen negatieve impact op overleving lijkt te hebben.

Atezolizumab, een immunoglobuline G1 (IgG1) monoklonaal antilichaam, wordt als immunotherapie toegediend bij NSCLC. Recent is de subcutane toediening (1875 mg elke drie weken) van atezolizumab goedgekeurd. Aangezien dit een vaste dosis gaat, is de enige manier om de dosering van atezolizumab te optimaliseren op basis van individuele patiëntkenmerken door het interval tussen toedieningen aan te passen. Bij de goedkeuring op de Amerikaanse markt in 2016 heeft de licentiehouder een uitgebreid populatie-farmacokinetisch (POPPK)-model ontwikkeld ter ondersteuning van het doseringsadvies. In **Hoofdstuk VI** gebruikten we dit model om alternatieve doseringsschema's te onderzoeken.

Aangezien de klaring van atezolizumab mede afhankelijk is van het lichaamsgewicht, hebben we in eerst gekeken naar het verlengen van het doseringsinterval a.h.v. lichaamsgewicht van de patiënt. Door ons te houden aan de FDA-richtlijn voor bio-equivalentieanalyse van PD-L1-blokkerende antilichamen via simulatie, zijn de mogelijke bevindingen direct implementeerbaar. We vonden een doseringsinterval verlenging tot 5 weken voor patiënten met een lichaamsgewicht <50 kg, een interval van 4 weken voor patiënten met een gewicht van 50-65 kg, en het standaard doseringsinterval van 3 weken voor patiënten met een lichaamsgewicht >65 kg. Het implementeren van deze op gewicht gebaseerde doseringsgroepen zou leiden tot een reductie van de geneesmiddelkosten van 12% voor de Europese populatie en 7% voor de Amerikaanse populatie (tot 11,7% als de bovengrens voor het gewicht van 65 kg naar

75 kg zou worden verhoogd). Onze gesimuleerde concentraties toonden een equivalente blootstelling aan de goedgekeurde intraveneuze dosis atezolizumab, in lijn met de FDA-richtlijnen, waardoor directe implementatie mogelijk is.

Daarnaast hebben we een tweede scenario geëvalueerd, waarbij we onderzochten of het verlengen van het dosisinterval – ongeacht het lichaamsgewicht – mogelijk is, waarbij een minimale effectieve blootstelling wordt behouden gedurende de gehele behandelingsperiode (minimale concentratie van 6 µg/mL, geassocieerd met 95% intratumorale PD-L1-receptorverzadiging). We vonden dat het verlengen van het interval tot 6 weken zou leiden voor het behoud van een constante minimale effectieve blootstelling, zowel voor de Europese als de Amerikaanse populaties. Door het verdubbelen van het doseringsinterval, zou dit een reductie van 50% in medicijnkosten kunnen opleveren, terwijl de minimale therapeutische werkzaamheid behouden blijft. Onze studie benadrukt de effectiviteit en het gemak van POPPK-studies bij het optimaliseren van doseringsstrategieën voor geneesmiddelen die worden gebruikt bij de behandeling van gevorderde NSCLC. Door deze methoden van simulatie vaker toe te passen, kunnen we de kosteneffectiviteit van kankerbehandelingen aanzienlijk verbeteren. Dit maakt nieuwe behandelingsopties toegankelijker en verlaagt de financiële druk op gezondheidszorgbudgetten.

SLOTOPMERKINGEN

Het optimaliseren van doseringsschema's door middel van *precision medicine* is een spannende en veelbelovende richting voor het verbeteren van de behandeling van gevorderde NSCLC. Door met POPPK-modellen verschillende patiëntpopulaties te stimuleren, en andere geïndividualiseerde strategieën toe te passen op basis van patiëntkenmerken, kunnen we bijwerkingen verminderen en tegelijkertijd de therapeutische werkzaamheid van cytotoxische middelen verbeteren. Daarnaast is POPPK-modellering met name effectief en eenvoudig in te zetten om, door het simuleren van verschillende populaties, het cumulatieve medicijngebruik en de bijbehorende kosten te verminderen, terwijl effectieve blootstelling behouden blijft, met name voor dure nieuwe medicijnen zoals atezolizumab.

Om deze strategieën echter op grote schaal te kunnen implementeren, moet toekomstig onderzoek zich richten op het verfijnen van deze modellen, het aanpakken van logistieke uitdagingen en grotere stappen maken in het vertalen van onderzoek naar de klinische praktijk. Alleen door voortdurende samenwerking tussen onderzoekers, clinici en regelgevende instanties kunnen we het potentieel

van precisiedosering volledig realiseren en de behandeling voor alle cytotoxische middelen en alle patiënten verbeteren.

Helaas blijft momenteel een groot deel van het werk en de inspanning voor dosisoptimalisatie een academische exercitie en worden gevonden resultaten en adviezen vaak niet geïntegreerd of overgenomen door licentiehouders of regelgevende instanties. De bevindingen van dit proefschrift, samen met andere dosisoptimalisatiestudies die binnen de academische context zijn uitgevoerd, zouden ook overheden, regelgevende instanties, licentiehouders en andere belangrijke betrokken zorgprofessionals moeten bereiken.

Daarom adviseer ik om academisch onderzoek nauwer af te stemmen op de ontwikkeling van klinische richtlijnen. Deze richtlijnen identificeren vaak gaten van kennis die kunnen worden aangepakt door gericht academisch onderzoek, waardoor de bevindingen directer relevant zijn voor en aansluiten op de praktische behoeften van het veld. Daarnaast stel ik, naast betere aansluiting aan klinische richtlijnen, voor dat onderzoeksvragen actiever worden aangestuurd door regelgevende instanties en zorgprofessionals. Deze belanghebbenden zijn het meest betrokken bij patiëntenzorg en zijn het beste in staat om kritieke problemen en uitdagingen te identificeren die moeten worden aangepakt.

Verder raad ik aan om het therapeutische bereik van chemotherapie medicijnen in de samenvatting van de productkenmerken van de licentiehouders toe te voegen, gezien de variabiliteit in patiënten zoals een verminderde nier- of leverfunctie. Bovendien zouden fabrikanten verplicht moeten worden om nieuw klinisch bewijs en doseringsaanbevelingen op te nemen in hun samenvatting van productkenmerken. Hierdoor blijft de informatie van medicijnen in de samenvatting van productkenmerken de nieuwste wetenschappelijke inzichten weerspiegelen. Dit is essentieel om patiëntresultaten te verbeteren en verouderde voorschrijfpraktijken te voorkomen.

Het komt er keer op keer neer dat het niet alleen gaat om het verkennen van mogelijkheden voor dosisoptimalisatie, maar ook om het vertalen van deze bevindingen naar de klinische praktijk. Uiteindelijk is het onze compassie voor de patiënt die ons verenigt, terwijl we allemaal streven naar een betere behandeling van (long)kanker en tegelijkertijd de hoogste kwaliteit van leven hooghouden. Laten we vandaag beginnen!

DATA MANAGEMENT PLAN

ETHICS AND PRIVACY

Chapters II, IV, and V of this thesis involve retrospective patient data. The Medical Research Ethics Committee United (MEC-U, Nieuwegein, the Netherlands) determined that these studies were not subject to the Medical Research Involving Human Subjects Act, granting ethical approval under codes MEC 2019-105 (**Chapter II**) and MEC W23.130 (**Chapters IV and V**). All three studies were multicenter in design.

Patient data were coded with unique research numbers to ensure data protection and processed pseudonymously using ResearchManager (Deventer, the Netherlands). The pseudonymization key was securely stored on a network drive within the hospital where the patient was treated, accessible only to local researchers. This key was stored separately from the research data to maintain confidentiality.

Chapter III describes a prospective study conducted in compliance with national and international regulations, guidelines, and Rijnstate policy (Arnhem, the Netherlands). This study received approval from the local medical ethics committee and adhered to the principles of the Declaration of Helsinki (version 10, October 2013). All participants provided written informed consent.

Chapter VI includes simulated data to model clinical scenarios and investigate potential outcomes under varying conditions. The analysis incorporates data simulation and statistical modeling scripts, which are available upon request.

DATA COLLECTION AND STORAGE

The data for **Chapters II, III, IV, and V** were collected through electronic Case Report Forms (eCRF) in ResearchManager. The data were subsequently exported from ResearchManager to Excel (v2108; Microsoft 2021, USA) and further processed using Statistical Package for the Social Sciences (SPSS v29.0; IBM Corp 2022, USA) and R statistical software (v4.4.2; R Core Team 2024) for analysis and interpretation. Pseudonymized data were securely stored and analyzed on the department server of the Catharina Hospital (Eindhoven, the Netherlands) and within ResearchManager, with access strictly limited to affiliated project members.

The data for **Chapter VI** were simulated. Data interpretation, along with scripts for simulation and modeling, were securely stored on the department server of Radboud University Medical Center (Nijmegen, the Netherlands), with a copy maintained at Catharina Hospital. Both raw and processed data from all chapters are not archived

in a Data Acquisition Collection (DAC) or Research Documentation Collection (RDC) within the Radboud Data Repository. This decision was made because the data involved patients treated in external hospitals and thus not owned by Radboudumc, and the patients did not provide consent for their data to be reused or shared.

In compliance with Dutch regulations, data collection from electronic patient files was carried out by personnel with a treatment relationship with the patient or by researchers with explicit consent from the study participants. All research data are securely stored in a restricted-access folder on the departmental server of the hospital pharmacy at Catharina Hospital.

AVAILABILITY OF DATA

All studies are published as open access. The data will be securely stored at Catharina Hospital and Rijnstate Hospital for a minimum of 15 years following the termination of the study these datasets are available for future research only after renewed permission is obtained from the participants.

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CURRICULUM VITAE

Mart Kicken werd geboren op 27 januari 1994 te Amsterdam. Na vier jaar in Noord-Holland te hebben gewoond, groeide hij verder op in Berlicum, nabij 's-Hertogenbosch. In 2013 behaalde hij zijn gymnasiumdiploma aan het Gymnasium Bernrode te Heeswijk-Dinther, met onder andere de extra vakken Grieks en wiskunde D.

Aansluitend begon hij aan de bacheloropleiding (bio)Medische Wetenschappen en Technologie (MWT) aan de Technische Universiteit Eindhoven, waar hij een brede natuurwetenschappelijke basis verwierf in scheikunde, natuurkunde en wiskunde. Zijn bachelorscriptie voerde hij uit in een chemisch laboratorium, met onderzoek naar de optimale vetzuurketenlengte voor micelvorming ten behoeve van siRNA-transport (A biodegradable polycarbonate platform for siRNA delivery). Naast zijn technische verdieping volgde hij keuzevakken op het gebied van nanomaterialen en neuropsychologie.

Na het afronden van zijn bacheloropleiding schreef Kicken zich in 2017, als eerste MWT-student van de TU Eindhoven, in voor de opleiding Farmacie aan de Universiteit Utrecht. De combinatie van natuurwetenschappelijke diepgang en klinische toepassing in de behandeling van patiënten maakte farmacie tot een logische vervolgstap. De opleiding bestond uit een premasterjaar gevolgd door een driejarige masterfase. Gedurende deze periode volgde hij aanvullende vakken op het gebied van farmaco-epidemiologie en gezondheidsfilosofie, en liep hij een extra 10-weekse stage bij de International Pharmaceutical Federation (FIP).

Zijn masterscriptie voerde hij uit binnen het oncologisch domein bij het Catharina ziekenhuis onder begeleiding van dr. Maarten Deenen, met specifiek onderzoek naar de invloed van de body mass index (BMI) op de behandeluitkomst van carboplatine-gebaseerde chemotherapie bij patiënten met uitgezaaide niet-kleincellige longkanker. Dit onderzoek vormt tevens onderdeel van dit proefschrift.

Begin 2022 rondde hij zijn opleiding tot apotheker af en trad hij in dienst als projectapotheker oncologie en bereidingen in het Elisabeth-TweeSteden Ziekenhuis te Tilburg. In 2023 startte hij formeel zijn promotieonderzoek bij het Catharina ziekenhuis en Radboudumc onder begeleiding van dr. Maarten Deenen, dr. Rob ter Heine, dr. Ben van den Borne en prof. dr. Michel van den Heuvel. Dit proefschrift is het bezinksel van dat promotietraject.

RIHS PORTFOLIO

Name PhD candidate: M.P. Kicken
Department: Pharmacy
Graduate School: Radboud Institute for Health Sciences (RIHS)

PhD period: 01-02-2023 until 01-02-2025
Promotors: Prof. dr. M. van den Heuvel
Co-promotors: Dr. R. ter Heine
Dr. M.J. Deenen (Catharina ziekenhuis)
Dr. B.E.E.M. van den Borne (Catharina ziekenhuis)

Training activities (1/2)	Year	Time [hours]	ECTS*
Courses & Workshops			
Radboudumc – Scientific integrity	2024	20	0.7
Radboudumc – Introduction to Pharmacokinetic and pharmacodynamic analysis (RSS00.25)	2023	90	3.2
Radboudumc – In the lead: introduction for PhD candidates	2023	12	0.4
Radboudumc – General introduction for research personnel	2023	9	0.3
Catharina Ziekenhuis Eindhoven – Advanced statistics	2023	20	0.7
Catharina Ziekenhuis Eindhoven – Good Clinical Practice (GCP) cursus	2023	48	1.7
Catharina Ziekenhuis Eindhoven – Advanced Scientific Writing	2023	26	0.9
Catharina Ziekenhuis Eindhoven – Scientific writing	2019	12	0.4
Catharina Ziekenhuis Eindhoven – Various courses Clic (e-learnings)	2023-2024	18	0.6
Amsterdam UMC – Practical Biostatistics (e-learning)	2022	60	2.1
Utrecht University – Pharmaco-epidemiology (FA-MA210)	2022	210	7.5
Radboud University – Effective Writing Strategies	2023	75	2.7
Various Courses Harvard Associated Schools on statistics and R-programming (online)	2022-2024	152	5.4
	SUBTOTAL	752.0	26.9

***1 EC = 28 hours**

Training activities (2/2)	Year	Time [hours]	ECTS*
Symposia & congresses			
Longkanker in perspectief (congress)	2023	6	0.2
Radboudumc - PhD Retreat (congress, including presenting)	2023-2024	25	0.9
Various different seminars	2023-2024	53.5	1.9
Various weekly meetings (including presenting)	2023-2024	192	6.9
Radboudumc - Thoracic oncology research meeting (including presenting)	2023-2024	48	1.7
Catharina Ziekenhuis Eindhoven – Journal club (including presenting)	2023-2024	56	2.0
Catharina Ziekenhuis Eindhoven – Journalclub (including presenting)	2019	26	0.9
Elisabeth TweeSteden Hospital – Journal club (including presenting)	2022	16	0.6
Monthly referrals Nederlandse Vereniging voor Klinische Farmacologie en Biofarmacie	2022	12	0.4
	SUBTOTAL	**434.5**	**15.5**

***1 EC = 28 hours**

Teaching activities	Year	Time [hours]	ECTS*
Symposia & congresses			
Cancer treatment lectures, Elisabeth TweeSteden Hospital, nurse specialists	2022	20	0.7
Cancer treatment lectures, Catharina Ziekenhuis Eindhoven, pharmacy assistants	2023-2024	20	0.7
Supervision of internships			
6-month research internship, MSc student, Pharmacy (2x)	2023-2024	80	2.9
Others activities	**Year**	**Time [hours]**	**ECTS***
Radboudumc – Member of the PhD Council	2023-2024	40	1.4
PhD retreat – Organization (2x)	2023-2024	80	2.9
	SUBTOTAL	**240.0**	**8.6**
Personal development – PhD candidate	**TOTAL**	**1426.5**	**50.9**

Dankwoord

Met het opstellen van dit dankwoord nadert de voltooiing van mijn proefschrift daadwerkelijk haar einde. De voorbije jaren vormden een intensieve doch bovenal leerzame en bezielende reis. Het was een periode van ontwikkeling en verrijking, waarvoor ik met grote dankbaarheid op terugkijk. Niettemin had ik dit proefschrift nooit kunnen voltooien zonder de onmisbare steun, kundige begeleiding en hartelijke aanmoediging van velen. In het volgende dankwoord wens ik dan ook enkele personen in het bijzonder mijn oprechte dank te betuigen.

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Naast de onschatbare bijdrage van de patiënten, had dit traject nooit tot stand kunnen komen zonder de onmisbare steun, inspiratie en het aanhoudende enthousiasme van mijn promotieteam, waarvoor ik oneindig veel dankbaarheid voel.

Maarten, jij bent gedurende het gehele promotietraject mijn dagelijkse sparringpartner geweest. Ik kon altijd bij je terecht met vragen, ideeën of twijfels, en tijdens onze wekelijkse overleggen hebben we een breed scala aan onderwerpen besproken. Wat mij bijzonder inspireert, is hoe jij je tijd weet te verdelen en daarbij zoveel kunt betekenen voor anderen. Jouw toewijding en beschikbaarheid waren nooit begrensd, en je passie voor onderzoek was altijd zichtbaar en voelbaar, van begin tot eind. Je straalt betrokkenheid en passie uit, je denkt in mogelijkheden, ziet geen obstakels of beren op de weg, maar mogelijkheden en uitdagingen. Je was voortdurend gericht op hoe je mij het beste kon ondersteunen. Voor jouw vertrouwen, energie, oplossingsgerichtheid en de onuitputtelijke bereidheid om te helpen bij welk vraagstuk dan ook, ben ik je diep dankbaar. Je inzet en enthousiasme hebben een blijvende indruk op mij gemaakt en mijn vuur van passie voor onderzoek alleen maar meer aangewakkerd. En ik zou nog steeds graag eens naar een optreden van je komen kijken, en vooral luisteren!

Rob, naast Maarten had ik wekelijks contact met jou. Wat mij telkens weer opviel, was jouw tomeloze energie. Van jou heb ik geleerd dat het loont om zaken direct op te pakken in plaats van uit te stellen tot vlak voor de deadline. De tijd die het kost blijft gelijk, maar door proactief te handelen, voorkom je onnodige stress. Je beantwoorde e-mails vrijwel altijd binnen het uur, gaf uitgebreid commentaar op stukken tekst vaak nog dezelfde dag terug, en had het geduld en de bereidheid om zaken telkens opnieuw helder uit te leggen. Een lopende encyclopedie: voor elke vraagstelling had jij wel een artikel paraat. Elke vergadering bracht nieuwe inzichten; je stuurde me relevante artikelen toe, stelde scherpe vragen die mij tot verder nadenken aanzetten, en daagde me telkens uit om een extra stap te zetten. Jouw benadering en werkethiek zijn voor mij een inspirerend voorbeeld. Niet alleen voorzag je mijn werk steevast van scherpe en waardevolle feedback, je had bovendien oog voor mijn ontwikkeling als onderzoeker in bredere zin. Ik neem die houding graag mee in mijn verdere carrière. Naast een uitstekende sparringpartner ben je bovendien altijd in voor wat luchtig- en vermakelijkheid. Er spreekt een aanstekelijke speelsheid uit jouw manier van doen, die ik zeer bewonder. Wees vooral heerlijk jezelf en je zult ongetwijfeld nog vele onderzoekers mee inspireren!

Ook Michel en Ben mogen hier vanzelfsprekend niet ontbreken. Hoewel onze contactmomenten wat minder frequent waren, was jullie feedback telkens van grote waarde. Waar Maarten, Rob en ik ons vaak bewogen binnen de wereld van de farmacotherapie, brachten jullie met regelmaat verfrissende en prikkelende perspectieven vanuit de klinische praktijk. Jullie opmerkingen wisten niet zelden mijn betoog aan te scherpen, en hielpen mij bij het slaan van een brug tussen mijn onderzoek en de klinische werkelijkheid. Juist die verbinding is essentieel, en jullie bijdrage daaraan is van grote betekenis geweest. Daarvoor ben ik jullie bijzonder dankbaar.

Aan mijn paranimfen Doortje en Ramon, en Sofía. Wat was het waardevol om met jullie niet alleen te kunnen sparren over de inhoud van onze onderzoeken, maar ook over de grotere levensvragen die zich tijdens het promotietraject aandienden.

Doortje, jouw toewijding aan een plantaardige en gezonde levensstijl is ronduit inspirerend. Ik heb genoten van onze levendige discussies over de beste olie om in te bakken, over slimme zuivelvervangers en de dagelijkse strijd om voldoende vitamines, calcium en ijzer binnen te krijgen. Jouw energie, enthousiasme en betrokkenheid hebben me steeds geraakt en aangestoken. Voor jou ligt de wereld aan je voeten. Ik

ben heel benieuwd naar waar jouw voeten en interesses je zullen brengen. Met elke stap vorm jij zo je eigen pad. Zoals je geweldige plantaardig kookboek, dankjewel voor deze culinaire inspiratiebron!

Ramon, jij bent een bron van onvermoeibare energie en betrokkenheid. Hoe je erin slaagt alles tegelijk te doen - met hart voor de farmacie én met zorg voor je privéleven - dwingt altijd bewondering bij mij af. Ik heb onze samenwerking altijd als bijzonder prettig en constructief ervaren. Gelukkig is deze nog steeds niet voorbij. Er liggen nog twee studies voor ons; ik twijfel er niet aan dat die tot een goed einde zullen komen. En ik zie ernaar uit om als coauteur met je samen te schrijven!

Sofía, samen begonnen wij aan dit traject, en wat hebben we veel meegemaakt. Jij vertrok naar Leiden, ik naar Nijmegen, maar telkens als we gelijktijdig in het Catharina Ziekenhuis waren, vonden we elkaar weer; voor een praatje, een lunch, of een sparsessie en inhoudelijk gesprek. Je staat nooit stil en bent altijd in beweging met boeken die je wilt lezen, films die je wilt zien. Het was prikkelend en leerzaam met je te kunnen sparren over survivalanalyse. Daarnaast heb ik vooral ook veel geleerd van jouw gestructureerde manier van werken; al je overzichtelijke mapjes, documenten, en het vermogen van je om altijd de orde te bewaren. Al ben je hier zelf volgens mij niet mee eens…

Aan alle longoncologen, (ziekenhuis)apothekers, verpleegkundig specialisten, (research)verpleegkundigen en trialmedewerkers hartelijk dank voor de plezierige, constructieve en voortdurende samenwerking. Jullie betrokkenheid, professionaliteit en toewijding hebben een onmisbare bijdrage geleverd aan het tot stand komen van dit onderzoek.

Aan de medeonderzoekers en coauteurs met wie het contact vooral via de e-mail verliep, spreek ik mijn diepste waardering uit. Jullie deskundige en scherpe feedback, gecombineerd met een prettige samenwerking, hebben het onderzoeksproces aanzienlijk versterkt en verrijkt.

Ik wil Angélique van het Wetenschapsbureau en Ramon van de researchafdeling van het Catharina Ziekenhuis in het bijzonder bedanken. Vanaf het eerste moment had ik een fijne klik met jullie. Angélique, jij was de eerste die mij, na een simpele mail, vrijwel direct belde om mee te denken. Altijd snel, doortastend, met veel inhoudelijke kennis in alle regelgeving rondom alles wat met onderzoek te maken heeft. Een oplossing was er dan ook altijd binnen dezelfde dag. Je toewijding, energie en opgewektheid waren aanstekelijk en zeer gewaardeerd. Ramon, jij was altijd bereid

om te helpen, mee te denken en praktische oplossingen aan te dragen. Ik kon je altijd bellen, en je stond altijd klaar. Jullie inzet en betrokkenheid waren voor mij van grote waarde. Ik waardeer jullie beiden enorm en kom graag nog eens langs voor een kop koffie.

Een andere, uiterst belangrijke schakel in mijn onderzoek en de dataverzameling is Anne Grotenhuis geweest; inmiddels mijn directe collega bij Santeon. Anne, dankjewel voor je enorme inzet: je constante beschikbaarheid voor vragen, het sparren samen, je snelle reacties op e-mails en inhoudelijke verzoeken. Ik had me geen betere ondersteuning kunnen wensen! Wat ik in het bijzonder waardeer, is hoe je altijd opgewekt en positief bleef, ook toen het proces steeds meer tijd in beslag nam. Je energie, je vrolijkheid, je vermogen tot relativeren en je gevoel voor het juiste moment om luchtigheid te brengen, hebben het hele traject niet alleen efficiënter, maar vooral ook gezelliger gemaakt. En dat waardeer ik tot op de dag van vandaag. Wat een voorrecht dat we nu collega's zijn binnen Santeon! Op volle kracht vooruit in een nieuw project. Ik heb er al helemaal zin in!

Marcel, al bij onze eerste ontmoeting bij het CZE voelde ik direct een klik. Je nuchtere benadering, je vermogen tot relativeren en je scherpe inzicht dat cijfers ook gewoon cijfers zijn, maakten diepe indruk. Ik heb intens genoten van onze inhoudelijke sparringsessies en de luchtige discussies over wat causaliteit nu eigenlijk wel en vooral niet is. Je begon destijds meteen over causaliteit, en hoe het in theorie onmogelijk is om alle causale relaties volledig te kennen. Terecht merkte je op dat de frequentie statistiek uitstekend is in tellen, associëren en correleren, maar moeite heeft met het leggen van causale verbanden. Dat gaf mij eindelijk de ruimte om mijn grote fascinatie voor Bayesiaanse statistiek met te delen en daarin begrepen te voelen. En ja ook in dit boekje heb ik veel gebruikgemaakt van frequentie statistiek. Maar jouw opmerkingen zijn blijven hangen. Direct na ons gesprek heb ik The Book of Why aangeschaft. En nu, gewapend met een pot koffie en een hoofd vol vermoedens, begin ik aan de reis waarvan niemand precies weet waar die eindigt; maar iedereen achteraf beweert dat ze het al die tijd al hadden zien aankomen.

Linda, dank voor het bieden van ruimte en rust, en voor het zijn van mijn rots in de branding. Jouw passie voor filosofie en wiskunde heeft tijdens mijn promotietraject geleid tot vele diepgaande discussies, vaak tot laat in de nacht. Wat is überhaupt causaliteit? Is logica een inherente eigenschap, of juist afhankelijk van de aannames die we maken ("maar dat is toch gewoon logisch!")? Onze gesprekken over wetenschap als een manier van waarnemen en begrijpen, hebben mijn perspectief verrijkt en mij tot nieuwe inzichten gebracht. Het leven is elke dag een feest en avontuur met jou.

Samen met jou ga ik het liefst op ontdekkingstocht. Met jou beklim ik de hoogste torens van abstractie, lach ik om de laagste banale grapjes, en verwonder ik mij over hoe snel onze gesprekken van hot naar her laten vliegen. Jij bent de keuze die ik elke dag opnieuw maak. Jij bent mijn zekerheid. Mijn eeuwige wederkeer, voor wie ik telkens opnieuw mijn leven zou willen overdoen. Jij bent mijn fatum en mijn armor. Mijn Ëarendil, de verste ster die schittert in het donker. Don't know much about history, don't know much about biology, don't know much about a science book, don't know much about the French I took, but I do know that… I… Love… You.

Lieve familieleden, dankzij jullie onvoorwaardelijke liefde en voortdurende steun sta ik waar ik nu ben. Van jullie heb ik geleerd wat het betekent om hard te werken, vastberaden te zijn in het nastreven van mijn doelen en trouw te blijven aan wat mij vreugde schenkt. Jullie stonden steeds klaar en toonden oprechte interesse in mijn reis. Daarvoor ben ik jullie diep dankbaar. Dank voor jullie liefde, aandacht en altijd warme thuis dat jullie voor mij zijn.

Aan Nietzsche en Foucault, voor het behouden van mijn mentale gezondheid op momenten dat ik dwaalde op de koude, eenzame hoogtes van het denken. Jullie boden geen antwoorden, maar perspectief en daarmee ruimte. Jullie brachten me terug naar de wereld, door me eraan te herinneren hoe weinig ik werkelijk weet. Hoe kennis geen neutrale zoektocht is, en hoe zelfs binnen de wetenschap de vraag bepaalt wat gevonden wordt: je alleen kan vinden wat je zoekt. Jullie lieten me zien dat de flamingo die achter een boom staat niet gevonden wordt, maar door ons zelf is neergezet; door wie zoekt, door wat gevraag wordt, door hoe gekeken wordt. In mijn zoektocht naar mogelijkheden tot optimalisatie van geneesmiddelbehandeling, in retrospectieve analyses zonder causale pretentie, hielpen jullie me de beperkingen en impliciete aannames van mijn eigen methoden onder ogen te zien. Juist daarin hielpen jullie mij te blijven zoeken, hielden jullie mij in beweging, niet op zoek naar een definitieve, vaste waarheid, maar richting scherpere, diepere vragen.

Tot slot wil ik ook Ludwig Wittgenstein en Jan Brouwer bedanken, mijn katten, welteverstaan. Niet alleen boden zij gezelschap tijdens de vele uren achter het scherm, ze herinnerden mij ook aan de waarde van het absurde, het onzegbare en het intuïtieve.

Wittgenstein, terwijl ik worstelde met definities, categorieën en correcte terminologie, lag en nestelde jij zich op het toetsenbord precies wanneer ik dacht een helder argument te hebben geformuleerd. Een ware taalfilosofie die tijdens mijn Teams-meetings met zijn spinnen mij eraan leek te willen herinneren dat "waarover

men niet spreken kan, men moet zwijgen" en dat sommige paragrafen beter gewoon helemaal verwijderd kunnen worden dan urenlang te veilen en te schuren. Met een blik vol absolute overtuiging eiste jij altijd je gelijk op wanneer het etenstijd is, zonder enige ruimte voor discussie. Wanneer jij je op de stoel nestelt, als ik even was opgestaan, en weigert ook maar één centimeter uit te wijken, is dat geen verzoek, maar een duidelijk signaal. Elke beweging van je staart, elke gefronste blik, straalt de zekerheid uit van een denker die zijn axioma's als onherroepelijk beschouwt. In jouw wereld bestaat geen nuance; jij bent het woord, de wet en de waarheid. Een stelligheid die je met koninklijke vanzelfsprekendheid uitdraagt.

Brouwer, met je voorkeur voor onnavolgbare slaapcycli en plotselinge sprongen over mijn literatuurlijst, jij belichaamt de intuïtionistische overtuiging dat wiskunde geen externe waarheid weerspiegelt, maar een constructie is van de menselijke geest. Je houding maakte me altijd duidelijk dat ook academisch werk ruimte moet laten voor intuïtie, voor het niet-weten, voor het creatieve moment dat zich niet in getallen of modellen laat vangen. Je schijnbaar willekeurige van sprongen en zachtaardigheid en tegelijkertijd onontkoombare aanwezigheid dwongen mij tot pauzes in mijn denken, waarin nieuwe inzichten onverwacht konden ontstaan.

Tezamen herinneren jullie mij er telkens aan dat er meer nodig is dan logica om een proefschrift te voltooien: geduld, aandacht, verwondering, en soms een warme vacht op schoot, een nieuwe zitplaats op mijn toetsenbord of een staart in mijn gezicht. Ja ja jullie willen eten, ik kom er al aan!

Radboudumc university medical center

IN DEI NOMINE FELICITER

Radboud University