Original Research

The association of cisplatin pharmacokinetics and skeletal muscle mass in patients with head and neck cancer: The prospective PLATISMA study

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Abstract *Background:* Locally advanced head and neck squamous cell carcinoma (HNSCC) is commonly treated with cisplatin-based chemoradiotherapy (CRT). Cisplatin is associated with severe toxicity, which negatively affects survival. In recent years, a relationship between low skeletal muscle mass (SMM) and increased toxicity has been described. This increased toxicity may be related to altered cisplatin distribution and binding in the fat-free body mass of which SMM is the largest contributor. This study aims to investigate the association between cisplatin pharmacokinetics and SMM in patients with HNSCC.

Methods: We performed a prospective observational study in patients with HNSCC treated with CRT. Patients received standard-of-care chemotherapy with three cycles of cisplatin at a dose of 100 mg/m^2 per cycle. Quantitative data on SMM, measured on computed tomography scans and cisplatin pharmacokinetics (total and ultrafilterable plasma concentrations) were collected, as well as data on toxicity.

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Results: A total of 45 evaluable patients were included in the study. A large proportion of the study population had a low SMM (46.7%). The majority of patients (57.8%) experienced cisplatin dose-limiting toxicities. Pharmacokinetic analysis showed a significant relationship between cisplatin pharmacokinetics and SMM, weight, fat-free mass and body surface area ($p < 0.005$). In a simulation, patients with a low SMM (<25.8 kg) were predicted to reach higher-bound cisplatin concentrations.

Conclusion: We found an association between cisplatin pharmacokinetics and SMM; however, this relationship was also seen between cisplatin pharmacokinetics and other body composition descriptors.

1. Introduction

Head and neck squamous cell carcinomas (HNSCCs) are among the most frequent tumours worldwide [1]. Two-thirds of patients with HNSCC present with advanced disease, which is commonly treated with cisplatin-based chemoradiotherapy (CRT) [2].

Acute toxicity of cisplatin, such as nephrotoxicity and ototoxicity, results in dose reductions, treatment delay or treatment cessation (chemotherapy dose-limiting toxicity, CDLT) in at least 30% of treated patients [3–5]. It has been described that patients who receive a lower cumulative dose of cisplatin have a worse oncological outcome [5]. It is, therefore, assumed that CDLTs negatively affect survival because patients receive suboptimal treatment. In recent years, a relationship between radiologically assessed low skeletal muscle mass (SMM) and CDLT has been described for HNSCC [6–8]. A retrospective study in patients with HNSCC undergoing CRT showed that patients with low SMM had a threefold higher risk of experiencing CDLT (44.3% versus 13.7%), which resulted in a significantly shorter overall survival than for patients who were able to complete CRT [7].

An explanation for the relationship between low SMM and toxicity might be that hydrophilic drugs, including cisplatin, mainly distribute into the fat-free body mass of which SMM is the largest contributor [9]. Cisplatin is a highly reactive drug, and on administration the drug will bind not only to tumour DNA causing its anti-cancer effect but also to tissue causing side effects (e.g. in the nephrons causing nephrotoxicity), and lastly to tissue without any pharmacodynamic effect (e.g. muscle tissue) [10]. We hypothesized that this latter compartment is highly related to SMM. In patients with a low SMM, less tissue is available to which cisplatin can bind relatively harmless, but more reactive cisplatin is available to bind to tissue related to toxicity. This might lead to increased CDLTs negatively affecting outcome.

The primary aim of this prospective observational study was to investigate the relationship between SMM and pharmacokinetic (PK) parameters of cisplatin in HNSCC patients. We hypothesized that an altered distribution of cisplatin, which is reflected by differences in cisplatin plasma concentrations, could explain why patients with low SMM are more prone to experience cisplatin toxicity. As a secondary objective, the relationship between SMM and toxicity was studied.

2. Materials and methods

2.1. Ethical considerations

The Medical Research Ethics Committee (METC) of the University Medical Center Utrecht has reviewed the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable Dutch and European regulations and has approved this study in June 2018 (METC 18–225/D). The study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent prior to inclusion in the study.

2.2. Study population, study design and sample size

This study was designed as a monocentre prospective observational cohort study in patients with HNSCC receiving 3-weekly high-dose (100 mg/m²) primary or adjuvant CRT. To estimate the sample size a clinical trial simulation (n = 200) was performed based on a previously published PK model on ultrafilterable cisplatin [11]. An allometric relationship between SMM and cisplatin clearance was assumed. Patient characteristics (SMM and body surface area (BSA)) were simulated in accordance with clinical practice. It was estimated that data from 45 patients was sufficient to find a significant relationship between cisplatin clearance and SMM with a power of >80%. As PK models with SMM and BSA are non-hierarchical, the difference between the two models cannot be statistically tested. However, in approximately 70% of the trials, this relationship showed better goodness-of-fit than a BSA-based relationship. Finally, the allometric exponent

could be estimated with acceptable precision (approximately 28% relative standard error) with a sample size of 45 patients.

2.3. Skeletal muscle mass measurement

Segmentation of SMM was manually performed using the SliceOmatic software (Tomovision, Canada). Skeletal muscle area (SMA) was measured on pre-treatment computed tomography (CT) imaging at the level of the third lumbar vertebrae (L3) by a validated method [12]. If no pre-treatment imaging was available at the level of L3, SMA was measured at the level of the third cervical vertebrae (C3) and then converted to SMA at the level of L3 by use of an earlier defined formula [12]. To correct for height, SMA was divided by squared height to yield the skeletal muscle mass index (SMI). Low SMM was defined as a lumbar SMI (LSMI) ≤ 43.2 cm^2/m^2. [13] The LSMI was used for analysis of demographic and anthropometric measurements. For PK analysis, the absolute volume of the muscle compartment was used, because cisplatin will distribute to this absolute volume after administration to a patient, by converting SMA to SMM with use of the following equations [14,15]:

$$\textit{Skeletal muscle volume } (L) = 0.166 L/cm^2$$
$$\times \textit{ skeletal muscle area in } cm^2 + 2.142\, L \qquad (1)$$

$$\textit{SMM } (kg) = \textit{skeletal muscle volume in } L \times 1.06 g/cm^3 \qquad (2)$$

For simulation purposes, the threshold value of low LSMI was converted to a threshold value for SMM in kilograms. Using the median height in our patient population, the threshold for low SMM was defined to be ≤ 25.8 kg. SMM was compared with the calculated fat-free mass (FFM), which is another way to estimate body composition. For calculation of FFM the equations of Janmahasatian et al. were used [16]:

$$\textit{FFM } (\textit{in males}) = \frac{9.27 \times 10^3 \times \textit{weight}}{6.68 \times 10^3 + 216 \times \textit{BMI}} \qquad (3)$$

$$\textit{FFM } (\textit{in females}) = \frac{9.27 \times 10^3 \times \textit{weight}}{8.78 \times 10^3 + 244 \times \textit{BMI}} \qquad (4)$$

In these equations, BMI is the body mass index (weight/height^2; weight in kg and height in m).

2.4. Cisplatin bioanalysis

Plasma and ultrafilterable (using a filter of 30 kDa) samples were collected from patients at different time points (pre-dose, end of infusion and 1 h, 3 h, 7 h and 20 h after end of infusion) during the first cycle of cisplatin. Both total and ultrafilterable plasma concentrations of platinum were measured by inductively coupled plasma-mass spectrometry (ICP-MS) by a previously described method [17]. For simplification, the terms free and bound cisplatin are used throughout to denote ultrafilterable and non-ultrafilterable platinum species, respectively.

2.5. Cisplatin-related toxicity

Toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) guidelines, version 4.03 [18]. CDLT was defined as any toxicity resulting in cisplatin dose-reduction of $\geq 50\%$, a treatment delay of ≥ 4 days, or cessation of cisplatin after the first or second cycle of therapy.

2.6. Pharmacokinetic analysis

For description of cisplatin PK a two-compartment model for free cisplatin, followed by one compartment for protein-bound cisplatin was used, as previously described by Urien et al. [11] Clearance of free cisplatin was considered negligible compared with binding to proteins and, therefore, not included in the model. More detailed information about the PK model can be found in the Supplementary materials.

The body composition descriptors weight, SMM, FFM and BSA were separately evaluated as covariates on clearance of free cisplatin (CL$_{\text{free}}$), volume of distribution of free cisplatin (V$_{\text{free}}$), intercompartmental clearance (Q) and volume of distribution of the peripheral compartment (V$_{\text{p}}$) of free cisplatin, clearance of bound cisplatin (CL$_{\text{bound}}$) and volume of distribution of bound cisplatin (V$_{\text{bound}}$). The body composition descriptors were evaluated using equation (5):

$$\theta_i = \theta_{pop} \times \left(\frac{body\ composition}{median\ body\ composition} \right)^k \qquad (5)$$

where θ_i represents the parameter estimate for individual i, θ_{pop} represents the typical parameter estimate for the population and k represents the exponent.

Based on the theory of allometric scaling the exponent was fixed to 0.75 for evaluation of clearance and to 1 for volume of distribution [19]. For both clearance and volume of distribution the exponent was also estimated.

The glomerular filtration rate (GFR; calculated using the creatinine-based Cockcroft−Gault formula [20], or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C equation and capped on a maximum value of 130 mL/min), and albumin were examined as additional relevant covariates, as described in the Supplementary materials.

In case the addition of the GFR and/or albumin resulted in a better fit of the baseline model (based on the objective function value (OFV), a drop in inter-individual variability (IIV) and a difference in effect size between the 25% and 75% quartile), body composition was also evaluated in combination with these covariates.

Lastly, the final model was used to simulate the effects of different SMMs on the population predicted

Table 1
Demographic and anthropometric measurements according to SMM status and DLT status.

	Total N = 45 N (%) or Mean (SD)	Without low SMM* n = 24 (53.3) Mean (SD)	With low SMM n = 21 (46.7) Mean (SD)	p	Without DLT ** n = 19 (42.2) Mean (SD)	With DLT n = 26 (57.8) Mean (SD)	p
Gender							
Male	32 (71.1)	23 (95.8)	9 (42.9)	**<0.01**	13 (68.4)	19 (73.1)	0.8
Female	13 (28.9)	1 (4.2)	12 (57.1)		6 (31.6)	7 (26.9)	
Age (diagnosis)	59.1 (6)	58 (5.2)	60.3 (6.6)	0.2	57.8 (4.6)	59.9 (6.7)	0.3
Weight (kg)							
	79.9 (18.8)	90.4 (17.4)	67.9 (12.16)	**<0.01**	79.7 (18.9)	80.0 (19.2)	1.0
Length (m)							
	1.8 (0.1)	1.8 (0.1)	1.8 (0.1)	0.3	1.8 (0.1)	1.8 (0.1)	0.8
BMI kg/m^2							
18.5−24.9	16 (35.6)	4 (16.7)	12 (57.1)	**<0.01**	4 (21.1)	12 (46.2)	0.2
<18.5	4 (8.9)	0 (0)	4 (19.0)		2 (10.5)	2 (7.7)	
25−29.9	18 (40.0)	14 (58.3)	4 (19.0)		11 (61.1)	7 (26.9)	
≥30	7 (15.6)	6 (25.0)	1 (4.8)		2 (10.5)	5 (19.2)	
LSMI cm^2/m^2 (median, IQR)	44.1 (37.7−50.9)	50.6 (5.2)	36.9 (4.1)	**<0.01**	45.0 (8.6)	43.7 (8.3)	0.6

*Low SMM is defined as an LSMI ≤43.2 cm/m^2.
**DLT is defined as any toxicity resulting in cisplatin dose-reduction of ≥50%, a treatment delay of ≥4 days, or cessation of cisplatin after the first or second cycle of therapy.
SMM: skeletal muscle mass.
BMI: body mass index.
LSMI: lumbar skeletal muscle mass index.
DLT: dose-limiting toxicity.

cisplatin concentrations. In this simulation, the effects of different SMMs around the threshold of 25.8 kg for low SMM were predicted. For the chosen SMMs, the corresponding BSAs were extracted from the data to calculate the given dose for the virtual patients.

2.7. Statistical analysis

Formal statistical testing for the PK model was performed using the likelihood ratio test (by means of the OFV which is minus twice the log likelihood) for the models without fixed coefficients, a *p*-value of 0.005 was used to take into account multiple testing [21,[22]], and the degrees of freedom were equal to the number of included relationships. For the models with fixed coefficients, the drop in OFV was used as a guidance. Other statistical analyses were performed using R (version 3.6.3) [23]. Correlation analysis was performed by use of Pearson's correlation analysis for variables with a normal distribution, and Spearman's correlation analysis was used for non-normally distributed variables. Chi-square statistics were used for analysing the differences between the frequencies of each categorical variable with the presence or absence of low SMM and DLT.

3. Results

3.1. Patient characteristics

In total, 50 patients were included between July 2018 and September 2020. Five patients eventually did not participate in the study, three due to the withdrawal of informed consent and two did not undergo CRT. Table 1 shows the characteristics of the 45 evaluable patients, 21 patients (46.7%) had low SMI. Median LSMI was 44.06 cm^2/m^2 (interquartile range (IQR) 37.7−50.9). Patients without low SMM were more likely to be overweight (58.3% versus 19%; *p* < 0.01) and obese (25.0% versus 4.8%; *p* < 0.01) compared with patients with low SMM.
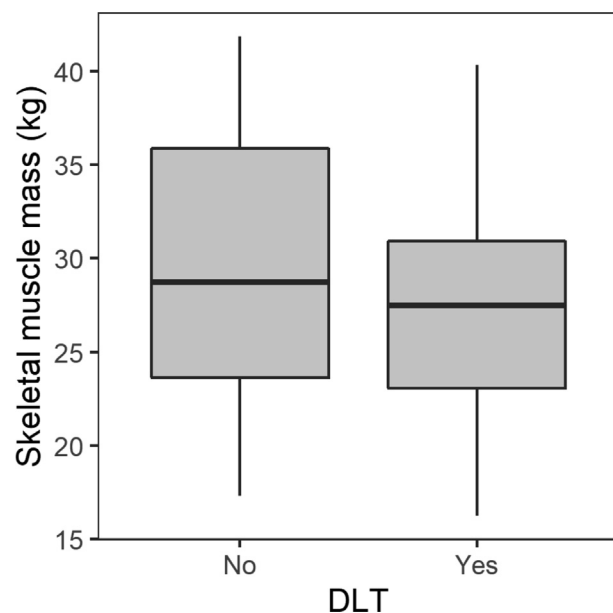

Fig. 1. Correlation between dose-limiting toxicities of cisplatin and skeletal muscle mass (unpaired t-test; *p* = 0.39).
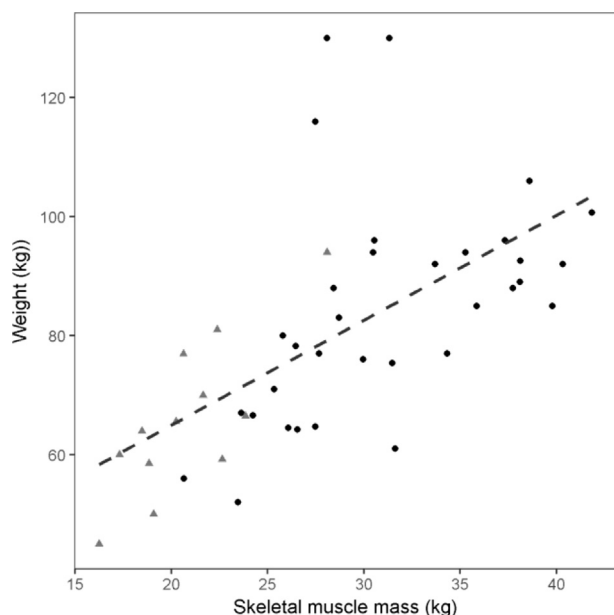
Fig. 2. Correlation between weight and skeletal muscle mass. Males are displayed by black circles and females by grey triangles. R = 0.63, *p* < 0.005.

The majority of patients were treated in a primary setting (n = 40, 88.9%) and had a tumour, node, metastasis (TNM) stage IV tumour according to the 8th edition TNM cancer staging criteria (n = 25, 55.5%). One patient received a weekly low-dose cisplatin schedule (40 mg/m² weekly) due to comorbidity.

3.2. Cisplatin dose-limiting toxicity

Of the 45 included patients, 26 patients (57.8%) did not complete three cycles of cisplatin. All were due to CDLT and consisted of creatinine increase grade 2 (n = 11) and grade 3 (n = 2), nausea grade 3 (n = 3), hearing impairment grade 2 (n = 6), neutropenia grade 3 (n = 1), heart failure grade 3 and increased creatinine grade 3

(n = 1), creatinine increase grade 2, hypomagnesaemia grade 3 and hyponatremia grade 3 (n = 1), hearing impaired grade 2 and neutropenia grade 4 (n = 1). In our data set, no correlation was found between CDLTs and SMM (unpaired T-test, *p* = 0.39), as illustrated in Fig. 1.

3.3. Pharmacokinetic results

SMM and weight were significantly correlated with a Pearson correlation coefficient of 0.6, as shown in Fig. 2. Based on goodness-of-fit plots the data were well described by the used PK model. For five patients, no SMA at the L3 slice was available; therefore, SMA at the C3 slice was used.

Firstly, albumin and GFR were tested as covariates on the baseline model. No effect of albumin on the PK model was found. Addition of the GFR as a covariate on CL_{bound} resulted in a drop in OFV of 28 and 33 points, for the GFR calculated based on creatinine and cystatin C, respectively (non-hierarchical models). Also, a drop in IIV and a relevant difference in effect size were encountered. Therefore, GFR was also evaluated in combination with SMM.

Secondly, the PK model was extended with SMM, weight, and FFM as covariates. Using estimated exponents, compared with fixed exponents based on the theory of allometric scaling, led to a substantially better description of the data, as indicated by the OFV. The exponent was unidentifiable for V_{free} and Q. Addition of GFR, next to SMM, had no effect on the PK model (additional dOFV −5 and −4, for creatinine and cystatin C, respectively), which could be explained by a relationship between weight and GFR (weight is even used to calculate creatinine clearance in the Cockcroft-Gault formula).

Therefore, SMM, weight and FFM were added as potential covariates on CL_{free}, CL_{bound} and V_{bound} of cisplatin while estimating the exponents. The OFV was significantly decreased by addition of SMM (dOFV −64, *p* < 0.005), weight (dOFV −77, *p* < 0.005) and
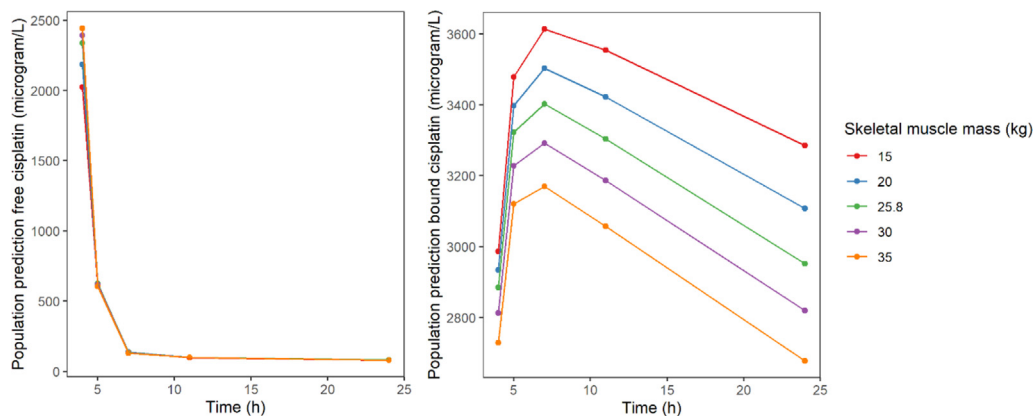

Fig. 3. Population predicted cisplatin concentrations versus time. The left panel shows predicted free cisplatin concentrations, and the right panel shows predicted bound cisplatin concentrations. Simulations were performed using the model in which skeletal muscle mass was added as covariate on clearance of free cisplatin, and on clearance and volume of distribution of bound cisplatin. Skeletal muscle mass was simulated around the threshold of 25.8 kg for a low skeletal muscle mass, with corresponding body surface area and thus dose given.
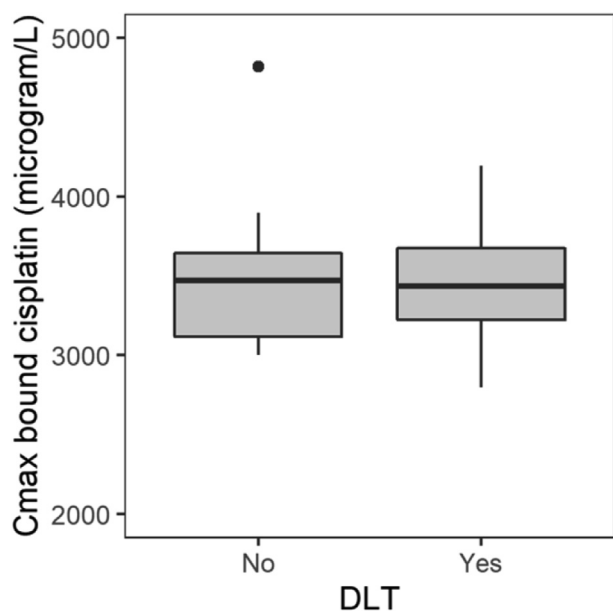
Fig. 4. Correlation between dose-limiting toxicities of cisplatin and the maximum plasma concentration (C_{max}) of bound cisplatin (Wilcoxon rank-sum test; $p = 0.85$).

FFM (dOFV -70, $p < 0.005$). Because cisplatin is dosed based on BSA, BSA was also tested as covariate in the final model, which resulted in a significant drop in OFV (dOFV -86, $p < 0.005$). The parameter estimates and estimated exponents for the model with SMM are shown in Supplementary materials S2.

Thirdly, a simulation was performed. Plots of the population predicted cisplatin concentrations versus time derived from this simulation are shown in Fig. 3, which shows that patients with a lower SMM are predicted to reach higher concentrations of bound cisplatin.

Lastly, the correlation between CDLTs and the maximum plasma concentration (C_{max}) of bound cisplatin was examined. The subject receiving a weekly low-dose cisplatin schedule was excluded in this analysis, because this subject received a lower dose of cisplatin compared with the other patients. No correlation between CDLTs and the C_{max} of bound cisplatin was found (Wilcoxon rank sum test; $p = 0.85$), which is illustrated by the boxplots in Fig. 4.

4. Discussion

In this prospective observational study, we investigated the relationship between cisplatin PK and SMM. We hypothesized that such relationship could explain the higher risk of toxicity in patients with a low SMM. As expected, we found an association between cisplatin PK, especially bound cisplatin, and SMM. A pharmacokinetic simulation showed that patients with low SMM reached higher concentrations of bound cisplatin, which could be a theoretical explanation for the higher toxicity in this patient group. The higher concentration of bound cisplatin could be seen as a reflection of the smaller volume of distribution. Because of this smaller volume, less tissue is available where, the hydrophilic and highly reactive, cisplatin can distribute to and bind with, without inducing toxicity.

We expected that patients experiencing CDLTs would have higher maximum concentrations of bound cisplatin in plasma; however, we did not find a correlation between these two parameters. Furthermore, no relationship was found between DLTs and a low LSMI, which was seen in previous studies [7,24]. These findings are most likely explained by the relatively low number of included patients. A relationship between SMM and toxicity has already been described. Wendrich et al. showed that patients with HNSCC with a low SMM undergoing CRT had a threefold higher risk of experiencing CDLTs. Therefore, we did not power our study to find a relationship between SMM and toxicity, but we aimed to find a relationship between PK of cisplatin and SMM. A relationship between PK of cisplatin and SMM was found, and we provided a hypothesis how this could explain the toxicity of cisplatin.

Although we found a relationship between cisplatin PK and SMM, there was also a significant relationship between cisplatin PK and the other body composition descriptors. Based on the findings in this study, both SMM and the other body composition descriptors are weakly predictive for cisplatin pharmacokinetics. With the used population pharmacokinetic method, the influence of each body composition descriptor could only be statistically compared with the baseline model and not compared with each other, because in that matter the models were non-hierarchical. Therefore, we were not able to draw a conclusion about which body composition descriptor predicts cisplatin PK best. However, the differences in model fit were only minor, highly suggestive that all body size descriptors were similarly predictive. We did find SMM to be correlated with weight, which might explain why cisplatin pharmacokinetics is also related to weight and FFM. In contrast to BSA and weight, only SMM provided an explanation for the toxicity of cisplatin.

A limitation of the study is that no data were available on the concentration of bound cisplatin in tissue. Therefore, the hypothesis that higher concentrations of bound cisplatin reflected the distribution and tissue binding of cisplatin, and thus could explain toxicity, could not be tested. A study in which cisplatin PK was studied in mice in whole blood, serum, kidney, liver, testis, brain and tumour tissue, suggested that platinum serum concentrations can be used to predict the concentrations in tumour and tissue [25]. This underlines our hypothesis. Measurement of platinum-DNA adducts in human tissue of patients treated with cisplatin is also possible [26]. However, this was only studied in a small number of patients (n = 3). To further investigate the relationship between a low SMM and PK of cisplatin, platinum-DNA adducts could be measured in

human tissue and the correlation with SMM could be studied. However, platinum-DNA adduct measurement is only feasible in surrogate tissue such as peripheral blood mononuclear cells (PBMCs).

5. Conclusion

Patients with HNSCC with low SMM reach higher-bound cisplatin concentrations, although no correlation was seen between cisplatin DLT and low SMM. Further studies that examine the level of bound cisplatin in tissue could further clarify the relationship between low SMM and cisplatin DLTs in patients with HNSCC.

Author contributions section

N. Chargi: Data curation; Formal analysis; Investigation; Methodology; Resources; Roles/Writing − original draft; Writing − review and editing.
L. Kuijsten-Molenaar: Data curation; Formal analysis; Investigation; Methodology; Resources; Roles/Writing − original draft; Writing − review and editing.
L.F.J. Huiskamp: Investigation; Resources; Roles/Writing − original draft; Writing − review and editing.
L.A. Devriese: Conceptualization; Funding acquisition; Supervision; Writing − review and editing.
R. de Bree: Conceptualization; Funding acquisition; Project administration; Supervision; Writing − review and editing.
A.D.R. Huitema: Conceptualization; Formal analysis; Funding acquisition; Methodology; Supervision; Writing − review and editing.

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Conflict of interest statement

The authors Najiba Chargi, Laura Kuijsten-Molenaar, Laura F.J. Huiskamp, Lot A. Devriese, Remco de Bree and Alwin D.R. Huitema of the manuscript *The association of cisplatin pharmacokinetics and skeletal muscle mass in head and neck cancer patients: the prospective PLATI-SMA study* have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.10.010.

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