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ORIGINAL ARTICLE

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# Carboplatin AUC8 in combination with etoposide and bleomycin in the treatment of intermediate and poor-risk metastatic germ cell tumours: a phase II study

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**Abstract** *Purpose:* Carboplatin has demonstrated significantly poorer response rates in non-seminomatous germ cell tumours. A phase II study of higher than standard doses of carboplatin was conducted because of suspicion that the poorer response might have been due to suboptimal dosing. *Patients and methods:* A group of 19 patients with advanced germ cell tumours (International Germ Cell Cancer Collaborative Group intermediate and poor prognosis) were treated with carboplatin at an AUC of 8 mg/ml·min (using Calvert's formula) on day 1, etoposide 120 mg/m$^2$ days 1–3 and bleomycin 60,000 U over 2 days (EBCa). Treatment was repeated every 3 weeks and a maximum of four courses was given. *Results:* Of the 19 patients, 7 (37%) achieved complete remission, of whom 6 (32%) remained long-term progression-free. Post-chemotherapy surgery and further chemotherapy salvaged an additional 26%, leading to an overall disease-free survival rate of 58%. No relationship between outcome and degree of myelosuppression could be established. *Conclusion:* Dose-escalated carboplatin in combination, although feasible, did not improve the results and led to poorer results than those expected with cisplatin-based therapy. There is no evidence that the patients relapsing following this were easier to salvage. Further investigation of this regimen cannot be recommended.

**Key words** Carboplatin · AUC 8 · Dose escalation · Germ cell cancer · Myelosuppression

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## Introduction

The substitution of carboplatin for cisplatin in the treatment of metastatic germ cell cancer has been associated with a 14% reduction in progression-free survival and a 7% reduction in overall survival [1, 2, 3]. Two observations suggest that carboplatin may have been given suboptimally in this trial. In the initial phase I/II study by Childs et al. [4] there was a steep dose response curve (AUC $<4.5$ mg/ml·min, 29% relapse rate; AUC 4.5–5.0 mg/ml·min, 4% relapse rate; AUC $>5.0$ mg/ml·min, 0% relapse rate). Secondly, in the TE09 study subgroup analysis demonstrated that patients who had significant myelosuppression during their first course appeared to do as well as those receiving cisplatin [1]. This does not mean that had all patients been given a dose that produced myelosuppression, the results would have been better, but did justify a dose-escalation study in carboplatin. This, together with the report that carboplatin can safely be given in ovarian cancer at a dose of AUC 12 mg/ml·min [5], justified an investigation of carboplatin at AUC 8 mg/ml·min with etoposide and bleomycin in patients whose risk factors put them outside the Medical Research Council TE20 good prognosis study. We report here the results and retrospectively classify the patients according to the International Germ Cell Cancer Collaborative Group (IGCCCG) criteria [6].

## Patients and methods

Between February 1995 and March 1997, 19 previously untreated patients (median age 27 years, range 18–37 years) with germ cell tumours (seven embryonal carcinomas, three teratocarcinomas,

seven nonspecified germ cell tumours) who were ineligible for MRC TE20 received carboplatin at AUC 8 mg/ml·min according to Calvert's formula [7] on day 1, etoposide 120 mg/m$^2$ days 1–3 and bleomycin 30,000 U over 8 h on days 1 and 2 (EBCa AUC8). Cycles were repeated every 21 days; a maximum of four cycles was given. Of the 19 patients, 13 had testicular primaries and 6 mediastinal primaries. Following retrospective classification according to the IGCCCG criteria [6], 6 patients fell into the intermediate group and 13 into the poor-risk group.

## Results

The treatment outcomes are shown in Table 1. Seven patients (37%) achieved a complete remission (in two this was surgically confirmed) of whom six remained long-term progression-free (32%). One received further chemotherapy on progression and was rendered free of disease. None of the five patients who achieved marker-negative partial remissions (PR) remained progression-free following EBCa treatment alone. Two (11%) were salvaged by surgery, i.e. surgically induced complete remissions with viable cancer at operation. Three patients (16%) were salvaged by further chemotherapy. Of these, one achieved complete remission (CR), one a marker-negative PR and one a marker-positive PR in response to EBCa, leading to an overall salvage rate of 38% (5 of 13) and an overall survival of 58%. Median progression-free survival was 10 months with a median follow up of 45 months.

### Toxicity

A total of 66 cycles of chemotherapy were given. Grade 3/4 neutropenia was seen in 34 cycles (52%), and grade 3/4 thrombocytopenia in 10 cycles (15%). There were three episodes requiring hospital admission (5%). Growth factors were used in a total of 17 cycles. In 10 cycles they were given during an infective episode and in 7 in subsequent prophylaxis.

White blood cell (WBC) and platelet counts were determined weekly during treatment. There was no difference between the mean or median nadir platelet or WBC counts during the first two cycles in those who were rendered progression-free in response to EBCa (122 and $108\times10^9$/l, and 2.3 and $2.3\times10^9$/l, respectively) than in those who were not. If this is expressed in terms of those whose platelets were $<100\times10^9$/l or WBC $<2.0\times10^9$/l as evidence of being myelosuppressed, this occurred in 11 patients, of whom 3 (27%) were long-term progression-free. It did not occur in 8, of whom 3 were long-term progression-free (38%).

## Discussion

In this study only 3 of 13 poor-risk patients (23%) were cured by primary therapy compared to 53% expected in a comparable mix of patients treated with cisplatin [6]. This result compares poorly with the 44% reported for carboplatin 500 mg/m$^2$ by Bosl and Bajorin [2] and the 58% reported by Tjulandin et al. [8] following a dose-escalation study up to 600 mg/m$^2$. The first suspicion that carboplatin might be inferior to cisplatin in germ cell cancer came from in vitro studies reported by Harstrick et al. [9] in 1990. This was 6 years before the MRC randomized trial was published. A recent review by Go and Adjei [10] confirmed that this degree of difference between cisplatin and carboplatin could also be demonstrated in vitro in 4 of 22 (18%) of cell lines tested. Furthermore, in ovarian, non-small-cell lung, head and neck and bladder cancer, the overall results are inferior with carboplatin- than with cisplatin-based regimens.

In vitro, Hongo et al. [11] have shown that carboplatin requires a 100 times higher drug concentration and a 7.5 times longer incubation to induce the same effects as cisplatin. Confirmation clinically that it may be necessary to give higher doses than AUC 8 mg/ml·min comes from the negative trial in ovarian cancer in which AUC 6 mg/ml·min and AUC 12 mg/ml·min were compared [5]. However, in this study delays in therapy due to myelosuppression meant that dose intensity was not increased significantly. The suggestion that the equivalent dosage of carboplatin and cisplatin may be less than the 100-fold difference suggested by Hongo et al. comes from a study of testis cancer patients treated at AUC 30 mg/ml·min (equivalent to 1500 mg/m$^2$) [12, 13], i.e. 15

**Table 1** Outcome in patients treated with EBCa AUC8 (*CR* complete remission, *PR* partial response, *SD* stable disease, *PD* progressive disease)

| Response | Number | Progression free | | | Currently alive and disease free |
|---|---|---|---|---|---|
| | | Following EBCa | Following surgery for viable cancer | Following further chemotherapy | |
| CR | 7 | 6 | 0 | 1 | 7 |
| Marker-negative PR | 5 | 0 | 2 | 1 | 3 |
| Marker-positive PR | 3 | 0 | 0 | 1 | 1 |
| Marker-positive SD | 1 | 0 | 0 | 0 | 0 |
| PD | 3 | 0 | 0 | 0 | 0 |
| IGCCCG poor prognosis | 13 | 3 | 2 | 3 | 8 |
| IGCCCG intermediate prognosis | 6 | 3 | 0 | 0 | 3 |

times the cisplatin dose, in combination with high-dose etoposide. Using this dose it is possible to salvage approximately one-third of patients failing conventional dose cisplatin.

In addition to the poor primary cure rate in this study, the results of salvage chemotherapy and surgery were not good: 5 of 13 (38%) were salvaged, 2 by surgery. This does not compare well with our results in patients who relapsed following first-line treatment with cisplatin (65% cumulative salvage rate) [14]. Despite these poor overall results which led to the abandonment of this study prematurely, there has been one recent report raising the question as to whether the difference between carboplatin and cisplatin becomes less as the patients' anticipated prognosis improves. The data supporting this view came from a report of 98% relapse-free survival in a group of 50 very good risk metastatic patients treated with bleomycin, etoposide and carboplatin combination chemotherapy using carboplatin at a dose of 400 mg/m$^2$ [15]. Though the numbers are small, this is not obviously worse than results from four courses of bleomycin, etoposide and cisplatin.

At present there are several new cisplatin analogues, such as oxaliplatin, with a good therapeutic index and low toxicity becoming available. However, following the negative experience with carboplatin in the MRC TE09 trial, several participants have expressed considerable reluctance to risk treating patients with a curable cancer using a drug that might only reduce toxicity. Information from pretrial in vitro work on cell lines such as that mentioned above [11] could help decision making in this area, but correlation between in vitro and in vivo results can be variable, so prolonged clinical trials with large numbers of patients are still required to be sure of a new drug's efficacy and safety. Despite this, given that there are long-term side effects with cisplatin including hypertension, vascular disease, loss of hearing and the as-yet-unascertained risk of late malignancies, there is still a need to look for alternatives.

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