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Therapy of Extragonadal Germ-cell Tumors

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Abstract—*Sixteen patients with primary extragonadal germ-cell tumors were treated at the Department of Chemotherapy, Finsen Institute, Copenhagen from* 1976 *to* 1982. *Twelve patients received a combination of* cis-*diamminedichloroplatinum (cisplatin), vinblastine and bleomycin (PVB). Eight patients had a complete remission and* 5 *had a partial response. Eighty-six percent of the patients achieving complete remission remain free of disease after a median follow-up of* 42 months. *The best results with PVB were obtained in teratocarcinomas and embryonal carcinomas, while more effective chemotherapy regimens are needed for the treatment of choriocarcinomas and endodermal sinus tumours.*

INTRODUCTION

MALIGNANT tumours having the same morphological appearance as germinal tumours of the testis are sometimes found in other anatomic locations such as the anterior mediastinum, retroperitoneum, pineal gland and presacral region.

The extragonadal origin of these tumours is generally accepted, although it seems likely that some of the reports of extragenital germ-cell primaries are fictitious or, at the very least, inadequately documented. However, in view of the many cases that are well documented, both clinically and histologically, it would appear that the extragonadal germ-cell tumor is a clinical fact.

Because of the rarity of these tumors, all reported series focusing on treatment have included relatively small numbers of patients. Hainsworth *et al.* [1] found that extragonadal germ-cell tumors are as curable as testicular germ-cell tumors when treated with intensive cisplatin containing combination chemotherapy regimens, while Feun *et al.* [2] reported that this group of patients responded less well than patients with disseminated testicular cancer.

With this discrepancy as a background, we reviewed 16 patients with extragonadal germ-cell tumors treated at the Department of Chemotherapy, Finsen Institute from 1976 to 1982.

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MATERIALS AND METHODS

Sixteen male patients with measurable disease were included in the review. In all patients the testes were negative on palpation for malignancy both before chemotherapy and during the follow-up periods. The testes were examined at autopsy in 2 patients and showed no evidence of neoplasm or scar formation. Four patients had negative testicular biopsies. Histologic specimens were reviewed by experienced pathologists at the Finsen Institute and in all cases were compatible with the diagnosis of germ-cell neoplasm. The ages of the patients at the time of diagnosis ranged from 19 to 44 yr (median 26 yr).

Histologic subtypes and the location of the primary tumor are shown in Table 1. There were 7 patients with tumor located in the mediastinum, 7 with tumor located in retroperitoneal space and 2 with tumor both in the retroperitoneal area and the mediastinum.

Metastatic sites were as follows: lung, 8 (2 with extensive disease and metastases to both lungs and mediastinum); lymph nodes, 4 (cervical nodes, 4; inguinal nodes, 1; axillary node, 1); bone, 1. Nine patients had more than one metastatic site (see Table 1). Twelve patients received treatment with cisplatin, vinblastine and bleomycin (PVB) in the following doses: cisplatin 20 mg/m^2 i.v., days 1–5 q. 3 weeks, vinblastine 6 mg/m^2 i.v., days 1 and 2 q. 3 weeks and bleomycin 15 mg/m^2 i.v., weekly for the first 10 weeks and then 5 mg/m^2 weekly for 8 weeks thereafter. This regimen was given for a period of 4 months. Three patients with pure seminoma received supervoltage radiotherapy and 1 also received chemotherapy

Table 1. Relationship of tumor markers to histologic subtypes

Patient No.	Age	Histologic subtypes						Tumor markers before therapy		Metastases before therapy
		Seminoma	Embryonal carc.	Choriocarc.	Endodermal sinus tumor	Teratocarc.	Germ-cell tumor	α-feto. (μg/l)	β-HCG I.E.	
1	31			X				125	148.000	both lungs, neck, axillary and inguinal lymph nodes
2	42			X				102	38.000	both lungs, bone
3	24				X			14.240	0	
4	21		X		X			4.040	0	lung
5	42	X						0	0	
6	44						X	0	0	
7	25		X					0	211.191	lymph node in the neck
8	38		⊠					0	0	lymph node in the neck
9	22						⊠	0	0	lung, lymph node in the neck
10	27				O			470	0	lung
11	21	O	O		O			950	0	lung
12	23					O		0	0	
13	33	O						0	0	
14	19		O		O	O		27.270	0	lung
15	19				O			62	0	
16	28	O						0	0	

O = Tumor located in mediastinum; X = tumor located in retroperitoneum; ⊠ = tumor located both in mediastinum and retroperitoneum; carc. = carcinoma; α-feto. = α-fetoprotein.

(PVB). The radiation dose ranged from 3500 to 4500 rad administered in 200-rad fractions. Two patients with non-seminomatous tumors received other chemotherapy than the PVB program; 1 patient was treated with vincristine, doxorubicin, methotrexate and bleomycin and the other patient received vincristine, CCNU, cyclophosphamide and methotrexate for 1 month before PVB. Four patients underwent debulking surgery before chemotherapy.

Renal function was evaluated primarily by the determination of Cr-EDTA clearance. Measurements were repeated after 3 series and at the end of treatment. The serum tumor markers alfa-fetoprotein and the beta subunit of human chorionic gonadotropin (β-HCG) were determined for all patients and measured serially. Hb, leucocytes, thrombocytes, S-bilirubin, S-alkaline phosphatases, S-creatinine and S-electolytes were also measured serially. Audiometry was performed prior to therapy and after 3 series. Appropriate X-rays together with measurement of lesions and pulmonary function tests were carried out every 3 weeks. Patients with disease in the retroperitoneum underwent abdominal computerized tomography at the start of chemotherapy and again after 3 and 6 series.

Tumor response to therapy was monitored by physical examination, serial serum tumor markers and appropriate radiologic studies. After 6 cycles of chemotherapy a complete re-evaluation was done, including tumor markers and repetition of all previously abnormal roentgenograms.

The criteria for response were in accordance with the definitions provided by the WHO [3] and included normalization of serum tumor markers. Progression was defined as greater than 25% increase in the sum of areas of all measurable lesions and/or the appearance of new lesions and/or increase in alfa-fetoprotein or β-HCG of more than 25% (two measurements) compared to the lowest hitherto.

With respect to the dosage of chemotherapy, vinblastine was reduced by 33% if leucocyte counts were between 2.5 and $3.0 \times 10^9/l$ and/or platelets between 75 and $99 \times 10^9/l$. Thirty-three percent of the dose was given if leucocyte counts were between 2.0 and $2.5 \times 10^9/l$ and platelets $>75 \times 10^9/l$. Bleomycin was discontinued if the patient developed pneumonitis which was evident either clinically or roentgenologically.

Patients in complete remission either received no further chemotherapy (6 patients) or maintenance vinblastine 6 mg/m^2 on day 1 and actinomycin-D 1.5 mg/m^2 on day 1 every month (2 patients). Patients who still had a residual active tumor after chemotherapy were treated with a variety of second-line chemotherapy. Palliative radiotherapy was applied in few cases.

RESULTS

The treatment results and follow-up data for the 16 patients are shown in Table 2. Six patients achieved complete remission after initial treatment. Three of these had a pure seminoma; 2 of the latter patients received radiotherapy alone and 1 received radiotherapy together with chemotherapy. Two patients treated with PVB obtained a complete remission only after maintenance therapy with actinomycin-D and vinblastine was

Table 2. Results of treatment

Patient No.	Reponse CR	PR	Progress	Duration of response in month	Status
1		X		5	dead after 8.5 months
2		X		3	dead after 13 months
3		X		4, 5	dead after 18.5 months
4		X		4	alive with disease 13 months after diagnosis
5	X			42+	NED
6	X			62+	NED
7	X			4	alive with disease 6 months after diagnosis
8	X			29+	NED
9	X			23+	NED
10			X		dead after 7 months
11			X		dead after 10.5 months
12	X			15+	NED
13	X			60+	NED
14			X		dead after 18 months
15		X		4	alive with disease 16 months after diagnosis
16	X			62+	NED

CR = Complete response; PR = partial response; progress = progression; NED = no evidence of disease.

instituted. Seven of the patients with complete response remain in continuous remission after follow-up ranging from 15 to 62 months (median 42 months) (Table 2).

The patient who relapsed 4 months after achieving complete remission is now receiving second-line treatment with cytostatic agents. He had a second-look operation performed 2 months after complete remission with no evidence of disease, but relapsed 2 months later with an increase in β-HCG.

Of the 5 patients with partial responses, 3 have since died from their disease and 2 are alive with progressive disease, despite treatment with a wide variety of second-line agents. The duration of response in this group was between 3 and 5 months (Table 2). At the time of diagnoses 9 patients had elevated tumor markers (alfa-fetoprotein, 6 patients; β-HCG, 1 patient; and both, 2 patients); see Table 1. Long-term complete remission was only observed in patients who initially had normal values of β-HCG and alfa-fetoprotein.

Toxicity was common in patients receiving PVB. Myelosupression ($<2.5 \times 10^9/l$ leucocytes) was seen in 11 patients, but there were no life-threatening infections. Thrombocytes $<100 \times 10^9/l$ were seen in 7, without any bleeding episodes.

DISCUSSION

Only small series of patients with extragonadal germ-cell tumor treated with PVB have been reported. Fox *et al.* [4] described the results of treatment in 3 patients. All of the patients died—2 from disease and 1 from septicemia caused by myelosuppression. Richardson *et al.* [5] reported on 10 patients. Four of these patients were alive with no clinical evidence of disease at the time of reporting, but only 2 of the patients had been followed for more than 1 yr.

The Southwest Oncology Group [2] have reported on 16 patients. In this study only 3 patients were complete responders, and 1 of these relapsed and died from metastatic disease; another patient died from septicemia (drug-induced myelosuppression) and post-mortem examination revealed residual tumor, while the third patient was lost to follow-up only 4 weeks after achieving complete remission.

In contrast, Funes *et al.* [6] reported on 14 patients with mediastinal germ-cell tumors treated with PVB, achieving a 46% complete remission rate with 1 relapse after median 16 months follow-up.

A higher response rate was observed by Hainsworth *et al.* [1] treating 31 patients. Chemotherapy and surgery resulted in a complete remission in 21 of 31 patients. Two of these relapsed after chemotherapy and surgery and 1 died from chemotherapeutic side-effects. Partial remissions were seen in 10 patients, of whom 7 died with progressive disease. Two patients are alive with progressive cancer and 1 died from an unrelated cause. In this study patients with endodermal sinus tumor were excluded because of the poor therapeutic response of these tumors.

Kuzur *et al.* [7] treated 10 patients with endodermal sinus tumor of the mediastinum. Four of these were treated with PVB. There was one complete remission lasting about 6 months and 3 partial responses. The median duration of initial response was 4 months for the 10 patients, with a range of 0–60+ months. One patient was still in complete remission more than 5 yr after diagnosis of the disease. The median survival of the 9 patients who relapsed was 10 months.

In our study there were 8 patients (50%) with complete remission and up to the time of reporting only 1 relapse. It is striking that only 1 patient with elevated tumor markers at the start of chemotherapy showed a complete remission; this patient has since relapsed.

Similarly, it has been observed that regardless of clinical staging, patients with disseminated testicular cancer and elevated pretreatment markers have a far worse prognosis than those with normal markers [8]. The small number of patients precludes further definite conclusions with respect to prognostic factors, but the histological subtypes do not appear to respond equally well.

In our study patients with choriocarcinomas and endodermal sinus tumors either had a partial response or progression of their disease. The same pattern is seen in the papers referred to above [1, 7].

With respect to seminoma, there is considerable evidence that radiotherapy alone or in combination with surgery may be curative in 66–81% of cases [9–11]. For this reason radiotherapy should be the treatment of choice for localized extragonadal seminoma. Chemotherapy should be reserved for those patients whose extragonadal seminomas are too widespread or too bulky to permit technically adequate radiotherapy.

The outlook for patients with teratocarcinomas and embryonal carcinomas has improved considerably, with the possibility of cure in some patients following the development of increasingly effective chemotherapy regimens. However, more effective regimens are obviously still needed for the treatment of choriocarcinomas and endodermal sinus tumors.

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