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# High-dose chemotherapy and stem cell transplantation for advanced testicular cancer

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## Abstract

High-dose chemotherapy (HDCT) with autologous stem cell support has been studied in both the salvage and first-line setting in advanced germ cell tumor (GCT) patients with poor-risk features. While early studies reported significant treatment-related mortality, introduction of peripheral blood stem cell transplantation, recombinant growth factors and better supportive care have decreased toxicity; and in more recent reports treatment-related deaths are observed in <3% of patients. Two to three cycles of high-dose carboplatin and etoposide is the standard backbone for HDCT, given with or without additional agents including ifosfamide, cyclophosphamide and paclitaxel. Three large randomized Phase III trials have failed to show a benefit of HDCT over conventional-dose chemotherapy (CDCT) in the first-line treatment of patients with intermediate- or poor-risk advanced GCT, and to date the routine use of HDCT has been reserved for the salvage setting. Several prognostic models have been developed to help predict outcome of salvage HDCT, the most recent of which applies to both CDCT and HDCT in the initial salvage setting. Patients that relapse after HDCT are usually considered incurable, and additional therapy is provided with palliative intent.

### Keywords

chemotherapy; germ cell tumors; high-dose chemotherapy; stem cell transplantation; testicular cancer

With an estimated 8500 annual cases in the USA, germ cell tumors (GCTs) account for less than 1% of all cancers; however, they represent the most common malignancy in young men between the ages of 15 and 35 years [1]. GCTs were recognized early as a model for curable cancers [2], and over the past three decades, major advances – first and foremost the introduction of cisplatin in the mid 1970s [3] – have helped increase cure rates to more than 95% [4]. Approximately 70% of patients with advanced disease are cured with conventional-dose, platinum-based chemotherapy, and efforts have been focused on directing treatment according to risk classification. For patients with advanced disease and poor prognosis criteria per the International Germ Cell Cancer Collaborative Group (IGCCCG) Classification [5], the current standard of care in first-line therapy is combination chemotherapy with four cycles of cisplatin, etoposide and bleomycin (BEP), which results in

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5-year overall survival (OS) rates of less than 60% in this group [6,7]. Patients who do not achieve long-term remission with initial chemotherapy are still curable with second- and even third-line treatment strategies. Options include Centre for Developmental Cancer Therapeutics (CDCT) programs combining cisplatin and ifosfamide with either paclitaxel (TIP) [8] or vinblastine [9] with durable complete response (CR) rates of up to 63% in the Phase II setting in well-selected patients. Another approach that has been heavily investigated is the use of high-dose chemotherapy (HDCT) with autologous stem cell support.

In the 1970s high-dose combination chemotherapy followed by autologous stem cell rescue was found to be effective in the treatment of relapsed hematologic malignancies [10–15]. Based on these experiences, investigators started looking into the utility of such treatment in advanced solid tumors; the initial trials for this were undertaken in the early 1980s and enrolled pretreated patients of several tumor types [16–19]. It was logical to include GCT patients in such studies due to their chemosensitivity, as well as the dose–response phenomena of individual drugs with synergistic action, the rare occurrence of bone marrow (BM) metastasis, and a young patient population with a low incidence of significant comorbidities. Following encouraging results for some of the GCT patients in the aforementioned pilot studies, dedicated protocols for this tumor type were conducted both in Europe and the USA. Important characteristics of drugs chosen for these studies included:

- Anti-tumor activity in conventional doses without evidence that the dose effect plateau had been reached;
- Myelosuppression, even at high doses, being the dominant adverse effect, a toxicity that could be modulated by autologous BM infusion.

In the case of GCT, carboplatin, etoposide and cyclophosphamide (CE) were the main candidates that fulfilled these requirements. Carboplatin was chosen over cisplatin, since its predominant toxicity is myelosuppression, but other adverse effects such as neurotoxicity and nephrotoxicity are usually not observed. Phase I studies in other disease entities had established the safety of high-dose carboplatin up to 1600 mg/m$^2$ as a single agent [20,21]. The efficacy of HDCT using carboplatin in conjunction with stem cell transplantation was shown later [22]. For etoposide, a dose-response effect in GCT had been suggested for doses up to 2400 mg/m$^2$ [23], and the efficacy of combinations of high-dose etoposide with cyclophosphamide had been reported [24].

## High-dose chemotherapy in the salvage setting

The favorable outcomes achieved in a proportion of GCT patients treated during the initial studies led to more formal trials of salvage HDCT, specifically in GCT patients, published in the 1980s. These studies demonstrated hope in the treatment of patients, which were refractory to standard chemotherapy, but came at the price of significant morbidity and mortality, mostly related to infectious complications of severe myelosuppression. The first two published studies, one from the USA, one from Europe, used high-dose etoposide- and cyclophosphamide-based regimens, and yielded overall disappointing results with no long-term responses despite significant toxicity [18,25]. Better outcomes were seen with etoposide and carboplatin, a combination soon established as the backbone for further treatment programs. A sentinel report using this regimen was a Phase I/II trial conducted at the Indiana University (IN, USA) and Vanderbilt University (TN, USA) and published in 1989 [26]. A total of 33 patients, who had either demonstrated progression on salvage therapy with ifosfamide and cisplatin, or had primary cisplatin refractory disease, were enrolled. In the Phase I portion of the trial, all patients received 1200 mg/m$^2$ of etoposide per cycle of HDCT in combination with escalating doses of carboplatin, establishing a carboplatin dose of 1500 mg/m$^2$/cycle as the recommended dose for the Phase II portion.

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Patients received one (39%) or two (61%) cycles of HDCT followed by autologous stem cell rescue. The authors reported CRs in eight out of 32 patients (25%), three (9%) of whom remained in CR for >1 year. Toxicities in this heavily pretreated population were significant, as all patients developed severe myelosuppression, some complicated by neutropenic fever or bleeding. There were seven treatment-related deaths (21% of patients), all within 20 days of marrow infusion. Nonhematologic toxicity was mostly mild to moderate in the Phase II portion of the study. This was the first trial to suggest that HDCT could be curative even in the third-line setting, and in a subsequent publication describing the long-term follow-up of these plus several additional patients treated on this program, the authors reported sustained CR rates of 15% (Table 1) [27–31].

The encouraging results of this trial prompted further study of this treatment program (one or two cycles of carboplatin 1500 mg/m$^2$ and etoposide 1200 mg/m$^2$) in form of a multi-institutional Phase II protocol sponsored by the Eastern Cooperative Oncology Group (ECOG). Similar results were achieved (overall response rate: 44%, CR sustained >1 year 13% and treatment-related deaths 13%) [32]. Together, these studies helped establish the combination of high-dose carboplatin and etoposide as the backbone for high-dose protocols. Subsequent efforts have focused on confirming activity, increasing the number of patients who achieved durable responses and reducing toxicity.

In 2007, the group from the Indiana University published a large retrospective evaluation of their experience with HDCT using the combination of carboplatin and etoposide in 184 consecutive patients treated between 1996 and 2004 [33]. Most patients (73%) were treated in the initial salvage setting. The high-dose regimen consisted of two cycles of carboplatin 2100 mg/m$^2$ and etoposide 2250 mg/m$^2$, both administered over 3 days and supported by autologous stem cell reinfusion. Some patients received one or two cycles of conventional dose salvage chemotherapy with vinblastine/ifosfamide/cisplatin (VeIP) prior to HDCT. After a median of 4 years of follow-up, 63% of patients were continuously disease free. Notably, the patients in this series were in general more favorable than the other series. For example, patients with primary mediastinal nonseminomatous GCTs (NSGCTs) and late relapses were not included due to previously observed poor outcomes with HDCT in these subgroups [33].

## Addition of other agents to carboplatin & etoposide

Following the promising original report by Nichols *et al.* [26], several groups added an oxazaphosphorine (cyclophosphamide or ifosfamide) to high-dose carboplatin and etoposide in an effort to improve efficacy. In an early attempt in the 1990s, the German Testicular Cancer Cooperative Study Group treated patients with one cycle of high-dose etoposide, carboplatin and ifosfamide and reported 31% CR rates with 20% partial response (PR) with marker normalization, and 19% sustained remissions >12 months with substantially less treatment-related mortality (3%) [28]. This study did not confirm the concerns for significant renal toxicity raised by a previously reported small series of patients treated with the same triplet at the Indiana University [34]. Our group at the Memorial Sloan–Kettering Cancer Center (MSKCC) treated 58 treatment refractory patients with one or two cycles of high-dose carboplatin, etoposide, and CE with encouraging results (CR: 40%; 2 year OS: 31; 17% sustained CR: >24 months). Multivariate analysis identified the pretreatment level of human chorionic gonadotropin (HCG) and the status of retroperitoneal metastases as two independent predictive factors for survival [29]. During this time, two comprehensive reviews suggested that CR improved via the addition of oxazaphosphorines [35,36]. Alternatively, data using modified regimens with higher doses of carboplatin plus etoposide has suggested improved efficacy over the original carboplatin plus etoposide doublet [33,37].

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A Phase II trial published by German investigators in 2001 enrolled 80 patients with relapsed or cisplatin-refractory disease for treatment with three cycles of conventional dose paclitaxel, ifosfamide and cisplatin (TIP) followed by one cycle of high-dose carboplatin, etoposide and thiotepa [30]. The 3-year OS was reported as 30%, long-term remissions were observed in 25% of patients. In this study, 29% of HDCT patients developed sensorimotor toxicity ≥grade 2. Peripheral nerve damage from conventional-dose TIP was substantially aggravated by HDCT, which the authors contributed for high-dose thiotepa, either by itself or in combination with high-dose carboplatin.

Paclitaxel has been successfully incorporated in HDCT treatment programs, following studies showing efficacy as a single agent in the salvage setting [38], and synergism with cisplatin and oxazaphosphorines in preclinical models [39]. A salvage HDCT protocol developed at the MSKCC studied the sequence of two courses of rapidly recycled (every 14 days), conventionally dosed paclitaxel and ifosfamide for stem cell mobilization followed by three cycles of highdose carboplatin plus etoposide (1200 mg/m$^2$ per cycle) with stem cell support. High-dose carboplatin was dose escalated among patient cohorts, eventually determining a carboplatin dose of area under the curve (AUC) 24 per cycle [31,40,41]. This program was specifically designed to target previously treated patients with GCT who were unlikely to achieve a successful outcome with conventional-dose salvage chemotherapy. ‘Unfavorable prognostic features’ were defined as extragonadal primary site, progression after an incomplete response to first-line therapy, or progression after treatment with a prior ifosfamide plus cisplatin-based salvage regimen. Of the 107 patients included in the final analysis, 58% achieved a favorable response (CR or PR with normalized serum tumor markers), and there were only two (1.9%) treatment-related deaths. With a median follow-up of 5 years, the 5-year disease free survival (DFS) and OS rates in this unfavorable group of patients was 48 and 52%, respectively, with relatively high proportions considering the poor prognostic features of the patient population. In particular, five out of 21 (24%) patients with primary mediastinal (PM)-NSGCT, two out of seven (29%) with late relapses, each being subgroups with historically dismal outcomes to HDCT, were alive and disease free at last follow-up [31].

## Randomized prospective studies of HDCT in the salvage setting

The IT-94 randomized Phase III trial compared HDCT to CDCT in the salvage setting. This multicenter international study was conducted in Europe between 1994 and 2001, and enrolled 280 patients from 43 institutions in 11 countries [42]. The trial compared the efficacy of four cycles of CDCT using etoposide/ifosfamide/cisplatin (VIP)/VeIP versus three cycles of the same CDCT followed by one cycle of HDCT using carboplatin (200–550 mg/m$^2$), etoposide (1800 mg/m$^2$) and cyclophosphamide (200 mg/kg) followed by autologous stem cell rescue (Table 2) [42,43]. No survival benefit was observed for the high-dose arm. It is important to note that:

- The majority of patients were treated during the initial salvage setting, unlike most of the Phase II trials reported earlier;
- Patients refractory to first-line platinum-containing chemotherapy were excluded;
- Only one cycle of HDCT was provided, while those studies which reported an advantage of HDCT over historical results with CDCT included two or more HDCT cycles.

German investigators reported the results of a randomized trial that was designed to answer the question of whether multiple sequential HDCT cycles are superior to a single HDCT cycle [43]. In this study, 211 patients were randomly allocated to receive either three cycles of VIP followed by one cycle of high-dose carboplatin 2200 mg/m$^2$, etoposide 1800 mg/m$^2$

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and cyclophosphamide 6400 mg/m$^2$ (CECy), or one cycle of VIP followed by three high-dose carboplatin 1500 mg/m$^2$ and etoposide 1500 mg/m$^2$ without CE. These investigators found no statistically significant differences in event-free survival (EFS), Progression-free survival (PFS) or OS between the two groups. However, toxicity was more severe within the single high-dose CECy arm with 16% treatment-related deaths as compared with 4% in the sequential high-dose CE arm, which led to the premature closure of the trial and a nonsignificant trend toward improvement in OS for the sequential arm (80 vs 61%) [43]. The authors concluded that sequential therapy was superior in terms of better tolerability, but the significant differences in drug dosing between the high-dose portions of each arm, as well as the fact that one contained three drugs and the other only two, are the main critiques of this trial. Taking all of the above into consideration, two or three sequential high-dose cycles remain the standard of care when HDCT is used with curative intent during the treatment of GCT.

## HDCT for initial salvage

Limited data exist to guide the choice of HDCT versus CDCT for initial salvage treatment. An important point made early on in favor of HDCT as first salvage was the better tolerability of HDCT in less extensively pretreated patients [44]. In a retrospective study of 65 patients treated at the Indiana University with cisplatin-combination chemotherapy followed by two cycles of high-dose carboplatin and etoposide with autologous stem cell rescue as initial salvage, a continuous DFS rate of 57% was achieved with or without surgery at a median follow-up of more than 3 years [45]. It is noteworthy to mention that all patients on this trial had a testicular primary tumor; the majority had achieved a CR or marker-negative PR to first-line therapy and were classified as favorable-risk for HDCT according to the Beyer score (one of the prognostic models outlined later) [37]. A German study published by Rick *et al.* in 1998 retrospectively reported a heterogeneous population with respect to the timing of HDCT (initial salvage vs later salvage) [46]. A program of three cycles of CDCT followed by one cycle of high-dose VIP was used. For patients with good-risk Beyer scores [37], the 2-year OS was 66% for patients treated with HDCT as initial salvage as compared with only 47% for patients receiving HDCT as second or later salvage ($p < 0.05$).

More recently, data from a large multicenter, international retrospective analysis of initial salvage chemotherapy in approximately 1600 subjects were reported at the 2010 annual American Society of Clinical Oncology (ASCO) meeting [47]. Approximately equal numbers of patients were treated with CDCT and HDCT respectively. Overall, PFS and OS were found to be superior for patients treated with HDCT as compared with CDCT. On multivariate analysis, important prognostic factors were identified that allowed patient stratification into five well-defined prognostic categories. This data has since been used to develop a new prognostic model for initial salvage therapy (see later) [48]. Within these prognostic categories, PFS and OS remained superior for HDCT in each class with the exception of OS in the low-risk group. [47]. Owing to the retrospective nature of this analysis, a significant selection bias cannot be excluded as the explanation for the more favorable outcomes observed in patients treated with HDCT. An international, prospective trial comparing sequential HDCT with CDCT as initial salvage is being planned to answer this question.

Nevertheless, on the basis of these favorable results, HDCT is considered a standard approach for initial salvage treatment by some investigators. Others favor reserving HDCT for the third-line setting in order to avoid unnecessary toxicity in patients who could potentially be cured with CDCT. Another approach is to base initial salvage chemotherapy decisions on prognostic models for outcomes to CDCT and HDCT.

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## Prognostic models in HDCT

Several studies investigating prognostic factors for salvage HDCT have found specific variables predictive of a poor outcome, including pretreatment marker levels of HCG [29], mediastinal primary (PM) NSGCT [49,50] and absolute refractory disease (defined as no marker response to initial treatment) [51].

Several prognostic models have been developed to help risk stratify possible patients considered for HDCT. In 1996, Beyer and colleagues retrospectively performed a multivariate analysis of 310 patients treated at four centers in the USA and Europe with at least one cycle of high-dose carboplatin and etoposide with or without an oxazaphosphorine [37]. All had been pretreated with at least one cisplatin-based regimen. A nomogram was created with failure-free survival (FFS) after HDCT as the primary outcome variable. Progressive disease before HDCT, PM-NSGCT, refractory or absolute refractory disease to conventional-dose cisplatin, and HCG levels >1000 U/l were independent adverse prognostic indicators of survival after HDCT. A scoring system, referred to as the Beyer score (see also Table 3 [37]) based on these risk factors was established to categorize individual patients as good (0 points), intermediate (up to 2 points), or poor prognosis (>2 points) with reliable discrimination in regard to proportion of patients that relapsed, FFS and OS (all with $p < 0.001$). It is important to note, that more than 90% of the patients treated in Europe received a single HDCT course, and the majority were treated with two or more regimens before HDCT.

In a later retrospective review, investigators at Indiana University reported favorable outcomes for patients classified as poor-risk by the Beyer criteria [53]. Possible explanations for these discrepant results include selection of less heavily pretreated patients, more frequent administration of tandem rather than single HDCT, the use of growth factors, and autologous transplantation of peripheral blood stem cells rather than BM. Despite these favorable results, the authors noted that none of the patients with PM-NSGCT were alive and failure free at 2 years, leading them to conclude that such patients should not be offered HDCT [53].

In 2007, Indiana investigators developed a prognostic model for HDCT based on their experience in 184 testicular GCT patients treated between the years 1996 and 2004 [33]. PM-NSGCT were not included in this analysis, owing to the findings in the prior review mentioned earlier [53]. Similarly, patients with late relapses (>2 years) were also excluded due to historically poor outcomes with HDCT. Multivariate analysis identified three significant predictors of adverse DFS:

- An IGCCCG poor-risk classification at initial diagnosis;
- Platinum-refractory disease, defined as tumor progression within 4 weeks after the most recent cisplatin-based chemotherapy;
- Receipt of HDCT as third-line or subsequent chemotherapy.

Similar to the Beyer scoring system, points were assigned for each of these factors and patients were classified into three prognostic groups based on their total score (referred to as the Einhorn score, see Table 4 [33]). DFS was approximately 80, 60 and 40% for patients with low-risk, intermediate-risk and high-risk Einhorn scores, respectively [33]. The Beyer score was not confirmed to reliably predict DFS in this patient population ($p = 0.25$).

Memorial Sloan–Kettering Cancer Center investigators evaluated prognostic factors in the TI-CE series [31]. As previously described, this HDCT trial was targeted at patients predicted to have a poor prognosis to conventional salvage therapy with nearly half of

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patients achieving continuous DFS. Factors predicting unfavorable DFS or OS included mediastinal primary tumor site, HCG ≥1000 U/ml, two or more lines of prior therapy, three or more metastatic sites and IGCCCG intermediate- or poor-risk classification at diagnosis [31]. The study also tested both the Einhorn and Beyer prognostic models for their ability to predict DFS. Although this study did not include any patients who would have met criteria for the good-risk category per the Beyer score, this model still effectively separated patients into intermediate- and poor-risk groups with DFS rates of 54 and 23%, respectively. The Einhorn model only reached statistical significance when the low- and intermediate-risk groups were combined for comparison with poor-risk patients. It did, however, effectively identify a poor-risk group that had significantly inferior DFS compared with Einhorn good- or intermediate-risk patients. The lack of complete reproducibility of both the Einhorn and Beyer models in the TI-CE series demonstrates the limitations in the broad application of these prediction rules, each developed in specific patient populations, which vary in clinical features, prior management and HDCT regimen used.

Importantly, the TI-CE series also demonstrated remissions in patients with PM-NSGCT's, late relapse and CNS (pineal) and ovarian primary site GCTs. The authors concluded that in the absence of safety concerns, no patient group should be routinely excluded from consideration of HDCT. All of the aforementioned prognostic models were developed to specifically predict the likelihood of benefit from HDCT.

Recently, Lorch and colleagues presented the results of a large retrospective international multicenter analysis conducted by the International Prognostic Factor Study Group to identify prognostic groups for initial salvage therapy independent of regimen intensity (Table 5) [48]. Patients with salvage treatment administered as consolidation of first-line therapy without progression were excluded. This is the largest series ever reported and included approximately 2000 patients from 38 centers throughout 14 countries in Europe and North America. Seven factors were found to be significant for PFS on multivariate analysis including histology (seminoma vs nonseminoma); primary tumor site (mediastinal vs retroperitoneal vs gonadal); response to first-line chemotherapy (CR vs PR vs other); progression-free interval following first-line chemotherapy, α-fetoprotein (AFP) level at salvage, HCG level at salvage and the presence of nonpulmonary visceral metastases. Each factor was assigned a point value and a sum score calculated for each patient. Scores were divided into five groups (very low risk, low risk, intermediate risk, high risk and very high risk) with distinct PFS and OS rates [48]. The large, international and multicenter population of patients included in this study and the ability of the model to predict outcomes to both HDCT and CDCT initial salvage approaches will allow this model to be more widely applicable than the prior prognostic systems. Indeed, this is now widely considered the new standard predictive model in the relapsed/refractory setting.

## HDCT in the first-line therapy of GCT

The favorable results observed in the relapsed and refractory setting soon prompted investigators to expand their studies of HDCT to the first-line treatment of advanced GCT. This was facilitated further by more uniform pretreatment risk stratification, specifically the development of the universally accepted IGCCCG classification scheme [5] that enabled oncologists to identify poor-risk patients prior to the initiation of systemic therapy. Several groups have published single-arm Phase II trials of HDCT as first-line treatment in GCT patients with poor prognosis [54–59]. Response rates and survival data of early studies were encouraging, when compared with historical controls of studies using CDCT in poor risk patients. As expected, these studies reported less toxicity when using HDCT upfront rather than in the salvage setting [35,44,55,56]. A matched pair analysis of 147 consecutive patients treated with high-dose VIP in a German multicenter trial and 309 patients treated

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with CD VIP or BEP at the Indiana University was reported in 1999 [60]. Multivariate analysis indicated that first-line HDCT in patients with poor-prognosis GCT may result in a significant improvement of progression-free and overall survival. These findings led to Phase III trials which evaluated the role of HDCT in first-line treatment of poor-risk GCT.

In one randomized trial performed by the Genitourinary Group of the French Federation of Cancer Centers, 114 previously untreated patients with poor-prognosis nonseminomatous GCT received either three or four cycles of double-dose cisplatin in combination with vinblastine, etoposide and bleomycin (P200VeBV) or two cycles of modified P200VeBV followed by a single cycle of double-dose cisplatin (200 mg/m$^2$) in combination with high-dose etoposide (1750 mg/m$^2$) and cyclophosphamide (6400 mg/m$^2$) supported by autologous stem cell transplantation (ASCT) [61]. The initial report failed to demonstrate significant differences in relapse-free survival or OS (Table 6) [62–64]. This negative result was later confirmed after a median follow-up of 9.7 years [62]; in fact, there was a trend toward superior OS in the standard-dose arm. The study has been criticized in that the high-dose arm used double-dose cisplatin, which has been shown to have no greater efficacy than single-dose cisplatin [65]; the standard arm did not include BEP chemotherapy, the current standard of care for first-line treatment of poor-risk disease; and a significant proportion of patients in the high-dose arm did not complete HDCT. It is therefore felt that this trial did not adequately address the issue of first-line HDCT in poor-risk GCT.

The German Testicular Cancer Study Group developed a sequential high-dose VIP regimen composed of three to four cycles of conventional-dose cisplatin plus dose-escalated etoposide and ifosfamide followed by ASCT. In a Phase I/II trial treating 221 patients with IGCCCG poor-risk disease, PFS and disease-specific survival were 68 and 73%, respectively, at 5 years, with limited severe toxicity [57]. This Phase I/II trial demonstrated that high-dose VIP was tolerable, achieved more responses than historical controls with conventional-dose therapy, and could be administered at multiple centers [57]. Based on these results, a randomized Phase III trial (EORTC 30974) for patients with poor-risk GCT was designed in Europe to compare standard BEP versus one cycle of standard VIP plus three cycles of high-dose VIP (etoposide 1500 mg/m$^2$, ifosfamide 12 g/m$^2$ and cisplatin100 mg/m$^2$) with ASCT. This study closed prematurely due to slow accrual, and instead of the 222 patients estimated necessary to adequately prove superiority, only 137 patients were enrolled and treated. Preliminary data was reported at the 2010 ASCO meeting. With 4.4 year median follow-up, neither the 2-year FFS nor the 2-year OS differed significantly between the two treatment arms [63].

The largest randomized Phase III trial (n = 219) to evaluate the benefit of HDCT and autologous stem cell support in the first-line setting was published in the year 2007 [64]. This was a multi-institutional intergroup study (MSKCC, Southwestern Oncology Group, Eastern Cooperative Oncology Group, and Cancer and Leukemia Group B) comparing standard BEP × four to two cycles of BEP, followed by two sequential cycles of high-dose CECy (carboplatin 1800 mg/m$^2$, etoposide 1800 mg/m$^2$ and cyclophosphamide 200 mg/kg), each supported by autologous stem cell reinfusion. Similar to previous reports, accrual to this trial was challenging, and even with modification of the eligibility criteria to include intermediate-risk patients, this study did not reach its target accrual of 270 patients. No significant differences were observed between the two arms in the rate of CR, 2-year durable DFS or 2-year OS. In addition, toxicity was worse in the HDCT arm [64]. Secondary analysis in this study prospectively validated the prognostic significance of the rate of tumor marker decline following the initial two cycles of BEP, an adverse feature that these authors had used for patient selection in two prior Phase II trials [54,55]. In this Phase III study, patients with appropriate marker decline had a significantly longer survival and time to treatment failure compared with patients with an unsatisfactory rate of decline. The 1-year

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durable CR proportion for the 70 unsatisfactory decline patients was significantly higher with HDCT than with BEP (61 vs 34%; p = 0.03); however, 2-year OS only showed a trend towards better outcome (78 vs 55%; p = 0.1). Given the modest sample size of patients in this specific subgroup, these findings are not sufficiently robust to draw definite conclusions for clinical practice.

Scandinavian investigators have also examined the utility of using marker decline to help guide treatment selection in the first-line setting. Results of a multicenter protocol conducted by the Swedish Norwegian Testicular Cancer Group (SWENOTECA) were presented at the 2009 ASCO meeting [66]. Investigators treated 602 patients with metastatic NSGCT. Treatment was individually adjusted according to AFP and β-HCG decline (satisfactory decline defined as half-life for AFP ≤7 days and/or β-HCG ≤3 days), and patients with unsatisfactory response after two courses of standard BEP received intensified treatment with addition of ifosfamide. If marker decline remained unsatisfactory, treatment was further escalated to HDCT with stem cell rescue. A total of 19% of patients were intensified in the first step and 6% in the second step. In a preliminary analysis, the results were encouraging with 5-year PFS of 89.5, 85.4 and 64.9% for IGCCCG good-, intermediate- and poor-risk groups, respectively. The lack of significant difference between the good- and intermediate-risk group suggests that intermediate-risk patients may specifically benefit from this approach.

In the light of the overall disappointing Phase III data, there is currently no role for the routine incorporation of HDCT into the first-line treatment of patients with GCT. Further studies are ongoing testing new regimens; however, until adequately powered randomized Phase III trials demonstrate a superior outcome, the standard of care for intermediate- and poor-risk GCT remains four cycles of BEP chemotherapy.

## Reducing toxicity of high-dose regimens

Major advances that have helped reduce toxicity of high-dose regimens include the routine use of growth factor support as well as the use of peripheral blood stem cells (PBSCs) *in lieu* of autologous BM rescue. Again, randomized studies in hematologic malignancies had proven the efficacy of using recombinant granulocyte colony-stimulating factor (G-CSF) and granulocyte– macrophage colony-stimulating factor (GM-CSF) to accelerate leukocyte recovery after HDCT with autologous BM rescue [67–71], a concept that could easily be applied to HDCT in GCT.

A randomized study conducted by European investigators in the early 1990s assigned 47 patients to receive either PBSCs or autologous BM rescue following HDCT in the salvages setting. Rescue using PBSCs resulted in a significantly shorter recovery time of neutrophil and platelet counts, as well as fewer days to transfusion independence for both red blood cells and platelets. OS and event-free survival were no different in the two groups [37,72]. The use of G-CSF has been integral to the ability to collect stem cells from the peripheral blood; other growth factors have been evaluated for the purpose of stem cell mobilization in patients with inadequate response to G-CSF.

General improvements in supportive care and antibiotics have also diminished the toxicity associated with HDCT, and with all of the measures mentioned earlier, treatment-related mortality has been improved from >20% to now less than 3% [33,41,73]. Authors have recommended avoiding aminoglycosides when treating neutropenic fever after high-dose carboplatin to minimize otic toxicity [41,74]. Finally, the timing of HDCT in the salvage setting, that is, the amount of prior chemotherapy, has significance for tolerability and rate complications, as outlined earlier.

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## Managing progression after HDCT

There is no current standard of care for the treatment of patients with relapsed/refractory disease following HDCT, and it is well recognized that such patient currently have no curative treatment options. The exception to this rule is salvage surgery, which is seldom considered in carefully selected patients, and in these rare cases can achieve long-term remission.

## Expert commentary

In line with the data summarized in this article, we use HDCT in the salvage setting for carefully selected patients, recognizing that it is always administered with curative intent and that it can help achieve long-term remissions even in patients whose disease might not be cured with CDCT. That said, HDCT comes at the price of added toxicity, and the important challenge lies in selecting those patients that would fail to achieve a cure with CDCT. At MSKCC we use a risk-stratified approach at the time of initial relapse following cisplatin-based first-line therapy, based on the success observed with the conventional dose TIP regimen (paclitaxel, ifosfamide and cisplatin) in patients with favorable prognostic features for CDCT [8]. Accordingly, patients with gonadal or RP primary site, who have achieved a confirmed CR (any duration) or a marker-negative PR lasting >6 months prior to their first relapse, go on to receive CDCT, usually with TIP. Patients with incomplete response to first-line cisplatin-based therapy, primary platinum refractory disease, or who relapse 6 months or less after achieving a marker-negative PR, are usually considered for salvage HDCT with TI-CE (paclitaxel and ifosfamide every 14 days × two cycles followed by three cycles of high-dose carboplatin plus etoposide with stem cell support). For patients treated with CDCT in the initial salvage setting, HDCT remains an option in the third-line setting, should subsequent relapses occur. As outlined in this article, the degree of toxicity expected with HDCT is proportional to the amount of prior treatment. In accordance with the data summarized in this article, we do not use HDCT in the first-line treatment of advanced GCT, even in patients with primary mediastinal NSGCT or other poor prognostic features.

An area of controversy is the management of patients with primary mediastinal GCT or of those with late relapse, defined as recurrence of disease 2 years or longer following CR to cisplatin-based therapy. Both are known to predict for poor outcome, having led some investigators to exclude such patients from HDCT trials. As mentioned earlier, we have seen long-term responders within a small cohort of these groups when treated with TI-CE HDCT in the salvage setting and thus continue to study HDCT for these poor-risk patients.

Patients with teratoma with malignant transformation typically are not candidates for HDCT. Surgical resection is a key element in their management, if the disease is locally confined. If transformation is limited to a single cell type, tailored chemotherapy directed to that cell type may be effective [75].

For carboplatin, a key agent in virtually all high-dose programs currently in use, investigators have employed different approaches to dose calculation. Rather than dosage per body surface area, we prefer administering carboplatin according to the target AUC measured in ([mg per ml] × min) using the Calvert formula [76] (dose [mg] = target AUC × [glomerular filtration rate +25]). In prior studies, we have compared several methods of estimating renal clearance, and have found that the Jelliffe method [77] resulted in the highest correlation between target and measured AUC for carboplatin dosing [41].

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## Five-year view

In the upcoming years, we expect further efforts to establish a universal prognostic model for initial salvage therapy independent of treatment intensity, building on the efforts presented recently by the International Prognostic Factor Study Group [48]. With these tools at hand, investigators will be able to stratify patients in future studies, both for CDCT and HDCT, similar to the classification scheme developed by the IGCCCG for first-line therapies in advanced GCT [5]. While the Phase III study by Pico and colleagues failed to demonstrate the benefit to escalating initial salvage therapy with a single cycle of HDCT [42], an unanswered question remained: whether tandem or triplet HDCT improves outcome in the initial salvage setting. Only a large randomized trial would be appropriate to address this question.

Last, a number of novel agents, mostly targeted therapies, are currently under investigation in early clinical trials for patients with advanced GCT. Although unclear at this time, it is hoped that some of these might emerge as effective treatment options in the salvage setting, and that such agents might eventually be incorporated into high-dose chemotherapy programs.

### Key issues

- High-dose chemotherapy (HDCT) is potentially curative in second- and third-line therapy for patients with advanced germ cell tumor.
- Standard HDCT regimens include high-dose carboplatin and etoposide with or without additional agents, such as cyclophosphamide, ifosfamide and paclitaxel.
- Sequential therapy with two to three cycles is felt to be superior to single cycles of HDCT.
- Patients who are unlikely to achieve durable disease-free survival salvage chemotherapy with conventional-dose chemotherapy (CDCT) should be considered for first-line salvage with high-dose therapy.
- Currently, there is no role for HDCT in the first-line treatment of patients with germ cell tumor, as several Phase III trials have failed to confirm the benefit of such an approach over CDCT.
- Through routine use of peripheral blood stem cell transplantation and growth factor support, as well as improvements in supportive care, treatment-related mortality for HDCT has been greatly reduced and is reported as less than 3% in recent trials.
- Future trials investigating therapy in the initial salvage setting – whether to use CDCT or HDCT – should use the seven variable prognostic score developed by the International Prognostic Factors Study Group to stratify patients.
- Patients with refractory or relapsed disease despite treatment on high-dose protocols are generally considered to have incurable disease.

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**Table 1**

Selected Phase II trials for high-dose chemotherapy in the salvage setting.

| Study (year) | Regimen | high-dose part | Cycles of HDCT (n; patients receiving full %) | Patients (n) | Patient selection criteria | CR (%) | Other efficacy end points | Ref. |
|---|---|---|---|---|---|---|---|---|
| Broun *et al.* (1992) | HD CE × 2 (Phase I/II) | Carboplatin (900–2000 mg/m$^2$)<br>Etoposide (1200 mg/m$^2$)<br>Ifosfamide (10 g/m$^2$) in three patients | 2 (65) | 40 | Recurrence after second-line, or refractory to first-line cisplatin-based chemotherapy | 30 | CR: ≥2 years: 15% | [27] |
| Siegert *et al.* (1994) | PEI × 2, then HD CEI × 1 (Phase I/II) | Carboplatin (1500–2000 mg/m$^2$)<br>Etoposide (1200–2400 mg/m$^2$)<br>Ifosfamide (10 g/m$^2$) | 1 (92) | 68 | Recurrence after ≥1 cycle cisplatin-based chemotherapy, or IR to first-line | 51 | CR: ≥1 year: 19%<br>2-year OS (%): 44% | [28] |
| Motzer *et al.* (1996) | HD CECy × 2 (Phase I/II) | Carboplatin (1500 mg/m$^2$)<br>Etoposide (1200 mg/m$^2$)<br>Cyclophosphamide (60–150 mg/kg) | 2 (47) | 58 | IR to first-line cisplatin-based chemotherapy or IR to/relapse after cisplatin-based salvage | 40 | 2-year OS: 31% | [29] |
| Rick *et al.* (2001) | TIP × 3, ± T × 1, followed by HD CETh × 1 | Carboplatin (1500 mg/m$^2$)<br>Etoposide (2400 mg/m$^2$)<br>Thiotepa (450–750 mg/m$^2$) | 1 (78) | 80 | Relapse or progression after cisplatin-based chemotherapy | 45 | 3-year OS: 30%<br>3-year EFS: 25% | [30] |
| Feldman *et al.* (2010) | TI × 2, followed by HD CE × 3 | Carboplatin (AUC 24)<br>Etoposide (1200 mg/m$^2$) | 3 (77) | 107 | Recurrence after ≥1 cycle cisplatin-based chemotherapy, and one of the following: extragonadal primary, or IR to first-line, or prior CDCT salvage | 50 | 5-year DFS: 47%<br>5-year OS: 52% | [31] |

In all trials, high-dose therapy was followed by autologous stem cell rescue.

ASCT: Autologous stem cell transplantation; CR: Complete remission; DFS: Disease-free survival; HD CE: High-dose carboplatin/etoposide; HD CECy: High-dose carboplatin/etoposide/cyclophosphamide; HD CEI: High-dose carboplatin/etoposide/ifosfamide; HD CETh: High-dose carboplatin/etoposide/thiotepa; IR: Incomplete response; OS: Overall survival; PEI: Cisplatin/etoposide/ifosfamide; TI: Paclitaxel/ifosfamide; TIP: Paclitaxel/ifosfamide/cisplatin.

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**Table 2**

Phase III trials of high-dose chemotherapy in the salvage setting.

| Study (year) | Patient selection criteria | Regimen | Patients (n) | CR (%) | Median follow-up (months) | Other efficacy end points | Ref. |
|---|---|---|---|---|---|---|---|
| Pico *et al.* (2005) | First relapse after CR or PR with first-line cisplatin-based chemotherapy (100% first-line salvage) Primary cisplatin-refractory patients excluded | Arm A: PEI/VeIP × 4<br>Arm B: PEI/VeIP × 3, HD PECy × 1<br>**HD regimen:** HD PECy<br>carboplatin (200–550 mg/m$^2$)<br>etoposide (1800 mg/m$^2$)<br>cyclophosphamide (200 mg/kg) | Arm A: 128<br>Arm B: 135 | Arm A: 42<br>Arm B: 43<br>p = 0.71 | 45 | 3-year EFS:<br>Arm A: 35<br>Arm B: 42<br>p = 0.16<br>3-year DFS: for patients with CR:<br>Arm A: 55<br>Arm B: 75<br>p < 0.04 | [42] |
| Lorch *et al.* (2007) | Relapsed or refractory disease after ≥1 cycle of cisplatin-based chemo (86% first-line salvage) Late relapses (>2 years post-cisplatin) and PMGCT excluded | Arm A: VIP × 1, followed by HD CE × 3<br>Arm B: VIP × 3, followed by HD CEC × 1<br>**HD regimen Arm A:** HD CE<br>carboplatin (1500 mg/m$^2$)<br>etoposide (1500 mg/m$^2$)<br>**HD regimen Arm B:** HD CECy<br>carboplatin (2200 mg/m$^2$)<br>etoposide (1800 mg/m$^2$)<br>cyclophosphamide (6400 mg/m$^2$) | Arm A: 108<br>Arm B: 103 | Arm A: 47<br>Arm B: 45<br>Nonsignificant | 36 | 3-year EFS:<br>Arm A: 34<br>Arm B: 31<br>p = 0.44<br>3-year PFS:<br>Arm A: 47<br>Arm B: 45<br>p = 0.44<br>3-year OS:<br>Arm A: 48<br>Arm B: 46<br>p = 0.19 Study stopped prematurely for excess toxicity in Arm B | [43] |

In all trials, high-dose therapy was followed by autologous stem cell rescue.

CE: Carboplatin/etoposide; CECy: Carboplatin/etoposide/cyclophosphamide; CR: Complete response; DFS: Disease-free survival; EFS: Event-free survival; HD: High dose; PECy: Parboplatin/etoposide/cyclophosphamide; PEI: Cisplatin/etoposide/ifosfamide; PFS: Progression-free survival; PMGCT: Primary mediastinal germ cell tumor; PR: Partial response; VeIP: Vinblastine/ifosfamide/cisplatin; VIP: Etoposide/ifosfamide cisplatin.

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## Table 3

Prognostic models: Beyer score.

| **Factors** | | **Points** | | |
|---|---|---|---|---|
| Progressive disease before | | 1 | | |
| Progression ≤4 weeks after cisplatin | | 1 | | |
| No response to initial cisplatin therapy | | 1 | | |
| Mediastinal NSGCT | | 2 | | |
| Serum hCG level ≥1000 IU/l | | 2 | | |
| Stratification | Points | CR/PR | 2-year FFS (%) | 2-year OS (%) |
| Low risk | 0 | 77 | 51 | 61 |
| Intermediate risk | 1–2 | 59 | 27 | 34 |
| High risk | 3 or more | 22 | 5 | 8 |

All comparisons statistically significant with $p \leq 0.001$.

CR: Complete response; FFS: Failure-free survival; hCG: Human chorionic gonadotropin; NSGCT: Nonseminomatous germ cell tumor; OS: Overall survival; PR: Partial response.

Data taken from [37].

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## Table 4

Prognostic models: Einhorn score.

| Factors | Points | |
|---|---|---|
| Third-line or subsequent chemotherapy | 3 | |
| Progression ≤4 weeks after cisplatin | 2 | |
| IGCCCG high-risk stage | 2 | |
| Stratification | Points | |
| Low risk | 0 | DFS differs between three groups per log-rank test ($p < 0.05$) |
| Intermediate risk | 2–3 | |
| High risk | 4–7 | |

DFS: Disease-free survival; IGCCCG: International Germ Cell Cancer Collaborative Group.

Data taken from [33].

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## Table 5

Prognostic models: international prognostic factor study group score.

| Factors | | Points | |
|---|---|---|---|
| Primary site | Gonadal | 0 | |
| | Retroperitoneal | 1 | |
| | Mediastinal (NSGCT) | 3 | |
| Response to first-line therapy | CR/PR− | 0 | |
| | PR+/SD | 1 | |
| | PD | 2 | |
| Progression-free interval after first-line therapy | >3 months | 0 | |
| | ≤3months | 1 | |
| Serum hCG level | ≤1000 IU/l | 0 | |
| | >1000 IU/l | 1 | |
| Serum AFP level | Normal | 0 | |
| | ≤1000 ng/ml | 1 | |
| | >1000 ng/ml | 2 | |
| Liver, bone or brain metastases | Absent | 0 | |
| | Present | 1 | |
| *Add points for preliminary score (0–10); regroup into category score: (0): 0; (1–2): 1; (3–4): 2; (5 or more): 3 Add histology points as below to category score to determine final risk category* | | | |
| Histology | Seminoma | −1 | |
| | NSGCT/mixed | 0 | |
| Stratification | Points | 2-year PFS (%) | 3-year OS (%) |
| Very low risk | −1 | 75 | 77 |
| Low risk | 0 | 51 | 66 |
| Intermediate risk | 1 | 40 | 58 |
| High risk | 2 | 26 | 27 |
| Very high risk | 3 | 6 | 6 |

AFP: α-feto protein; CR: Complete response; DFS: Disease-free survival; FFS: Failure-free survival; hCG: Human chorionic gonadotropin; NSGCT: Nonseminomatous germ cell tumor; OS: Overall survival; PD: Progression of disease; PFS: Progression-free survival; PR−: Partial response with negative markers; PR+: Partial response with positive markers; SD: Stable disease.

Data taken from [48].

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**Table 6**

Phase III trials first-line high-dose chemotherapy.

| Study (year) | Patient selection criteria | Regimen | Patients (n) | CR (%) | Median follow-up (years) | Other efficacy end points (%) | Ref. |
|---|---|---|---|---|---|---|---|
| Droz *et al*. (2007) | Any IGCCCG risk category NSGCT. Any primary site other than ovarian. No prior treatment | Arm A: 4 × pVeB90V<br>Arm B: 2 × PVeB60V, 3 × HD PECy<br>**HD regimen:** HD PECy<br>Cisplatin (200 mg/m$^2$)<br>Etoposide (1750 mg/m$^2$)<br>Cyclophosphamide (6400 mg/m$^2$) | Arm A: 57<br>Arm B: 57 | Arm A: 56<br>Arm B: 42<br>p = 0.099 | 9.7 | 5-year CR:<br>Arm A: 75<br>Arm B: 61 | [62] |
| Daugaard *et al.* (2010) | IGCCCG poor risk GCT. No prior treatment | Arm A: 4 × BEP<br>Arm B: 1 × VIP, 3 × HD VIP<br>**HD regimen:** HD VIP<br>Etoposide (1500 mg/m$^2$)<br>Ifosfamide (12 g/m$^2$)<br>Cisplatin (100 mg/m$^2$) | Arm A: 66<br>Arm B: 65 | Arm A: 30<br>Arm B: 43<br>p = 0.18 | 4.4 | 2-year FFS:<br>Arm A: 45<br>Arm B: 58<br>p = 0.06<br>2 year OS:<br>Arm A: 66<br>Arm B: 73<br>p > 0.05 | [63] |
| Motzer *et al.* (2007) | IGCCCG intermediate and poor risk GCT. Any primary site. No prior treatment | Arm A: 4 × BEP<br>Arm B: 2 × BEP, 2 × HD CECy<br>**HD regimen:** HD CECy<br>Carboplatin (1800 mg/m$^2$)<br>Etoposide (1800 mg/m$^2$)<br>Cyclophosphamide (200 mg/kg) | Arm A: 111<br>Arm B: 108 | Arm A: 55<br>Arm B: 56<br>p = 0.89 4.3 | 4.3 | 1-year OS:<br>Arm A: 48<br>Arm B: 52<br>p = 0.53<br>TTF (months):<br>Arm A: 11.3<br>Arm B: 23.2<br>p = 0.4 | [64] |

In all trials, high-dose therapy was followed by autologous stem cell rescue.

BEP: Bleomycin/etoposide/cisplatin; CR: Complete response; FFS: Failure-free survival; GCT: Germ cell tumor; HD: High-dose; HD CECy: High-dose carboplatin/etoposide/cyclophosphamide; HD PECy: High-dose cisplatin/etoposide/cyclophosphamide; HD VIP: High-dose etoposide/ifosfamide/cisplatin; IGCCCG: International Germ Cell Cancer Collaborative Group; NSGCT: Nonseminomatous germ cell tumor; pVeBV: Cisplatin/vinblastine/bleomycin/etoposide; TTF: Time to treatment failure; VIP: Etoposide/ifosfamide/cisplatin.