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Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group

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Summary We investigated the efficacy and toxicity of induction chemotherapy with cisplatin and etoposide with either bleomycin or ifosfamide in patients with intermediate-prognosis testicular non-seminoma. A total of 84 eligible patients were randomized to receive four cycles of etoposide, ifosfamide, cisplatin (VIP), or four cycles of bleomycin, etoposide, cisplatin (BEP). Intermediate prognosis was defined as any of the following: lymph node metastases 5–10 cm in diameter, lung metastases more than four in number or > 3 cm, HCG 5000–50 000 IU l^{-1}, AFP > 1000 IU l^{-1}. The complete response (CR) rates to VIP and BEP were similar, 74% and 79% respectively ($P = 0.62$). Including the cases in whom viable cancer was completely resected with post-chemotherapy debulking surgery, the percentages of patients who achieved a no-evidence-of-disease status were 80% on VIP and 82% on BEP ($P = 0.99$). In addition, there were no differences in relapse rate, disease-free and overall survival after a median follow-up of 7.7 years. The 5-year progression-free survival was 85% (95% CI 74–96%) in the VIP arm and 83% (95% CI 71–96%) in the BEP arm, hazard ratio (VIP/BEP) 0.83 (95% CI 0.30–2.28). The VIP regimen was more toxic with regard to bone marrow function; the frequency of leucocytes below 2000 μl^{-1} throughout four cycles was 89% on VIP and 37% on BEP ($P < 0.001$). Our study does not indicate that ifosfamide is superior to bleomycin in combination with cisplatin and etoposide. The sample size in this study is small as the study was prematurely discontinued when data became available from a competing study that showed no improved effectiveness of VIP compared with BEP. Taken together with these data, bleomycin should not be replaced by conventional-dose ifosfamide.

Keywords: testicular cancer; non-seminatous germ cell cancer; chemotherapy

The treatment of metastatic germ cell tumours with modern cisplatin-based chemotherapy results in cure in approximately 70–80% of patients (Einhorn et al, 1981; Einhorn et al, 1990). Factors associated with treatment failure have been analysed in several large studies and include large tumour volume, the presence of liver, bone or brain metastases, grossly elevated tumour markers and an extragonadal primary site, particularly in the mediastinum (Einhorn et al, 1980; Bajorin et al, 1988; Mead et al, 1992). Based on these prognostic factors, during the past decade, clinical trials have attempted to decrease the toxicity of the standard of four bleomycin, etoposide, cisplatin (BEP) cycles in patients with good-risk disease, or to improve the results by intensifying therapy or by the incorporation of new agents in the chemotherapeutic regimen in patients with one or more adverse risk factors. After the demonstration of the effectiveness of ifosfamide in germ cell cancer and reports on long-term survival of cisplatin–ifosfamide-based salvage regimens (Loehrer et al, 1988; Motzer et al, 1990; Munshi et al, 1990; McCaffrey et al, 1997), the Eastern Cooperative Oncology Group (ECOG) and the European Organization for Research and Treatment of Cancer (EORTC) simultaneously began trials testing the substitution of ifosfamide for bleomycin in the induction regimen in patients with adverse prognostic features. Here, we report the results of the randomized study of four cycles of induction chemotherapy comparing BEP with cycles comprising cisplatin, ifosfamide and etoposide (VIP), conducted by the EORTC in patients with intermediate-prognosis disease. The definition of intermediate prognosis was derived from the preceding EORTC multivariate prognostic factor analysis (Stoter et al, 1987).

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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 5–10 cm, lung metastases more than four in number or > 3 cm, HCG 5000–50 000 IU l^{-1} or AFP > 1000 IU l^{-1}. Patients with extragonadal primary tumours or metastatic sites other than lymph nodes and lung (liver, bone, brain, etc.) were excluded as they were considered to have a poor prognosis. Other ineligibility criteria were pure seminoma (unless accompanied by elevated HCG levels > 200 IU l^{-1} or elevated AFP levels), 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 randomized to receive four cycles of BEP or four cycles of VIP. 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 day

Table 1 Relative dose intensity

Relative dose intensity[a]	BEP (*n* = 38) *n*	(%)	VIP (*n* = 46) *n*	(%)	*P*-value[b]
Cisplatin (%)					
70–90	1	(3)	8	(17)	0.095
90–110	37	(97)	38	(83)	
Etoposide (%)					
< 70	2	(5)	16	(35)	< 0.001
70–90	12	(31)	20	(44)	
90–100	24	(63)	10	(22)	
Bleomycin (%)					
< 90	6	(16)			
90–100	32	(84)			
Ifosfamide (%)					
< 70			19	(41)	
70–90			16	(35)	
90–100			11	(24)	

[a]Numbers and percentages of patients with a dose intensity relative to the planned protocol dose intensity. [b]Wilcoxon rank-sum test.

Table 2 Haematological toxicity

Toxicity	BEP *n*	(%)	VIP *n*	(%)	*P*[a]
Leucocytes (WHO grade)[b]					
0	0	(0)	1	(2)	
1	3	(8)	1	(2)	
2	21	(55)	3	(7)	
3	11	(29)	29	(63)	
4	3	(8)	12	(26)	< 0.001
Thrombocytes (WHO grade)					
0	23	(61)	14	(30)	
1	5	(13)	6	(13)	
2	4	(11)	13	(28)	
3	5	(13)	7	(15)	
4	1	(3)	6	(13)	0.20
Blood culture-proven sepsis	0	(0)	1	(2)	
Leucocytopenic fever (WBC < 2000 μl^{-1}, T > 38°C)	3	(8)	5	(11)	

[a]*P*-values reflect comparisons of grade 3/4 toxicity between the two study arms. [b]Denotes World Health Organization grade.

Table 3 Post-chemotherapy surgery

Variable	BEP (*n* = 38) *n*	(%)	VIP (*n* = 46) *n*	(%)
Surgery performed	28	(74)	30	(65)
Complete macroscopic resection	23	(61)	27	(59)
Partial macroscopic resection	5	(13)	3	(7)
Histological findings				
Viable cancer	5	(13)	4	(9)
Mature teratoma	11	(29)	16	(35)
Necrosis/fibrosis only	9	(24)	10	(22)
Unspecified	3	(8)	0	(0)

1, 3 and 5 every 3 weeks; and bleomycine 30 mg i.v. on day 1, weekly for 12 weeks. The VIP schedule was the same concerning the schedule and dose of cisplatin and etoposide; ifosfamide was given at 1.2 g m^{-2} i.v. on days 1–5 every 3 weeks. Before the infusion of ifosfamide, a bolus of mesna 200 mg m^{-2} was given, followed by ifosfamide as a 4-h infusion in combination with mesna at a dose of 600 mg m^{-2}. After completion of ifosfamide, an additional dose of mesna 400 mg m^{-2} was administered over the next 4 h.

If at the start of a treatment cycle the WBC was below 1500 μl^{-1} or platelets below 50 000 μl^{-1}, treatment was delayed. Blood counts were then repeated every 3 days until these thresholds were reached and retreatment was given. Doses of etoposide and ifosfamide were reduced by 25% were made if the total WBC was between 2000 and 3000 μl^{-1}, and by 50% if the total WBC was between 1500 and 2000 μl^{-1} or if the platelet count was between 50 000 and 100 000 μl^{-1}.

Cisplatin, bleomycin and ifosfamide were withheld if the creatinine clearance fell below 40 ml min^{-1}. If renal function recovered, cisplatin was resumed at 75% and bleomycin and ifosfamide at 100%. 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 radiological evidence of any residual lesions were classified as complete responders and were monitored without further therapy.

Patients in whom markers were normalized, but who showed evidence of residual tumour mass, underwent explorative surgery. The protocol required complete macroscopic resection of all tumour remnants. Those patients were classified as complete responders if the histological examination showed no viable cancer cells. If viable malignancy was found, and it was considered that it had been resected completely, the patients were classified as having been rendered disease free by chemotherapy plus post-chemotherapy surgery. In these cases, the protocol advised two additional cycles of the protocol chemotherapy. Patients in whom the surgical resection of residual disease was incomplete in the presence of viable cancer, and/or those who had continuing elevation of tumour markers, and/or those who had disease progression while on chemotherapy, were classified as incomplete responders. Rising tumour markers or an increase in tumour volume were considered to indicate disease progression.

Response rates to the treatment regimens were compared using the two-sided Fisher exact test (Agresti, 1990). The same test was used for comparing the frequencies of grade 3/4 toxicity. The dose intensities achieved on the two arms were compared using the Wilcoxon rank-sum test (Lehmann, 1975). Survival and time to progression curves were estimated using the Kaplan–Meier technique and compared with a two-sided log-rank test (Kalbfleisch and Prentice, 1980). A significance level of 0.05 was used.

The randomization was stratified by institute. Approval of the ethics committee of the participating hospitals was obtained. All patients gave informed consent.

RESULTS

Between September 1987 and June 1990, 87 patients were entered, of whom 41 were randomized to BEP and 46 to VIP. Three patients on BEP (7%) were ineligible: one was because of pure seminoma histology, one had no testicular cancer, and one had a

Table 4 Treatment results

Variable	BEP (*n* = 38)		VIP (*n* = 46)		*P*[a]
	n	(%)	*n*	(%)	
Response rate (all eligible patients)					
Complete response					
After chemotherapy	30	(79)	34	(74)	0.62
After chemotherapy and debulking surgery	1	(3)	3	(7)	
Total of patients rendered disease free	31	(82)	37	(80)	0.99
Incomplete response/progression	6	(16)	4	(9)	
Early death due to malignant disease	0	(0)	1	(2)	
Insufficient data to evaluate response[b]	0	(0)	3	(7)	
Progression status (all eligible patients)					
Progression during chemotherapy	1	(3)	2	(4)	
Relapse	7	(18)	5	(11)	
Treatment failure	8	(21)	7	(15)	
Progression-free survival and survival (intent to treat)	(*n* = 41)		(*n* = 46)		
Time to progression, events	8	(20)	7	(15)	0.72
Deaths	2	(5)	1	(2)	

[a]Log-rank test. [b]Patients with residual lesions not surgically evaluated.

HCG value at entry of 459 000 IU l^{-1}. Out of the 84 eligible patients, three patients on VIP were not evaluable for response as a result of omitted explorative surgery. The analysis is based on all eligible patients. However, all randomized patients were included in the progression-free survival and survival analyses.

Patient characteristics

Patient characteristics (age, histology, stage, markers) were well balanced between the two treatment groups (data not shown). Overall, 50% of the patients had retroperitoneal lymph node metastases only, 6% had mediastinal and/or supraclavicular lymph node metastases, and 43% had pulmonary metastases. According to the current risk classification (IGCCCG, 1996) 15 (40%) of the patients on BEP fulfilled the criteria for intermediate-prognosis disease, nine (24%) qualified for poor-prognosis disease, while nine patients (24%) had good-prognosis disease. On the VIP arm, these numbers were: intermediate prognosis 18 (39%); poor prognosis eight (17%); good prognosis 15 (33%). From five patients on each arm, data were lacking, predominantly LDH values at entry, to properly classify patients according to the international criteria.

Treatment administered

All but one patient on VIP had four cycles of treatment. This patient died of massive pulmonary embolism 10 days after the start of the first cycle of chemotherapy.

The relative dose intensity of the agents over all cycles is listed in Table 1. The total doses per m^2 delivered over all cycles and the relative dose intensity of etoposide were less in the VIP arm than in the BEP arm ($P < 0.001$). A similar, but non-significant trend was seen in the relative dose intensity of cisplatin ($P = 0.095$).

Toxicity

The haematological toxicity throughout the four cycles is presented in Table 2. The frequency of leucocytes grade 3 and/or 4 toxicity was significantly higher in the VIP arm ($P < 0.001$). There was slightly more thrombocytopenia grade 3 and/or 4 in the VIP arm, but the difference was not significant ($P = 0.20$). Three patients on BEP and five patients on VIP had leucocytopenic fever during the course of their treatment ($P = 0.71$). One patient on VIP developed a sepsis. Pulmonary function tests were performed in 32 patients on BEP and in 33 patients on VIP. The carbon monoxide diffusion capacity declined by a median of 14% from the baseline value in the patients on BEP, whereas there was no decline in the patients on VIP. Out of all 38 patients treated with BEP, four developed clinical symptoms of pulmonary toxicity; two cases had grade 1 (5%), one case grade 2 (3%) and one case grade 3 (3%) toxicity. There were no other differences in non-haematological toxicities between the two treatment arms (data not shown).

Surgery

Post-chemotherapy surgery was performed in 58 patients: 28 patients treated with BEP and 30 with VIP (Table 3). Histological findings were essentially the same for the two treatment groups. Overall, viable cancer was found in 16% of the surgical specimens, mature teratoma in 47% and necrosis/fibrosis only in 33% (unspecified 4%).

Response

Responses to chemotherapy are listed in Table 4. Of the 38 patients on BEP, 30 (79%) achieved a complete response to chemotherapy alone. In the VIP arm, 34 of 46 (74%) achieved a complete response. This result is not significantly different ($P = 0.62$). In addition, one patient on BEP (3%) and three patients on VIP (7%) had viable cancer completely resected at surgery. Therefore, the numbers of patients who were rendered disease free (NED) after chemotherapy plus post-chemotherapy surgery were 31 (82%) on BEP and 37 (80%) on VIP. Again, there was no difference between the two arms ($P = 0.99$).

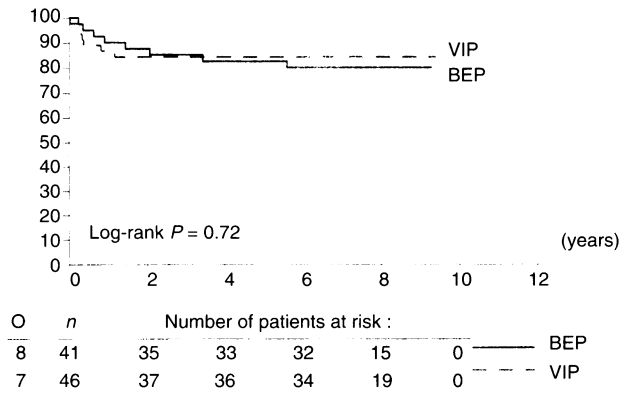

Figure 1 Progression-free survival

Progression-free survival

After a median follow-up duration of 7.7 years, seven patients (18%) on BEP and five (11%) on VIP relapsed (Table 4). Of these relapses, three (two on BEP and one on VIP) had occurred in the nine patients who had viable cancer detected at post-chemotherapy surgery. Including the patients who progressed during induction chemotherapy, a total of eight patients (20%) treated with BEP, and seven (15%) patients treated with VIP developed treatment failure ($P = 0.72$). The hazard ratio (VIP/BEP) was 0.83 (95% CI 0.30–2.28). At 5 years, there was 83% progression-free survival (95% CI 71–96%) in the BEP arm and 85% (95% CI 74–96%) in the VIP arm. Figure 1 shows the progression-free survival for all patients.

In the BEP arm, two patients died of malignant disease; on the VIP arm, one patient died of massive pulmonary embolism 10 days after the start of the chemotherapy. During follow-up, no patients developed a secondary malignancy.

DISCUSSION

We investigated the efficacy and toxicity of induction chemotherapy with cisplatin and etoposide with either bleomycin or ifosfamide. Four cycles of VIP were compared with the standard of four cycles of BEP with 360 mg m^{-2} of etoposide per cycle. The study began in 1987. During the course of the study, data became available from ECOG showing no improved effectiveness of VIP compared with BEP with 500 mg m^{-2} of etoposide per cycle in a study in 304 patients with advanced stage (= poor prognosis) germ cell cancer, according to Indiana criteria (Loehrer et al, 1993). At that time, 87 patients had been entered into the study presented here. In view of the outcome reported by ECOG and our data pointing in the same direction, i.e. no indication of improved efficacy, but increased toxicity by VIP, it was decided to close the study.

The final report from the ECOG study with a median follow-up of 5 years showed that 63% of the VIP-treated patients and 60% of the BEP-treated patients remained free of disease (Nichols et al, 1998) in our study reported here, we observed a 5-year progression-free survival of 83% with BEP and 85% with VIP. The fact that these progression-free survival rates are higher than in the ECOG study is explained by the fact that we selected a more favourable prognostic category of patients. This may also be indicated by the high salvage rate in our relapsing patients, resulting in no more than two disease-related deaths. Although there were no treatment-related deaths in our study, there was significantly greater myelotoxicity associated with VIP. WHO grade 3 and/or 4 leucocytopenia at any time during the course of the four cycles was observed in no more than 37% of patients treated with BEP compared with 89% of patients on VIP ($P < 0.001$). Of note, both treatment arrms included etoposide at a dose of 360 mg m^{-2} per cycle, which was used by EORTC during that period.

When we take the results of the ECOG and EORTC together, we conclude that there is no role for this dose of ifosfamide in the induction chemotherapy regimen in non-seminomatous germ cell cancer. Further evidence of the lack of increased efficacy of VIP over BEP was recently obtained in a collaborative study of the Medical Research Council (MRC) and EORTC that compared three closely spaced cycles of bleomycin, vincristine and cisplatin (BOP) followed by three cycles of VIP, vs four cycles of BEP plus two cycles of EP, in patients with poor-prognosis disease (Kaye et al, 1998). In that study, complete response rates to BEP/EP and BOP/VIP were 57% and 54% respectively ($P = 0.69$). Progression-free survival rates for BEP/EP and BOP/VIP were 60% and 53% respectively.

Recent data have shown that the doses of both ifosfamide and etoposide can be increased two to three times during multiple cycles of chemotherapy, when bone marrow support is realized by repetitive administration of autologous blood progenitor cells (Bokemeijer et al, 1996). In view of the substantially increased dose intensity of these two agents, there appears a rationale to investigate whether the use of high-dose VIP plus autologous progenitor cell support after each cycle of chemotherapy can result in an improved disease-free survival in patients with poor-prognosis disease according to the current international classification, which shows that these patients have less than 50% survival rate with conventional cisplatin combination chemotherapy (IGCCCG, 1996).

We conclude that the combination of cisplatin, etoposide and bleomycin remains the standard induction chemotherapy and that ifosfamide should not replace bleomycin.

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