New concepts for relapsed Hodgkin’s disease

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Introduction

Depending on stage and risk factor profile, up to 95% of patients with Hodgkin’s disease (HD) at first presentation reach complete remission (CR) after the initial standard treatment including radiotherapy, combination chemotherapy (CT) or combined modality therapy. Patients who relapse after a first CR can achieve a second CR with salvage treatment including radiotherapy for localized relapse in previously non-irradiated areas, conventional salvage chemotherapy, or high-dose CT with autologous stem-cell transplantation (autoSCT) [1].

The survival of patients treated with conventional CT after relapse of irradiated early stage disease is at least equal to that of advanced-stage patients initially treated with CT. Overall survival (OS) and disease-free survival (DFS) range from 57 to 71% [2, 3]. Patients who relapse following radiation therapy alone for localized HD have satisfactory results with combination CT and are not considered candidates for high-dose CT and autoSCT.

The optimum treatment for recurrence after primary CT is less clear. Different modalities such as salvage radiotherapy, conventional CT, second-line CT and high-dose CT with autoSCT are being employed.

High-dose CT followed by autoSCT has been shown to produce 30–65% long-term DFS in selected patients with refractory and relapsed HD [4–8]. In addition, the reduction of early transplant-related mortality from 10 to 25% reported in earlier studies to <5% in more recent studies has led to the widespread acceptance of high-dose CT and autoSCT.

High-dose CT followed by autoSCT has been shown to produce 30–65% long-term DFS in selected patients with relapsed or refractory HD [9]. The actuarial 3-year event-free survival (EFS) was significantly better in patients who received high-dose CT (53% versus 10%). In the BNLI trial, patients with relapsed or refractory HD were treated with a combination of carmustine (BCNU), etoposide, cytarabine and melphalan at a conventional-dose level (mini-BEAM) or a high-dose level (BEAM) with autologous bone marrow transplantation (ABMT) [9]. The actuarial 3-year event-free survival (EFS) was significantly better in patients who received high-dose CT (53% versus 10%).

The largest randomized, multicenter trial was performed by the GHSG/EBMT to determine the benefit of high-dose CT in relapsed HD. Patients with relapse after polychemotherapy were randomly assigned between four cycles of Dexa-BEAM (dexamethasone, BCNU, etoposide, Ara-C and melphalan) or two cycles of Dexa-BEAM followed by high-dose CT (BEAM) and ABMT/peripheral blood stem cell transplantation (PBSCT). The final analysis of 144 evaluable patients revealed that of 117 patients with partial (PR) or complete remission (CR) after two cycles of CT, freedom from treatment failure (FFTF) in the high-dose CT group was 55%, compared with 34% for the patients receiving an additional two cycles of CT. OS was not significantly different [10].

Sequential high-dose CT

In recent years, sequential high-dose CT has increasingly been employed in the treatment of solid tumors, and hematological and lymphoproliferative disorders. Initial results from phase I/II studies indicate that this kind of therapy offers safe and effective treatment [11–16]. In accordance with the Norton–Simon hypothesis [17], following initial cytoreduction, few non-cross-resistant agents are given at short intervals. In general, the transplantation of PBSC and the use of growth factors allow the application of the most effective drugs at the highest possible doses at intervals of 1–3 weeks. Sequential high-dose CT thereby enables the highest possible dosing over the minimum period of time (dose intensification).

In 1997, a multicenter phase II trial with a high-dose sequential CT program and a final myeloablative course was started in order to evaluate the feasibility and efficacy of this novel regimen in patients with relapsed HD [18]. Eligibility
Allogeneic transplantation after reduced conditioning in HD

Allogeneic bone marrow transplantation (alloBMT) has clear advantages compared with autologous transplantation: donor marrow cells uninvolved by malignancy are used, thus avoiding the risk of infusing occult lymphoma cells that may contribute to relapse in patients who undergo autologous transplantation. In addition, donor lymphoid cells can potentially mediate a graft-versus-lymphoma effect.

Generally, donor availability and age constraints have limited a broader application of alloBMT in HD. Moreover, alloBMT is associated with a high treatment-related mortality rate of up to 75%, observed in patients with induction failure, which casts doubt on the feasibility of this approach in HD patients [19–22]. In most cases, allogeneic transplantation from human leukocyte antigen (HLA)-identical siblings is not recommended for patients with HD. The reduced relapse rate associated with a potential graft-versus-tumor effect is offset by lethal graft-versus-host toxicity.

Nevertheless, patients with induction failure and relapsed patients with additional risk factors also have a poor prognosis after high-dose CT and autoSCT. Therefore, the role of alloBMT should be further evaluated in these patients, taking advantage of new developments like non-meloaablative conditioning regimens and alloPBSCT.

To circumvent the problems inherent to the toxicity and treatment-related mortality associated with allografting, the possibility of achieving engraftment of allogeneic stem cells after immunosuppressive therapy combined with myelo-spressive but nonmyeloablative therapy has been assessed. Several groups have recently updated their experience with non-myeloablative conditioning regimens and alloPBSCT.

The EBMT, together with the Grupo Espanol de Linfomas – Transplante Autologo de Medula Osea (GEL/TAMO) and the GHSG, activated a multicenter phase II study to evaluate the treatment-related mortality of patients with primary progressive or relapsed HD (early relapse, multiple relapse and relapse after autoSCT). Patients with an HLA-compatible sibling donor or an HLA-matched unrelated donor will initially be treated with one to two cycles of DHAP or other salvage protocols to reduce tumor burden before alloPBSCT. PBSCs will be collected after G-CSF priming of the donor and reinforced after conditioning with fludarabine and melphalan.

Future directions

Alternative strategies have been developed to improve the outcome of relapsed and resistant HD. These approaches include the development of new cytostatic drugs and biological agents with proven efficacy in pre-clinical models.

One of the most promising new cytostatic drugs is the new vinca alkaloid vinorelbine, which has demonstrated activity in HD even in patients pre-treated with vincristine or vinblastine [26]. The use of vinorelbine in first- and second-line therapy

HDR-2 protocol

In January 2001, the GHSG together with the European Organisation for Research and Treatment of Cancer (EORTC) and the EBMT started a prospective randomized study to compare the effectiveness of a standard high-dose CT (BEAM) with a sequential high-dose CT after initial cytoreduction with two cycles of DHAP (HD-R2 protocol, see Figure 1).

Patients with histologically confirmed early or late relapsed HD, and patients in second relapse with no prior high-dose CT fulfilling the entry criteria receive two cycles of dexamethasone, high-dose cytarabine and cisplatin (DHAP) followed by granulocyte colony stimulating factor (G-CSF).

Patients achieving no change (NC), PR or CR after DHAP are centrally randomized to receive either BEAM followed by PBSCT (arm A of the study) or HD cyclophosphamide, followed by high-dose methotrexate (HD-MTX) + vincristine, followed by HD etoposide and a final myeloablative course with BEAM (arm B of the study).
for HD in order to improve frequency and duration of response is still under investigation. The pyrimidine analog gemcitabine is the only drug currently under investigation that represents a new cytostatic mechanism of action: the ‘self-potentiating’ mechanism of action leads to an enhanced accumulation and prolonged retention of gemcitabine in the malignant cell. The preliminary results of gemcitabine in advanced relapsed HD are promising, with an overall RR of

Figure 1. HDR-2 protocol.
53% in heavily pre-treated patients [27]. If these results can be confirmed, gemcitabine must be evaluated in combination regimens.

Although some clinical efficacy has been demonstrated in clinical trials with immunotoxins, none that is currently available seems to be suited for a clinical phase III study [28–30]. Bispecific monoclonal antibodies (BiMoab) such as the recently reported CD30xCD64 BiMoab look more promising, and clinical development programs are scheduled, including phase III trails. The use of recombinant DNA technology for site-directed modifications of the immunotoxins and the development of humanized immunotoxins and BiMoabs might optimize their efficacy [31]. In the future, combining standard chemotherapy/radiotherapy with biological agents might result in the elimination of residual tumor cells, and subsequently more relapse-free, long-term survivors.

References


