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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 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. Secondary safety endpoints were thrombocytopenia and toxicity-related hospitalizations.

Materials 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 (n=51) compared to normal weight patients. However, obesity was associated with significantly higher incidences of thrombocytopenia grade ≥3 (aOR=3.47, 95%-CI:1.75-6.90).

Conclusion: This study shows a significantly longer survival for overweight compared to normal weight patients. Obese patients have an increased risk for grade ≥3 thrombocytopenia without a difference in survival following carboplatin-based chemotherapy. The implications for clinical practice are to use the Cockcroft-Gault formula with caution in patients with BMI≥30.0 kg/m^2, and to verify calculated dosing of carboplatin for appropriateness.

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

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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 result in a potential overdose of carboplatin in patients with high weight categories [13]. 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 $\geq$ 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.

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. In order to gain more insight into the association between BMI treatment outcomes, the primary objective of the study was to determine the association 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 association between BMI and toxicity-associated hospitalization and thrombocytopenia.

Materials and methods

Study design and patient population

This was a retrospective, multi-center cohort study to determine the association of BMI with 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.* [18]. 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 [19].

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 $\geq$ 30.0 kg/m^2 as obese [20]. 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)). CCI was used to compensate for potential confounders regarding comorbidities. It categorizes comorbidities of patients using the International Classification of Diseases (ICD) diagnosis codes and assign different weights to it (ranging from 1-6) based on adjusted risk of 1-year mortality. 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) [21]. 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.

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

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 [22].

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 type of distribution. 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 association of BMI with 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.* [23]. Likewise, the subdivision in concomitant chemotherapy was based on differences in survival for triplet treatment with bevacizumab against doublet therapies with carboplatin [24–28]. 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 bivariate 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).

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 2019-105). Furthermore, obtainment of informed consent was waived given the retrospective character of the study including a large number of patients, of which most patients were already deceased. For personal data protection, all patient data was coded with a research number and processed anonymously in the research database (Castor, Amsterdam, the Netherlands).

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

Table 1
Baseline characteristics of stage IV NSCLC patients treated with carboplatin-based chemotherapy by BMI.

Characteristics	TOTAL (n=493)	<25.0 kg/m^2 (n=268)	25.0-29.9 kg/m^2 (n=174)	≥30.0 kg/m^2 (n=51)	p-value
Sex, n (%)					
Male	312 (63%)	154 (58%)	128 (74%)	30 (59%)	<0.001
Female	181 (38%)	114 (43%)	46 (26%)	21 (41%)	
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/m^2], 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%)	0.05
6	132 (27%)	83 (31%)	40 (23%)	9 (18%)	
Charlson Comorbidity Index, n (%)					
0	230 (47)	136 (51%)	80 (46%)	14 (28%)	0.06
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%)	
ECOG performance status, n (%)0					
0	202 (41%)	107 (40%)	73 (42%)	22 (43%)	0.88
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%)	
Primary tumor, n (%)					
Adenocarcinoma	299 (61%)	169 (63%)	103 (59%)	27 (53%)	0.27
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%)	
Concomitant chemotherapy, n (%)					
Etoposide	7 (1%)	4 (2%)	1 (1%)	2 (4%)	<0.001
Gemcitabine	160 (32%)	79 (30%)	58 (33%)	23 (45%)	
Paclitaxel	13 (3%)	6 (2%)	7 (4%)	0 (0%)	
Pemetrexed	201 (41%)	106 (40%)	76 (44%)	19 (37%)	
Docetaxel	38 (8%)	26 (10%)	10 (6%)	2 (4%)	
Paclitaxel + bevacizumab	74 (15%)	47 (18%)	22 (13%)	5 (10%)	

[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

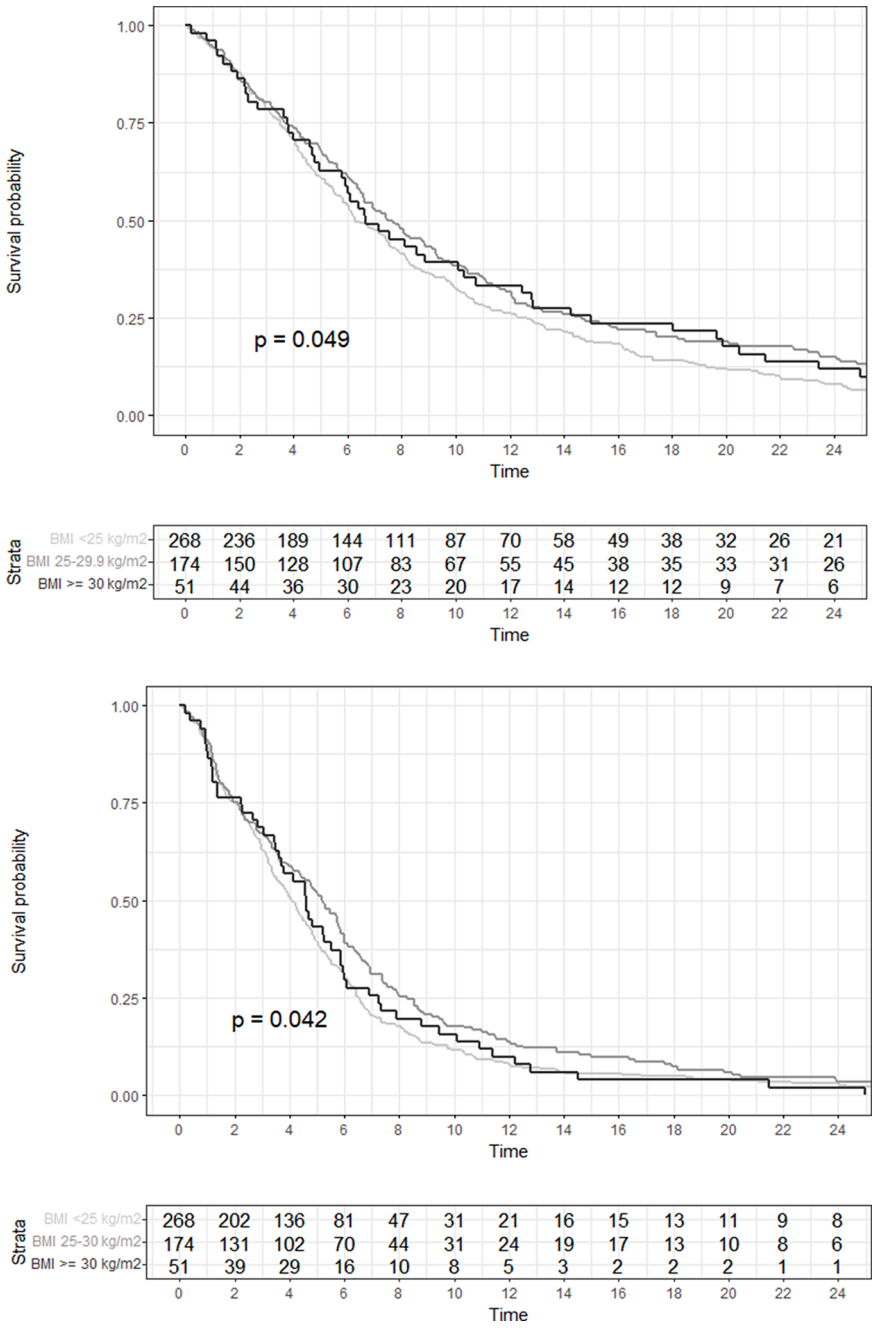

Fig. 1. a: Overall survival from start chemotherapy to 24 months. Black lines represent normal weight (BMI<25 kg/m^2) patients, dark grey overweight (25.0-30.0 kg/m^2) and light gray obese (≥30.0 kg/m^2). **b:** Progression free survival from start chemotherapy to 24 months. Black lines represent normal weight (BMI<25 kg/m2) patients, dark grey overweight (25.0-30.0 kg/m2) and light gray obese (≥30.0 kg/m2).

493 patients eligible for analysis. The median follow-up was 7 (0.03 - 127) months.

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 ($p = 0.042$); Fig. 1 provides the survival curves. In bivariate 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 association 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.

Table 2
Bivariate and multivariate analysis of overall survival and progression free survival in stage IV NSCLC patients.

Characteristics	No	%	Progression free survival Bivariate analysis[1] HR (95% CI)	p-value[2]	Multivariate analysis aHR (95% CI)	p-value[3]	Overall survival Bivariate analysis[1] HR (95% CI)	p-value[2]	Multivariate analysis aHR (95% CI)	p-value[3]
BMI [kg/m^2]										
< 25.0	268	54%	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
25.0-29.9	174	35%	0.78 (0.65-0.95)	0.01	0.74 (0.61-0.90)	0.003	0.78 (0.65-0.95)	0.01	0.72 (0.59-0.89)	0.002
≥ 30.0	51	10%	0.95 (0.70-1.28)	0.72	0.90 (0.66-1.22)	0.49	0.91 (0.67-1.23)	0.54	0.84 (0.62-1.14)	0.26
Sex										
< 25.0	154/114	58/43%	1.00 (ref)				1.00 (ref)			
25.0-29.9	128/46	74/26%	0.76 (0.62-0.92)	0.01			0.76 (0.62-0.93)	0.01		
≥ 30.0	30/21	59/41%	0.96 (0.71-1.29)	0.77			0.91 (0.68-1.23)	0.56		
male (ref) vs female			0.82 (0.68-0.99)	0.04	0.84 (0.70-1.02)	0.09	0.84 (0.69-1.01)	0.06	0.88 (0.72-1.06)	0.18
Age	[mean (SD)]									
< 25.0	63 (9)		1.00 (ref)				1.00 (ref)			
25.0-29.9	67 (9)		0.78 (0.64-0.95)	0.01			0.75 (0.61-0.91)	0.004		
≥ 30.0	66 (7)		0.94 (0.70-1.27)	0.70			0.88 (0.65-1.19)	0.42		
Age [year]			1.00 (0.99-1.01)	0.75			1.01 (1.00-1.02)	0.03	1.01 (1.00-1.02)	0.15
CCI										
< 25.0	210/58	78/22%	1.00 (ref)				1.00 (ref)			
25.0-29.9	127/47	73/27%	0.78 (0.64-0.95)	0.01			0.77 (0.64-0.94)	0.01		
≥ 30.0	33/18	65/35%	0.94 (0.69-1.27)	0.44			0.89 (0.66-1.20)	0.44		
<2 (ref) vs ≥ 2			1.08 (0.88-1.33)	0.74			1.21 (0.98-1.49)	0.07	1.13 (0.91-1.40)	0.27
ECOG PS										
< 25.0	226/38	83/14%	1.00 (ref)				1.00 (ref)			
25.0-29.9	144/24	83/14%	0.77 (0.64-0.94)	0.01			0.78 (0.64-0.95)	0.01		
≥ 30.0	44/7	86/14%	0.93 (0.69-1.26)	0.63			0.89 (0.66-1.20)	0.43		
<2 (ref) vs ≥ 2			1.35 (1.05-1.75)	0.02	1.35 (1.04-1.75)	0.02	1.43 (1.11-1.85)	0.01	1.39 (1.07-1.80)	0.01
Primary tumor										
< 25.0	169/99	63/37%	1.00 (ref)				1.00 (ref)			
25.0-29.9	103/71	59/41%	0.78 (0.64-0.94)	0.01			0.78 (0.64-0.95)	0.01		
≥ 30.0	27/24	53/47%	0.92 (0.68-1.25)	0.61			0.89 (0.66-1.21)	0.46		
Adenocarcinoma (ref) vs Large cell + squamous + other			1.18 (0.98-1.41)	0.08	1.15 (0.95-1.38)	0.16	1.14 (0.95-1.37)	0.17		
Concomitant chemotherapy										
< 25.0	47/221	18/83%	1.00 (ref)				1.00 (ref)			
25.0-29.9	22/152	13/87	0.77 (0.64-0.94)	0.01			0.78 (0.64-0.94)	0.01		
≥ 30.0	5/46	10/90%	0.92 (0.69-1.24)	0.56			0.88 (0.65-1.20)	0.42		
Paclitaxel/bevacizumab (ref) vs Gemcitabine + pemetrexed + paclitaxel + etoposide + docetaxel			1.29 (1.01-1.66)	0.04	1.21 (0.93-1.56)	0.15	1.25 (0.97-1.60)	0.09	1.14 (0.89-1.48)	0.32

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

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 Fig. 2, where the percentual

Table 3
Carboplatin dose intensity, thrombocytopenia, and hospitalization by BMI of carboplatin in stage IV NSCLC patients.

Characteristics	<25.0 kg/m^2 (n=268)	25.0-30.0 kg/m^2 (n=174)	≥ 30.0 kg/m^2 (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%)	0.34
No	147 (55%)	94 (54%)	22 (43%)	
1 cycle	39 (15%)	26 (15%)	9 (18%)	
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%)	0.01
RDI cycle 1 < 0.80, n (%)				0.004
Yes	45 (17%)	32 (18%)	18 (35%)	
No	179 (67%)	114 (66%)	23 (45%)	
RDI cycle 2, [%] mean (SD)	93% (17%)	90% (18%)	85% (19%)	0.13
RDI cycle 2 < 0.80, n (%)				0.12
Yes	27 (10%)	28 (16%)	9 (18%)	
No	104 (39%)	72 (41%)	14 (28%)	
RDI cycle 3, [%] mean (SD)	91% (18%)	90% (20%)	91% (33%)	0.93
RDI cycle 3 < 0.80, n (%)				0.77
Yes	28 (10%)	24 (14%)	7 (14%)	
No	81 (30%)	56 (32%)	16 (31%)	
a RDI (1-3), [%] mean (SD)	92% (15%)	89% (17%)	85% (19%)	0.02
RDI cycles 1-3 < 0.80, n (%)				0.02
Yes	78 (29%)	59 (34%)	24 (47%)	
No	146 (55%)	87 (50%)	17 (33%)	
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 109/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%)

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.

Discussion

Under the hypothesis that patients with higher BMI would be more likely at risk for overdosing of carboplatin, this study investigated the association 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 a difference in survival outcomes.

These findings support the hypothesis that BMI is significantly associated with treatment outcomes of carboplatin-based chemotherapy regarding toxicity and survival parameters. 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, 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 [16,17,14,15,29]. 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 association 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) [29]. 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 [30]. 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 association 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. Namely, this study design did not allow to establish the causality of the association. 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 [31]. 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 association of BMI on the treatment 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.

Furthermore, the Cockcroft-Gault formula was initially based on the regression line between mean 24-h creatinine excretion/kg body weight

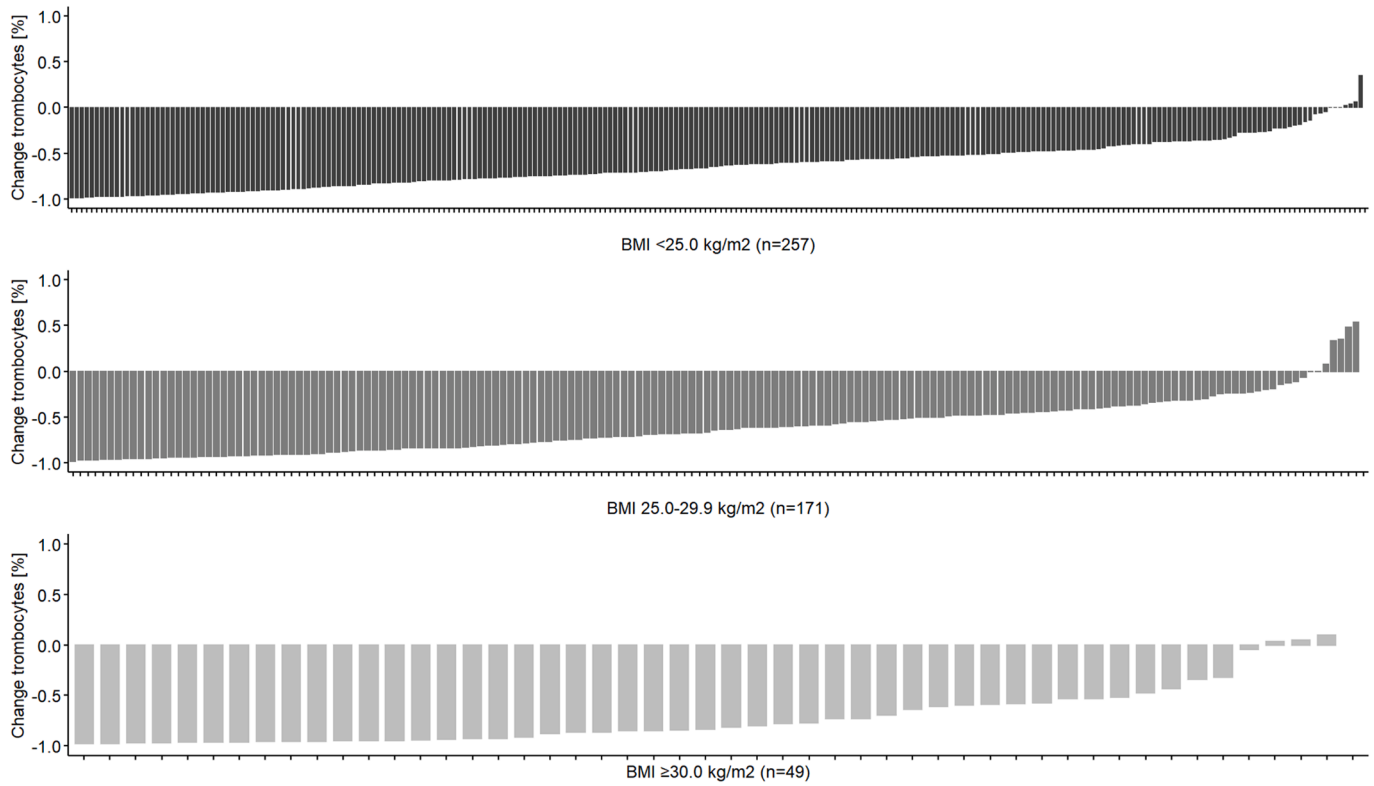

Fig. 2. Change in percentage (-1 = -100% to 1 = 100%) of lowest nadir in cycles 1-3 relative to baseline thrombocyte count.

plotted against the mean age [32]. Next to weight, the CG formula uses creatinine. However, 24-h urine collection is inaccurate and cumbersome. In addition, urine creatinine concentration may be unreliable in cancer patients due to confounding factors such as muscle mass, rate of metabolism of the creatine to creatinine, absorption of dietary creatine, filtration of creatinine by the renal glomeruli and its secretion by the proximal renal tubuli. Our study mainly focused on the weight part of the CG-equation and did not go into potential lower creatinine concentration.

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 $\geq$ 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.

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 $\geq$3 thrombocytopenia without a difference in survival following carboplatin-based chemotherapy.This association of BMI on survival and toxicity was significant even after adjusting for possible confounders, indicating a large and potent association of BMI specifically for obese patients. Notwithstanding, causality regarding BMI as a predictive or prognostic variable could not be established. The implications for clinical practice are that the Cockcroft-Gault formula should be used with caution in patients with BMI $\geq$ 30.0 kg/m^2, and the calculated dose of carboplatin 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 potentially enable safer therapy without negatively affecting treatment effectiveness.

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

Characteristics	No	%	Grade ≥3 Thrombocytopenia Bivariate analysis[2] OR (95% CI)	p-value[3]	Multivariate analysis aOR (95% CI)	p-value[4]	Hospitalization Bivariate analysis[1] OR (95% CI)	p-value[3]	Multivariate analysis aOR (95% CI)	p-value[4]
BMI [kg/m^2]										
< 25.0	268	54%	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
25.0-29.9	174	35%	1.51 (0.97-2.36)	0.07	1.20 (0.73-1.97)	0.47	1.20 (0.80-1.80)	0.37	1.18 (0.78-1.77)	0.44
≥ 30.0	51	10%	3.81 (2.04-7.12)	<0.001	3.47 (1.75-6.90)	<0.001	1.44 (0.77-2.67)	0.25	1.34 (0.72-2.51)	0.36
Sex										
< 25.0	154/114	58/43%	1.00 (ref)				1.00 (ref)			
25.0-29.9	128/46	74/26%	1.39 (0.88-2.19)	0.15			1.21 (0.81-1.83)	0.35		
≥ 30.0	30/21	59/41%	3.86 (2.06-7.26)	<0.001			1.44 (0.78-2.67)	0.25		
male (ref) vs female			0.57 (0.36-0.90)	0.02	0.74 (0.45-1.21)	0.22	1.06 (0.71-1.57)	0.79		
Age										
< 25.0	63 (9)		1.00 (ref)				1.00 (ref)			
25.0-29.9	67 (9)		1.20 (0.75-1.91)	0.44			1.16 (0.77-1.77)	0.47		
≥ 30.0	66 (7)		3.35 (1.77-6.34)	<0.001			1.40 (0.75-2.61)	0.29		
Age [years]			1.06 (1.03-1.09)	<0.001	1.04 (1.01-1.07)	0.01	1.01 (0.99-1.03)	0.50		
CCI										
< 25.0	210/58	78/22%	1.00 (ref)				1.00 (ref)			
25.0-29.9	127/47	73/27%	1.46 (0.93-2.29)	0.11			1.18 (0.79-1.77)	0.42		
≥ 30.0	33/18	65/35%	3.53 (1.87-6.67)	<0.001			1.37 (0.74-2.56)	0.32		
<2 (ref) vs ≥ 2			2.21 (1.41-3.47)	0.001	2.09 (1.27-3.42)	0.003	1.43 (0.94-2.19)	0.10	1.45 (0.94-2.22)	0.09
ECOG PS										
< 25.0	226/38	83/14%	1.00 (ref)				1.00 (ref)			
25.0-29.9	144/24	83/14%	1.54 (0.98-2.42)	0.06			1.18 (0.78-1.78)	0.43		
≥ 30.0	44/7	86/14%	3.92 (2.09-7.35)	<0.001			1.41 (0.76-2.63)	0.28		
<2 (ref) vs ≥ 2			1.27 (0.68-2.38)	0.45			1.43 (0.85-2.42)	0.18		
Concomitant chemotherapy										
< 25.0	47/221	18/83%	1.00 (ref)				1.00 (ref)			
25-29.9	22/152	13/87%	1.55 (0.97-2.48)	0.07			1.20 (0.80-1.81)	0.38		
≥ 30.0	5/46	10/90%	4.09 (2.10-7.99)	<0.001			1.41 (0.76-2.63)	0.28		
Gemcitabine + paclitaxel + paclitaxel/bevacizumab (ref) vs pemetrexed + etoposide+ docetaxel			4.54 (2.85-7.24)	<0.001	4.51 (2.78-7.29)	<0.001	1.54 (1.05-2.24)	0.03	1.54 (1.06-2.26)	0.03

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

However, this should be subject of further investigation.

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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CRediT authorship contribution statement

M.P. Kicken: Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft. **H.D. Kilinc:** Data curation, Investigation, Methodology. **C.M. Cramer-van der Welle:** Data curation, Investigation, Validation, Writing – review & editing. **S. Houterman:** Methodology, Supervision, Writing – review & editing. **B.E.E.M. van den Borne:** Methodology, Validation, Writing – review & editing. **A.A.J. Smit:** Methodology, Validation, Writing – review & editing. **E.M.W. van de Garde:** Methodology, Investigation, Supervision, Writing – review & editing. **M.J. Deenen:** Conceptualization, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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