

# High-Dose Chemotherapy and Autologous Peripheral-Blood Stem-Cell Transplantation for Relapsed Metastatic Germ Cell Tumors: The Indiana University Experience

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## ABSTRACT

### Purpose

Patients with relapsed metastatic germ cell tumor (GCT) can be cured with second-line and even third-line regimens. We report survival outcomes of patients treated with high-dose chemotherapy (HDCT) and peripheral-blood stem-cell transplantation (PBSCT) at Indiana University between 2004 and 2014.

### Patients and Methods

We conducted a retrospective analysis of 364 consecutive patients with GCT who progressed after cisplatin-based combination chemotherapy and were subsequently treated with HDCT and PBSCT. Three hundred forty-one patients received two consecutive courses of HDCT consisting of 700 mg/m<sup>2</sup> carboplatin and 750 mg/m<sup>2</sup> etoposide, each for 3 consecutive days, and each followed by PBSCT. Twenty-three patients received only a single course of HDCT because of progressive disease or toxicity. Cox proportional hazards models were used to test predictors of disease progression.

### Results

The median age was 32 years (range, 17 to 70 years). With a median follow-up of 3.3 years, the 2-year progression-free survival (PFS) was 60% (95% CI, 55% to 65%) and the 2-year overall survival was 66% (95% CI, 60% to 70%). Three hundred three patients received HDCT as second-line therapy with a 2-year PFS of 63% (95% CI, 57% to 68%), and 61 patients received HDCT as third-line or later therapy with a 2-year PFS of 49% (95% CI, 36% to 61%). In a multivariable analysis, factors associated with disease progression included use of HDCT as third-line or later therapy, platinum-refractory disease, mediastinal primary tumor site, nonseminoma histology, intermediate- or poor-risk disease at the time of GCT diagnosis, and human chorionic gonadotropin  $\geq$  1,000 mIU/mL at initiation of HDCT. There were nine treatment-related deaths. Secondary leukemia developed in five patients.

### Conclusion

This large single-institution study demonstrates that patients with relapsed metastatic GCT are curable by HDCT plus PBSCT even when used in third-line or later therapy.

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## INTRODUCTION

Germ-cell tumors (GCT) are the most common cancer in men between 15 and 35 years of age and the incidence has risen during the past several decades.<sup>1</sup> Patients with metastatic GCT are curable even in the presence of metastatic disease.<sup>2</sup> The International Germ Cell Cancer Collaborative Group (IGCCCG) classified patients with metastatic GCT into good, intermediate, and poor risk disease on the basis of specified prognostic criteria.<sup>3</sup> Per the IGCCCG, the good risk

category represents 60%, intermediate risk represents 26%, and poor risk represents 14% of patients with metastatic GCT. Using contemporary cisplatin-based front-line combination chemotherapy, cure rates at our institution for good, intermediate, and poor risk disease are 90%, 84%, and 51%, respectively.<sup>4</sup> Patients who relapse after initial chemotherapy, with anatomically confined disease, can still be cured by salvage surgery.<sup>5</sup> The vast majority of patients, however, will be treated with salvage chemotherapy; the most effective regimen for these patients remains unsettled. Second-line standard-dose chemotherapy options include

### ASSOCIATED CONTENT



See accompanying Oncology Grand Rounds on page 1036



Appendix  
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etoposide plus ifosfamide plus cisplatin (VIP), vinblastine plus ifosfamide plus cisplatin, or paclitaxel plus ifosfamide plus cisplatin.<sup>6-8</sup>

High-dose chemotherapy (HDCT) followed by bone marrow transplant was first investigated at Indiana University in 1986.<sup>9</sup> Bone marrow transplantation was replaced by peripheral-blood stem cells in 1996. This allowed for more rapid engraftment and hence fewer delays in delivering a second course of HDCT. In our previous series of 184 consecutive patients with relapsed metastatic GCT treated with HDCT and peripheral-blood stem-cell transplant (PBSCT) between 1996 and 2004, long-term disease-free survival was achieved in 70% of patients in the second-line setting, and in 45% of patients who received a third-line or subsequent regimen.<sup>10</sup>

Investigators at Memorial Sloan Kettering Cancer Center (MSKCC) pioneered another widely used HDCT regimen, which incorporates paclitaxel and ifosfamide as induction chemotherapy and stem-cell mobilization followed by high-dose carboplatin and etoposide with PBSCT for three cycles (TI-CE regimen).<sup>11</sup> In a phase I/II trial that enrolled 107 patients, the reported 5-year disease-free survival was 47% and overall survival (OS) was 52%. Given the lack of definitive phase III data for salvage therapy and limited outcome data reported from the past 10 years, we now report survival outcomes and prognostic criteria in 364 consecutive patients with relapsed metastatic GCT treated at Indiana University between 2004 and 2014 with HDCT followed by PBSCT for a planned two successive courses.

## PATIENTS AND METHODS

### Patients

Eligible patients had metastatic GCT that progressed after one or more standard cisplatin-etoposide-based combination chemotherapy regimens.<sup>2,12</sup> After institutional review board approval was obtained, we conducted a retrospective analysis of 364 patients with relapsed metastatic GCT who received HDCT and PBSCT at Indiana University between December 2004 and December 2014. Clinical data were collected from electronic medical records, physical charts, and patient interviews. Abstracted data included patient and disease characteristics, prior surgical and chemotherapy treatment, date of HDCT, and survival outcomes. This study used the secure Web-based, Title 21 Code of Federal Regulations Part 11-compliant Research Electronic Data Capture system for data input. Patients with primary mediastinal nonseminomatous germ cell tumor (PMNSGCT) were included in this study. Patients with late relapse of GCT, defined as > 2 years after previous therapy, were excluded.

Patients who had platinum-refractory disease, defined as tumor progression within 4 weeks of cisplatin-based chemotherapy, proceeded directly to HDCT. Patients who had platinum-sensitive disease received one or two cycles of standard-dose chemotherapy, most commonly vinblastine plus ifosfamide plus cisplatin, before proceeding to HDCT. This was done in an attempt to reduce the bulk of tumor while preventing further disease progression before initiating HDCT.

Peripheral-blood stem cells were harvested after the patient's bone marrow was stimulated using granulocyte colony-stimulating factor. These cells were then purified using a technique that has been previously described.<sup>13</sup> Two courses of HDCT were planned for all patients. Each course consisted of carboplatin 700 mg/m<sup>2</sup> body-surface area plus etoposide 750 mg/m<sup>2</sup> intravenously on days 5, 4, and 3. Stem-cell infusion was performed on day 0.

Patients received bacterial, viral, and fungal prophylaxis according to the following regimen: ciprofloxacin 500 mg orally twice per day, acyclovir 400 mg orally twice per day, fluconazole 400 mg orally once per day, and vancomycin intravenously. Infectious prophylaxis was initiated on the day before stem-cell infusion and continued until neutrophil count recovery. Granulocyte colony-stimulating factor was delivered once per day after

stem-cell infusion until neutrophil count recovery. After engraftment and end-organ recovery, the second cycle of HDCT was initiated. Some patients who achieved a complete or partial remission after HDCT were treated with maintenance oral etoposide delivered at a dose of 50 mg/m<sup>2</sup> once per day for 21 days of 28-day cycles for a total of three cycles.<sup>14,15</sup> This was given to patients with nonseminoma who achieved a serological complete remission and had hematologic recovery after HDCT.

The primary end point of this study was to estimate the 2-year PFS of patients with relapsed GCT treated with HDCT. Secondary end points were to estimate 2-year OS, to identify clinical factors prognostic for disease progression after HDCT, and to assess safety and toxicity.

### Statistical Analysis

Analyses were performed using SAS software, version 9.4. Patient and disease characteristics at the beginning of HDCT were tabulated. PFS was calculated from the date of HDCT initiation to the date of relapse or date of death. Otherwise, the patient was censored at the date of last follow-up. PFS was estimated using Kaplan-Meier methods.

Univariable analysis was performed to identify prognostic factors for disease progression using the Wald  $\chi^2$  test. Using a significance level of  $P < .05$ , factors that were significant in the univariable analysis for PFS were incorporated in a multivariable Cox proportional hazards model. This model was used to identify important clinical factors in predicting PFS and to estimate the hazard ratio for each variable while adjusting for other covariates.

Variables that were tested in the univariable analysis were use of HDCT as third-line or later regimen versus second-line therapy, platinum-refractory versus platinum-sensitive disease, primary tumor site (mediastinal v testes/retroperitoneal), tumor histology, risk per IGCCCG criteria at the time of GCT diagnosis,<sup>3</sup> serum tumor marker level at initiation of HDCT including alpha-fetoprotein and human chorionic gonadotropin (hCG), and age at the time of HDCT initiation. Age was used as a continuous variable in this analysis.

## RESULTS

### Patient and Disease Characteristics

Three hundred sixty-four consecutive patients with relapsed metastatic GCT received HDCT and PBSCT at Indiana University between 2004 and 2014. The median age was 32 years (range, 17 to 70 years). Three hundred forty-two patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 at initiation of HDCT. The primary tumor site was testis in 316 patients, retroperitoneum in 28 patients, and mediastinum in 20 patients. All patients with primary mediastinal primary tumor site had nonseminoma histology. Seventy-nine patients had pure seminoma and 285 had nonseminomatous GCT. Two hundred forty-two patients had platinum-sensitive disease and 122 patients had platinum-refractory disease, defined as tumor progression within 4 weeks of cisplatin-based chemotherapy. Three hundred three patients received HDCT in the second-line setting and 61 received HDCT in the third-line or later setting. Table 1 lists patient and disease characteristics at the time of starting the first course of HDCT.

### Treatment Administration and Survival Outcomes

Two hundred forty-two patients received a single course of standard-dose chemotherapy before proceeding with HDCT. Three hundred forty-one patients (94%) received the planned two courses of HDCT. The median time between HDCT courses was 28 days (range, 18 to 58 days). Twenty-three patients received only a single course of HDCT because of progressive disease in 12

**Table 1.** Patient and Disease Characteristics at the Beginning of High-Dose Chemotherapy

Characteristic	No. of Patients (N = 364)	%
Median age, years (range)	32 (17-70)	
Location of primary tumor		
Testis	316	87
Retroperitoneum	28	8
Mediastinum	20	5
Tumor histology		
Seminoma	79	22
Nonseminoma	285	78
Metastatic site(s)		
Retroperitoneum	281	77
Pulmonary	217	60
NPVM	122	34
Liver	75	21
Brain*	64	18
Bone*	25	7
Brain metastasis		
None	300	82
Inactive/previously treated	44	12
Progressive	20	6
Initial IGCCCG risk		
Good	151	41
Intermediate	39	11
Poor	174	48
Progression-free interval after first-line chemotherapy, weeks		
< 4	118	32
4-12	54	15
> 12	192	53
Platinum sensitivity		
Sensitive	242	66
Refractory	122	34
No. of previous chemotherapy regimens		
1	303	83
2	55	15
≥ 3	6	2
Median serum AFP ng/mL (range)	7.5 ng/mL (1-21,347)	
Serum AFP level < 1,000	336	92
Serum AFP level ≥ 1,000	28	8
Median serum hCG mIU/mL (range)	37.1 mIU/mL (0.5-178,140)	
Serum hCG < 1,000	274	75
Serum hCG ≥ 1,000	90	25
ECOG performance status		
0	305	84
1	37	10
2	22	6
Risk per IPFSG criteria (N = 303)		
Very low	34	11
Low	55	18
Intermediate	77	25.5
High	77	25.5
Very high	60	20

Abbreviations: AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; hCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group; IPFSG, International Prognostic Factors Study Group; NPVM, nonpulmonary visceral metastasis.  
\*Brain/bone imaging was not mandatory.

patients and toxicity in 11 patients. One hundred thirty-four patients received maintenance etoposide after HDCT. Among these patients, 15 received one cycle, 14 received two cycles, and 105 received three cycles of oral maintenance etoposide.

With a total of 364 patients and a median follow-up of 3.3 years, the estimated 2-year PFS was 60% (95% CI, 55% to 65%; Fig 1A).

The estimated 2-year OS was 66% (95% CI, 60% to 70%; Fig 1B). Among the 143 patients who had disease recurrence after HDCT, the median time to relapse was 4.3 months (range, 1 to 30 months).

In breaking down the PFS by line of therapy, patients who received HDCT as second-line treatment had a 2-year PFS of 63% (95% CI, 57% to 68%) and patients who received HDCT as third-line or later therapy had a 2-year PFS of 49% (95% CI, 36% to 61%;  $P = .03$ ). The 2-year OS rates for these subsets were 67% (95% CI, 61% to 72%) and 60% (95% CI, 46% to 71%), respectively ( $P = .05$ ). Patients with platinum-refractory disease had 2-year PFS rates of 33% (95% CI, 24% to 41%)  $\nu$  75% (95% CI, 69% to 80%) for platinum-sensitive patients ( $P < .001$ ). Two-year OS rates for these subsets were 37% (95% CI, 30% to 45%) and 80% (95% CI, 75% to 85%), respectively ( $P < .001$ ). Figure 2 depicts Kaplan-Meier estimates of PFS for patients who received HDCT according to the line of treatment and according to platinum sensitivity.

Patients with pure seminoma had 2-year PFS of 90% (95% CI, 81% to 95%) compared with 52% (95% CI, 46% to 58%) for nonseminomatous GCT ( $P < .001$ ; Appendix Fig A1, online only). Two-year PFS rates for patients with PMNSGCT versus testicular/retroperitoneal primary tumor sites were 23% (95% CI, 7% to 43%) versus 63% (95% CI, 57% to 68%;  $P < .001$ ), respectively (Appendix Fig A2, online only). Two-year PFS and 2-year OS for patients receiving HDCT in the second-line setting stratified per the International Prognostic Factors Study Group criteria are shown in Appendix Table A1 (online only).

Some patients with brain metastasis in this study were treated with radiation therapy before or after HDCT. Among the 64 patients with brain metastasis, 20 had progressive brain metastasis at initiation of HDCT. Eight of these 20 patients achieved remission and were disease-free after HDCT without additional surgery or radiation therapy. In addition, five of 20 patients with PMNSGCT were continuously disease-free after HDCT.

### Univariable and Multivariable Analyses

Univariable and multivariable analyses were performed to evaluate the impact among the predictors on PFS while adjusting for other covariates. The results of the Cox regression analysis of all 364 patients are presented in Tables 2 and 3. The variables that were significant in the univariable analysis and included in the multivariable analysis were line of therapy (third-line or later regimen  $\nu$  second-line therapy), platinum-refractory versus platinum-sensitive disease, serum tumor marker level at initiation of HDCT including alpha-fetoprotein and hCG, histologic type (nonseminoma  $\nu$  seminoma), risk per IGCCCG criteria at the time of GCT diagnosis, and primary tumor site (mediastinal  $\nu$  testis/retroperitoneal).

Significant variables that retained statistical significance in the multivariable analysis and had an adverse effect on PFS were use of HDCT as third-line or later therapy, platinum-refractory disease, mediastinal primary tumor site, nonseminoma histology, intermediate or poor risk disease per IGCCCG criteria,<sup>3</sup> and hCG  $\geq$  1,000 mIU/mL at initiation of HDCT.

### Toxicity

Grade 3 or higher nonhematologic toxic effects of HDCT are listed in Table 4. Renal toxicity was defined as a serum creatinine greater than three times the upper limit of normal range, GI

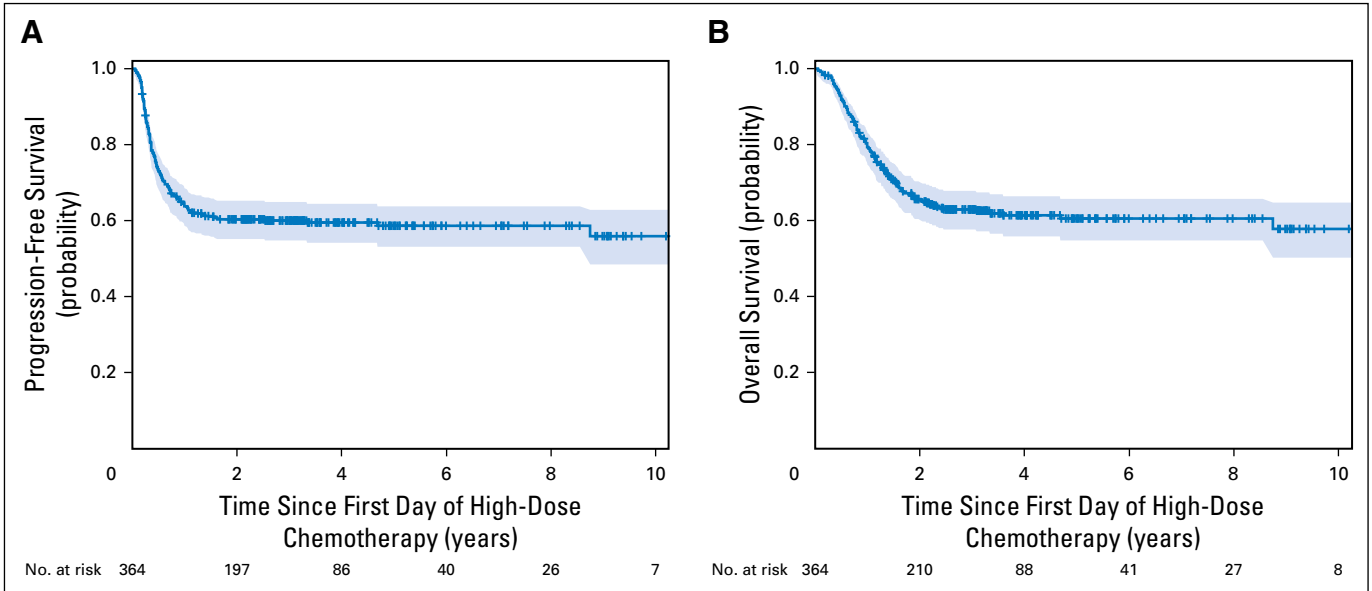


Fig 1. Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival for 364 patients.

defined as severe pain interfering with oral intake, neurologic defined as severe symptoms limiting self-care, pulmonary defined as dyspnea or hypoxia interfering with daily activities, and hepatic toxic effects included a value for liver-function tests that was greater than three times the upper limit of normal range. The most frequent adverse events were mucositis, nausea, and vomiting. Long-term adverse effects included peripheral neuropathy and ototoxicity.

There were nine treatment-related deaths. Six deaths occurred during or within 30 days of completion of HDCT: four as a result of infectious complications of HDCT and two as a result of hepatic failure. Three deaths occurred > 30 days after completion of HDCT and were as a result of complications from secondary leukemia.

Secondary leukemia developed in five patients and the intervals from HDCT to diagnosis of leukemia were 17, 27, 36, 51, and 120 months. Among these five patients, four received HDCT as second-line and only one received HDCT as third-line therapy. Three patients who developed secondary leukemia had received maintenance oral etoposide after HDCT. Three of these five patients died as a result of complications related to leukemia and two are currently experiencing complete remission for their relapsed GCT and secondary leukemia. One patient developed a solid malignancy 6 months after HDCT in the form of metastatic mucinous adenocarcinoma of the GI tract. He died as a result of complications related to his solid malignancy.

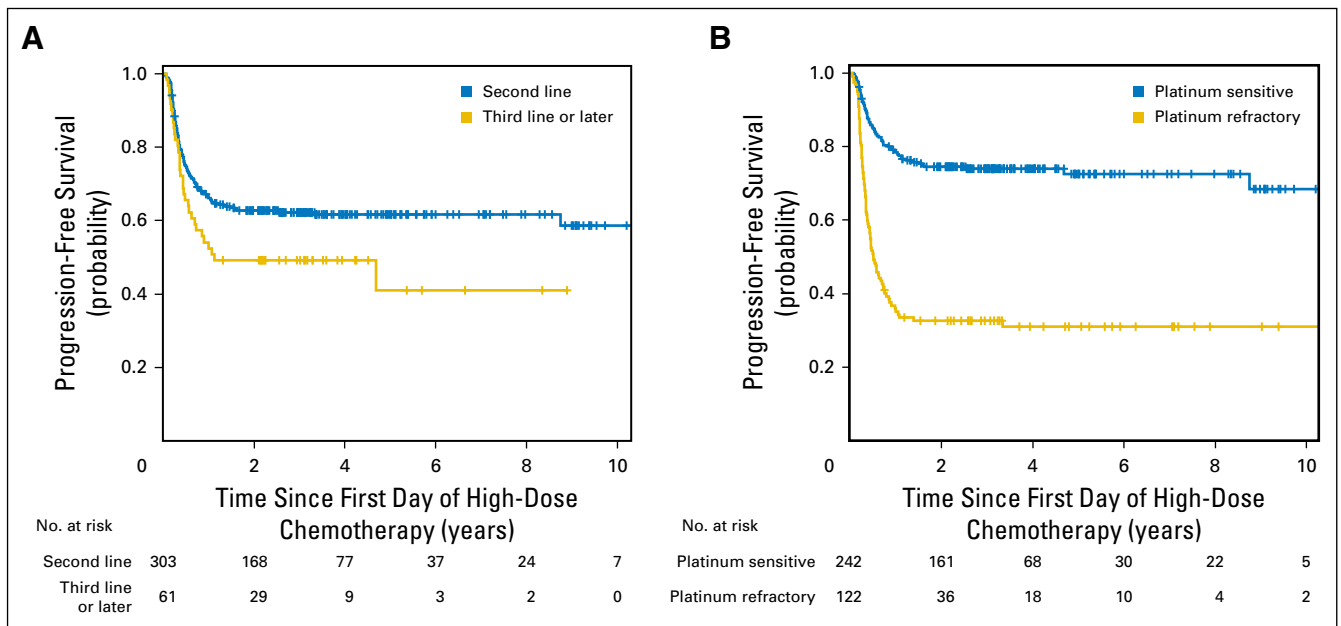


Fig 2. Kaplan-Meier estimates of (A) progression-free survival according to line of therapy and (B) platinum sensitivity.

**Table 2.** Univariable Analysis for Prognostic Variables in 364 Patients

Variable (no. of patients)	2-Year PFS, %	Hazard Ratio (95% CI)	P*
High-dose chemotherapy			.03
Second line (303)	63	1.00	
Third line or later (61)	49	1.53 (1.03 to 2.26)	
Platinum sensitivity			< .001
Sensitive (242)	75	1.00	
Refractory (122)	33	3.77 (2.72 to 5.24)	
Location of primary tumor			< .001
Testis/RP (344)	63	1.00	
Mediastinum (20)	23	2.71 (1.58 to 4.63)	
Tumor histology			< .001
Seminoma (79)	90	1.00	
Nonseminoma (285)	52	4.90 (2.58 to 9.32)	
Initial IGCCCG risk			< .001
Good (151)	82	1.00	
Intermediate (39)	58	2.8 (1.55 to 5.07)	
Poor (174)	43	4.09 (2.69 to 6.22)	
Serum AFP, ng/mL			.05
< 1,000 (336)	62	1.00	
≥ 1,000 (28)	42	1.69 (1.01 to 2.84)	
Serum hCG, mIU/mL			< .001
< 1,000 (274)	69	1.00	
≥ 1,000 (90)	37	2.76 (1.97 to 3.85)	
Age (continuous variable)	NA	0.99 (0.98 to 1.01)	.44

Abbreviations: AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group; NA, not applicable; PFS, progression-free survival; RP, retroperitoneum.  
\*P value for hazard ratio.

## DISCUSSION

In the current era, cisplatin-based combination chemotherapy will cure 83% of patients with metastatic GCT.<sup>16</sup> Ninety percent of

patients with IGCCCG good risk disease will achieve cure with front-line chemotherapy. Patients with intermediate and poor risk disease have less favorable outcomes, and a significant proportion will relapse and require salvage therapy.<sup>4</sup> This study evaluates 364 consecutive patients with relapsed metastatic GCT treated with HDCT at our center between 2004 and 2014. To our knowledge, this is the largest single-institution study evaluating HDCT in patients with relapsed GCT.

With a median follow-up of 3.3 years, the 2-year PFS was 60% (95% CI, 55% to 65%) and 2-year OS was 66% (95% CI, 60% to 70%). These outcomes are similar to results reported from MSKCC using the TI-CE regimen.<sup>11</sup> Although this study included a high proportion of patients with poor prognostic factors at initiation of HDCT, survival outcomes seem superior compared with previous studies evaluating standard-dose salvage chemotherapy.<sup>6,7,17</sup>

The multivariable analysis reported in this study identifies key prognostic factors in patients with relapsed GCT undergoing HDCT. Receiving HDCT in the third-line or subsequent setting, platinum-refractory disease, nonseminoma histology, mediastinal primary tumor site, IGCCCG intermediate or poor risk disease at the time of GCT diagnosis, and hCG ≥ 1,000 mIU/mL at start of HDCT were all independent predictors of progression after HDCT. These prognostic criteria are consistent with previous studies that reported prognostic factors in patients with relapsed GCT treated with HDCT.<sup>10,18,19</sup> Importantly, a significant proportion of patients who had poor prognostic features achieved remission and were disease-free after HDCT.

Long-term remissions were achieved in patients receiving HDCT as third-line or subsequent therapy (2-year PFS, 49%) and in patients with platinum-refractory disease (2-year PFS, 33%). Switching from bone marrow transplant to PBSCT allowed for

**Table 3.** Multivariable Analysis for Prognostic Variables in 364 Patients

Variable	Hazard Ratio (95% CI)	P*
High-dose chemotherapy		.003
Second line	1.00	
Third line or later	1.85 (1.23 to 2.78)	
Platinum sensitivity		.001
Sensitive	1.00	
Refractory	2.05 (1.33 to 3.18)	
Location of primary tumor		.03
Testis/RP	1.00	
Mediastinum	1.94 (1.06 to 3.55)	
Tumor histology		.02
Seminoma	1.00	
Nonseminoma	2.28 (1.11 to 4.68)	
Initial IGCCCG risk		.04
Good	1.00	
Intermediate	2.05 (1.12 to 3.78)	
Poor	1.72 (1.05 to 2.82)	
Serum hCG, mIU/mL		.003
< 1,000	1.00	
≥ 1,000	1.76 (1.22 to 2.55)	
Serum AFP, ng/mL		.46
< 1,000	1.00	
≥ 1,000	1.23 (0.71 to 2.15)	

Abbreviations: AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group; IU, international unit; RP, retroperitoneum.  
\*P value for hazard ratio.

**Table 4.** Grade 3 or Higher Nonhematologic Toxicity of High-Dose Chemotherapy in 364 Patients

Toxicity	No. of Patients	%
GI	50	13.8
Hepatic	12	3.3
Pulmonary	12	3.3
Renal	11	3
Neurologic	9	2.5
Secondary leukemia	5	1.4

more rapid delivery of the second course of HDCT and improved outcomes in patients with PMNSGCT. This study included 20 patients with PMNSGCT. Five of these 20 patients (25%) were disease-free after HDCT. These results seem similar to those of patients with PMNSGCT in the MSKCC series, where five of 21 patients (24%) were disease-free after HDCT.<sup>11</sup> In addition, this study included 64 patients with brain metastasis; among these, 20 patients had progressive brain metastasis at initiation of HDCT. Eight of these 20 patients achieved remission and were disease-free after HDCT.

The choice of initial salvage chemotherapy for relapsed metastatic GCT remains controversial. One of the challenges is determining which patients should be treated with salvage standard-dose chemotherapy versus HDCT. A randomized phase III study comparing sequential with a single course of HDCT showed superior OS in the arm receiving sequential HDCT.<sup>20</sup> A prospective phase III trial did not show a difference in survival when comparing VIP for four cycles versus VIP for three cycles followed by HDCT with carboplatin and etoposide plus cyclophosphamide for one cycle.<sup>21</sup>

In 2011, Lorch et al<sup>17</sup> reported outcomes from a large multi-institutional database evaluating 1,594 patients with relapsed GCT. This retrospective study included a diverse patient population stratified to prognostic subgroups according to the International Prognostic Factors Study Group.<sup>19</sup> Patients were treated with heterogeneous salvage chemotherapy regimens between 1990 and 2008. In this study, HDCT achieved superior outcomes compared with standard-dose chemotherapy and there was an overall 56% decrease in the risk of progression after first salvage treatment, favoring HDCT. This translated into statistically significant improvement in OS with HDCT in all prognostic subgroups except the low-risk group. The superior outcomes with HDCT were more pronounced in patients with intermediate, high, or very high risk disease.

In the current study, patients with seminoma had the highest cure rate, with a 2-year PFS of 90% (95% CI, 81% to 95%). Even more importantly, cures were achieved in patients with platinum-refractory disease, PMNSGCT, progressive brain metastases, and

in patients receiving HDCT as third-line or subsequent therapy. These patients have low chance of cure with standard-dose chemotherapy.<sup>17</sup>

Although this study had a large sample size of consecutive patients and long follow-up, there are limitations to report. Patients in this study were treated at an experienced high-volume referral center for metastatic GCT; hence survival outcomes for patients treated at other institutions might vary. In our opinion, these patients require multidisciplinary expertise and thus should be cared for at centers of testicular cancer excellence. Other studies have reported improved outcomes when patients with testicular cancer were treated at tertiary care centers.<sup>22,23</sup> Patients who were treated with salvage HDCT had adequate performance status and end-organ function, and these factors might have contributed to selection bias. In addition, some prognostic groups had a small number of patients, prohibiting statistical significance in the multivariable analysis.

In conclusion, HDCT followed by PBSCT is effective salvage therapy for patients with relapsed GCT, delineating remarkable chemosensitivity of this disease. Patients with platinum-refractory disease and patients with poor prognostic features are prime candidates for HDCT. Treatment with high-dose carboplatin and etoposide was associated with low treatment-related mortality. Although potentially curative, HDCT has both short- and long-term quality-of-life issues, reflecting a burden of the patients who are cured. Optimal patient selection for HDCT versus standard-dose chemotherapy as initial salvage is currently being studied in a randomized phase III trial as part of an international collaboration ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02375204) identifier, NCT02375204).

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [jco.org](https://jco.org).

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**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**High-Dose Chemotherapy and Autologous Peripheral-Blood Stem-Cell Transplantation for Relapsed Metastatic Germ Cell Tumors: The Indiana University Experience**

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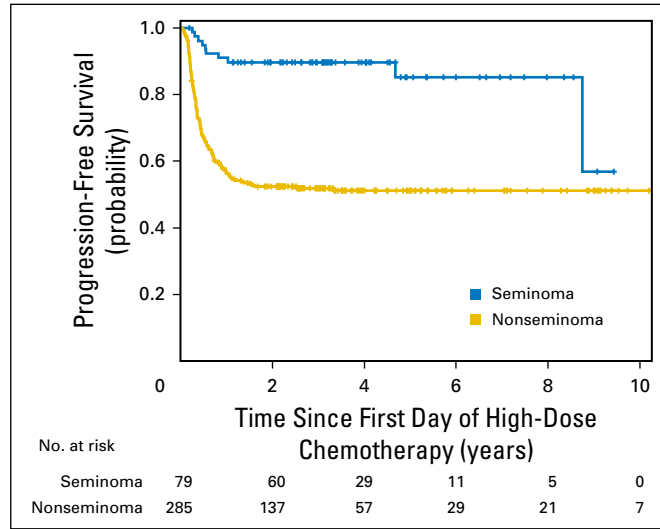
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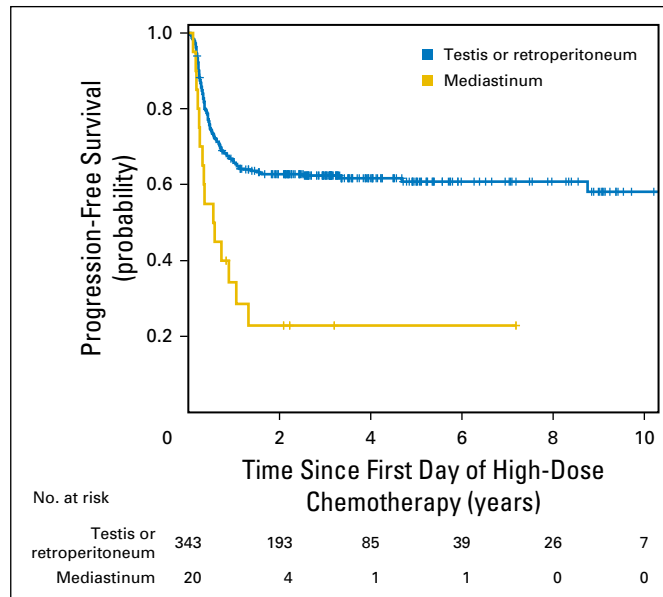
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Appendix



**Fig A1.** Kaplan-Meier estimates of progression-free survival for seminoma versus nonseminoma.



**Fig A2.** Kaplan-Meier estimates of progression-free survival for primary tumor site: testis/retroperitoneum versus mediastinum.

## High-Dose Chemotherapy for Relapsed Metastatic Germ Cell Tumors

**Table A1.** Progression-Free Survival and Overall Survival for Subgroups of Patients Receiving High-Dose Chemotherapy as Second-Line Therapy per the International Prognostic Factors Study Group Criteria

IPFSG Risk (no. of patients)	2-Year PFS, % (95% CI)	2-Year OS, % (95% CI)
Very low (34)	94 (79 to 99)	94 (79 to 99)
Low (55)	80 (67 to 88)	85 (72 to 92)
Intermediate (77)	75 (64 to 83)	77 (66 to 85)
High (77)	52 (40 to 62)	61 (49 to 71)
Very high (60)	27 (16 to 39)	28 (17 to 40)

Abbreviations: IPFSG, International Prognostic Factors Study Group; OS, overall survival; PFS, progression-free survival.