High dose chemotherapy with autologous hematopoietic stem cell support for solid tumors other than breast cancer in adults

On behalf of the European Group for Blood and Marrow Transplantation (EBMT) Solid Tumors Working Party

1Falck Division of Medical Oncology, Ospedale Niguarda Ca’ Granda, Milano, Italy; 2Department of Oncology, UCL, London, UK; 3Hôpital Tenon, Department of Clinical Oncology, Paris France; 4Centre Pluridisciplinaire d’Oncologie, Lausanne, Switzerland; 5Division of Medical Oncology, University of Turin, IRCC Candiolo, Turin, Italy; 6Medical Oncology, Ospedale Santa Maria delle Croci, Rovenna, Italy; 7EBMT Central Office, University College London Hospitals, London, UK; 8Ankara University Medical School, Ibn Sina Hospital Dept. of Hematology, Ankara, Turkey

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Since the early 1980s high dose chemotherapy with autologous hematopoietic stem cell support was adopted by many oncologists as a potentially curative option for solid tumors, supported by a strong rationale from laboratory studies and apparently convincing results of early phase II studies. As a result, the number and size of randomized trials comparing this approach with conventional chemotherapy initiated (and often abandoned before completion) to prove or disprove its value was largely insufficient. In fact, with the possible exception of breast carcinoma, the benefit of a greater escalation of dose of chemotherapy with stem cell support in solid tumors is still unsettled and many oncologists believe that this approach should cease. In this article, we critically review and comment on the data from studies of high dose chemotherapy so far reported in adult patients with small cell lung cancer, ovarian cancer, germ cell tumors and sarcomas.

Key words: high dose chemotherapy, solid tumors, stem cell transplantation

introduction

Autologous hematopoietic stem cell transplantation (AHCT) allows the administration of chemotherapy (CT) with a several-fold increase in the drug dose. The goal is to achieve a higher tumor cell kill than possible with standard-dose CT with the aim of improving long-term disease free (DFS) and overall survival (OS). Early trials of high dose chemotherapy (HDC) with stem cell support, based on favorable laboratory and clinical indicators [1] were initiated in the early 1980s and suggested that this approach might favorably affect the course of chemosensitive solid tumors. The replacement of autologous bone marrow (BM) support by peripheral blood progenitor cell (PBPC) transplantation [2] resulted in reduced morbidity and mortality, a shortened hospitalization, reduced costs [3, 4], and allowed a more widespread use of this procedure outside specialized and academic centers.

However, with the exception of breast carcinoma (BC) [5], very few randomized trials have been conducted in solid tumors. Fluctuations in the enthusiasm for this procedure [6] have been due to many reasons, including the positive expectations created by early trials, the toxicity of the procedure and the availability of new drugs for clinical trials. As a result only a minority of the 4450 transplants for adult patients with small cell lung cancer (SCLC), ovarian cancer (OC), germ cell tumors (GCT) and sarcomas registered at the European Group for Blood and Marrow Transplantation (EBMT) were performed within prospective controlled trials. In this article, we review and comment on the data from studies of HDC so far reported in these diseases.

small cell lung cancer (SCLC)

SCLC is a very chemosensitive tumor, although the prognosis is poor. Since the 1970s there have been many attempts to improve its outcome by increasing the intensity of CT. Over the years, it has become clear that doses of CT that induce myelosuppression are of greater benefit to patients and a further increase in dose-intensity supported by hematopoietic growth factors, could improve the outcome further [7–9].

The possibility of using hematopoietic stem cells to increase the dose of chemotherapeutic agents further led to the development of phase II studies. Initiated in the early 1980s, when BM was the source of stem cells, they demonstrated that
HDC was feasible and that there was a high complete response (CR) rate, even in patients with relapsed or refractory disease [10]. Most of these studies were designed as a ‘late intensification’ strategy, where only responding patients were treated, and often using multiple sequential high-dose cycles of CT [11–17] (Table 1). Elias et al. reported impressive results in 36 patients with limited disease (LD) [18]. All had responded to previous standard CT and 29 were in complete remission (CR). They received high-dose cyclophosphamide, cisplatin and carmustine, followed by chest and prophylactic cranial radiotherapy. At 5 years, 41% of the patients were still alive. Fletcher et al. reported a 56% 4-year survival rate among 30 patients with LD treated with high-dose ifosfamide, carboplatin, etoposide (ICE) given after two cycles of conventional dose CT [19]. Kiura et al. reported a 61% and 55% CR and 3-year survival rate in 18 patients with LD who received three cycles of conventional CT followed by high-dose ICE [20]. One randomized trial suggested an improvement in median survival among patients with LD (14 versus 19 months). However, this difference was not significant; the sample size was small and the toxic death rate was 18% [21].

The group from Manchester has pioneered the technique of whole blood collection as a source of PBPC to support the administration of multi-cyclic dose-dense CT [22]. Preliminary results of a randomized study comparing the standard 4-weekly to a 2-weekly ICE regimen with whole blood support in 318 SCLC patients of which 87% had LD did not show a survival benefit [23]. A smaller randomized trial from a single German institution enrolled 70 patients, almost all with LD, to receive either standard ICE every 4 weeks or every 2 weeks with stem cell support [24]. The response rate (RR) was improved in the dose-dense arm (49% versus 37%), leading to a significant advantage of overall survival (OS) at 2 years (54% versus 34%). Compared to the British study, these better results might be due to factors such patient selection (performance status, disease extension) and improved standardized administration of CT, radiotherapy and follow-up in a single institution compared with a multi-institution study.

An EBMT study, including 69 (30 with LD) tested the ‘upfront’ strategy in which three cycles of high-dose ICE were administered at 4 week intervals in previously untreated patients [25, 26]. Seventy-two percent of patients completed the treatment. The CR rates were 70% and 36% in patient with limited and extensive disease, respectively. At 2 years, 32% of the patients with LD and 5% of the ones with extensive disease were alive. A high rate of tumor cell contamination could be demonstrated not only in BM but also in the leukapheresis products from SCLC patients using immunohistochemistry or RT-PCR techniques [27]. This might have contributed to tumor recurrence. For this reason, in the ongoing EBMT randomized HDC trial (Random-ICE), two cycles of standard CT are given before HDC to produce in vivo purging of circulating tumor cells before stem cell collection.

So far, in the absence of large randomized trials, the benefit of HDC by escalation of the dose of CT, i.e. by multiple HDC cycles given sequentially with AHSCT, is still unsettled in SCLC.

### Ovarian Carcinoma (OC)

The majority of patients with OC present with advanced disease and there has been little change in the OS over the last 20 years. Surgery and CT are the main treatments for stage III/IV disease. Although around 75% of patients respond to CT, the expected 5-year survival is about 30% [28] due to frequent relapses as a result of the emergence of drug-resistant disease.

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**Table 1.** Studies of intensified chemotherapy in small cell lung cancer: reports of at least 20 patients were considered

<table>
<thead>
<tr>
<th>Investigator year [Ref.]</th>
<th>Number of patients</th>
<th>Stage LD/ED</th>
<th>Intensification strategy</th>
<th>High-dose regimen (no. of cycles)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall response rate %</td>
<td>2 year survival %</td>
</tr>
<tr>
<td>Banham et al. 1982 [11]</td>
<td>20</td>
<td>9/11</td>
<td>Late</td>
<td>Cy (1)</td>
<td>100</td>
</tr>
<tr>
<td>Smith et al. 1985 [12]</td>
<td>36</td>
<td>29/7</td>
<td>Late</td>
<td>Cy (1)</td>
<td>91</td>
</tr>
<tr>
<td>Cunningham et al. 1985 [13]</td>
<td>22</td>
<td>16/6</td>
<td>Late</td>
<td>Cy-VP16 (1)</td>
<td>73</td>
</tr>
<tr>
<td>Spitzer et al. 1986 [14]</td>
<td>32</td>
<td>32/0</td>
<td>Late</td>
<td>Cy-VP16-MTX (1)</td>
<td>100</td>
</tr>
<tr>
<td>Humblet et al. 1987 [15]</td>
<td>23</td>
<td>16/7</td>
<td>Late</td>
<td>Cy-VP16-BNU (1)</td>
<td>69</td>
</tr>
<tr>
<td>Souhami et al. 1989 [16]</td>
<td>25</td>
<td>21/4</td>
<td>Early</td>
<td>Cy (1)</td>
<td>84</td>
</tr>
<tr>
<td>Souhami et al. 1989 [16]</td>
<td>26</td>
<td>26/0</td>
<td>Early</td>
<td>Cy-VP16 (2)</td>
<td>88</td>
</tr>
<tr>
<td>Pettengell et al. 1995 [17]</td>
<td>25</td>
<td>20/5</td>
<td>Early</td>
<td>Ifo-Ch-VP16 (6)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100</td>
</tr>
<tr>
<td>Elias et al. 1999 [18]</td>
<td>36</td>
<td>36/0</td>
<td>Late</td>
<td>Cy-BNCU-P (1)</td>
<td>100</td>
</tr>
<tr>
<td>Fetscher et al. 1999 [19]</td>
<td>30</td>
<td>19/11</td>
<td>Late</td>
<td>Ifo-Ch-VP16 (2)</td>
<td>97</td>
</tr>
<tr>
<td>Leyvraz et al. 1999 [20]</td>
<td>69</td>
<td>30/39</td>
<td>Early</td>
<td>Ifo-Ch-VP16 (3)</td>
<td>86</td>
</tr>
<tr>
<td>Woll et al. 2001 [22]</td>
<td>25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17/8</td>
<td>Early</td>
<td>Ifo-Ch-VP16 (6)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>80</td>
</tr>
<tr>
<td>Kiura et al. 2003 [20]</td>
<td>18</td>
<td>14/4</td>
<td>Late</td>
<td>Ifo-Ch-VP16 (1)</td>
<td>94</td>
</tr>
<tr>
<td>Buchholz et al. 2003 [24]</td>
<td>35</td>
<td>32/3</td>
<td>Early</td>
<td>Ifo-Ch-VP16 (6)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100</td>
</tr>
<tr>
<td>Lorigan et al. 2005 [23]</td>
<td>159&lt;sup&gt;a&lt;/sup&gt;</td>
<td>136/22</td>
<td>Early</td>
<td>Ifo-Ch-VP16 (6)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>81</td>
</tr>
</tbody>
</table>

LD, limited disease; ED, extensive disease; NR, not reported; Cy, cyclophosphamide; VP16, etoposide; Ch, carboplatin; Ifo, ifosfamide, MTX, methotrexate; P, cisplatin; BNU, carmustine.

<sup>a</sup> Patients in the high dose/dose-dense arm of randomized study.

<sup>b</sup> Conventional chemotherapy given in a dose-dense manner (q 2 weeks) with stem cell support.
A retrospective analysis of randomized trials by Levin et al. [29] demonstrated that dose-intensification has a statistically significant effect on response rate and survival in patients with advanced disease. This association was mainly shown for cisplatin, especially if administered in combination with other drugs. However, prospective randomized trials of increased dose intensity have failed to demonstrate a benefit in survival [30]. Significant toxicity was noted in practically all 'double dose' studies, to the extent that it was not possible to deliver the intended dose to all patients.

Very high doses of alkylating drugs such as melphalan or carboplatin, supported by autologous BM or PBPC have been used to treat OC for two decades. Early reports of HDC in OC were in patients with refractory or relapsed disease. These studies have shown that the overall RR can be very favorable, but the duration of the response is short. There have been a substantial number of non-randomized phase I/II studies most commonly using high-dose melphalan, cyclophosphamide, thiotepa and carboplatin [31]. Studies were often in a heterogeneous patient population and too small to draw firm conclusions. More recently Stiff et al. analyzed their single center experience in 100 patients with relapsed or persistent disease treated with various high-dose regimens [32]. The median OS times were 9.6 and 23.1 months for patients with platinum-resistant and sensitive disease, respectively, leading to the now widely accepted conclusion that platinum sensitivity and tumor bulk are the two most important predictors of survival following HDC in relapsed OC. Patient age was an additional prognostic factor for survival. Furthermore, the outcome of patients who were not in remission at the time of HDC was poor. The median survival was 14 months post treatment.

Even fewer patients have been given HDC in the first-line setting. The largest non-randomized study was published by Legros and colleagues [33] who observed a 5-year OS rate of 59.9% from the time of diagnosis. However, disease-free survival (DFS) was only 23.6%. Interestingly, 38 out of a total of 53 who were treated for relapse responded to second-line cisplatin CT, with a reported median survival of 17.3 months. Only three women went on to have a second high-dose procedure.

Further information on the activity of HDC in OC comes from the analysis of transplant registries. Between 1991 and 2002 OC represented 3% of reported AHSCT in Europe (845 transplants). Although these numbers are small compared with the total reported AHSCT during the same period (27,902 transplants in solid tumours in Europe), retrospective analysis has clearly demonstrated that the survival of OC patients is significantly better if they are treated with consolidation HDC whilst the disease is chemosensitive [34]. Patients treated with bulky residual disease or in resistant relapse do less well. Furthermore, remission was longer if patients were transplanted in first rather than in second remission.

The encouraging results from the registry data strongly supported the need for randomized phase III clinical trials. The French GINEECO group has compared high-dose carboplatin and cyclophosphamide with PBPC support with three cycles of conventional doses of these drugs following as initial induction course of platinum-based CT and surgical debulking. Early results suggested a significant improvement in DFS but the trial results failed to confirm an improvement in OS [35]. Late 1998 the EBMT launched a phase III study of multi-cycle HDC in optimally debulked, stage III or IV disease. The control arm consisted of six courses of standard dose platinum–paclitaxel. The intensified arm included two courses of cyclophosphamide and paclitaxel followed by three HD cycles; two of carboplatin, paclitaxel, and one course of carboplatin, paclitaxel, and melphalan. In 2002 this study was merged with a very similar trial, designed by the German Cancer Society. The new study (HIDOC-European Intergroup Study) has recently closed, prematurely due to slow recruitment over the last 2 years, after enrolling 149 patients, 72% of the required total. Significantly, HIDOC-EIS is the largest randomized trial in this patient population. Seventy-five patients completed all cycles of HDC and there was only one case of transplant-related death. The progression-free survival (PFS) was 21.7 months in the control group and 24.5 months after HDC, which was not statistically significant [36]. Similarly there was no significant survival benefit. Two other randomized trials, conducted by the Gynaecological Oncology Group and by a Finnish group closed early due to poor recruitment. The randomized trials were small and failed to demonstrate a significant benefit for HDC in OC. They do not exclude a small benefit for HDC but this could only be demonstrated if very large trials were performed. Currently, treatment of patients with HDC remains experimental and should be in the context of a clinical trial.

The results from the principal studies of HDC in OC are reported in Table 2 [37–39].

**germ cell tumors (GCT)**

Because GCT are the most chemo-sensitive tumors in adults, the concept of HDC has been rapidly developed worldwide and intensively investigated through a number of phase II studies. These have been performed in a variety of clinical situations, ranging from resistant or absolute refractory disease to chemosensitive relapse. The term refractory disease is applied to patients with at least stable disease or better followed by tumor progression within 4 weeks of the last cisplatin-containing CT. Absolute refractory disease is defined by the group who progress despite cisplatin-based CT. Principal studies on HDC with AHSCT for GCT are reported in Table 3.

**salvage therapy of refractory disease**

For patients who relapse or have an inadequate response after a conventional-dose salvage regimen, HDC is able to overcome resistance to conventional CT. In the early 1980s, HDC regimens contained etoposide and cyclophosphamide [40]. Carboplatin was used as ‘high-dose’ cisplatin did not improve survival and was far too toxic [41]. It was combined with etoposide and occasionally with ifosfamide [42]. The ICE regimen was subsequently proposed in tandem courses and earlier in the course of the disease [43, 44]. HDC has also been given as first-salvage treatment in platinum-sensitive patients with the purpose of increasing RR and survival [45]. However, despite the use of HDC, long-term remissions can only be expected in 10–40% of resistant patients, depending on risk factors, notably location of the primary tumor and degree of sensitivity to platinum compounds [46] (Table 4).
Sequential HDC using paclitaxel, ifosfamide, carboplatin, etoposide has been recently successfully used [47] in very poor-prognosis setting. Patients were selected if they had progressive tumor after conventional chemotherapy with unfavorable prognostic features (extra-gonadal primary site, incomplete response to first-line therapy), or relapse or incomplete response to ifosfamide/cisplatin conventional dose salvage. A high RR has been achieved with this sequential dose-intensive approach (56% CR rate) allowing 77% of the patients having a CR to be disease-free with a median follow-up of 33 months.

**salvage therapy of absolute refractory disease**

For absolute refractory patients the optimal salvage treatment remains controversial [48]. Despite high response rates to HDC, most authors consider that this approach is unable to offer a real chance of cure for these patients. To improve the results in this setting, the use of both old and new drugs have been explored. Epirubicin and paclitaxel have produced a RR of 50% in refractory diseases [49, 50] and their combination with G-CSF is able to mobilize peripheral blood stem cells [51]. Thiotepa and cyclophosphamide, which can be given in very high doses and are effective in GCT, have also been used [52]. In view of these data, the French Genito-Urinary Tract Tumors Study Group (GETUG) conducted an HDC study combining two courses of epirubicin and paclitaxel as front-line therapy, followed by three HDC cycles (thiotepa plus cyclophosphamide for the first one and high dose ICE for the second and the third courses) [53]. Among 45 previously treated patients enrolled, 22 completed the whole treatment, 25 died from PD and five (11%) for the first one and high dose ICE for the second and the third courses) [53]. Among 45 previously treated patients enrolled, 22 completed the whole treatment, 25 died from PD and five (11%) from toxic side effects. The overall RR was 37.7%, including 8.9% CR. The median OS was 11.8 months while the 3-year survival and PFS rates were 23.5%. No relapses have occurred after 1.5 years from HDC, as previously reported [54].

According to the Bayer score (Table 4), the 3-year PFS was 62%, 13% and 0% for patients graded 0, 1–2 and >2, respectively. These results confirm that highly refractory patients and particularly patients with resistant/refractory primary mediastinal GCTs, clearly do not benefit from HDC and should be treated in clinical trials with new drugs. Three others studies [55-57] have investigated the use of multiple paclitaxel-based salvage therapy showing a RFS at 30–40 months ranging from 34 to 41% (Table 3). Indeed, the use of paclitaxel in this setting seems promising, and moreover, paclitaxel can be given at higher doses, i.e. in combination with thiotepa [58].

### Table 2. Studies of high-dose chemotherapy in ovarian carcinoma

<table>
<thead>
<tr>
<th>Investigator year [Ref.]</th>
<th>Characteristics of patient/number</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mulder et al. 1989 [37]</td>
<td>Persistent after 2nd look laparotomy/11</td>
<td>Cy-VP16</td>
<td>Median OS = 23 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CR 6; median duration = 15 months</td>
</tr>
<tr>
<td>Viens et al. 1990 [38]</td>
<td>First-line consolidation/35</td>
<td>L-PAM</td>
<td>Projected survival = 47% at 4.5 years</td>
</tr>
</tbody>
</table>
| Benedetti-Panici et al. 1995 [39] | FIGO III-IV, previously untreated/20 | Induction: Cy-P; HDC: P-VP16-Cb | OR = 84% (CR 37%; PR 47%)
|                          |                                   |           | Estimated OS/PFS at 4 years = 62%/57% |
|                          |                                   |           | Median PFS = >24 months |
| Legros et al. 1997 [37]  | FIGO IIA-IV consolidation/53       | Melphalan or Cy-Cb | DFS at 5-years = 23.6% (median 30.4 months) |
| Stiff et al. 2000 [32]   | Relapsed (41% platinum resistant)/421 | Various | OS at 5-yrs = 59.9% (median 65.8 months) |
|                          |                                   |           | DFS at 2-yrs = 22%; OS at 2-yrs = 35% |
| Ledermann et al. 2001 [34]| Advanced or recurrent disease (90% FIGO III-IV) First line consolidation = 105; recurrent = 149 | Various (86% platinum-based) | DFS (1st remission) = 18 months |
| Cure et al. 2004 [35]    | FIGO III-IV, post SLO/110          | Cb-Cy versus Conventional maintenance | DFS of 2nd remission = 9 months |
|                          |                                   |           | OS (105 in 1st + 27 in 2nd remission) = 33 months |
|                          |                                   |           | OS (no remission) = 14 months |
| Ledermann et al. 2005 [36]| First-line optimally debulked     | Multi cycle HDC | DFS = 17.5 versus 12.2 months |
|                          |                                   | Cb-TXL-L-PAM vs Conventional CT | OS = 49.7 versus 42.5 months |
|                          |                                   |           | HDC versus conventional |

OS, overall survival; PFS, progression free survival; DFS, disease free survival; OR, overall response; CR, complete response; PR, partial response; Cb, carboplatin; T, thiotepa; Cy, cyclophosphamide; L-PAM, melphalan; P, cisplatin; TXL, paclitaxel; VP16, etoposide; Nov, mitoxantrone; HDC, high dose chemotherapy; TRM, transplant-related mortality.
In the 1990s several phase II studies explored the earlier administration of HDC as consolidation therapy. Bhatia et al. 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 vinblastine, ifosfamide, cisplatin (VeIP) followed by two of high dose carboplatin–etoposide [44]. Subsequent outcome after HDC was correlated with the response to first-line therapy, and the disease status after HDC predicted long-term survival. Similarly, Rodenhuis et al. reported a RFS of 54% at 37 months in a population of 35 previously complete responder patients treated by conventional induction and two high-dose regimens combining carboplatin, thiotepa and cyclophosphamide [51]. However, the first prospective randomized study (EBMT-IT-94) failed to demonstrate the superiority of a single course of high-dose carboplatin, etoposide and cyclophosphamide (CarboPEC), administered after three courses of conventional dose cisplatin, ifosfamide and etoposide (or vinblastine) over four such conventional cycles for patients with advanced GCT, who had relapsed after previous CR, or achieved an incomplete remission, or failed to have normal levels of tumor markers after first-line therapy [59]. However, complete responders in the CarboPEC arm had a significant improvement in disease free survival (DFS).

The survival rate of patients with metastatic disease fulfilling the ‘poor prognosis’ criteria of the International Germ Cell Cancer Collaborative Group [60] is still only 50 to 60% following conventional cisplatin-based CT. The German Testicular Cancer Study Group started a large multicenter phase I/II trial with stepwise dose escalation of high dose carboplatin–etoposide [44]. Subsequent outcome after HDC was correlated with the response to first-line therapy, and the disease status after HDC predicted long-term survival. Similarly, Rodenhuis et al. reported a RFS of 54% at 37 months in a population of 35 previously complete responder patients treated by conventional induction and two high-dose regimens combining carboplatin, thiotepa and cyclophosphamide [51]. However, the first prospective randomized study (EBMT-IT-94) failed to demonstrate the superiority of a single course of high-dose carboplatin, etoposide and cyclophosphamide (CarboPEC), administered after three courses of conventional dose cisplatin, ifosfamide and etoposide (or vinblastine) over four such conventional cycles for patients with advanced GCT, who had relapsed after previous CR, or achieved an incomplete remission, or failed to have normal levels of tumor markers after first-line therapy [59]. However, complete responders in the CarboPEC arm had a significant improvement in disease free survival (DFS).

### Table 4. (A) Prognostic index for patients with germ cell tumors undergoing high dose chemotherapy as salvage therapy and (B) treatment outcome according to prognostic categories [46]

#### A Independent adverse prognostic variables for disease-free survival after high dose chemotherapy (HDC) Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease before HDC</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal primary site</td>
<td>1</td>
</tr>
<tr>
<td>Refractory disease before HDC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Absolute refractory disease before HDC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>HCG before HDC &gt; 1.000 IU/L</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup>See text.

#### B Prognostic categories 2 years disease-free survival 2 years overall survival

<table>
<thead>
<tr>
<th>Category</th>
<th>2 years disease-free survival</th>
<th>2 years overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good (score 0)</td>
<td>51%</td>
<td>61%</td>
</tr>
<tr>
<td>Intermediate (score 1 and 2)</td>
<td>27%</td>
<td>34%</td>
</tr>
<tr>
<td>Poor (score 2)</td>
<td>5%</td>
<td>8%</td>
</tr>
</tbody>
</table>

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**high dose chemotherapy as consolidation therapy**

In the 1990s several phase II studies explored the earlier administration of HDC as consolidation therapy. Bhatia et al. 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 vinblastine, ifosfamide, cisplatin (VeIP) followed by two of high dose carboplatin–etoposide [44]. Subsequent outcome after HDC was correlated with the response to first-line therapy, and the disease status after HDC predicted long-term survival. Similarly, Rodenhuis et al. reported a RFS of 54% at 37 months in a population of 35 previously complete responder patients treated by conventional induction and two high-dose regimens combining carboplatin, thiotepa and cyclophosphamide [51]. However, the first prospective randomized study (EBMT-IT-94) failed to demonstrate the superiority of a single course of high-dose carboplatin, etoposide and cyclophosphamide (CarboPEC), administered after three courses of conventional dose cisplatin, ifosfamide and etoposide (or vinblastine) over four such conventional cycles for patients with advanced GCT, who had relapsed after previous CR, or achieved an incomplete remission, or failed to have normal levels of tumor markers after first-line therapy [59]. However, complete responders in the CarboPEC arm had a significant improvement in disease free survival (DFS).
first-line therapy with multiple cycles of high-dose etoposide, ifosfamide, and cisplatin plus AH SCT that enrolled 221 poor-prognosis patients [61]. In 70% of patients, the primary tumor was located in the testis, in 17% it was in the retroperitoneum, and 13% presented with a primary mediastinal tumor. After 4-year median follow-up, PFS and disease-specific survival rates were 69% and 79% at 2 years, and 68% and 73% at 5 years. This dose intense CT was associated with high but acceptable acute toxicity without long-term toxicities. Bokemeyer et al. [62] reported their experience of first-line sequential high-dose VIP chemotherapy for 28 patients with primary mediastinal nonseminomatous GCTs. They obtained a 2-year PFS and OS rates of 64% and 68%, respectively, and concluded that these results may indicate that this approach results in an approximately 15% survival improvement. Finally, Rosti et al. [63] reported in 2004 the EBMT experience on 22 patients with poor prognosis extragonadal GCTs who received HDC as first-line therapy. At a median follow-up of 50 months, 15 patients (68%) were disease-free.

In conclusion, several studies suggest that it would clearly make sense to concentrate the administration of high-dose salvage chemotherapy, as currently conceived, to those most likely to benefit from it [54, 61–66], i.e., based on the risk categories suggested by Beyer [46]. Furthermore, other forms of HDC consolidation treatment, the role of sequential HDC and the role of surgery for residual tumors after HDC [67] must be stressed in future trials. With this in mind, the Department of Medical Oncology of Tenon Hospital in Paris, on behalf of the Assistance Publique-Hôpitaux de Paris, have recently started the TAXIF-II protocol targeting poor-prognosis patients with sensitive relapse (excluding patients with a Beyer score ≥3), in which a higher dose of paclitaxel (360 mg/m²), combined with a higher dose of thiotepa (720 mg/m²), replaces cyclophosphamide in the first HD sequence. Also, the dose of ifosfamide is escalated to 12 g/m² during the second and the third high-dose sequences of the ICE regimen.

**sarcomas**

**soft tissue sarcomas**

The prognosis of patients with unresectable or advanced metastatic soft tissue sarcoma (STS) remains poor [68], with a median survival of about a year, and less than 10% of patients are alive at 5 years [69]. In general, dose-intensive regimens based on doxorubicin and ifosfamide have yielded higher response rates, prolonged the DFS but failed to show any OS advantage [70–72]. On the other hand, it has been shown that patients with a CR will have a longer survival and a small chance of cure [73]. These data, along with the dismal prognostic of STS, prompted different phase I and II trials during the 1990s in the attempt to improve outcome [74–83].

The results of the most relevant published studies on HDC are summarized in Table 5. From a methodological point of view, these data are closer to case reports than to formal phase I or II clinical trials. This is mainly due to the heterogeneity of both tumor subtypes and conditioning regimens used. In addition, there are striking differences in chemosensitivity and prognosis of pediatric and adult sarcomas. Therefore, it is difficult to draw evidence-based conclusions from these studies, but a few worthwhile comments can be made. HDC yielded an overall RR ranging from 20% to 65% with a CR from 10% to 43%. The best reported 5-year OS and PFS were 32% and 21%, respectively. Finally, it is evident that CT intensification has no value in chemoresistant or chemorefractory patients just as it is in other neoplastic diseases [75, 83].

The only possible conclusion is that the data derived so far are insufficient either to reject or support the clinical use of HDC in adult STS. A large French prospective randomized trial is ongoing to address this issue (J. Blay, pers. comm.). At this point HDC in chemosensitive adult STS is not recommended outside a clinical trial.

**rhabdomyosarcomas, Ewing family of tumors, osteosarcomas**

HDC has been used to treat small round-cell sarcomas and osteosarcoma, which in the vast majority of cases occur in the pediatric and young adult population. Although these histological subtypes have a better outcome, patients presenting with metastatic or unresectable tumors have a dismal prognosis. There is no clear evidence for the use of HDC in rhabdomyosarcomas [84] or osteosarcomas [85]. For the Ewing Family of Tumours (EFT) more data are available and deserve some comment. Meyers et al. [86] reported the use of HDC with melphalan and etoposide plus total body irradiation (TBI) in high-risk EFT. Among 32 eligible patients only 23 proceeded to HDC because of either progression or toxicity to standard therapies; three transplant-related deaths occurred (13%) and 24% of patients were disease free at 2 years. Burdach et al. [87] reported on 54 patients treated according to two different protocols of high dose melphalan-etoposide, one of which included TBI. The 2-year EFS ranged from 22 to 29%, but with considerably higher transplant-related deaths in patients receiving TBI (23% versus 4%).

Important information on the activity of HDC in EFT comes from the analysis of the EBMT registry [88]. The 5-year probability of surviving is significantly influenced by: transplant performed in 1st or 2nd CR, age younger than 16, or a busulfan-melphalan conditioning regimen. In contrast, TBI produced significantly worse results compared to busulfan-melphalan.

A considerable effort to define the role of HDC with AH SCT in EFT is currently being pursued in Europe and North America through multicenter prospective trials enrolling patients with chemosensitive, high-risk disease [89–91]. HDC has still to be considered an investigational treatment in small round-cell sarcomas and osteosarcoma and every effort should be made to treat these patients in prospective clinical trials.

**conclusion**

Over a 20-year period since the early 1980s HDC with AH SCT was adopted as a therapeutic option for solid tumors, only supported by a strong rationale from laboratory studies and apparently positive results of early non-randomized studies. As a result, the number and size of phase III trials comparing HDC with conventional CT initiated (and often abandoned before completion) to prove or disprove its value was largely
insufficient. In fact, after more than two decades of clinical research and thousands of patients receiving HDC, the benefit of a greater escalation of dose of CT with AHSCT in solid tumors, with the possible exception of BC [5], is still unsettled. For this reason many oncologists believe that this approach should cease [92]. However, such a conclusion could be just as premature and thoughtless as the uncritical use of HDC that was so common 10 years ago. It is important to note that: (i) the prognosis of solid tumors discussed in this article has changed very little in the past 25 years and it is still based on the use of old drugs such as doxorubicin and platinum compounds; (ii) HDC with AHSCT has become a safe and reasonably well-tolerated treatment modality that can even be administered in the outpatient setting. It can be hypothesized that greatly increasing the total dose of CT may prove effective in a subgroup of patients with defined clinical and biological characteristics, as demonstrated for BC [93]. We know that HDC is more effective in patients with sensitive disease and low tumor burden, but no information is available on other predictive factors, such as histopathologic and biomolecular characteristics. Moreover, the optimal timing and schedule of administration of HDC (up-front, consolidation, single course, multiple cycles given sequentially) has not been defined yet.

The more pressing question is whether we should continue to pursue programs of HDC now that cancer therapy has entered the era of molecular-targeted therapy. In other words, if we have smart bombs, do we need to refine the blunderbuss? [94]. Perhaps the answer is still yes. So far, novel targeted therapies have had little impact on the diseases discussed in this article. Moreover, synergy data between targeted therapies (including new drugs and modern forms of immunotherapy) and CT suggest that a long period of co-existence between these diverse approaches is needed [95, 96], and as such, refinement of CT dose and schedule might yet offer advantages.

Finally, the experience of HDC with AHSCT in solid tumors demonstrates the importance of adopting an internationally co-ordinated approach to the investigation of this treatment modality. There needs to be an increased emphasis on prospective trials that are statistically robust and have well defined criteria for patient selection. This task is made harder by the rarity of some of the tumors considered for HDC. However, it is only through clinical trials that we will be able to demonstrate whether HDC, alone or incorporated into programs with novel therapeutic modalities, is worthwhile in patients for whom conventional treatments have often a limited impact on survival.

In conclusion, data available to date do not support the routine use of HDC with AHSCT for solid tumors other than BC in adults. Outside randomised clinical trials we find that there is some evidence from the studies we have reviewed to support the use of intensified therapy in selected and well-informed patients.

Table 5. Studies of high-dose chemotherapy in advanced adult-type soft tissue sarcomas. Reports lacking adequate data on histology were not considered.

<table>
<thead>
<tr>
<th>Investigator year [Ref.]</th>
<th>Number of patients</th>
<th>Response to standard CT</th>
<th>Conditioning regimen</th>
<th>Response to HDC</th>
<th>Study endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kozuka et al. 2002 [80]</td>
<td>2</td>
<td>2 PR</td>
<td>Ifosfamide, carboplatin, etoposide (ICE)</td>
<td>CR</td>
<td>RFS</td>
<td>40 months</td>
</tr>
<tr>
<td>Blay et al. 1998 [75]ab</td>
<td>30</td>
<td>8 CR, 19 PR, 3 SD</td>
<td>Cisplatin, ifosfamide, Etoposide</td>
<td>12 CR, 3 PR, 11 SD, 3 PD</td>
<td>OS</td>
<td>26 months</td>
</tr>
<tr>
<td>Dumontet et al. 1992 [78]</td>
<td>22</td>
<td>4 CR 1, 8 CR 2 or 3, 6 PR 1 or 2, 3 &lt;PR</td>
<td>Melphalan + TBI</td>
<td>DFS, OS 5 years, 32%</td>
<td>15 months</td>
<td></td>
</tr>
<tr>
<td>Schlemmer et al. 2004 [81]c</td>
<td>55</td>
<td>3 CR, 17 PR</td>
<td>ICE</td>
<td>4 CR, 5 PR</td>
<td>OS 5 years, 26 months</td>
<td></td>
</tr>
<tr>
<td>Kessinger et al. 1994 [76]c</td>
<td>13</td>
<td>Various</td>
<td>ICE</td>
<td>3 CR, 4 PR</td>
<td>OS, Short lasting</td>
<td></td>
</tr>
<tr>
<td>Mesia et al. 1994 [82]</td>
<td>9</td>
<td>4 CR</td>
<td>Various</td>
<td>4 CR</td>
<td>DFS, OS, 2 CR maintained at +41 and +27 months</td>
<td></td>
</tr>
<tr>
<td>Kasper et al. 2004 [83]a</td>
<td>12</td>
<td>5 &lt;PR, 2 CR, 5 PR</td>
<td>ICE, Melphalan-based</td>
<td>5 PR, 3 CR, 4 PR, 4 &lt;PR</td>
<td>PFS, OS 12 months</td>
<td></td>
</tr>
</tbody>
</table>

OS, overall survival; DFS, disease-free Survival; PFS, Progression-free survival; CR, complete response; PR, partial response; <CR, partial response or less; <PR, minor response/stable disease/progressive disease; TBI, total body irradiation.
|*Series with long-term survivors (potentially cured). |
|**Pediatric histotypes: Ewing’s family of tumors or rhabdomyosarcomas. |
|**Information lacking in some patients. }
References


