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Papers

Combination Chemotherapy with Bleomycin, Etoposide and Cisplatin (BEP) for Metastatic Testicular Teratoma: Long-term Follow-up

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127 men with previously untreated non-seminomatous germ cell tumours (NSGCT) of the testis were given BEP chemotherapy (bleomycin, etoposide and cisplatin) between 1979–1986. Long-term follow-up (median 65 months) has shown an overall 5 year survival of 87.2% (95% confidence limits 81.1%–93.3%). Outcome was related to both tumour volume and serum marker levels of alpha-fetoprotein (αFP) and beta human chorionic gonadotropin (HCG), with 5 year actuarial survivals of 97.8%, 72.2% and 26.7% respectively for small, large and very large volume disease defined by Medical Research Council criteria, and 91.2% and 60.8%, respectively, for men with low (αFP≤500 kU/l and HCG≤1000iU/l) or high serum marker levels. 79 men (62%) had a complete radiological and serum marker response to chemotherapy alone; residual masses postchemotherapy were resected in 39 patients (31%), showing undifferentiated tumour in only 6 (15%). 23 of the 127 patients (18%) failed to respond or developed recurrent disease after BEP; only 5 were successfully salvaged. Myelotoxicity of treatment was mild with grade 4 toxicity in 2% of chemotherapy courses and 3 episodes of neutropenic sepsis. Mean glomerular filtration rates fell by 15.6% between courses 1 and 4 of BEP. Bleomycin pneumonitis developed in 13% of cases with 1 fatality. So far 21 men have had children following chemotherapy, but semen analysis 12 months or more (median 36 months) after treatment showed azoospermia in 11 out of 54 (20%) men tested. BEP chemotherapy can be regarded as standard treatment for patients with metastatic NSGCT in low-risk categories, but more intensive therapy is required for advanced presentations. Strategies to develop "risk related" treatment are under investigation.
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INTRODUCTION

BLEOMYCIN, ETOPOSIDE AND CISPLATIN (BEP) combination chemotherapy was introduced into the management of metastatic testicular cancer at the Royal Marsden Hospital in 1979 [1]. Initially the combination was used in a successful attempt to reduce the bowel toxicity caused by the then standard cisplatin, vinblastine and bleomycin (PVB) regimen [2–4], particularly in patients who had relapsed after previous irradiation for stage I disease. The excellent initial results led to the adoption of BEP as standard management at the Royal Marsden Hospital and subsequently this combination has been extensively used worldwide. This report details long-term follow-up and morbidity in 127 previously unirradiated patients with metastatic non-seminomatous germ cell tumours (NSGCT) treated between 1979 and 1986.

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PATIENTS AND METHODS

127 patients with metastatic NSGCT of the testis previously treated by orchidectomy only were given BEP chemotherapy between July 1979 and September 1986. Patients' ages ranged between 15–60 years (median 27.8 years). The initial diagnosis was established by orchidectomy in all cases and histological specimens were reviewed in the Royal Marsden Hospital Department of Histopathology. 86 patients were treated for metastases demonstrated at the time of initial presentation and 41 following recurrence after surveillance for stage I disease. 8 patients had malignant teratoma trophoblastic (MTT—pure choriocarcinoma or with other cell types), 48 malignant teratoma undifferentiated (MTU—embryonal carcinoma), 42 malignant teratoma intermediate (MTI—teratocarcinoma), 26 combined teratoma and seminoma and 2 patients differentiated teratoma alone in the orchidectomy specimen. In 1 patient the primary histology was of seminoma but alpha-fetoprotein (αFP) was raised at 430 kU/l and biopsy of an abdominal mass showed MTU. Staging investigations included full physical examination, assay of serum αFP and the β subunit of human chorionic gonadotropin (βHCG), chest X-ray and computed tomography (CT) of thorax and abdomen. Patients were then classified according to the Royal Marsden Hospital staging system [5] (Table 1). Those cases with multiple lung metastases or serum βHCG levels

Table 1. Royal Marsden Hospital staging classification [5]

Stage	
I	No metastases evident outside testis
IM	No clinical evidence of metastases but persistent elevation of serum αFP and/or βHCG levels after orchidectomy
II	Infradiaphragmatic nodal metastases
IIA	Metastases < 2 cm diameter
IIB	Metastases 2–5 cm diameter
IIC	Metastases > 5 cm
III	Supradiaphragmatic nodal metastases Abdominal status A, B, C as for Stage II
IV	Extranodal metastases
IVL1	Pulmonary metastases, ≤ 3 in number
IVL2	Multiple small pulmonary metastases < 2 cm diameter
IVL3	Multiple pulmonary metastases. One or more > 2 cm diameter
IVH+ B+ Br+	Hepatic, bone or brain involvement Abdominal status A, B, C as for Stage II

>50 000iU/l had central nervous system staging using CT of the brain and cerebrospinal fluid cytology and marker estimations for αFP and βHCG. Details of the extent of the disease are given in Table 2. 11 patients (8.7%) had raised tumour markers only with no evidence of disease on CT. 97 cases (76%) had abdominal lymph-node involvement, which was bulky (>5 cm)

Table 2. Histology, extent of disease, tumour marker levels and prognostic categories in patients treated with BEP chemotherapy

Histopathology			
Differentiated teratoma (TD)			2
Malignant teratoma intermediate (MTI)			42
Malignant teratoma undifferentiated (MTU)			49
Malignant teratoma trophoblastic (MTT)			8
Mixed teratoma/seminoma			26
Stage			
IM	11		
II	60	Abdominal mass >5 cm	32
III	5		
IV	51	Lung metastases	51
		Liver, bone, brain metastases	6
Tumour markers			
HCG (iU/l)	>1000	25	
	>10 000	9	
αFP (kU/l)	>50 000	4	
	>500	17	
	>1000	15	

MRC prognostic groups [5]	Tumour markers* Low	High
Small volume (n = 90) (IM, IIA/B, IIIA/B, IVA/B L1/2)	75	15
Large volume (n = 22) (IIC, IIIC, IVC L1/2)	12	10
Very large volume (n = 15) (L3, liver, bone, brain)	6	9

*Low markers: HCG ≤1000 iU/l and αFP ≤500 kU/l; high markers: HCG >1000 iU/l and αFP >500 kU/l.

in 32 (25%) cases. 51 patients (40%) had pulmonary involvement which was extensive (L3) in 14 (11%). 6 patients had liver (3), bone (1), or brain (2) involvement. βHCG or αFP marker levels were raised in 92 patients (αFP 75 cases, βHCG 74 cases) and 34 patients had high levels according to the Medical Research Council (MRC) criteria [6] with βHCG >1 000 iU/l or αFP >500 kU/l. For analysis patients have been stratified according to tumour bulk and marker levels (Table 2) using the MRC prognostic groups [6].

Chemotherapy was given on three weekly cycles as previously described [1] using cisplatin 20 mg/m^2 per day on days 1–5, etoposide 120 mg/m^2 per day on days 1–3 and bleomycin 30 mg on days 2, 9 and 16. Hydration was maintained with 4 litres of normal saline per day. Mannitol was given prior to each 6 hourly infusion of cisplatin to induce diuresis. Renal function was estimated using chromium-51 labelled EDTA clearance before each course of chemotherapy and blood counts were undertaken weekly throughout treatment. Of the 127 patients, 104 received four courses of treatment, 21 patients with large volume disease or unsatisfactory initial response received five or six courses and 2 patients received only two courses, 1 patient dying from bleomycin lung toxicity and the second having surgical resection of a small cystic para-aortic lymph-node. Surgical resection of residual masses was undertaken following chemotherapy in 39 patients and the 2 patients with brain metastases were treated with whole cranial radiotherapy to a dose of 40 Gy in 20 fractions over 4 weeks. For the purpose of recurrence and survival analysis, entry to the study was from the start of chemotherapy. Time to recurrence was defined as the period from start of chemotherapy to any evidence of progressive disease; patients who were never disease free were considered to have a zero time to recurrence. Relapse free survival was defined by the time to recurrence or time to death if patients had not recurred. Median time of follow-up of survivors is 65 months (range 24–111 months).

RESULTS

The overall 5 year survival for the whole group of patients is 87.2% (95% confidence limits, 81.1–93.3%). Of the 19 deaths, 18 were in patients with disease recurrence and the remaining man died from bleomycin lung toxicity. A total of 23 patients (18%) developed disease progression. 19 patients relapsed after completion of chemotherapy, and 4 had evidence of disease progression during initial treatment. Recurrence was related to both initial disease bulk and tumour marker levels. 5 year actuarial recurrence free survival was 94.2%, 68.2% and 26.7% for patients with small, large and very large volume disease respectively (P<0.005) and 89.1% and 60.6% for patients with low and high tumour markers respectively (P<0.005). 14 of these failures occurred within 12 months of commencing chemotherapy, 7 within the second year after treatment and 1 each in the third and fourth year of follow-up. Median time to disease recurrence for all relapsing patients was 10 months, but was longer for patients who had presented with small volume disease—median 18 months, than large volume disease—median 12 months or very large volume disease—median 7 months (Spearman rank correlation, P<0.1). 5 patients with recurrent disease were salvaged (see below) and 5 year actuarial survival (Table 3) for patients with small, large and very large volume disease was 97.8%, 72.2% and 26.7%, respectively, and 91.2% and 66.1% for patients with low and high tumour markers, respectively. Of the 19 deaths, 5 occurred within 12 months of treatment, 7 in the second year of follow-up, 2 in the third year

Table 3. Prognostic groups and 5 year survival probability for NSGCT treated by BEP chemotherapy

	n	Probability of 5 year survival (%)		95% CL	
All cases	127	87		80–92	
Small volume low markers	75	97	98	89–99	91–99
Small volume high markers	15	100		100	
Large volume low markers	12	83	72	48–96	48–86
Large volume high markers	10	60		25–83	
Very large volume low markers	7	43	27	10–73	8–50
Very large volume high markers	8	12		1–42	
All volumes low markers	94	91		83–96	
All volumes high markers	33	66		47–80	

Small vs. large vs. very large volume, $P < 0.005$ (trend); low vs. high markers, $P < 0.005$.
CL = confidence limits.

and 5 in the fourth year after initial treatment. All deaths have occurred within 4 years of initial treatment and have been disease or treatment related; no cases of leukaemia, other second malignancy or cardiovascular deaths have occurred. Actuarial relapse free and overall survival curves are shown in Fig. 1 with survival probabilities for the different prognostic groups in Table 3.

Table 4. BEP chemotherapy in NSGCT: results of surgery for post chemotherapy residual masses

	No. of resections	Patients relapsing after surgery
Total	39	10
Teratoma differentiated	28	4
Necrosis/fibrosis	5	2
Teratoma undifferentiated	6	4*
Incomplete resection	7	7+

*Incomplete resection in 2.
+Positive histology in 2.

Surgery for post-chemotherapy residual masses

39 patients had resection of residual masses following completion of chemotherapy. Para-aortic masses were resected in 34 patients, mediastinal or neck lymphadenopathy in 5 patients and 7 cases had thoracotomy for residual pulmonary lesions. Differentiated teratoma was found in 28 out of 39 patients, necrosis or fibrosis alone in 5 and 6 had residual malignancy (Table 4). 32 patients had complete surgical clearance of disease, histology showing undifferentiated malignancy in 4 cases, but in the remaining 7 men complete surgical clearance was not possible although only 2 patients had undifferentiated teratoma identified histologically. 10 of the 39 patients subsequently recurred: these included all 7 patients who had had incomplete resections and in 2 of the others resected masses had shown

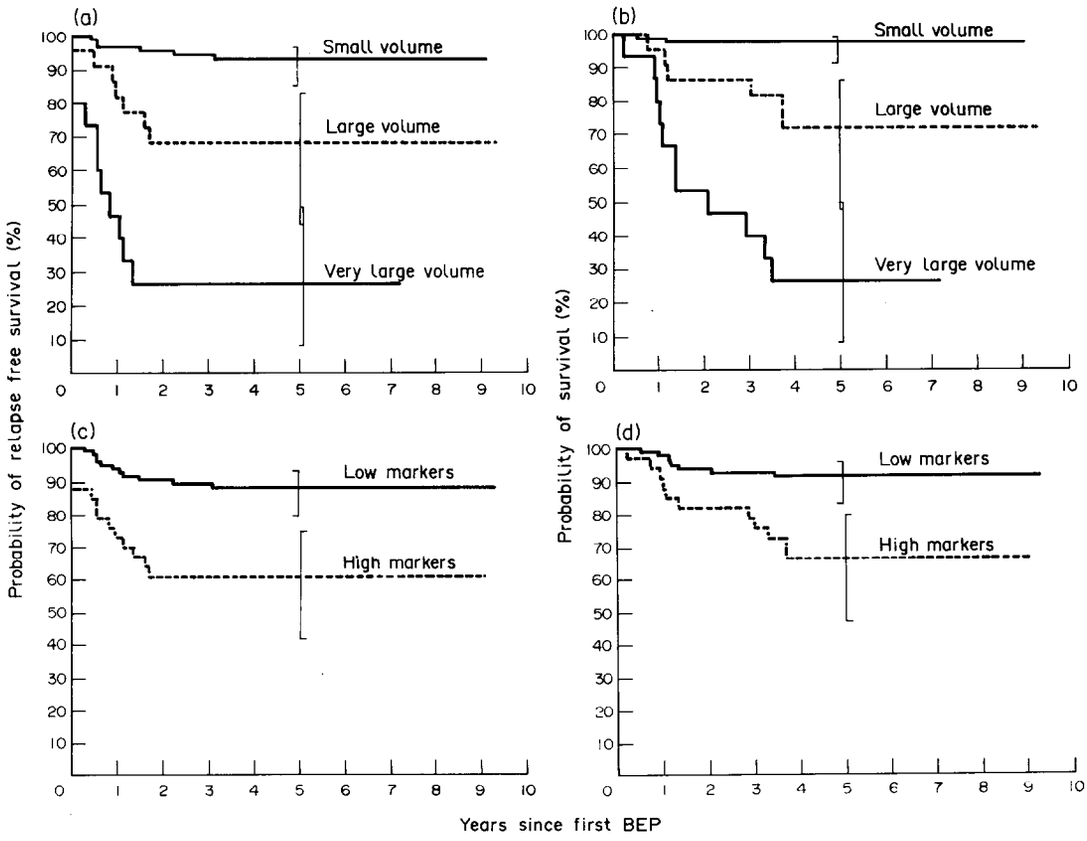

Fig. 1. Actuarial relapse free and overall survival following BEP chemotherapy stratified according to tumour volume and serum marker levels [5]. Relapse free survival and (a) tumour volume, (b) marker levels. Overall survival and (c) tumour volume, (d) marker levels.

Table 5. BEP chemotherapy in NSGCT: factors affecting outcome after relapse

		Proportion salvaged			
Initial volume*	Small	4/5	Large	1/7	Very 0/11
Initial markers*	Low	3/8	High	2/15	large
Residual mass	No	4/9	Yes	1/14	
No. sites relapse	1	4/10	>1	1/13	
Disease free interval	>6 mos	4/10	≤6 mos	1/13	
Relapse chemotherapy	BOP+	2/5	Other	2/16	
All cases			5/23		

*MRC definitions [6].
+See text [7, 8].

undifferentiated teratoma (Table 4). Only 1 out of 28 patients who had apparent complete resections of residual masses without histological evidence of undifferentiated teratoma developed recurrent disease, and this man was salvaged with chemotherapy (carboplatin, vinblastine) and further para-aortic node dissection.

Salvage of patients relapsing after chemotherapy

Only 5 of 23 patients relapsing after BEP chemotherapy were salvaged, and these patients remain well and disease free 40–68 months after retreatment. Further chemotherapy was given in 21 out of 23 cases using cisplatin, carboplatin, methotrexate, vinblastine, ifosfamide, actinomycin D and cyclophosphamide in various combinations, but latterly the intensive weekly bleomycin, vincristine and cisplatin (BOP) regimen has been used [7, 8]. When possible recurrent masses were either surgically excised or irradiated after salvage chemotherapy. Initial volume of disease, presence of a residual mass following initial chemotherapy and surgery, disease free interval, number of sites at relapse and possibly type of relapse chemotherapy were predictors of outcome (Table 5). 4 out of 5 patients with small volume disease at presentation were salvaged compared to only 1 out of 18 with large or very large volume disease. Of patients with only one site of disease at recurrence, 4 out of 10 were salvaged compared to only 1 out of 13 who relapsed at more than one site. Recurrent disease was surgically excised or irradiated in all of the survivors as well as 11 out of 18 patients who died. As all of these patients were treated on an individual basis with various combinations of chemotherapy, surgery and irradiation, it is not possible to be precise about the role of each treatment modality. 4 of the 5 salvaged cases had disease recurrence confined to the para-aortic area, all were completely resected after further chemotherapy (histology showed residual undifferentiated teratoma in 2) and the fifth patient with mediastinal and lung recurrence remains disease free after intensive weekly chemotherapy [7, 8] and mediastinal irradiation. All patients retreated with the intensive weekly (BOP) regimen responded: 2 remain disease free 51 and 57 months postrecurrence and the remaining 3 patients had survivals of 23, 34 and 44 months after retreatment.

Toxicity of treatment

Bone marrow. Myelosuppression was generally mild. White cell count nadirs $<2.0 \times 10^9$/l occurred in 20.5% of 482 courses analysed with counts of $<1.0 \times 10^9$/l in only 2%. There were six episodes of infection requiring antibiotics, three treatment unrelated (appendicitis, salmonellosis, infected toe) and three episodes of neutropenic sepsis with one death in a patient who had received additional high dose methotrexate for poorly responding bulky disease. Toxicity became more marked with later courses of chemotherapy, grade 3 toxicity occurring in 12%, 13%, 22.5% and 34.5%, respectively, of courses 1, 2, 3 and 4. Significant thrombocytopenia was rarely seen and platelet counts $<50\,000 \times 10^9$/l occurred in 2% of 482 courses, 10 out of the 12 episodes occurring in course 4. No problems with haemorrhage were encountered. Haemoglobin levels fell below 8 g/dl in 4% of courses, on all but 1 of 18 occasions during course 4. 18 patients had treatment delays of more than 2 weeks but only 3 cases had a delay of more than 3 weeks between the start of chemotherapy and the expected date of completion of the fourth course of therapy. Delays occurred predominantly in the earlier part of the series (1979–1983) when chemotherapy was withheld with total white cell counts $<2.5 \times 10^9$/l. Subsequently treatment has been given without complications providing the white cell count has been $>2.0 \times 10^9$/l and rising. There was no relationship between these short treatment delays and stage of disease and no effect on recurrence or survival was apparent (actuarial 5 year recurrence free survival was 79% for no delay compared to 85% for delay >1 week).

Renal toxicity. Pretreatment EDTA renal clearances ranged from 41–206 ml/min (mean 134 ml/min). Before the fourth course of chemotherapy there was a mean fall of clearance of 15.6% to 113 ml/min (range 56–171 ml/min). 13% of patients had a greater than 30% fall of EDTA but in only 1 case did the EDTA reduce to less than half of its pretreatment value. In 14 patients who went on to receive six courses of therapy EDTA levels fell by 25% (mean pretreatment EDTA 123 ml/min reducing to 92 ml/min before sixth course) and 3 patients had higher than 50% decreases in glomerular filtration rate.

Pulmonary toxicity. Symptomatic bleomycin lung toxicity with radiographic changes occurred in 17 out of 127 cases (13%). 14 men complained of dyspnoea alone, 2 of chest pain and 1 patient had both symptoms. The changes were usually minor; 13 cases required no intervention. 4 patients required treatment with high-dose steroids because of dyspnoea and 1 of these men died from bleomycin-induced respiratory failure. The mean dose given to the 17 cases who developed bleomycin lung toxity was 450 mg (range 180–690 mg) compared to a mean dose of 360 mg bleomycin for the entire group of patients. The 4 cases requiring intervention received a mean dose of 383 mg of bleomycin (range 180–480 mg), but the patient who died received only 180 mg in total.

Fertility. 75 patients had sperm counts prior to chemotherapy and approximately half (37) were normal (sperm count $>20 \times 10^6$/ml); only 4 men were azoospermic. A total of 54 cases were tested more than 12 months (median 36 months, range 12–89 months) after commencing chemotherapy. 11 men had normal counts, 32 were oligospermic having counts $<20 \times 10^6$/ml and 11 were azoospermic (median time after chemotherapy 43 months, range 13–89 months). The 47 patients who were tested both prechemotherapy and postchemotherapy showed a similar pattern (Table 6). 21 men had a series of sperm counts taken postchemotherapy. Of 11 patients who were azoospermic 12 months or more after treatment, 4 became oligospermic and one normospermic. 3 patients who were oligospermic at 12 months or more after treatment regained normal sperm counts. All the improvements in sperm counts were seen

Table 6. Sperm counts in patients tested before and after BEP chemotherapy

		Postchemotherapy*		
Prechemotherapy	Total	Normal	Oligospermic	Azoospermic
Normal	24	8	13	3
Oligospermic	20	1	13	6
Azoospermic	3	0	2	1
Total	47	9	28	10

*All tested more than 12 months after commencement of treatment.

by 34 months and in the 10 patients tested more than 3 years after chemotherapy (4 azoospermic, 6 oligospermic) no further improvements were seen.

Prior to chemotherapy 42 men had fathered 80 children, and so far following treatment 21 men have had a further 26 children and additionally 3 pregnancies have miscarried. No congenital abnormalities have been seen apart from 1 child with a Wolff–Parkinson–White conduction defect. Postchemotherapy sperm counts were available in 12 of the men who had children (1–58 months before estimated date of conception) and showed oligospermia in 10 and normospermia in the remaining 2.

DISCUSSION

Cisplatin, vinblastine and bleomycin (PVB) combination chemotherapy was established by the end of the 1970s as effective treatment for the majority of patients with metastatic non-seminomatous germ cell tumours with approximately 70% long-term disease free survival [2–4]. Myelotoxicity was noted as a particular problem in previously irradiated patients [1, 4] and our experience suggested a high risk of gastrointestinal morbidity in this group. Etoposide had been reported as an active single agent in patients relapsing after first line chemotherapy with an approximate 30% response rate [9–14]. In 1979 the BEP regimen was introduced at the Royal Marsden Hospital [1] for previously irradiated men with recurrent germ cell tumours, and following early experience which suggested reduced toxicity and maintained efficacy compared to PVB, BEP became established as first-line management in metastatic NSGCT. Long-term follow-up of this single institution series of patients confirms our initial reports that BEP is an effective regimen with an overall 5 year survival probability of 87% (95% confidence levels 81.1%–93.3%). Survival correlated with both disease volume and serum levels of HCG and αFP as previously shown by the MRC [6]. Results were excellent (97.5% 5 year survival) in patients with small volume disease, but poorer survivals were seen with more advanced presentations (72.2% and 26.7% for large volume and very large volume disease, respectively). The long-term relapse free survival following complete remission after chemotherapy alone was 94% (74 out of 79) and 3 of these 5 relapsing patients have been salvaged. We have regarded surgical excision of residual masses as an essential component of treatment whenever feasible [15, 16]. Only 3 out of 32 (9%) of patients who had complete resections have recurred and 2 of these had residual undifferentiated teratoma in the resection specimen. The other 2 patients with residual undifferentiated teratoma who had complete surgical clearance remain disease free. Of the patients whose complete resection showed differentiated teratoma or necrosis and fibrosis, only 1 out of 28 has recurred when excision was complete whereas all 5 cases with incomplete resection have relapsed. These observations strongly support the therapeutic role of postchemotherapy surgery. Although 61% (14/23) of recurrences were within 12 months of commencing chemotherapy, late recurrence (14–38 months post treatment) occurred in 9 men and time to recurrence correlated inversely with bulk of disease at presentation. It may be that patients presenting with small volume disease have tumours of slower growth rate [17] which is then reflected in a longer disease free interval [18]. This would caution against early interpretation of studies in patients with small volume disease (see below). 37% of deaths (7 out of 19) occurred more than 2 years after chemotherapy. This figure is similar to that seen by other groups who have reported long-term results using either PVB [19, 20] or the Charing Cross Hospital POMB-ACE regimen [21] and emphasises the importance of adequate follow-up in reporting survival data in NSGCT.

Salvage following recurrence after BEP chemotherapy was disappointing with only 5 out of 23 (22%) survivors. Factors determining the likelihood of successful retreatment were the extent of disease, both at initial presentation and at relapse, the presence of unresectable masses following initial treatment, and the interval between first treatment and recurrence. Our recent experience using the weekly BOP chemotherapy regimen [7, 8] as well as that of other groups using intensive drug schedules [22, 23] suggest that these approaches may improve salvage.

Some degree of nausea and vomiting and alopecia was universal in patients treated with BEP. Significant haematological toxicity was uncommon and the 3 day etoposide schedule (120 mg/m^2 per day) was associated with only a 2% incidence of total white cell count below 1.0×10^9/l and only 3 episodes of neutropenic sepsis occurred. This compares with incidences of granulocytopenic fever of 35% and 15% using PVB regimens with 0.4 mg/kg and 0.3 mg/kg, respectively [2, 4, 24] and 15–23% using 5 day schedules of etoposide with 100–120 mg/m^2 per day [1, 25]. Cisplatin therapy produced a mean fall of renal clearance of 16% prior to the fourth course of chemotherapy. Our previous studies [26] on a subset of these patients, as well as reports from other groups [27–29], suggest these changes are permanent in the majority of patients and recent reports suggesting long-term side-effects of hypertension, hyperuricemia, hypercholestorolemia and increased cardiovascular morbidity are of concern [19, 20, 30, 31]. In common with other series [25, 32, 33] we saw a 13% incidence of bleomycin lung toxicity with 1 death. Increasing bleomycin dose, renal impairment and age are known risk factors for the development of toxicity [34, 35] and recovery of pulmonary function after cessation of treatment is incomplete [29, 36]. Although of low incidence such morbidity assumes considerable importance in patients in low risk categories when the probability of chemotherapy cure is near 100%.

Recovery of sperm counts was seen in the majority of our patients up to 3 years after treatment. However, of the 44 men tested prechemotherapy who were normospermic or oligospermic, 9 (20%) remain azoospermic on last testing (median 43 months post-treatment) and our routine policy is to offer sperm banking to all men pretreatment who have adequate sperm counts, providing chemotherapy is not urgently indicated. Prior to treatment 42 of 127 (33%) of men were fathers and so far post-therapy 21 of the 108 survivors (19%) have had children, although the denominator wishing to have families is not known. This figure is similar to other series using BEP or PVB chemotherapy; Bissett and colleagues [30] reported that 18 out of 74

men (24%) became fathers after treatment and with longer follow-up (median 8.5 years) Roth and colleagues [19] reported that 51 out of 146 (35%) of men had children. We have seen a single congenital cardiac abnormality in children born after chemotherapy—this case has previously been reported as part of a larger series [37] which showed 9 out of 96 of first born children had abnormalities (relative risk 1.0, 95% confidence limits 0.4–2.4 compared to matched controls). Prospective parents should be reassured that there is no evidence of teratogenicity following BEP therapy, although we continue to advise against conception for 12 months after treatment.

It is now clear that chemotherapy for metastatic NSGCT should be risk related [1, 38–41]. A variety of prognostic classifications [6, 21, 38, 41–43] are in use but for patients with low risk disease—for example small volume disease defined on MRC criteria [6]—the prognosis is excellent following properly delivered treatment (in this series 2 deaths out of 90 patients). The challenge has become to reduce treatment related morbidity from myelotoxicity, bleomycin pneumonitis, renal damage, ototoxicity, neurotoxicity and Raynaud's phenomenon. Approaches have included the reduction of number of treatment courses, reduction of drug dosage and number of chemotherapy agents used and the use of less toxic drug analogues. Preliminary analysis of a randomised prospective study comparing 3 and 4 courses of BEP (with 5 days etoposide giving 100 mg/m^2/day) in good risk patients has shown no difference in efficacy [44]. A prospective study from the Indiana University group comparing 0.4 mg/kg with 0.3 mg/kg of vinblastine showed equivalent results [4] and in small volume disease our results using BEP with the 3 day etoposide schedule are entirely adequate, although the higher doses in the 5 day schedule may produce improved results in patients with more advanced disease [25, 32].

Lower doses of etoposide may produce less good results [45] and for cisplatin the randomised study of Samson and colleagues [46] demonstrated a clear dose response relationship for cisplatin comparing doses of 75 and 120 mg/m^2. The Royal Marsden Hospital Testicular Tumour Unit has piloted the use of the analogue carboplatin [47] in combination with etoposide and bleomycin (CEB) in patients with good prognosis NSGCT [40, 48]. Renal toxicity, neurotoxicity and ototoxicity are avoided and with appropriate dose adjustment to allow for variations in renal excretion [47] results using CEB appear equivalent to BEP. The current MRC prospective randomised study in good prognosis patients is comparing CEB and BEP chemotherapy. Bleomycin may be an unnecessary component in good risk patients, although our initial experience using the 2 drug combination of etoposide and cisplatin (EP) was unfavourable with four out of 17 recurrences in good risk patients [49]. However, preliminary results of an EORTC study [50] comparing BEP with EP in good prognosis patients (using 3 days of etoposide at 120 mg/m^2/day) showed 94% and 92% disease free survivals, respectively, and Bosl and colleagues [51] have shown the equivalence of EP (5 days of etoposide at 100 mg/m^2 per day) to the VAB-6 regimen in terms of overall and event free survival with a substantial reduction in toxicity. Conversely an Eastern Cooperative Oncology Group prospective randomised study [52] comparing 3 courses of BEP (5 days of etoposide) with EP in patients with minimal or intermediate disease according to the Indiana classification has shown an unfavourable response in 32% of patients using the 2 drug schedule compared to 15% with 3 drugs ($P<0.01$). These results emphasise the value of randomised studies in testing variations of standard treatment regimens, but long-term follow-up will be required before final conclusions can be drawn. Reducing toxicity is of no benefit to patients if treatment efficacy is compromised and even in good prognosis groups the risk of dying from uncontrolled malignant disease outweighs the risk from treatment toxicity.

Although the number of patients treated by BEP chemotherapy in this study with advanced disease (MRC very large volume) was small (15 cases) it has been our strong impression that improved results have subsequently been seen with more intensive drug regimens. Attempts at improving treatment efficacy can be made by (1) increasing the number of drugs used, (2) increasing the frequency of drug administration, (3) using alternating and non-cross resistant drugs combinations and (4) increasing drug doses. We have studied the addition of vinblastine to BEP at a dose of 0.3 mg/kg (BEVIP) in 17 patients with very large volume disease [53] and produced long-term disease free survival (follow-up 68–110 months) in 8 cases (43%) but at the cost of markedly increased bone marrow and gastrointestinal toxicity. Since 1985 our approach has been to intensify therapy using weekly induction treatment with the BOP-BEP regimen [7, 8] which has given a 67% 2 year actuarial survival in 61 patients with advanced disease (74% for large volume, 61% for very large volume). Improved results have also been claimed by other groups using more intensive drug combinations including POMB-ACE [21], CISCA-VB [54] and BOP-VIP [55], but apparently similar results have been obtained by Pizzocaro *et al.* [25] using the BEP regimen with a 5 day etoposide schedule with an 82.5% survival at 2 years in high risk patients. Since the prospective randomised study by Williams and colleagues [32] showed that BEP using the 5 day etoposide schedule gave a significantly improved outcome in poor risk patients compared to PVB therapy (2 year survival probability of 76% for patients with advanced disease according to the Indiana system) this regimen has been generally accepted as standard treatment for advanced presentations of metastatic NSGCT.

Randomised studies are now required comparing BEP with more intensive regimens in high risk patients. Preliminary results have demonstrated no advantage for "double dose" cisplatin (200 mg/m^2) compared to the standard BEP regimen (100 mg/m^2) despite an increase in toxicity [56]. The MRC are currently performing a multicentre randomised trial to compare the intensive BOP-VIP regimen [55] with BEP containing etoposide 100 mg/m^2 per day for 5 days. Alternative approaches include the use of high dose schedules with autologous bone marrow transplant [57–60], and the use of bone marrow support factors [61] which may allow dose escalation of drugs such as carboplatin, etoposide and ifosfamide for which myelosuppression is dose limiting. Any benefits from these approaches in improved tumour control will need to be weighed against increases in toxicity and careful patient selection is paramount in restricting such intensive treatment approaches to patients who can not be adequately managed with more conventional treatment.

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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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