British Journal of Cancer (1995) 71, 1311-1314

Four cycles of BEP versus an alternating regime of PVB and BEP in patients with poor-prognosis metastatic testicular non-seminoma; a randomised study of the EORTC Genitourinary Tract Cancer Cooperative Group

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Summary We have investigated whether an alternating induction chemotherapy regimen of PVB BEP is superior to BEP in patients with poor-prognosis testicular non-seminoma. A total of 234 eligible patients were randomised to receive an alternating schedule of PVB/BEP for a total of four cycles or four cycles of BEP. Poor prognosis was defined as any of the following: lymph node metastases larger than 5 cm, lung metastases more than four in number or larger than 2 cm, haematogenic spread outside the lungs, such as in liver and bone, human chorionic gonadotrophin $>10\,000$ IU l^{-1} or alphafetoprotein >1000 IU l^{-1}. The complete response (CR) rates to PVB/BEP and BEP were similar, 76% and 72% respectively ($P = 0.58$). In addition, there was no significant difference in relapse rate, disease-free and overall survival at an average follow-up of 6 years. The 5-year progression-free and survival rates in both treatment groups were approximatley 80%. The PVB BEP regime was more toxic with regard to bone marrow function; the frequencies of leucocytes below 1000 μl^{-1}, leucocytopenic fever and platelets below 25 000 μl^{-1}, throughout four cycles were 28% *vs* 5% ($P < 0.001$), 16% *vs* 5% ($P = 0.006$), and 10% *vs* 1% ($P = 0.001$) respectively. Neuropathy also occurred more often in the PVB BEP arm: 47% *vs* 25% ($P = 0.001$). This study shows that an alternating regimen of PVB BEP is not superior to BEP and that it is more myelo- and neurotoxic.

Keywords: germ cell cancer; non-seminoma; chemotherapy

Cisplatin combination chemotherapy has increased the long-term survival rates of patients with disseminated testicular non-seminoma from 10% to approximately 70% (Einhorn, 1981; Stoter *et al.*, 1989). Variables associated with a poor prognosis include extent of metastases and serum levels of β-subunit of human chorionic gonadotrophin (HCG) above 10 000 IU l^{-1} and/or alphafetoprotein (AFP) above 1000 IU l^{-1} (Medical Research Council, 1985; Bosl *et al.*, 1983; Birch *et al.*, 1986; Stoter *et al.*, 1987). Several studies have shown that complete (CR) rates fall by 30-50% in the presence of one or more poor-prognosis factors (Bajorin *et al.*, 1988; Mead *et al.*, 1992).

Etoposide has been shown to be active against cisplatin-resistant germ cell tumours, indicating non-cross-resistance (Williams *et al.*, 1980; Bosl *et al.*, 1985). Moreover, the combination of cisplatin, etoposide and bleomycin (BEP) has greater anti-tumour activity in poor-prognosis patients than the combination of cisplatin, vinblastine and bleomycin (PVB) (Williams *et al.*, 1987). To improve the results of induction chemotherapy in patients with poor-prognosis criteria, both the introduction of new active agents and the concept of alternating chemotherapy combinations could be exploited (Goldie *et al.*, 1982; Goldie and Coldman, 1984). Therefore, the Genitourinary Group of the European Organization for Research and Treatment of Cancer (EORTC) decided to perform a randomised study of four cycles of induction chemotherapy comparing BEP as the standard regimen with alternating cycles of PVB and BEP in poor-prognosis patients. The definition of poor prognosis was derived from the preceding EORTC study in which PBV-treated patients with lymph node metastases >5 cm or lung metastases >2 cm achieved a CR rate of only 56% as compared with 88% in patients with less extensive metastases (Stoter *et al.*, 1986).

Materials and methods

Patients were eligible for the study if they had metastatic testicular non-seminoma with any of the following characteristics: lymph node metastases >5 cm, lung metastases >4 in number or >2 cm, haematogenic spread outside the lungs such as in liver or bone, HCG $>10\,000$ IU l^{-1} or AFP >1000 IU l^{-1}. These cut-off levels of serum markers were based on prognostic factors analyses of EORTC (Stoter *et al.*, 1986) and MRC (Medical Research Council, 1985). Patients were not accepted for the study if they had pure seminoma in the primary tumour, brain metastases, prior radiotherapy or chemotherapy, white blood count (WBC) below 2000 μl^{-1}, platelet count below 100 000 μl^{-1} or a creatinine clearance below 40 ml min^{-1}.

Patients were randomised to receive four cycles of BEP or alternating treatment cycles with PVB/BEP PVB/BEP. BEP consisted of cisplatin 20 mg m^{-2} intravenously (i.v.) on days 1-5 every 3 weeks; etoposide, 120 mg m^{-2} i.v. on days 1,3 and 5 every 3 weeks; and bleomycin 30 mg i.v. on day 2, weekly for 12 weeks. For PVB the schedule was the same as for cisplatin and bleomycin, with vinblastine 0.15 mg kg^{-1} i.v. on days 1 and 2 every 3 weeks. If at the start of a

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Received 27 October 1994; revised 12 January 1995; accepted 13 January 1995

treatment cycle the WBC was below 1500 μl^{-1} or platelets below 50 000 μl^{-1}, treatment was delayed for 1 week. If after 1 week the WBC was not above 3000 μl^{-1} and platelets above 100 000 μl^{-1}, dose modifications of etoposide and vinblastine were applied. Cisplatin and bleomycin were withheld if creatinine clearance fell below 40 ml min^{-1}. If renal function recovered, cisplatin and bleomycin were resumed at 75% and 100% respectively. Severe skin toxicity and signs of lung toxicity were reasons for termination of bleomycin.

After four cycles, patients with normal levels of tumour markers and no clinical or roentgenographic evidence of residual masses were classified as complete responders and were followed without further therapy. Patients in whom markers were normalised but who showed evidence of residual tumour mass underwent debulking surgery. They were classified as complete responders if histological examination showed no viable cancer cells. Patients who still had elevated tumour markers after four cycles and those with viable cancer in the resected specimens were classified as treatment failures.

Rising tumour markers or an increase in tumour volume was considered as an end point indicating progression of disease. Response rates to the treatment regimens were compared by using the standard chi-square test for contingency tables. For comparison of toxicity, a chi-square test for linear trend was used. Time to progression and duration of survival curves were computed using the Kaplan–Meier product limit method and were compared using the log-rank test (Breslow, 1984). The percentage of patients for whom follow-up was available after 5 years was decreased owing to the policy of several institutions to dismiss patients after 5 years. Informed consent was obtained from all patients.

Results

Between March 1983 and August 1987, 250 patients were entered, of whom 125 were randomised to BEP and 125 to PVB/BEP. Sixteen patients (seven on BEP and nine on PVB/BEP) were ineligible, predominantly because of histology other than non-seminoma. Out of the 234 eligible patients, 26 (13 on each treatment) were not evaluable for response, predominantly as a result of omitted explorative surgery. However, all 234 eligible patients were included in the time to progression and the survival analysis. Two patients on the BEP arm died of malignant disease before the completion of chemotherapy. On the PVB/BEP arm two patients died of treatment related toxicity. These four patients were considered treatment failures.

Patient characteristics

Patient characteristics in the 234 eligible patients were well balanced between the two treatment groups, except that trophoblastic tumour elements were diagnosed in 20% of the primaries in the patients on BEP compared with 13% on the PVB/BEP arm. Sixty-five per cent of patients had retroperitoneal lymph node metastases >5 cm, 18% had mediastinal and 16% had supraclavicular metastases. Forty- five per cent of the patients had >4 lung metastases and 31% had lung metastases >2 cm. Liver and bone metastases were present in 6% and 1% of the patients respectively.

According to currently accepted poor prognosis criteria (Birch *et al.*, 1986; Stoter *et al.*, 1990; Mead *et al.*, 1992), 17% of patients had abdominal masses >10 cm and 14% had 20 or more lung metastases. Nine per cent of patients had an HCG $\geqslant$ 10 000 IU l^{-1} and 23% had an AFP $\geqslant$ 1000 IU l^{-1}.

Response to treatment

A total of 105 patients on BEP and 103 patients on PVB/BEP were evaluable for response. The CR were similar: 72% and 76%, respectively ($P = 0.58$) (Table I). When the inevaluable patients are included in the response analysis as treatment failures, the CR rates were again not statistically different: 64% on BEP and 67% on PVB/BEP ($P = 0.65$). After an average follow-up of 6 years (maximum 10 years) the relapse rates from CR were 16% on BEP and 12% on PVB/BEP ($P = 0.50$).

Time to progression and survival

There were no significant differences in time to progression ($P = 0.27$) or duration of survival ($P = 0.32$) between the treatment groups. Figure 1 gives the duration of survival by treatment group for all 234 eligible patients. The 5 year progression-free and survival rates in both treatment groups are approximately 80%. When the log-rank survival analysis is restricted to the group of complete responders, the 5 year survival is 92%. Nine complete responders have died on BEP and six on PVB/BEP, thus there is again no significant difference between the two groups ($P = 0.41$).

Surgery

A total of 138 (67%) of the 204 fully evaluable patients underwent explorative surgery to assess the response to treatment. Twenty-four (17%) still had viable cancer cells, that is 14 (20%) of 71 patients on BEP and 10 (15%) of 67 patients on PVB/BEP. In 61 patients (44%), the resected specimen showed mature teratoma. The remaining 53 patients had fibronecrotic remnants or normal architecture. Eight (33%) of the patients with residual cancer and eight (13%) of the patients with mature teratoma relapsed and died of cancer.

Toxicity

The haematological toxicity throughout four cycles in the 234 eligible patients is presented in Table II. The frequencies of leucocytes below 1 000 μl^{-1} (28% *vs* 5%), leucocytopenic fever (16% *vs* 5%) and platelets below 25 000 μl^{-1} (10% *vs* 1%) are all significantly higher on the PVB/BEP arm.

Table III presents the non-hematological toxicity. Nausea, vomiting, paraesthesia, skin reactions and mucositis were the most frequent side-effects. Neuropathy occurred significantly more frequently in the PVB/BEP arm: 47% *vs* 25% ($P = 0.001$). As a result of toxicity, chemotherapy dosages were reduced in 60% of patients on PVB/BEP and in 68% of

Table I Response to treatment

	BEP	*PVB/BEP*	*p-value*
Eligible	118	116	
Inevaluable	13	13	
Early death	2	2	
CR/eligible	76 (64%)	78 (67%)	0.65
CR/evaluable	76 (72%)	78 (76%)	0.58

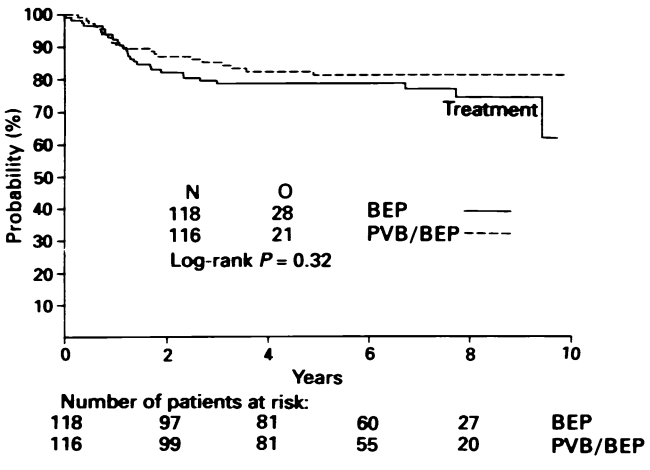

Figure 1 Duration of survival.

Table II Haematological toxicity

Side-effects	*BEP*	*PVB BEP*	*p-value*
Leucocytes $<1\,000\,\mu l^{-1}$ (WHO grade 4)	6 118 (5%)	32 116 (28%)	<0.001
Leucocytopenic fever (leucocytes $<2\,000\,\mu l^{-1}$ $T>38°C$)	6 118 (5%)	19 116 (16%)	0.006
Platelets $<25\,000\,\mu l^{-1}$ (WHO grade 4)	1 118 (1%)	12 116 (10%)	0.001

Table III Non-haematological toxicity

	BEP	*PVB BEP*	*p-value*
Renal (creatinine >1.25 N)	3 118 (3%)	3 116 (3%)	
Allergic reactions	6 118 (5%)	6 116 (5%)	
Gastrointestinal	112 118 (97%)	114 116 (98%)	
Neuropathy	29 118 (25%)	54 116 (47%)	<0.001
Mucosal	19 118 (16%)	32 116 (28%)	<0.05
Skin	56 118 (47%)	50 116 (43%)	
Pulmonary (fibrosis)	4 118 (3%)	3 116 (3%)	

patients on BEP. Chemotherapy was postponed in 24% of patients on PVB/PEB and in 20% of patients on BEP.

Discussion

The rationale for alternating administration of different chemotherapy combinations is based on the assumption that a tumour contains cell populations that are sensitive to one drug but resistant to another agent. Such heterogeneity may either exist at the initiation of cytostatic treatment or develop during treatment as a result of biochemical modulation or genetic mutation (Goldie *et al.*, 1982; Goldie and Coldman, 1984). In the case of germ cell cancer it is likely that natural resistance is involved since these tumours proliferate rapidly and the duration of induction chemotherapy is restricted to 3 or 4 months. These considerations favour the approach with alternating chemotherapy as the initial treatment in patients with poor-prognosis germ cell tumours.

This randomised study comparing four cycles of BEP with an alternating regimen of PVB/BEP for a total of four cycles in poor-prognosis patients shows no differences in CR rates, time to progression and survival. PVB/BEP proved to be considerably more toxic with regard to bone marrow suppression, leucocytopenic fever and neuromuscular symptoms.

It is concluded that the alternating regimen of PVB/BEP does not yield better treatment results than BEP, but is accompanied by more toxicity. This is in agreement with the results of a phase II study of EP/VAB-6 at Memorial Sloan Kettering Cancer Center, which yielded a relapse-free survival rate of 37% in a group of patients for whom a relapse-free survival rate <50% was predicted (Bosl *et al.*, 1987), but is in contrast to the results of two single-institution phase II studies including the POMB/ACE regimen at the Charing Cross Hospital (Cullen *et al.*, 1988; Hitchins *et al.*, 1989) and the CISCA/VB schedule at the M.D. Anderson Hospital (Logothetis *et al.*, 1986), with which survival rates of 70–85% have been achieved in poor-prognosis patients, defined as bulky abdominal, mediastinal or pulmonary disease, or the presence of liver, bone or brain metastases. It is difficult to judge the relative merits of these alternating regimens as the studies were not randomised and different prognostic selection criteria were used. The study here reported is the first testicular cancer trial which investigated the concept of alternating chemotherapy in a randomised fashion. Of note, the standard arm in this study comprised BEP rather than PVB to avoid the possibility that an eventual treatment advantage of PVB/BEP could be due to the addition of etoposide (Williams *et al.*, 1987; Ozols *et al.*, 1988). The explanation for a lack of benefit of PVB/BEP over BEP may be mainly that cisplatin resistance is the crucial factor for treatment failure in testicular cancer. Since vinblastine and etoposide are not cross-resistant, the alternation of these drugs may not be an adequate method to test the concept of cross-resistance (Pastan and Gottesman, 1987). Other agents with significant activity in refractory disease such as ifosfamide (Loehrer *et al.*, 1989, 1993; Motzer *et al.*, 1992), and in particular the taxanes (Hutter *et al.*, 1994), are new candidates for alternating drug combinations which may merit further testing. In addition to the testing of alternating chemotherapy, short intervals between courses may also be further investigated. Data from the Royal Marsden Hospital suggest that the dose intensity of cisplatin at the beginning of the treatment may be important (Horwich *et al.*, 1989). The design of BOP/BEP involved four cycles of bleomycin, vincristine and cisplatin given over the initial 4 weeks, followed by three courses of BEP at conventional 3 week intervals, yielding an 85% persistingly disease-free survival rate in patients with poor-prognosis disease, defined by large volume disease and/or liver, bone or brain metastasis. This study was followed by the testing of three BOP cycles, followed by three VIP cycles (Lewis *et al.*, 1991), and this design has recently been investigaged in a randomised prospective MRC/EORTC collaborative trial comparing BOP/VIP with the 'gold standard therapy' using BEP. The results of this trial are awaited.

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