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Accelerated Chemotherapy for Poor Prognosis Germ Cell Tumours

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A pilot study has been completed of an innovative dose intensive chemotherapy schedule for poor prognosis patients with metastatic germ cell tumours referred to the Royal Marsden Hospital between August 1989 and January 1992. The rationale underlying the regimen was the use of an extremely short intercycle interval in order to counteract the potential of these tumours for rapid proliferation. The drug combination in the first phase incorporated a combination of cisplatin and carboplatin, infusional bleomycin and vincristine and this was followed by three cycles of bleomycin, etoposide and cisplatin (C-BOP/BEP). 21 patients with adverse presentations were treated with C-BOP/BEP. The median follow-up of surviving patients is 36 months (range 18–52 months). 1 patient died of disease, 1 died of a treatment complication while in remission and 1 further patient relapsed, and is in remission after radiotherapy and surgery. The 2-year overall survival rate was 90% [95% confidence interval (CI) = 77–100%]. We conclude that this approach may represent an improvement over standard chemotherapy and should be assessed in a multicentre setting.
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INTRODUCTION

THE OVERALL cure rate of patients with metastatic testicular non-seminoma is high. A recent survey of 895 patients treated with chemotherapy between 1982 and 1986 indicated a 3-year survival probability of 85% and multifactorial survival analysis defined the major independent prognostic factors to be high tumour markers, the presence of liver bone or brain metastases, presence of a mediastinal mass >5 cm in diameter or the presence of >20 lung metastases [1]. Presence of only one of these adverse factors indicated a 3-year survival probability of 68% compared with 94% of patients with none of the adverse factors. Since these factors were independently significant, the adverse prognostic category could be divided further by summating the number of adverse features such that the predicted 3 year survival probability for a patient with two adverse factors was 55%, with three adverse factors was 35% and with all four adverse factors, no patients survived.

There is both clinical and laboratory evidence that germ cell tumours have a high proliferative capacity [2–4], and additionally there is some evidence that those germ cell tumours with the highest rates of proliferation may be more likely to fail chemotherapy [5]. We have therefore investigated intensive induction chemotherapy of poor risk germ cell tumours using a sequence of regimens since 1985 [6, 7], and the bleomycin, etoposide and cisplatin (C-BOP) regimen represents the latest stage of this development. The regimens were based on that originally described by Wettlaufer and colleagues 1984 [8] who employed cisplatin, vincristine and bleomycin on a weekly schedule. The modifications underlying the C-BOP pilot schedule include the combination of cisplatin and carboplatin during the intensive induction phase as well as infusional bleomycin and weekly bleomycin and vincristine. There is some evidence that infusional bleomycin may be highly effective and less toxic than bolus injections [9]. A 6-week induction is then followed by three cycles of conventional chemotherapy employing bleomycin, etoposide and cisplatin. The purpose of this report is to review the efficacy and toxicity in the first 21 patients treated with this regimen.

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PATIENTS AND METHODS

Between August 1989 and January 1992, 21 patients referred to the Testicular Tumour Unit of the Royal Marsden Hospital (RMH) for first-line chemotherapy fulfilled the clinical criteria for categorisation as poor prognosis defined by the Medical Research Council Prognostic Factor Analysis [1]. Stage distribution by the RMH Classification [10, 11] is illustrated in Table 1; 1 patient was difficult to categorise using MRC cirteria, but was regarded as adverse because at presentation he had five bulky lung metastases together with large volume pleural deposits. This series contained 4 patients with mediastinal primary germ cell tumours, none of whom had evidence of metastases. 2 of these were biopsied. One was seminoma presenting with a HCG (human chronic gonadotrophin) of 16 000 U/l, the second was malignant teratoma undifferentiated with a AFP (alpha feto protein) of 10 000 U/l; the others presented with bulky mediastinal masses, 1 associated with HCG of 4000 and the other with an AFP of 2000.

Of the remaining 17 patients, pretreatment histology was obtained following orchidectomy in 15 cases; in the other 2, orchidectomy was performed following the first month of therapy. The histopathology sections were always reviewed

within the RMH Department of Histopathology. The distribution of pathology and clinical stage is shown in Table 1.

Patients in this series were also classified using the Indiana University (IU) Classification System [12]. 19 patients would have been classified as advanced disease, however, 1 patient was classified as intermediate using this system. He had a 7 cm palpable abdominal mass, 5 cm supraclavicular node and serum AFP concentration at presentation of 27000 U/l. A further patient would have been classified as having minimal disease using the IU System, and he had a 4 cm diameter retroperitoneal node mass associated with a serum HCG concentration of 46000 U/l. These would be classified as high risk using the MRC Classification because of the high marker concentration.

Tumour therapy was based on the C-BOP/BEP regimen which is illustrated in Figure 1. This regimen has two parts. It begins with an accelerated schedule based on that first described by Wettlaufer (1984) [13] in which platinum-based chemotherapy is administered every seven days for the first four cycles. It can be seen that cisplatin and carboplatin were combined on weeks 2 and 4. Carboplatin was administered just after completion of the cisplatin 6 h infusion. Also on weeks 2 and 4, a 5-day infusion of bleomycin was administered, usually via an intravenous (i.v.) access line using a mobile pump in order to allow treatment to be continued out of hospital. On weeks 1 and 3, cisplatin was administered at a dose of 20 mg/m^2/day on each of the first 5 days (or more recently 50 mg/m^2/day on days 1 and 2) associated with a minimum of 3 l hydration with normal saline containing 20 mmol potassium chloride and magnesium chloride. On weeks 2 and 4, a cisplatin dose of 40 mg/m^2 was administered in a 6-h infusion with similar hydration. Carboplatin was administered

Table 1. Patients' details

Patients	RMH stage	Prechemotherapy Histology	AFP (U/l)	HCG (U/l)	MRC risk factors	Failure
1	IVC $L_2M_+N_+$	MTU	–	–	L	
2	Mediastinum	MTU	A	–	M	
3	IVC L_3M_+	MTI	–	H	L	
4	IVC L_2	MTU	–	H	–	
5	IIIC M_+N_+	MTU	A	H	–	
6	IIC	MTU	A	–	–	
7	IVC L_2	MTU	A	H	L	
8	IIB	MTU	–	H	–	
9	IVC L_3	–	–	H	L	
10	Mediastinum	–	A	–	M	
11	IVC L_2	–	–	–	L	
12	IVC L_3	MTU/S	–	–	–	
13	IVC L_2	MTU/S	–	–	L	
14	IVC L_2	Seminoma	–	–	Hep L	F
15	IVB L_2	MTU	–	–	L	
16	UVC $L_1H_+B_+$	MTI	A	–	B Hep T	
17	Mediastinum	–	–	–	M	
18	IVC M_+L_2	MTU	–	H	M T	F
19	Mediastinum	Seminoma	–	–	M	
20	IVC L_2H_+	–	A	–	Hep	
21	IVC L_3	MTT	–	H	L T	

MTU, malignant teratoma undifferentiated; MTI, malignant teratoma intermediate; MTT, malignant teratoma trophoblastic. A, AFP >1000 U/l, H, HCG >1000 U/l, Hep, liver involvement, L, ≥20 lung metastases, M, mediastinum >5 cm, T, ≥10 cm abnominal mass, B, bone. Late relapse from stage I, unusual site pleura.

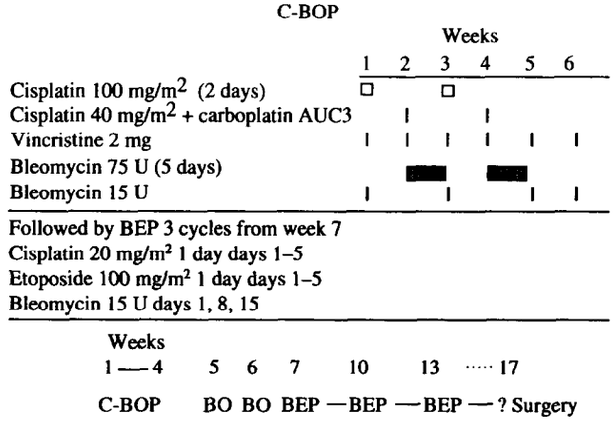

Figure 1. The C-BOP/BEP regimen.

as a 60-min infusion in 500 ml of 5% dextrose, and in the first 13 patients this was at a dose calculated to achieve a serum concentration × time of 2 mg/ml × min and in the remaining patients to achieve a serum concentration × time of 3 mg/ml × min. These dose calculations are based on the formula derived by Calvert and colleagues (1989) [14] such that dose in mg = AUC(25 + GFR) where AUC = the desired serum concentration × time in mg/ml × min and GFR = the glomerular filtration rate assessed by clearance of chromium-51-labelled EDTA. Vincristine was administered at dose of 2 mg by push injection. Bleomycin doses other than the 5-day infusions were always 15-U administered by push injection together with 100 mg of hydrocortisone. Etoposide doses were via 30-min i.v. infusions. Chemotherapy was administered routinely with antiemetics, initially a combination of meoclopramide 10 mg, dexamethasone 8 mg and lorazepam 1 mg. Patients with persisting emesis were given a combination of ondansetron 8 mg i.v. and dexamethasone 8 mg i.v.

Following chemotherapy patients with residual masses were considered for surgical resection. If there were residual masses at multiple sites, these were monitored rather than immediately resected. In 10 patients, there were persisting abnormalities and resection was undertaken. In 8, this revealed necrosis only, and in 2, there was teratoma differentiated, 1 of whom subsequently relapsed, and is now in complete remission after radiotherapy and further surgery.

Following completion of treatment, patients were reassessed every two months for 1 year, then every 3 months for 1 year, every 4 months for 1 year, every 6 months for 1 year then annually. No patients have been lost to follow-up.

Data collection was from computer records. All patients were registered prospectively, and data on radiological and haematological investigations was recorded directly on the record by the appropriate laboratory. Toxicity data was predominantly derived from symptom assessment during follow-up visits. Haematological toxicity was assessed weekly during the course of chemotherapy, and renal function was assessed regularly at 3–4 week intervals during and on completion of chemotherapy by EDTA clearance. Data on spermatogenesis is not available.

Treatment modifications

In 3 patients, week 4 chemotherapy was omitted because of thrombocytopenia. In this setting, subsequent chemotherapy was brought forward by 1 week. 2 patients had omission of week

5 or 6 chemotherapy because of low counts with no change in the subsequent schedule. 4 patients had carboplatin rather than cisplatin-based chemotherapy on week 1 in order to avoid the saline hydration regimen. In 3 cases, this was because of dyspnoea associated with either multiple lung metastases or with superior venal caval obstruction, and in the other case, the patient had hydronephrosis secondary to a large retroperitoneal mass.

RESULTS

21 patients treated with C-BOP chemotherapy have been followed for a minimum of 18 months, range 18–52 months, median 36 months, from the start of the chemotherapy regimen. 18 patients have remained continuously free from progressive disease. 1 patient died from treatment-related toxicity 3 months after the beginning of chemotherapy. This patient had presented with a large retroperitoneal mass associated with multiple small volume lung metastases, an AFP of 8000 U/l and HCG of 20 000 U/l. His GFR at presentation was 81 ml/min, and his initial chemotherapy was with carboplatin rather than cisplatin. After completing the 4-week induction schedule, he proceeded with chemotherapy based on carboplatin, etoposide and bleomycin rather than cisplatin. Following the second cycle of CEB chemotherapy, his white count fell to 0.6×10^9/l on day 15, and he was admitted to his local district general hospital with a fatal septicaemia. No viable tumour was found at the post-mortem examination.

2 patients in this series developed tumour progression. 1 presented with stage IIIC disease associated with very high serum HCG concentration. He achieved marker remission, but had multiple persistent cystic masses. These could be only partially resected and revealed residual mature teratoma (teratoma differentiated), however, he has suffered both marker and radiological relapse, and was treated with local radiotherapy and surgery; he is currently in complete remission.

The second patient to suffer disease progression after chemotherapy has died of progressive tumour. This patient presented with stage IVC L2 H+ germ cell tumour, characterised from the testicular primary as a pure seminoma, but associated with serum AFP concentration of 20 U/l. He had an excellent response to a full standard course of C-BOP chemotherapy, and reassessment after chemotherapy revealed only minimal residual abnormalities <1 cm in size in the liver and retroperitoneal area. Unfortunately, 5 months later he suffered both marker and radiological relapse. Both his AFP and his HCG concentrations

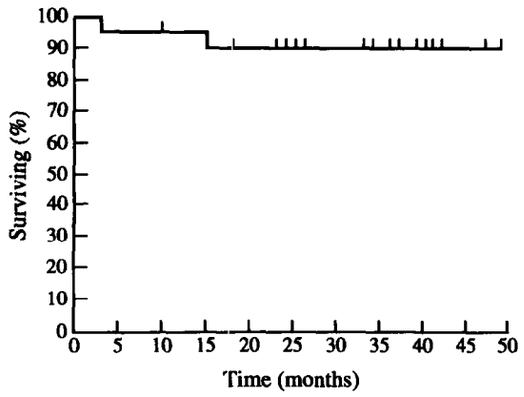

Figure 2. Overall survival of 21 patients followed for a median of 36 months (range 18–52 adults).

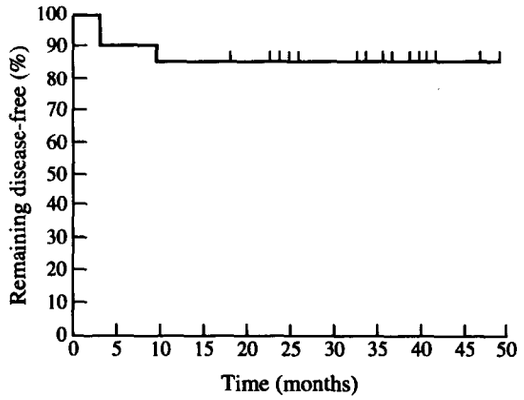

Figure 3. Continuous failure-free survival.

rose and new lesions appeared in the lungs and the liver. He declined any further chemotherapy and died after 7 months following relapse. Thus, 19 out of 21 (90%) patients are currently alive, with no evidence of active disease. The overall survival of 21 patients is illustrated in Figure 2 and the failure-free survival is shown in Figure 3. The 2-year overall survival rate was 90% (95% CI from 77 to 100%). The failure-free survival rate at 2 years was 86% (95% CI from 71 to 100%).

The 2 patients who developed progressive disease were assessed in relation to the extent of disease at presentation; 1 patient had stage IIIC teratoma and 1 had stage IVC L2 H+ seminoma associated with raised serum AFP. Using the Medical Research Council definition of adverse prognosis, the patient with stage IIIC disease had two risk factors only (serum HCG concentration of 100 000 U/l and a mediastinal mass 6 cm in diameter). The patient with stage IV disease, who died from tumour progression, had one MRC risk factor (liver involvement). In the remaining 18 evaluable patients, 1 patient had no risk factors, 10 had one risk factor and 7 had two risk factors. Using the Indiana University Prognostic Classification, both of the patients who relapsed had advanced presentations, 1 defined on the basis of liver involvement and the other on the basis of palpable abdominal mass associated with mediastinal mass. Of the remaining 18 evaluable patients, 16 would have been classified as having advanced disease, 1 moderate disease and 1 minimal disease.

With regard to toxicity, the regimen was associated with marked bone marrow toxicity especially at week 6 when 7 patients had total white count $<1 \times 10^9$/l, and a further 4 had a total white count $\leq 1.5 \times 10^9$/l. Also, at this time point, 8 patients had platelets counts $<50 \times 10^9$/l of whom 3 were treated with prophylactic platelet transfusions. 7 patients suffered a total of 11 episodes of neutropenic sepsis. The regimen as a whole was associated with significant renal toxicity, and the distribution of initial and final measurements of glomerular function are shown in Figure 4. The final glomerular filtration rate ranged from 60 ml/min to 129 ml/min, median 81 ml/min. 9 patients suffered peripheral neuropathy, 7 grade I and 2 grade II using WHO criteria. Audiometry was not routinely performed, however, 1 patient noted symptomatic high tone hearing loss and 2 patients suffered transient tinnitus. 2 patients have experienced Raynaud's phenomenon. Alopecia was universal, but has recovered in all evaluable patients.

DISCUSSION

Approaches to improving the chemotherapy of poor prognosis, germ cell tumours have included dose escalation, the

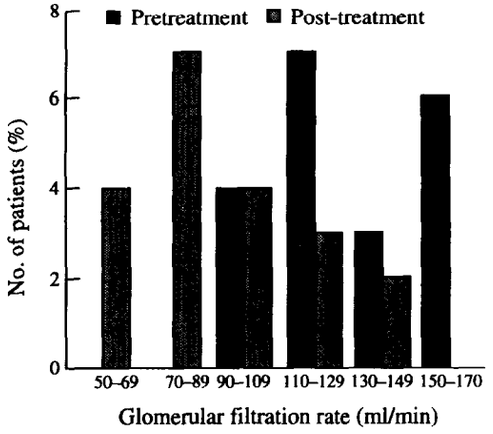

Figure 4. Renal function before and after C-BOP/BEP chemotherapy in 20 patients.

incorporation of new agents, alternating schedules and the use of intensively cycled drugs [15]. The use of etoposide in place of vinblastine appeared to improve the prognosis of more advanced cases [16]; any further potential improvements in the chemotherapy of poor prognosis germ cell tumours should be tested against the combination of bleomycin, etoposide and cisplatin. Simple dose escalation of cisplatin has not proved fruitful [17, 18]. Good results have been reported from some centres using alternating regimens [19, 20]. However, results are not always repeatable at other centres [21], and randomised trials have not confirmed the superiority of this approach [22, 23].

Frequent cycling of chemotherapy (accelerated chemotherapy) can most easily be achieved by the use of vincristine rather than a more myelosuppressive alternative drug in the initial combination chemotherapy of patients, and this approach was first described by Wettlaufer and collagues 1984 [8], who achieved a 93% complete response rate in 29 patients. The approach was consolidated by surgery and further chemotherapy, including cisplatin, actinomycin-D and vincristine, and also maintenance chemotherapy was continued for 12 months: an overall survival of 83% was reported after a median follow-up of 31 months. Early results of frequently-cycled chemotherapy have also been reported by Murray and colleagues [24] and Daniel and colleagues [25].

An investigation of a more modest acceleration of chemotherapy has been undertaken in a joint Medical Research Council/European Organisation for research in the treatment of cancer (EORTC) trial comparing BOP/VIP-B chemotherapy [26] with standard BEP. The BOP/VIP-B schedule comprises three cycles of bleomycin, vincristine and cisplatin administered once every 10 days, followed by a more conventionally cycled chemotherapy based on a combination of bleomycin, etoposide, ifosfamide and cisplatin; results should be available early in 1995.

Our initial experience with intensively cycled induction chemotherapy followed by three cycles of more standard chemotherapy gave encouraging results [6, 7], and we have therefore developed this approach further by combining modest doses of carboplatin with cisplatin in order to maintain an approximately even weekly platinum dose during the first 4 weeks of treatment in the C-BOP/BEP regimen. Although the results reported in this manuscript are good, every caution should be observed in the interpretation of single centre pilot studies and we believe that this approach should be investigated in a multicentre setting.

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Double Modulation of 5-Fluorouracil in Advanced Colorectal Cancer With Low-dose Interferon-α2b and Folinic Acid. The "GISCAD" Experience

R. Labianca, G. Giaccon, S. Barni, G. Ambrosini, A. Iirillo, G. Fiorentini, M. Duro, E. Piazza, C. Oliani, G. Pancera, S. Cascinu, G. Martignoni, A. Zaniboni, G. Dallavalle and G. Luporini on behalf of GISCAD (Italian Group for the Study of Digestive Tract Cancer)

In advanced colorectal cancer the addition of folinic acid (FA) has been shown to lead to increased activity, at least in terms of response rate, in comparison with 5-fluorouracil (5FU) alone. Similarly, interferon-α (IFN) is able to potentiate 5FU, although high doses cause heavy toxicity. Given the different mechanisms of action of the two agents, the double modulation of 5FU deserves clinical evaluation. In a multicenter study (involving both primary care and referral institutions) 63 patients with advanced colorectal cancer, previously untreated with chemotherapy, received, in an outpatient setting, FA (200 mg/m² i.v. bolus) + 5FU (400 mg/m² i.v. in 15 min) for 5 consecutive days every 4 weeks + IFN 3 × 10⁶ U on alternate days, starting 1 week before chemotherapy. During the 5 days of 5FU + FA, IFN was administered daily. The antitumour activity, the impact on response duration and survival and toxicity of the combination were evaluated according to WHO criteria. Of the 63 enrolled patients, 56 were evaluable: there were 2 complete responses (3%) and 13 partial responses (21%), giving an objective response rate of 24% (95% confidence interval 13–35%); no change was observed in 17 cases and progressive disease in 24. Median duration of response was 9 months and median survival (all patients) 13 months. Toxicity was acceptable, even though 4 patients presented reversible grade 4 side-effects (2 mucositis and 2 diarrhoea). With this schedule and these doses, addition of IFN did not lead to any increase in the activity of 5FU + FA. In colorectal cancer, further clinical studies with these drugs should be based on a deeper experimental knowledge of their mechanisms of interaction.

Keywords: 5-fluorouracil, interferon-α2b, folinic acid, colorectal cancer
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INTRODUCTION

THE BIOCHEMICAL modulation of 5-fluorouracil (5FU) with folinic acid (FA) led to the most significant advance in the systemic chemotherapy of metastatic colorectal cancer of the last decade. A recent meta-analysis of nine phase III published trials [1], including a GISCAD study [2], has confirmed the clear advantage of the combination over 5FU alone in terms of objective response rate, although overall survival is no longer than with 5FU alone.

The possibility that the activity of 5FU might be improved by the addition of interferon-α (IFN) was suggested by experimental observations [3] of a decrease in thymidine kinase activity, with a reduction in the rate of phosphorylation of thymidine and consequent inhibition of thymidine incorporation into DNA. Pharmacokinetic studies showed a decrease in 5FU clearance (and an increase in the 5FU area under the curve) when the drug was administered concomitantly with IFN [4]. Furthermore, the induction of thymidylate synthase (TS) associated with fluoropyrimidine exposure (which can be an important mechanism of cell resistance) can be eliminated by IFN [5]. In the