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Clinical Trial

A phase II study of carboplatin AUC-10 guided by positron emission tomography−defined metabolic response in metastatic seminoma

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Abstract *Introduction:* Carboplatin monotherapy for metastatic seminoma at a dose of AUC-10 has shown promising activity. Three or four cycles have been given with most haematological side-effects seen with the 4th cycle. An early response might allow de-escalation of therapy.

Methods: Forty-eight patients with metastatic seminoma (International Germ Cell Cancer Collaborative Group good prognosis) were recruited. Positron emission tomography (PET) scanning was performed before and after one cycle of carboplatin. Those with a Deauville score of 3 or less were given a total of three cycles of carboplatin, the rest received four.

Results: PET scanning allowed 44% to receive three cycles of carboplatin. With a median follow-up of 31.2 months, 95.6% (95% confidence interval: 83.5%−98.9%) were progression free. The overall survival at 2-years was 100%. Lower stage (2A and 2B) disease was significantly (*P* = 0.001) associated with the better metabolic response, but the association was not strong (correlation coefficient = −0.48). Over a third of the blood products given were used to support the 4th cycle. The regimen was well tolerated with a low incidence of grade III neutropenic sepsis or nausea and vomiting (<3% cycles).

Conclusion: Carboplatin AUC-10 monotherapy is effective with low toxicity. Early changes

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during PET scanning may allow de-escalation of therapy in high volume disease—comparison against combination therapy is warranted.

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1. Introduction

Metastatic seminoma is very responsive to current therapies. It is both very chemosensitive and radiosensitive. Seminomas appear more sensitive to both these modalities than non-seminomas. Attempts to reduce toxicity of combination chemotherapy in seminoma using carboplatin was first attempted in the early 1990s. Studies comparing carboplatin 400 mg/m^2 [1] or AUC-5 [2] to combination cisplatin- and etoposide-based chemotherapy with either ifosfamide or bleomycin yielded similar findings namely a lower progression-free survival (PFS) with carboplatin although overall survival in the two studies was not significantly worse. A meta-analysis suggested however that there might be a reduction in overall survival as well [1]. Inadequate dosing of carboplatin might be the reason for this.

Long-term studies looking at the effect of combination cisplatin-based chemotherapy in germ cell tumours have highlighted the significant long-term side-effects—in particular cardiovascular, neurological and second malignancies as well as the predictable but significant acute side-effects. This, despite the excellent overall outcomes using cisplatin and etoposide with or without a third drug, has made the further evaluation of carboplatin monotherapy attractive. In addition, qualitative assessments suggest better physical and psychological functioning with reduced time off work during single-agent carboplatin for metastatic seminoma [3].

We previously conducted a pilot study of carboplatin AUC-10 in metastatic seminoma [4]. In this study, patients were re-scanned at 21 days, those who were in complete remission received a further two cycles and the rest received a further three. The response rate and overall survival was impressive, but it was clear that a lot of the transfusion requirements were concentrated in the 4th cycle. It was also evident that only patients with 2A disease were attaining a complete response (CR) after one cycle. An initial overview of outcome of an unselected group of patients treated by our group showed reassuring PFS and overall survival [5].

We postulated that this was because of the volume of disease at the start and that positron emission tomography—computerised tomography (PET-CT) scanning would allow us to identify patients who had responded well but still had residual masses after 21 days. It was therefore proposed to prospectively evaluate PET scanning in metastatic seminoma. As there were no data to use to define what constituted a complete metabolic response in this disease, we chose to adopt the Deauville criteria used to assess response in lymphoma [6]. We therefore set up the Car-PET study with the primary end-point of PFS rate at 2 years and the secondary end-points of toxicity and metabolic response rate.

2. Material and methods

2.1. Study population

Patients with metastatic chemotherapy and radiotherapy naïve seminoma who had International Germ Cell Cancer Collaborative Group (IGCCCG) good prognosis disease (i.e. no non-pulmonary visceral metastases) were recruited into the study at two centres, St Bartholomew's Hospital and Mount Vernon Hospital, both in London, United Kingdom. Inclusion criteria included creatinine clearance of over 25 ml/min (assessed preferably using an ethylenediaminetetraacetic acid [EDTA] clearance), performance status 0–3, male sex and age range between 18 and 75 years. Exclusion criteria included any patient with non-pulmonary visceral metastases, previous chemotherapy or retro-peritoneal radiotherapy and raised alpha-fetoprotein. Patients were required to give written informed consent. The trial had ethical review and is registered on clinicaltrials.gov, identifier NCT02272816, and with https://www.clinicaltrialsregister.eu, EudraCT number 2009-009882-33.

2.2. Study design

Patients required a fluorodeoxyglucose PET-CT scan prior to study entry and a formal EDTA clearance to measure glomerular filtration rate (GFR). Carboplatin AUC-10 according to the Calvert formula ($10 \times$ GFR (ml/min) $+ 25$) mg was given in 5% glucose over 1 h every 21 days. Standard antiemetics were employed (5HT3 antagonist and dexamethasone prior to therapy followed by two days of oral dexamethasone and metoclopramide). A repeat PET-CT scan was carried out on day 17–21 of the first cycle. The PET-CT scans were centrally reviewed. If the PET-CT scan showed a CR (Deauville ≤3), the patient would stop after three cycles. If the PET-CT showed persistent activity

(Deauville >3), then patients went on to have four cycles in total, see Figure 1. There was no routine use of growth factors. Filgrastim was given in cases where white cell recovery was delayed or in symptomatic neutropenia only.

2.3. Overall response

Overall treatment responses were measured using the same criteria described in our previous phase II study [4], which are consistent with other published reports. Progressive disease (PD) was defined as the development of new sites of disease with rising tumour markers if present. Stable disease was defined as the lack of any new sites of disease and a <90% reduction in tumour markers, 28 days after chemotherapy. Marker-positive partial response (M + ve PR) was defined as a >90% reduction in tumour markers (without normalisation) for ≥ 28 days, and no new sites of disease. Marker-negative PR (M-ve PR) was defined as a normalisation of tumour markers and no new sites of disease for ≥ 28 days. For those patients who had normal
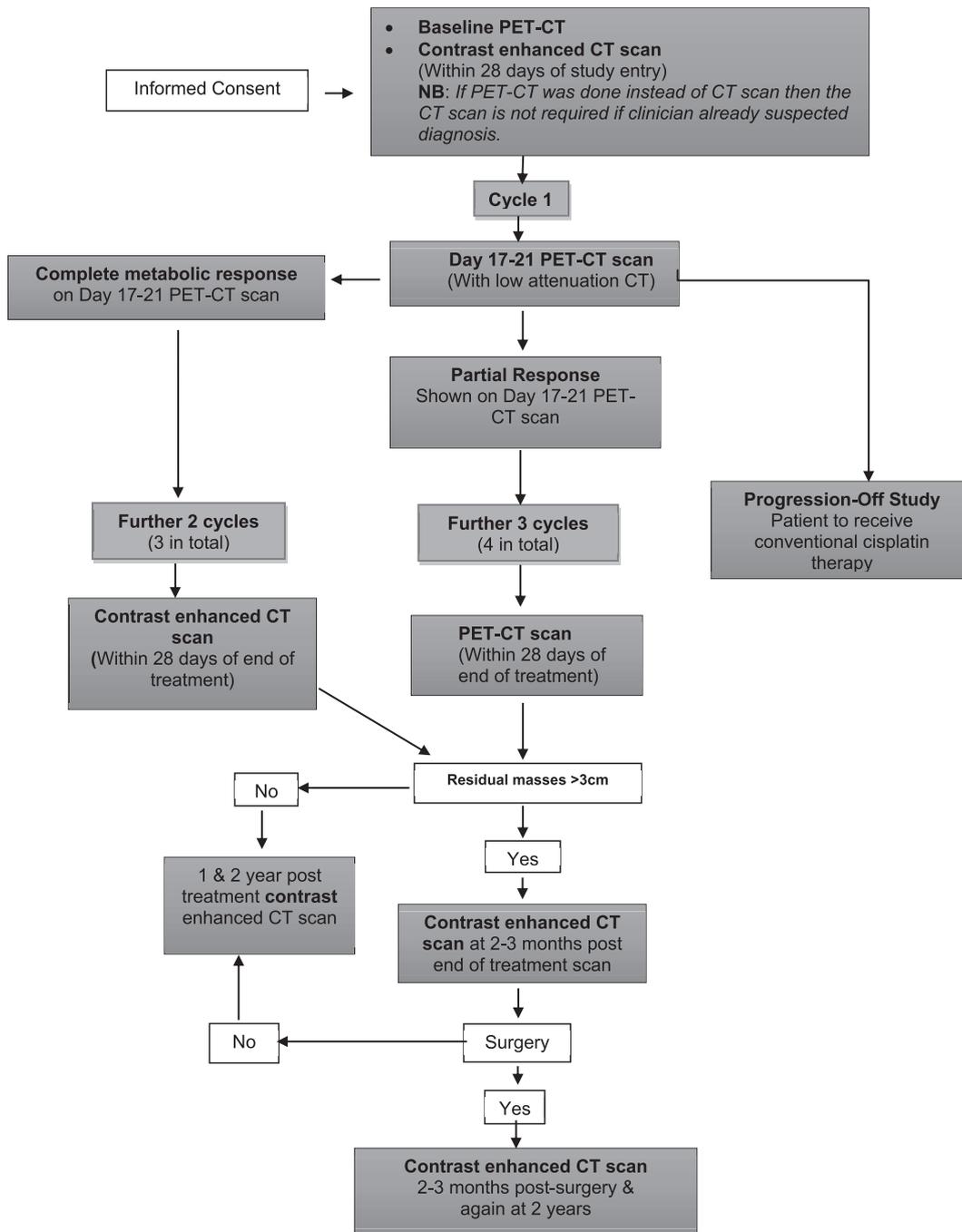

Fig. 1. Treatment flowchart. PET-CT, positron emission tomography−computerised tomography.

tumour markers before chemotherapy, a M-ve PR required a ≥ 50% reduction in the bidimensional measurements of the residual masses to be maintained for ≥28 days. CR was defined as a normalisation of tumour markers with a complete resolution of all sites of disease. Postsurgical outcome was defined as outcome after surgery performed to remove all sites of disease, and patients who achieved a radiological CR to chemotherapy alone or had a surgically induced CR were deemed to have no evidence of disease.

2.4. PET-CT assessment

There are currently no validated metabolic response criteria for PET-CT in seminoma. Hence, we used the Deauville criteria for assessment of response developed for the evaluation of lymphoma [6]. This is shown in Table 1. All PET-CT scans were centrally reviewed at University College London Hospitals NHS Foundation Trust.

2.5. Dose reductions and delays

These are shown in Figure 2. If the bloods were not up to treatment on the planned date, a dose delay of 48 h was permitted according the schedule below. Importantly, dose reductions were only made for platelet counts of $<20 \times 10^9$/l.

2.6. Statistical analysis

The primary objective was to gain a preliminary indication on whether carboplatin AUC-10 is worthwhile considering in a phase III study, using the PFS rate as a criterion. A'Hern's single-stage procedure is used to estimate the number of patients required [7]. The primary outcome was the percentage of patient's progression-free at 2 years. Therefore, all patients had at least 2-years follow-up (unless they had died or their disease had progressed). Previous studies [1,2] showed that carboplatin AUC-10 should not have a 2-year PFS rate of 75% or less, and it would only be worth considering in a phase III study if the true rate were 90% or more. Based on this information A'Hern's single-stage design

Table 1
Deauville criteria.

Degree of glucose uptake	Deauville criteria	Metabolic response
No uptake	1	Complete
Equal to mediastinal blood pool	2	Complete
Equal to the liver	3	Complete
Moderately increased > liver	4	Partial
Markedly increased > liver and/or new lesions	5	Progressive disease

yield a sample size of 45 patients, with 80% power and one-sided test of significance at the 5% level. To allow for a 10% drop-out rate, the intention was to recruit up to a maximum of 50 patients if needed.

The primary efficacy end-point was the PFS rate at 2 years measured from the date of study enrolment to the date of disease progression or death. Patients who did not complete 2-year follow-up for reasons other than death were censored at the last date of follow-up. The PFS rate was determined for the carboplatin AUC-10, along with a one-sided 95% confidence interval according to the Kaplan-Meier method. Standard techniques of descriptive statistics were used. The association between disease stage and metabolic response was calculated using Spearman and Kendall's rank correlation coefficients and tested using Fisher's exact test.

The analysis of safety included all patients who received at least one cycle of treatment. Safety and tolerability of carboplatin AUC-10 are determined by an evaluation of changes in laboratory parameters, vital signs, the incidence and severity of adverse events and of toxicities according to the Common Terminology Criteria for Adverse Events classification (version 4.03).

3. Results

Between February 2012 and May 2015, 48 patients were consented and started treatment with carboplatin. One patient was withdrawn from treatment after cycle 1.

Patient demographic and tumour characteristics are shown in Table 2. Out of 48 patients, 46 were testicular and two were extragonadal. Twenty-seven percent (13) patients had stage 2A disease, 48% (23) had stage 2B disease and 23% (11) had stage 2C disease. The median age was 36 years (24–66). One patient had a mediastinal primary seminoma. Twenty-five percent (12) of patients had a raised beta-human chorionic gonadotropin, and 27% had raised lactate dehydrogenase. Forty-three patients had their GFR calculated from a formal EDTA clearance. The EDTA clearance range was large (68–236 ml/min) with a median of 106 ml/min. All patients had a PET-CT scan prior to cycle 2.

Twenty-one had a metabolic CR with the first cycle of treatment and went on to receive a total of three cycles. Twenty-six (excluding the patient who dropped out) had a PR and went on to receive a total of four cycles.

Eight of the 21 metabolic CRs had at least a radiological PR prior to cycle 2, and the overall results are shown in Table 3. Of note, the number of patients with 2A, 2B and 2C disease having three or four cycles were respectively (9, 4); (12, 10) and (0, 11). Fisher's exact test showed a significant association between lower stage disease and lower cycles of treatment received ($P = 0.001$). Similarly, Fisher's exact test between disease stage and metabolic response at the end of cycle 1 showed that there was a significant association between
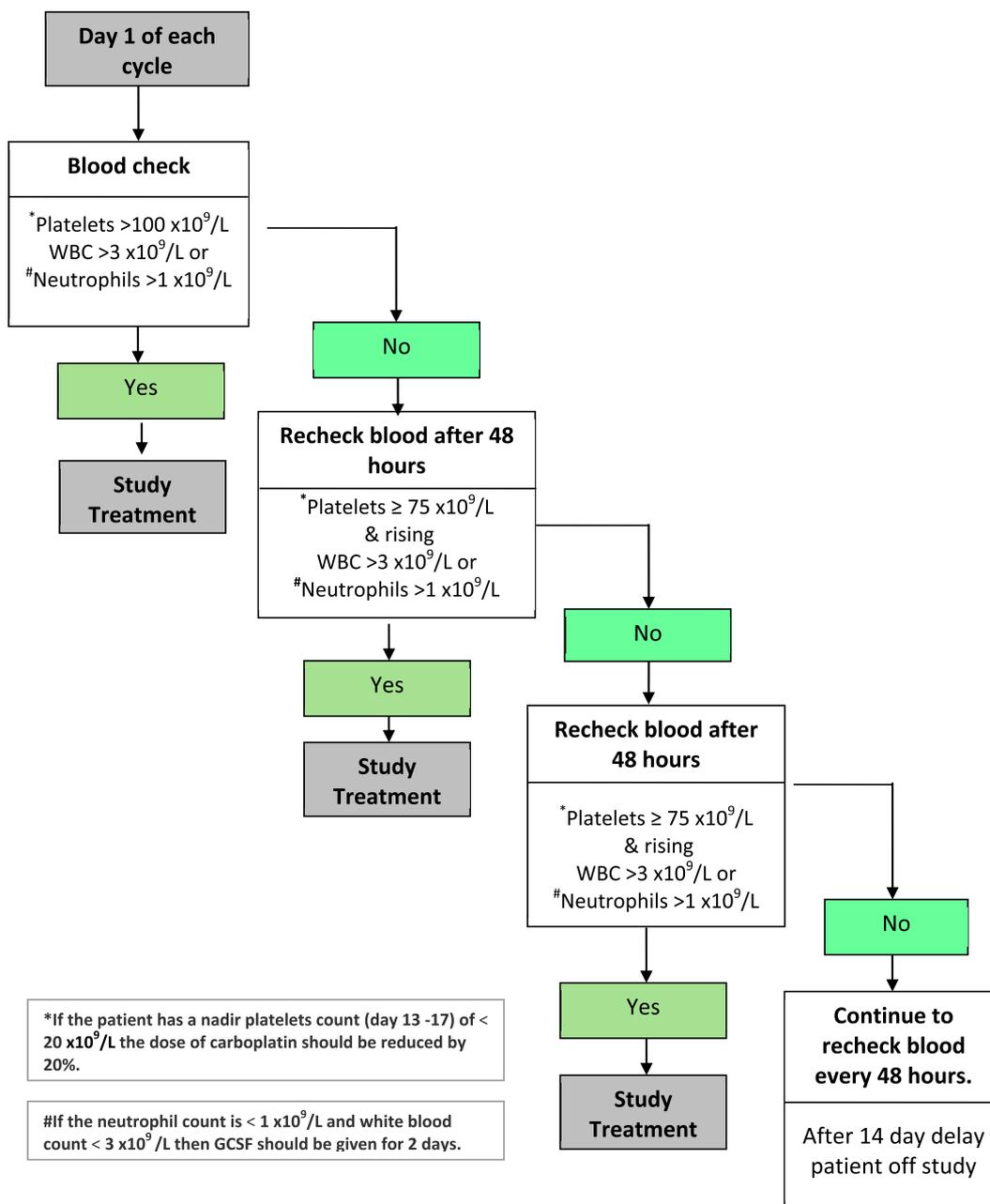
Fig. 2. Blood count guide prior to treatment. WBC, white blood cells.

lower stage disease and better metabolic response ($P = 0.001$), see Table 3; however, the association was not strong (Spearman rank correlation rho $= -0.48$, $P < 0.001$; Kendall's tau-b $= -0.46$, $P = 0.001$).

In the trial, 95.6% (46/48) (1-sided 95% CI: $\leq$ 98.6% and 2-sided 95% CI: 83.5%–98.9%) patients were progression-free at 2 years. Two patients progressed at 14 and 24 months, respectively, and both patients had had a partial metabolic response to carboplatin and a radiological partial response overall. One patient aged 39 years with stage 2B disease had previous traumatic spinal damage and poor bladder emptying requiring intermittent self-catheterisation; he had a large bladder stone which was a source of infection. He received four cycles of carboplatin relapsed 24 months later with an isolated dural metastasis presenting with headaches, and this radiologically appeared to be a meningioma but when excised was found to be seminoma. He had no other sites of progression; he received bleomycin, etoposide and platinum (BEP) chemotherapy and is currently progression-free. The other patient aged 59 years had stage 2C disease, he received 4 cycles of carboplatin. He relapsed 14 months later, and went on to have further treatment initially with BEP which failed and then high dose chemotherapy and stem cell transplant and was alive with disease at the time of data lock.

Table 2
Patient demographic and tumour characteristics at baseline.

Characteristic	Statistics
Number of patients	48
Age in years: median (range)	36 (24 − 66)
Primary tumour	
Testis	46
Mediastinum	1
Retroperitoneum	1
Sites of metastases	
Lung	2
Lymph nodes	29
Other	9
ECOG PS	
0	41
1	2
Missing	5
Stage, number (%)	
2A	13 (27%)
2B	23 (48%)
2C	11 (23%)
NA (Mediastinal)	1
Tumour markers	
AFP:	All normal
BHCG: median (range)	1 (1-102)
normal (<3)	36
Raised	12 (3-7: 8, 8-100: 3 and >100:1)
LDH: median (range)	406 (<190-2657)
Normal (LDH<ULN:480)	34 (71%)
Raised (LDH≥ULN & LDH<3xULN)	11 (23%)
Raised (LDH≥3xULN)	2 (4%)
Missing	1 (2%)
GFR: median (range)	106ml/min (68-236)
EDTA	43 (GFR>120ml/min: 9)
Calculated clearance	05 (GFR>120ml/min: 4)

ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; LDH, lactate dehydrogenase; GFR, glomerular filtration rate; EDTA, ethylenediaminetetraacetic acid; BHCG, beta-human chorionic gonadotropin.

There were no deaths at the time of data lock. The patient withdrawn from the treatment after cycle 1 (partial metabolic response) had developed severe Raynaud's phenomenon and gastrointestinal bleeding due to gastric antrum vascular ectasia. He had stage 2A disease and completed treatment with paraaortic irradiation and is progression free.

The number of patients requiring a dose reduction was nine. This was because of low platelets ($<20 \times 10^9$/l) in cycle 3 or 4. The median cycle length was 22 days between cycle 1 and 2 (range: 21−28), and 45% received treatment on time, 21% were delayed by up to 2 days, 28% by 2−5 days and 6.4% by more than 5 days. The median cycle length between cycle 2 and 3 was 23 days (range: 21−27); 40% received the treatment on time, 30% were delayed by up to 2 days, 28% by 3−5 days and 2% by more than 5 days. The median cycle length between cycle 3 and 4 was 23 days (range: 21−31); 32% received the treatment on time, 36% were delayed by up to 2 days, 24% by 3−5 days and 8% six more than 5 days.

In the first three cycles, eight out of 47 patients required blood products: six required red cells alone, and two required red cells and platelets. Of the 26 patients requiring four cycles, five required blood products: red cells in four and platelets alone in one.

Grade III and IV toxicities are shown in Table 4. Non-haematological toxicity was very low. The number of grade III febrile neutropenic episodes was in 2.4% of cycles. This was despite the absence of prophylactic antibiotics or routine use of growth factors. The number of cycles complicated by significant nausea/vomiting (grade III) was 3%.

The neurological toxicity was low, and there was no grade II or higher neuropathy. There were six occurrences of grade I sensory neuropathy. The number of cycles complicated by tinnitus was 7% by grade I and 2% by grade II. There was only one occurrence of grade III ototoxicity (tinnitus), three occurrences of grade II tinnitus and 12 occurrences of grade I tinnitus. Although 13 patients reported tinnitus, it had resolved in 11 by cycle 4. In the single patient who reported grade III tinnitus, it had reduced to grade I by cycle 4.

Haematological toxicity was predominantly anaemia. A total of 27 units of blood were given to eight patients, four received blood on the 4th cycle. Platelet transfusions were required by four patients.

Overall, patients with EDTA>120 ml/min experienced less than half of the toxicities than those with EDTA≤120 ml/min. For example, grade III anaemia, neutropenia and thrombocytopenia occurrences were 5.4%, 15.5% and 15.5% of cycles, respectively, among the patients with EDTA≤120 ml/min while the respective occurrences were 1.2%, 6.5% and 2.4% of cycles in patients with EDTA>120 ml/min.

Table 3
Association between disease stage and patient responses at the end of cycle 1 and the final radiological response at the end of treatment.

Metabolic response assesment after cycle 1 and overall radiological response at end of treatment		Disease stage			
		2A	2B	2C	Total
Metabolic response at cycle 1	CR	9	12	0	21
	PR	4	11	11	26
	Total	13	23	11	47
Overall response	CR	11	18	3	32
	PR-ve	2	3	7	11
	SD-ve	0	1	1	2
	Total	13	22	11	46

CR, complete response; PR, partial response.
Fisher's exact test (between metabolic response and disease stage) $P = 0.001$.

4. Discussion

This study has demonstrated excellent efficacy in metastatic seminoma using single-agent carboplatin AUC-10.

Table 4
Grade III/IV toxicities per cycle delivered and the number of patients affected.

Grade III/IV toxicity	Number of cycles—affected (%)[a]	Number of patients by grade III/IV toxicity
		48
Neutropenia	43 (25.6)	24
Thrombocytopenia	33 (19.6)	21
Anaemia	12 (7.1)	9
Fatigue	3 (1.8)	3
Febrile neutropenia	4 (2.4)	3
Vomiting	3 (1.8)	3
Nausea	2 (1.2)	2
Mucositis (oral)	2 (1.2)	1
Pain	2 (1.2)	2
Diarrhoea	1 (0.6)	1
Headache	1 (0.6)	1
Insomnia	1 (0.6)	1
Tinnitus	1 (0.6)	1
GI toxicity bleed	1 (0.6)	1
Total	109 (65%)	

[a] Percentages are calculated based on total 168 cycles of treatment.

The results are comparable with those using combination cisplatin-based therapy but with more modest non-haematological toxicity. The use of PET-CT allowed the number of patients receiving four cycles to be reduced to 43% compared with the approach we had previously used using radiological CR after one cycle. This suggests that using PET-CT in this way was effective in sparing patients a final cycle of chemotherapy. However, we do not know whether the 4th cycle was needed at all. There was a significant association between the volume of disease prior to therapy and the chance of achieving a metabolic CR. A pragmatic argument can be made for using the volume of disease at the start and deciding on how many cycles a patient is going to have rather than relying on a PET-CT during therapy. This would mean simply giving all patients with stage 2A and 2B disease three cycles and those with greater disease four cycles. However, the association was not strong enough (rho = −0.48) to rely on simply volume of disease rather than PET-CT. Both patients who relapsed in this study and the patient who relapsed in our pilot study had received four cycles of carboplatin—suggesting that underdosing in terms of cycles was not the cause of relapse.

The lack of acute toxicity within this study was striking—the fact that these results were achieved with a simple 1-h infusion makes this therapy very patient friendly. Most patients had minimal delay between cycles and few required dose reductions during treatment (9 patients). There was no hair loss with this therapy.

Previous studies have demonstrated good outcome with lower doses of carboplatin but with the addition of other agents (e.g. cyclophosphamide)—this is likely to be less attractive because haematological toxicity is still significant with many patients requiring platelet transfusions [8] and the increased risk of infertility.

Metastatic seminoma is becoming more frequent. Stage 1 disease is increasingly managed by surveillance. Adjuvant therapy in the stage 1 setting reduces risk of recurrence [9], although some have claimed that single agent carboplatin in this setting is not effective enough for it to become standard of care [10].

The use of radiotherapy in this setting is associated with second cancers. Surveillance for stage 1 disease means that there will be more recurrences requiring therapy. For stage 2A/B disease, the low volume mean's high cure rates can be obtained using radiotherapy or induction chemotherapy followed by radiotherapy [11]—both present problems in terms of the risk of secondary malignancies—a situation analogous to Hodgkin's lymphoma [12]. For more advanced disease (2C and above) combination chemotherapy is usually used [13].

To date carboplatin at least in the adjuvant setting has not been associated with secondary malignancies or raised cardiovascular risk—unlike the situation with combination cisplatin-based therapies. A majority of patients failing single-agent chemotherapy can be salvaged with combination chemotherapy (most frequently BEP).

This study has shown that haematological toxicity remains a weakness for this approach; however, a stricter transfusion policy—limiting red cell transfusion to patients with haemoglobin less than 70 g/l, would probably reduce this further. Some treatment delays were due to slow recovery of neutrophil counts—again as so few episodes of neutropenia were accompanied by fever—reducing the lower limit to proceeding with the treatment to 0.5×10^9/l would probably reduce delays.

The range of renal function in this study was quite broad, and there was no suggestion that patients with uncorrected (for surface area) renal function with GFR> 120 ml/min were more likely to develop low blood counts. This confirms the validity of using uncorrected GFR when using the Calvert formula and no cap on total carboplatin dosage should be used.

This study has obvious shortcomings, and it is a single-arm phase II study limiting the confidence we can have that the results would not have been better with combination chemotherapy. The ototoxicity recorded was symptomatic, and formal audiograms were not carried out, and it is clear that carboplatin at this dose is not free from ototoxicty. The absence of formal audiograms is clearly a weakness of this study. We cannot directly comment on long-term toxicity.

In conclusion, carboplatin monotherapy is an effective for metastatic seminoma, the convenience and low number of acute side-effects make it worthy of consideration in the management of metastatic good prognosis seminoma. PET scanning after one cycle may allow a reduction in therapy, but the case for this has not been proven.

Ethics approval and consent to participate

Ethics approval for the study was obtained from the London—City & East Research Ethics Committee. All patients provided written informed consent prior to participation in the study. The study was performed in accordance with the declaration of Helsinki.

Consent for publication

The manuscript does not include any personal data.

Availability of data and material

Data is held centrally by the Centre for Experimental Cancer Medicine, Queen Mary University of London.

Authors' contributions

J.S. was the Chief Investigator of the study.

C.C. coordinated operational aspects of the study.

J.S., R.S., N.S., A.S., K.M. and G.R. were involved in recruitment, clinical care and data returns.

R.S. performed central review of PET scans for the study.

P.W. provided statistical support for the study.

S.J.S. was the study statistician and performed the main analysis for the study.

J.S. and S.J.S. compiled the manuscript with input and support from R.S., N.S., A.S., K.M., C.C., P.W. and G.R.

Conflict of interest statement

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.04.013.

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