TI-CE High-Dose Chemotherapy for Patients With Previously Treated Germ Cell Tumors: Results and Prognostic Factor Analysis

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A B S T R A C T

Purpose

We previously reported a dose-finding and phase II trial of the TI-CE regimen (paclitaxel [T] plus ifosfamide [I] followed by high-dose carboplatin [C] plus etoposide [E] with stem-cell support) in germ cell tumor (GCT) patients predicted to have a poor prognosis with conventional-dose salvage therapy. We now report the efficacy of TI-CE with prognostic factors for disease-free survival (DFS) and overall survival (OS) in our full data set of 107 patients.

Patients and Methods

Eligible patients had advanced GCTs with progressive disease following chemotherapy and unfavorable prognostic features (extragonadal primary site, incomplete response [IR] to first-line therapy, or relapse/IR to ifosfamide-cisplatin-based conventional-dose salvage). Univariate and multivariate analyses (MVAs) of prognostic factors were performed. The predictive ability of the Einhorn and Beyer prognostic models was assessed.

Results

Most patients were platinum refractory and had an IR to first-line chemotherapy. There were 54 (50%) complete and eight (8%) partial responses with negative markers; 5-year DFS was 47% and OS was 52% (median follow-up, 61 months). No relapses occurred after 2 years. Five (24%) of 21 primary mediastinal nonseminomatous GCTs are continuously disease free. On MVA, primary mediastinal site ($P < .001$), two or more lines of prior therapy ($P < .001$), baseline human chorionic gonadotropin $\geq 1,000$ U/L ($P = .01$), and lung metastases ($P = .02$) significantly predicted adverse DFS. Poor-risk patients did worse than good- or intermediate-risk patients according to both Beyer ($P < .002$) and Einhorn ($P < .05$) models.

Conclusion

TI-CE is effective salvage therapy for GCT patients with poor prognostic features. Mediastinal primary site and two or more lines of prior therapy were most predictive of adverse DFS. Beyer and Einhorn models can assist in predicting outcome.

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INTRODUCTION

Germ cell tumors (GCTs) are considered a model for curable cancers¹ with expectations of cure in more than 95% of patients.² Even with advanced disease, 70% are cured with standard chemotherapy consisting of etoposide and cisplatin with or without bleomycin.³ Treatment options for the remaining 30% include conventional-dose chemotherapy programs combining cisplatin and ifosfamide with either paclitaxel⁴ or vinblastine⁵ or high-dose chemotherapy (HDCT) with autologous stem-cell support.^{6,7}

Prognostic factors have been identified for both salvage conventional-dose chemotherapy and HDCT. Patients with gonadal primary tu-

mors and a partial response (PR) or complete response (CR) lasting > 6 months to first-line chemotherapy have a $> 60\%$ chance of achieving cure with conventional-dose chemotherapy.^{4,8} Other patients, such as those with primary refractory disease or remissions of short duration (< 6 months) have durable disease-free survival (DFS) and overall survival (OS) rates of less than 10% with similar regimens.⁸ In contrast, HDCT can achieve durable CRs in 30% to 60% of such patients.^{6,7,9,10}

Two models that predict outcome to HDCT were reported by Beyer¹¹ and Einhorn.⁶ These differ both in the patient populations studied and in the variables they incorporate. The predictive ability of the Beyer model was confirmed in several small

studies^{12,13} but not in a larger series.⁶ The Einhorn model was only recently published, and attempts at external validation produced mixed results.¹⁴

In 1993, with recognition of the activity of paclitaxel in GCTs, we began using the TI-CE regimen, including two cycles of paclitaxel (T) + ifosfamide (I) for stem-cell mobilization followed by three cycles of high-dose carboplatin (C) and etoposide (E), each with autologous stem cell support targeted to patients predicted to have a poor outcome to conventional-dose chemotherapy. The dosing schedule and safety have been previously described.⁷ Herein, we report the final efficacy data for the 107 patients treated at our institution between 1993 and 2006. We also identify relevant prognostic factors and evaluate the ability of the Beyer and Einhorn models to predict DFS and OS in this population.

PATIENTS AND METHODS

Patients

Eligible patients had GCT histology confirmed by pathologic review at Memorial Sloan-Kettering Cancer Center (MSKCC), progressive GCT, assessable disease, progressive disease (PD) after one or more cisplatin-based chemotherapy regimens, and one or more unfavorable prognostic features for achieving a CR with conventional-dose chemotherapy. Unfavorable prognostic features included extragonadal primary site, PD following an incomplete response (IR) to first-line therapy, and PD after a conventional-dose salvage (cisplatin + ifosfamide-based) regimen.

The initial intent of the phase I trial was to escalate the target carboplatin area under the concentration-time curve (AUC) in patients who had received six or fewer cycles of prior cisplatin-based combination therapy. However, after recognizing TI-CE to be relatively well tolerated compared with prior HDCT regimens, we sought additional pharmacologic data and expanded eligibility in the phase II trial to include patients treated with more than six cycles of prior cisplatin, administering a fixed-dose level of carboplatin to these patients. Additional eligibility criteria have been published.⁷

Study Design

This prospective, single-institution, phase I/II trial was approved by the MSKCC institutional review board. Pretreatment evaluation has been described.¹⁵ Two cycles of TI + mesna were given 14 days apart (cycles 1 and 2) followed by three cycles of CE with autologous stem-cell support every 21 to 28 days (cycles 3 to 5; Appendix Table A1, online only). Carboplatin dosing was by target AUC and varied during phase I¹⁵ by cohort. In phase II, an AUC of 24 mg/mL/min divided over 3 days (days 1 through 3) was administered to patients who had received six or fewer prior cycles of cisplatin and an AUC of 21 mg/mL/min to more heavily pretreated patients.¹⁵ Etoposide dosing was fixed at 400 mg/m² daily on days 1 through 3 for all patients. Granulocyte colony-stimulating factor was administered to enhance leukapheresis and rapidity of engraftment.¹⁵

Evaluation of Response and Toxicity

Toxicity and response assessments were previously described.⁷ Responses were categorized as IR or CR, with CR divided into those achieved with chemotherapy alone or with chemotherapy plus surgery. IR included patients achieving PR with negative tumor markers (PR-negative) as well as those with stable disease or PD as previously defined.¹⁵ CR and PR-negative were considered favorable responses.

Supportive Care

Management of complications included platelet and RBC transfusions. Neutropenic fevers were treated with broad-spectrum antibiotics.

Statistics

The primary end point in phase I was to determine the maximum-tolerated dose of carboplatin in the TI-CE regimen in patients who had received six or fewer cycles of prior cisplatin. The phase II portion was designed

to estimate the proportion of patients (with 95% CIs) achieving a CR using the maximum-tolerated dose of carboplatin determined in phase I. Secondary end points included DFS, OS, and description of adverse events. Thirty-seven patients completed the phase I portion. Fifty patients were planned for accrual in phase II to allow estimation of a response proportion to $\pm 20\%$ (95% CI). Since results indicated a higher response rate and lower toxicity than historical HDCT studies, TI-CE became standard therapy at our institution, and the trial was amended to allow continued accrual for additional efficacy and safety information. Twenty additional patients were accrued in this manner, for a total of 71 patients in phase II. Data collected from these additional patients together with data from patients on the original trial serve as the source for this report.

Univariate analysis of prognostic factors for DFS and OS was performed using the Kaplan-Meier method, and hazard ratios were estimated using

Table 1. Patient Characteristics

Characteristic	No.	%
Sex		
Male	104	97
Female	3	3
Age, years		
Median	31	
Range	16-54	
Histology		
Nonseminoma	94	88
Seminoma	13	12
Primary site		
Testis	72	67
Mediastinum	21	20
Retroperitoneum	6	6
Ovary	2	2
Pineal gland	2	2
Unknown	4	4
Sites of metastatic disease		
Lung	65	61
Retroperitoneum	66	62
Mediastinum	49	46
Liver	24	22
Bone	8	7
Brain	3	3
Other	13	12
No. of metastatic sites		
1	2	2
2	20	19
3+	85	79
Elevated markers		
HCG ≥ 2.2 U/L	58	54
Median elevated	15.8	
Range	2.3-93,501	
AFP > 15 ng/mL	52	49
Median elevated	280	
Range	16.7-69,957	
LDH > 200 U/L	44	41
Median elevated	389	
Range	203-2,770	
Number of prior lines of therapy		
1	81	76
2	22	21
3+	4	4
Late relapse	7	7

Abbreviations: HCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; LDH, lactate dehydrogenase.

univariate Cox regression analysis. To examine prognostic factors in a multivariate analysis (MVA), Cox regression models were fit using stepwise regression (entry P value = .10; elimination P = .05). Further pruning of the multivariate model was done to keep only those variables significant at $P < .05$. DFS was defined as the time from treatment start until the first documented progression of disease, death, or date of last follow-up. OS was defined as the time from treatment start until death or date of last follow-up. In addition, two established prognostic models for GCT patients receiving HDCT (those reported by Einhorn et al⁶ and Beyer et al¹¹) were assessed for their ability to predict DFS in patients treated with TI-CE.

RESULTS

Patient Characteristics

Of 108 patients enrolled, one (not included in results) withdrew consent within 3 days of enrollment and never received treatment. Patient demographics for the remaining 107 patients are shown in Table 1. Seventy-nine (74%) were platinum refractory (progression within 4 weeks of the last cisplatin-based therapy), including two who were absolute platinum refractory (did not even achieve transient stable disease to the last platinum-based therapy). In addition, 26 (24%) had received two or more prior lines of chemotherapy, 21 (20%) had mediastinal primary tumors (all nonseminomas), and seven had late relapses (> 2 years).

Treatment Administered

Eighty-two (77%) patients received all five treatment cycles; only seven did not receive any high-dose cycles (Table 2). The most common reason for not completing therapy was PD. Target carboplatin AUCs ranged from 12 to 32 mg/mL/min during phase I. Most ($n = 73$; 68%) received an AUC of 21 or 24 mg/mL/min, including all patients

treated on the phase II portion of the study. An AUC of 24 mg/mL/min was administered to patients with six or fewer cycles of prior cisplatin therapy, whereas more heavily pretreated patients received an AUC of 21 mg/mL/min (Table 2).

Treatment Outcome

There were two (2%) treatment-related deaths (grade 5 toxicities), including one fatal cerebral hemorrhage and one fatal pulmonary hemorrhage. All patients experienced grade 4 neutropenia, but serious infectious complications were uncommon, as reported previously.¹⁶ Grade 4 thrombocytopenia (86%) and anemia (37%) were also common. The safety profile has been previously reported.¹⁵

Fifty-four (50%) patients achieved a CR: 45 (42%) to chemotherapy alone and nine (8%) to chemotherapy plus surgery. Eight (7%) additional patients achieved PR-negative status, for a total favorable response rate of 58% (Table 2). Fifty deaths occurred among the 107 patients including the two related to treatment. After a median of 61 months, 57 remained alive at last follow-up. The 5-year OS rate was

Variable	No.	%
Cycles received		
1	2	2
2	5	5
3	7	7
4	11	10
5	82	77
Target total AUC of carboplatin*		
12	3	3
15	3	3
18	9	8
21*	24	22
24*	56	52
28	9	8
32	3	3
Best response		
CR (chemotherapy alone)	45	42
CR (chemotherapy + surgery)	9	8
PR-negative	8	8
Incomplete response	45	42

Abbreviations: TI-CE, paclitaxel + ifosfamide and carboplatin + etoposide; AUC, area under the time-concentration curve; CR, complete remission; PR-negative, partial remission with negative tumor markers.
 *Three patients with target AUC of 21, and four patients with target AUC of 24 did not receive high-dose therapy.

Fig 1. Kaplan-Meier curves of (A) disease-free survival and (B) overall survival for patients treated with paclitaxel + ifosfamide and carboplatin + etoposide high-dose chemotherapy.

Table 3. Univariate Analysis of Prognostic Factors for DFS

Variable	Total No.	No. of Failures	Median DFS (months)	95% CI	P
Primary site					
Gonadal/retroperitoneal	80	36	NR		.003
Mediastinal	21	16	8.6	7.6 to 12.4	
Other/unknown	6	4	9.2	6.0 to NR	
Platinum response					
Platinum sensitive	28	12	NR		.52
Platinum refractory	77	42	21.6	12.4 to NR	
Absolute refractory	2	2	20.3	17.0 to 23.5	
Platinum response*					
Platinum sensitive	28	12	NR		.30
Any platinum refractory	79	44	21.6	12.4 to NR	
Marker values					
HCG, U/L					
< 1,000	87	42	NR		.02
≥ 1,000	20	14	10.1	5.5 to NR	
AFP, ng/mL					
< 1,000	93	45	NR		.10
≥ 1,000	14	11	14.1	8.6 to 23.2	
LDH, U/L					
< 1,000	98	51	23.2	15.2 to NR	.39
≥ 1,000	9	5	8.1	5.9 to NR	
Prior lines of therapy					
1	81	36	NR		.004
2+	26	20	11.7	8.6 to 21.7	
IGCCCG risk at initial chemotherapy					
Good	27	8	NR		.03
Intermediate	22	14	10.8	7.4 to NR	
Poor	52	30	16.7	9.9 to NR	
Not evaluable	6	4	14.5	6.4 to NR	
Histology					
Seminoma	13	6	NR		.59
Nonseminoma	94	50	22.3	12.5 to NR	
No. of metastatic sites					
1 or 2	22	7	NR		.03
3+	85	49	17.0	11.7 to NR	
Location of metastases					
NPVM					
Absent	36	22	17.0	8.5 to NR	.20
Present	71	34	NR		
Lung metastases					
Absent	42	15	NR		.004
Present	65	41	13.1	8.6 to NR	
Liver metastases					
Absent	83	43	22.3	12.7 to NR	.65
Present	24	13	21.7	8.1 to NR	
BBL metastases					
Absent	75	37	23.5	12.6 to NR	.33
Present	32	19	17.3	8.1 to NR	
Node-only metastases					
Yes	24	8	NR		.02
No†	83	48	16.3	9.9 to NR	
Mediastinal metastases					
Absent	58	26	NR		.052
Present	49	30	12.7	8.5 to NR	
Retroperitoneal metastases					
Present	65	28	NR		.01
Absent	42	28	11.5	8.5 to 21.6	

(continued in next column)

Table 3. Univariate Analysis of Prognostic Factors for DFS (continued)

Variable	Total No.	No. of Failures	Median DFS (months)	95% CI	P
Late relapse					
No	100	51	22.3	12.7 to NR	.55
Yes	7	5	22.4	10.8 to 23.5	
Responder to initial chemotherapy					
Yes	36	20	22.3	12.7 to NR	.92
No	71	36	23.4	12.4 to NR	
Target AUC					
≤ 21	39	24	16.4	9.2 to NR	.21
≥ 24	68	32	NR		
Hazard Ratio					
Continuous variables					
Age			0.99	0.96 to 1.02	.59
(Log) baseline HCG			1.18	1.05 to 1.33	.006
(Log) baseline AFP			1.06	0.97 to 1.16	.23
(Log) baseline LDH			1.47	1.07 to 2.02	.02

Abbreviations: DFS, disease-free survival; NR, not reached; HCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; LDH, lactate dehydrogenase; IGCCCG, International Germ Cell Cancer Collaborative Group; NPVM, nonpulmonary visceral metastases; BBL, bone, brain, and liver; AUC, area under the concentration-time curve.

*In this assessment of prior platinum response, platinum refractory and absolute refractory are combined into one category entitled "any platinum refractory."

†Indicates the presence of non-nodal sites of metastases.

52% with median OS not reached (Fig 1B). Fifty-six patients experienced disease progression with a median DFS of 22 months. With a median follow-up of 61 months, 51 remained disease-free and the 5-year DFS was 48%. All progression events after TI-CE occurred within 2 years from the start of treatment (Fig 1A).

Prognostic Factors Analysis

Characteristics previously reported to have prognostic importance for outcome to HDCT were subjected to univariate analysis for both DFS (Table 3) and OS (Appendix Table A2, online only). Characteristics at initial diagnosis that portended poor DFS included mediastinal primary site ($P = .003$) and International Germ Cell Cancer Collaborative Group (IGCCCG) risk status before first-line chemotherapy ($P = .03$). Features at trial enrollment that significantly worsened DFS included human chorionic gonadotropin (HCG) $\geq 1,000$ U/mL ($P = .02$), two or more lines of prior systemic therapy ($P = .004$), three or more metastatic sites ($P = .03$), and lung metastases ($P = .004$). Patients with lymph-node-only metastases ($P = .02$) and any retroperitoneal metastasis ($P = .01$) had improved DFS. Cisplatin sensitivity ($P = .52$), histology (seminoma *v* nonseminoma), and target carboplatin AUC did not have a significant impact on DFS. Similar results were found for OS (Appendix Table A2).

Of 21 patients with primary mediastinal nonseminomatous GCT (PM-NSGCT), five (24%) achieved long-term DFS and six (29%) achieved OS. Only seven patients had late relapse, limiting its evaluation as a negative prognostic factor. However, two remain continuously disease-free suggesting a lack of complete resistance to HDCT. One of three female patients also achieved long-term DFS and OS, whereas both patients with pineal gland primary tumors are alive, with one continuously disease-free.

Table 4. Multivariate Analysis of Prognostic Factors for DFS and OS

DFS Variable	Hazard Ratio	95% CI	P
Primary site			
Gonadal/retroperitoneal	Reference		.001
Mediastinal	3.2	1.7 to 6.0	
Other/unknown	1.5	0.5 to 4.3	
HCG, U/L			
< 1,000	Reference		.003
≥ 1,000	2.4	1.2 to 4.6	
Prior lines of chemotherapy			
1	Reference		.001
≥ 2	2.7	1.5 to 4.8	
Lung metastases			
Absent	Reference		.02
Present	2.1	1.1 to 3.8	
OS Variable	Hazard Ratio	95% CI	P
Primary site			
Gonadal/retroperitoneal	Reference		.01
Mediastinal	2.8	1.3 to 5.9	
Other/unknown site	2.7	0.7 to 10.0	
No. of metastatic sites			
1-2	Reference		.02
3+	3.2	1.2 to 8.8	
Prior lines of chemotherapy			
1	Reference		.001
≥ 2	3.0	1.6 to 5.6	
IGCCCG risk at initial chemotherapy			
Good	Reference		.006
Intermediate	6.0	2.2 to 16	
Poor	2.8	1.0 to 7.8	
Unknown	3.3	0.80 to 14	

Abbreviations: DFS, disease-free survival; OS, overall survival; HCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group.

Six patients were excluded from the MVA of DFS and OS (Table 4) because their IGCCCG risk classification could not be determined: one had missing baseline information and five were either female ($n = 3$) or had CNS primary tumors ($n = 2$), groups excluded from the model. On MVA for DFS, four variables retained statistical significance: mediastinal primary site ($P = .001$), two or more lines of prior therapy ($P = .001$), HCG $\geq 1,000$ U/mL ($P = .003$), and the presence of lung metastases ($P = .02$). For OS, four factors were again significant on MVA (Table 4): two from the DFS analysis (mediastinal primary site [$P = .01$] and two or more lines of prior therapy [$P = .001$]) and two additional variables (IGCCCG risk classification at diagnosis [$P = .006$] and three or more metastatic sites [$P = .02$]).

Evaluation of Einhorn and Beyer Prognostic Models

Two established prognostic models for HDCT were tested for their ability to predict DFS. The Beyer model¹¹ uses five prognostic features to predict outcome: progressive disease before HDCT (1 point), mediastinal primary site (1 point), refractory disease (1 point), absolute refractory disease (2 points), and HCG $> 1,000$ U/mL (2 points). Patients with 0 points were predicted to achieve a good outcome (good-risk); those with 1 or 2 points, an intermediate outcome (intermediate-risk); and those with 3 or more points, a poor outcome (poor-risk) with respect to both OS and DFS.

Eligibility to our study required PD to prior therapy. Therefore, all 107 patients had Beyer scores of ≥ 1 with none being classified as Beyer good-risk. Nevertheless, the Beyer model effectively separated patients into intermediate-risk ($n = 85$; 79%) and poor-risk ($n = 22$; 21%) groups ($P < .001$) with DFS of 54% and 23%, respectively (Fig 2A). Reclassification based on Beyer score allowed patient stratification into three risk groups: those with 1 point had DFS of 65%, those with 2 points had DFS of 50%, and those with ≥ 3 points had DFS of 23% ($P = .01$; Fig 2B).

The Einhorn model⁶ assigns 3 points for two or more prior lines of therapy, and 2 points each for platinum-refractory disease and initial IGCCCG poor-risk status at diagnosis. Patients are separated into three groups on the basis of their point total (low-risk = 0, intermediate-risk = 2 to 3, high-risk = 4 to 7). IGCCCG risk status could not be determined for six patients, and an additional 28 patients would have been excluded from HDCT at Indiana University because of mediastinal primary site ($n = 21$) or late relapse ($n = 7$).⁶ The remaining 73 patients had a 62% 5-year OS and 57% 5-year DFS, higher than for the entire population but not statistically significant. Separating these 73 patients by Einhorn score yielded 11 (15%) low-risk, 28 (38%) intermediate-risk, and 34 (47%) high-risk patients. Median DFS was 16.4 months for the high-risk group and was not reached for the low- and intermediate-risk groups. This stratification was not significant ($P = .14$), primarily because of a lack of separation between the intermediate- and low-risk groups (Fig 2C). However, by combining the low- and intermediate-risk patients into a single cohort, the model reached statistical significance ($P < .05$; Fig 2D).

Applying the Einhorn model to all 101 patients (including those with PM-NSGCTs or late relapses) for whom a score could be calculated resulted in similar findings. Again, outcomes for intermediate-risk ($n = 35$) and low-risk ($n = 11$) patients overlapped, but both groups achieved significantly better DFS than those classified as Einhorn high-risk ($n = 55$; $P = .02$; Appendix Fig A1, online only). Of note, neither the Beyer nor Einhorn models identified a subgroup of patients with $< 20\%$ 5-year DFS.

DISCUSSION

This prospective trial demonstrates the effectiveness of TI-CE HDCT in GCT patients predicted to have a poor outcome to conventional-dose chemotherapy. The major findings include a 52% 5-year OS and 47% 5-year DFS—encouraging results for this group. These rates improve to 62% (5-year OS) and 57% (5-year DFS) when patients with PM-NSGCTs and late relapses are excluded, approximating the outcomes reported by Einhorn et al⁶ despite a higher proportion of TI-CE patients being platinum refractory, achieving an IR to first-line therapy, and having higher Beyer and Einhorn scores (Appendix Table A3, online only).

Although the Einhorn regimen and TI-CE are both based on administration of high-dose CE, important differences with TI-CE include using preparative chemotherapy (cycles 1 and 2) before stem-cell collection in all patients, administering three rather than two high-dose cycles, dosing carboplatin by target AUC rather than body surface area, and not using adjuvant oral etoposide (prescribed for 3 months following HDCT at Indiana University).⁶ The current

Fig 2. Kaplan-Meier curves of disease-free survival stratified by (A) Beyer risk group classification, (B) Beyer raw score, (C) Einhorn risk group classification, and (D) Einhorn risk classification with the low- and intermediate-risk cohorts combined into one group. Figures 2C and 2D include only the 73 patients who would have met criteria for high-dose chemotherapy at Indiana University.

doses and schedule of TI-CE (as reflected by National Comprehensive Cancer Network [NCCN] guidelines¹⁷) are provided in Appendix Table A3.

While TI-CE patients were more similar to those reported by Beyer, some differences should be emphasized. First, the Beyer model was published 13 years ago, when HDCT was less standardized and bone marrow-derived rather than peripheral blood stem cells were used for support. Second, Beyer's data were derived from a heterogeneous group of patients treated with several different HDCT regimens at multiple institutions. Third, larger proportions of Beyer's patients were cisplatin-sensitive and achieved favorable responses to first-line chemotherapy. Finally, some of Beyer's patients received HDCT without PD, whereas all of our patients (and those reported by Einhorn) were required to have PD in order to receive HDCT.

Despite these differences, three of the four factors predicting DFS in this study were previously identified by either Beyer¹¹ (mediastinal

primary site, HCG $\geq 1,000$ U/mL) or Einhorn (two or more lines of prior chemotherapy).⁶ In contrast, we found no relationship between cisplatin refractoriness and outcome as reported by both Beyer and Einhorn. This could reflect population differences or a specific effect of TI-CE in overcoming platinum resistance.

Rather than developing another prognostic classification, we chose to apply the Beyer and Einhorn models to our population and found both effectively stratified patients into good- and poor-risk groups. Limitations of the Einhorn model in our cohort included a lack of applicability to 34 patients with PM-NSGCT or late relapse or for whom initial IGCCCG risk group could not be determined. In addition, no significant separation in DFS curves was observed between Einhorn low- and intermediate-risk groups. The model did however identify a high-risk group of patients distinct from these other two subsets.

Disadvantages of the Beyer model relate to inclusion of two variables with limited clinical applicability. As previously mentioned,

today's standards recommend that HDCT be reserved for patients with PD, eliminating the utility of this factor and resulting in none of our patients qualifying as Beyer good-risk. Similarly, absolute refractory disease is quite rare (< 2% in this series), limiting the contribution of this variable. Nevertheless, the Beyer system effectively separated TI-CE patients into intermediate- and poor-risk cohorts, likely because of population similarities and the strength of remaining variables in the model. Furthermore, refining the point cutoffs to account for TI-CE patients uniformly having PD before HDCT yielded three distinct prognostic groups with DFS of 65%, 50%, and 23%.

Importantly, a significant proportion of patients within even the worst Beyer (23%) and Einhorn (40%) risk groups achieved long-term DFS. Therefore, neither identifies a patient subset for which HDCT should be completely disregarded. This is supported by the encouraging finding of 24% long-term DFS for patients with PM-NSGCTs treated with TI-CE. Indiana University abandoned salvage HDCT for PM-NSGCT in the mid-1990s after no durable CRs were achieved among the first 13 patients.⁶ Similarly, Beyer et al¹¹ reported a failure-free survival of only 12% for PM-NSGCT patients undergoing HDCT. It is unclear whether our more favorable results relate to general improvements in HDCT and postchemotherapy surgery over the past decade or to a specific benefit of our regimen. Nevertheless, these findings support continued consideration of such patients for HDCT since no other available therapy offers this degree of success.

Selection of optimal salvage treatment for relapsed or refractory GCT patients remains limited by the multiple different prognostic models available for both conventional and HDCT, each developed from distinct patient populations. A multi-institutional international collaboration¹⁸ was recently formed with the goal of establishing a universally accepted prognostic model for initial salvage treatment. Incorporating tumor biology into future prognostic models might also enhance utility and applicability. We recently identified a GCT gene signature that predicted 5-year OS independent of IGCCCG classification and distinguished patients within the same IGCCCG group.¹⁹ Combining such analyses with clinical features could improve on existing prognostic systems.

In summary, TI-CE HDCT is highly effective for patients predicted to have poor outcomes with conventional-dose chemotherapy and represents our standard approach for this patient population at MSKCC. Mediastinal primary tumor site, HCG $\geq$ 1,000 U/mL, two or more lines of prior therapy, three or more metastatic sites, and IGCCCG intermediate- or poor-risk classification at diagnosis are independently predictive of DFS and/or OS. Einhorn and

Beyer models effectively distinguish good-risk from poor-risk patients and therefore may provide useful information for patients considering HDCT. However, our data suggest that in the absence of safety concerns, no subgroup of patients, including those with mediastinal primaries, is so unfavorable that consideration of HDCT should be excluded.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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