High-Dose Chemotherapy in Adult Solid Tumors and Lymphoproliferative Disorders: The Need for Randomized Trials

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Key Words. Solid tumors · Non-Hodgkin’s lymphoma · Myeloma · High-dose chemotherapy · Randomized trials

ABSTRACT

The demonstration of a dose-effect relationship in a wide spectrum of malignancies including solid tumors and lymphoproliferative disorders, along with the development of new techniques of hematopoietic stem cell support, have given rise to a growing interest for high-dose chemotherapy in recent years. Results in more than 3,000 patients included in nonrandomized trials have been reported in the literature. However, only nine randomized trials addressing the issue of the impact of high-dose chemotherapy on survival have been published: three in non-Hodgkin’s lymphoma, one in multiple myeloma, two in metastatic breast cancer, one in germ-cell tumors, one in melanoma, and one in small-cell lung cancer. Firm, reliable conclusions can only be drawn from studies conducted in the salvage treatment of non-Hodgkin’s lymphoma and in the first-line treatment of multiple myeloma: high-dose chemotherapy used in a consolidation setting after conventional chemotherapy leads to a survival advantage in chemosensitive patients. Promising but not firmly conclusive results were reported in metastatic breast cancer. The results of the sixteen ongoing randomized trials as well as studies addressing the issue of cost-effectiveness will be critical in establishing definite conclusions on the role of high-dose chemotherapy. With the exception of multiple myeloma and relapsed non-Hodgkin’s lymphoma, there is no evidence for treating patients with high-dose chemotherapy outside randomized clinical trials. The Oncologist 1997;2:83-93

INTRODUCTION

Despite recent progress in modern chemotherapy, only specific subgroups of patients are likely to be cured by chemotherapy alone or chemotherapy combined with surgery or radiotherapy. Therefore, metastatic solid tumors and advanced-stage non-Hodgkin’s lymphomas (NHL) still have poor outcome. In the last two decades, the delivery of increased doses or dose intensities of cytotoxic agents has been developed with the aim of improving these rather disappointing cure rates. Such an approach has been allowed by the development of new techniques of hematopoietic stem cell support and recent advances in the knowledge of hematopoiesis regulation. The use of hematopoietic growth factors along with the collection of peripheral blood stem cell progenitors actually supports the management of hematological toxicities induced by the administration of high-dose chemotherapy (HDCT).

There has been a growing interest in HDCT as shown by the number of patients treated by these techniques in recent years, both in the U.S. and in Europe. However, few randomized trials addressing the issue of the impact of these regimens on survival compared to conventional treatment have been published to date.

MATERIALS AND METHODS

Different materials were reviewed to ensure the inclusion of all appropriate trials. Recent general reviews were published on the occasion of the International Consensus Conference on intensive chemotherapy plus hematopoietic stem cell transplantation in malignancies held in Lyon on June 4-6, 1993 [1, 2], as well as in the second edition of the textbook: High-Dose Cancer Therapy by J.O. Armitage and K.H. Antman [3]. Another important source of information was the review on high-dose chemotherapy with autologous bone-marrow transplantation in metastatic breast cancer by Eddy [4]. Finally, we updated our review of high-dose chemotherapy in germ-cell tumors [5]. We selected references in Medline from January 1990 to December 1995 with
the following crosslinked key words: stem cell transplantation, autologous bone marrow transplantation, and chemotherapy. In total, 2,260 references were found. Personal reference files and pertinent bibliographic lists in review articles were studied. This material was supplemented by data collected in the EBMT (European Bone Marrow Transplantation) registry, current protocols declared in the PDQ (Physician Data Query) system of the National Cancer Institute [6], and personal communications received from oncologists involved in hematopoietic stem cell transplantation programs. Previously published and ongoing randomized trials are reported in Tables 1 and 2, respectively.

RESULTS

Dose-Response Relationship and Conventional Chemotherapy

The importance of dose intensity was pointed out in 1984 by Hryniuck and Bush [7]. These authors showed a statistically significant relationship between responses to chemotherapy and dose intensity (dose per unit of time of each drug expressed as mg/m²/week) of conventional regimens used in breast cancer. Moreover, the greater the complete response (CR) rate, the longer the median survival [7]. This relationship was observed in other retrospective studies involving different chemotherapy regimens where drug dosages were in the range of conventional protocols. Lepage retrospectively studied the survival of patients with NHL who received either ≥70% or <70% of the planned dose intensity of cytotoxic agents. The survival of the former was better than that of the latter [8]. Two prospective trials confirmed these observations. Suboptimal drug dosage in the cyclophosphamide, methotrexate and fluorouracil (CMF) regimen was less active than standard dosage in breast cancer patients [9]. Samson showed that 19 mg/m²/week cisplatin dose intensity was less active than 30 mg/m²/week standard dose intensity in germ-cell tumors [10].

Other studies attempted to investigate the role of increased dose intensities with or without hematopoietic growth factor support. In most solid tumors and NHL, no data support the hypothesis of better results within the range of 50% to 100% increased dose intensity above conventional doses. For example, the increase of epirubicin dose from 50 to 75 mg/m² in the fluorouracil, epirubicin and cyclophosphamide (FEC) regimen failed to increase the response rate and the overall survival in breast cancer [11]. The increase of cisplatin dose intensity from 33 to 66 mg/m²/week in the bleomycin, etoposide and cisplatin (BEP) regimen increased toxicity but did not lead to a higher survival rate in germ-cell tumors [12].

It can be concluded from these studies that there is a dose-response relationship when suboptimal to standard conventional doses are considered. However, no further benefit is observed when moderately increased dose intensities beyond standard conventional doses are considered.

High-Dose Chemotherapy with Hematopoietic Stem Cell Support

Background

Are the results of conventional dose chemotherapy likely to be increased by the use of higher dose intensities? Preclinical in vitro models have shown that the higher the dose of a drug, the greater the cytotoxic effect. Such a phenomenon is primarily observed with alkylating and intercalating agents. Moreover, the use of very high doses (two- to fivefold the conventional dose) may reverse the resistance to chemotherapeutic agents [13]. This hypothesis was supported by preliminary in vivo observations. As an example, HDCT with single nonalkylating agents in refractory breast cancer induced a 16% response rate in 45 patients (but no CR), while alkylating agents obtained a 36% response rate in 74 patients (with an 8% CR rate). However, all responding patients progressed within 6 months [14].

Non-Hodgkin’s Lymphomas

Intermediate and High-Grade NHL

Combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP regimen) and its variants are the standard chemotherapy regimens in high- and intermediate-grade NHL (excluding Burkitt’s and lymphoblastic histological patterns) [15]. Thirty percent to 40% of patients are expected to achieve long-term no-evidence-of-disease (NED) status. Second generation conventional regimens delivering higher dose intensities failed to improve these results in a prospective randomized multicenter study [16]. Therefore, 60% to 70% of patients will either fail to enter in CR or relapse after achieving CR status. Results of conventional salvage regimens are poor—the three-year disease-free survival is only 28% with the combination of etoposide, methylprednisone, cytarabine and cisplatin (ESHAP) [17].

The most important compilation of results of HDCT was reported in the EBMT registry, which included 1,762 NHL patients [1]. Survival was clearly better in patients with chemosensitive disease (45% survival rate at five years) than in patients with chemorefractory disease (15% survival rate at five years). Moreover, the procedure-related mortality varied according to disease status at the time of HDCT. Several retrospective studies suggested that intensification of chemotherapy with hematopoietic stem cell support may increase the cure rates in patient subgroups. As an example, patients who received salvage treatment after either relapse, incomplete response, or progressive disease in the NHL84 protocol were
<table>
<thead>
<tr>
<th>Disease (reference)</th>
<th>Status at time of HDCT</th>
<th>High-dose arm treated/eligible for randomization</th>
<th>Statistical method</th>
<th>Statistical hypothesis</th>
<th>Toxic deaths</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL/first line [19]</td>
<td>Complete response</td>
<td>174/464</td>
<td>1-sided</td>
<td>2-year DFS 50% → 65%</td>
<td>2</td>
<td>No survival advantage</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>(\alpha = 0.05)</td>
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<td>(\beta = 0.10)</td>
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<tr>
<td>NHL/first line [22]</td>
<td>Slow response</td>
<td>34/106</td>
<td>1-sided</td>
<td>2-year EFS 35% → 70%</td>
<td>2</td>
<td>No survival advantage</td>
</tr>
<tr>
<td></td>
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<td>(\alpha = 0.05)</td>
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<td></td>
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<td></td>
<td>(\beta = 0.20)</td>
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<tr>
<td>NHL/first salvage [23]</td>
<td>Complete or partial response</td>
<td>49/109</td>
<td>2-sided</td>
<td>None</td>
<td>3</td>
<td>Overall survival advantage</td>
</tr>
<tr>
<td>Multiple myeloma/first-line [31]</td>
<td>All patients</td>
<td>74/200</td>
<td>2-sided</td>
<td>5-year overall survival 10% → 50%</td>
<td>2</td>
<td>Response rate and overall survival advantage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\alpha = 0.05)</td>
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<td>(\beta = 0.20)</td>
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<tr>
<td>Poor-risk NSGCT/first-line [39]</td>
<td>All patients</td>
<td>42/115</td>
<td>1-sided</td>
<td>2-year overall survival 50% → 70%</td>
<td>2</td>
<td>No survival advantage</td>
</tr>
<tr>
<td></td>
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<td>(\alpha = 0.10)</td>
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<td>(\beta = 0.20)</td>
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</tr>
<tr>
<td>Metastatic breast/first-line [42]</td>
<td>All patients</td>
<td>43/90</td>
<td>(\alpha = 0.05)</td>
<td>CR + 30%</td>
<td>0</td>
<td>Overall survival advantage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\beta = 0.20)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Small cell lung cancer/first-line [46]</td>
<td>Complete or partial response</td>
<td>23/45</td>
<td>2-sided</td>
<td>None</td>
<td>4</td>
<td>No survival advantage</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Melanoma high-risk/stage II [48]</td>
<td>All patients</td>
<td>15/39</td>
<td>(\alpha = 0.05)</td>
<td>Time to progression (\times 2)</td>
<td>1</td>
<td>No survival advantage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\beta = 0.20)</td>
<td></td>
<td></td>
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</tbody>
</table>

NHL = non-Hodgkin’s lymphoma; NSGCT = non-seminomatous germ-cell tumors; DFS = disease-free survival; EFS = event-free survival; HDCT = high-dose chemotherapy.
retrospectively studied [18]. The overall survival of the patients who received HDCT as consolidation to conventional salvage chemotherapy was significantly higher than that of the patients who received conventional chemotherapy only (35% versus 10% three-year survival rate, respectively). Moreover, a multivariate analysis determined the prognostic factors of poor outcome: high-serum lactic dehydrogenase, low serum albumin, high-grade lymphoma histology, progressive disease, and treatment other than HDCT [18].

Two randomized trials addressed the issue of the role of high-dose consolidation chemotherapy in the first-line treatment of aggressive NHL (Table 1). The first one studied the potential benefit of a high-dose regimen containing cyclophosphamide, carmustin, and etoposide versus sequential consolidation conventional chemotherapy with ifosfamide, etoposide, asparaginase, and cytarabine in non-pretreated patients with intermediate and high-grade NHL who achieved CR status after conventional induction chemotherapy. In total, 464 patients were eligible for the consolidation phase. After a median follow-up of 28 months, the three-year survival rate was 70% in both treatment arms [19]. However, recent analyses stratifying patients into subgroups have shown that there could be a benefit of HDCT for patients with high-risk characteristics and those with partial response (PR) after induction treatment [20, 21]. Another study addressed the issue of the role of HDCT in patients with aggressive lymphomas who responded slowly to CHOP [22]. In total, there were 110 patients (38%) with a rapid response and 133 patients (47%) with slowly responding disease. The later group was eligible for randomization, 69 of whom were actually randomized. There was no difference as to response rate and overall, disease-free and event-free survivals. It can be concluded from these two studies that there is no evidence for the standard use of HDCT as consolidation treatment in patients who respond to first-line chemotherapy. Two ongoing European studies are addressing the role of high-dose consolidation therapy in the first-line treatment of high- and intermediate-grade non-pretreated NHL (Table 2).

In the salvage setting, the recently published results of the PARMA protocol demonstrated the benefit of consolidation chemotherapy [23]. Two hundred and fifteen patients with intermediate and high-grade relapsing NHL were included into a randomized prospective study between 1987 and 1994. All registered patients received two cycles of the DHAP salvage regimen. The patients with progressive and stable disease were taken off-study while patients with CR or PR (109 patients) were considered for randomization to either four additional cycles of the DHAP regimen or one cycle of high-dose carmustine, etoposide, cytarabine, cyclophosphamide. All patients received post-chemotherapy irradiation of all involved fields. After a median follow-up at 63 months, the five-year overall survival rate was 53% in the high-dose treatment arm and 32% in the conventional treatment arm ($p = 0.038$). This is the only study which favors the use of high-dose consolidation chemotherapy in responding patients with relapsing intermediate- and high-grade NHL.

Low-Grade NHL

Patients with advanced-stage low-grade NHL are considered incurable by conventional chemotherapy despite objective responses to chemotherapy. Even when CR is observed, median duration of the CR is short. However, this disease still remains sensitive to chemotherapy after relapse. Among 201 patients who received HDCT outside randomized trials in the EBMT registry, the five-year overall survival was 60% [24]. There was no difference in survival whether the bone marrow was purged or not. No randomized trial has been published to date. A European trial randomizes patients to either high-dose cyclophosphamide and total body irradiation or the same regimen plus immunomagnetic ex vivo purge of marrow or conventional chemotherapy. A French study compares standard treatment versus HDCT (Table 2).

Only a few reports concern HDCT in chronic lymphocytic leukemia [25]. Forty patients were reported, 27 of whom entered CR. No randomized trial has been published to date.

Hodgkin’s Disease

Standard chemotherapy achieves a high cure rate in advanced stage Hodgkin’s disease [26]. However, patients who fail conventional chemotherapy have poor outcome [27]. HDCT has been given in this group of poor-risk patients. In a survey of 512 patients who received salvage HDCT, 35% to 80% entered CR [28]. Half of these patients received a combination of high-dose cyclophosphamide, carmustine, and etoposide. The other patients received other drug combinations with or without total body irradiation. No randomized study currently supports the use of HDCT in the standard treatment of patients with Hodgkin’s disease. There is no ongoing randomized trial.

Multiple Myeloma

Only limited progress has occurred in the conventional chemotherapy of multiple myeloma during the last two decades [29]. A compilation of the results of HDCT in 400 patients treated in two institutions demonstrated a 31% CR rate, a 3% toxic death rate, and a median overall survival of 30 months [30]. The favorable prognostic factors for survival were a short interval between diagnosis and HDCT, low β2-microglobulin serum levels as well as a non-IgA isotype. The median survival of good-risk group patients (those with two or three good-risk factors) was four years. These results were confirmed by other studies: 571 patients

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### Table 2. Ongoing randomized trials addressing the role of HDCT in patients with solid tumors and lymphoproliferative disorders

<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease</th>
<th>Regimen</th>
<th>Endpoints</th>
<th>Projected accrual/duration</th>
<th>Institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 20901</td>
<td>Intermediate and high-grade NHL</td>
<td>( S = CC ) and ( E = CC + HDCT + RT )</td>
<td>DFS</td>
<td>300/5 years</td>
<td>EORTC</td>
</tr>
<tr>
<td>EU 92028</td>
<td>Adult lymphoblastic lymphoma</td>
<td>( S = CC ) and ( E = CC + HDCT )</td>
<td>Overall survival</td>
<td>200/?</td>
<td>MRC</td>
</tr>
<tr>
<td>EU 93009</td>
<td>Low-grade NHL Relapsed</td>
<td>( S = CC ) and ( E = CC + HDCT + TBI )</td>
<td>Time to progression</td>
<td>400/?</td>
<td>MRC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( E = CC + HDCT + TBI ) with ex vivo immunomagnetic marrow purge</td>
<td>Time to relapse</td>
<td></td>
<td>European trial</td>
</tr>
<tr>
<td>GELF 94</td>
<td>Low-grade NHL First-line II bulky, III, IV</td>
<td>( S = CC + IFN\alpha )</td>
<td>Overall survival</td>
<td>391/4 years</td>
<td>GELF</td>
</tr>
<tr>
<td></td>
<td>One adverse prognostic factor Less than 60 years</td>
<td>( E = CC + HDCT + TBI )</td>
<td>Response rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG 9321</td>
<td>Any stage myeloma</td>
<td>( S = CC ) and ( E = CC + HDCT + TBI )</td>
<td>Overall survival</td>
<td>500/4 years</td>
<td>Intergroup study</td>
</tr>
<tr>
<td>INT 0141</td>
<td>Any stage myeloma</td>
<td>( S = CC ) and ( E = CC + HDCT + TBI )</td>
<td>Overall survival</td>
<td>750/?</td>
<td>MRC</td>
</tr>
<tr>
<td>EU 94030</td>
<td>Any stage myeloma</td>
<td>( S = CC ) and ( E = CC + HDCT + TBI )</td>
<td>Overall survival</td>
<td>300/3 years</td>
<td>IFM</td>
</tr>
<tr>
<td>IFM 94</td>
<td>Any stage myeloma</td>
<td>( S = CC ) and ( E = CC + HDCT + TBI )</td>
<td>Response rate</td>
<td>200/4 years</td>
<td>MSKCC</td>
</tr>
<tr>
<td>NCI T94-0086D</td>
<td>Germ cell tumors Poor-risk</td>
<td>( S = CC ) and ( E = CC + HDCT \times 2 )</td>
<td>Response rate</td>
<td>240/4 years</td>
<td>ECOG SWOG</td>
</tr>
<tr>
<td>IT94</td>
<td>Germ cell tumors First relapse</td>
<td>( S = CC ) and ( E = CC + HDCT \times 2 )</td>
<td>2-year overall survival</td>
<td>800/7 years</td>
<td>IGR CALGB</td>
</tr>
<tr>
<td>CLB 9082</td>
<td>Breast cancer I/II/IIIA ≥ 10 nodes</td>
<td>( S = CC ) and ( E = CC + HDCT )</td>
<td>DFS</td>
<td>800/7 years</td>
<td>SWOG Toronto</td>
</tr>
</tbody>
</table>

Continued on next page
Table 2. Ongoing randomized trials addressing the role of HDCT in patients with solid tumors and lymphoproliferative disorders (continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease</th>
<th>Regimen</th>
<th>Endpoints</th>
<th>Projected accrual/duration</th>
<th>Institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI T90-0180D</td>
<td>Metastatic breast cancer</td>
<td>S = CC, E = CC + HDCT</td>
<td>Time to progression, Overall survival, Toxity, Cost, Quality of life</td>
<td>549/3 years</td>
<td>ECOG, NCCTG, SWOG</td>
</tr>
<tr>
<td></td>
<td>PR/CR</td>
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<tr>
<td>FNCLCC 94006</td>
<td>Breast cancer, all T, ≥ 8 nodes</td>
<td>S = CC, E = CC + HDCT</td>
<td>Time to relapse, Overall survival, Toxity, Quality of life, Cost</td>
<td>240/3 years</td>
<td>FNCLCC and other university hospitals</td>
</tr>
<tr>
<td>FNCLCC 94008</td>
<td>Metastatic breast cancer</td>
<td>S = CC, E = CC + HDCT</td>
<td>Time to relapse, 3-year overall survival, Quality of life</td>
<td>180/3 years</td>
<td>FNCLCC and other university hospitals</td>
</tr>
<tr>
<td>—</td>
<td>Ovarian cancer, stage III and IV</td>
<td>S = CC, E = CC + HDCT</td>
<td>3-year overall survival, Toxity</td>
<td>140/?</td>
<td>GINECO, FNCLCC, SFGM</td>
</tr>
<tr>
<td>INT-0121</td>
<td>Breast cancer, II/III ≥10 nodes</td>
<td>S = CC, E = CC + HDCT</td>
<td>DFS, Overall survival, Toxity, Quality of life</td>
<td>429/3 years</td>
<td>ECOG, CALG-B, SWOG</td>
</tr>
<tr>
<td>INT-0127</td>
<td>Metastatic breast cancer</td>
<td>S = CC, E = CC + HDCT</td>
<td>Overall survival, Toxity</td>
<td>300/2.5 years</td>
<td>SWOG</td>
</tr>
<tr>
<td>(closed 1/1/94)</td>
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</tbody>
</table>

S = standard treatment; E = experimental treatment; MRC = Medical Research Council; EORTC = European Organization on Research and Treatment of Cancer; MSKCC = Memorial Sloan-Kettering Cancer Center; IGR = Institut Gustave Roussy; CALG-B = Cancer and Leukemia Group-B; SWOG = South West Oncology Group; ECOG = Eastern Cooperative Oncology Group; NCCTG = North Central Cancer Treatment Group; FNCLCC = French Federation of Cancer Centers; GELF = Follicular Lymphoma Study Group; IFM = French Myeloma Intergroup; GINECO = Groupe d’Investigateurs Nationaux pour l’Etude des Cancers de l’Ovaire; SFGM = Société Française de Greffe de Moelle; NHL = Non-Hodgkin's Lymphoma; CC = conventional chemotherapy; HDCT = High-dose chemotherapy; IFN-α = interferon-α; DFS = disease-free survival; TBI = total body irradiation.
were treated with HDCT in seven trials. Forty-two percent of these patients entered CR. The median overall survival was four to five years [30].

Only one randomized trial has been published to date [31]. Two hundred non-pretreated patients were randomized to receive either conventional chemotherapy only or four to six cycles of conventional chemotherapy followed by high-dose melphalan and total body irradiation with hematopoietic support. The objective response rates of patients who received conventional treatment and HDCT were 57% and 81%, respectively. Moreover, the five-year survival rate of patients with HDCT was 52% and that of patients with conventional chemotherapy was only 12%. The treatment-related toxicity was the same in both treatment arms [31].

These important results clearly support the use of consolidation HDCT as a standard procedure in the first-line treatment of multiple myeloma. Three important randomized trials are ongoing (Table 2). Two trials are addressing the issue of the role of high-dose melphalan and interferon-α. The US Intergroup trial successively studies the role of high-dose melphalan consolidation chemotherapy versus conventional chemotherapy in a first randomization, and the role of interferon-α versus no treatment as a maintenance therapy in a second randomization. The English trial compares conventional chemotherapy to a combination of high-dose melphalan and interferon-α. The French trial studies the role of two different HDCT procedures.

Germ Cell Tumors

Background

The results of treatment in germ cell tumors (GCT) have been dramatically improved by cisplatin-containing chemotherapy. Treatment with bleomycin, etoposide, and cisplatin (BEP) and the surgical removal of residual masses constitutes the standard treatment for disseminated disease [32]. According to prognostic classifications, patients can be allocated to either good-risk or poor-risk groups. Three cycles of BEP in good-risk patients and four cycles of BEP in poor-risk patients provide 80%-100% and 50%-70% complete remission rates, respectively. Moreover, 10% of the patients in complete remission relapse. Therefore, about 30% of patients with GCT will need a salvage chemotherapy for refractory or recurrent disease. Currently available salvage chemotherapy with ifosfamide and cisplatin is predicted to cure about 30% of patients who failed first-line treatment [33].

Studies in the Salvage Setting

The study of HDCT in GCT began in the early 1980s in order to improve the results of salvage treatment. High-dose chemotherapy regimens were based on etoposide, cisplatin, and, more recently, carboplatin. In several regimens, an oxazaphosphorine derivative was added to the former combination, either cyclophosphamide or ifosfamide. The HDCT was administered as consolidation treatment after conventional cisplatin-based chemotherapy. Promising prospective single center and multicenter studies have been published [5]. The reported 40% to 50% cure rates in patients who are treated with HDCT during first-line salvage treatment was higher than that observed with conventional ifosfamide-based chemotherapy. A recently published prognostic factor analysis identified progressive disease before HDCT, disease refractory to conventional-dose cisplatin (as defined by an increase in serum tumor marker levels during cisplatin-based chemotherapy or within one month after the last cycle of chemotherapy), mediastinal primary and high serum human chorionic gonadotrophin levels as independent adverse prognostic variables for survival after HDCT. Patients with good prognosis (no adverse prognostic factor) at time of HDCT had a predicted 51% two-year survival while patients with poor prognosis (more than two adverse prognostic factors) had a 5%-35% one-year remission rate [34]. It is thus necessary to consider prognostic factors in interpreting long-term results of HDCT in the salvage setting.

No randomized trial currently supports the use of HDCT in the standard salvage treatment of GCT. An ongoing international randomized trial compares four cycles of salvage conventional VIP (etoposide or vinblastine, ifosfamide, and cisplatin) to three cycles of the same VIP regimen followed by one cycle of high-dose etoposide, cyclophosphamide and carboplatin in the salvage setting of GCT (Table 2).

First-Line Chemotherapy

Only a few studies have focused on the role of HDCT in first-line treatment of patients with poor-risk disease. Three nonrandomized studies were in favor of HDCT as consolidation therapy: the reported 50% long-term NED rate compared favorably to the 30%-40% long-term NED rate which was observed in the same institutions after conventional chemotherapy regimens [35-37]. Unfortunately, the conventional regimen used in one study [36] did not include etoposide, a drug which has become a major tool in modern chemotherapy regimens of GCT [38].

Only one randomized trial has been reported in the first-line treatment of poor-risk GCT to date [39]. Patients were randomized to receive either three to four cycles of a combination of vinblastine, etoposide, bleomycin, and double-dose cisplatin or two cycles of a slightly modified similar protocol followed by one cycle of high-dose etoposide, cyclophosphamide and double-dose cisplatin.
In total, 114 eligible patients were randomized between 1988 and 1991. After a median follow-up of three years, 40/57 patients (70%) were progression-free in the standard treatment arm compared to 33 out of 57 patients (58%) in the HDCT arm (Table 1). This trial failed to demonstrate a survival advantage for HDCT. However, the high-dose arm used in this trial is no longer considered as a standard HDCT. The results obtained in the salvage setting by carboplatin-based high-dose regimens favor a trial including HDCT in the first-line treatment of poor-risk GCT patients. An ongoing U.S. randomized trial compares the results of conventional BEP chemotherapy regimen (four cycles) to two cycles of the same regimen followed by two cycles of HDCT (Table 2).

**Breast Cancer**

**Stage IV Disease**

A compilation of trials including more than 10 patients in relapsed or refractory breast cancer shows a 61% response rate and a 15% CR rate among 155 patients treated with HDCT. Median duration of response rarely exceeded six months [40]. Conversely, in 865 responding patients after a conventional induction chemotherapy regimen, consolidation HDCT induced a 59% CR rate. However, it is noteworthy that the CR rate after conventional chemotherapy was 41% with an overall response rate of 79%. Prognostic factor studies of outcome after HDCT showed that disease status, tumor bulk and disease-free interval were the most important factors [41].

**Stage II and III Disease and Inflammatory Breast Cancer**

A compilation of trials shows that 22 studies including 428 patients were reported to date. Only seven reports concerned trials with more than 20 patients (285 patients in total) [40]. The continuous NED rate at two to three years was 7%-93% in stage II disease with five or more involved lymph nodes depending on the inclusion criteria. In stage III and inflammatory breast cancer, the NED rate was 54%-70% and 96%, respectively [40]. No firm conclusion can be drawn from these results regarding the impact of HDCT on overall survival as compared to conventional chemotherapy. The most reliable conclusion is the toxic death rate of 6% in stage II disease and 2% in stage III and inflammatory disease [40].

**Randomized Trials in Breast Cancer**

Bezwoda recently reported a comparison of conventional chemotherapy to immediate HDCT in metastatic breast cancer patients. Ninety patients were randomized to receive either conventional CNV regimen (cyclophosphamide, mitoxantrone, vincristine) or high-dose CNV regimen for two cycles. There were 43 (95%) responses including 23 CRs in 45 patients treated with high-dose CNV, as compared to only 24 (53%) responses including two CRs in 45 patients who received conventional CNV. Both duration of response and overall survival were significantly longer for patients who received high-dose CNV [42].

**Ovarian Cancer**

Experience with HDCT in ovarian cancer is limited: 145 patients were reported in nine studies, only three of which concerned more than 20 patients. Results in refractory patients are poor. However, two papers reported 30% and 50% three-year survival rates, respectively, after consolidation HDCT in responding patients [44]. Although these results may compare favorably with those observed after conventional chemotherapy, no firm conclusion can be drawn. A French randomized trial comparing consolidation HDCT to conventional chemotherapy in patients with chemosensitive disease is ongoing (Table 2).

**Small Cell Lung Cancer**

Fourteen studies including 52 patients reported the results of HDCT in relapsed and refractory small cell lung cancer (SCLC); survival was very short [45]. Among 103 untreated SCLC patients who were reported in 10 studies, 73 had localized disease and only 15 patients were alive more than two years after treatment initiation. When only responding patients are taken into account (66% with localized disease), 37 out of 282 patients achieved a long-term NED status in 19 studies. The overall survival is in the order of that observed with conventional chemotherapy. Only one randomized study was published to date. Humblet
studied the role of alkylating-based HDCT as consolidation therapy in patients with responding SCLC [46]. There was no survival advantage of high-dose treatment in this study. However, the toxic death rate was high (20% of treated patients) (Table 1). There are no data supporting the role of HDCT in the standard management of HDCT.

Malignant Melanoma

The results of HDCT were reported in numerous studies: 14 studies including 208 patients (five studies with more than 20 patients) with single-agent chemotherapy, and 10 studies including 129 patients (only one study with more than 20 patients) with combination chemotherapy [47]. The objective response rate was 47% with the former and 57% with the latter. No evaluation of survival was available. However, duration of response was short (median less than four months). In 1993, Meisenberg published the only randomized trial of adjuvant high-dose chemotherapy in high-risk malignant melanoma [48]. A prospective randomized trial studied the efficacy of immediate high-dose cyclophosphamide, BCNU, cisplatin regimen versus the same treatment at relapse in high-risk stage II melanoma (patients with more than four involved lymph nodes). The time to disease progression was significantly longer in the immediate high-dose treatment arm as compared to the delayed treatment arm (35 weeks versus 16 weeks). However, the overall survival was not different between the two treatment arms. This trial failed to demonstrate any survival advantage of adjuvant HDCT.

High-Grade Glioma

The results of HDCT were assessed in the adjuvant setting after surgical resection and radiotherapy in 178 patients in five separate reports [49]. The two-year survival varied from 25% to 65%, but it was 25% in the largest three studies which totaled 129 patients. No randomized trial has been reported.

DISCUSSION

There is clear evidence of a growing interest for using HDCT in the treatment of patients with solid tumors and lymphoproliferative disorders. Results on more than 3,000 patients have been reported in more than 200 publications. However, there is also a clear absence of scientific background to apply this procedure in the standard management of most tumors. Nine randomized trials have been published to date, three of which have suggested a survival advantage for HDCT: one in the first-line treatment of metastatic breast cancer [42], one in the salvage treatment of aggressive NHL [23], and one in multiple myeloma [31].

The results observed in metastatic breast cancer are clearly insufficient to support the use of HDCT in standard treatment. Indeed Bezvoda's study is the subject of very strong criticisms. The first criticism comes from the choice of chemotherapy regimens. Conventional CNV was not completely comparable to high-dose CNV: vincristine was used in the conventional arm as compared to etoposide in the high-dose arm. The second criticism concerns the reported survival data in the high-dose CNV arm which are comparable to those observed in prospective trials with conventional chemotherapy. For example, the two-year survival rate was 40% in the experience of the French Epirubicin Group which reported the results of a large three-arm randomized trial with conventional epirubicin-based chemotherapy [11]. In the South African trial, the two-year overall survival of patients treated with conventional CNV and high-dose CNV was 0% and 50%, respectively. Therefore, the results of conventional chemotherapy in this study are surprisingly poor.

The patient selection is another important point to consider, as suggested by a retrospective study performed at the M.D. Anderson Cancer Center [50]. Patients who fulfilled the eligibility criteria to enter HDCT consolidation trials but actually received a conventional chemotherapy had a longer median survival (28 months) than that observed in patients who were unlikely to be candidates for HDCT (17 months). Thus, it is possible to consider that the better results of HDCT as compared to conventional chemotherapy which are reported in nonrandomized trials are related to patient selection only.

Interpretation of randomized trials may also be influenced by statistical designs. It is noteworthy that the majority of published randomized trials concerned small patient populations. Indeed, only about 50 patients were treated in the HDCT arm: 53 patients in the T87 protocol [39], 50 patients in the PARMA protocol [23], and 45 patients in the South African trial [42]. Therefore, the statistical power of such trials is rather low. A 20% two-year survival difference between the two arms was expected to be detected with a power of 80%. Prospective clinical randomized trials addressing the role of HDCT should clearly be designed with accurate statistical considerations in order to draw firm conclusions regarding survival.

The cost of the procedure is high, approximately $50,000. Only a few studies have addressed both the issues of efficacy and cost-effectiveness of HDCT. For example, a six-month increase in survival of metastatic breast cancer patients leads to a cost per life-year of $115,800. A decrease in mortality from 23% to 10% in second relapse Hodgkin's disease only leads to a cost per life-year of $37,000 [51]. It is thus very important to incorporate cost-effectiveness
studies in trials with HDCT and to carefully select the population of patients who are likely to benefit from HDCT as it was demonstrated in relapsed NHL [23].

From this review we concluded that there is no evidence to support HDCT as a routine treatment. The results published in the literature are only encouragements to perform trials with accurate design in carefully selected chemosensitive tumor patients.

**REFERENCES**


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