Eur J Cancer, Vol. 27, No. 11, pp. 1376–1379, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Specialist Interest Articles

Alternating Cycles of PVB and BEP in the Treatment of Patients with Advanced Seminoma

Jourik A. Gietema, Pax H.B. Willemse, Nanno H. Mulder, Jan Oldhoff, Elisabeth G.E. de Vries and Dirk Th. Sleijfer

33 patients (median age 39 years) with advanced seminoma were treated with 4 courses of alternating cisplatin-containing chemotherapy PVB/BEP (cisplatin, vinblastine and bleomycin; bleomycin, etoposide and cisplatin). Patients were classified as stage IIC ($n = 7$), IID ($n = 9$), III ($n = 13$) and IV ($n = 4$). 8 had had prior radiotherapy; 9 had an elevated beta human chorionic gonadotropin (βHCG). 30 patients were evaluable for response and 33 for toxicity. During chemotherapy 3 patients died, 1 due to malignant disease, another due to a cardiac arrest, and 1 patient of a bleomycin pneumonitis. 13 (43%) had a complete remission and 17 (57%) had a clinical partial remission (residual radiographic mass). At a median follow-up of 28 months (range 16–88), 3 patients relapsed, 6–8 months after entry. After completion of therapy there were 2 deaths, 1 due to bleomycin pneumonitis and 1 neither tumour nor treatment related. 26 of 33 (79%) patients achieved a continuously disease-free status. Leucocytopenia and thrombocytopenia of WHO grade 3/4 occurred in, respectively, 32/33 (97%) and 20/33 (61%) of the patients. This study shows that alternating PVB/BEP in this group yields comparable response rates with non-alternating schedules but at the expense of considerable toxicity.
Eur J Cancer, Vol. 27, No. 11, pp. 1376–1379, 1991.

INTRODUCTION

THE SUCCESSES of treatment with cisplatin-based combination chemotherapy of non-seminomatous germ cell tumours are well known [1]. Chemotherapy for patients with seminoma has generally been reserved for the patient who presents with extensive disease, or for the patient who relapses following primary radiotherapy. The general treatment philosophy has been to treat these patients with combination chemotherapy in a fashion similar to those with metastatic non-seminomatous testicular cancer [2–4].

Various regimens containing cisplatin, vinblastine and bleomycin, with or without other agents, have become standard [5, 6]. Recently, Williams *et al.* [7] concluded in a large comparative group study that a regimen with bleomycin, etoposide and cisplatin (BEP) is superior to cisplatin with vinblastine and bleomycin (PVB) in treatment of disseminated germ-cell tumours because of diminished toxicity and, among patients with advanced disease, better efficacy. Since salvage chemotherapy with etoposide and cisplatin has shown to be effective in some patients failing induction chemotherapy with PVB [8, 9], one may conclude that these combination regimens are not completely crossresistant. Therefore, it seems to be attractive to treat patients with advanced disease with an alternating regimen of BEP and PVB.

In an attempt to improve the complete response rate and survival of patients with advanced seminoma, a regimen of a total of four cycles alternating PVB and BEP was administered to patients with advanced seminoma.

Correspondence to J.A. Gietema.
J.A. Gietema, P.H.B. Willemse, N.H. Mulder, E.G.E. de Vries and D.Th. Sleijfer are at the Division of Medical Oncology, Department of Internal Medicine; and J. Oldhoff is at the Department of Surgical Oncology, University Hospital, Oostersingel 59, 9713 EZ Groningen, The Netherlands.
Revised 17 June 1991; accepted 9 July 1991.

PATIENTS AND METHODS

Between March 1983 and August 1989, 33 consecutive patients were entered in this study. Patients with advanced seminoma (≥ stage IIC) considered to be unsuitable for radiotherapy, and patients relapsing from previous radiotherapy were treated with cisplatin-based chemotherapy. All patients had histological confirmation of seminoma and were thoroughly evaluated by means of various studies, including measurement of beta human chorionic gonadotropin (βHCG) and alpha fetoprotein (αFP) levels. Additional pretreatment evaluation included liver and renal function tests, pulmonary function studies (including diffusion capacity), and computed tomography (CT) of the abdomen and chest. Radionuclide bone scanning was performed as clinically indicated. These data were used to categorise patients according to the Royal Marsden classification [10], with the modification that retroperitoneal adenopathy > 10 cm was stratified as stage IID.

The intravenously given induction chemotherapy consisted of four alternating courses of PVB and BEP administered at 3-week intervals, starting with PVB. Cisplatin (20 mg/m^2) was given over 4 h on days 1–5. Vinblastine (0.15 mg/kg) was given as a bolus on days 1 and 2; bleomycin (30 mg) was given over 30 min on days 2, 9 and 16; etoposide (120 mg/m^2) over 30 min on days 1, 3 and 5. Dose modifications were not routine and were permitted only after life-threatening complications. 1 patient who had prior radiotherapy on the chest did not receive bleomycin. Bleomycin was discontinued if lung toxicity (clinical signs of pulmonary fibrosis or a vital capacity drop below 80% of pretreatment baseline value) was observed.

Table 1. Patients' characteristics .

No. of patients	33
Median age (yr) (Range)	39 (23–62)
Stage at diagnosis	
IIC	8
IID	8
III	13
IV	4
Sites of disease	
Retroperitoneal	24
Mediastinum	10
Lung	4
Bone	1
Total sites per patient	
One	21
Two	9
Three	3
Prior radiotherapy	
Yes	8
No	25
Serum markers elevated (%)	
αFP	0
βHCG	9 (27)
LDH	26 (79)
Follow-up (months)	
Median (range)	28 (16–88)

During the fourth course of chemotherapy (i.e. at weeks 9–12) restaging of patients was performed on the basis of repeat measurements of serum markers and repeat radiography of all previously abnormal sites. A complete remission (CR) was defined as complete resolution of known sites of disease including normalisation of serum levels of lactate dehydrogenase (LDH) and βHCG. A partial remission (PR) was defined as a > 50% reduction of the sum of the products of the longest diameter and its perpendicular for all measurable lesions. Patients were divided into three groups based on an arbitrary diameter for residual disease [11]. Group 1 patients had normal imaging studies after chemotherapy. Group 2 consisted of patients with a residual mass < 3 cm, documented radiographically after chemotherapy. Group 3 had a residual mass ≥ 3 cm. Toxicity was measured according to WHO criteria [12].

Remission was dated from the beginning of a response; survival was calculated from the first day of treatment. The curves were plotted with the technique of Kaplan and Meier [13]. All univariate comparisons were made using a χ^2 test; the Wilcoxon test was used for continuous data comparisons.

RESULTS

Patients' characteristics

33 patients were entered in this trial; 30 were evaluable for response and all patients for toxicity. 1 patient died due to malignant disease, 19 days after starting chemotherapy. Another patient died of a cardiac arrest 14 days after starting chemotherapy. As no autopsy was performed, the death was considered to be treatment-related. An additional patient died of a bleomycin pneumonitis during the third cycle of therapy.

Table 1 shows the characteristics of the patients. All 8 patients who received previous radiotherapy had relapsed after an initial response. Site of prior radiotherapy in these patients was abdomen in 6 and chest plus abdomen in 2. LDH was the most commonly elevated serum tumour marker. The median elevated value was 695 U/l (range 296–7500). βHCG was elevated in 27% of patients. The median elevated value was 12.9 ng/ml (normal < 2.0; range 2.9–255). AFP was not elevated in any patient.

After chemotherapy, 13 patients had normal imaging studies and 17 had a definable residual mass.

Table 2. Responses and outcome of all 33 patients related to presentation, disease extent and age

		Death		Response		
	n	Toxic	Early	CR	PR	Relapsed
All patients	33	2	1	13	17	3†
Newly diagnosed	25	2	1	9	13	2*
Relapsed after radiotherapy	8	0	0	4	4	1*
Stage						
IIC	8	1	0	3	4	1*
IID	8	1	1	1	5	0
III	13	0	0	6	7	2*
IV	4	0	0	3	1	0
Age (yr)						
≤ 40	18	2	0	5	11	1*
> 40	15	0	1	8	6	2*

* 1 patient died during salvage treatment.
† 2 patients died during salvage treatment.

Response and survival

The response to therapy and outcome is outlined in Table 2. Of 30 patients evaluable for response, 13 achieved a CR (1 patient with a residual mass underwent surgery and was found to have only retroperitoneal fibrosis-necrosis, and was considered to have a CR). No relapses occurred in patients who achieved a CR. The CR rates did not differ significantly in the various subgroups of age over 40 years, or prior radiotherapy. The other 17 evaluable patients had a PR. There was no difference in survival between patients obtaining a complete response and those obtaining a partial response. In 18 patients a residual mass was found with normal serum tumour marker values after chemotherapy; only 1 had surgery to define response status. The influence of the size of the radiological residual mass on the occurrence of relapse is shown in Table 3. 3 patients relapsed from PR, all having a residual mass ≥ 3 cm. The first had a relapse 6 months afrom the start of therapy, with a progressive residual mass and increasing βHCG levels. He died during ablative chemotherapy and autologous bone marrow transplantation. The second patient had a relapse on the initial metastatic site 7 months from study entry, but achieved another

Table 3. Patients with a residual mass after chemotherapy during follow-up

	n	Relapses
Residual mass		
None	13	0
< 3 cm	5	0
≥ 3 cm	12	3

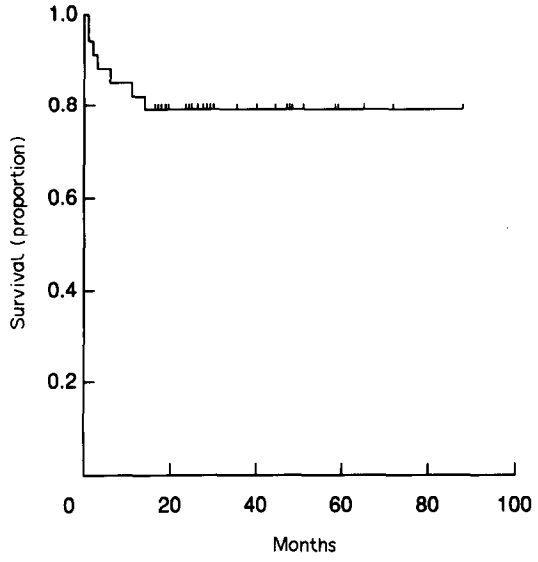

Fig. 1. Overall survival for all 33 eligible seminoma patients.

PR after radiotherapy. The third patient had a relapse 8 months after start of induction, presenting with an enlarged supraclavicular lymph node. He died during radiotherapy of respiratory insufficiency due to pulmonary fibrosis. The first and second patient had both had prior radiotherapy.

Figure 1 shows the survival of all 33 eligible patients in this study. Different subgroups revealed no difference in survival. After a median follow-up duration of 28 months, 26 of 33 patients (79%) are currently alive with no evidence of disease (NED).

Toxicity

Toxicity of this regimen is summarised in Tables 4 and 5. There were 3 treatment-related deaths. 1 patient died during chemotherapy and 1 patient 3 months after start of treatment. Both patients died of complications of bleomycin induced pulmonary fibrosis. Another patient died of a cardiac arrest during the chemotherapy treatment period. An additional patient (aged 51 years, with a history of ischemic myocardial disease before chemotherapy) in CR died of a cardiac arrest 6 months after the start of chemotherapy. This was considered to be not treatment-related.

The haematological toxicity was more apparent than expected. Leukopenia and thrombocytopenia of WHO grade 3/4 occurred in, respectively, 97% and 61% of the patients. Although thrombocytopenia was more severe in patients over 40 years, this difference was not significant ($P > 0.05$). Previous radiotherapy did not result in more severe haematological toxicity. All patients experienced nausea and vomiting requiring intravenous antiemetic treatment. Bleomycin lung toxicity occurred in 27% of the patients. It was not more frequent in patients previously treated with radiotherapy.

Table 4. Haematological toxicity

	All patients	Age (yr)		Previous radiotherapy	
		≤ 40	> 40	No	Yes
Nadir values*					
WBC (10^9/l)	0.4 (0–2.9)	0.4 (0.1–2.9)	0.5 (0–1.7)	0.4 (0–2.9)	0.6 (0.2–1.7)
Platelet count (10^9/l)	33 (7–229)	57 (12–229)	28 (7–131)	35 (7–229)	28 (12–61)
Patients requiring dose reduction†	20/33	10/18	10/15	15/25	5/8

* Median (range)
† No./total.

Table 5. Non-haematological toxicity

	All patients	Age (yr)		Previous radiotherapy	
		≤ 40	> 40	No	Yes
Vital capacity < 80% baseline	10/33	5/18	5/15	8/25	2/8
Bleomycin-induced lung fibrosis	9/33	5/18	4/15	8/25	1/8
Neuromuscular abdominal cramps	10/33	6/18	4/15	6/25	4/8

No./total.

Renal function expressed as creatinine clearance decreased during chemotherapy in all but 1 patient: mean clearance before chemotherapy was 113 ml/min (S.D. 25) vs. after chemotherapy 92 ml/min (20); (Student's t test, $P < 0.01$).

DISCUSSION

In this study, 13 of 30 (43%) evaluable patients achieved a CR after PVB/BEP. In previously reported series using cisplatin-containing regimens in patients with advanced seminoma, complete response rates between 76 and 100% were obtained [14–16]. This difference is likely to reflect the use of consolidation of the response by postchemotherapeutic surgery, radiotherapy or both, to the site of original tumour bulk in several of these trial patients. In the present study only one CR was obtained by additional retroperitoneal lymph node dissection. Therefore, our CR rate is considerably lower compared with other reported results. Using only conventional radiological methods to define the response status after chemotherapy, reported CR rates vary from 32 to 41%; this is comparable with our rate [11, 17]. Whether further treatment or observation in patients not obtaining a radiographical CR is needed is still unclear. Surgical resection of a residual mass following chemotherapy may be difficult because of the severe fibrotic reaction frequently noted in the retroperitoneum, along with an enhanced perioperative mortality in this older patient population [15]. Most investigators have the feeling that surgical resection of residual disease rarely produces findings that would alter the patient's prognosis. Because only 14% of the residual mass patients had persistent seminoma during postchemotherapy surgical resection, researchers at Indiana University recommended close follow-up for patients with seminoma and persistent radiographical masses after completion of induction chemotherapy [18]. In the present series it seems therefore justified to use no evidence of disease (NED) as an overall response assessment, rather than the percentage of CR. 26 of 30 patients who completed four cycles of cisplatin-based chemotherapy achieved a NED status, and the total survival was 79%. These figures are comparable with those earlier reported for advanced seminoma [14–16, 19].

Factors of prognostic importance in the outcome of chemo-

therapy in this patient group such as the extent of disease, expressed in the modified Royal Marsden classification system, age, and prior radiotherapy [14, 17, 19] could not be analysed sufficiently because of the small numbers of patients at different stages and in the different subgroups.

After induction chemotherapy, only 3 of 30 (10%) patients relapsed. All 3 patients relapsed within 1 year after the start of chemotherapy and had a residual mass greater than 3 cm. 1 patient who relapsed after chemotherapy achieved another response after radiotherapy and is alive, and 2 patients died due to subsequent treatment-related complications. As previously mentioned, the optimal management of a postchemotherapy residual mass in patients with advanced seminoma remains unresolved. Motzer *et al.* [11] identified a subgroup of patients with a residual mass of 3 cm or greater who were at high risk for residual viable tumour. They found in their series that 6 of 14 patients with a residual mass $\geq$ 3 cm who underwent surgery had viable residual tumours. According to these investigators additional therapy is indicated for those patients. More recently, Schultz *et al.* reported no relation between size of untreated residual mass and relapse rate or survival; they therefore recommended close observation instead of additional surgery [18]. Although it has been our policy not to perform postchemotherapy surgery for a residual mass in patients with pure seminoma, this series show that patients with a residual mass greater than 3 cm were more likely to relapse than patients with a smaller residual mass. Close observation after treatment during follow-up, especially in this subgroup, is certainly necessary.

As anticipated, the toxicity of the PVB/BEP regimen predominantly involved myelosuppression. Remarkable, however, is the difference in myelotoxicity of the same regimen used in patients with non-seminomatous testicular cancer. Preliminary results of that study revealed that 64% of the patients experienced leucocytopenia greater than WHO grade 2 and 23% experienced thrombocytopenia greater than WHO grade 2 [20]. In the current series these percentages were 97% and 61%, respectively. The reason for this more severe myelotoxicity could partially be explained by the higher age of our study population. Although patients with an age higher than 40 years suffered more severe thrombocytopenia compared with younger patients, due to the relatively small number of patients this was not significant. It has been claimed that irradiated patients tolerate chemotherapy relatively poorly [17, 19]. Although the number of irradiated patients was only 8, we cannot confirm this statement. Others have stated that limited abdominal radiotherapy alone does not reduce the chemotherapy tolerance significantly [14, 16].

In summary, the regimen with four alternating cycles of PVB and BEP has a curative potential in patients with advanced seminoma as 79% of the patients achieved a continuous disease-free status. Although the results of different studies are difficult to compare because of differences in stages, previous treatment and use of additional surgery or irradiation, the PVB/BEP regimen has yielded comparable response rates with PVB or BEP alone [14, 16]. The high incidence of serious adverse events, however, makes this regimen a very toxic one and of questionable use in advanced seminoma patients. In the light of exploration of equally effective but less toxic regimens, there are recent reports of single-agent treatments with carboplatin suggesting similar results to combination therapy [17, 21]. There is also a trend to abolish the use of bleomycin and to employ other active chemotherapeutic drugs such as vincristine [22] and cyclophosphamide [23] in the treatment of seminoma. We are currently treating patients with advanced seminoma with a combination of carboplatin, vincristine and cyclophosphamide. The present study also showed that careful observation without additional treatment in patients with a limited residual mass after chemotherapy is a viable option.

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