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Long Term Results of Treatment in Patients with Extragonadal Germ Cell Tumours

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From 1979 to 1991 56 patients with extragonadal germ cell tumours (EGCT) received cisplatin based chemotherapy. From 16 patients with seminomatous EGCT 13 achieved complete remission (CR) with chemotherapy alone, 2 with additional radiotherapy with final CR rate of 94%. 5 (31%) patients developed relapses and at a median follow-up of 38 (5–103) months 11 (69%) are alive and 10 (62%) have no evidence of disease (NED). Only 7 patients with non-seminomatous EGCT reached CR with chemotherapy alone and 8 more with additional chemotherapy or surgery. Overall CR was 37% and 3 (20%) relapses have been observed. At a median follow-up of 26 (3–114) months 14 (35%) are alive and remain free of disease, 26 (65%) have died. By univariate analysis seminomatous EGCT patients had a significantly greater likelihood of achieving a CR, for non-seminomatous EGCT *BEP* induction chemotherapy was superior to VAB-6, and NSEGCT patients with serum levels > 2000 ng/ml had worse prognosis. Current staging systems are insufficient to predict the treatment outcome in EGCT.
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INTRODUCTION

EXTRAGONADAL GERM cell tumours (EGCT) are uncommon neoplasms. They share serological and morphological characteristics with the primary germ cell tumours of the testis and consequently their treatment is similar. Considerable success has been achieved since introduction of cisplatin based chemotherapy in the treatment of testicular cancer, but results are inferior for EGCT [1–9]. This report describes the clinical experience of the Cancer Research Center (CRC) of the Russian Academy of Medical Sciences in patients with ECGT.

MATERIALS AND METHODS

From 1979 to 1991, 56 patients with EGCT and a mean age of 29 (16–60) years, were treated and evaluated for response and survival. We defined EGCT as a germ cell tumour (GCT) arising in the mediastinum, retroperitoneum and other sites, without demonstrable gonadal tumour at presentation as determined by testicular ultrasound and/or negative testicular biopsy specimens. Patients with undifferentiated tumour or with histological diagnosis of the mediastinal, or retroperitoneal tumour with elevated serum markers, have been included in the analysis. Before treatment all patients had a complete history and physical examination, blood chemistry and complete blood count, chest X-ray and computed tomography (CT) scans of the lungs and abdomen, as well as an abdominal ultrasound. Radioimmunoassay techniques were used for quantitative determination of alpha fetoprotein (AFP) and human chorionic gonadotrophin (HCG). Serum values of less than 13 ng/ml and 10 ng/ml, respectively, were considered normal. Estimations of extent of the disease were based on the Indiana staging system [10] and the probability of treatment outcomes was calculated as previously described [11].

Characteristics of the patients are summarised in Table 1. The mean and range AFP levels (ng/ml) for each subgroup were: 9 patients with different subtypes of non-seminomatous EGCT (NSEGCT): 6880 (18–16000); 6 patients with GCT: 1014 (14–4000); 5 patients with undifferentiated tumours: 1388 (14–1600); and for 5 patients with unknown histology: 1826 (14–8000). In all patients the tumour was localised in either the mediastinum, or retroperitoneum. However, 2 patients had EGCT of axillary or cervical lymph nodes and pelvic lymph node involvement was also observed in 1 case.

26 patients had been previously treated with chemotherapy, debulking surgery and radiotherapy or a combination thereof. None had been previously treated with cisplatin-based combination chemotherapy and were referred after failing initial treatment. The patients were treated with various cisplatin-based regimens previously described for the treatment of primary testicular cancer, VAB-6 [12], PVB+ doxorubicin [13], BEP [14], CP [15], and with other combinations (cisplatin + ifosfamide, cisplatin + vinblastine + cyclophosphamide).

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Table 1. Patients' characteristics

	SEGCT	NSEGCT	Total
No. of patients	16	40	56
Histology			
Germ cell tumours	16	30	46
Undifferentiated (AFP positive)	0	5	5
Unknown (AFP positive)	0	5	5
Primary site			
Mediastinum	6	16	22
Retroperitoneum	5	21	26
Mediastinum + retroperitoneum	4	1	5
Other sites	1	2	3
Extent of disease*			
Minimal	1	2	3
Moderate	4	5	9
Advanced	11	33	44
Pretreatment elevated markers			
AFP positive (patients)	0	26	26
Mean level (ng/ml)		2103	
Range		(14–16000)	
HCG positive (patients	4	24	28
Mean level (ng/ml)	150	184	
Range	(22–501)	(12–2700)	
LDH positive (patients)	8	19	27
Mean level (u/l)	801	1751	27
Range	(500–2013)	(644–3935)	
Prior treatment			
None	6	24	30
Surgery (S)	5	10	15
Chemotherapy (CT)	0	3	3
Radiotherapy (RT)	1	1	2
S+CT+RT	4	2	6
Treatment regimens			
VAB-6	6	19	25
PVB	1	11	12
BEP	1	10	11
CP	6	0	6
Others	2	0	2

*Indiana staging system [10]. LDH = lactate dehydrogenase; AFP = alpha fetoprotein.

Toxicities were classified according to WHO criteria [16]. A complete remission (CR) was defined as complete resolution of tumour masses and normalisation of tumour markers. A partial remission (PR) was defined as > 50% reduction in the diameter of measurable lesion. All patients with responses less than PR were considered non-responders. Patients who were in CR after induction chemotherapy received no further treatment. Patients with SEGCT who had residual masses following induction chemotherapy have been referred for radiotherapy or alternative chemotherapy. In patients with NSEGCT, surgical excision of all sites of disease was performed if evidence of residual disease was found. Surgical resection of fibrosis or necrotic tissues or elements of mature teratoma alone was also considered CR to chemotherapy and the patients received no further therapy. CR to chemotherapy and surgery was defined as the excision of all masses, any one of which contained viable GCT, and these patients received two additional courses of chemotherapy. Patients who still had an active residual tumour after chemotherapy were treated with a variety of second-line chemotherapies.

Survival was calculated from the onset of chemotherapy to the date of last follow-up or death. Remission duration was calculated from the date of remission to the date of relapse or last follow up. Survival curves were calculated by the Kaplan–Meier method and the log-rank test was used to compare survival curves. All univariate comparisons of proportions were made using a χ^2 test.

RESULTS

SEGCT group

CR was achieved with chemotherapy alone in 13 out of 16 patients. Additionally 2 patients who had an initial PR after chemotherapy received radiotherapy and achieved CR. The overall CR was 94%. 5 patients had a relapse from complete remission (mean 8 months, range 1–18). 4 of these 5 patients received salvage chemotherapy. 1 patient did not respond. 3 patients achieved a secondary CR but relapsed again after 8, 12 and 54 months, respectively, and each subsequently died. The remaining patient received additional radiotherapy, but did not achieve CR. At a median follow-up of 38 (5–103) months, 11 patients are alive and 10 (62%) have no evidence of disease. 5 have died of disease progression. The response to therapy is outlined in Table 2.

NSEGCT group

7 patients achieved CR with chemotherapy alone. Of the 15 patients with PR, 2 had CR with subsequent chemotherapy. Surgical resection of residual masses was performed after chemotherapy in 6 patients and revealed necrosis in 1 and mature teratoma in 2. In 3 patients viable carcinoma within residual masses was completely resected. Thus overall CR rate was 37%. 3 patients have relapsed 2, 2 and 4 months after CR. 2 of these patients achieved secondary CR with salvage chemotherapy alone and chemotherapy plus surgery, respectively. At a median follow-up of 26 (3–114) months 14 (35%) patients remain alive and disease-free. 26 patients have died of disease progression.

Prognostic factors

A variety of potential prognostic factors and treatment results are shown in Tables 3 and 4. The most important prognostic factor was the tumour histology and patients with NSEGCT had a lower chance of achieving a CR on treatment (37% vs. 94%, $P = 0.0001$). This factor had no significant influence on the proportion of the patients with current NED in both groups (35% vs. 62%, $P = 0.57$) due to the high relapse rate and the small number of patients in the SEGCT group. In the SEGCT group we did not observe a significant influence of the different prognostic factors. By univariate analysis statistically significant differences were noted only in relation to elevated levels of AFP

Table 2. Results of treatment

	SEGCT	NSEGCT	Total
No of patients (%)	16 (100)	40 (100)	56 (100)
Overall CR (%)	15 (94)	15 (37)	30 (54)
Relapses (%)	5 (31)	3 (20)	8 (14)
Currently NED (%)	10 (62)	14 (35)	24 (43)
Died (%)	5 (31)	26 (65)	31 (55)

CR = complete response; NED = no evidence of disease.

(> 2000 ng/ml) in the NSEGCT group. This factor influenced achievement of CR (P = 0.01) and NED (P = 0.03). Patients with minimal and moderate disease presented better CR and NED rates but the differences were not significant due mainly to the small number of patients with such disease extent. Also the BEP induction chemotherapy in NSEGCT was superior to VAB-6 in CR and NED rates (16% vs. 60%) chemotherapy, although the probability of CR was similar in both groups.

Survival

Survival curves for 16 patients with SEGCT and 40 patients with NSEGCT were constructed independently (Fig. 1). SEGCT patients had an improved survival in comparison with NSGCT group (P = 0.017). Median survival for SEGCT and NSEGCT was 57 and 15 months, respectively.

Toxicity

Myelosuppression and nephrotoxicity were tolerable in most patients, but in 14% leukopenia (III–IV) was observed. None had infectious complications. 8 patients developed transitory renal dysfunction, but in all cases renal function returned to normal. Hepatic toxicity was transitory in 3%. 1 patient demonstrated pulmonary fibrosis on PVB chemotherapy (total bleomycin dose was 300 mg), which required corticosteroid administration. Symptomatic ototoxicity and peripheral neuropathy was observed in 2 patients. None of the patients presented fatal complications.

Table 3. Prognostic factor analysis: SEGCT group

	CR	Alive NED
No. of patients.	15/16 (94)	10/16 (62)
Primary site		
Mediastinum	6/6 (100)	5/6 (83)
Retroperitoneum	5/5 (100)	3/5 (60)
Mediastinum + retroperitoneum	3/4 (75)	1/4 (25)
Other sites	1/1 (100)	1/1 (100)
Extent of disease		
Minimal	1/1 (100)	1/1 (100)
Moderate	3/4 (75)	2/41 (50)
Advanced	11/11 (100)	7/11 (64)
Markers		
HCG (ng/ml)		
0–10	11/12 (92)	7/12 (58)
11–100	3/3 (100)	2/3 (67)
> 500	1/1 (100)	1/1 (100)
LDH (units/l)		
0–450	8/8 (100)	6/8 (75)
451–1000	6/6 (100)	3/6 (50)
1001–2000	0/1 (0)	0/1 (0)
Prior treatment		
None	6/6 (100)	4/6 (67)
Surgery	5/5 (100)	2/5 (40)
S+CT+RT	4/5 (80)	4/5 (80)
Chemotherapy regimen		
VAB-6	6/6 (100)	3/6 (50)
CP	5/6 (83)	4/6 (67)
Others	4/4 (100)	3/4 (75)

Figures in brackets are percentages.

Table 4. Prognostic factor analysis: NSEGCT group

	CR	NED	Probability CR§ (mean) MSKCC
No. of patients	15/40 (37)	14/40 (35)	0.54
Primary site			
Mediastinum	6/16 (37)	6/16 (37)	0.62
Retroperitoneum	7/21 (33)	6/21 (29)	0.45
Med. + retrop.	0/1 (0)	0/1 (0)	0.42
Other sites	2/2 (100)	2/2 (100)	0.89
Extent of disease			
Minimal	2/2 (100)	2/2 (100)	0.55
Moderate	3/5 (60)	3/5 (60)	0.61
Advanced	10/33 (30)	9/33 (27)	0.53
Markers			
AFP (ng/ml)			
0–13	5/14 (36)	5/14 (36)	0.50
14–500	8/12 (67)*	7/12 (58)†	0.55
501–1000	0/0 (0)	0/0 (0)	–
1001–2000	1/5 (20)	1/5 (20)	0.48
> 2000	1/9 (11)	1/9 (11)†	0.54
HCG (ng/ml)			
0–10	6/16 (37)	6/16 (37)	0.58
11–100	7/19 (37)	6/19 (32)	0.53
101–500	2/3 (67)	2/3 (67)	0.47
> 500	0/2 (0)	0/2 (0)	0.18
LDH (units/l)			
0–450	10/21 (48)	10/21 (48)	0.69
451–1000	2/6 (33)	2/6 (33)	0.51
1001–2000	2/10 (20)	1/10 (20)	0.28
> 2000	1/3 (33)	1/3 (33)	0.21
Prior treatment			
None	10/24 (42)	9/24 (37)	0.52
Surgery	3/10 (30)	3/10 (30)	0.64
S+CT+RT	2/6 (33)	2/6 (33)	0.43
Chemotherapy regimen			
VAB-6	3/19‡ (16)§	3/19 (16)§	0.51
PVB	6/11‡ (54)	5/11 (45)	0.51
BEP	6/10 (60)§	6/10 (60)§	0.62
Histology			
Embryonal carcinoma	3/8 (37)	3/8 (37)	0.49
Teratoma	5/11 (45)	5/11 (45)	0.62
Choriocarcinoma	1/1 (100)	1/1 (100)	0.87
Yolk sac tumour	1/4 (25)	1/4 (25)	0.59
Germ cell tumour	1/6 (17)	1/6 (17)	0.45
Undifferentiated	2/5 (40)	1/5 (20)	0.49
Unknown	2/5 (40)	2/5 (40)	0.50

*P = 0.1; †P = 0.03; ‡P = 0.03; §P = 0.02.
Figures in brackets are percentages.

DISCUSSION

Our results confirm previous reports of improved survival for patients with EGCT treated with chemotherapy based on cisplatin, however the results remain inferior when compared with those obtained in primary testicular cancer [1–9].

EGCT are generally considered poor risk tumours. Bajorin *et al.* [17] compared current "poor risk" germ cell tumours definition by four selected criteria and showed that, the MSKCC

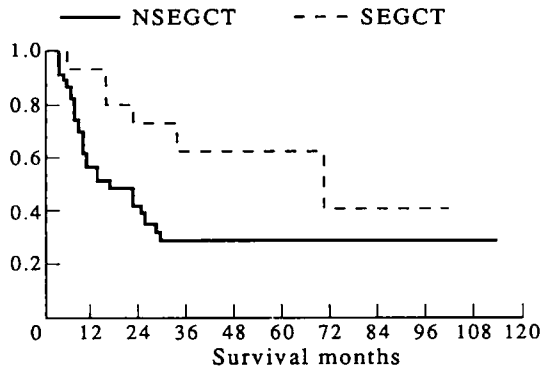

Fig. 1. Survival curves for SEGCT and NSEGCT patients. ($P = 0.017$ for SEGCT vs. NSEGCT.)

and Indiana criteria more accurately predict the outcome of treatment. In an attempt to identify prognostic factors we tested the Indiana and MSKCC criteria systems. Obviously, patients with SEGCT have significantly greater chance of achieving CR (and better survival) than NSEGCT patients. This study also showed that NSEGCT patients with AFP serum levels more than 2000 ng/ml had significantly less chance of achieving CR and NED status. At the present time, no other prognostic factors for EGCT patients are known. The results of this study, as well as others published previously [18], suggest that current staging systems developed for primary testicular cancer can be utilised with difficulty in EGCT patients. Assessment of new prognostic factors and a new staging system is obviously necessary for EGCT to identify the factors that predict better CR rate, early relapses and survival.

The best treatment for EGCT has generated disagreement.

Radiotherapy as a primary treatment of SEGCT was reviewed in a series by Hainsworth and Greco [19], in spite of that 60% of patients had long-term disease-free survival after radiation therapy, a substantial proportion of cases are not cured by radiation alone and need further therapy. Only recently has there been a trend to treat these patients with initial chemotherapy. In our series we corroborated the high sensitivity of SEGCT to chemotherapy alone. But from 13 (81%) patients, who reached a CR with chemotherapy, 5 (31%) developed relapses and all but one had advanced disease before treatment. On the basis of these results and others reported previously [20, 21] we suggest that cisplatin-based chemotherapy should be the initial treatment for SEGCT and radiotherapy and/or surgery should be added for patients with advanced disease who achieve CR status.

For NSEGCT patients the treatment should be started with cisplatin-based chemotherapy followed by surgical resection of residual mass. From our experience the BEP combination chemotherapy was superior to alternative regimens and permitted achievement of CR or NED status in 60%. Randomised studies and longer follow-up are necessary to determine the best regimen of induction chemotherapy according to prognostic subgroups of patients.

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