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Carboplatin dose based on actual renal function: no excess of acute haematotoxicity in adjuvant treatment in seminoma stage I

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ABSTRACT

Introduction The practice of carboplatin dosing is not concordant among different centres and oncologists. Some clinical guidelines recommend capping of the carboplatin dose at, for example, creatinine-clearance (Crea-Cl) of 125 mL/min because of concerns of excessive toxicity. Clinical data to support such recommendations are lacking, especially in patients with seminoma.

Methods This is a retrospective analysis of acute haematotoxicity of patients with stage I seminoma treated with adjuvant carboplatin area under the curve (AUC) 7 in routine practice in two Swiss centres in 2005–2015, and a comparison of incidence and grade (according to Common Terminology Criteria for Adverse Events v4.0) of haematological adverse events (hAEs) in patients with Crea-Cl <125 mL/min vs >125 mL/min without dose capping.

Results 74 patients with 229 documented measurements were included (median 3/patient). A total of 151 hAEs occurred. Platelet nadir occurred earlier than median white cell/neutrophil count (median day 15 vs day 22; P<0.0001). The majority of hAEs were mild, with more than 80% being of grade 1. Only two (2.7%) clinically relevant hAEs necessitating subsequent interventions occurred (one patient received platelet transfusion, one patient with febrile neutropaenia). Haematological toxicities were not statistically different in patients dosed with Crea-Cl >125 mL/min versus those with Crea-Cl <125 mL/min. No hAEs other than grade 1 occurred before day 10 and after day 24.

Conclusions Toxicity after single-dose carboplatin AUC 7 is generally mild. No excess of toxicity occurs in patients with high Crea-Cl above 125 mL/min, and therefore dose capping is not routinely necessary. In addition, this study provides a rationale for efficient use of healthcare services without compromising patients' safety.

Key questions

What is already known about this subject?

- Some experts and clinical guidelines (Food and Drug Administration, American Society of Clinical Oncology, Gynecologic Oncology Group) recommend capping of the carboplatin dose at a creatinine-clearance (Crea-Cl) of 125 mL/min because of concerns of excessive toxicity. Patients with stage I seminoma receiving adjuvant carboplatin often have high Crea-Cl, but there is a paucity of data on acute haematological toxicities in relation to the different clinical practices and recommendations.

What does this study add?

- Toxicity after single-dose carboplatin area under the curve 7 is generally mild with a low rate (2.7%) of haematological adverse events (hAEs) necessitating clinical interventions.
- No excess of toxicity occurs in patients with carboplatin dosing based on Crea-Cl greater than 125 mL/min.
- No new hAEs other than grade 1 occurred before day 10 and after day 24.

How might this impact on clinical practice?

- This study provides a rationale for efficient use of healthcare services without compromising patients' safety: either omitting routine blood count controls in view of the very low rate of clinically relevant adverse events or timing of regular blood count control at the time of lowest platelet and neutrophil counts (eg, around days 15–22) and omitting any further blood count analyses.

INTRODUCTION

The practice of carboplatin dosing is not concordant among different centres and oncologists—for example, some may use measured actual glomerular filtration rate (GFR) by a radioisotope method, while others prefer to use formula-based estimations of creatinine-clearance (Crea-Cl) from a single serum-creatinine value for the dose calculation according to the 'Calvert-formula'[1 2]; in addition, the issue of dose capping versus non-capping in patients with very high GFR is not resolved. Some experts and clinical guidelines recommend capping of the carboplatin dose at a Crea-Cl of 125 mL/min because of concerns of excessive toxicity in view of changes in assays used to measure

serum-creatinine and alerts by the Food and Drug Administration (FDA) and Gynecologic Oncology Group (GOG).[3 4]

Stage I seminoma is the most commonly diagnosed testis cancer and accounts for ~40%–45% of all testis cancers.[5] The risk of recurrence after tumour orchiectomy is 10%–20%; active surveillance and adjuvant treatment are possible management options.[6] Contemporary guidelines favour active surveillance for seminoma stage I and single-dose carboplatin is listed as adjuvant treatment option.[6 7] Many of the patients receiving single-dose carboplatin area under the curve (AUC) 7 have a very good renal function, and hence high absolute doses of carboplatin are frequently administered: about 50% of patients treated on study protocols and reported in cohorts had a GFR of 125 mL/min and higher.[8 9]

However, there is a paucity of data on acute haematological toxicities in relation to the different clinical practices and recommendations of carboplatin dosing in patients with very high GFR in general and in particular in the adjuvant treatment of patients with seminoma stage I. As a consequence, great variations in monitoring for haematological toxicities, frequency and timing of follow-up visits and insecurity of expectable haematological acute adverse events (hAEs) exist.

In order to fill this gap of knowledge, we conducted a retrospective analysis of haematological toxicities in patients with seminoma stage I and GFR >125 mL/min having received carboplatin without capping compared with those with GFR <125 mL/min and/or having received capped doses. In addition, we analysed the pattern of acute hAEs to offer guidance for monitoring.

METHODS

This is a retrospective analysis of a cohort of patients with stage I seminoma treated with adjuvant carboplatin AUC 7 in routine practice in two Swiss centres between 2005 and 2015.

The main inclusion criteria were a normal blood count at treatment and a minimum of two documented blood count measurements during the first 8 weeks after treatment. The main exclusion criterion was a documented denial by patients to use their data for research purposes.

The following factors were analysed: incidence of hAE, grade of hAE according to common clinical toxicity criteria for adverse events (V.4.0) and time of nadir of hAEs. All factors were separately analysed for patients with Crea-Cl <125 mL/min vs >125 mL/min without dose capping, respectively. Moreover hAEs in patients with and without capping were compared.

Statistical analysis was performed with GraphPad InStat V.3.1a for Macintosh computer software using Tukey-Kramer multiple comparisons test, Fisher's exact test and X^2 test.

Table 1 Baseline characteristics: subgroups according to Crea-Cl (median; range)

	Crea-Cl <125 mL/min n=36	Crea-Cl >125 mL/min No dose capping, n=29	
Age (years)	47 (22–71)	33 (23–53)	P=0.0001
SCr (µmol/L)	79 (51–117)	77 (52–92)	NS
Crea-Cl (mL/min)	109 (70–120)*	143 (125–184)*	
Carboplatin dose (g)	950 (700–1020)*	1200 (1050–1480)*	

*Significant differences due to definition of subgroup.
Crea-Cl, creatinine-clearance; SCr, serum-creatinine.

RESULTS

A total of 92 patient charts were screened, but 18 were excluded for not fulfilling the criteria of two or more documented follow-up blood counts. Seventy-four patients with 229 documented follow-up measurements (median of 3 measurements per patient, range 2–6) were included. Ten patients had carboplatin dosing based on radioisotope measurement of GFR after a change of institutional practice in 2014. The remaining majority of 64 patients had formula-based estimation (Cockroft-Gault) of Crea-Cl.

Sixty-five patients were dosed without capping according to the Crea-Cl received by formula calculation from a single serum-creatinine value (n=55) or measured GFR by radioisotope method (n=10), respectively. In nine patients with Crea-Cl >125 mL/min based on the Cockroft-Gault formula, the carboplatin dose was capped at 1000 or 1050 mg, respectively.

The median age was 41 years (range 22–71), the median Crea-Cl (Cockroft-Gault) was 126 mL/min (range 70–206) and the median carboplatin dose was 1013 mg (700–1477). The characteristics of patients in different subgroups are shown in table 1.

With a median follow-up time of the whole cohort of 60 months (22–136 months), one patient (1.3%) experienced a relapse 24 months after adjuvant treatment and was salvaged with combination chemotherapy.

Overall, a total of 151 hAEs occurred in 70 patients. Four (5.4%) patients had no hAEs. The hAEs were of grade 1 only in 49 (66%) patients, maximum of grade 2 in 15 (22%) patients, maximum of grade 3 in 5 (6.8%) patients and of grade 4 in 1 (1.4%) patient, respectively. Overall, clinical relevant hAE necessitating subsequent clinical interventions occurred in two (2.7%) patients. Decreased platelet count of any grade (69%) was significantly more frequent than decreased neutrophil (43%) and white cell count (36%) (P=0.0027 and P=0.0001, respectively). More detailed information is found in table 2.

Decreased platelet count occurred also significantly earlier than decreased neutrophil and white cell count: the median platelet nadir was on day 15 and the median white cell/neutrophil count nadir was on day 22

Table 2 Haematological adverse events after carboplatin AUC 7: patients with Crea-Cl <125 mL/min vs >125 mL/min and no dose capping

	Crea-Cl <125 mL/min n=36	Crea-Cl >125 mL/min No dose capping, n=29
Anaemia overall	71% (25)	52% (15)
Anaemia grade 1	71% (25)	52%(15)
Thrombocytopaenia overall	56% (20)	76% (22)
Thrombocytopaenia grade 1	44% (16)	55% (16)
Thrombocytopaenia grade 2	11% (4)	18% (5)
Thrombocytopaenia grade 4	–	3% (1)
Leucopaenia overall	36% (13)	48% (14)
Leucopaenia grade 1	33% (12)	41% (12)
Leucopaenia grade 2	3% (1)	7% (2)
Neutropaenia overall	39% (14)	35% (10)
Neutropaenia grade 1	22% (8)	24% (7)
Neutropaenia grade 2	6% (2)	7% (2)
Neutropaenia grade 3	11% (4)	3% (1)
Adverse events with clinical interventions	3% (1 hospitalisation with febrile neutropaenia grade 3)	3% (1 platelet transfusion in thrombocytopaenia grade 4)

The sum of percentages of different grades may differ from percentage of overall due to rounding.
Crea-Cl, creatinine-clearance.

(P<0.0001). Before day 10 and after day 24, no new toxicities higher than grade 1 were documented.

In 36 patients with Crea-Cl <125 mL/min, a total of 74 hAEs (81% grade 1) were documented, corresponding to a mean of 2.1 (95% CI 1.8 to 2.6) hAEs per patient. In 29 patients with Crea-Cl >125 mL/min and no dose capping, a total of 64 hAEs (80% grade 1) were found, corresponding to a mean of 2.2 (95% CI 1.8 to 2.5) hAEs per patient (P=0.84when compared with group with Crea-Cl <125 mL/min). In each group one clinically relevant hAE with subsequent interventions occurred: one case of febrile neutropaenia grade 3 in a patient with Crea-Cl <125 mL/min, and one patient with Crea-Cl >125 mL/min and thrombocytopaenia grade 4 and absence of haemorrhage received one prophylactic platelet transfusion in accordance with institutional guidelines (thrombocyte nadir was 14×10^9/L followed by a rapid increase to 89×10^9/L 1 week later). Overall, this corresponds to a rate of severe, clinically relevant hAEs of 2.8% in patients with Crea-Cl <125 mL/min vs 3.4% in patients with Crea-Cl >125 mL/min, respectively (P=0.89). No statistically significant differences between groups of Crea-Cl <125 mL/min vs Crea-Cl >125 mL/min (no capping) were found (for further details see table 2).

There were no statistically significant differences nor trends between different cohorts.

A capped carboplatin dose at 1000 mg or 1050 mg had been administered in nine patients with Crea-Cl >125 mL/min, which is in line with some recommendations to limit the carboplatin dose to a Crea-Cl maximum of 125 mL/min but consequently results in an AUC <7. This decision was at the individual discretion of the treating physician. In retrospect, the main reasons to apply dose capping were consideration of the alerts by the FDA and GOG on the one hand, and concerns of excessive toxicity in older patients with numerically very high doses (if uncapped) on the other hand. These nine cases were analysed separately: the mean age was 37 years (range 22–56), and the mean carboplatin dose administered was 12.9% lower than the full dose calculated for AUC 7 (median difference 148 mg; range 45–344 mg). A total of 15 hAEs occurred, with a mean of 1.7 hAEs per patient, 87% (13/15) of them were of grade 1 and no clinical interventions were necessary. No statistically significant differences between Crea-Cl >125 mL/min (no capping) versus capping at Crea-Cl 125 mL/min were found. Due to the relatively small number of patients with Crea-Cl >125 mL/min and dose capping (n=9), these results should be interpreted with caution.

In the subgroup of patients with radionuclide GFR measurement (n=10), the mean age was 41 years (range 23–54), and the mean carboplatin dose administered was 1.9% higher (median difference +74.5 mg, range −228 to +178 mg) than if it would have been if based on Crea-Cl from formula estimation (Cockroft-Gault).

A total of 22 hAEs occurred, with a mean of 2.2 hAEs per patient, 77% (17/22) of them were of grade 1. No clinical interventions were necessary. No statistically significant differences between patients with radionuclide measurement of GFR and formula-based estimation of Crea-Cl were found. Due to the relatively small number of patients with carboplatin dose based on GFR measurement (n=10), these results should be interpreted with caution.

In terms of non-haematological adverse events, no signals were observed for relevant acute renal dysfunction as serum-creatinine values in the weeks 1–4 after treatment remained within normal limits with a median of 83 µmol/L (range 48–115) and not significantly different from before treatment with a median at baseline of 79 µmol/L (range 51–117) (P=0.12). No chemotherapy-induced nausea and emesis of grade 3 or greater occurred in this cohort.

DISCUSSION

According to our knowledge, this is the first study to assess toxicities associated with capping versus non-capping of carboplatin doses in patients with seminoma stage I and a very high GFR. It is also the first comparison of hAEs in patients with Crea-Cl above versus below 125 mL/min.

In this patient population the majority of haematological toxicities were very mild and of relatively short duration, with more than 80% of documented hAEs being of grade 1 and more than 70% of patients with no hAEs or grade 1 hAEs only. Of note, grade 1 haematological toxicities are usually asymptomatic and hardly ever affect patients—for example, anaemia with haemoglobin level below normal but >100 g/L. Among 74 patients, only in two patients (2.7%) clinically relevant hAEs necessitating subsequent clinical interventions occurred.

The American Society of Clinical Oncology clinical guidelines as well as some other experts and organisations recommend that capping of the carboplatin dose calculated with the Calvert formula should occur at a Crea-Cl of 125 mL/min due to concerns of excess of toxicity.[3 4] However, our data do not support any of these recommendations in patients with seminoma stage I receiving adjuvant carboplatin: there was no excess of haematological toxicity in patients with Crea-Cl >125 mL/min without dose capping, and there were neither statistically significant nor relevant differences in patients with Crea-Cl >125 mL/min (and no dose capping) compared with below 125 mL/min. In the small subgroup of patients with Crea-Cl >125 mL/min and capped carboplatin dose, the rate of hAEs per patient was numerically lower when compared with those without capping. But the pattern of hAEs with more than 80% being grade 1 was similar in both groups, and the differences are not statistically significant. However, due to the small number of patients in this subgroup (n=9), these results should be interpreted with caution.

Our results should be interpreted with caution in regard to the weaknesses and strengths of this study. The heterogeneity of our data reflects the variations in clinical practice by different oncologists and centres over time. On the other hand this facilitates the generalisability of our results and conclusions for daily clinical practice. It is a retrospective study with a small number of patients. Nevertheless, our conclusions can be substantiated due to the very similar proportion and equal distribution of low-grade toxicities as well as the very few severe hAEs between the different groups with Crea-Cl>125 mL/min or <125 mL/min and capping versus no capping, respectively.

With all the limitations that apply to retrospective studies, it is unlikely that the data are prone to a selection bias of patients with a more favourable post-treatment course. The patients excluded due to missing documentation of blood counts were followed up at their general practitioners, who were instructed to immediately report any toxicities of higher grade. In addition, any clinically relevant complications of higher degree would have been retrospectively captured and documented at the first surveillance visit scheduled at 3 months after treatment.[10] This was not the case in any of the patients excluded due to incomplete documentation of follow-up blood counts during the first 8 weeks after treatment. Taken together these measures are more likely to result in overestimation of severe, relevant hAEs rather than underestimation.

This study focused on acute toxicities, and it was neither designed nor powered to elucidate on chronic and long-term toxicities of single-dose carboplatin AUC 7. However, in the follow-up of the large Medical Research Council (MRC) TE19/European Organisation for Research and Treatment of Cancer (EORTC) 30982 trial, no safety signals concerning long-term toxicities were reported.[8] Therefore it seems unlikely that chronic toxicities after single-dose carboplatin are significantly different between patients with capped or uncapped carboplatin doses.

Our data are also in line with a single-centre retrospective study that identified no significant toxicity in an even smaller number of patients receiving carboplatin with GFR >110 mL/min, who did not have their doses capped. The authors concluded that carboplatin doses should be based on actual GFR and that dose titration at subsequent carboplatin treatments should occur in case of myelotoxicity.[11]

Although radionuclide measurement of GFR is the reference standard for the calculation of the carboplatin dose in patients with seminoma stage I, the majority of our patients had estimations of Crea-Cl from serum-creatinine values by the Cockcroft-Gault formula before radioisotope measurement was introduced at our institutions in 2014.[12–16] According to the published literature, it is reasonable to conclude that the rates of adverse events could be further improved by basing the carboplatin dose on radioisotope-measured GFR, as this eliminates the inaccuracy associated with formula-based Crea-Cl estimations.[12 17–19] In addition, a post-hoc analysis of the large prospective MRC TE19/EORTC 30982 trial revealed that lowering carboplatin doses by 10% was associated with a trend for an increased rate of recurrences (in those patients in whom the carboplatin dose calculation was based on a Crea-Cl estimate from a 24-hour urine collection).[8] However, this has not been reproduced in a cohort from routine clinical practice so far and has been challenged recently.[1]

Using healthcare services efficiently without compromising patients safety will become increasingly important in the future in view of rising healthcare costs, economic constraints and other limitations for healthcare services. In this study we did not find any onset of new hAEs other than grade 1 before day 10 and after day 24. Therefore this study provides a rationale to concentrate any blood count analyses at the time when the thrombocyte nadir and white cell/neutrophil nadir are most likely to occur (median day 15 and day 22, respectively)—if the treating physician regards a routine analysis necessary. In view of the very low rate of clinically relevant toxicities in this series, one could consider to completely abstain from any routine blood count analyses after single-dose adjuvant carboplatin in informed patients with unrestricted access to emergency services. In any case, outside the days 10–24 period, routine blood count analyses can be omitted without compromising patients' safety.

CONCLUSIONS

Toxicity after single-dose carboplatin AUC 7 in the adjuvant treatment of seminoma stage 1 is generally mild. According to our data, no excess of toxicity occurs in patients with higher Crea-Cl above 125 mL/min and therefore dose capping is neither necessary nor indicated and may negatively impact outcome in patients with seminoma stage 1.

In addition, this study provides a rationale for an efficient use of healthcare services with regard to limiting and timing of blood count analysis during the immediate follow-up period without compromising patients' safety.

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