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Treatment of Persistent or Relapsing Advanced Germ Cell Neoplasms with Cisplatin, Etoposide and Bleomycin

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Abstract—*Twenty-six patients, previously treated with cisplatin, vinblastine and bleomycin (pVB) had residual or recurrent germ cell tumors and were treated with cisplatin, etoposide and bleomycin (peB). Six patients obtained complete response and 11 patients partial response. Of the 11 patients with partial response 5 were disease free after post-chemotherapy surgery. Seven patients are still alive without evidence of disease with a median follow-up of 40 months (range 14+ – 57+ months). One patient died from acute non-lymphocytic leukemia without evidence of germ cell cancer. Toxicity was modest with only three patients having leukopenic fever. Retrospectively, the patients were analyzed in two groups according to their initial prognostic features. Thirteen patients were considered to have unfavourable prognostic factors and all had progress/relapse after treatment with peB. It is concluded that peB might be useful as first line therapy because of modest toxicity and considerable activity in pretreated patients and that more intensive therapy is necessary in patients with unfavourable prognostic features.*

INTRODUCTION

SINCE the introduction of cisplatin in treatment of disseminated non-seminomatous testicular cancer impressive results have been obtained with response rates from 80–100% [1–3].

Approximately 60–70% of all patients remain without evidence of disease, while 30–40% of the patients will relapse and some of these eventually die from the disease [1–3]. Therefore salvage therapy and even more effective first line therapy are still needed in subsets of patients.

The epipodophyllin derivative etoposide has shown considerable activity in patients with germ-cell cancer [4–7]. Furthermore the combination of cisplatin and VP-16 has been shown to act synergistically in *in vitro* studies [8]. Accordingly we decided to treat all patients who had progressive disease or relapsed after initial treatment with cisplatin, vinblastine plus bleomycin with the combination of cisplatin, etoposide and bleomycin.

MATERIAL AND METHODS

From September 1977 to December 1983 all patients with malignant germ-cell tumors, non-seminomatous stage II and III, relapse after initial stage I and extragonadal disease were treated with cisplatin, vinblastine and bleomycin. Stage I is defined as disease limited to the testis, stage II involvement of retroperitoneal lymph nodes while stage III is subdivided in stage III a and b. Stage III a indicates involvement of supradiaphragmatic lymph nodes and stage III b disease outside the lymph nodes.

Cisplatin was given in a dosage of 20 mg/m^2 for 5 days every 3 weeks for six courses, vinblastine in a dosage of 6 mg/m^2 day 1 and 2 every 3 weeks and bleomycin weekly for 18 weeks with a dosage of 15 mg/m^2 for 12 weeks and thereafter 5 mg/m^2 for the last 6 weeks (pVB) [1]. If a patient had progressive disease during or relapsed after pVB, treatment with cisplatin, etoposide and bleomycin (peB) was initiated.

One cycle of peB consisted of cisplatin given in a dosage of 50 mg/m^2 days 1 and 2, etoposide in a dosage of 120 mg/m^2 day 1–5, and bleomycin 15 mg/m^2 day 1. The treatment was given every 3 weeks and a total of four cycles was planned.

'Complete blood cell count' (cbc) was performed every week while chest X-ray, clinical examination, ^{51}Cr-EDTA-clearance, lung function tests and alfa-foetoprotein and HCG-beta in serum were performed every 3 weeks. Bleomycin was omitted

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diffusion capacity and/or clinical or radiological signs of lung toxicity was found. Cisplatin was reduced according to ^{51}Cr-EDTA-clearance.

If serum-markers normalized during the four courses of peB, CT-scan of the abdomen, and in selected cases of the thorax, was performed. If the patient had residual tumor he was submitted to surgery with the purpose of removing the tumor radically and obtaining a histological diagnosis. peB was given for two additional courses if malignant tissue was found in the tumor. Response was defined according to the WHO recommendations [9]. During follow-up chest X-ray, cbcs and serum-markers were obtained every month for the first year and then the intervals were widened.

When evaluating the response to peB therapy special attention was made to previous response to pVB treatment. Furthermore patients were retrospectively evaluated with regard to initial prognostic factors. The poor prognosis group was defined as patients having one or more of the following features: supradiaphragmatic lymph nodes ≥ 5 cm in diameter, lungmetastases ≥ 5 cm in diameter, intraabdominal tumor ≥ 10 cm in diameter, livermetastases, HCG-beta ≥ 100,000 IE or extragonadal germ cell cancer with elevation of alfa-foetoprotein and/or HCG-beta in serum.

Table 1.

Age: median	28
range	16–57
Initial stage of disease	*No. of pts.*
II	2 (8%)
III a	6 (23%)
III b	14 (54%)
extragonadal	4 (15%)
Histological components:	
embryonal carcinoma	19 (76%)
endodermal sinus carcinoma	9 (36%)
malignant teratoma	9 (36%)
seminoma	6 (24%)
chorioncarcinoma	5 (20%)
mixed tumors	13 (50%)
Initial elevation in s-markers:	
HCG-beta	17 (65%)
alfa-foetoprotein	14 (54%)

RESULTS

During the 6-yr period a total of 26 patients were treated with peB. Twenty-two patients had testicular cancer and four patients had extragonadal germ-cell tumor. The characteristics of these patients, when submitted to the Finsen Institute, are shown in Tables 1 and 2 while response and duration of response to pVB and peB are shown in Table 3. All patients but two relapsed within 1 yr after pVB treatment, median 5 months (range 1–28 months).

Seventeen of the 26 patients (65.4%) achieved regression during peB therapy and details are shown in Table 4. Seven patients are still alive without evidence of disease after peB treatment with a median follow-up of 40 months (range 14+ to 57+ months). Two of these patients had a complete response while five obtained partial remission and were submitted to surgery. In three of these patients malignant tissue was found at the operation while two patients only had fibrosis. One patient who obtained CR during peB died 13 months later because of acute non-lymphocytic leukemia. Autopsy showed no residual germ-cell tumor. This case has been reviewed in an earlier publication [10].

Of the eight patients without evidence of germ cell cancer five originally obtained CR during pVB therapy while three only obtained PR. When evaluating the patients with regard to prognostic factors 13 were in group 1 (poor prognosis) and 13 in group 2 (good prognosis). All patients in group 1 relapsed or had progressive disease after peB while the above mentioned eight patients all belonged to group 2.

The toxicity to peB treatment was modest and only three patients had leukopenic fever. No patient died due to toxicity. Bleomycin was omitted in one or more cycles in four patients because of decreased lung function and in five patients the dose of cisplatin was reduced.

Sixteen patients later received experimental chemotherapy. Five of these received combination chemotherapy including high-dose cisplatin (40 mg/m^2 for 5 days). Three of these patients are still alive. Two have been observed for 11+ and 21+ months without evidence of disease, while the third patient still has active disease and is currently treated with the cisplatin analogue JM-8.

DISCUSSION

In this study 17 patients (65.4%) achieved regression. This is in accordance with other studies [11–14]. Recently the Southeastern Cancer Study group reported 23% long-term survivors without evidence of disease among 44 evaluable patients [14]. In this study lung toxicity due to bleomycin was severe and frequent. In our study 8 of 26 patients (31%) were disease-free and seven of these (27%) are still alive without evidence of disease. Follow-up in these seven patients is median 40 months (range 14+–57+ months). No toxic deaths were seen and lung toxicity was not a major problem when bleomycin was given every 3 weeks.

Table 2. Characteristics of patients including initial response to pVB, response to peB, and surgery

Patients initials	Age	Sites of disease	Response to pVB and duration	Response to peB and duration	Surgery after peB and histologic diagnosis	Third line therapy	Response — outcome
JWJ	30	testis, neck, retroperitoneum	CR — 6 months	CR — 3 months	laparotomy embryonal carcinoma	high-dose DDP, VP-16, actinomycin D, bleomycin	CR, died due to sepsis
BCH	30	testis, mediastinum, retroperitoneum	CR — 4 months	CR — 13 months	laparotomy seminoma		died due to ANNL
GHH	27	testis, neck, lungs	PR — 8 months	PR — 5 months	thoracotomy embryonal carcinoma	high-dose DDP, VCR, VP-16, VM-26, JM-8 TGU	initial PR expired
MF	29	testis, mediastinum, retroperitoneum	PD	NC — 2 months		VP-16, actinomycin	Dinitial PR expired
HO	28	testis, lungs, neck	PR — 9 months	PR — 4 months		progesterone, DDP, actinomycin D,	PD expired TNO-6
JFS	34	testis, retroperitoneum, neck	PD	PD	laparotomy immature teratoma		expired
LR	23	testis, lungs, neck	PD	PD	thoracotomy chorian carcinoma	high-dose DDP actinomycin D	PD expired
JBH	31	testis, lungs	PR — 5 months	PD		progesterone actinomycin D	PD expired
JH	28	testis, lungs	PR — 4 months	PR — 32+ months	thoracotomy fibrosis		alive
JBC	29	testis, lungs	CR — 8 months	CR — 28+ months			alive
JG	57	testis, lungs	CR — 1 month	CR — 40+ months			alive
JLP	26	testis, retroperitoneum, lungs	CR — 12 months	PR — 57+ months	laparotomy undifferentiated carcinoma		alive
SJM	25	testis, lungs	CR — 7 months	PR — 57+ months	thoracotomy fibrosis		alive
SEB	27	testis, lungs	CR — 3 months	PR — 56+ months	thoracotomy embryonal carcinoma		alive
BHJ	34	testis, retroperitoneum, mediastinum, neck	CR — 23 months	CR — 8 months		high-dose DDP VP-16, bleomycin JM-8	PR alive
CF	26	testis, retroperitoneum, mediastinum, lungs, neck	CR — 1 month	CR — 2 months	laparotomy fibrosis (elevated) markers)	high-dose DDP, VP-16, bleomycin, vincristine	CR, alive 21+ months
EFJ	47	testis, retroperitoneum, neck	PR — 7 months	PD		high-dose DDP, VP-16, bleomycin	CR, alive 11+ months
KJJ	45	testis, retroperitoneum, lungs, neck	CR — 7 months	PR — 13 months			expired
LV	18	testis, lungs	CR — 28 months	PR — 14+ months	laparotomy embryonal carcinoma		alive
JM	42	testis, neck	CR — 4 months	PD		actinomycin progesterone	PD expired
OJ	16	testis, retroperitoneum	CR — 1 month	PD		actinomcyin D, progesterone, cyclophosphamide, methotrexate	PD expired
PEJ	25	testis, lungs	PR — 4 months	PR — 2 months		actinomycin D	PD expired
MS	21	retroperitoneum	PD	PR — 2 months		actinomycin D progesterone	PD expired
CSP	25	retroperitoneum neck	PR — 6 months	PR — 3 months		actinomycin D TNO-6	PD expired
TW	20	mediastinum	PR — 5 months	PD		progesterone, actinomycin D, adriamycin, cyclophosphamide	PD expired
EG	50	retroperitoneum mediastinum	PD	PD		actinomycin D	PD expired

+ High-dose DDP: cisplatin 40 mg/m^2 for 5 days every 3 weeks.
Cisplatin analogues: JM-8 and TNO-6.

Table 3. peB response according to initial response to pVB

pVB treatment	No. of pts.	peB treatment PD	PR	CR
PD	5	4	1	0
PR	9	3	6	0
CR	12	2	4	6
Total	26	9	11	6

Table 4. peB treatment, response and duration of response

No. of cycles:	
Median	4
Range	(1–6)

Response:	*No. of pts.*
Complete remission, chemotherapy only	6
Complete remission, chemotherapy and surgery	
Partial remission	6
No change or progressive disease	9
Continuously disease free after peB	7
Currently disease free	9

Response:	*No. of pts.*	*Duration*
CR, chemotherapy	6	3 – 40+ months
CR, chemotherapy + surgery	5	14+ – 57+ months
PR	6	2 – 13 months

Bosl *et al.* have described that the combination of cisplatin and etoposide is only effective in patients who had previously obtained CR during pVB therapy [13]. In this study three patients who had partial remission during pVB are disease-free after peB and surgery.

When we analysed the patient population according to prognostic features none of the patients from the 'poor' prognostic group obtained long disease-free survival after peB. Therefore we conclude that it is the prognostic factors before initial therapy rather than the response to pVB that indicate the efficiency of second line treatment.

The impressive response rates obtained with a regimen which only differs from initial therapy by replacement of vinblastine with etoposide indicates great activity and as toxicity was modest and manageable this combination of cisplatin, etoposide and bleomycin might be useful as first line therapy in patients with good prognostic factors. Preliminary results from trials comparing pVB with peB indicates that peB is at least as active as pVB [15]. It is clear, however, that the group of patients with poor prognostic factors needs more intensive therapy. This can be achieved by increasing the dosages of cisplatin and etoposide while bleomycin (due to cumulative lung toxicity) probably cannot be given in higher doses [16, 17]. Another option is to add additional active drugs to the antineoplastic regimen as suggested by the Charing Cross Group [18].

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