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Intensive Chemotherapy with Autologous Peripheral Blood Stem Cell Transplantation During a 10-Year Period in 64 Patients with Germ Cell Tumor

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ABSTRACT

Despite gratifying cure rates in germ cell tumors, conventional-dose chemotherapy achieves long-term remissions in less than 50% of patients at high risk. High-dose chemotherapy followed by autologous (auto) peripheral blood stem cell transplantation (PBSCT) has shown impressive remission rates in high-risk and relapsed germ cell tumors. We report on 64 consecutive patients with high- (n = 39), intermediate- (n = 18), and refractory or relapsed low- (n = 7) risk germ cell tumors who underwent auto-PBSCT between January 1993 and February 2003. PBSCTs were performed as a single (n = 40) or repeated (n = 24) transplantation using either etoposide, ifosfamide, and carboplatin (n = 80) or related protocols (paclitaxel, ifosfamide, carboplatin, etoposide [n = 7]; carboplatin, etoposide, thiotepa [n = 4]). With a median follow-up of 6 years, estimated 2- and 5-year overall survivals were 77.2% (95% confidence interval [CI] 66.7-87.7) and 73.1% (95% CI 61.7-84.5), respectively. We observed unfavorable results in those patients showing refractoriness to cisplatin (hazard ratio 20.36; 95% CI 6.64-62.47) or no response to induction chemotherapy (hazard ratio 10.67; 95% CI 1.37-83.37). Auto-PBSCT was well tolerated, showed objective antitumor activity, and achieved long-term survival in patients at high risk and with relapse. Our data suggest that auto-PBSCT can increase response rates and may improve the outcome in these patients.
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INTRODUCTION

The introduction of platinum-based combination chemotherapy in the 1970s has substantially improved the outcome of patients with germ cell tumors (GCT). With advanced or relapsed disease, conventional-dose chemotherapy (CDCT) can cure 70% to 80% of patients with disseminated disease [1,2]. However, subgroups of patients with GCT have a poor prognosis with cure rates less than 50% [3]. A particularly unfavorable outcome is observed in patients refractory to platinum [4,5], with short relapse-free interval or mediastinal primary site [3,6-8]. Initial studies of high-

dose chemotherapy (HDCT) with autologous (auto) stem cell transplantation (SCT) included heavily pretreated relapsed or refractory cases, in which a complete remission (CR) was achieved in 24% and long-term remission in 15% to 20% [9]. In addition to its use in patients with second or subsequent relapse, HDCT has also shown encouraging results with early intensification. Because prospective randomized trials are still underway, unequivocal recommendations on the use of HDCT are not yet available.

The aim of our study on 64 patients with advanced GCT was to: (1) describe the overall outcome and toxicity after auto peripheral blood stem cell (PBSC)

transplantation (PBSCT); (2) explore clinical factors prognostic for response and survival; and (3) compare our results with those from previous trials.

METHODS

Patients and Eligibility

Sixty-four consecutive patients with GCT, receiving HDCT with auto-PBSCT between January 1993 and February 2003, were analysed using medical charts and electronic records. Follow-up (FU) relating to survival information was obtained from the tumor and PBSCT database. All patients fulfilled the criteria of high- or intermediate-risk disease at diagnosis, inappropriate or delayed response after first treatment, or relapsed disease. Diagnosis of GCT was histologically proven in all cases and included seminoma and nonseminoma (NS) of gonadal and extragonadal origin. With the development of the International Germ Cell Cancer Collaborative Group (IGCCCG) classification in 1997, patients treated before this date were reclassified and it is this classification that has been used prospectively ever since [3]. Bulky disease was defined as tumor mass greater than 5 cm. For each patient, the following data were obtained: (1) pre-HDCT: age, histology, primary site, disease stage, location of metastases, tumor markers, type and number of cisplatin-based chemotherapy regimens, and platinum-refractoriness; (2) HDCT: regimen, number of cycles, response, engraftment, and complications; and (3) post-HDCT: type of treatment, progression, cause of death, event-free survival (EFS) and overall survival (OS). HDCT was performed in patients at high and intermediate risk or with inappropriate response to CDCT as primary PBSCT (n = 31), or with relapsed disease as a subsequent salvage attempt (n = 33). The study and analysis were carried out according to the guidelines of the Declaration of Helsinki and good clinical practice. All patients gave their written informed consent for institutional-initiated research studies and specifically for retrospective analyses of transplantation outcomes conforming to our institutional review board guidelines. For this analysis, living patients were censored as of May 15, 2003, which was the specified date (with definite contact to the patient, physician, or relative) for the statistical analysis of our patient cohort.

Treatment Schedule and PBSCT

Median number of CDCT cycles before first PBSCT was 4.5 (range: 1-15). All patients had received platinum-based chemotherapy. High-dose regimens (n = 91) were etoposide (1500 mg/m^2), ifosfamide (12,000 mg/m^2), and carboplatin (1500 mg/m^2) (n = 80) or other combinations (paclitaxel [175 mg/m^2], ifosfamide I [9000 mg/m^2], carboplatin [1200 mg/m^2], and

etoposide [900 mg/m^2] [n = 7] or carboplatin [1500 mg/m^2], etoposide [2400 mg/m^2], and thiotepa [450 mg/m^2] [n = 4]). After PBSC collection, cells were cryopreserved unmanipulated in all patients and reinfused on day (d) 0. Recombinant human granulocyte colony-stimulating factor was administered for rapid neutrophil recovery, starting on day 7 (d+7) post-PBSCT and continued until achievement of an absolute white blood cell count of greater than 1×10^9/L. In patients with residual tumor mass after HDCT, if technically feasible, complete surgical resection was

Table I. *Patient Characteristics (n = 64)*

	n	%
Age at PBSCT (y; range)	32 (18-54)	
Histology (n; %)		
Seminoma	5	8
Nonseminomatous GCT	59	92
Mixed	38	59
Embryonic	10	16
Teratoma	7	11
Yolk sac	2	3
Chorionic	1	1.5
Anaplastic Ca	1	1.5
Primary tumor location		
Testis	52	81
Mediastinum	10	16
Retroperitoneum	2	3
Extranodal metastasis	45	70
Lung only	21	33
Extrapulmonary viscerally	24	37
Lung	42	66
Liver	13	20
Bone	9	14
CNS	8	12
Kidney	2	3
Pancreas	1	2
Bulky disease	48	75
Lugano stage at PBSCT		
IIB	3	5
IIC	10	15
IID	2	3
IIIA	5	8
IIIB	21	33
IIIC	23	36
IGCCCG risk		
Low	7	11
Intermediate	18	28
High	39	61
Time of PBSCT		
Upfront	31	48
First relapse	23	36
≥Second relapse	10	16
Serum tumor markers	n-fold	range
β-HCG	682	3-115,904
≥5,000 mIU/mL	19	
>50,000 mIU/mL	10	
AFP	103	1-7346
≥1,000 ng/mL	21	
>10,000 ng/mL	9	
LDH	2	1-29

AFP indicates alpha fetal protein; β-HCG, human chorionic gonadotropin; GCT, germ cell tumor; IGCCCG, International Germ Cell Cancer Collaborative Group; LDH, lactate dehydrogenase; PBSCT, peripheral blood stem cell transplantation.

attempted. Radiotherapy was considered for sites of residual disease, where surgical excision was not possible, and when tumor markers had failed to normalize at the end of chemotherapy.

Response Criteria

Toxicity and response were defined according to World Health Organization criteria [10]. Sensitivity to platinum was classified according to the response after the last cisplatin-based chemotherapy before HDCT. The disease was considered cisplatin-refractory with evidence of tumor progression within 4 weeks of the last cisplatin-based chemotherapy.

Statistical Analysis

Descriptive data analysis was performed using the median and the range except where otherwise stated. EFS was defined as the time from the date of PBSC infusion until the date of treatment failure as defined by progressive disease (PD), relapse, or death from any cause. For censored observations, survival state as reported on May 15, 2003, was used. Estimates of EFS and OS were obtained using the Kaplan-Meier method. Univariate analyses were performed for the prognostic factors. Univariate Cox proportional hazard regression models were applied where possible to obtain hazard ratio (HR) with a 95% confidence interval (CI). The corresponding test procedure used was the Wald's test. In situations where strata with no events occurred the log rank test was applied. Associations between

different prognostic factors were investigated by use of frequency tables. Multivariate analyses were performed using the Cox proportional hazard model. Because of the small number of events, a parsimonious model was considered. Only some variables selected to their significance in the univariate analysis and their relevance were chosen as candidate prognostic factors in the multivariate model. Statistical analysis system software (Version 8.2, SAS Institute Inc, Cary, NC) was used. Data was analyzed as of May 15, 2003.

RESULTS

Patient Characteristics

As summarized in Table 1, most patients (92%) had NS GCT. Primary tumor locations were the testis in 81%, the mediastinum in 16%, and the retroperitoneum in 3%. Extranodal metastases were present in 70% of patients. Median β-human chorionic gonadotropin (β-HCG), alpha fetal protein (AFP), and lactate dehydrogenase (LDH) level increases leading to PBSCT (as calculated from the upper normal value) were 682-, 103-, and 2-fold, respectively. Twelve cases were defined as cisplatin refractory. Bulky disease was observed in 75% of patients. According to IGCCCG, 89% were at high or intermediate risk, and 11% at low risk, the latter receiving HDCT because of relapsed disease.

Table 2. *Clinical Response in Patients with Germ Cell Tumor: Summarized and Detailed Analyses*

	Response		
Before PBSCT	Immediately after PBSCT (1 mo)	Best after PBSCT (with Multimodal post-PBSCT Treatment)	Current
Summarized analysis			
CR: 4 (3/1)	CR: 38 (20/18)	CR: 50 (25/25)	CR: 47* (24/23)
PR: 47 (26/21)	PR: 17 (9/8)	PR: 6 (4/2)	PR: 1† (1/0)
SD: 8 (1/7)	SD: 7 (1/6)	SD: 6 (1/5)	SD: 0
PD: 5 (1/4)	PD: 2 (1/1)	PD: 2 (1/1)	PD: 1*/15† (6/10)
Detailed analysis			
CR: 4	CR: 4	CR: 4	CR: 3
			PD: 1
PR: 47	CR: 31	CR: 41	CR: 39
	PR: 15	PR: 5	PR: 1
	SD: 1	SD: 1	PD: 7
SD: 8	CR: 3	CR: 5	CR: 5
	PR: 1	SD: 3	PD: 3
	SD: 4		
PD: 5	PR: 1	PR: 1	PD: 5
	SD: 2	SD: 2	
	PD: 2	PD: 2	

In parentheses number of patients receiving PBSCT as upfront versus salvage treatment.
*Alive.
†Deceased.
PBSCT, peripheral blood stem cell transplantation; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Table 3. *Univariate Analysis of Prognostic Factors on Overall Survival*

Variables		n	1-y OS (95% CI)	5-y OS (95% CI)	Estimated HR (95% CI)	P value
Cisplatin	Sensitive	52	94.1% (87.6-100)	89.0% (79.8-98.2)	1.00	
	Refractory	12	33.3% (6.7-60.0)	8.3% (0-24.0)	20.36 (6.64-62.47)	<.0001
Remission at PBSCT	CR	11			1.00	
	PR	35			1.19 (0.13; 10.67)	.0003
	SD/PD	18			10.67 (1.37; 83.37)	
β-HCG, mIU/mL	<50,000	54			1.00	.028
	>50,000	10			1.82 (1.07; 3.10)	
AFP, ng/mL	<10,000	55				
	>10,000	9			n.e.	.16 (logrank)
Seminoma	Yes	5	100% (–)	100% (–)		
	No	59	80.8% (70.6-91.0)	70.7% (58.5-82.9)	n.e.	.2 (logrank)
IGCCCG risk at Dx	Low	7				
	Intermediate	18			n.e.	.29 (logrank)
	High	39				
Visceral metastases	Non	19	94.7% (84.7-100)	88.0% (72.2-100)	1.00	
	Pulmonary	21	79.4% (61.3-97.4)	74.1% (54.5-93.7)	2.65 (0.51; 13.67)	
	Extrapulmonary	24	74.5% (56.8-92.2)	58.7% (37.5-79.9)	4.54 (0.98; 21.06)	.14
Primary tumor location	Testis + retroperoneal	54	84.8% (75.1-94.5)	76.1% (64.3-88.0)	1.00	
	Mediastinal	10	68.6% (38.9-98.3)	57.1 (25.0-89.2)	2.20 (0.71; 6.85)	.17
No. PBSCTs	1	40	89.9% (80.4-99.3)	78.5% (65.1-91.8)	1.00	
	>1	24	69.1% (49.9-88.2)	64.5% (44.6-84.4)	1.93 (0.72; 5.17)	.19
Time of PBSCT	Upfront	31	83.2% (69.7-96.6)	79.0% (63.9-94.1)	1.00	
	Relapse	33	81.7% (68.5-94.9)	67.6% (50.9-84.4)	1.62 (0.59; 4.47)	.35
Age	<30 y	26			1.00	.88
	≥30 y	38			0.92 (0.34; 2.49)	
Bulk	No	16			1.00	.999
	Yes	48			1.001 (0.32; 3.11)	

AFP indicates alpha fetal protein; β-HCG, human chorionic gonadotropin; CI, confidence interval; CR, complete remission; Dx, primary diagnosis; HR, hazard ratio; IGCCCG, International Germ Cell Cancer Collaborative Group; n.e., not estimable: strata with no events; OS, overall survival; PBSCT, peripheral blood stem cell transplantation; PD, progressive disease; PR, partial remission; SD, stable disease.

Apheresis Results and Posttransplantation Course

A median of one apheresis (range: 1-7) was sufficient to harvest median CD34$^+$ cell numbers of 6 × 10^6/kg body weight (range: 1.1-34). With infusion of a median of 3.9 × 10^6/kg CD34$^+$ cells (range: 1.1-16.9) hematopoietic engraftment with white blood cell count greater than 1 × 10^9/L and platelets greater than 20 × 10^9/L were observed on d+10 (range: 7-17) and d+11 (range: 7-27) after PBSC infusion (d 0), respectively. Infections, mostly fever of unknown origin, were documented in 48 patients (75%). These were successfully treated in all, but one patient developed septic pneumonia and adult respiratory distress syndrome during neutropenia and died on d +6 post-PBSCT, leading to a treatment-related mortality (TRM) of 1.6%. Another patient developed a self-limiting transient tachyarrhythmia and one patient with cerebral metastases had a grand mal seizure after PBSCT. In all others, the HDCT was well tolerated, resulting in a median hospital discharge on d+14 (range: 9-47).

Treatment Response and Current Remission

After CDCT and before PBSCT, achievement of CR or partial remission (PR) was observed in 80% of patients. Table 2 depicts responses immediately before and after PBSCT and current remissions status.

Eleven patients required post-PBSCT therapy to achieve a CR. This treatment consisted of radiation (n = 5), operation (n = 4), chemotherapy plus operation (n = 1), or chemotherapy alone (n = 1). Six patients each achieved a PR and stable disease (SD) as best response after PBSCT. Two patients showed PD despite PBSCT and interdisciplinary treatment modalities. None of these 14 patients achieved long-term remission (Table 2). Five patients, initially in CR after PBSCT, showed recurrent disease: one patient with high-risk disease relapsed 15 months after the first PBSCT. A second PBSCT was performed, again leading to CR; however, relapse occurred 4 months later. This patient is currently progressive and receiving further CDCT. Two patients with recurrent GCT who relapsed 11 and 30 months after the first PBSCT underwent a second PBSCT and are in ongoing CR at 5.6 and 7.5 years, respectively. Two other patients, who received a transplantation for disease recurrence, relapsed 12 and 8 months after PBSCT. Both died of PD. The current remission status is an ongoing CR in 47 patients (73%) (Table 2).

Subgroup Analysis

Seminoma versus NS GCT. Patients with seminoma were all disease free (four after one PBSCT, one after two PBSCTs) and had an estimated OS of 100%.

Patients with NS GCT (n = 59) had an estimated 1-year EFS of 74.2% (95% CI 63.0-85.5) and 1-year OS of 80.8% (Table 3), with 42 patients being in ongoing CR.

Primary versus Secondary (With Relapsed Disease) PBSCT. Because of high- (n = 22) or intermediate- (n = 9) risk disease, 31 patients (48%) received HDCT as a first-line therapy and 33 patients as a subsequent salvage treatment. Of those patients undergoing upfront transplantation, 58% (n = 18 of 31) received one cycle and 42% (n = 13 of 31) two PBSCTs. As salvage treatment, single transplantation was performed in 67% (n = 22 of 33) and repetitive transplantations in 33% (n = 11 of 33). All patients had cisplatin-based CDCT regimen before HDCT to reduce tumor mass and mobilize stem cells. In patients with first-line as compared with secondary PBSCT, β-HCG and AFP were increased in the former group by 2- and 16-fold, and high-risk disease was present in 71% (22 of 31) versus 48% (16 of 33), respectively. With retransfusion of 4 and 3.8×10^6/kg CD34$^+$ cells in both groups, white blood cell count and platelet engraftment was 1 day earlier in the first-line PBSCT versus secondary transplantation group (d+9 versus d+10). In addition, fewer platelet transfusions (3 versus 4) were used and earlier discharge from hospital (d+14 versus d+15) was possible. Table 2 depicts disease status before and after PBSCT for the upfront and salvage groups. Response with currently ongoing CR in both groups was 77.4% versus 69.7%. The estimated 1-year EFS was 83.5% (95% CI 70.3-96.7) and 1-year OS 83.2% for patients undergoing first-line

PBSCT versus an EFS of 69.4% (95% CI 53.6-85.2) and OS of 81.7% for those who underwent transplantation with relapsed disease (Table 3, Figure 1).

Single versus Repetitive PBSCT. Single PBSCT was performed in 63% and tandem or repetitive PBSCTs in 24 patients (37%). Response rates (CR/PR) were obtained in 77.5% of patients undergoing single versus 66.7% with repetitive PBSCTs. The estimated 1-year EFS was 82.3% (95% CI 70.3-94.2) versus 66.7% (95% CI 47.8-85.5) and 1-year OS 89.9% versus 69.1%, respectively (Table 3). The second PBSCT was applied in 3 different clinical settings. First, as an upfront intended tandem transplantation to increase dose intensity in 6 of 24 patients. The median time between both transplantations was 30 days (range: 21-46). Of these patients, all but one are currently in CR. Second, with inadequate response (either residual tumor mass or persisting elevation of serum tumor markers) to the first HDCT cycle, 12 of 24 patients received a second PBSCT, with a median time interval of 76 days (2.3 months; range: 27-239 days) between both transplantations. Of this group with incomplete response to the first cycle, currently 67% are in CR. One patient died on d+6 after PBSCT because of sepsis (TRM) and 3 patients died of tumor progression despite a second cycle of HDCT. Finally, with relapsed disease (after having achieved a CR with the first cycle of HDCT) a second PBSCT was performed in another 6 of 24 patients. The median time interval between these transplantations was 13 months (4-, 5-, 9-, 17-, 34-, and 43-month time interval). Four patients, who were at high
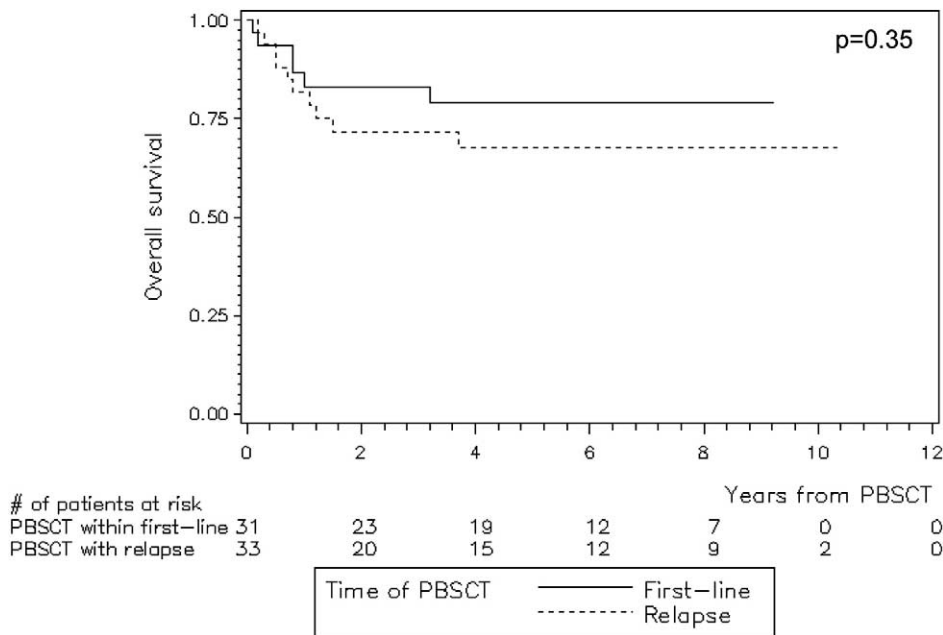
Figure 1. Primary versus secondary (with relapsed disease) PBSCT. Because of high-risk disease, 31 patients received HDCT as first-line, and 33 patients as first- or subsequent salvage treatment. Response with currently ongoing CR in both groups was 77.4% versus 69.7%, and estimated 5-year OS 79.0% versus 67.6%, respectively.
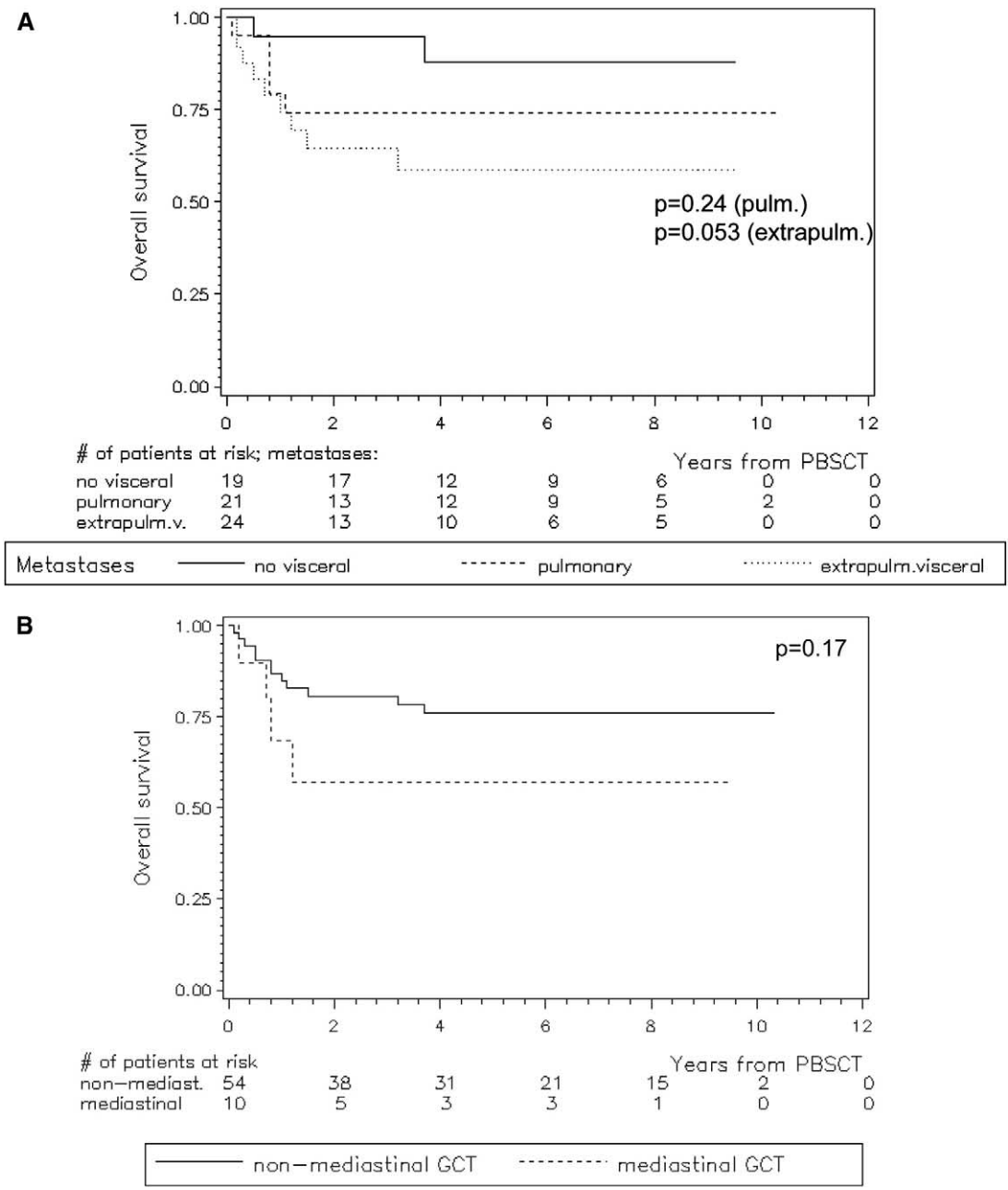
Figure 2. A, Visceral (pulmonary and extrapulmonary) versus nodal metastases. Forty-five patients had visceral metastases, with extrapulmonary and pulmonary manifestation in 24 and 21 patients, respectively. Estimated 5-year OS for nonpulmonary, pulmonary, and extrapulmonary visceral metastases was 88.0%, 74.1%, and 58.7%, respectively. B, Mediastinal versus nonmediastinal GCT. Ten patients had primary mediastinal tumor location. As compared with those with nonmediastinal GCT, 5-year OS was 57.1% versus 76.1%, respectively.

risk at primary diagnosis, died of PD, but two patients regained a CR with repetitive PBSCT.

Patients with Visceral Metastases and Primary Mediastinal Tumor Location. Forty-five patients had visceral metastases, with extrapulmonary visceral metastases in 24 patients (37%). Of those patients, 67% are currently alive and disease free (Figure 2A). Of note is that 3 of 9 patients with central nervous tumors are in ongoing CR.

Ten patients with primary mediastinal tumors underwent single (n = 4) or tandem (n = 6) PBSCTs as upfront or salvage treatments in 5 patients each, respectively. Of 10 patients, 6 are disease free and alive. Of those 4 patients showing SD and PD after the first PBSCT, two received a second PBSCT after 1 and 4 months, respectively, but nevertheless died of PD (Figure 2B). Of those receiving PBSCT as upfront treatment, one died of PD, whereas 4 of 5 patients are in CR. Notably, 2 of 5 patients with relapsed mediastinal GCT are in an ongoing CR after PBSCT.

Patients Not Reaching CR after PBSCT and Cisplatin Response. Of 64 patients, 26 did not reach a CR directly

after PBSCT (PR: n = 17; SD: n = 7; PD: n = 2). In those patients, PBSCTs had been performed in 11 as primary and in 15 patients as secondary PBSCT. High-risk disease was present in 69.2% (18 of 26); 15 cases were classified as cisplatin sensitive and 11 as refractory. The former group achieved in 12 of 15 (80%) a CR after further treatment, the latter progressed in 10 of 11 patients (91%). In all, 12, 1, and 13 patients are in CR, PR, and PD, respectively.

A total of 31 patients underwent operation after PBSCT for residual tumor mass. In 6 patients (19%), viable tumor cells were detected, in 5 (16%) teratoma, and in the remaining (n = 20; 65%) only necrotic tissue.

Of all cases, 12 were cisplatin refractory. Of those patients with refractory disease, 9 were at high risk and 3 were at intermediate risk. Best response after PBSCT in these patients was a CR in one, a PR in 3, SD in 6, and PD in two patients, leading to an ongoing CR in only one patient, the others dying of PD. Cisplatin response had a significant effect on survival, with estimated 1-year EFS in sensitive versus refractory cases of 92.1% (95% CI 84.7-99.5) versus 8.3% (95% CI 0-24.0), and 1-year OS of 94.1% versus 33.3% (Table 3, Figure 3), respectively.

Survival, Prognostic Factors, and Long-Term FU

All 64 patients were included in the analysis showing 5-year OS and EFS of 73.1% (95% CI 61.7-84.5%) and 72.3% (95% CI 60.9-83.6%), respectively. With a median FU of 6 years (range: 0.2-10.6),

48 patients are alive and 47 are disease-free. FU was longer for patients with single PBSCT (7.65 years) as compared with those undergoing repetitive transplantations (4.7 years). Estimated OS after 1, 2, and 5 years were 82.3% (95% CI 72.8-91.8), 77.2% (95% CI 66.7-87.7), and 73.1% (95% CI 61.7-84.5), respectively. Patients with IGCCCG low-, intermediate-, or high-risk disease had an estimated 1-year EFS of 100%, 71.4% (95% CI 50.2-92,7), and 74.4% (95% CI 60.7-88.1) and 1-year OS of 100%, 76.7% (95% CI 56.7-96.7), and 81.6% (95% CI 69.3-94.0), respectively. Elevated β-HCG of less than 50,000 versus 50,000 mU/mL or more resulted in an estimated 1-year OS of 86.7% (95% CI 77.6-95.9) versus 58.3% (95% CI 26.8-89.9), respectively. Patients reaching a CR or PR versus SD/PD before PBSCT had an estimated 1-year OS of 100%, 94.2% (95% CI 86.4-100.0) versus 47.4% (95% CI 23.4-71.4), respectively. Univariate analysis of prognostic factors on OS showed a highly significant risk for patients with cisplatin-refractory disease and those achieving only SD or PD (Table 3). Other prognostic factors showed elevated HR, but did not reach statistical significance. Univariate analyses of prognostic factors on EFS showed similar results as those on OS, reaching statistical significance for cisplatin refractoriness (P < .0001) and remission at PBSCT (P = .0001). In a multivariate regression model for selected prognostic variables, only cisplatin refractoriness reached statistic significance with a HR of 22.24 (P < .0001; 95% CI 6.2-79.77) as compared with visceral extrapulmo-
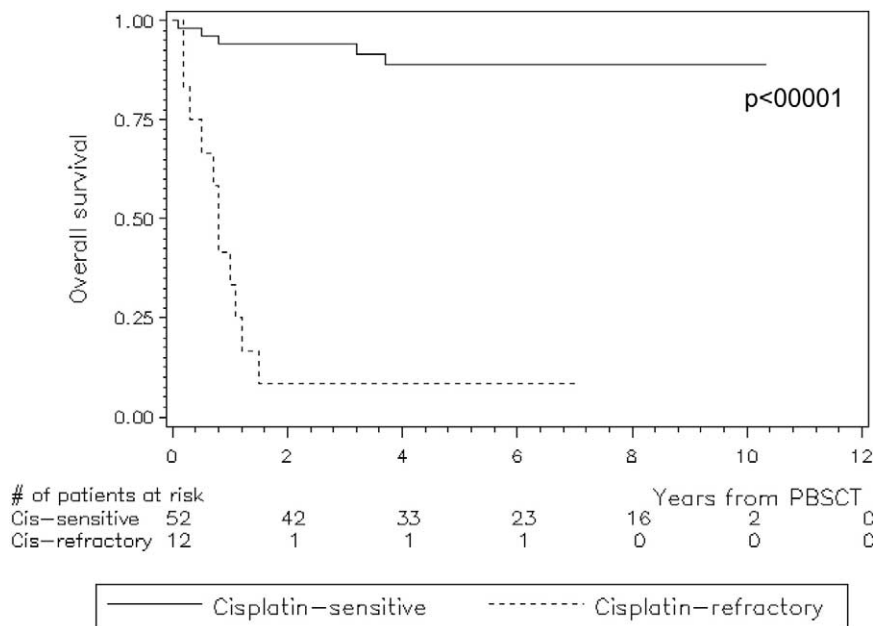
Figure 3. Cisplatin response. Of all cases, 12 were cisplatin refractory and 52 were cisplatin sensitive. Of those with refractory disease, 9 were at IGCCCG high risk and 3 at intermediate risk. Best response after PBSCT in these patients was CR in one, PR in 3, SD in 6, and PD in two patients, leading to ongoing CR in only one patient, others dying of PD. Cisplatin response had significant effect on survival, with estimated 1- and 5-year OS in sensitive versus refractory patients of 94.1% and 89% versus 33.3% and 8.3%, respectively.

Table 4. *Summary of Selected Series Using Autologous Peripheral Blood Stem Cell Transplantation in Germ Cell Tumor*

Indication	No.	No. HDCT	HDCT Regimen	Response	FU (mo)	Reference
Rel/ref	58	1	CEC	CR 40% OS 31% (2y)	28 (10-65)	Motzer, 1996 [11]
Rel/ref	25	1 = 6 2 = 19	CEI	PFS 52% (3y)	26 (14-36)	Broun, 1997 [12]
Rel/ref	150	1	CEI	EFS 29% OS 39%	55 (21-88)	Rick, 1998 [13]
Rel	35	1 = 10 2 = 25	HD-CTC	PFS 51.3% (2y) OS 64.9% (2y)	37 (12-56)	Rodenhuis, 1999 [14]
Rel/ref	65	2	CE	DFS 57%	39 (16-91)	Bathia, 2000 [15]
Rel/ref	80	1	CET	EFS 25% (3y) OS 30% (3y)	36 (22-46)	Rick, 2001 [16]
Rel/ref	74	1	CEI	n.g.	60 (12-96)	Beyer, 2002 [17]
Rel/ref	80	1 = 24 2 = 56	CE/CEI	FFS 32% (2y) OS 40% (2y)	56 (11-166)	Vaena, 2003 [18]
Rel/ref	36	1	Carbo-EC-T	EFS 48% (2y) OS 58% (2y)	29 (4-89)	McNeish, 2004 [19]
1st-line in HR	147	1	HD-VIP	PFS 75% (2y) OS 82% (2y)	21 (0-70)	Bokemeyer, 1999 [20]
1st-line in HR	221	3-4	HD-VIP	PFS 68% (5y) OS 71% (5y)	47 (0-118)	Schmoll, 2003 [21]
1st-line in HR	18	1 = 11 2 = 7	CE/CEI/CEC	CR 67% DFS 67%	111 (20-194)	De Giorgi, 2004 [22]
1st-line/rel/ref	64	1 = 40 ≥2 = 24	VIC/TICE/CET	EFS 72% (5y) OS 73% (5y)	72 (2.4-127)	Müller, 2005

Carbo-EC-T indicates carboplatin, etoposide, cyclophosphamide, paclitaxel; CE, carboplatin, etoposide; CEC, carboplatin, etoposide, cyclophosphamide; CET, carboplatin, etoposide, thiotepa; DFS, disease-free survival; EFS, event-free survival; FFS, failure-free survival; FU, follow-up; GCT, germ cell tumor; No. HDCT, number of HDCT-cycles; HD-CTC, carboplatin, thiotepa, cyclophosphamide; HDCT regimen, high-dose chemotherapy regimen for PBSCT; HD-VIP, cisplatin, etoposide, ifosfamide; 1st-line in HR, HDCT within first-line treatment in patients with high-risk/poor prognosis (IGCCCG) or advanced disease (Indiana); n.g., not given; PFS, progression free survival; Rel/ref, relapse or refractory GCT; TICE, paclitaxel, ifosfamide, carboplatin, etoposide; Upfront, PBSCT as first line therapy; VIC or CEI, carboplatin, etoposide, ifosfamide.

nary metastases (HR 2.8; P = .21; 95% CI 0.56-13.96), visceral pulmonary metastases (HR 2.36; P = .33; 95% CI 0.43-13.04), or time of PBSCT (upfront versus with relapse) with a HR of 0.72 (P = .56; 95% CI 0.24-2.17).

Table 4 summarizes selected earlier trials on HDCT (1996-2004) performed mostly as salvage therapy in patients with relapse or refractory GCT (n = 9 trials) [11-19], but also as first-line treatment (n = 3 trials) [20-22]. In these previous studies, a median number of 70 patients per study were included and their median FU was 3.2 years. Six of these trials included patients undergoing repetitive PBSCTs. In comparison with these HDCT trials, our study included a considerable number of patients and with 6 years, our FU was above average.

DISCUSSION

Although most patients with metastatic GCT can be cured, 20% to 30% will require salvage treatment [1,2]. In patients with NS GCT, those showing high tumor markers, extrapulmonary visceral metastases, mediastinal primary sites, or cisplatin-refractory disease have an unfavorable outcome when treated with CDCT alone [3]. Patients with relapsed metastatic NS GCT can achieve remission in 30% to 60%; however, only 20% to 50% are long-term survivors [5,8]. Second- or third-line salvage CDCTs no longer lead to cure. A particularly unfavorable prognosis is observed with relapsed primary mediastinal tumors, leading to long-term disease-free survival with CDCT in less than 10% [8]. To improve cure rates, various multiagent regimens have been used, but have failed to perform better than standard dose bleomycin, etoposide and cisplatin (BEP) in randomized trials. Moreover, increased doses of cisplatin, vincristine, or bleomycin have resulted in higher toxicity [23-25].

Encouraging preclinical and clinical data for a dose-response relationship for etoposide and ifosfamide were the rationale for HDCT regimen in GCT [9,26,27]. Initial studies included patients with heavily pretreated and mostly cisplatin-refractory disease and achieved objective responses in 24% to 45%, with long-term disease-free survivors (15%-20%) even in unfavorable subgroups [9,11]. Successive HDCT trials investigated its role earlier in the treatment course, showing response rates of 30% to 60% in patients with relapsed or refractory GCT [15,28,29]. A matched pair analysis comparing HDCT with CDCT as first

salvage treatment in patients with NS GCT suggested a benefit with HDCT, with an estimated absolute improvement in OS of 9% to 11% at 2 years [17]. With earlier use of HDCT, response rates have improved with simultaneous decline of treatment-related deaths. HDCT as first-line therapy in high-risk GCT has achieved OS of 67% to 82% [20,30]. A matched pair analysis on HDCT as first-line treatment compared with CDCT with standard-dose bleomycin, etoposide and cisplatin or standard-dose etoposide, ifosfamide and cisplatin (BEP/VIP) alone revealed a significant improvement in OS (82% for HDCT versus 71% with CDCT at 2 years) [20]. Tandem HDCT in poor prognosis and relapsed GCT has suggested a benefit of repetitive HDCT cycles in selected patients, demonstrating that 52% can survive progression free for a median of 26 months [12,31]. However, despite the frequent use of HDCT in poor prognosis GCT for more than a decade, comparative data on HDCT and CDCT are scarce and prospective analyses on auto-SCT not yet available.

Our analysis describes the outcome of 64 consecutive patients with GCT after HDCT and auto-PBSCT during a 10-year period. We determined clinical factors predictive for response and compared our results with those of previous trials. Patients showed high- or intermediate-risk according to IGCCCG criteria, relapsed disease, and unfavorable characteristics, such as mediastinal primary tumor location, refractoriness to cisplatin, extrapulmonary visceral metastases, and bulky disease.

Single PBSCT was performed in 63% and tandem or repetitive PBSCTs in 24 patients (37%). Transplantation was performed as single or repetitive PBSCTs with response rates (CR/PR) of 77.5% versus 66.7%, respectively. The second PBSCT was applied: (1) as an actual tandem transplantation for increased dose intensity (25%); (2) with incomplete response to the first HDCT cycle (50%); or (3) with relapse, but initial response to the first cycle of HDCT (25%). Those with dose-dense tandem PBSCT (1) had a notably better response with 83% responders as compared with those relapsing after the first PBSCT (3) (33% response rate). Of those patients undergoing a second PBSCT as consolidation for residual tumor after the first transplantation (2), 67% are currently in CR, which may support the use of repetitive PBSCTs in this clinical context, but nevertheless needs to be fully evaluated in prospective trials before definite recommendations can be provided.

We confirmed that HDCT is well tolerated: adverse effects consisted mainly of infections, which were well controlled with standard treatment. Moreover, our overall response was favorable, achieving an estimated 5-year OS of 73.1%. With a median FU of 6 years, 48 patients (75%) are alive, 47 of whom are disease-free. Of note is the difference in FU between

the patients who underwent single transplantation (FU 7.65 years) versus repetitive transplantations (4.7 years). This seems to be a result of the fact that 13 of 24 patients (54%) undergoing repetitive transplantation had received this treatment in 1999 or later, whereas only 14 of 40 (35%) single transplantations were performed in the same time period. Another possible reason is that repetitive PBSCTs were performed for heterogenous reasons, as relapse and progression after the first cycle of HDCT, and/or refractoriness to cisplatin. Therefore, this group included the majority of patients with most unfavorable prognostic features, which led to a shorter FU because of death.

Ten patients with primary mediastinal tumor location underwent HDCT as first-line (n = 5) or salvage (n = 5) therapy. Of these patients, 60% are alive and disease-free. Of note is that IGCCCG subgroup analysis did not reveal a statistically significant difference in survival for patients at intermediate versus high risk. Therefore, the favorable overall outcome of our patient cohort did not seem to be positively biased by the inclusion of patients with intermediate-risk GCT.

We have also confirmed cisplatin response as the most important adverse prognostic variable. OS after auto-PBSCT was 0.8 years in patients with platinum-unresponsive versus 5.3 years in platinum-sensitive disease. This matched the significantly better results in patients achieving a CR or PR versus SD/PD before PBSCT with an estimated 1-year OS of 100% and 81% versus 47%, respectively. Of those receiving HDCT as first-line treatment, 80% are alive, and 70% are disease free. Of those patients undergoing HDCT with relapse, 57% are alive and disease free. This is concordant with previous observations, again suggesting that earlier PBSCT may improve response rates.

Our analysis may be criticized for the retrospective character of the study, the heterogeneity in therapy regimens, and the PBSCT use as first-line and salvage therapy. Nevertheless, this analysis sought to include all consecutive patients with GCT receiving auto-PBSCTs at two university centers during a 10-year period, providing long-term FU in patients with intermediate risk, high risk, and relapse. Compared with previous HDCT trials [11-22], our study has included a considerable number of patients and our FU of 6 years was well above average. Encouraging results with auto-PBSCT were also obtained in patients with unfavorable characteristics, which may in part be a result of our early use of HDCT, consolidation treatment post-HDCT when necessary, and low TRM. Although these and previous results are intriguing, prospective randomized studies on HDCT with PBSCT are lacking and will only allow a determination of its significance compared with CDCT: one ongoing study is an European Organization for

Research and Treatment of Cancer phase III trial, where standard cisplatin, etoposide, and ifosfamide are followed by sequential high-dose cisplatin, etoposide, and ifosfamide with PBSCT versus BEP alone in chemotherapy-naive men with poor prognosis GCT. Another randomized intergroup trial in poor-risk GCT compares 4 cycles of BEP with two cycles of BEP followed by HDCT.

In conclusion, we observed impressive EFS and OS with HDCT and auto-PBSCT in GCT with unfavorable prognostic factors. Toxicity and TRM of HDCT were remarkably low. Subgroup analysis showed that poor response and cisplatin-refractory disease are the most adverse prognostic factors. Our results support the significance and efficacy of auto-PBSCT in advanced GCT as first-line and subsequent therapy, achieving remarkable responses and thereby potentially improving cancer prognosis. This needs to be fully determined in ongoing randomized prospective trials on HDCT as compared with CDCT. Until these trials are completed, detailed analyses such as ours seem to be of significance.

ACKNOWLEDGEMENT

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