Relaps and Refractory Hodgkin`s Diseases

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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, 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 chemotherapy (HDCT) with stem cell transplantation (SCT).[1]

Prognostic factors in relapsed and refractory Hodgkin`s disease

It was first noted in 1979 that the length of remission to first-line chemotherapy had a marked effect on the ability of patients to respond to subsequent salvage treatment.[2] In 1992 the National Cancer Institute (NCI) updated their experience with the long-term follow up of patients who relapsed after polychemotherapy.[3] Derived primarily from investigations involving failures after MOPP and MOPP variants, the conclusions are thought to be relevant to other chemotherapy programs as well. On this basis, chemotherapy failures can be divided into three subgroups:

- Primary progressive Hodgkin`s disease, i.e. patients who never achieve a complete remission
- Early relapses within 12 months of CR
- Late relapses after CR lasting > 12 months

Using conventional chemotherapy for patients with primary progressive disease, virtually no patient survives more than eight years. In contrast, the projected 20-year survival for patients with early relapse or late relapse was 11% and 22%, respectively.[3]

Primary progressive Hodgkin`s disease

Patients with primary progressive disease, defined as progression during induction treatment or within 90 days after the end of treatment, have a particularly poor prognosis. Conventional salvage regimens have given disappointing results in the vast majority of patients: response to salvage treatment is low and the duration of response is often short. The 8-year OS ranges between 0% and 8%.[3,4]

The German Hodgkin`s disease Study Group (GHSG) retrospectively analysed 206 patients with PD to determine outcome after salvage therapy and identify prognostic factors.[5] The five year freedom from second failure (FF2F) and OS for all patients was 17% and 26%. As reported from transplant centers, the five year FF2F and OS for patients treated with HDCT is 42% and 48%, respectively, but only 33% of all patients received HDCT. The low percentage of patients who received HDCT was due to rapidly fatal disease or life-threatening severe toxicity after salvage therapy. Other reasons not to proceed to HDCT were insufficient stem cell harvest, poor performance status and older age.

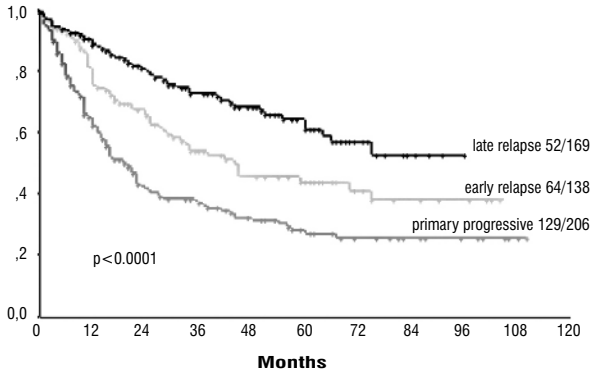

Figure 1. Actuarial OS of patients with primary progressive, early or late relapsed HD registered in the GHSG from 1988 to 1999 (n = 513)

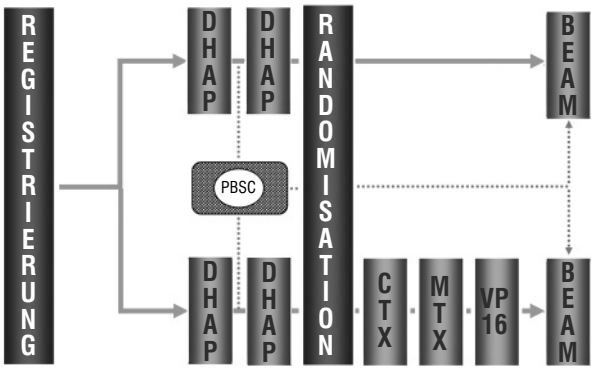

Figure 2. HDR-2 protocol. A European multicenter study for relapsed Hodgkin lymphoma (GHSG, EORTC, EBMT, GEL/TAMO)

In a multivariate analysis, Karnofsky performance score at progress (p < 0.0001), age (p = 0.019), and attainment of a temporary remission to first-line chemotherapy (p = 0.0003) were significant prognostic factors for survival. Patients with none of these risk factors had a 5-year OS of 55% compared with 0% for patients with all three of these unfavorable prognostic factors.

Early and late relapsed Hodgkin`s disease

The overall prognosis is bad for patients relapsing after first-line chemotherapy when treated with conventional chemotherapy. At present, HDCT followed by ASCT is the treatment of choice for patients with relapsed HD after first-line polychemotherapy. Although the results reported with HDCT in patients with late relapse have been superior to those reported in most series of conventional chemotherapy, the use of HDCT in late relapses had been an area of controversy because patients with late relapse have satisfactory second CR rates when treated with conventional chemotherapy with OS ranging from 40% to 55%. However, the HDR-1 trial of the GHSG showed improved FFTF after HDCT compared with conventional chemotherapy also in patients with late relapse.[6]

Many prognostic factors have been described for patients relapsing after first-line chemotherapy. These include age, sex, histology, relapse sites, stage at relapse, bulky disease, B symptoms, performance status, and extranodal relapse. The impact of these factors is difficult to assess due to confounding factors such as small number of patients and inclusion of primary progressive HD. In addition, multivariate analysis were not performed systematically.[7,8,9]

Brice et al performed one of the largest studies evaluating prognostic factors in relapsed HD. One-hundred and eighty seven patients who relapsed after a first complete remission were included. At first relapse, treatment was conventional (chemo- and/or radiotherapy) in 44% and HDCT followed by ASCT in 56%. Two prognostic factors were identified by multivariate analysis as correlating with both FF2F and OS. These factors were the initial duration of first remission (i.e. < 12 months or > 12 months; p < 0.0001) and stage at relapse (I-II vs. III-IV); p = 0.0013). FF2F was 62% and 32%, respectively, OS was 44% and 87% according to the presence of 0 or 2 parameters, respectively. Laboratory data were not available in this retrospective analysis.[10]

The GHSG has recently performed a retrospective analysis including a much larger number of relapsed patients (n=422) than previous reported (Figure 1). The analysis of prognostic factors suggests that the prognosis of a patient with relapsed HD can be estimated according to several factors. The most relevant factors were combined into a prognostic score. This score was calculated on the basis of duration of first remission, stage at relapse and the presence or absence of anemia at relapse. Early recurrence within 3 to 12 months after the end of primary treatment, relapse stage III or IV and haemoglobin <10.5g/dl in female or < 12g/dl in male patients comtribute to a score with possible values 0, 1, 2 and 3 in order of worsening prognosis.[11] This prognostic score allows distinguishing patients with different FF2F and OS. The actuarial 4-year FF2F and OS for patients relapsing after chemotherapy with three unfavorable factors were 17% and 27%, respectively. In contrast, patients with none of the unfavorable factors had FF2F and OS at 4-year of 48% and 83%, respec-

tively. In addition, the prognostic score was also predictive for patients relapsing after radiotherapy, for patients relapsing after chemotherapy who were treated with conventional therapies or with HDCT followed by ASCT, and for patients under 60 years and a Karnofsky performance status ≥ 90% being the major candidate groups for dose intensification. Our prognostic factor score uses clinical characteristics which can be easily collected at the time of relapse. It separates groups of patients with substantially different outcomes.

The prognostic factors identified may be useful to tailor the therapy for subgroups of patients, to define homogeneous cohorts for prospective randomized trials, and to identify more precisely patients with poor-risk relapse who should be treated with innovative approaches.

Treatment strategies

The survival of patients treated with conventional chemotherapy after relapse of irradiated early-stage disease is at least equal to that of advanced-stage patients initially treated with chemotherapy. Overall survival (OS) and disease-free survival (DFS) range from 57% to 71%.[12,13] Patients who relapse following radiation therapy alone for localized Hodgkin's disease have satisfactory results with combination chemotherapy and are not considered candidates for HDCT and ASCT.

HDCT followed by ASCT has been shown to produce 30%-65% long-term disease-free survival in selected patients with refractory and relapsed HD.[14-17] In addition, the reduction of early transplant-related mortality from 10% - 25% reported in earlier studies to less than 5% in more recent studies has led to the widespread acceptance of HDCT and ASCT.

Although results of HDCT have generally been better than those observed after conventional-dose salvage therapy, the validity of these results has been questioned due to the lack of randomized trials. The most compelling evidence for the superiority of HDCT and ASCT in relapsed HD comes from two reports from the British National Lymphoma Investigation (BNLI) and the German Hodgkin's Lymphoma Study Group (GHSG) together with the European Group for Blood and Marrow Transplantation (EBMT).

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.[18] The actuarial 3-year event-free survival (EFS) was significantly better in patients who received high-dose chemotherapy (53% vs 10%).

The largest randomized, multicenter trial was performed by the GHSG/EBMT to determine the benefit of HDCT in relapsed HD. Patients with relapse after polychemotherapy were randomly assigned between four cycles of Dexa-BEAM (dexamethasone, BCNU, etoposide, Ara-C and melphalan) and two cycles of Dexa-BEAM followed by HDCT (BEAM) and ABMT/PBSCT. The final analysis of 144 evaluable patients revealed that from 117 patients with PR or CR after two cycles of chemotherapy, FFTF in the HDCT group was 55% versus 34% for the patients receiving an additional two cycles of chemotherapy. OS was not significantly different.[6]

Sequential high-dose chemotherapy

In recent years, sequential high-dose chemotherapy has increasingly been employed in the treatment of solid tumors, hematologic and lymphoproliferative disorders. Initial results from phase-I/II studies indicate that this kind of therapy offers safe and effective treatment.[19-24] In accordance with the Norton-Simon hypothesis,[25] 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 one to three weeks. Sequential high-dose chemotherapy thereby enables the highest possible dosing over a minimum period of time (dose intensification).

In 1997 a multicenter phase-II trial with a high-dose sequential chemotherapy program and a final myeloablative course was started to evaluate the feasibility and efficacy of this novel regimen in patients with relapsed HD.[26] Eligibility criteria included age 18-60 yrs., histologically proven relapsed or primary progressive HD, second relapse with no prior HDCT and ECOG performance status 0-1.

The treatment program consists of two cycles of DHAP (dexamethasone, ara-C, cisplatin) in the first phase in order to reduce tumor burden before HDCT. Patients with partial remission (PR) or complete remission (CR) after two cycles of DHAP,

receive sequential high-dose chemotherapy consisting of cyclophosphamide 4 g/m^2 iv, methotrexate 8 g/m^2 iv plus vincristine 1.4 mg/m^2 iv; and etoposide 2 g/m^2 iv. The final myeloblative course was BEAM followed by PBSCT with at least 2 x 10^6 CD34+ cells/kg.

At the last interim analysis 102 patients were available for the final evaluation. State of remission was multiple relapse in 10 patient, progressive disease in 16 patients, early relapse in 29 patients and late relapse in 44 patients. At 18 months of median follow-up (range 3-31 months) results are as follows: Response rate (RR) after DHAP 87% (23% CR, 64% PR) and RR at final evaluation 77% (68% CR, 9% PR). Toxicity was tolerable with no treatment related deaths. FFTF and OS for patients with early relapse were 64%/87% for early relapse; 68%/81% for late relapse; 30%/58% for patients with progressive disease and 55%/88% for patients with multiple relapse.[26]

In conclusion, sequential administration of high doses of cyclophosphamide, methotrexate and etoposide is feasible and did not affect the tolerability of final myeloablative BEAM. This new, three-phase treatment regimen is well tolerated and feasible in patients with relapsed and primary progressive HD. The preliminary data suggests a high efficacy in relapsed HD patients, warranting further randomized studies.

HDR-2 Protocol

In January 2001, the GHSG together with the EORTC, the GEL/TAMO and the EBMT started a prospective randomized study to compare the effectiveness of a standard HDCT (BEAM) with a sequential HDCT after initial cytoreduction with 2 cycles DHAP (HD-R2 protocol, Fig. 2).

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

Patients achieving NC, PR or CR after DHAP are centrally randomized to receive either BEAM followed by PBSCT (arm A of the study) or HD cyclophosphamide + G-CSF, followed by HD-MTX + vincristine, followed by HD etoposide + G-CSF and a final myeloablative course with BEAM (arm B of the study).

Allogeneic transplantation after reduced conditioning in HD

Allogeneic transplantation (alloBMT) has clear advantages compared with autologous transplantation: Donor marrow cells uninvolved by malignancy are used avoiding the risk of infusing occult lymphoma cells, which 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 upon the feasibility of this approach in HD patients.[27-30] In most cases, allogeneic transplantation from 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 have a poor prognosis also after HDCT and ASCT. Therefore, the role of alloBMT should be further evaluated in these patients taken advantage of new developments like non-meloablative conditioning regimens and alloPBSCT.

To circumvemt the problems inherent to the toxicity and treatment related mortality associated to allografting, the posibility to achieve engraftment of allogeneic stem cells after immunosuppressive therapy combined with myelosuppressive but non-myeloablative therapy has been assessed. Several groups have recently updated their experience with non-myeloablative conditioning regimens.[31-33]

The EBMT together with the GEL/TAMO, the EORTC and the GHSG activated a multicenter phase II study to evaluate the treatment-related mortality (TRM) of patients with primary progressive or relapsed HD (early relapse, multiple relapse and relapse after autologous SCT). Patients with an HLA compatible sibling donor or an HLA matched unrelated donor will be initially treated with 1-2 cycles of DHAP or other salvage protocols to reduce tumor burden before alloPBSCT. PBSC will be collected after G-CSF priming of the donor and reinfused 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 preclinical models.

One of the most promising new cytostatic drugs is the new vinca alkaloid vinorelbine, which has demonstrated activity in HD even in patients pretreated with vincristine or vinblastine.[34] The use of vinorelbine in first and second-line therapy of HD in order to improve frequency and duration of response is still under investigation. The pyrimidine analogue 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 results of gemcitabine in advanced relapsed HD are promising, with an overall response rate of 53% in heavily pretreated patients.[35]

Although some clinical efficacy has been demonstrated in clinical trials with immunotoxins (IT) none of the current available IT seems to be suited for a clinical phase-III study.[36-38] Bispecific monoclonal antibodies (BiMoab) such as the recently reported CD30xCD64 BiMoab look more promising with clinical development programs scheduled including phase III. The use of recombinant DNA technology for site-directed modifications of the IT and the development of humanized IT and BiMoabs might optimize their efficacy.[38] In the future, combining standard chemo-/radiotherapy with biological agents might result in the elimination of residual tumor cells and subsequently more relapse-free long term survivors.

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