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High-Dose Cisplatin and VP-16 with Bleomycin, in the Management of Advanced Metastatic Germ Cell Tumors

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Abstract—*Intensive combination chemotherapy consisting of cisplatin* 40 mg/m^2 *daily* × 5, *VP*-16 200 mg/m^2 *daily* × 5 *and bleomycin* 15 mg/m^2 *every week was administered to* 29 *patients* (22 *previously untreated and seven previously treated) with poor prognosis germ cell tumors. Eighty-six per cent of the previously untreated patients obtained CR and* 5% *PR. Seventeen patients* (77%) *are alive without evidence of disease after a median observation time of* 11 *months* (*range* 1+ – 19+ months) *after treatment. Seventy-one per cent of the previously treated patients obtained CR and* 14% *PR. Six patients are still alive and four* (57%) *without evidence of disease after a median observation time of* 9 months (*range* 3+ – 12+ months) *after treatment. Toxicity was severe in both groups. In* 73% *of the cycles WBC was below* 1.0 × 10^9/1, *and in* 74% *of the cycles trombocytes was below* 25 × 10^9/1. *Ninety-one per cent had at least one incidence with culture negative neutropenic fever, and in four patients bacteriemia was documented. Kidney function decreased* (*median* 33%) *in previously untreated patients as measured by* ^{51}Cr-*EDTA clearance. Ototoxicity was observed in around* 60% *of the patients* (*two patients has required the use of a hearing aid) and neurotoxicity in around* 40%. *Neurotoxicity was mild in most cases. The results of the present investigation are encouraging and justify an aggressive therapeutic approach to patients with poor prognosis germ cell tumors. The toxicity is substantial, but manageable, and only a prospective randomized study can substantiate whether this excess in toxicity can be translated into an improved survival and cure.*

INTRODUCTION

APPROXIMATELY 70% of patients with testicular cancer treated with cisplatin based combination chemotherapy regimens will achieve a complete remission, and most of these patients will be cured of their disease as the relapse rate is as low as 10% [1, 2]. However, the 'standard' cisplatin chemotherapy is ineffective for the subgroup of patients with bulky disease in abdomen or thorax, visceral metastases, extragonadal primaries or marked elevation of the serum levels of the beta-subunit of human chorionic gonadotropin (HCG) or alpha-fetoprotein (AFP) [1–4].

Ozols *et al.* [5] showed in 1983 that cisplatin could be administered in twice the dose used in current schedules, if administered in 3% NaCl, without any increase in renal toxicity [6]. They found that 'high-dose' cisplatin in combination with vinblastine, bleomycin and VP-16 produced an 88% complete response rate in patients with advanced bulky lung or abdominal disease. Similarly, Schmoll *et al* [7] treated 15 patients with bulky disease and found a complete response rate of 87% using a combination of cisplatin 40 mg/m^2 i.v. day 1–5, VP-16 140 mg/m^2 day 1–5 and bleomycin 15 mg/m^2 i.v. day 1, 8 and 15 q. 21 days.

Since November 1983 we have used a similar treatment in previously untreated patients with poor prognosis germ cell tumors and in patients who had relapsed after primary therapy.

MATERIALS AND METHODS

Twenty-nine patients with poor prognosis germ cell tumors were treated with a 3 drug combination chemotherapy regimen consisting of cisplatin, VP-16 and bleomycin (Table 1). The patients were extensively hydrated throughout the 5 days of platinum treatment receiving 200 ml/hr of isotonic saline. The cisplatin was mixed in 250 ml of 3% sodium chloride and was administered over 30 min followed by 500 ml of 20% mannitol. VP-16 was administered i.v. over 30–60 min following the

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mannitol. At least three courses of this combination were given to all patients.

Twenty-eight of the patients had histologically documented germ cell tumors. Histology of the primary tumor was: seminoma, eight (one pure seminoma, three seminomas with elevated tumor-markers); embryonal carcinoma, 19; choriocarcinoma, three; endodermal sinus tumor, six; teratocarcinoma, three; unclassified germ cell tumors, two; tumors with more than one element, 12. Twenty-two patients were previously untreated (included in this group are two patients who were previously treated with radiotherapy and bleomycin in 1974 and 1975) and seven patients had relapsed after prior radio- and/or chemotherapy. Two of these seven patients had previously received radiotherapy (lumboiliacal field in two patients, and brain irradiation in one patient). Seven patients had previously been treated with cisplatin (median 1200 mg accummulated dose, range 900–2060) and three of these patients had also received VP-16 (median accumulated dose 2000 mg, range 1800–5300) (Table 2). All patients without previous cisplatin treatment had at least one of the following poor prognostic characteristics: 1. Advanced abdominal disease (≥ 10 cm in diameter), 2. Liver metastases, 3. Supradiaphragmatic lymphnode metastases (≥ 5 cm in diameter), 4. Multiple lung metastases with at least one ≥ 5 cm in diameter, 5. HCG ≥ 100.000 U/l and 6. Extragonadal primary with elevated tumor markers (AFP and/or HCG). The age for the whole group of patients ranged from 16 to 52 yr (median 33 yr).

Table 1. *Treatment regimen*

Cisplatin 40 mg/m^2 day 1–5 every 3 weeks
VP-16 200 mg/m^2 day 1–5 every 3 weeks
Bleomycin 15 mg/m^2 every week

Renal function was evaluated primarily by ^{51}Cr-EDTA clearance, which was repeated before and after each series. AFP and HCG in serum were measured at least once a week. Hb, leucocytes, thrombocytes, *s*-creatinine, *s*-sodium, *s*-potassium and *s*-magnesium were measured at least every second day. BUN, *s*-bilirubin, *s*-alkaline phosphatase and *s*-LDH were also measured serially. Audiometry, pulmonary-function tests and appropriate X-rays with measurements of lesions were carried out every 3 weeks. All patients underwent abdominal and/or chest computerized tomography (CT-scan) at the start of chemotherapy and after three series, if tumormarkers were negative.

Tumor response to therapy was monitored by physical examination, serial tumor markers and appropriate radiologic studies. After three cycles of chemotherapy a complete re-evaluation was done, including tumormarkers and repetition of all previously abnormal roentgenograms. Patients who had residual masses following three series of PEB and negative tumormarkers underwent surgical exploration and resection, if possible, of all abnormal tissue. If the resected tissue had any malignant elements or if the patient had elevated markers following three cycles of PEB, the patients were treated with one or more additional series of chemotherapy. Patients who were in complete remission after three cycles of PEB or who had no evidence of residual cancer in the resected specimen received no further treatment.

In order to compare the treatment results of PEB with the platinum–vinblastine–bleomycin chemotherapy regimen (pVB) ('Einhorn regimen'), all patients treated at the Finsen Institute with pVB in the period 1979–1983 were reviewed. Patients with one or more of the poor prognostic characteristics listed above were included in this study (Table 3).

The treatment results of the previously treated patients have been compared with the results obtained after treatment with cisplatin 50 mg/m^2

Table 2. *Prior treatment in the previously treated group. CR = complete remission, PR = partial remission, PD = progressive disease, NED = no evidence of disease, pVB and peB see text.*

Patient no.	Prior radiotherapy	Prior chemotherapy	pVB	No. of cycles	Response	peB	No. of cycles	Response	Response to PEB
1	Lumboiliacal field brain irradiation		x	3	PD	x	2	PD	PD
2			x	6	PR	x	2	PD	CR, NED 11+ months
3			x	6	CR				CR, NED 12+ months
4	Lumboiliacal field	cyclophosphamide	x	6	CR	x	4	CR	CR, relapse after 12 months
5			x	6	CR				CR, NED 7+ months
6			x	6	CR				CR, NED 3+ months
7			x	6	CR				PR, still disease in liver and retroperitoneum after 4 cycles of PEB

Table 3. Comparison between previously untreated patients, treated with highdose cisplatin/VP-16 (PEB) and previously untreated patients treated with pVB(Einhorn regimen). The median follow-up for patients with no evidence of disease in the PEB group is 10 months *after termination of treatment, and in the pVB group it is the number of patients without evidence of disease* 10 months *after termination of treatment that is mentioned.*

	Sites of metastatic disease						No evidence of disease (CR + "CR")	Progression	Patients dead		
	1	2	3	4	5	6			Of toxicity	With disease	Other reasons
PEB $n = 22$	13 (59%)	4 (18%)	7 (32%)	4 (18%)	3 (14%)	4 (18%)	17 (77%)		3 (14%)	2 (9%)	
pVB $n = 26$	14 (54%)	3 (12%)	11 (42%)	3 (12%)	7 (27%)	9 (35%)	4‡ (15%)	11* (42%)	1 (4%)	9 (35%)	1† (4%)

* One of these patients is now in CR after treatment with PEB.
† Died of purulent meningitis.
‡ One of these patients had a relapse 4 yr after the initial treatment, and is now in CR after treatment with PEB.
1 = Advanced abdominal disease (tumor ≥ 10 cm in diameter). 2 = Livermetastases. 3 = Supradiaphragmatic lymphnode metastases (tumor ≥ 5 cm in diameter). 4 = Multiple lung metastases with at least one ≥ 5 cm in diameter. 5 = HCG ≥ 100.000 U/l. 6 = Extragonadal primary with elevated tumor markers (HCG and/or AFP). CR = Complete remission, 'CR' = Complete remission with biopsy verified necrotic tissue in the lungs or mediastinum.

Table 4. Comparison between previously treated patients, treated with highdose cisplatin/ VP-16 (PEB) and previously treated patients, treated with conventional doses of cisplatin/ Vp-16 (peB)

	CR *n* (%)	PR *n* (%)	NC or PD *n* (%)	Relapse *n* (%)	Dead *n* (%)	NED *n* (%)
PEB $n = 7$	5 71%	1 14%	1 14%	1 14%	1 14%	4* 57%
peB $n = 26$	11 (42%)	6 (23%)	9 (35%)†	10 (38%)‡	15 (58%)§	7 (27%)‖

* Median observation time 9 months (range 3+–12+ months).
† One patient have obtained CR after treatment with PEB.
‡ Two patients have obtained CR after treatment with highdose cisplatin, in one patient combined with highdose VP-16, the other patient with conventional doses of VP-16.
§ One patient died of leukemia, without evidence of germ cell tumor (20).
Median observation time 34 months (range 9+–51+ months).
CR = complete remission after chemotherapy and surgery, PR = partial remission, NC or PD = no change or progression, NED = no evidence of disease.

i.v. day 1 and 2 q. 3 weeks, VP-16 120 mg/m^2 p.o. day 1–5 q. 3 weeks and bleomycin 5 mg/m^2 i.m. every 3 weeks (peB). This regimen was used for patients with relapse after pVB treatment at our institution between 1979 and 1983 (Table 4). Standard response criteria according to WHO were employed (8).

RESULTS

Previously untreated patients

Characteristics of the 22 patients previously untreated with cisplatin, are shown in Table 5.

All patients responded to the PEB treatment. Nineteen patients obtained CR (86%) and one patient PR (5%). One patient died of respiratory failure within 10 days after start of chemotherapy, but had a marked decrease in HCG, and one patient died of cardiac failure after one cycle. Two patients in CR died with trombo- and leucocytopenia after 1 and 1.5 series, one of these patients refused hospitalization. The last patient died after six series of PEB with mycotic infection in the lung and heart. Post-mortem examination showed small elements of embryonal carcinoma in the liver and retroperitoneum. Seventeen patients are alive 1+–19+ months after completion of therapy without evidence of disease (median observation 11 months).

At the completion of three cycles of PEB, 10 of

Table 5. Tumor load and tumor markers in previously untreated patients

Patient no.	Testicular cancer	Extragonadal primaries	Liver metastases	Greatest diameter of tumor in					HCG U/L (normal: <8U/l)	AFP nmol/l (normal: <0.07 nmol/l)	LDH U/l (normal: <450U/l)	Status
				Abdomen (cm)	Supradiaphragmatic glands (cm)	Lungs (cm)	Mediastinum (cm)	Others				
1	x		x	14		3			< 8	8.28	4240	CR, NED 12+ months
2	x			12					< 8	2.61	948	CR, NED 15+ months
3	x					6.5			204.422	0.73	1164	'CR', NED 14+ months
4	x			11	1	5			750	2.59	÷	'CR', NED 16+ months
5	x			20	10				82	< 0.07	729	CR, NED 9+ months
6	x			10	1.5	2		brain metastases	401.778	0.26	4500	'CR', NED 3+ months
7	x			7			12		260	0.11	1218	CR, NED 1+ months
8	x			8	3	12			< 8	< 0.07	2930	'CR', NED 5+ months
9	x			16	8	1.5			< 8	304.30	2380	CR, NED 3+ months
10	x				8	3			72.000	< 0.07	1083	'CR', NED 11+ months*
11	x			20	5	1			< 8	0.36	1198	CR, NED 5+ months

12	x				8		9.5	29.000	< 0.07	2390	CR, NED 9+ months*
13	x		x	8				3030	88.00	708	PR, died after 6 cycles in penia with small tumor in the liver
14	x		x	5	4	7		2856.000	< 0.07	÷	Died 10 days after start of chemo-therapy with metastases in all organs
15	x			13	3			< 8	< 0.07	1268	Died after 1 cycle of cardiac failure without penia
16		x		13				21	0.42	463	CR, NED 11+ months
17		x		13				< 8	< 0.07	59	CR, NED 15+ months
18		x		12	1			< 8	< 0.07	1286	CR, NED 16+ months
19		x		12				1510	4.15	÷	CR, NED 19+ months
20		x	x			3	11	< 8	138.00	1012	'CR', NED 6+ months
21		x		13				< 8	< 0.07	330	CR, died in penia after 1.5 cycles
22		x		6		?		< 8	0.62	1060	CR, refused hospi-talization and died in penia

CR = Complete remission, 'CR' = Complete remission with biopsy verified necrotic tissue in the lungs or mediastinum, PR = Partial remission, NED = No evidence of disease. *Previously treated with radiotherapy and bleomycin.

these 17 patients had normal markers, and eight patients had persistent roentgenographic abnormalities at the site of bulk disease. At surgery five patients were found to have fibrosis, two a mature teratoma and one small elements of teratocarcinoma. The latter patient received two additional cycles of platinum and VP-16 (at decreased dose) and is now without evidence of disease. Four patients were tumormarker negative after four cycles of PEB. One of these patients had residual disease on the CT-scan, but no evidence of disease at surgery, two patients were found to have fibrosis and the last patient still had multiple pulmonary infiltrates but numerous biopsies in connection with a thoracotomy have shown necrotic tissue only. The same picture was seen in one patient after five cycles of PEB. Another patient had a fibrotic tumor in the abdomen. The last patient had a teratoma in the mediastinum after five cycles of PEB.

A total of 74 cycles of PEB have been administered to previously untreated patients. Seventy-two per cent of the cycles were given without dose modification and 80% of the cycles were administered within 3 weeks from the last cycle. The major toxicity of PEB was myelosuppression. In 73% of the cycles the WBC was below $1.0 \times 10^9/l$ (for median 7 days, range 1–15 days) and in 74% of the cycles thrombocytes were below $25 \times 10^9/l$ (for median 6 days, range 1–18 days). Twenty patients (91%) had at least one incidence with culture negative neutropenic fever, and 68% of the patients had two to five cases of neutropenic fever. In four patients bacteriemia was documented during treatment.

Twenty-one patients received blood transfusions (median 16, range 7–64) and 14 patients received platelet transfusions (median 17, range 1–67).

Glomerular filtration rate decreased from 104 ± 6 ml/min to 71 ± 4 ml/min (X ± S.E.M.) after three cycles. Seventy-nine per cent of the patients developed a high frequency hearing loss of more than 30 dB in the 2–8000 Hz area. Two patients had a functional hearing impairment that has required the use of a hearing aid. Eleven patients developed paresthesia in distal extremities which are gradually resolving. All patients had gastrointestinal toxicity with nausea, vomiting and mucositis. Diarrhoea was observed in 31% of the cycles, but was not a major problem in most of the cases. All patients developed hypomagnesemia and received magnesium chloride i.v.. No significant pulmonary toxicity was seen.

Previously treated patients

This group consisted of five patients with testicular cancer, one patient with an extragonadal primary tumor and one patient with an embryonal carcinoma in the ovary. These patients were primarily diagnosed between 1979 and 1983. Six patients had elevated tumormarkers (HCG in six, AFP in five and both in four patients).

The previous treatments are listed in Table 2. One patient relapsed 4 yr after treatment with the 'Einhorn' (pVB) regimen. Six of seven patients responded to the PEB treatment. Five patients obtained CR (71%) and one patient PR (14%). One patient became marker negative but died after 1.5 cycles with progression in previously irradiated brain metastases and with decreasing lung and kidney function.

Six patients are still alive, four without evidence of disease after a median follow-up of 9 months (range 3+ – 12+ months) after completion of therapy. One patient with CR had a relapse after 12 months with increase in HCG and evidence of disease in the liver. The patient with PR was not disease free at the surgical exploration performed after four cycles of PEB.

At the completion of three cycles of PEB four of the seven patients had normal markers and no roentgenographic abnormalities. One patient became marker negative after extirpation of a lymph node containing malignant germ cells in the neck and did not receive further treatment. This patient is still without disease (observation time 11+ months)

A total of 21 cycles of PEB has been administered to previously treated patients. Fifty-two per cent of the cycles were given without dose modifications and 76% of the cycles were administered within 3 weeks from the last cycle.

In 71% of the cycles the leucocyte count was below $1.0 \times 10^9/l$ (median 5 days, range 1–13 days) and in 71% of the cycles the platelets count was below $25 \times 10^9/l$ (median 6 days, range 1–15 days).

All patients had at least one incidence with culture negative neutropenic fever, four patients had two incidences and one patient three cases. All patients received blood transfusions (median 22, range 3–33) and six patients received platelet transfusions (median 15, range 2–55).

Glomerular filtration rate decreased from 85 ± 11 ml/min to 57 ± 16 ml/min (X ± S.E.M.) after three cycles. Ototoxicity (50%), neurotoxicity (33%) and gastrointestinal toxicity were a little less than in the previously untreated patients. No significant pulmonary toxicity was seen.

The comparison between PEB and pVB treatment (Table 3) shows that the number of patients without evidence of disease after treatment with PEB is significantly higher ($P < 0.01$) than the number in the pVB group (after a median observation time of 10 months in the PEB group and an observation time of 10 months in the pVB group).

Likewise the comparison between PEB and peB (Table 3) shows that the resposne rate of PEB is somewhat higher than that of peB (CR + PR) (86% vs. 65%), but the observation time in the PEB group is short and the numbers are small.

DISCUSSION

The platinum–vinblastine–bleomycin (pVB) combination chemotherapy and similar platinum based combination regimens have greatly improved the outlook for patients with disseminated germ cell tumors. However, there is a clinically definable subset of patients in whom current combination chemotherapy regimens have been markedly less effective, and likewise treatment of patients failing front-line chemotherapy has been rather unsuccessful, even though long disease-free survival has been reported in some cases [9].

In a report from the British Medical Research Council Working Party on Testicular Tumors (10) a poor prognostic group with a 3-yr survival rate of 47% was defined. The prognostic factors concerning liver metastases and supradiaphragmaticlymphnode involvement were similar to the ones applied in the present study. We have used, however, a higher limit for the size of retroperitoneal tumor masses ($\geq$ 10 cm diameter vs. $\geq$ 5 cm diameter), for lung metastases (multiple, one or more $\geq$ 5 cm diameter vs. multiple, one or more $\geq$ 2 cm diameter) and for the HCG level (100,000 U/l vs. 1000 U/l). This implies that the patients in our series belongs to a group, with an even worse prognosis, than those included in the poor prognostic group of the British study.

The comparison between patients treated with pVB and PEB shows that this is probably correct (Table 2). The results listed in the PEB group are those obtained after median 10 months observations after treatment and in the pVB group 10 months after treatment. Twenty patients in the pVB group were dead or showed progressive disease at that time and all these patients had their first relapse within 6 months after treatment with pVB. Only five patients in the PEB group have not reached this observation time. The treatment results with PEB are apparently superior to the pVB treatment in this group of patients with advanced metastatic germ cell tumors. A strict comparison obviously requires a randomized trial, however.

Pizzocarro *et al.* [11] have shown that they can obtain the same results as we have with half the doses of cisplatin and VP-16 used in this study in patients with bulky disease. This is in contrast to the results reported by Williams *et al.* [12] who found equivalent therapeutic responses between pVB and cisplatin 20 mg/m^2 for 5 days, VP-16 100 mg/m^2 for 5 days and 30 units of bleomycin every week, but only 34% of the patients with advanced disease obtained a favorable response.

Several approaches directed at improving treatment results in high-risk patients are being explored. They fall broadly into three categories: the use of multi-drug regimens; schedules employing existing drugs in higher doses; and the investigation of new drugs. The first approach has been explored by Newlands *et al.* [13]. Sixty-nine patients were treated with a combination of vincristine, bleomycin, cisplatin, VP-16, actinomycin D, cyclophosphamide and methotrexate and the overall survival was 83%. Eight of the 69 patients had liver involvement of whom six went into complete remission. These patients would fulfil the entrance criteria, while it is not possible to assess from the published data, how many of the other patients who would actually fall into our category of 'high risk' patients.

There are several reasons why we have chosen a combination of high-dose cisplatin/VP-16 to patients with poor prognosis germ cell tumors. Firstly cisplatin has a steep dose–response curve in testicular cancer. Hayes *et al.* [14] showed that increasing the dose of cisplatin from 40 mg/m^2 to 120 mg/m^2 produced a 55% response rate in patients, who had failed the lower dose. The initial results from Ozols and co-workers using 40 mg/m^2 $\times$ *d* for 5 days to this group of patients have also been encouraging [5].

Secondly VP-16 is an active agent against germ cell tumors [15]. Using VP-16 in combination with other drugs, Hainsworth *et al.* [9] reported a 23% long-term survival in previously treated patients. In a phase II study of high-dose VP-16 monotherapy for refractory germinal malignancies two of six patients, previously treated with VP-16 in lower doses, responded with one CR and one PR [16]. The responses were of short duration (5 and 3 months). In addition to this VP-16 and cisplatin have been shown to be synergistic in several animal tumor models [17]. Three of the previously treated patients in our study have received prior treatment with VP-16. One patient with brain metastases did not respond to treatment either with pVB in conventional doses or 'low-dose' cisplatin and VP-16. This patient also showed progression on high-dose cisplatin/VP-16. The two other patients had received six cycles of pVB with one CR and one PR. After relapse both received cisplatin 50 mg/m^2 for 2 days and VP-16 120 mg/m^2 p.o. for 5 days. One patient obtained CR (6 months) and the other had progressive disease. Both obtained CR after treatment with high-dose cisplatin/VP-16 (11+ and 12 months). Our data from the previously treated patients support the theory about a steep dose–response curve for both cisplatin and for VP-16 in patients with germ cell tumors. The

comparison of PEB and peB in previously treated patients shows a superiority of PEB with respect to the response rate (CR + PR) which is 86% for the PEB and 65% for peB. The observation time in the PEB group is only 9 months compared with the median follow-up in the peB group which is 34 months, and the numbers in the PEB group are still to small to allow for a meaningful comparison.

In a retrospective study from the Finsen Institute [4] we found that long-term complete remissions in patients with extragonadal germ cell primaries treated with pVB were only observed in patients who initially had normal values of HCG and AFP. In the present study of 7 of 22 previously untreated patients had extragonadal primaries, and four of these had elevated tumor markers. All four obtained CR and three are still alive 6+ - 19+ months after completion of therapy.

Some authors have included obstructive uropathy [6] and others high concentrations in serum of LDH as poor prognostic features. In the present material 18% of previous untreated patients had obstructive uropathy and 95% increased concentration of LDH (Table 5).

With respect to the nephrotoxicity, Ozols *et al.* found that high-dose cisplatin (40 mg/m^2 body surface area × *d* for 5 days) can be administered without any increase in nephrotoxicity in previously untreated patients using vigorous saline hydration and 3% saline as the vehicle for drug delivery [6]. This is in contrast to the results of this study where all previous untreated patients had a decrease in the glomerular filtration rate (median 33%, range 17–53%). Also Legha *et al.* [18] have questioned the protection of nephrotoxicity by hypertonic saline, stressing that *s*-creatinine and creatinin-clearance are not suited for exact determination and follow-up of the kidney function in these patients [19].

In our study 86% of the previously untreated patients obtained CR and 5% PR. Seventy-seven per cent are still alive without evidence of disease. Of previously treated patients 71% obtained CR and 14% PR, and 57% are still alive without evidence of disease. The data from both groups are very encouraging compared with the retrospective data and indicate a superiority of the PEB regimen in the treatment of very advanced metastatic germ cell tumors. The toxicity, especially the hematologic toxicity is, however, very severe, and necessitates a well equipped and well trained clinical back-up setting. Many of the patients should stay hospitalized during most of the treatment period. Toxicity is, however, generally manageable. The therapeutic approach to these high-risk patients should be very aggressive, as a realistic goal of such therapy is long-term disease-free survival and potential cure.

In spite of the toxicity, the results obtained in this group of often young patients with very poor prognosis are sufficiently encouraging and therefore it is indicated to further explore this aggressive treatment in larger series. Only when the results of such series and longer follow-up of the present series are available, can final conclusions be made.

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