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Transplantation for Refractory Germ Cell Tumors: Does It Really Make A Difference?

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Abstract

High-dose chemotherapy (HDC) has been used over the past 25 years for germ-cell tumors in a variety of clinical scenarios. There is consensus at this point that its use as part of first-line treatment does not benefit patients with high-risk tumors. Long-term results of prospective trials in patients with relapsed or with refractory disease indicate that a fraction of them achieve long-term remissions consistent with cures. While HDC constitutes for many oncologists in the US an accepted treatment modality for relapsed or refractory GCT, controversy surrounds its use in those settings. Prognostic models have been developed that allow to prospectively identify poor prognosis patients that might benefit from novel HDC-based approaches.

Keywords

Germ cell tumors; high-dose chemotherapy; autologous stem cell transplant

INTRODUCTION

Germ-cell tumors (GCT) represent the most common malignancy in young men between the ages of 15 and 35 years. Since the advent of modern cisplatin-based chemotherapy cure rates for metastatic disease has reached 70-80%. The standard first-line regimen of bleomycin/etoposide/cisplatin (BEP) yields long-term EFS rates of 90% in advanced-disease good-risk patients, as defined by the International Germ Cell Consensus Classification (IGCCC), which decreases to 80% for intermediate-risk GCT and 50% for poor-risk patients (Table 1). [1] Standard salvage regimens, based on ifosfamide and cisplatin, plus either vinblastine (VeIP),[2] etoposide (VIP)[3] or paclitaxel (TIP)[4] result in CR rates of 50-60% and long-term EFS of 20-30% of patients in first relapse. Patients in second relapse are largely incurable with standard treatment.

High-dose chemotherapy (HDC) has been investigated for patients with poor-risk or relapsed GCT. The use of autologous hematopoietic progenitor-cell support (AHPCS), derived from bone marrow or from peripheral blood progenitor cells (PBPCs), allows for the dose escalation of chemotherapy up to 10 fold, exploiting the dose-response effect of

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Conflict of Interest

Yago Nieto declares no conflict of interest.

alkylators and other drugs. Widespread substitution of PBPC for bone marrow support and other improvements in patient care have increased the safety of HDC to current treatment-related mortality (TRM) rates below 5%.

HDC for Refractory/Relapsed NSGCT

The use of tandem high-dose cycles of carboplatin/etoposide (CE) with AHPCS as salvage therapy was pioneered by Nichols and colleagues at Indiana University in the 1980's. In sequential studies, this treatment resulted in long-term EFS rates of 15% for patients in second relapse,[5,6,7] and 38% for those transplanted in first relapse.[8,9] The introduction of PBPC and improvement of supportive measures allowed the re-escalation of the dose of these drugs and improvement of results.[10] Einhorn et al., subsequently reported 68% EFS at median follow-up of 48 months in a more recent report from the Indiana group in 184 patients (135 transplanted in second-line therapy and 49 in third-line or later therapy) who received tandem cycles of carboplatin (2100 mg/m^2) and etoposide (2,250 mg/m^2).[11] The EFS rates in patients transplanted in first or in second or later relapse were 70% and 45%, respectively. The outcome was similar in patients with seminoma and non-seminoma histologies (74% *v* 60%). These excellent results partly reflect patient selection, with no patients with late relapses or primary mediastinal tumors included, and around one third of the patients presenting features predictive of good outcomes with SDC alone.

Several investigators have tested the addition of a third drug to the CE backbone. Motzer et al. treated 58 cisplatin-refractory patients with two cycles of carboplatin/etoposide/cyclophosphamide (CEC), with a 40% CR rate and 21% EFS rate at a median follow-up of 28 months.[12] Siegert et al. treated 74 patients with recurrent disease with two SDC cycles followed by one cycle of HDC with ifosfamide/carboplatin/etoposide (ICE), with 50% 2-year EFS rates among patients with sensitive tumors, but only 4% EFS in those with refractory disease.[13] Margolin et al. reported a 45% EFS rate after tandem cycles of high-dose ICE in 20 patients with relapsed, cisplatin-sensitive tumors.[14] These investigators subsequently treated 31 relapsed patients with sequential cycles of HDC with paclitaxel (425 mg/m^2 over 24 hours)/carboplatin/etoposide (cycle 1) and ICE (cycle 2).[15] At median follow-up of 5.5 years, twelve (39%) patients remained free of disease. Rick et al. treated 80 patients, most with cisplatin-sensitive disease, with 3-4 cycles of SDC followed by one cycle of high-dose carboplatin/etoposide/thiotepa.[16] At median follow-up of 3 years, the EFS rate was 26%. Overall, high-dose triplets achieve 40-50% EFS rate in patients with cisplatin-sensitive tumors, and 4-20% in those with refractory disease.[17,18]

Feldman et al., have tested the use of 3 cycles of HDC, and reported encouraging results in 107 patients with relapsed disease and unfavorable prognostic features treated with 2 biweekly cycles of paclitaxel/ifosfamide followed high-dose CE x 3 (TICE), with 47% DFS at 5 years.[19]

Can we predict the outcome of patients with relapsed GCT receiving HDC?

Beyer et al. analyzed 283 relapsed/refractory patients treated with CE.[20] They identified the following independent adverse predictors: refractoriness to cisplatin (progression within 4 weeks after treatment with cisplatin), absolute refractoriness to cisplatin (no response to

initial platinum chemotherapy), primary mediastinal tumor, and high tumor markers (HCG >1,000 U/L) at the time of HDC. A prognostic score based on these variables was developed (Table 2). The resulting good, intermediate, and poor risk groups presented 2-year EFS of 51%, 27% and 5%. This model was externally validated in a group of 45 patients with cisplatin-refractory relapsed disease, treated with HDC using ICE x 2, where the subsets with good, intermediate and poor risk had 62%, 13% and 0% EFS rates, respectively, at median follow-up of 32 months.[21] The Beyer model was based on patients treated between 1984 and 1993, and most of them had received a single course of HDC. Ninety-one percent of these patients had failed at least one prior salvage regimen.

Einhorn et al. developed a different prognostic model based on their experience in 184 patients treated at Indiana University with tandem CE.[59] Patients with primary mediastinal tumors were not included for this analysis due to their prior findings that none of the patients those authors had treated were alive and free of disease at 2 years.[22] Three independent adverse prognostic factor were identified: an IGCCCG poor-risk classification at initial diagnosis, cisplatin-refractory disease (defined as PD within 4 weeks of most recent cisplatin-based chemotherapy) and administration of HDC as 3rd- line or later treatment. Patients in the low, intermediate and high-risk categories had EFS rates of approximately 80%, 60% and 40%, respectively.

The International Prognostic Factor Study Group (IPFSG) analyzed 1,594 patients treated after 1990 with HDC (N=821) or SDC (N=773) as first salvage therapy.[23, ●] Among patients receiving HDC, half received a single cycle and the other half received tandem cycles. Seven factors were found to be independent predictors of outcome, both after SDC or HDC: primary tumor site (mediastinal vs. retroperitoneal vs. gonadal), response to first-line therapy, length of prior progression-free interval, AFP at salvage, B-HCG at salvage and presence of nonpulmonary visceral metastases. A composite score based on these factors assigns patients to a very low (only seminoma), low, intermediate, high or very high risk categories. Within each prognostic category, PFS at 2 years was significantly superior after HDC compared to SDC, which translated into improved OS (Table 3). The strengths of this international analysis are its very large sample size and the requirements of a well-documented unequivocal progression or relapse, as well as of prior use of modern first-line and salvage treatments. It is applicable to patients receiving either SDC or HDC at the time of first recurrence, a setting in which it seems more applicable than the other two models. In both the IPFSG and Beyer models, HDC was administered in either one (50% and 91% of the patients, respectively) or tandem (50% and 9%, respectively) cycles. In contrast, all patients in the Indiana model received tandem cycles.

Both the Beyer and the Indiana models are applicable to patients in second or later relapses. While the Indiana model does reflect better the common US practice of using tandem HDC cycles, the Beyer score seems better capable of detecting a very poor prognosis subset of patients, for which novel approaches are clearly needed.

Randomized trials of HDC in the salvage setting

Retrospective matched pair comparisons of HDC versus SDC for patients in first relapse have suggested a large benefit from transplant.[24,25 ●] Pico and colleagues of the EBMT

have conducted the only randomized trial to date comparing HDC to SDC in relapsed patients. These investigators randomized 280 relapsed patients to receive three cycles of SDC followed by one more cycle (SDC arm) or a single course of high-dose CEC with ASCT (HDC arm).[26] At median follow-up of 45 months, no differences in EFS (35% vs. 42%, P=0.16) or OS (53% in both arms) were apparent. This trial has been criticized because of a 30% drop-out rate in the HDC arm, the higher than expected treatment-related mortality in both study arms (3% and 7%, respectively), and the use of a single rather than sequential cycles of HDC.

Lorch et al. randomized 216 patients with relapsed or refractory disease to receive one cycle of high-dose CE or two sequential cycles of those drugs at slightly lower doses, requiring in both arms AHPCS.[27] Accrual to this study stopped after an excessive 14% TRM was detected in the single cycle arm. At median follow-up of 3 years, the differences in favor of the sequential HDC arm in EFS (40% *v* 37%) and OS rates (80% *v* 61%) did not reach statistical significance.

In summary, there is no consensus yet as to whether HDC should be considered for all patients at the time of first relapse. Results of tandem cycles of HDC as salvage treatment appear superior to those expected with SDC, which have prompted many to consider HDC the standard salvage treatment,[28] despite the absence of evidence of benefit from randomized studies. It is possible that more than one cycle of HDC is necessary to achieve a favorable outcome, and that a single cycle, as administered in the European randomized study, may not be sufficient to improve results. Of note, in the IPFSG analysis, the 2-year DFS rates of patients receiving sequential HDC cycles appeared superior to those receiving a single high-dose cycle (55% *v* 44%, P<0.001). An international randomized phase III trial comparing TICE, with 3 cycles of HDC, to SDC with 4 cycles of TIP, will soon address this important question.[29]

Other Areas of Uncertainty

It is unclear whether patients with relapsed primary mediastinal GCT can achieve benefit from HDC. Results of HDC in this population have been historically poor, which has led some investigators to abandon it for these patients.[30] Others, in contrast, have reported long-term CRs within this population in their HDC studies.[67,79]

Late relapses, defined as recurrence 2 years or longer following a CR to cisplatin-based first-line therapy, are a disconcerting syndrome characterized for a poor response to chemotherapy. While surgery is the preferred approach,[31] it remains unclear whether patients with unresectable late relapses might benefit from HDC as some have recently suggested.[79]

First-Line HDC for Poor-Risk NSGCT

Motzer and colleagues at Memorial Sloan Kettering Cancer Center developed a strategy of switching to HDC those patients showing a reduced clearance and prolonged half-life of tumor markers during SDC.[32] This approach yielded a CR rate of 57%, 50% EFS at a median follow-up of 30 months, and significantly longer OS than historical controls from the same institution.

Schmoll and colleagues reported long-term results of HDC in 221 patients with advanced poor-prognosis disease, who received one cycle of SDC followed by three cycles of high-dose VIP (high-dose etoposide/ifosfamide + standard dose cisplatin).[33] At median follow-up of 4 years, the EFS rate was 69%. Non-randomized matched-pair comparisons of patients enrolled in this trial with others enrolled in trials of SDC suggested superiority of HDC.[34]

The role of HDC in first-line therapy has been evaluated in three randomized studies. A European randomized trial conducted in the 1980's failed to show a therapeutic benefit for HDC in 115 untreated poor-risk patients, who were randomized to receive 3-4 cycles of SDC or two cycles followed by one cycle of a stem-cell-supported high-dose cisplatin-containing regimen.[35] Patients randomized to the transplant arm received less total cisplatin than those on the standard-dose arm, as well as a HDC regimen that can be considered substandard by present criteria. It is therefore felt that this study did not appropriately address the role of first-line HDC in poor-risk GCT.

A European study compared SDC with BEP x 4 cycles to one cycle of VIP followed by 3 cycles of high-dose VIP with ASCT in patients with poor-risk features by the IGCCCG.[36] This study closed prematurely after slowly enrolling only 137 of the 222 planned patients. At its first analysis with 4.4 year median follow-up, the 2-year EFS (45% vs. 58%, P=0.06) and 2-year OS (66% vs. 73%, P>0.05) differences did not reach statistical significance.

In an US Intergroup trial Motzer et al. randomized 219 patients with newly diagnosed disease with intermediate or poor risk features according to the IGCCCG criteria to receive 4 cycles of BEP or 2 cycles of BEP followed by 2 cycles of HDC with CEC.[37] The 1-year durable CR rates did not differ significantly between the transplant and control arms (48 vs 52%, P=0.5). There were no significant differences in EFS (p=0.4) or OS (p=0.9). A planned subset analysis according to early tumor marker clearance suggested a significant benefit of HDC among those patients experiencing a slow marker decline (61% vs 34% 1-year EFS, P=0.03), in contrast with similar outcomes in both arms in the group of patients with a satisfactory marker drop (P=0.5). Given the small size of this subset analysis, these provocative observations are not robust enough to allow firm conclusions.

In summary, the available data from randomized trials indicate that there is currently no standard role for HDC in first-line treatment of GCT.

Special considerations

Surgical management after HDC—A retrospective review of the German experience identified 216 patients treated on three consecutive HDC trials between 1989 and 1999.[38] Partial remissions with negative or positive tumor markers after high-dose chemotherapy were achieved in 128 patients (59%). Of these patients, 57 (45%) proceeded to residual tumor resection; the remaining 71 (55%) could not be operated on because of progressive disease, unresectability of the tumor masses, poor performance status, or patient refusal. With a median follow-up of 87 months, 37/57 patients (65%) were alive, 34 of whom (59%) remained continuously disease free. Viable cancer was documented in the resected specimen of 26 (46%) of the 57 patients. The 5-year EFS rates in patients with and without viable cancer were 42% and 84%, respectively (P<0.01). Of note, all patients in this series had

been treated with a single cycle of high-dose chemotherapy, which likely influenced the incidence of viable cancer in resected specimens. This report indicates that postchemotherapy resection can significantly contribute to overall treatment outcome, and that residual tumor resection should be considered in patients in partial remission after HDC.

Management of relapse post HDC—A retrospective review of the Indiana University experience identified 101 patients relapsed after HDC after a median interval of 10 months. Forty-seven of them subsequently received salvage SDC, with an overall RR of 18.2% and a CR rate of 5%. Seven patients underwent surgery alone, with only one long-term survivor.[39]

Two prospective trials have studied salvage SDC for relapse after HDC. In a phase II trial at Indiana University, 32 patients with progressive disease after CE x2 received paclitaxel/gemcitabine.[40] Patients who had received either agent prior to HDC were ineligible. A response was achieved by 10 patients (31%), including 6 CRs and 4 PRs (of 2–6 months' duration). Four patients in CR (12.5%) were continuously disease free without any additional treatment at 20 to 57 months from paclitaxel/gemcitabine. One additional CR patient was rendered disease free after two subsequent resections of tumor. A German study enrolled 32 patients with relapse after HDC and 9 patients with cisplatin-refractory disease who were rescued with gemcitabine/oxaliplatin/paclitaxel.[41] Two patients (6%) achieved a CR, 34% achieved a marker-negative PR, and 12% achieved marker-positive PR, for an overall RR of 51%.

Therefore, while outcomes have been largely unfavorable for patients who relapse after HDC, these trials point to some possibility of successful chemotherapeutic salvage even in heavily pretreated and cisplatin-refractory patients.

Novel HDC-based strategies: A novel strategy to improve results attempts to modulate the effect of HDC with biologic agents. Germ-cell tumors are highly vascularized and express vascular endothelial growth factor (VEGF) prominently. The expression of this angiogenic factor correlates closely with microvessel density within metastatic GCT lesions, which has been associated with prognosis.[42,43] Use of a single dose of the anti-VEGF monoclonal antibody bevacizumab before chemotherapy decreases tumor interstitial fluid pressure and enhances access of the cytotoxic drugs into the solid tumor lesions.[44] Attempting to exploit their synergy, we are conducting at MD Anderson Cancer Center a phase 2 trial of sequential cycles of bevacizumab combined with high-dose gemcitabine/docetaxel/melphalan/carboplatin followed by bevacizumab-ICE in patients in either poor-risk first relapse (Beyer model) or with more than 1 prior relapses. Preliminary results in the first 30 patients enrolled were recently reported.[45] These patients had experienced 3 median prior relapses with a median Beyer score of 3 (range, 1-5). At median follow up of 25 months the EFS and OS rates are 66% and 70%, respectively. Accrual continues to confirm these encouraging results in this very poor prognosis population.

CONCLUSIONS

In conclusion, there is currently no standard role for HDC in first-line treatment of GCT. Definition of its role as part of first-line salvage awaits completion and analysis of the

upcoming international randomized trial. HDC is widely considered a valid treatment option for patients with refractory disease or in second relapse or later.

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Table 1.

Risk stratification of newly diagnosed patients (International Germ Cell Consensus Classification)

	Non-seminoma		Seminoma	
Low risk	• Testis or retroperitoneal primary, *and* • No non-pulmonary visceral metastases *and* • Good markers (AFP<1,000 ng/mL *and* B-HCG<5,000 IU/L *and* LDH<1.5 ULN)	• 56 % patients • 90 % EFS at 5 years	• Any primary site, *and* • No non-pulmonary visceral metastases *and* • Normal AFP, any B-HCG, any LDH	• 90 % patients • 80 % EFS at 5 years
Intermediate risk	• Testis or retroperitoneal primary, *and* • No non-pulmonary visceral metastases *and* • Intermediate markers (AFP 1,000-10,000 ng/mL *or* B-HCG 5,000-50,000 IU/L *or* LDH 1.5-10 ULN)	• 28 % patients • 80 % EFS at 5 years	• Testis or retroperitoneal primary, *and* • Non-pulmonary visceral metastases *and* • Normal AFP, any B-HCG, any LDH	• 10 % patients • 67 % EFS at 5 years
Poor risk	• Mediastinal primary, *or* • Non-pulmonary visceral metastases *or* • Poor markers (AFP >10,000 ng/mL *or* B-HCG >50,000 IU/L *or* LDH >10 ULN)	• 56 % patients • 50 % EFS at 5 years		

ULN: Upper limit of normal

Table 2.

Prognostic Models for HDC for NSGCT

Model		Factor		Points	2-year EFS
Beyer	Variables	Progressive disease before HDC		1	
		Mediastinal primary tumor		1	
		Cisplatin-refractory disease (relapse within 4 weeks of completion of first-line chemotherapy)		1	
		Absolute cisplatin-refractory disease (PD as best response to prior therapy)		2	
		B-HCG > 1,000 IU/L before HDC		2	
	Stratification	**Low risk**		0	51%
		Intermediate risk		1-2	27%
		High risk		>2	5%
Einhorn	Variables	HDC at third-line or subsequent line of treatment		3	
		Refractory disease before HDC (relapse within 4 weeks of completion of first line chemotherapy)		2	
		High-risk IGCCCG stage		2	
	Stratification	**Low risk**		0	80%
		Intermediate risk		2-3	60%
		High risk		>3	40%
International Prognostic Factors Study Group	Variables	Histology	Seminoma	−1	
			Nonseminoma	0	
		Primary tumor site	Mediastinal	3	
			Retroperitoneal	1	
			Gonadal	0	
		Response to first-line chemotherapy	CR/PRm−	0	
			PRm+/SD	1	
			PD	2	
		Progression-free interval following first-line chemotherapy	>3 months	0	
			≤3 months	1	
		AFP at salvage	Normal	0	
			≤1,000	1	
			>1,000	2	
		B-HCG at salvage	≤1,000	0	
			>1,000	1	
		Liver/brain/bone metastases	No	0	
			Yes	1	
	Stratification	**Very low risk (seminoma + low risk)**		−1	92%
		Low risk		0	64%

Model		Factor		Points	2-year EFS
		Intermediate risk		1-2	53%
		High risk		3-4	33%
		Very high risk		>4	22%

Table 3.

EFS and OS rates in patients treated with HDC or SDC (International Prognostic Factors Study Group)

		2-yr EFS	*P* value	5-yr OS	*P* value
All patients (*N*=1594)	SDC	28 %	<0.001	41 %	<0.001
	HDC	50 %		53 %	
Very low risk (*N*=76)	SDC	58 %	<0.001	64 %	<0.01
	HDC	92 %		89 %	
Low risk (*N*=257)	SDC	40 %	<0.001	66 %	0.98
	HDC	64 %		64 %	
Intermediate risk (*N*=646)	SDC	32 %	<0.001	45 %	<0.001
	HDC	53 %		58 %	
High risk (*N*=351)	SDC	17 %	<0.001	23 %	<0.005
	HDC	33 %		35 %	
Very high risk (*N*=105)	SDC	2 %	<0.001	3 %	<0.001
	HDc	22 %		27 %	