

## ORIGINAL ARTICLE

# High-Dose Chemotherapy and Stem-Cell Rescue for Metastatic Germ-Cell Tumors

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## ABSTRACT

**BACKGROUND**

Metastatic testicular tumors that have not been successfully treated by means of initial chemotherapy are potentially curable with salvage chemotherapy.

**METHODS**

We conducted a retrospective review of 184 consecutive patients with metastatic testicular cancer that had progressed after they received cisplatin-containing combination chemotherapy. We gave 173 patients two consecutive courses of high-dose chemotherapy consisting of 700 mg of carboplatin per square meter of body-surface area and 750 mg of etoposide per square meter, each for 3 consecutive days, and each followed by an infusion of autologous peripheral-blood hematopoietic stem cells; the other 11 patients received a single course of this treatment. In 110 patients, cytoreduction with one or two courses of vinblastine plus ifosfamide plus cisplatin preceded the high-dose chemotherapy.

**RESULTS**

Of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up of 48 months (range, 14 to 118). Of the 135 patients who received the treatment as second-line therapy, 94 were disease-free during follow-up; 22 of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer that was refractory to standard-dose platinum, 18 were disease-free. A total of 98 of 144 patients who had platinum-sensitive disease were disease-free, and 26 of 35 patients with seminoma and 90 of 149 patients with nonseminomatous germ-cell tumors were disease-free. Among the 184 patients, there were three drug-related deaths during therapy. Acute leukemia developed in three additional patients after therapy.

**CONCLUSIONS**

Testicular tumors are potentially curable by means of high-dose chemotherapy plus hematopoietic stem-cell rescue, even when this regimen is used as third-line or later therapy or in patients with platinum-refractory disease.

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**G**ERM-CELL TUMORS ARE CURABLE EVEN in the presence of metastatic disease.<sup>1-3</sup> An international collaboration has established that metastatic germ-cell tumors can be classified into good-, intermediate-, and poor-risk disease, with corresponding cure rates of 90 to 95%, 75%, and 40 to 50%, respectively.<sup>4</sup> Hereinafter, we refer to these categories as low-, intermediate-, and high-risk disease, respectively. Patients with tumors that relapse or with tumors that progress despite initial chemotherapy are candidates for salvage therapy. The few patients with anatomically confined disease are amenable to surgical extirpation.<sup>5</sup> For most patients, however, the options include salvage chemotherapy with cisplatin plus ifosfamide plus vinblastine<sup>6</sup> or paclitaxel<sup>7</sup> for four courses, or high-dose chemotherapy with autologous hematopoietic stem-cell transplantation to rescue the bone marrow from the myeloablative effects of chemotherapy.<sup>8-10</sup> We began treating patients with carboplatin-based high-dose chemotherapy in 1986.<sup>11</sup> Earlier studies of such treatment based on high-dose cyclophosphamide were unsuccessful.<sup>12</sup>

Initially, we used autologous bone marrow cells to rescue the hematopoietic system after high-dose chemotherapy. In February 1996, we shifted to peripheral-blood stem cells, which rapidly engrafted, thereby permitting a second course of high-dose chemotherapy with fewer delays. In this article, we present a retrospective study of 184 consecutive patients treated at Indiana University with high-dose carboplatin plus etoposide (high-dose chemotherapy) and rescue of the hematopoietic system by infusion of peripheral-blood stem cells. Our goal was to examine the efficacy of this treatment for cisplatin-resistant, progressively growing testicular cancer.

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## METHODS

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### PATIENTS

We conducted a review of 184 consecutive patients who received high-dose chemotherapy and peripheral-blood stem-cell rescue between February 1996 and December 2004. Patient interviews and medical charts were used to obtain the data analyzed in this study. The institutional review board at Indiana University approved the study. The requirement for informed consent was waived.

Before high-dose chemotherapy was initiated, peripheral-blood stem cells were collected and purified according to a technique that has been

described previously.<sup>8</sup> We harvested the cells after stimulation of the patient's marrow with granulocyte colony-stimulating factor and enriched these cells for CD34+ hematopoietic cells. Patients who received high-dose chemotherapy as initial salvage treatment and whose tumor had not progressed within 4 weeks after the last round of this treatment received standard doses of vinblastine plus ifosfamide plus cisplatin<sup>6</sup> to reduce the bulk of the tumor and prevent progression before we administered high-dose chemotherapy. Patients who had already received ifosfamide-based salvage chemotherapy were offered high-dose chemotherapy without any further treatment. Patients with primary mediastinal nonseminomatous germ-cell tumors or tumors with late relapse (>2 years after previous therapy) were not offered high-dose chemotherapy during the specified period.

All patients received therapy in the outpatient clinic except for patients with complications requiring inpatient care. Antibiotics, including prophylactic acyclovir, fluconazole, ciprofloxacin, and either penicillin or vancomycin, were used routinely.

High-dose chemotherapy consisted of two cycles of 700 mg of carboplatin per square meter of body-surface area plus 750 mg of etoposide per square meter, both given intravenously 5, 4, and 3 days before the infusion of peripheral-blood stem cells. A minimum of 1 million CD34+ cells per kilogram of body weight was required for each cycle of high-dose chemotherapy. There were no planned reductions or escalations in the doses of chemotherapy. The second cycle of high-dose chemotherapy was given after recovery of granulocyte and platelet counts, unless there was a grade 4 nonhematologic toxic effect or no response to the first course. Most patients who had a complete or partial remission after the two cycles of high-dose chemotherapy and who had normal serum levels of human chorionic gonadotropin (hCG) and alpha-fetoprotein received a maintenance oral dose of 50 mg of etoposide per square meter daily for 21 consecutive days every 4 weeks for three cycles.<sup>13</sup>

Complete remission was defined as no clinically or radiographically detectable disease and normal serum levels of hCG and alpha-fetoprotein. Patients with a resectable residual mass after high-dose chemotherapy were offered surgery. Disease-free survival, defined as no evidence of disease at all follow-up visits after high-dose chemotherapy,

was the primary end point for this analysis. Survival time was measured from the first day of high-dose chemotherapy. Disease-free survival was measured from the initiation of high-dose chemotherapy to tumor progression or death.

#### STATISTICAL ANALYSIS

Analyses were carried out with the use of SAS (version 9.1) and S-PLUS (version 7.0) software.

The Kaplan–Meier method<sup>14</sup> was used to calculate overall and disease-free survival according to the risk group (low, intermediate, or high), which was defined on the basis of the prognostic scoring algorithm described below. The association of disease-free survival with each prognostic variable was assessed with the use of Fisher's exact test.

A multivariate proportional-hazards regression analysis was used to construct a prognostic scoring algorithm for disease-free survival. Because the individual prognostic variables correlated with each other significantly, and because our goal was to devise a prognostic scoring algorithm that was easy to implement clinically, we used the branch-and-bound algorithm of Furnival and Wilson<sup>15</sup> to find the best model among all possible models that contained three prognostic variables. This algorithm fits all possible three-variable models and identifies the model with the highest likelihood score (chi-square statistic). The best four-variable model was also obtained to determine whether the value added by including a fourth variable was meaningful. This model did not perform better than the best three-variable model. We used a bootstrap method in which 1000 samples of 184 patients were randomly selected from the original patient cohort.<sup>16</sup> For each sample, the branch-and-bound algorithm was applied.

Next, the model with the highest frequency of selection among the 1000 samples was identified. The best three- and four-variable models identified by the bootstrap algorithm were both identical to the best three- and four-variable models for the original sample, providing support for the validity of the final model. With the use of the method of Rassi et al.,<sup>17</sup> the  $\beta$  regression coefficients from the final model applied to the original sample were used to develop prognostic scores (with low scores reflecting a greater probability of disease-free survival) for each variable in the model. These prognostic scores were then summed and split three ways (by comparing the overall patterns of survival according to prognostic score with a Kaplan–Meier plot and forming three groups with similar patterns) to create an overall stratification of patients into low-, intermediate-, and high-risk groups.

## RESULTS

We analyzed the disease-free and overall survival of patients who received high-dose chemotherapy for at least 1 day. The one patient who was lost to

**Table 1. Characteristics of 184 Patients at the Beginning of High-Dose Chemotherapy.\***

Characteristic	No. of Patients (%)
No. of previous chemotherapy regimens	
1	135 (73.4)
2	45 (24.4)
≥3	4 (2.2)
Histologic type	
Seminoma	35 (19.0)
Nonseminomatous germ-cell tumor	149 (81.0)
Response to initial chemotherapy	
Complete remission (with or without resection of tumor)	75 (40.8)
Partial remission (normal hCG and alpha-fetoprotein levels)	9 (4.9)
Other (less than complete remission or partial remission with normal hCG and alpha-fetoprotein levels)	100 (54.3)
Initial IGCCCG stage	
Low risk	71 (38.6)
Intermediate risk	38 (20.7)
High risk	75 (40.8)
Platinum sensitivity	
Sensitive	144 (78.3)
Refractory	40 (21.7)
Serum hCG level	
≥1000 IU/liter	22 (12.0)
<1000 IU/liter	162 (88.0)
Serum alpha-fetoprotein level	
≥1000 μg/liter	8 (4.3)
<1000 μg/liter	176 (95.7)
Beyer score†	
0	136 (73.9)
1	24 (13.0)
2	9 (4.9)
3–4	15 (8.2)

\* IGCCCG denotes International Germ Cell Cancer Collaborative Group, and hCG human chorionic gonadotropin. Percentages may not sum to 100 because of rounding.

† A score of 1 point was given for platinum-refractory or absolute platinum-refractory disease, and 2 points were given for each primary mediastinal tumor and for a serum hCG level ≥1000 IU/liter.

follow-up was counted in the group of patients in whom treatment failed.

Table 1 lists characteristics of the patients at the start of high-dose chemotherapy. The median age was 31 years (range, 15 to 58). Patients with a low Eastern Cooperative Oncology Group (ECOG) performance status were not excluded, but most patients had an ECOG performance status of 0 or 1. Thirty-five patients had seminoma only, with no elements of nonseminomatous germ-cell tumor, and the remaining 149 patients had nonseminomatous germ-cell tumors. The Beyer score was used to stratify patients in low-, intermediate-, or high-risk categories.<sup>18</sup> With this scoring system, 1 point was assigned for platinum-refractory or absolute platinum-refractory disease and 2 points were assigned for each primary mediastinal tumor and for a serum hCG level greater than or equal to 1000 IU per liter. Platinum-refractory disease was defined as tumor progression within 4 weeks after the most recent cisplatin-based chemotherapy. Absolute platinum-refractory disease was defined as no response to the initial cisplatin-based chemotherapy.

Eleven patients did not receive the scheduled second course of high-dose chemotherapy; five had progressive disease, and four of these five patients died within 10 months after the initiation of high-dose chemotherapy. The fifth patient has no evidence of disease more than 33 months after two salvage surgeries. Five of the 11 patients did not receive a second course of high-dose chemotherapy because of grade 4 toxic effects (nephrotoxicity in 2, hepatotoxicity in 2, and pulmonary toxicity in 1). Of these five patients, two remained continuously disease-free 65 and 43 months after recovering from the toxic effects of the single course of high-dose chemotherapy. One patient who received a single course had apparently false elevations of serial serum alpha-fetoprotein levels in the absence of liver disease; he has been disease-free for more than 100 months.

During a median follow-up of 48 months (range, 14 to 118), 116 of 184 patients (63%) were continuously disease-free. Of these 116 patients, 104 (90%) were disease-free for more than 2 years. Six additional patients had complete remission of disease, four after receiving paclitaxel plus gemcitabine<sup>19</sup> and two after undergoing subsequent resection of a germ-cell tumor. Figure 1 shows the Kaplan–Meier estimate of survival.

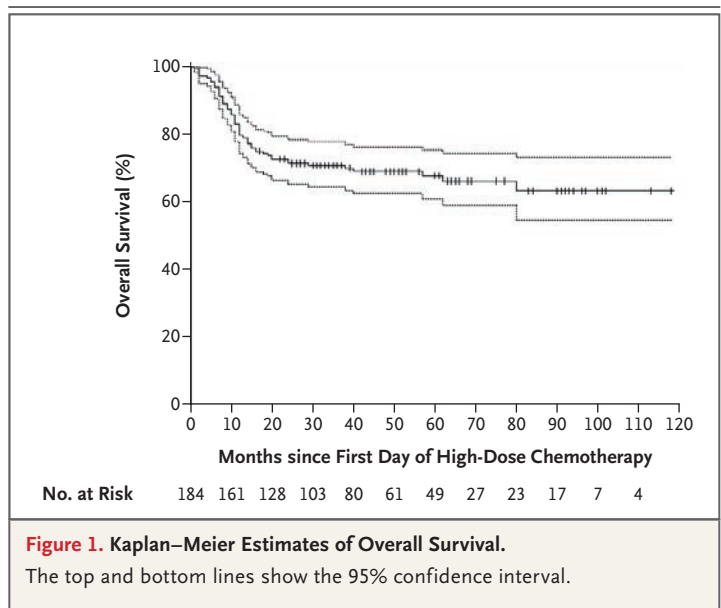


Table 2 lists prognostic variables for the 184 patients in our study. Variables that were significantly associated with progression-free survival were the use of high-dose chemotherapy as second-line as compared with third-line chemotherapy, response of the tumor to cisplatin (platinum sensitivity), response to initial chemotherapy, favorable prognosis,<sup>20</sup> and favorable International Germ Cell Cancer Collaborative Group (IGCCCG) score.<sup>4</sup> Of the 61 patients who had favorable prognostic features, 49 had disease that was in continuous remission for a median of 46 months (range, 25 to 112). A total of 18 of 40 patients with progressive metastatic disease and tumors that were refractory to platinum remained disease-free for a median of 49 months (range, 22 to 110).

To develop the prognostic scoring algorithm with the use of multivariate proportional-hazards regression, we included all individual variables (timing of high-dose chemotherapy, hCG level, platinum sensitivity, response to initial chemotherapy, histologic types, and IGCCCG score) in the branch-and-bound algorithm except for an alpha-fetoprotein level greater than or equal to 1000  $\mu$ g per liter, since only eight patients had an alpha-fetoprotein level of that elevation. The best three-variable model included timing of high-dose chemotherapy, platinum sensitivity or refractoriness, and IGCCCG stage (Table 3). The prognostic scoring algorithm, based on the three-variable model, assigned a score of 3 points

<b>Table 2. Prognostic Variables in 184 Patients.*</b>				
<b>Variable</b>	<b>Disease-free Survival (N=116)</b>	<b>Death or Survival with Disease (N=68)</b>	<b>P Value†</b>	<b>Hazard Ratio (95% CI)‡</b>
	<i>no./total no. (%)</i>			
<b>High-dose chemotherapy</b>				
Second-line	94/135 (69.6)	41/135 (30.4)		1.00
Third-line or subsequent	22/49 (44.9)	27/49 (55.1)	0.003	2.22 (1.37–3.62)
<b>Markers</b>				
hCG <1000 IU/liter	102/162 (63.0)	60/162 (37.0)		1.00
hCG ≥1000 IU/liter	14/22 (63.6)	8/22 (36.4)	1.00	1.05 (0.50–2.20)
Alpha-fetoprotein <1000 µg/liter	113/176 (64.2)	63/176 (35.8)		1.00
Alpha-fetoprotein ≥1000 µg/liter	3/8 (37.5)	5/8 (62.5)	0.15	2.40 (0.96–5.99)
<b>Platinum sensitivity</b>				
Sensitive	98/144 (68.1)	46/144 (31.9)		1.00
Refractory	18/40 (45.0)	22/40 (55.0)	0.01	2.16 (1.30–3.60)
<b>Response to initial chemotherapy</b>				
Complete remission or partial remission with normal serum markers	61/84 (72.6)	23/84 (27.4)		1.00
Less than complete remission or less than partial remission with normal serum markers	55/100 (55.0)	45/100 (45.0)	0.01	1.85 (1.12–3.05)
<b>Histologic type</b>				
Seminoma	26/35 (74.3)	9/35 (25.7)		1.00
Nonseminomatous germ-cell tumor	90/149 (60.4)	59/149 (39.6)	0.17	1.56 (0.77–3.14)
<b>IGCCCG stage (at start of initial chemotherapy)</b>				
Low risk	54/71 (76.1)	17/71 (23.9)		1.00
Intermediate risk	24/38 (63.2)	14/38 (36.8)		1.62 (0.80–3.29)
High risk	38/75 (50.7)	37/75 (49.3)	0.006	2.39 (1.35–4.25)
<b>Prognosis</b>				
Favorable§	49/61 (80.3)	12/61 (19.7)		1.00
Unfavorable	67/123 (54.5)	56/123 (45.5)	<0.001	2.76 (1.48–5.16)
<b>Beyer score¶</b>				
0	90/136 (66.2)	46/136 (33.8)		1.00
1–2	19/33 (57.6)	14/33 (42.4)		1.37 (0.75–2.49)
3–4	7/15 (46.7)	8/15 (53.3)	0.25	2.02 (0.95–4.29)

\* IGCCCG denotes International Germ Cell Cancer Collaborative Group, and hCG human chorionic gonadotropin. Percentages may not sum to 100 because of rounding.

† P values were calculated with the use of Fisher's exact test and are for the comparison of the patients with disease-free survival with patients who died or survived with disease.

‡ The hazard ratio for disease progression was calculated with the use of the univariate proportional-hazards regression model.

§ Patients with a favorable prognosis had complete remission or partial remission with normal serum markers and received high-dose chemotherapy as initial salvage therapy.

¶ A score of 1 point was given for platinum-refractory or absolute platinum-refractory disease, and 2 points were given for each primary mediastinal tumor and for a serum hCG level ≥1000 IU/liter.

**Table 3. Results of Multivariate Cox Proportional-Hazards Analysis and Prognostic Score.\***

Prognostic Variable	Hazard Ratio (95% CI)	P Value	$\beta$ Regression Coefficient	Prognostic Score†
Third-line or subsequent chemotherapy	2.19 (1.35–3.56)	0.002	0.78	3
Platinum-refractory disease	1.74 (1.01–3.00)	0.05	0.55	2
IGCCCG high-risk stage	1.67 (1.00–2.78)	0.05	0.51	2

\* The hazard ratio is for disease progression. IGCCCG denotes International Germ Cell Cancer Collaborative Group.

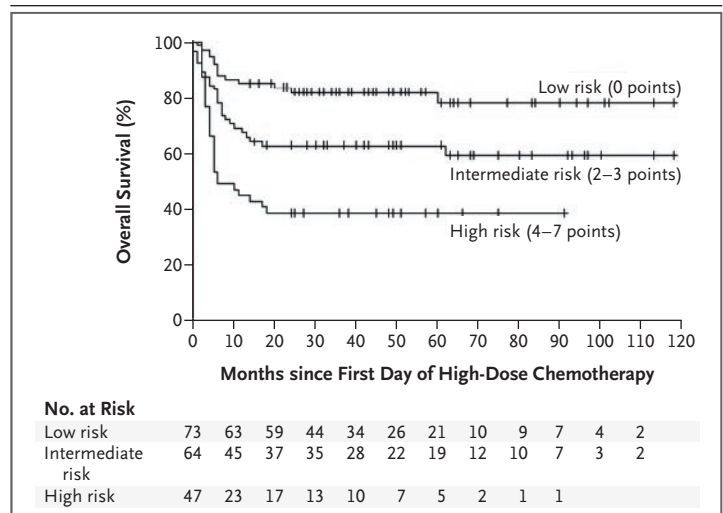
† The score was calculated by dividing the regression coefficient by 0.51, multiplying by 2.0, and rounding to the nearest whole number.

for third-line chemotherapy, 2 for platinum refractoriness, and 2 for advanced IGCCCG stage. High scores indicated a low probability of disease-free survival. Figure 2 illustrates overall survival according to this scoring algorithm, which stratifies patients according to the level of risk (low, 0 points; intermediate, 2 to 3 points; or high, 4 to 7 points). The results of log-rank tests comparing the disease-free survival curves among the three risk groups were all statistically significant ( $P < 0.05$ ).

The toxic effects of high-dose chemotherapy were primarily myelosuppression, mucositis, nausea, vomiting, dehydration, peripheral neuropathy, and otologic abnormalities.<sup>8</sup> There were three sudden drug-related deaths; two were due to hepatic failure, and one was due to pulmonary toxic effects. Table 4 lists the toxic effects that were grade 3 or higher. Acute leukemia developed in three patients 11, 21, and 60 months after high-dose chemotherapy. None of these patients had received maintenance therapy with oral etoposide. All three had been treated with high-dose chemotherapy as third-line or later chemotherapy. Two of these patients died during follow-up; the third remained alive with cancer that was in complete remission after antileukemia therapy plus allogeneic bone marrow transplantation. Two of these three patients have been described previously.<sup>21</sup> Glioblastoma multiforme developed in one patient 6 years after high-dose chemotherapy. He had received radiation therapy for brain metastases of the germ-cell tumor at the time of the initial diagnosis.

## DISCUSSION

Cisplatin-containing combination chemotherapy cures 70% of patients with newly diagnosed meta-

**Figure 2. Disease-free Survival.**

The prognostic scoring algorithm, based on the three-variable model, assigned a score of 3 points for third-line chemotherapy, 2 points for platinum refractoriness, and 2 points for advanced International Germ Cell Cancer Collaborative Group stage. High scores indicated a low probability of disease-free survival.

static germ-cell tumors. Prognostic factors, based on data from more than 5000 such patients, are well established.<sup>4</sup> The factors associated with long-term survival after salvage therapy, however, are less well established.

In 1996, Beyer et al.<sup>18</sup> reported a multivariate analysis of factors that can predict cure after high-dose chemotherapy. Adverse prognostic variables in the 283 patients in that study included refractoriness to platinum (progression within 4 weeks after treatment with cisplatin), absolute refractoriness to platinum (no response to initial platinum-based chemotherapy), mediastinal non-seminomatous germ-cell tumor, and a serum hCG level greater than or equal to 1000 IU per liter.

**Table 4. Toxic Effects of High-Dose Chemotherapy (Grade 3 or Higher) among 184 Patients.\***

Toxic Effect	No. of Patients	No. of Deaths
Hematologic (leukemia)	3	2
Renal (serum creatinine, 3–6× ULN)	4	0
Gastrointestinal	30	0
Hepatic	6	2
Neurologic	9	0
Pulmonary	3	1

\* Gastrointestinal toxic effects included colitis, diarrhea, mucositis, nausea, and vomiting. Hepatic toxic effects included a serum albumin level that was less than 2 g per deciliter; a value for alkaline phosphatase, aspartate aminotransferase, or alanine aminotransferase that was >5 to 20 times the upper limit of the normal range (ULN); and a bilirubin level that was >3 to 10 times the ULN. Two patients died from acute hepatic failure that developed after the first course of high-dose chemotherapy. Neurologic toxic effects included sensory alterations, paresthesias, and weakness interfering with daily activity. Pulmonary toxic effects included dyspnea interfering with daily activity and symptomatic hiccups interfering with sleep. The acute respiratory distress syndrome developed in one patient.

A prognostic score based on these variables was developed. Primary mediastinal tumors and an hCG level greater than or equal to 1000 IU per liter were each assigned 2 points, whereas all other variables were each assigned 1 point. For patients with a score of 3 or higher, the rate of disease-free survival at 2 years was only 5%, as compared with 51% for patients with a Beyer score of 0. This scoring system, however, was based on data from patients who were treated between 1984 and 1993; most of these patients had received only a single course of high-dose chemotherapy. A total of 91% of these patients received two or more induction regimens before receiving high-dose chemotherapy.

There are some similarities between the prognostic variables in our study (Table 2) and the Beyer scores, but our list of variables reflects some additions and deletions. Beyer and colleagues assigned 2 points for “absolute refractory disease,” defined as progression with initial cisplatin-based chemotherapy. Forty-three of the 283 patients (15%) in that study were assigned to this category. In our series, only 2 of 184 patients had absolute refractory disease. In the study reported by Beyer et al., serum hCG levels greater than or equal to 1000 IU per liter were assigned 2 points. In our series, there was no difference in disease-free survival on the basis of hCG levels ( $P=1.00$ ).

The improved results in our series, as compared with the 283 patients in the analysis by Beyer et al., reflect the benefit of high-dose chemotherapy given as second-line rather than third-line chemotherapy and the administration of two consecutive rounds of high-dose chemotherapy with hematopoietic stem-cell rescue. We did not use a third agent such as cyclophosphamide, ifosfamide, or thiotepa, as others have,<sup>22-27</sup> because adding a third agent requires dose reductions of the two most active drugs, carboplatin and etoposide. Only a randomized study could show whether the addition of a third agent is beneficial.

Some variables were associated with very high rates of continuous disease-free survival. Of 35 patients with a pure seminoma (defined as no other cell types and normal serum alpha-fetoprotein levels) that relapsed after first- or second-line chemotherapy, 26 remained disease-free for a median of 43 months (range, 19 to 118). Sixty-one patients had favorable prognostic features; these features included cancer that was in complete or partial remission and normal serum hCG and alpha-fetoprotein levels for more than 6 months after the first chemotherapy treatment and then high-dose chemotherapy as the initial salvage therapy.<sup>7</sup> Of these 61 patients, 49 had disease that was in continuous remission for a median of 46 months (range, 25 to 112). In a recently reported series, 29 of 46 similar patients had disease that was in a durable complete remission (median, 69 months) after treatment with paclitaxel plus ifosfamide plus cisplatin.<sup>20</sup> The minimum follow-up was 2 years.

Patients with primary mediastinal nonseminomatous germ-cell tumors were not eligible for high-dose carboplatin plus etoposide during this study. From 1988 to 1996, 13 patients with this tumor received high-dose chemotherapy with bone marrow transplantation. None of them survived disease-free for more than 2 years.<sup>28</sup> A larger international study had poor results with any type of salvage chemotherapy, with only 9 of 79 patients (11%) alive and disease-free for more than 2 years.<sup>29</sup>

In a recent study, 219 patients in the high-risk group were randomly assigned to receive initial treatment with four courses of bleomycin plus etoposide plus cisplatin or two courses of this initial treatment followed by two courses of high-dose chemotherapy with stem-cell rescue.<sup>30</sup> There was no benefit from the high-dose chemotherapy.

Pico et al. randomly assigned 280 patients to receive salvage chemotherapy with either four courses of vinblastine (or etoposide) plus ifosfamide plus cisplatin or three similar cycles followed by a single course of high-dose carboplatin plus etoposide plus cyclophosphamide.<sup>31</sup> The single cycle of high-dose chemotherapy had no effect on the outcome. To our knowledge, these two studies are the only randomized trials of high-dose chemotherapy in patients with germ-cell tumors, and it is disappointing that they did not show an advantage of such treatment.

There should be little or no debate on the use of high-dose chemotherapy for a patient with a

germ-cell tumor that is refractory to platinum-based chemotherapy or that is not cured by a cisplatin-ifosfamide regimen as salvage chemotherapy. In our study, 18 of 40 patients with progressive metastatic disease and tumors that were refractory to platinum remained disease-free for a median of 49 months (range, 22 to 110), and 22 of 49 patients who received high-dose chemotherapy as third-line or later therapy remained disease-free for a median of 46 months (range, 25 to 112).

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