Original Article

Management of Advanced Germ Cell Cancer in Patients With Unfavorable Prognosis

Kim Margolin, MD, *Duarte, California*

Key Words

Germ cell cancer, high dose chemotherapy, hematopoietic cell transplant

Abstract

Advanced germ cell cancer can be cured in most patients using chemotherapy with or without surgery. A small fraction of patients with nonseminomatous tumors (NSGCT) and an even smaller percentage of seminoma patients are destined to have a less favorable outcome, due to an inadequate response to first-line chemotherapy (failure to achieve remission, finding of residual viable carcinoma at post-chemotherapy surgery, or relapse after achieving a remission). Despite the apparent salvage potential for regimens containing ifosfamide or paclitaxel, no proof exists that such combinations are superior to the standard regimen of four cycles of cisplatin, etoposide, and bleomycin (PEB) in the front-line therapy of patients with advanced NSGCT. Other modifications of first-line therapy, such as the addition of paclitaxel or the use of escalated doses of cisplatin, also have failed to increase the cure rate. The use of single or tandem cycles of high-dose chemotherapy (HDT with autologous hematopoietic cell transplant [aHCT]) in various settings (for selected patients with poor prognostic features before therapy, patients predicted to have a poor outcome based on the rate of serum tumor marker decline while on therapy, and patients in relapse or failure to achieve adequate response to standard therapy) has been evaluated in many phase II and a limited number of phase III trials, which are summarized in this review. Important questions that remain to be answered include the role of new agents and the use of more sophisticated techniques to understand prognostic and predictive factors in selecting therapy for GCT. (*JNCCN* 2005;3:77–83)

From the Departments of Medical Oncology and Therapeutics Research and Hematology/Hematopoietic Cell Transplantation, City of Hope National Medical Center, 1500 E. Duarte Road, Duarte, California.

Submitted October 15, 2004; accepted for publication November 5, 2004.

The author has no financial interest, arrangement, or affiliations with the manufacturers of any products discussed in the article or with their competitors.

Correspondence: Kim Margolin, MD, Departments of Medical Oncology and Therapeutics Research and Hematology/Hematopoietic Cell Transplantation, City of Hope National Medical Center, 1500 E. Duarte Road, Duarte, CA 91010. E-mail: kmargolin@coh.org

Since the advent of cisplatin combinations in the therapy of germ cell tumor (GCT) 30 years ago, more than 90% of all patients with nonseminomatous histologies (NSGCT) are cured using carefully selected sequences of surgery and/or chemotherapy. An even higher percentage of patients with seminoma are cured using radiotherapy and/or chemotherapy.[1] About 60% of patients with advanced-stage nonseminomatous NSGCT and the vast majority of those with advanced seminoma present with favorable prognostic features that confer a 90% likelihood of cure with chemotherapy, with or without post-chemotherapy surgery. The remaining patients with seminoma and about 30% of patients with NSGCT have an intermediate prognosis, associated with an 80% likelihood of cure. The remaining patients (all with NSGCT) fall into the poor-risk category, with less than 50% probability of cure from current approaches.[2]

General Principles and History of High-Dose Chemotherapy in Germ Cell Tumors

The use of high-dose chemotherapy (HDT) with autologous hematopoietic cell transplant (aHCT) in GCT began at a time when several features of the disease and its treatment were considered as an ideal testing ground for this approach. First, the very high rate of cure using cisplatin-based combinations with bleomycin and either vinblastine or etoposide led to the routine use of these regimens in non-selected patients with advanced GCT. Patients who experienced relapse after initial chemotherapy often showed response to second-line combinations containing cisplatin in combination with other active agents that had not been given initially (most commonly vinblastine and ifosfamide).[3,4] As experience with the use of aHCT increased, this modality began to be explored in patients with highly chemoresponsive solid tumors who had experienced

relapse after initial and sometimes second-line chemotherapy.

Drugs with activity in GCT were also ideal for aHCT in having only low-to-moderate extramedullary dose-limiting toxicities. Thus, carboplatin and etoposide formed the backbone of most regimens, with or without the addition of cyclophosphamide or ifosfamide in some centers. In the United States, double ("tandem") cycles of HDT/aHCT were generally used, based on oncologic principles that a single exposure would be suboptimal and on the favorable characteristics of the drugs used for HDT. Some European centers continued to use single cycles of HDT/aHCT, but a randomized comparison of single versus tandem regimens has never been performed in GCT (reviewed by Motzer and Bosl[5]).

In the earliest studies, only patients with heavily pretreated, multiply relapsed GCT went on to HDT/aHCT, so the toxicities and treatment-associated mortality were substantial, and the long-term cure rate was only about 15% to 20%. As experience grew with this modality in hematologic and solid tumors, the encouraging results of the earlier studies prompted several groups to move this modality into an earlier position in the therapy of GCT, so the second wave of reports consisted of patients whose response to standard-dose therapy for relapsed GCT was "consolidated" with HDT/aHCT. In this group of patients, the reported long-term remission rates were in the 40% to 50% range and have remained there through the most recent studies.[6–8] One important observation to emerge from all of these studies was that cases of primary mediastinal NSGCT in relapse could virtually never be salvaged using HDT/aPSCT, and most investigators now exclude these patients from their studies.[9]

Classification Systems for Advanced Germ Cell Tumors and the Selection of Therapy

The improvements in safety and promising activity of HDT/aHCT in relapsed GCT patients led investigators, primarily at Memorial Sloan-Kettering Cancer Center, to consider introducing this approach earlier in the treatment of patients predicted to have a poor outcome from standard therapy. Based on an initial report suggesting the singular importance of tumor marker response in predicting a favorable outcome during initial therapy and statistical analyses of the patient databases from several large U.S. centers, a predictive model was developed in which the rate of decline of serum tumor markers during initial therapy stood out in multivariate analysis as the most important predictor of patient outcome.[10] Other analyses have not uniformly agreed with this model, and a validation study was incorporated prospectively into the recently-completed trial to assess the role of HDT/aHCT in first-line therapy of poor- and intermediate-risk GCT (detailed below). Similarly, prognostic systems for outcome based on clinical and laboratory characteristics have evolved from the original Indiana University system—based on radiographic extent and location of disease and serum tumor markers[11]—to an international system based on sites of involvement and tumor markers (alpha-fetoprotein [AFP], beta-human chorionic gonadotropin [HCG], and lactate dehydrogenase [LDH]). This system, derived from a large European and U.S. database by the International Germ Cell Cancer Collaborative Group (IGCCCG) and shown in Table 1, has gained wide acceptance based on the large size and features of the database used to create it, as well as its ease of use and clear identification of three distinct prognostic groups (poor, intermediate, and good risk) with significantly different outcomes from standard therapies.[2] Soon after the publication of the IGCCCG system for categorizing patients based on presenting characteristics, a German multicenter group reported a similar system for predicting the outcome of patients with GCT in relapse who underwent HDT/aHCT. This "Beyer index"[12] (Table 2) has been adopted for use in many studies of this modality for relapse patients and is used descriptively in the demographic results of reports from trials of second- and third-line HDT/aHCT for GCT. Much like the lymphomas, however, the IGCCCG and Beyer systems, while of prognostic importance and thus of value for stratification and description of patients in therapeutic trials, lack true predictive value for the interaction between the therapy and the target. These systems, analogous to lymphoma and, more recently, in solid tumors such as breast cancer, are likely to be replaced by molecular staging and prognostic systems that also provide a greater understanding of the potential therapeutic targets and agents most likely to be effective.

Table 1 International Germ Cell Cancer Collaborative Group (IGCCCG) Prognostic System

***Good Prognosis**	
Non-seminoma	**Seminoma**
Testis/retroperitoneal primary AND No non-pulmonary visceral metastases AND Good markers; all of: AFP < 1000 ng/mL hCG <5,000 IU/L (1,000 ng/mL) LDH < 1.5 × upper limit of normal	Any primary site AND No non-pulmonary visceral metastases AND Normal AFP, any hCG, any LDH
Intermediate Prognosis	
Non-seminoma	**Seminoma**
Testis/retroperitoneal primary AND No non-pulmonary visceral metastases AND Intermediate markers; any of: AFP ≥ 1,000 and ≤ 10,000 ng/mL OR hCG ≥ 5,000 IU/L and ≤ 50,000 IU/L OR LDH ≥ 1.5 × N and ≤ 10 × N	Any primary site AND Non-pulmonary visceral metastases AND Normal AFP, any hCG, any LDH
Poor Prognosis	
Non-seminoma	**Seminoma**
Mediastinal primary OR Non-pulmonary visceral metastases OR Poor markers; any of: AFP > 10,000 ng/mL OR hCG > 50,000 IU/L (10,000 ng/mL) or LDH > 10 × upper limit of normal	No patients classified as having poor prognosis

Data from the International Germ Cell Cancer Collaborative Group.[2]

Moving HDT/aHCT into First-Line Therapy

The application of dynamic characteristics to therapeutic decision-making has been exemplified by the series of studies from the GCT group at Memorial Sloan-Kettering. Based on their initial models for selection of poor-risk patients and the data supporting the importance of the rate of decline of serum tumor markers during initial chemotherapy, patients were treated with one of two standard induction regimens (initially the "VAB-6" regimen consisting of vinblastine, actinomycin, bleomycin, etoposide, and cisplatin; subsequently, the widely-used "VIP" regimen developed at Indiana University, consisting of etoposide, ifosfamide, and cisplatin). Patients whose serum tumor markers did not decline at the optimal half-life rate (3 days for HCG, 7 days for AFP).[10] were assigned after two cycles of their initial therapy to switch to 2 cycles of HDT/aHCT using carboplatin and etoposide (in the first report) or the same drugs plus cyclophosphamide (in the subsequent report). The results of these trials, in which approximately half of the patients with the most unfavorable predicted outcome achieved durable complete remission, suggested

Table 2 Beyer Prognostic Index

Patient Characteristic	Score
Progressive disease before HDT/aHCT	1
Mediastinal primary tumor	1
Refractory disease before HDT/aHCT	1
Absolute refractory disease before HDT/aHCT	2
HCG >1000 U/L before HDT/aHCT	2

Data from Beyer et al.[12]

superiority over that which would be predicted from historical controls.[13,14] These results formed the basis for an important randomized Intergroup trial (T94-0086, in which all three U.S. cooperative groups participated) evaluated the role of HDT/aHCT as part of first-line therapy and provided data to validate the importance of tumor marker half-life as a dynamic prognostic factor in IGCCCG high- and intermediate-risk patients.

In this trial, which accrued 219 patients and is expected to undergo analysis in late 2004, patients were randomly assigned before any treatment to receive four cycles of PEB chemotherapy or two cycles of PEB followed by two cycles of HDT/aHCT using the Memorial Sloan-Kettering regimen of high-dose carboplatin, etoposide, and cyclophosphamide. Prestratification for high versus intermediate risk assured equal representation of patients from each prognostic group in the two treatment arms, and close monitoring of serum tumor markers will provide the opportunity to detect a possible interaction between tumor marker half-life and therapy.

A similar study under development in the Southwest Oncology Group for IGCCCG intermediate-risk patients addresses the poor prognosis for patients with a persistently elevated serum tumor marker after two cycles of PEB chemotherapy.[15] In this study, all patients will receive initial therapy with two cycles of PEB, and patients whose marker remains above the upper limit of normal will be randomized to complete therapy with two additional cycles of PEB or to switch to a second-line regimen consisting of paclitaxel, ifosfamide and cisplatin (TIP).

In a recently reported phase III trial of the European Group for Bone Marrow Transplant (EBMT), the benefit of adding a single cycle of HDT/aHCT using carboplatin, etoposide, and cyclophosphamide to standard-dose salvage therapy was assessed in 280 patients in non-refractory relapse or incomplete response to first-line therapy. No difference was found between the treatment groups in the one-year event-free survival, and the regimen-related mortality was 9% among patients randomized to HDT/aHCT versus 2% for patients randomized to standard therapy.[16] Pitfalls in this study included the heterogeneity of patient characteristics, variability of first- and second-line therapies, lack of prestratification for known prognostic or predictive factors, and the very high regimen-related mortality in the HDT/aHCT cohort, which may have masked a potential therapeutic benefit. Despite this sobering result, the role of this form of therapy intensification for patients in first relapse remains worthy of further investigation, taking advantage of reduced regimen-related mortality and costs as well as new agents and schedules of administration (see later discussion). In light of such improvements in the tolerability of HDT/aHCT or related high-dose regimens, even a modest improvement in outcomes (the EBMT trial had only an 80% power to detect a 15% difference in 1-year EFS) would be associated with a favorable risk to benefit ratio for the more intensive salvage approach.

Current Approaches for Patients with Unfavorable Risk

Investigators in the U.S. and Europe have recently considered moving newer drugs into first-line regimens, with particular interest in the use of paclitaxel, gemcitabine, and oxaliplatin, all of which have shown promising activity in relapsed GCT.[17–20] Although lessons from the past and in other tumor types would raise some concern that adding agents to highly active therapy may simply increase toxicity and potentially limit the safe exposure to the known most active agents, only a carefully designed randomized clinical trial can answer this question in GCT. The feasibility of this approach will be tested in an ongoing trial by the Hoosier Oncology Group using a five-drug regimen (cisplatin, etoposide, bleomycin, paclitaxel, and gemcitabine) in patients with IGCCC poor-risk GCT.

Another variation on the theme of using HDT/aHCT in early relapsed GCT has been an innovative regimen using two cycles of paclitaxel and ifosfamide as both initial cytoreductive therapy and as mobilization for the collection of high numbers of HCT, followed by three cycles of high-dose etoposide

and carboplatin, each supported by the previously collected stem cells. The group at Memorial Sloan-Kettering applied this regimen to a group of 37 patients in relapse with features predictive of a poor outcome, such as failure to achieve a marker remission from first-line therapy. The response rate of 62% and long-term (>2.5 years) survival of 41% suggested a potential improvement over more standard second-line regimens, such as cisplatin plus ifosfamide and either paclitaxel or vinblastine.[3,4]

Current Status of HDT/aHCT in Relapsed GCT

The optimal timing of this modality remains to be determined, but at present, experts generally agree that for patients in relapse with favorable features by the Beyer system[12] or related criteria, tandem cycles of HDT/aHCT have the potential to cure 20% to 40% of patients who would not otherwise be cured. Deciding whether to consolidate a response to second-line therapy for first relapse using this form of therapy requires reconciling the negative results of the Italian study[16] with uncontrolled U.S. and European data regarding treatment of first or second relapse (reviewed).[5] This is a setting in which further randomized studies may be difficult to perform. Nevertheless, experts generally agree that the morbidity, mortality, and expense of this approach make it worthwhile only for cases with curative intent. Therefore, patients with mediastinal primary NSGCT should not be offered this form of therapy outside of a clinical trial, and for patients believed to be candidates for HDT/aHCT, the lower the markers and the less refractory the tumor, the greater the likelihood of benefit.

The question of which agents are most appropriate in HDT remains to be fully elucidated. Variations in the regimens based on currently available agents may have the least impact on outcome, which depends heavily on the above-mentioned factors. The hope is that, with the development of more active agents with unique mechanisms of action, the choice of drugs (and perhaps a shift in emphasis away from HDT) will have greater impact on the outcome. Until then, current regimens using drugs selected for their activity and their favorable risk to benefit relationship in the high-dose setting are recommended when patients are treated with HDT/aHCT outside of a clinical trial.

The most commonly used agents, the toxicities of which are predominantly myelosuppression, include: carboplatin, which possesses mild hepato-, neuro-, and nephrotoxicity in high doses;[21] etoposide, which is also highly active, synergistic with carboplatin, and limited mainly by gastrointestinal toxicity;[22] and cyclophosphamide or ifosfamide, both of which can cause hemorrhagic cystitis because of the elimination of the aldehyde metabolite that can be avoided by the reducing agent MESNA. Ifosfamide can also contribute to nephrotoxicity and neurotoxicity (encephalopathy), which can generally be avoided when the total dose is fractionated and adequate alkalinization and volume diuresis are provided.[23–27] Recently, paclitaxel in high doses that are limited by peripheral neurotoxicity and exacerbation of mucosal toxicity has been added to the therapeutic armamentarium.[8,28,29]

The relative increment in activity based on escalating doses of these agents within the range that is safe when protected by aHCT (ranging in each cycle between 2.5 and 5 times the standard dose) is unlikely to overcome drug resistance in the most refractory clones, but appears to suffice in the 20% to 40% of patients with long-term disease-free survival after this form of therapy. Although cytoprotective agents such as amifostine have shown some evidence of protection against the nephrotoxicity of cisplatin and the neurotoxicity of both cisplatin and paclitaxel in other settings, the reversibility of these toxicities and the possibility that the cytoprotective agent could also reduce antitumor activity has limited the use of agents other than MESNA, which is required to avoid the high risk of hemorrhagic cystitis from ifosfamide and high-dose cyclophosphamide.[30] Several new agents (for example, recombinant keratinocyte growth factor) have been developed to reduce stomatitis and its secondary complications such as airway compromise. These agents have not yet been investigated in these regimens but may hold promise for reducing the risks and morbidities of this form of therapy.

Conclusion

Most patients with GCT have an excellent prognosis, so therapeutic investigations are directed toward the reduction of short- and long-term toxicities. However, treatment and cure of patients with high-risk

disease and relapse remains an essential goal for the design of new therapeutic strategies. Novel agents with promising activity in these diseases will probably be selected on the basis of improvements in our precise understanding of the molecular biology of germ cell malignancies and the availability of more targeted agents. Until that time, researchers must continue to refine existing techniques, including the study of new agents, doses, schedules, and cytoprotective agents, to improve the safety and efficacy of all forms of systemic therapy for patients with poor-prognosis germ cell malignancies.

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