Intensified chemotherapy with stem-cell rescue in germ-cell tumors

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Received 21 December 2010; revised 21 March 2011; revised 3 July 2011; accepted 13 July 2011

Background: Based on the high chemosensitivity of germ-cell tumors (GCTs), the concept of high-dose chemotherapy (HDCT) has been developed and investigated through many clinical trials. It has been carried out in different clinical settings, ranging from resistant or absolute refractory disease to chemosensitive relapse. HDCT with stem-cell support has also been explored as a part of first-line strategy for poor-prognosis patients.

Patients and methods: Our review summarized results from clinical trials evaluating the role of HDCT in patients with advanced GCTs. So far available data were obtained through a Medline search of English-language literature.

Results: Several phase II trials and retrospective series have shown a possible benefit for GCT patients with recurrent disease as well as in first-line setting. Despite these results, data derived from randomized phase III studies failed to demonstrate any survival advantage for HDCT over conventional chemotherapy.

Conclusions: The role of HDCT in GCTs remains controversial. We need new prospective studies based on prognostic factors with multiple transplants of carboplatin and etoposide as the preferred high dose regimen. At present, based mainly on retrospective and phase II studies, HDCT may represent a therapeutic option for patients with primary refractory disease or for those with a second or further relapse.

Key words: autologous stem-cell transplantation, germ-cell tumors, high-dose chemotherapy

introduction

Germ-cell tumors (GCTs) are neoplasms accounting for only 1% of male cancers but are the most common solid tumor type in men between the ages of 20 and 35 years [1]. Thanks to the development of effective cisplatin-based chemotherapy (CT), disseminated GCTs have become a model of a highly curable malignant disease with an overall cure rate approaching 80% [2, 3]. However, 20%–30% of patients with advanced disease do not achieve a durable remission after first-line CT, with only a proportion being cured with a standard salvage CT regimen [4, 5].

Early trials of high-dose chemotherapy (HDCT) with autologous stem-cell transplantation (ASCT) based on encouraging laboratory and clinical indicators were first introduced in the late 1970s and suggested that this approach might favorably affect the course of chemosensitive malignancies [6]. The replacement of autologous bone marrow support by peripheral-blood progenitor cell transplantation [7] along with the use of hematopoietic growth factor resulted in reduced morbidity and mortality, a shortened hospitalization, reduced costs [8, 9], and allowed a more widespread use of this procedure outside specialized and academic centers [10].

Because of the extremely high chemosensitivity of GCTs, the concept of HDCT in this disease has been rapidly developed worldwide and intensively investigated. Clinical trials have been carried out in a variety of settings, ranging from resistant or absolute refractory disease to chemosensitive relapse. The role of dose intensification with stem-cell support has also been explored as a part of first-line strategy for patients at higher risk of recurrence.

This paper, reviewing the available data so far, will try to define the current status and the future perspectives of HDCT in patients with advanced GCTs. For simplicity, we have divided the existing literature into three categories: HDCT given (i) up front as first-line treatment option for poor-risk patients, (ii) as second line for recurrent/refractory disease, and (iii) for patients with the poorest prognosis (including those that receive HDCT as third or subsequent line, those with absolute refractory disease, and those with primary mediastinal location).

HDCT given within first-line treatment programs for poor-risk patients

In 1997, the International Germ Cell Cancer Cooperative Group (IGCCCG) provided a prognostic classification for advanced GCT patients, at the time of their diagnosis [11]. The 5-year survival rate of patients in the poor-prognosis group with standard-dose CT and surgery, when indicated, is ~50%, which

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doi:10.1093/annonc/mdr403
makes the development of novel treatment options of pivotal importance. Early studies of HDCT with ASCT published by investigators from the Memorial Sloan-Kettering Cancer Center [12, 13] suggested that poor-risk patients, selected for a high likelihood of failure by predicted markers of half-life, had both a significantly improved overall survival (OS) and event-free survival (EFS) compared with historical controls.

In 1999, Bokemeyer et al. [14] published the results of a multivariate and matched-pair analysis, comparing the outcome of 147 consecutive poor-prognosis patients treated with first-line sequential high-dose (HD) etoposide, ifosfamide, and cisplatin (VIP) versus 309 patients treated with conventional-dose CT. Two-year progression-free survival (PFS) and OS were significantly prolonged in the HDCT group (\(P = 0.0056\) and \(P = 0.0184\), respectively).

A few years later, the German Testicular Cancer Study Group (GTCSG) reported on a large multicenter phase II/I study with multicyle stepwise VIP dose escalation in 221 patients with either Indiana ‘advanced disease’ (\(n = 39\)) [15] or IGCCCG ‘poor prognosis’ criteria (\(n = 182\)) [11]. After a median follow-up of 4 years, PFS and disease-specific survival rates were 68% and 73%, respectively, which compare favorably with historical controls [16]. This intense-dose approach resulted associated with high but acceptable acute toxicity without long-term sequelae.

More recently, based both on laboratory studies suggesting synergy of paclitaxel and ifosfamide against cisplatin-resistant teratocarcinoma cell lines [17] and clinical studies reporting high response with the use of paclitaxel in cisplatin-resistant patients [18, 19], the GTCSG conducted a multicenter study investigating the addition of escalating doses of paclitaxel to the HD-VIP regimen in patients with poor-prognosis GCTs [20]. In addition to demonstrating that paclitaxel up to dose of 225 mg/m² can be safely added to HD-VIP, authors reported both a high response rate (79%) and a favorable 5-year PFS and OS outcome (64.1% and 75.2%, respectively).

The only randomized phase III trial so far published has been reported by Motzer et al. [21] on 219 previously untreated GCT patients with intermediate- or poor-prognosis features, who were randomly assigned up front either to four cycles of standard bleomycin, etoposide, and cisplatin (BEP) or to two cycles of BEP followed by a tandem transplant with HD-carboplatin, etoposide, and cyclophosphamide (CEC). OS and PFS did not differ significantly in the two arms. Among 67 patients with unsatisfactory marker decline, the 1-year durable complete remission (CR) proportion was significantly better in the HDCT arm (61% versus 34%; \(P = 0.03\)), suggesting that early-CT resistance, as detected by slow marker decline, may be overcome by late dose intensification.

Di Nicola et al. [22] reported the results of the Italian, multicenter, randomized phase III trial, comparing four cycles of BEP versus two cycles of BEP followed by a sequence of HD-cyclophosphamide (7 g/m²), HD-VIP16 (2.4 g/m²), and HD-carboplatin (AUC 25) with ASCT as first-line treatment of poor-prognosis patients. The target sample was not reached and the trial was stopped after enrolling 89 patients over a 10-year period. No differences in 2-year PFS and OS were seen among the two treatment groups. At the 2010 American Society of Clinical Oncology (ASCO) annual meeting, the European intergroup presented the final data of a phase III trial comparing one cycle of standard-dose VIP followed by three cycles of HD-VIP with four cycles of standard BEP in poor-prognosis GCT patients [23]. The study, designed to show a 15% improvement in 1-year failure-free survival (FFS), closed prematurely in June 2007 with 137 patients enrolled due to slow accrual. At 1 year, the FFS rate was 48% in the conventional arm and 66.1% in the HDCT arm (\(P = 0.035\)). Two-year FFS (44.8% versus 58.2%), CR rates (33.3% versus 44.6%), and OS were not statistically different in the two arms (\(P = 0.060\), \(P = 0.18\), and \(P > 0.1\), respectively).

Data from relevant studies of HDCT given within first-line treatment programs are reported in Table 1.

### HDCT as second-line treatment of recurrent/refractory disease

Among the 20%–30% of patients who fail to achieve a durable CR after first-line cisplatin-based CT, ~25% may be cured by standard salvage regimens as VIP or cisplatin, vinblastine, and ifosfamide (VeIP), with or without subsequent surgery [4, 5]. While the use of paclitaxel along with ifosfamide and cisplatin (TIP) in a selected patient population appeared to yield better results [24], the prognosis of such patients remains poor and most of them will eventually die of their disease.

Over the last three decades, HDCT with ASCT has been utilized as a salvage treatment option potentially able to overcome resistance to conventional CT. Earlier use of HDCT in heavily pretreated and multiple-relapsed patients was supported by bone marrow infusion. Reported long-term survival rates ranged through 15% to 25% with formidable acute toxicity and with ~10% of treatment-related deaths [25–30]. Toxicity has been subsequently reduced by the use of peripheral blood instead of bone marrow as the source of stem cells, together with treating patients earlier in their clinical course.

In 1996, Beyer et al. [31], through a multivariate analysis of 283 patients, produced a prognostic index for GCT patients receiving salvage HDCT; patients were stratified into good-, intermediate-, and poor-risk categories on the basis of a cumulative score scale. Independent adverse variables for FFS after HDCT were identified to be nonseminomatous mediastinal primary site, progressive disease before HDCT, refractory or absolute refractory disease to standard-dose cisplatin, and high serum levels of β-human chorionic gonadotropin. Predicted FFS rate at 2 years was 51%, 27%, and 5% in the good-, intermediate- and poor-risk categories, respectively (\(P < 0.001\)). The increased risk for treatment failure was due to both a significantly lower rate of favorable responses and a significantly higher rate of relapses. Other variables, including the type of HDCT regimen, the maximal response durations to the conventional-dose treatment, number of salvage regimens used, or minimal marker elevations before HDCT, were found to have no prognostic significance for disease-free survival (DFS). One of the relevant conclusions of the study was that all patients of the poor-prognosis category progressed immediately after HDCT and had no benefit from the dose-intensive strategy. This scoring system, however, was based on data from patients who were treated from 1984 to 1993, most having received a single course of HDCT.
Table 1. Studies of first-line HDCT for poor-prognosis GCTs

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of trial</th>
<th>No. of patients</th>
<th>Definition of poor prognosis</th>
<th>Treatment</th>
<th>OS (%)</th>
<th>PFS (%)</th>
<th>mFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motzer et al. [12]</td>
<td>Prospective, phase II</td>
<td>28</td>
<td>MSKCC</td>
<td>VAB-6 × 2 + HD-CE × 2</td>
<td>57</td>
<td>46</td>
<td>31 months</td>
</tr>
<tr>
<td>IGCCCG [11]</td>
<td>Retrospective</td>
<td>832</td>
<td>IGCCCG</td>
<td>Various HDCT regimens</td>
<td>48 (at 5 years)</td>
<td>67</td>
<td>5 years</td>
</tr>
<tr>
<td>Motzer et al. [13]</td>
<td>Prospective, phase II</td>
<td>30</td>
<td>IGCCCG</td>
<td>MSKCC</td>
<td>41 (at 5 years)</td>
<td>50</td>
<td>30 months</td>
</tr>
<tr>
<td>Bokemeyer et al. [14]</td>
<td>Retrospective, comparative</td>
<td>147 (HDCT) versus 309 (SDCT)</td>
<td>Indiana University or IGCCCG</td>
<td>VIP + HD-VIP × 3–4 versus BEP × 4 or VIP × 4</td>
<td>64 (at 5 years)</td>
<td>72 versus 72 (at 2 years), P = 0.0184</td>
<td>33 months</td>
</tr>
<tr>
<td>Schmoll et al. [16]</td>
<td>Prospective, phase I/II</td>
<td>221</td>
<td>Indiana University or IGCCCG</td>
<td>VIP + HD-VIP × 3–4</td>
<td>73 (at 5 years)</td>
<td>68 (at 5 years)</td>
<td>4 years</td>
</tr>
<tr>
<td>Hartmann et al. [20]</td>
<td>Prospective, phase I/II</td>
<td>52</td>
<td>IGCCCG</td>
<td>VIP + T-HD-VIP</td>
<td>75 (at 5 years)</td>
<td>64 (at 5 years)</td>
<td>41 months</td>
</tr>
<tr>
<td>Motzer et al. [21]</td>
<td>Prospective, phase III</td>
<td>111 (SDCT) versus 108 (HDCT)</td>
<td>IGCCCG</td>
<td>BEP × 4 versus BEP × 2 + HD-CE × 2</td>
<td>72 versus 71 (at 2 years)</td>
<td>57 versus 60 (at 2 years)</td>
<td>51 months</td>
</tr>
<tr>
<td>Di Nicola et al. [22]</td>
<td>Prospective, phase III</td>
<td>46 (SDCT) versus 43 (HDCT)</td>
<td>IGCCCG</td>
<td>BEP × 4 versus BEP × 2 + HD-carboplatin</td>
<td>66.8 versus 60.5 (at 2 years)</td>
<td>58.5 versus 55.8 (at 2 years)</td>
<td>33.5 months</td>
</tr>
<tr>
<td>Daugaard et al. [23]</td>
<td>Prospective, phase III</td>
<td>66 (SDCT) versus 65 (HDCT)</td>
<td>IGCCCG</td>
<td>BEP × 4 versus VIP + 3 HD-VIP</td>
<td>83 versus 86.1 (at 2 years)</td>
<td>48 versus 66.8 (at 1 year), P = 0.035</td>
<td>NR</td>
</tr>
</tbody>
</table>

Unless specified, OS and PFS rates refer to mFU.
*Analysis of response and survival was limited to the 182 patients with IGCCCG ‘poor prognosis’ criteria.
*Data referred to relapse-free survival rates.

BEP, bleomycin, etoposide, and cisplatin; GCTs, germ-cell tumors; IGCCCG, International Germ Cell Cancer Collaborative Group; HD, high dose; HD-CE, high-dose carboplatin and etoposide; HD-CEC, high-dose carboplatin, etoposide, and cyclophosphamide; HDCT, high-dose chemotherapy; HD-VIP, high-dose etoposide, ifosfamide, and cisplatin; mFU, median follow-up; MSKCC, Memorial Sloan-Kettering Cancer Center; NR, not reported; OS, overall survival; PFS, progression-free survival; SDCT, standard-dose chemotherapy; T, Taxol; VAB, actinomycin D, vinblastine, cyclophosphamide, bleomycin and cisplatin; VIP, etoposide, ifosfamide, and cisplatin.

The GTCSG explored a treatment strategy combining intensive conventional-dose salvage CT with TIP followed by a single shot of HD-carboplatin, etoposide, and thiopeta. Among the 62 patients that completed the whole program, 41 (66%) responded whereas 20 (32%) had stable disease (n = 3) or tumor progression (n = 17). The projected OS and EFS rates at 3 years were 30% and 25%, respectively [32]. There were no long-term survivors in the poor-prognosis group.

After the ‘single-shot’ period, several investigators embarked on trials with double (‘tandem’) or multiple transplants [19], following the Norton–Simon model [41].

Bhatia et al. [33] obtained a 57% relapse-free survival (RFS) at 39 months in a series of 65 patients treated in first relapse by one or two cycles of VeIP followed by two cycles HD-CE. The response to first-line therapy and the disease status after HDCT predicted long-term survival. Similarly, Rodenhuis et al. [34] reported a RFS of 54% at 37 months in a population of 35 previously complete responder patients treated by conventional induction and two courses of HD-carboplatin, thiopeta, and cyclophosphamide.

In 2002, Beyer et al. [35] carried out a retrospective matched-pair analysis comparing HDCT with conventional-dose CT as first-salvage treatment in 193 patients with relapsed or refractory nonseminomatous GCTs. HDCT was administered as intensification of first-salvage treatment. Patients were matched based on primary tumor location, response to the first-line treatment, duration of this response, and serum levels of tumor markers. The results suggested a potential benefit from HDCT approach, with an estimated absolute improvement in 2-year EFS and OS from 6% to 12% and from 9% to 11%, respectively.

In 2007, Einhorn et al. [36] retrospectively reviewed a large single-institution series of patients who had received tandem HD-CE after progressing to first-line cisplatin-based CT. Patients with primary mediastinal location and those experiencing late relapse were excluded from this analysis. A two-drug regimen was employed due to concerns that using a third agent would result in dose reduction of the two most active drugs, carboplatin (2100 mg/m²) and etoposide (2250 mg/m³). Among the 135 patients that received HDCT as second-line treatment, this study reported an impressive 70% 4-year DFS. One may argue that results are biased by patient selection. This does not seem to be the case as patients with very poor prognosis, including 50% with high-risk stage by IGCCCG classification and 45% with platinum refractory disease, were long-term disease-free survivors. It is important to note that all patients in this series received enriched CD34+ peripheral-blood progenitors as the source of stem cells, which
allowed a rapid engraftment, thereby permitting the administration of two courses of high-dose CE at a 3-week interval with acceptable toxicity. In addition, enriching for CD34+ peripheral-blood progenitors may have eliminated cancer cells present in the graft. The source of stem cells and their *in vivo* manipulation, along with 6 months of oral etoposide (given for unclear reasons), may have contributed to the positive results of the study, although at present there are no evidence-based data to support this hypothesis. Recently, Feldman et al. [37] reported on a prospective phase II trial investigating the efficacy of two cycles of paclitaxel–ifosfamide followed by three cycles of HD-CE in 107 GCT patients predicted to have a poor outcome with conventional-dose salvage therapy. Most of these patients were platinum refractory and were given HDCT as first-salvage treatment; 21 had mediastinal primary tumors and 26 had received two or more CT lines before HDCT. With a median follow-up of 61 months, the 5-year OS and DFS rates were 52% and 47%, respectively, all progressions occurring within 2 years. Excluding patients with primary mediastinal nonseminomatous germ-cell tumors (PMNSGCTs) or late relapses, survival rates improved to 62% and 57%, respectively, similar to the outcomes reported by Einhorn et al. [36]. The authors applied the Beyer [31] and the Einhorn [36] models to their series finding that both effectively stratified patients into good- and poor-risk groups. A significant percentage of patients within the worst Beyer (23%) and Einhorn (40%) risk categories achieved long-term remission suggesting that there may exist a subset of poor-risk patients for whom HDCT should not be completely disregarded.

The only phase III trial in this setting available to date, the EBMT-IT-94, randomly assigned 280 patients who had relapsed after a prior CR, had an incomplete remission or had failed to normalize levels of tumor markers by first-line therapy to receive three courses of conventional-dose VIP (or VelP) plus single course of HD-CEC versus four conventional cycles [38]. Similar complete and partial response rates were observed in the two treatment arms and no significant differences were observed in EFS and OS at 3 years. The major weakness of this trial, designed in the early 90s, is the use of a single course of HDCT including cyclophosphamide, which would not be currently considered as standard intensification strategy. Moreover, the study design required an unrealistic improvement of EFS in the HDCT arm. However, it is worth noting that a post hoc subgroup analysis showed that for patients who were complete responders after two cycles of conventional CT, HDCT provided a significant improvement in DFS.

Finally, in an effort to establish the most appropriate mode of administration of HDCT as salvage treatment of relapsed/refractory GCTs, Lorch et al. [39] conducted a prospective multicenter phase II trial comparing directly a single versus sequential HDCT approach. Two hundred and sixteen patients were randomly assigned to receive one cycle of conventional VIP followed by three cycles of HD-CE (arm A) or three cycles of conventional VIP followed by a single cycle of HD-CEC (arm B). Unexpectedly, recruitment was closed early due to excessive treatment-related mortality in the single HDCT arm. For this reason, no definitive conclusions can be drawn as for the efficacy of the two approaches and sequential treatment at submaximal doses of the most established drugs, carboplatin and etoposide, might be a safer strategy to deliver HDCT in pretreated patients. At the 2011 ASCO annual meeting were presented the survival results of this trial 6 years after randomization of the last patient and sequential HDCT was superior to single HDCT with respect to long-term OS [5-year OS is 49% [95% confidence interval (CI) 40% to 59%] in arm A and 39% [95% CI 30% to 49%] in arm B (95% CI 0.99–2.05, P = 0.057)] [40].

Data from relevant studies of HDCT given as second-line treatment programs are reported in Table 2.

Very recently, Lorch et al. have conducted a large international retrospective analysis (1984 patients) [42] aimed at developing a prognostic model applicable to clinical practice in GCT patients who experienced treatment failure with cisplatin-based first-line CT (Tables 3 and 4). The authors found large differences in PFS and OS ranging from >70% in the best prognostic category to slightly >10% in the most unfavorable one. When comparing the results of conventional-dose CT and HDCT, they found a significant PFS and OS advantage of HDCT in all risk groups except for OS in the low-risk category [43]. This new prognostic model will help to shape prospective efforts, i.e. the proposed TIGER study [44], in optimizing the treatment of refractory and/or relapsed GCT as well as assisting clinical treatment decisions in this highly complex patient population.

**HDCT for patients with the poorest outcome**

Patients with absolute platinum-refractory disease (defined by patients who progress despite cisplatin-based CT), those in whom second or subsequent CT lines failed and those with primary mediastinal location at diagnosis have the worse prognosis. Available data on the use of HDCT in these subgroups are sparse.

For absolute refractory patients and for those in whom a second standard CT attempt failed, the optimal salvage treatment remains controversial [45]. Although high response rates to HDCT have been reported, several authors consider that this approach is unlikely to offer a real chance of cure. The French Genito-Urinary Tract Tumors Group conducted a study combining two courses of epirubicin–paclitaxel followed by three courses of HDCT with stem-cell support (thiotepa–cyclophosphamide in the first course and ifosfamide–carboplatin–etoposide in the other two) [46]. Among 45 patients enrolled, 22 completed the whole treatment, 25 died of progressive disease, and 5 (11%) due to toxicity; the overall response rate was 37.7%. The median OS was 11.8 months, while the 3-year OS rate (equal to PFS) was 23.5%. No relapses occurred after 1.5 years from HDCT. In a retrospective series of 80 patients with at least one poor-prognosis feature, who received salvage HDCT from 1988 to 2001, Vaena et al. [47] reported a median OS of 14.7 months and a 2-year PFS of 32% with no relapses occurring 2 years after HDCT.

A novel sequential dose-intensive approach based on dose-dense paclitaxel–ifosfamide followed by three cycles of HD-CE has been successfully employed in a very poor-prognosis setting [18]. Patients were selected if they had tumor progression after conventional CT together with unfavorable prognostic features or relapse/incomplete response to ifosfamide–cisplatin salvage.
Table 2. Studies of HDCT as second line for recurrent/refractory disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>OS (%)</th>
<th>PFS (%)</th>
<th>mFU (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodenhuis et al. [34]</td>
<td>Prospective, phase II</td>
<td>35</td>
<td>Conventional induction chemotherapy followed by two cycles of HD-CTC</td>
<td>Not reported</td>
<td>54</td>
<td>37</td>
</tr>
<tr>
<td>Bhatia et al. [33]</td>
<td>Prospective, phase II</td>
<td>65</td>
<td>One to two cycles of conventional VeIP followed by two cycles of HD-CE</td>
<td>Not reported</td>
<td>57</td>
<td>39</td>
</tr>
<tr>
<td>Motzer et al. 2000 [19]</td>
<td>Prospective, phase II</td>
<td>37</td>
<td>Two cycles of TI followed by three cycles of HD-CE</td>
<td>54</td>
<td>49</td>
<td>31</td>
</tr>
<tr>
<td>Rick et al. 2001 [32]</td>
<td>Prospective, phase II</td>
<td>62</td>
<td>Three cycles of standard TIP followed by one cycle of HD-CET</td>
<td>30 (at 3 years)</td>
<td>25 (at 3 years)</td>
<td>36</td>
</tr>
<tr>
<td>Pico et al. [38]</td>
<td>Prospective, randomized, phase III</td>
<td>128 (SDCT) versus 135 (HDCT)</td>
<td>Four cycles of conventional VeIP or VIP versus three cycles of conventional VeIP or VIP followed by one cycle of HD-CE</td>
<td>53 versus 53 (at 3 years)</td>
<td>35 versus 42 (at 3 years)</td>
<td>45</td>
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<tr>
<td>Einhorn et al. [36]</td>
<td>Retrospective</td>
<td>135</td>
<td>Two cycles of HD-CE VIP + three cycles HD-CE versus three cycles of VIP + one cycle of HD-CE</td>
<td>Not reported</td>
<td>70</td>
<td>48</td>
</tr>
<tr>
<td>Lorch et al. [40]</td>
<td>Prospective, randomized, phase II</td>
<td>111 (sequential HDCT) versus 105 (single HDCT)</td>
<td>Two cycles of HD-CE VIP versus three cycles of HD-CE</td>
<td>Not reported</td>
<td>47 versus 45 (at 5 years)</td>
<td>49 versus 39 (at 5 years), ( P = 0.057 )</td>
</tr>
<tr>
<td>Feldman et al. [37]</td>
<td>Prospective, phase I–II</td>
<td>107</td>
<td>Two cycles of TI followed by three cycles of HD-CE</td>
<td>52 (at 5 years)</td>
<td>48 (at 5 years)</td>
<td>61</td>
</tr>
</tbody>
</table>

Unless specified, OS and PFS rates refer to mFU.
HD-CE, high-dose carboplatin and etoposide; HD-CEC, high-dose carboplatin, etoposide, and cyclophosphamide; HD-CET, high-dose carboplatin, etoposide, and thiopeta; HDCT, high-dose chemotherapy; HD-CTC, high-dose carboplatin, thiopeta, and cyclophosphamide; mFU, median follow-up; OS, overall survival; PFS, progression-free survival; SDCT, standard-dose chemotherapy; TI, paclitaxel and ifosfamide; TIP, paclitaxel, ifosfamide, and cisplatin; VeIP, vinblastine, ifosfamide, and cisplatin; VIP, etoposide, ifosfamide, and cisplatin.

Table 3. IGCCCG-2 Lorch–Beyer prognostic score for first-line salvage treatment—score construction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
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<td>0</td>
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Histology  
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<th>Seminoma</th>
<th>Nonseminoma</th>
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<tr>
<td>Primary site</td>
<td>Retropertoneal</td>
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<tr>
<td>Response</td>
<td>CR/PRm−</td>
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<tr>
<td>PFI</td>
<td>&gt;3 months</td>
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<td>AFP salvage</td>
<td>Normal</td>
</tr>
<tr>
<td>HCG salvage</td>
<td>&lt;1000</td>
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<tr>
<td>LBB</td>
<td>No</td>
</tr>
</tbody>
</table>

AFP, alpha-fetoprotein; CR, complete response; HCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group; LBB, liver, bone, brain; PD, Progressive disease; PFI, progression-free interval; PRm+, partial response with positive markers; PRm−, partial response with negative markers; SD, stable disease.

CT. Among 47 assessable patients, nearly half obtained CR and six were rendered disease free following subsequent surgery leading to an overall CR rate of 55%. At median follow-up of >3 years, 51% are alive without disease.

In the previously mentioned Indiana experience [36], 49 patients received two consecutive courses of HD-CE as third or subsequent line of CT. The authors reported a remarkable 50% 4-year DFS in this specific subgroup of patients.

Lorch et al. [48] retrospectively evaluated the outcome of 49 patients who underwent HDCT as second-salvage treatment. The overall rate of favorable responses (CR with or without surgery and partial response with negative markers) was 55%; progression occurred in 36 patients (74%), while 9 (18%) are disease free at 4 years.

Extranodal germ-cell tumors (EGCTs) account for 2%–5% of all GCTs [49]. With conventional cisplatin-based CT, long-term survival rates of retropertoneal GCTs approach those of patients with advanced metastatic gonadal GCTs [50], while PMNSGCTs have the poorest outcome with 5-year OS ranging from 40% to 45%. Indeed, the presence of mediastinal location defines per se a poor-prognosis category according to the IGCCCG classification [11]. This clinically and biologically distinct disease entity is associated with lower CR rates to CT, high rates of relapse and disappointing results from salvage CT. Nevertheless, current standard first-line treatment of patients with mediastinal primary location is still four cycles of BEP, as for all IGCCCG poor-prognosis patients [3].

Among studies that investigated the role of HDCT for poor-prognosis patients, PMNSGCTs usually represent a small subpopulation that is rarely discussed or evaluated separately.

In 2003, Bokemeyer et al. [51] reported a subgroup analysis of 28 patients with PMNSGCTs, within the previously mentioned German multicenter trial [16], who were treated up front with HD-VIP. These patients showed 2-year PFS and OS rates of 64% and 68%, respectively, which compared favorably.
with historical controls of the International Extragonadal Germ Cell Tumor Study Group. According to this retrospective comparison, the authors suggested that HDCT may produce a 15%–20% absolute improvement in survival.

Rosti et al. [52] presented the European Bone Marrow Transplantation (EBMT) experience on 22 patients with poor-prognosis EGCTs who received as first-line therapy one to four courses of HDCT after induction therapy. Among 11 patients with PMNSGCTs, 7 (64%) were disease free, although the data referred only to patients with responsive disease after induction therapy.

Banna et al. [53] evaluated the feasibility and activity of a single course of HD-CEC after conventional induction CT in 21 patients with PMNSGCT. Thirteen patients were not treated with HDCT mainly due to PD and poor physical condition, while eight who underwent HDCT (followed by residual surgery in four cases) were reported disease free with a median follow-up of 52 months.

In a retrospective study of 142 patients with relapsed extragonadal nonseminomatous germ-cell tumors (EGNSGCTs) treated with second-line HDCT at 11 European

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<th>Table 4. IGCCCG-2 Lorch–Beyer prognostic score for first-line salvage treatment—PFS and OS estimates for all patients according to prognostic score</th>
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<tr>
<td>Score</td>
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<tr>
<td>Very low (score −1)</td>
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<tr>
<td>Low (score 0)</td>
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<tr>
<td>Intermediate (score 1)</td>
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<tr>
<td>High (score 2)</td>
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<td>Very high (score 3)</td>
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CI, confidence interval; HR, hazard ratio; IGCCCG, International Germ Cell Cancer Collaborative Group; OS, overall survival; PFS, progression-free survival.

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<th>Table 5. Studies of HDCT for patients with the poorest outcome (absolute refractory, third line, and further, mediastinal GCTs)</th>
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<td>Lotz et al. [46]</td>
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<td>Hartmann et al. [54]</td>
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<td>De Giorgi et al. [55]</td>
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</table>

Unless specified, OS and PFS rates refer to mFU.

*Survival data referred only to primary mediastinal GCTs treated with HDCT.

BEP, bleomycin, etoposide, and cisplatin; CyT, cyclophosphamide and thiotepa; EGCTs, extragonadal germ-cell tumors; EGNSGCTs, extragonadal nonseminomatous germ-cell tumors; ET, etoposide and paclitaxel; GCTs, germ-cell tumors; HD-CE, high-dose carboplatin and etoposide; HD-CEC, high-dose carboplatin, etoposide, and cyclophosphamide; HDCT, high-dose chemotherapy; HD-VIP, high-dose etoposide, ifosfamide, and cisplatin; ICE, ifosfamide, carboplatin, and etoposide; mFU, median follow-up; NR, not reported; OS, overall survival; PFS, progression-free survival; PMNSGCTs, primary mediastinal nonseminomatous germ-cell tumors; SD-VIP, standard-dose etoposide, ifosfamide, and cisplatin; TI, paclitaxel and ifosfamide; VIP, etoposide, ifosfamide, and cisplatin.
and American centers from 1975 to 1996, those with primary retroperitoneal tumors achieved a long-term survival rate of 30%, whereas those with mediastinal primary had salvage rates of <10% [54].

Similar results come out by the analysis of the EBMT data regarding HDCT as second-line treatment of patients with EGNSGCTs [55]. The 3-year OS for patients with retroperitoneal primary tumors (n = 37) and with PMNSGCTs (n = 22) were 48% and 14%, respectively.

Data from relevant studies of HDCT for patients with the poorest outcome are reported in Table 5.

conclusions

The role of HDCT in GCTs remains controversial mainly due to the heterogeneity of patient population and treatment approaches, the lack of well-defined prognostic variables, and the limited number of randomized trials conducted.

HDCT cannot be proposed for poor-risk patients, neither as frontline therapy nor as consolidation, in patients achieving CR by conventional CT. The two randomized studies conducted in this patient population [21, 23] failed to demonstrate an OS benefit. Albeit supported by limited data, first-line ‘consolidation’ HDCT may be considered in selected patients with chemosensitive primary mediastinal disease [51, 52].

Intensified treatments have been more widely investigated as a salvage therapy for patients with an incomplete response to initial CT and for those with relapsed GCTs. Despite the robust data from the Indiana group and from other retrospective/phase II studies, the role of HDCT as second-line treatment of relapsed GCTs remains today uncertain. Also in view of the recent data produced by Lorch et al. [43], the most pressing issues in GCT treatment are defining standards of HDCT and optimizing outcomes of salvage treatment. The proposed TIGER study, comparing four cycles of conventional-dose TIP versus paclitaxel–ifosfamide followed by multiple HD-CE as first-line salvage treatment in refractory/relapsed GCT patients, goes in this direction.

HDCT is a treatment option for patients that are (primary) refractory to platinum-based CT or for those with a second or further relapse. Multiple intensified cycles with carboplatin–etoposide [18, 36] is recommended as the standard HD treatment also due to concerns that using a three-drug regimen would require dose reductions of the two most active drugs in this setting.

A potential limitation in the use of HDCT in previously treated patients, especially when multiple cycles are planned, is the reduced capacity to collect an adequate number of peripheral-blood stem cells (PBSCs). Indeed, the transfusion of a large number of PBSCs allows a faster hematopoietic recovery, thus limiting the risk of infection and bleeding, and permits the safe administration of repeated cycles of HDCT [9]. Mobilization with disease-specific CT plus granulocyte colony-stimulating factor (G-CSF), rather than G-CSF alone, is particularly recommended in these patients since the greater efficacy of mobilization is combined with the antitumor effect of the drug. When, despite this measure, the collection of PBSCs is poor, either the recently developed inhibitor of the CXCR4 chemokine receptor plerixafor (if available) [56] or the collection of bone marrow cells could be considered.

In conclusion, HDCT with ASCT is a therapeutic option for selected patients with advanced GCT. Issues that remain unresolved include optimum timing of therapy, the number of high-dose cycles, and patient selection on the basis of prognostic characteristics. Patients should be treated wherever possible in experienced centers and should be entered into multicenter randomized trials.

disclosure

The authors declare no conflict of interest.

references


44. Pedrazzoli P, De Giorgi U, Bregni M. High-dose chemotherapy (HDCT) and autologous stem cell transplantation in relapsed germ cell tumors: do we need a randomized study? Bone Marrow Transplant 2010; 45 (Suppl 2): S30.


