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Carboplatin Dose in Combination Chemotherapy for Testicular Cancer

Stephen J. Harland, Lindsay A. Gumbrell and Alan Horwich

Carboplatin was given in escalating doses in combination with etoposide and bleomycin (CEB) to 36 patients with testicular cancer. The platelet nadirs but not the white cell nadir correlated significantly with the dose of carboplatin administered. The best correlation was seen with area under the curve (AUC) calculated from a knowledge of the glomerular filtration rate (GFR). A further 40 patients were treated with a carboplatin dose calculated to give an AUC of 4.6 or 5.0 mg.min/ml. From the first part of the study it was predicted that 5–10% of the patients would have significant thrombocytopenia with the first course of treatment. The observed incidence was in fact 5%. When dose escalation and reduction were carried out for platelet nadirs falling outside the range 50–100×10⁹/l the average cumulative dose after four courses of carboplatin was very similar to four times the starting dose. Furthermore, as many reductions as escalations were carried out. Thus a starting dose for carboplatin calculated to give an AUC of 5.0 mg.min/ml in the CEB combination is one which will produce an acceptable level of thrombocytopenia. The CEB combination was found to produce a cumulative suppression of platelet nadirs. A mean net fall in haemoglobin of 7.5–9.5% was seen with each cycle.
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INTRODUCTION

THE COMBINATION of bleomycin, etoposide and cisplatin (BEP) is frequently successful in curing metastatic testicular cancer [1–3]. The schedule is toxic and much of the toxicity relates to the inclusion of cisplatin which can damage the kidney and the acoustic and peripheral nerves. In addition it is necessary to accompany the administration of cisplatin with large volumes of intravenous saline and it is customary to spread the drug administration over several days. Carboplatin, an analogue of cisplatin, causes less of the above toxicities and requires no saline infusion [4]. Used in ovarian cancer, the two drugs appear to havecn equivalent efficacy [5,6]. If the same is true for testis cancer substitution of carboplatin for cisplatin in the BEP combination would be desirable.

Carboplatin, however, is more myelotoxic than cisplatin and it is to be anticipated that combination with etoposide — also myelotoxic — may not allow its use at full dosage. It is likely that the dose of cisplatin used in testicular cancer regimes is critical for its efficacy [7]. Studies of the CEB regime (carboplatin, etoposide, bleomycin) suggest that this is also true for carboplatin. There may be a dose of carboplatin in this combination at which the myelosuppression is acceptable and where the efficacy is equivalent to that of cisplatin.

We describe here a study to determine an appropriate dose by analysis of the haematological response first to a range of doses and subsequently to two selected dose levels. Doses were initially given on the basis of body surface area but when haematological outcome was shown to be more closely related to patients' renal function they were calculated from the glomerular filtration rate (GFR).

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Table 1. Correlation between carboplatin exposure and haematological indices

Variables	*r*	*P*
Dose and first platelet nadir	0.47	0.002
AUC and first platelet nadir	0.67	<0.00001
AUC and first platelet nadir, %*	0.51	<0.002
Dose and lowest platelet count	0.37	<0.05
AUC and lowest platelet count	0.47	0.002
AUC and lowest platelet count, %	0.39	<0.05
Dose or AUC and first WBC nadir	–	NS
Dose or AUC and first WBC nadir	–	NS
Dose or AUC and lowest WBC	–	NS
AUC and lowest WBC %	0.008	0.96
Dose and % fall in Hb†	0.42	<0.02
AUC and % fall in Hb	0.45	<0.01

Dose in mg/m^2. AUC calculated from equation (1). Hb = haemoglobin, WBC = white blood cells.

*Percent of pretreatment value.

†Comparison was made between the values of Hb before treatment and before the third cycle of chemotherapy, to avoid the influence of transfusion.

METHODS

Patients with testicular cancer were given four courses of etoposide (120 mg/m^2 intravenously daily for 3 days) together with carboplatin on day 1, every 3 weeks. Bleomycin 30 mg was given intravenously for 12 weeks. The dose of carboplatin was given in an escalating fashion between 300 and 450 mg/m^2 in the first 36 patients. The dose in individual patients did not vary unless dangerously low white cell and platelet counts resulted.

Subsequent patients received a dose of carboplatin calculated to give an area under the plasma concentration × time curve (AUC) of 4.6 (20 patients) and 5.0 (20 patients) mg.min/ml. This dose was derived from the formula of Calvert *et al.* [8]

$$\text{dose (mg)} = f(\text{GFR} + 25) \qquad (1)$$

where f is the desired AUC (mg.min/ml) and GFR is glomerular filtration rate in ml/min.

The dose in the latter 40 patients was commonly altered in 10% increments in the second, third and fourth courses if the platelet nadir fell outside the range 50–100 × 10^9/l.

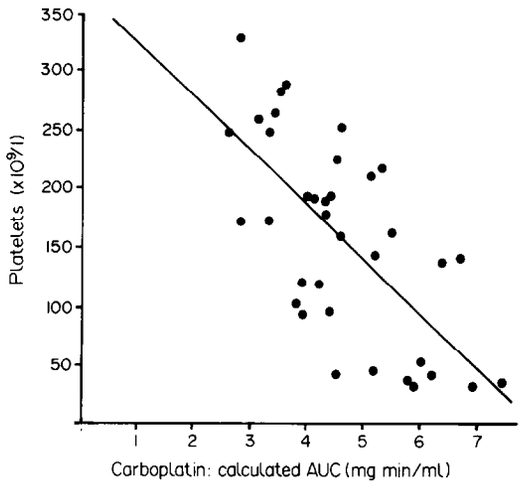

Fig. 2. Correlation of first platelet nadir with calculated AUC.

GFR was determined before treatment in all cases by ^{51}Cr EDTA clearance measurement. Haemoglobin, white cell and platelet counts were performed at weekly intervals. Body surface areas were derived from height/weight nomograms. For the purposes of analysis the carboplatin AUC of the first 36 patients was calculated from equation (1) with knowledge of the other variables. Linear regression analysis and calculation of prediction limits was by standard techniques.

RESULTS

Patients treated with escalating doses

Both dose in mg/m^2 and calculated AUC [from equation (1)] correlated with the first platelet nadir and the lowest platelet count throughout the treatment course (Table 1). Neither expressing the counts as a logarithm nor as a percentage of the pretreatment levels improved the correlation coefficient when compared to the crude platelet nadir. Correlation with dose in mg/m^2 (shown for first platelet nadir in Fig. 1) was worse than with calculated AUC (Figs 2 and 3).

The dose of carboplatin was not a determinant of the degree of leukopenia, but was significantly correlated with the percentage fall in haemoglobin.

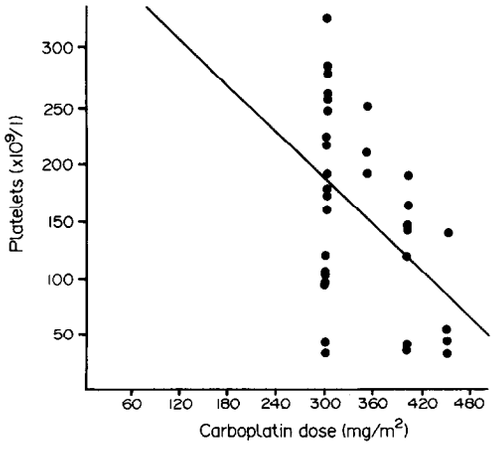

Fig. 1. Correlation of first platelet nadir with dose in mg/m^2.

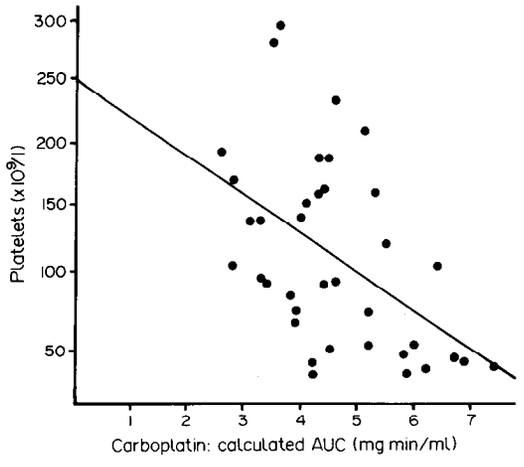

Fig. 3. Correlation of lowest platelet nadir with calculated AUC.

Table 2. Predicted risk of developing thrombocytopenia ($50 \times 10^9/l$)

	Carboplatin AUC (mg.min/ml) 4.6		5.0	
	Predicted	Observed*	Predicted	Observed*
Following first course	5%	5%	10%	5%
With all courses	17.5%	39%†	25%	50%†

The predicted figures were derived by setting the linear regression programme with different confidence limits.
*In 20 patients.
†Doses were varied in the majority of patients if a platelet nadir outside the range of 50–100 × 10^9/l was seen.

Patients treated with AUC = 4.6 and 5.0 mg.min/ml

The data from the first 37 patients, shown in Figs 2 and 3, led to the decision to treat patients with a dose of carboplatin calculated to produce an AUC of first 4.6 and subsequently 5.0 mg.min/ml. The predicted risks of thrombocytopenia at these two dose levels are shown in Table 2. The incidence of thrombocytopenia observed (Table 2) matched the predicted values well for the first course of treatment. Thrombocytopenia occurred more often than predicted in subsequent courses. The majority of patients whose platelet nadir fell above 50–100 × 10^9/l after the first course had received a dose escalation, and this may account for the discrepancy.

The actual platelet nadirs at the two dose levels were not significantly different from each other (Fig. 4). There was a wide scatter of values.

A rigid policy of dose reduction for a platelet nadir of less than 50 × 10^9/l and escalation for a nadir of more than 100 × 10^9/l was applied in 26 patients and it can be seen in Fig. 5 that escalation and reduction were applied equally often.

In one third of cases where an escalation took place the dose was revised down again in a subsequent course. The mean dose per course for each patient — which would suggest the ideal starting dose — was very similar to the starting dose in the majority of cases (Fig. 6).

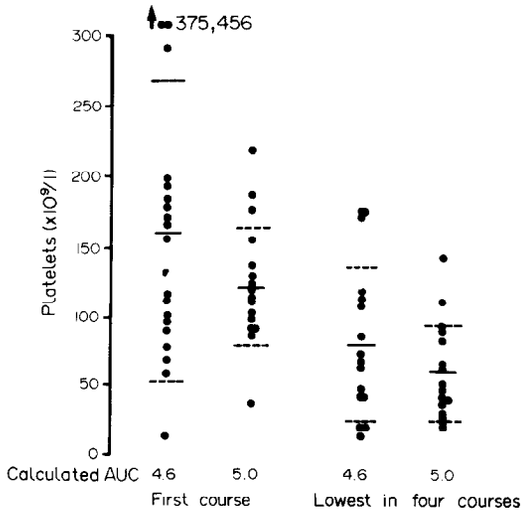

Fig. 4. Platelet nadirs on CEB chemotherapy at two dose levels. Means and standard deviations are shown.

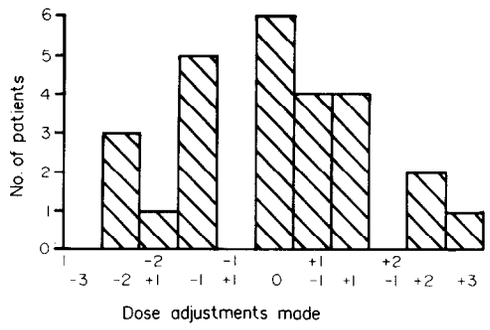

Fig. 5. Number of 10% dose adjustments made in individual patients when this policy, based on the preceding platelet nadir, was practised. + indicates increase(s) in dosage; − indicates decrease(s).

Cumulative haematological toxicity

The question of whether haematological toxicity was cumulative was addressed using data from patients from both parts of the study whose initial carboplatin dose had a calculated AUC between 4.3 and 5.3 mg.min/ml and in whom dose escalation was not practised. Mean platelet nadirs following the third and fourth courses were significantly lower than that seen after the first course by 37% and 34%, respectively (Fig. 7).

Whereas there was a tendency for mean total white cell count to fall further (up to 19%) with the third and fourth courses compared to the first, this difference did not reach significance (Fig. 8). Each cycle of chemotherapy produced a mean net fall of 7.5–9.5% in haemoglobin level (Fig. 9).

Of 34 patients treated with a dose of carboplatin of 4.6 or 5.0 mg.min/ml, 15 (44%) received red cell transfusions. The usual indication was a haemoglobin level of less than 9.5 g/dl.

Despite the high frequency of thrombocytopenia in this study, only 1 patient, who had advanced poor prognosis disease and renal impairment, required a platelet transfusion — at a time when he had a septicaemia. 1 other patient suffered a septicaemic illness.

DISCUSSION

In comparative single agent and combination studies, carboplatin appears at clinically tolerable doses to be as efficacious

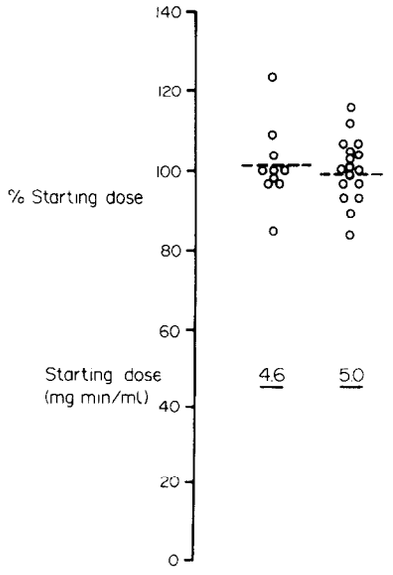

Fig. 6. Mean dose per course of carboplatin received when a policy of dose adjustment according to platelet nadir was pursued.

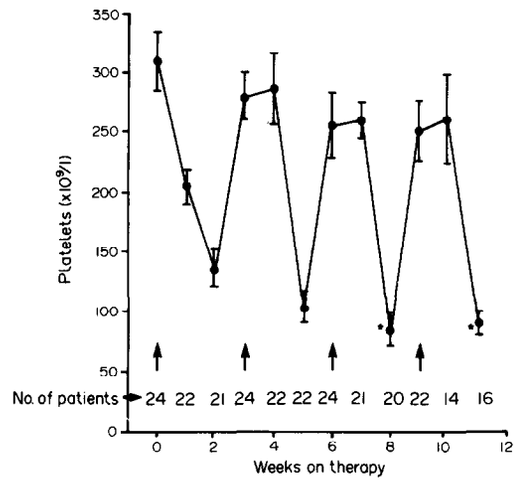

Fig. 7. Platelet counts on CEB chemotherapy (mean, S.E.). Only patients treated at a constant carboplatin dose (4.3–5.3 mg.min/ml) included. Heavy arrows indicate the administration of chemotherapy. *P=<0.05 compared to week 2 (Student's t test).

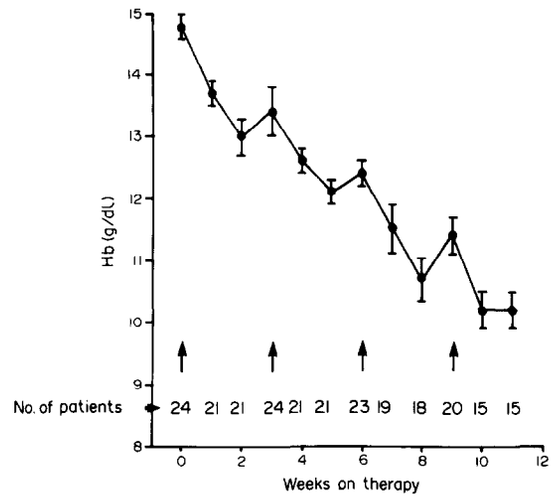

Fig. 9. Haemoglobin levels on CEB chemotherapy (mean, S.E.). The patients and the symbols are the same as in Fig. 7. Patients were censored when they had been transfused.

as cisplatin [5,6]. Its limiting toxicity — thrombocytopenia — is reversible, whereas in the case of cisplatin renal and neurotoxicity are largely irreversible. The desirability of using carboplatin in patients with good prognosis is therefore apparent, aside from any consideration of subjective toxicity and duration of hospital stay which also favour the newer analogue. Giving a platinum compound with more haematological toxicity in combination with bleomycin and etoposide might involve reducing the dose from that given in single agent studies. This in turn might compromise the efficacy of the combination.

The dose of carboplatin given in the CEB combination is critical to its success or failure [9]. Randomised studies currently in progress are evaluating whether CEB is as efficacious as BEP in testicular cancer — the response data on the patients described here [9] suggests that this is indeed the case when good prognosis disease is considered. This study has addressed the problem of the optimum dose for carboplatin given with etoposide 120 mg/m^2 daily for 3 days and bleomycin. The findings may not be the same when the dose of etoposide is different. Cytotoxic drugs are usually prescribed on the basis of a patient's surface area. In large populations both renal and hepatic function are related to this but the variability is considerable. For carboplatin there appears to be no hepatic metabolism. Calvert *et al.* [8,10] have demonstrated that AUC can be calculated from a knowledge of the glomerular filtration rate alone, patient size not being a determinant. Thus a patient with a large volume of distribution will have a low initial plasma level which will fall relatively slowly, whilst the same kidneys in a patient with a small volume of distribution would cause the more rapid fall of an initially high plasma level. In both cases the total drug clearance and AUC will be very similar, differences being accounted for by the greater covalent binding to tissues in the larger patient.

In this study covering a limited dose range no relationship between white cell nadir and dose of carboplatin has been demonstrated. It has been shown, however, that thrombocytopenia is related to dose of carboplatin and that this relationship is closer when dose is expressed in terms of calculated AUC based on a GFR measurement, than in mg/m^2. Egorin *et al.* [11] using carboplatin alone showed that the AUC correlated better with the percentage fall in platelet count than the absolute nadir count. This was not shown to be the case here. Using a starting dose where the calculated AUC is 4.6 or 5.0 mg.min/ml produces a dose nearer to the ideal than one based on mg/m^2. Clearly discrepancies between the two methods arise when small men have very good renal function and *vice versa*.

There is still a lot of variation in the first platelet nadir (Fig. 4). 6 out of 26 patients whose doses were adjusted after inspection of the platelet nadir in the previous course required a 20% or more change in dose to achieve a nadir of 50–100 × 10^9/l (Fig. 5). As 3 of them were adjusted upwards, and 3 downwards it is likely that these starting doses are about right.

Finally it should be noted that although thrombocytopenia was a frequent occurrence in this series (Table 2) a platelet transfusion was given on only one occasion. Thrombocytopenia appears to be well tolerated in otherwise fit young men.

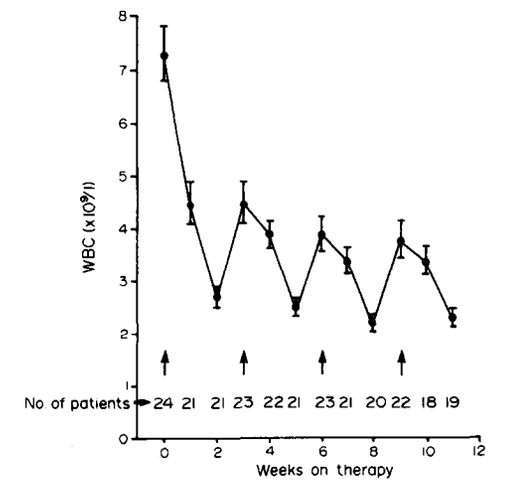

Fig. 8. Total white cell counts on CEB chemotherapy (mean, S.E.). The patients and the symbols are the same as in Fig. 7.

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Long-term Follow-up of Non-seminomatous Testicular Cancer Patients with Mature Teratoma or Carcinoma at Postchemotherapy Surgery

Rob L.H. Jansen, Richard Sylvester, Dirk T. Sleyfer, Wim W. ten Bokkel Huinink, Stan B. Kaye, William G. Jones, Jan Keizer, Allan T. van Oosterom, Sybren Meyer, Cornelis P.J. Vendrik, Marleen de Pauw and Gerrit Stoter for the EORTC Genitourinary Tract Cancer Cooperative Group (EORTC GU Group)

From 1979 to 1983 the EORTC GU Group treated 239 patients with disseminated non-seminomatous testicular cancer with combination chemotherapy comprising cisplatin, vinblastine and bleomycin in a prospectively controlled trial. The protocol required complete resection of residual masses after induction chemotherapy, provided that serum tumour markers were normal. 102 patients were operated on. 27 patients had mature teratoma (teratoma differentiated) in the resected specimens and 23 had viable cancer. Follow-up data were available for 26 and 22 of these patients, respectively. 23 of 26 patients (88%) with mature teratoma are alive and disease free after a follow-up of 53–110 months (median 92 months). 3 patients developed progressive disease; 1 died. A peculiar case of growing mature teratoma on the forearm is described. 13 of 22 patients (59%) with residual carcinoma are alive and disease free after a follow-up of 74–112 months (median 95 months). The prognosis of patients with carcinoma is shown to be correlated with the completeness of surgery, which in turn is correlated with the initial tumour mass before chemotherapy.
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INTRODUCTION

THE TREATMENT results of metastatic non-seminomatous germ-cell tumours have improved dramatically with the introduction of cisplatin combination chemotherapy. Survival rates beyond 3 years are reported to be 63–89% [1–5]. About half of the patients undergo postchemotherapy surgery, although the percentages in different series vary from 24%–70% [6, 7]. In about 20% of patients carcinoma is found in the resected specimens, 40% have mature teratoma (teratoma differentiated) and 40% have fibronecrotic tissue and normal architecture [6, 8–11]. Patients with residual viable cancer appear to have a high probability of disease progression [12, 13]. However, few reports are available about the long-term prognosis of patients with residual carcinoma [6, 13, 14] or mature teratoma [6, 15]. This report presents the analysis of such patients initially treated with cisplatin, vinblastine and bleomycin (PVB) in an EORTC GU Group Study [9].

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