Carboplatin in the combination chemotherapy of non-seminomatous germ cell tumours

The investigation of new drugs in a curable tumour places great responsibility on the oncologist to be particularly rigorous in ascertaining efficacy. The story of the evaluation of carboplatin in germ cell tumours emphasises the importance of a good prospective randomised trial design in the provision of secure evidence of efficacy equivalent to that of cisplatin.

At the time carboplatin became available for investigation in germ cell tumours, the standard chemotherapy in these tumours in most centres was based on the combination of cisplatin, etoposide and bleomycin [1]. Prognostic factor analysis had allowed definition of a particularly good prognosis subgroup of patients with metastatic disease with a survival probability of more than 90% [2-4]. In those patients clinical trials were designed to develop regimens of reduced toxicity and included evaluations of the need for bleomycin [5] in order to avoid lung toxicity, as well as evaluations of carboplatin to avoid the renal toxicity, neuro-toxicity and ototoxicity risks of cisplatin [6]. Additionally because intensive i.v. fluid hydration is unnecessary, the administration of carboplatin is a simple outpatient procedure. The pharmacokinetics of carboplatin differ from cisplatin. It is less extensively protein-bound [7], has a longer plasma half-life and a larger percentage is excreted via the kidneys [8]. Pharmacological studies have suggested that in vivo biological effects of a dose of this drug are determined by renal function [9].

The major pilot study of carboplatin in the combination chemotherapy of germ cell tumours was carried out in the Royal Marsden Hospital between 1984 and 1989 and involved the chemotherapy of patients with good prognosis metastatic non-seminomatous germ cell tumours treated with 4 cycles of the combination of carboplatin, etoposide and bleomycin (CEB). Bleomycin was administered at 30 U i.v. per week for 12 weeks. Etoposide was given intravenously at a dose of 120 mg/m² per day on days 1 to 3 inclusive of each of 4 cycles with cycles repeated every 21 days. The dosage of carboplatin was initially based on body surface area in a dose escalation study ranging between 300 mg/m² and 450 mg/m². However, following pharmacological studies confirming the accuracy of predicting the serum concentration x time [10], the carboplatin dose was calculated to achieve a serum concentration x time (AUC) of 4.6 mg/ml x min in 20 patients and subsequently an AUC of 5 mg/ml x min in 75 patients [11, 12].

With a median follow-up of 40 months from the start of chemotherapy, 118 of 121 patients remained alive and no patients had died from progressive germ cell tumour. One death was from ischaemic heart disease 3 years following chemotherapy, 1 from haemorrhage following replacement of aortic graft 6 years following chemotherapy and 1 from bleomycin pneumonitis. Nine patients were considered to have failed CEB chemotherapy of whom 5 had undifferentiated tumour resected following chemotherapy and a further 4 relapsed following apparent complete clinical remission. The study permitted comparison of the relationship between carboplatin dose and toxicity, comparing a dose based on body surface area and a dose given to achieve a particular serum concentration x time deriving from the glomerular filtration rate. At a carboplatin dose of 400 mg/m² or greater, 2 of 58 patients (3.4%) failed treatment, while 7 out 63 patients (11%) treated as a lower carboplatin dose than this failed (P > 0.1). At an AUC of 5 mg/ml x min or greater, 2 of 74 patients (2.7%) failed, while 7 out 47 patients (40.9%) who had an AUC less than this failed (P < 0.05). The failure rate rose to 26% for doses <4.5 mg/ml x min and in view of the more precise determination of toxicity and efficacy it was recommended that carboplatin dose be based on careful measurement of the glomerular filtration rate and that further evaluation of the combination be undertaken at a carboplatin dose to achieve a serum concentration x time of 5 mg/ml x min using the formula derived from Calvert et al. (1989) [9].

Dose = AUC (GFR + 25)

where the dose was in mg and GFR in ml/min.

Despite the excellent results achieved in this single-centre pilot study, there have now been reports from two substantial prospective randomised trials indicating that in the chemotherapy of good prognosis germ cell tumours, carboplatin combinations were inferior to those based on cisplatin. The first trial to be reported was based on 270 patients treated between October 1986 and December 1990 and was mainly a collaboration between the Memorial Sloan-Kettering Cancer Centre and the Southwestern Oncology Group. The patients were randomised to receive 4 cycles of either etoposide cisplatin (EP) or etoposide carboplatin (EC). The etoposide dose in all patients was 100 mg/m² per day on days 1 through 5. EP patients received cisplatin 20 mg/m² per day on days 1 through 5 and chemotherapy was recycled at 21-day intervals. For patients receiving EC the carboplatin dose was 350 mg/m² in the first 17 patients, 400 mg/m² in the next 5 patients and 500 mg/m² in the remaining 108 patients and the
chemotherapy recycling interval was 28 days [13]. In contrast to most European studies, the analysis did not define the finding of undifferentiated tumour at post-chemotherapy surgery as either failure of remission or an adverse event. Thirty-two patients (24%) receiving EC had either incomplete response or relapse compared with 17 of 134 patients (13%) treated with EP \( (P = 0.02) \). No difference in complete remission rate or survival was evident, but it was concluded that two-drug therapy with EC on these schedules was inferior to EP.

Between September 1989 and May 1993, a total of 598 patients with good prognosis metastatic non-seminomatous germ cell tumours were randomised to receive 4 cycles of either BEP or CEB within a multi-institutional MRC/EORTC trial reported in abstract in 1994 [14] and a full report of this is currently in press [15]. This differed from the MSKCC/SWOG trial described above, (1) in the classification of good prognosis patients, (2) in confining the trial to non-seminomatous tumours, (3) in incorporation of bleomycin in both arms of the trial at a dose of 30 U once every 3 weeks, (4) in the etoposide dose which was at 120 mg/m² per day on days 1 to 3 and (5) in the carboplatin dose which was based on a measurement of renal function and calculated to achieve an AUC of 5 mg/ml × min. The abstract reported a higher chemotherapy failure rate in patients treated with CEB (56/299 versus 29/299, \( P = 0.002 \)) and an inferior 1-year event-free survival 80% (95% CI 75%–85%) versus 90% (95% CI 86%–94%) where events included the finding of undifferentiated tumour at post-chemotherapy surgery. The full report with longer follow-up has confirmed a survival advantage for the patients treated with BEP [15]. Thus, the MRC/EORTC trial addressed a concern with the design of the MSKCC/SWOG trial in which the EC had been administered on a 4-week cycle, whereas EP had been given on a 3-week cycle. Despite equivalent cycle intervals, carboplatin-based chemotherapy appeared inferior.

A hypothesis to explain the inferior results of CEB in the MRC/EORTC trial compared to the Royal Marsden Hospital pilot study was that in the pilot study the slightly inferior activity of carboplatin was compensated for by the inclusion of full-dose bleomycin. At the time the trial was started, preliminary evidence had suggested that bleomycin contributed little to the chemotherapy of patients with good prognosis non-seminoma [5, 16, 17], but subsequent analyses have proved its value [18, 19]. The prospective randomised trial reported by Bokemeyer et al., in this issue, compared carboplatin with cisplatin-based chemotherapy in germ cell tumours and incorporated full-dose bleomycin for the first 3 of the 4 CEB cycles, such that a total of 270 mg of bleomycin was given to patients in each arm of the trial. The authors conclude that carboplatin is inferior even in the setting of full bleomycin dosage, but before accepting this, it is reasonable to examine the validity of the analysis. In fact, there are important weaknesses in the trial report deriving principally from the small numbers (only 54) of patients analysed. The major problems are as follows:

1. The principal analysis method reported in the article which also resulted in early stopping of the trial is invalid, since it was based on the total number of negative events observed per treatment arm, which included up to 3 in a single patient. The analysis is invalid since the statistical methods used require that each of the events be independent. Obviously, events occurring in the same individual are linked. The paper contains analysis of these events using denominators either of the number of patients in the trial or of the total possible number of events and neither are appropriate.

2. The power calculations and strategy for interim analysis appear inappropriate, but are inadequately described. The paper states that the statistical analysis was based on the assumption of a 1-year relapse-free survival of 90% in both treatment arms; however, the anticipated patients required were only 154 on each treatment arm, which is inadequate for an equivalence trial. In fact, the interim analysis did not use the endpoint specified in the sample size calculation (1-year relapse-free survival) or indeed any of the endpoints listed in the analysis section. If these endpoints had been used it seems exceedingly unlikely that the trial would have been stopped prematurely.

3. In the analysis of results shown in the paper, there are no significant differences between the two treatment groups for any of the valid endpoints if we simply consider the number of patients experiencing a particular event. For 1-year progression-free survival this would be 4/29 versus 4/27, \( P = 0.88 \) (chi-squared test with continuity correction). For response rate this would be 23/29 versus 19/25, \( P = 0.97 \) (chi-squared test with continuity correction). For relapse 4/29 versus 8/25, \( P = 0.21 \) (chi-squared test with continuity correction). For number of patients with a negative event, 7/29 versus 11/25, \( P = 0.21 \) (chi-squared test with continuity correction). In support of this, Figure 1 which illustrates the most informative analysis, the proportion of patients without a negative event, showed no significant difference between the treatment groups according to the figure legend and in contrast to the interpretation of this figure reported in the second paragraph of the discussion.

4. The invalid analysis of total number of negative events is wrongly attributed also to other reports listed in Table 4. The analyses of adverse events in the MSKCC/SWOG trial [13] was based correctly on the number of patients who experienced an event.

The relevance of the question as to whether standard
dose bleomycin might compensate for a slightly lower efficacy of carboplatin in the chemotherapy of germ cell cancers makes it particularly unfortunate that this trial was stopped too early. Even with prolonged follow-up, this trial will not have the statistical power to answer the questions reliably. At present, the standard first-line chemotherapy of metastatic germ cell cancers should be based on cisplatin.

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References


