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Dose Intensity and Outcome with Combination Chemotherapy for Germ Cell Carcinoma

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Abstract—*Two hundred and fifty-three patients with advanced stage germ cell carcinoma received induction chemotherapy with vinblastine, bleomycin and cisplatin, sometimes with subsequent surgical resection of residual masses. Overall,* 191 *patients* (76%) *achieved complete remission or no evidence of disease after surgery* (*CR + NED*). *With* 64 *months median follow-up only* 24 *patients have relapsed* (13%) *and* 68% *of all patients treated are long-term survivors and* 84% *of patients entering CR + NED are alive. Toxicity with this chemotherapy was considerable, including seven deaths from leukopenia and septicaemia and eight deaths from bleomycin lung toxicity. Dose reductions or omissions of the drug from the treatment programme was necessary with cisplatin in* 8% *of patients, with vinblastine in* 37% *and with bleomycin in* 35% *of patients. Analysis of these alterations in dose intensity for each drug revealed that initial treatment response and subsequent survival were not compromised by reductions in intended doses of drug administered for either vinblastine or bleomycin. Too few patients had dose reductions of cisplatin for meaningful analysis. This apparent lack of major dose–response effect for either vinblastine or bleomycin in the present treatment programme for germ cell carcinoma has prompted the initiation of a randomized study to determine whether deletion of bleomycin from treatment for patients with good prognostic pretreatment characteristics improves the therapeutic index of this very successful therapy.*

INTRODUCTION

MODERN chemotherapy regimens for advanced stage germ cell malignancies are based on the drug combination of cisplatin, vinblastine and bleomycin (PVB). Complete remission rates of 70–80% are regularly reported and with 2–3 years follow-up only 8–16% of patients have relapsed [1–4]. Analysis of pretreatment factors reveals that patients with low volume disease achieve complete remission in up to 90% of cases while remission rates of 50% or less are reported for patients with less favourable pretreatment characteristics [5–7].

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However, these encouraging results have been achieved at the expense of significant morbidity and even a drug related mortality rate as high as 5% [2, 8, 9]. Both the dose of each drug administered per cycle of treatment as well as the total dose of drug given during therapy determine these life-threatening toxicities.

In this report of a multi-institutional prospective study, described in detail elsewhere [10], 253 patients with advanced stage germ cell malignancy received induction chemotherapy with cisplatin, vinblastine and bleomycin. The data have been analysed to determine whether reductions in doses of each of the drugs administered (to ameliorate toxicity) thereby lessening intended dose intensity, compromised treatment outcome.

PATIENTS AND METHODS

From May 1979 to February 1983, 260 patients from 23 Institutions in Australia and New Zealand were entered onto study and 253 were evaluable. All patients had a histologically confirmed germ cell carcinoma other than pure seminoma and had either inoperable stage II or stage III disease. None

of the patients had received prior chemotherapy with any of the study agents. Before each cycle of chemotherapy, all patients had a complete workup as reported previously [10]. Informed consent was obtained from each patient prior to entry into the trial. The trial was approved by the respective Institutional Review Boards for Clinical Trials.

All patients received induction chemotherapy with cisplatin 100 mg/m^2 on day 1 by i.v. infusion, vinblastine 6 mg/m^2 days 1 and 2 by i.v. injection and bleomycin 30 mg i.m. on day 1 and weekly thereafter. Cisplatin and vinblastine were repeated at three weekly intervals and bleomycin administered for a maximum of 12 weeks (360 mg). Doses of vinblastine were reduced by 25% if the white cell or platelet counts before each treatment cycle were less than 3000/μl, or 100,000/μl respectively, by 50% if the white cell or platelet counts were less than 2000/μl or 75,000/μl respectively and omitted for that cycle if the white cell or platelet counts were less than 1000/μl or 50000/μl respectively. If moderate to severe peripheral or autonomic neuropathy developed, further doses of vinblastine were reduced by 50% or omitted. If the serum creatinine level rose above 0.20 mmol/l further doses of cisplatin were withheld until renal function improved. Serial DLCO levels were performed whenever possible and for the last 153 patients treated was a compulsory test every 3 weeks during induction therapy. If the DLCO fell by >25% baseline levels or if radiographic evidence of pulmonary toxicity developed, bleomycin was withdrawn from treatment. Bleomycin doses were also reduced by 50% or temporarily ceased if moderate or severe mucosal toxicity occurred.

The number of courses of induction chemotherapy given was determined by clinical and tumour marker response without any empirical limit. If complete remission was achieved as defined by complete disappearance of all evidence of disease and return to normal of elevated tumour markers for at least 1 month, then two further courses of induction chemotherapy were administered before consideration of maintenance therapy. Patients with stable residual tumour masses underwent attempted surgical resection of these. If the resected specimens contained fibrosis or benign teratoma, the patients were considered to be in complete remission. If viable carcinoma was found and completely removed, the patients were classified as having no evidence of disease (NED), received two further courses of induction chemotherapy and observed thereafter. Patients in whom surgical resection of residual disease was not undertaken or was incomplete had continued elevation of tumour markers or obvious progression of overt disease while on induction chemotherapy were classified as incomplete responders and received alternative treatment. Relapse was defined as clinical or radiographic evidence of recurrent disease or if a persistent rise in HCG and AFP by more than one log above normal values occurred after complete response or NED.

For statistical purposes, response data were divided according to the categories of complete response and NED, incomplete responses and complete responses with subsequent relapse. Within each category doses of each drug actually administered were listed by percentiles of the protocol defined treatment, e.g. 100%, 90–100%, 80–90%, etc. and then compared by chi-square analysis. Durations of response and survival were calculated from the date of initiation of chemotherapy until relapse, death or the date of last follow-up. Again using the categories described above and the percentiles of doses of each drug, durations of response and survival were compared by log-rank analysis and survival curves constructed according to the method of Kaplan–Meier [11].

RESULTS

Of the 253 patients who received induction chemotherapy, 183 (72%) achieved complete remission (CR) and surgical resection of residual masses revealing fibrosis, necrosis or benign teratoma confirmed this in 63 of these patients. A further eight patients were found by surgery to have viable carcinoma within the residual masses which was completely resected rendering these patients NED. Thus, the combined CR + NED rate was 76%. As described in detail elsewhere [10], multivariate regression analysis revealed that extent of disease was the dominant influence on response and patients with advanced lung and combined advanced lung and abdominal disease (as defined by Samuels' criteria [12]) had a significantly lower probability of achieving CR + NED.

Of the 191 patients who achieved CR + NED, 43 received subsequent maintenance therapy with 6 months of vinblastine 10 mg/m^2 every 4 weeks and the remainder no further treatment. At a median follow-up of 64 months relapses occurred in 24 patients (13%) with 20 of these occurring within the first 2 years of commencing induction chemotherapy and the remaining four at 28, 29, 38 and 60 months after commencing treatment. Overall, 68% of all patients treated are long-term survivors and 84% of patients entering CR + NED are alive.

Toxicities encountered with this induction chemotherapy were detailed in the earlier report [10]. Severe leukopenia (nadir white cell count <1000/μl) in 23% of patients including seven deaths from septicaemia, moderate to severe nausea and vomiting in 97% of patients, cumulative peripheral and autonomic neuropathy in 48% of patients and bleomycin-related pulmonary toxicity in 46%

Table 1. Response characteristics and percentage of drug doses administered

Drug	Number of patients	Drug dose in percentiles (as a % of patients) 100	90–100	80–90	70–80	60–70	50–60	<5
A. *Complete responses plus NED**								
Cisplatin	167	92.6	0.6	2.5	2.5	1.2	0.6	0
Vinblastine	167	60.7	1.2	18.4	11.0	5.5	3.2	0
Bleomycin	167	66.3	3.7	4.8	12.9	3.1	8.0	1.2
B. *Incomplete responses**								
Cisplatin	62	90.4	1.6	3.2	3.2	1.6	0	0
Vinblastine	62	59.7	4.8	14.5	3.2	11.3	6.5	0
Bleomycin	62	62.9	3.2	11.3	9.7	4.8	8.1	0
C. *Relapses**								
Cisplatin	24	87.4	4.2	4.2	0	0	0	4.2
Vinblastine	24	75.0	0	16.7	0	8.3	0	0
Bleomycin	24	58.2	4.2	4.2	25.0	4.2	4.2	0

*See Patients and Methods for definitions.

of patients with eight deaths, were the predominant toxicities. In relation to these toxicities, reductions in the dose or withdrawal of the drug from the treatment programme was undertaken with cisplatin in 8% of patients, with vinblastine in 37% and with bleomycin in 35% of patients. Table 1 reviews these data according to the response characteristics of this patient population. Analysing the doses of cisplatin given, among the 167 patients who achieved CR + NED and did not subsequently relapse, 155 (92.6%) received the total intended dose of cisplatin. This compared with 90.4% of the 62 patients who failed to achieve complete remission or NED and 87.4% of the 24 patients who initially entered complete remission but subsequently relapsed. In constrast, with vinblastine, the total intended dose of this drug was given in 60.7%, 59.7% and 75% of the three groups of patients and for bleomycin, the total intended dose was given in 66.3%, 62.9% and 58.2% of the three patient groups. Nevertheless, when these dose reductions were analysed by chi-square analysis according to the influence of any dose reduction on outcome and also the extent of that dose reduction by percentile, no significant differences were observed with any group. The data were also analysed relating the dose reductions of each drug to various pretreatment characteristics. Again, no significant differences were observed. In particular, drug dose intensity for the patients with advanced lung and abdominal disease, was comparable to those with less extensive disease.

Further analyses of these alterations in dose intensity were undertaken according to duration of response and survival. No significant differences were observed whether the data were analysed according to any dose reduction or percentile of dose reduction for each of the individual drugs for the total patient population or when the patients were classified within the three groups described above and comparing the influence of dose reduction of each drug within the groups and between the groups. Figure 1 illustrates the comparable survival of the two patient groups analysed according to the dose intensity of bleomycin administered.

DISCUSSION

This large study has shown that intensive chemotherapy achieves high complete remission rates (76%) and very favourable long term disease-free survival (84% at 64 months follow-up) for patients with advanced stage germ cell carcinoma, confirming the results of other generally smaller studies [1, 4, 13]. However, toxicity was a significant problem and 15 deaths occurred which were directly drug related. These included seven deaths from neutropenia and septicaemia attributable principally to the influence of vinblastine and eight deaths due to bleomycin-related pulmonary toxicity. These data prompt an assessment of the contribution each drug is making towards the efficacy and toxicities of the combination chemotherapy programme and what measures, if any, may be taken to reduce morbidity and maintain efficacy.

It has recently been proposed that the dose intensity of each drug given in any cancer chemotherapy combination is of great importance in obtaining optimal outcome [14]. Data to support this have come from studies in experimental leukaemia, advanced stage carcinomas and adjuvant chemotherapy for early stage malignancies [15–18]. Detailed analyses undertaken by Hryniuk *et al.* in advanced stage carcinoma of the breast and ovary have directly correlated the amount of drug given, either as a single agent or in combination, with outcome and Carde *et al.* have produced similar data for advanced Hodgkin's disease [16, 17, 19].

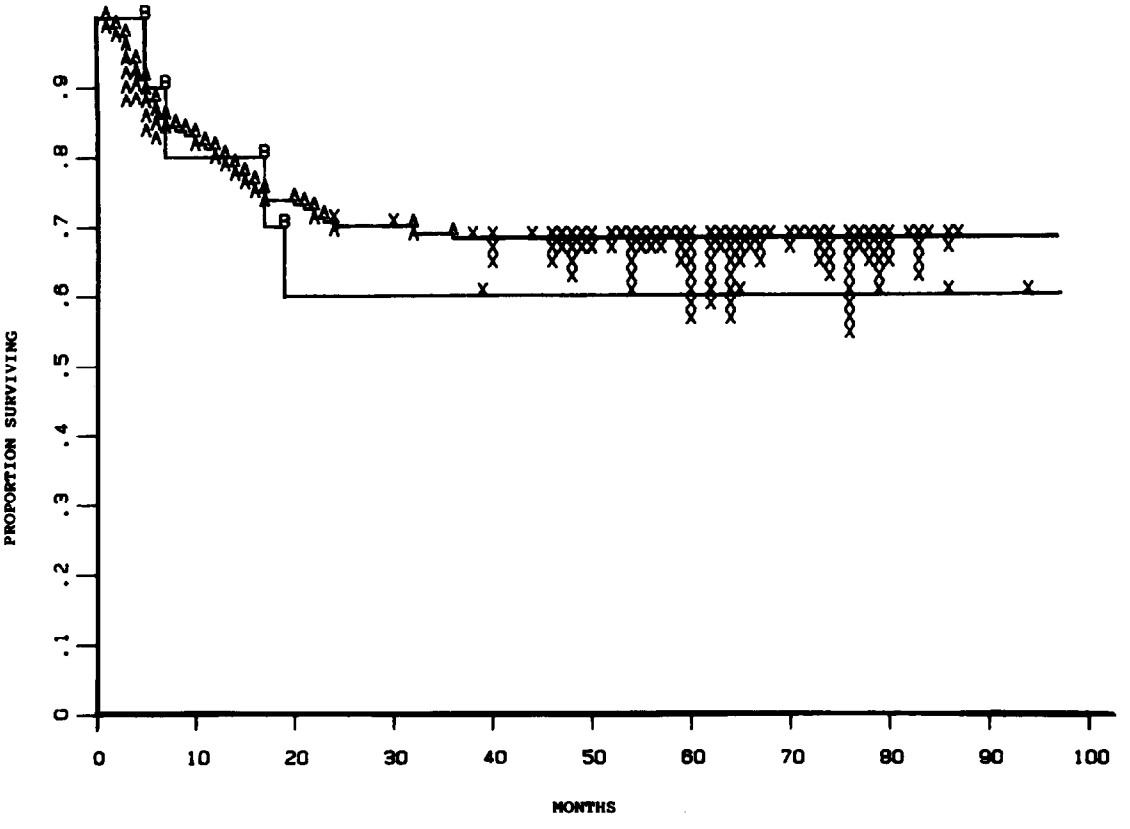

Fig. 1. Duration of survival for total patient population according to dose of bleomycin administered. A = patients receiving > 90% of intended dose of bleomycin; B = patients receiving < 90% of intended dose of bleomycin. Log-rank analysis P = 0.65.

Further, analysis of results of adjuvant chemotherapy in patients with early stage breast carcinoma and osteogenic sarcoma has also emphasized that the greater the dose intensity of drugs given the better the long-term outcome [20, 21].

It is of some interest then to determine whether the same can be said for advanced stage germ cell carcinoma. Only limited data are available from other studies. Einhorn *et al.* demonstrated in a randomized trial that reduction in the dose of vinblastine did not adversely influence results and now routinely recommend the lower dose of vinblastine in their treatment regimens [1]. Samson *et al.* have shown that 120 mg/m^2 of cisplatin monthly was superior to 75 mg/m^2 in the PVB combination [22]. Other studies which make passing reference to dose reductions in the reported treatment programmes do not indicate an adverse effect on results [23, 24].

This study has carefully evaluated the influence of reductions of dose intensity for each drug in the treatment combination as a function of the total dose administered over time and has not been able to show that treatment efficacy has been adversely affected. This applies to the proportions of initial treatment responses and long-term remission duration and survival. This is particularly valid for vinblastine and bleomycin where reductions in dose intensity were undertaken in 37% and 35% of patients respectively. However, with cisplatin, 92% of patients received the full intended dose and so no conclusions can be drawn from this study as to whether major reductions in dose intensity of cisplatin would influence treatment outcome.

It is pertinent to consider further the known data on the relative contribution of each drug within this treatment combination. Both vinblastine and bleomycin have moderate activity as single agents achieving response rates of 37–43% (10% complete remissions) in previously untreated patients with advanced germ cell carcinoma [25]. Cisplatin, however, appears more active with reported responses in 71% of patients incuding 52% complete remissions and essentially all these patients had received prior chemotherapy [25]. When vinblastine and bleomycin were combined by Samuels *et al.*, a complete response rate of 57% was reported [12]. As the current three-drug combination achieved a complete remission rate of 76%, it is likely that not all three drugs are contributing equally to the efficacy of the programme.

In this context, and in view of our data that reduced dose intensity of both vinblastine and bleomycin did not adversely affect outcome, the question must be asked as to whether either bleomycin or vinblastine could be safely omitted from the treatment regimen. This is particularly pertinent for patients in whom the presence of low volume disease predicts for a high rate of cure.

As a direct result the Australasian Germ Cell Neoplasm Group has now embarked on a study in 'good prognosis' disease randomly comparing the standard three-drug combination with the two drugs vinblastine and cisplatin, omitting bleomycin. Preliminary data suggest that initial response rates are equivalent without any differences in proportion of relapses, but with a marked lessening in toxicities for the two-drug arm, particularly related to pulmonary toxicity but also, to a lesser extent, myelosuppression and alopecia [26]. Should long-term follow-up confirm these results, then a definite advance towards optimal management of these patients will have been achieved.

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