High-dose thiotepa, etoposide and carboplatin as conditioning regimen for autologous stem cell transplantation in patients with high-risk Hodgkin's lymphoma

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Background: Autologous stem cell transplantation (ASCT) generally provides good results in Hodgkin's lymphoma (HL). We studied a high-dose chemotherapy regimen based on thiotepa, etoposide and carboplatin (TECA).

Methods: Fifty-eight patients with advanced HL were treated with thiotepa, etoposide and carboplatin for transplant induction.

Results: The overall response rate was 79.3% (39 CR: 67.2%; and 7 PR: 12.1%); 12 patients (20.1%) were non-responders. The 5-year overall survival rate was 77.6%; five initially responder patients relapsed within the first 5 years of follow-up and underwent salvage therapy.

Conclusion: The TECA conditioning regimen for ASCT in HL results in a good anti-HL effect, positive response to treatment and high 5-year overall survival rate. It was also well tolerated and did not induce excessive toxicity, suggesting that TECA may be a very useful conditioning regimen for HL.

Keywords: Autologous stem cell transplantation, conditioning regimen, high-dose chemotherapy, Hodgkin's lymphoma, survival

Introduction

Hodgkin's lymphoma (HL) is a malignant disease with an annual incidence of 2 to 3 cases per 100 000 persons in Europe and the United States, with a peak occurring in the third decade.[1] After first-line combined therapy, the relapse free-survival rate at 5 years of patients with early-stage disease or advanced-stage disease is about 75–80% and 65–70%, respectively. Patients failing after first-line chemotherapy can be divided into three subgroups: (i) patients with primary progressive disease, defined as progression during treatment or within 90 days after the end of therapy; (ii) patients with early relapsing disease, defined as relapse within 12 months after the end of treatment; and (iii) patients with late relapsing disease, defined as relapse occurring after 12 months from the end of therapy.

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The treatment of patients with primary progressive and relapsed HL remains particularly difficult. Conventional salvage regimens, particularly in poor prognosis HL, show a low-response rate with short duration of response. These patients are candidates for high-dose chemotherapy followed by autologous or allogeneic stem cell transplantation (ASCT). Early studies using ASCT in patients with refractory or relapsed Hodgkin's disease (HD) reported complete response rates of 48–69% and prolonged disease-free survivals. In two of the studies, 27% of patients were disease-free at approximately 4 years; the treatment-related mortality was high, ranging from 4% to 23%. Several advances in supportive care and the use of peripheral-blood progenitor cells during ASCT have subsequently reduced the treatment-related mortality to less than 3%.[2–6]

In an attempt to improve the results of patients with HL failing after first-line chemotherapy, we studied a high-dose chemotherapy regimen which included

DOI 10.1179/102453312X13221316477534

thiotepa, etoposide and carboplatin (TECA). A similar high-dose schedule is commonly used for the treatment of retinoblastoma in children,[7] breast cancer,[8] or in germ cell tumors.[9]

Patients and methods

Patients characteristics and selection criteria

From March 1999 to December 2005, 58 patients (34 M, 24 F) with relapsed (47 patients) or primary progressive (11 patients) HL after induction therapy with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) were selected for high-dose chemotherapy and ASCT, and were consecutively included in this phase II study. The selection criteria included: age <70 years, creatinine <2 mg/dL, cardiac ejection fraction $>50\%$, carbon monoxide diffusion capacity (DLCO) $>50\%$, no active infectious disease or other co-morbidity conditions. Prior high-dose chemotherapy was an exclusion criterion. The median age at transplantation was 39 years (range 19–64 years).

The study was carried out in accordance with the Declaration of Helsinki (Hong Kong Amendment, 1989). The protocol met the requirements of the European Good Clinical Practice Guidelines (July 1990). The study was approved by the Local Ethics Committee and all patients gave their informed consent.

Treatment program

All patients received previous first-line induction therapy with ABVD and all received various types of second-line chemotherapy before HDT (EVAP, MINE, HAM, BEACOPP, intensified BEACOPP, COPP/ABVD, IEV, DHAP). Then, 35 patients received mobilization therapy with 7 g/m^2 cyclophosphamide and 7 patients received mobilization with 2 g/m^2 VP-16. Ten patients were mobilized at the third cycle of IEV and 6 patients at the third cycle of DHAP. From day 2 after the end of therapy, recombinant Human Granulocyte Colony-Stimulating Factor (rHuG-CSF) was given at doses of 10 μg/kg per day subcutaneously (s.c.) until hematological recovery. CD34-positive peripheral blood progenitor cells (PBPCs) were separated by leukapheresis during the recovery phase when circulating CD34-positive cells increased to $\geqslant 10/\mu L$. The aim was to collect a minimum of 4×10^6 PBPCs per kg body weight, sufficient for transplantation procedures.

The transplant-conditioning regimen included etoposide 250 mg/m^2 days 1–4, thiotepa 166 mg/m^2 days 2–4 and carboplatin 266 mg/m^2 days 2–4. CD34+ cells were reinfused at day 7. All patients received 5 μg/kg/day rHuG-CSF from day 4 after reinfusion of PBSCs until bone marrow recovery.

Response criteria and follow-up

Complete staging procedures were applied to each patient at study entry, at interim staging after induction therapy on day 30, and at the final evaluation requiring physical examination, biological and virological blood parameters, lung and kidney function tests, bone marrow biopsy and cytology, electrocardiography and imaging with at least CT scans of neck, chest and abdomen. The extent of disease was assessed at study entry and after completing ASCT.

Responses were evaluated at 100 days after transplant by clinical and laboratory evaluation, bone marrow biopsy and total body CT or PET scan. Follow-up was performed every 6 months with clinical and laboratory evaluation, abdomen ultrasonography and chest radiography. Complete restaging, including clinical and laboratory evaluation, bone marrow biopsy and total body CT or PET scan, was performed every 12 months.

Complete response (CR) was defined as the disappearance of all clinical and radiographic evidence of disease for at least 6 months. Partial response (PR) was defined as a $>50\%$ reduction in the product of the largest diameter and its perpendicular of measurable disease lasting longer than 6 months. Any other response less than PR was considered treatment failure.

Definitions of toxicity

Early regimen-related toxicity was evaluated according to established transplantation-specific criteria.[10]

Statistical methods

The final follow-up was completed on December 20, 2007, and event-free survival (EFS) and overall survival (OS) were estimated with the method of Kaplan and Meier[11] and calculated from the day of bone marrow or peripheral blood hematopoietic cells infusion until the date of final follow-up examination. The relationships between clinical parameters and survival were evaluated using Cox univariate and multivariate analysis.

Results

All patients completed the therapy protocol.

Debulking, mobilization of peripheral blood progenitor cells and transplant

After mobilization, collected CD34+ PBPCs ranged from 3.26 to 14.5×10^6/kg (median 8.22×10^6/kg). No significant differences were seen as regards type of savage or mobilization therapy as well as response to previous therapy.

All patients underwent ASCT within 60 days from mobilization and no drop out or consent withdrawal were recorded. At transplantation, 30 patients were in CR, 16 in PR and 12 showed chemoresistance to salvage chemotherapy. The 11 patients with primary progressive disease presented unfavorable prognostic factors according to Josting of the GHSG:[12] 3 patients presented all three prognostic factors, 4

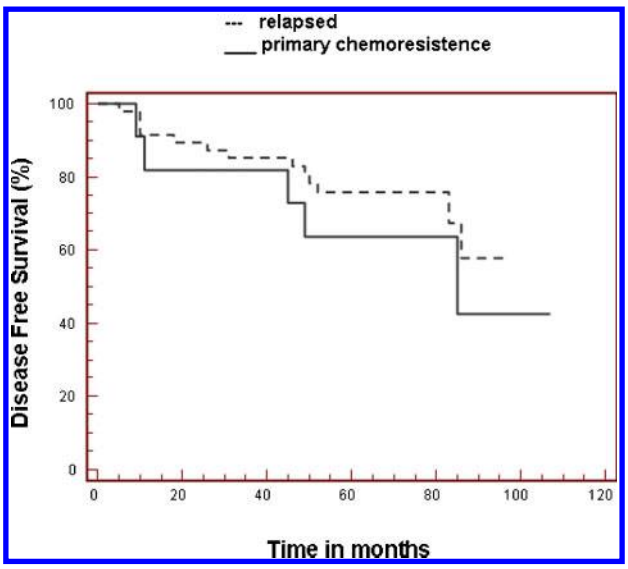

Figure 1 Kaplan-Meier curves for disease-free survival in transplanted HL patients

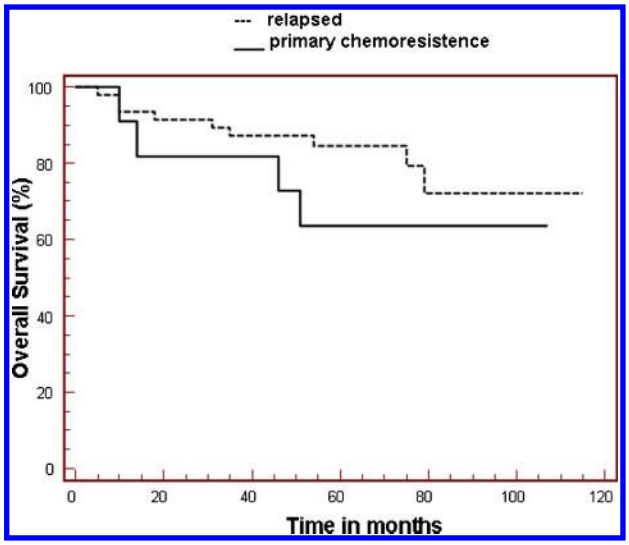

Figure 2 Kaplan-Meier curves for overall survival in transplanted HL patients

patients two, 2 patients one, and 2 patients no negative prognostic factor. The 47 patients with relapsed disease presented unfavorable prognostic factors according to Josting of the GHSG:[13] 10 patients presented all three prognostic factors, 16 patients two, 12 patients one and 9 patients no negative prognostic factor. No significant differences related to savage or mobilization therapy were seen.

The transplant-conditioning regimen was etoposide 250 mg/m^2 days 1–4, thiotepa 166 mg/m^2 days 2–4 and carboplatin 266 mg/m^2 days 2–4. CD34+ cells were reinfused at day 7. All patients received 5 μg/kg/day rHuG-CSF from day 4 after reinfusion of PBSCs.

Hematological reconstitution and toxicity

Engraftment was achieved in all 58 patients. Median time to recovery of an absolute neutrophil count >500/μL ranged from 9 to 15 days (median 11 days). Similarly, median time to platelet recovery >20 000/μL independent of transfusion in all 58 patients ranged from 9 to 18 days (median 13 days). Median number of days of hospitalization was 21 (range 18–26 days).

Hematological toxicity was acceptable and the duration of leukopenia WHO grade 4 (<500/mm^3) ranged from 4 to 7 days (median 5.2 days).

Table 1 Toxic events

Event	Grade 1–2	Grade 3–4
Fever of undetermined origin	32	14
CMV infections	18	5
Staphylococcus infections	1	0
Pseudomonas infections	2	1
Mucositis	29	14
Acute renal failure	5	1
Hepatic failure	3	0

The incidence of transplant-related infective and non-infective complications, shown in Table 1, was similar to other conditioning regimens. Infections were well controlled with antibiotics and resolved after engraftment. Non-infective complications resolved spontaneously after neutrophil recovery. No transplant-related deaths were observed.

Outcome of patients

The global overall response rate was 79.3% (37 CR: 67.2%, and 7 PR: 12.1%); 12 patients (20.1%) were non-responders. No significant differences were seen between primary progressive and relapsed patients (ORR: 72.7% and 80.8%, respectively).

Survival analysis

The 5-year disease-free survival (Fig. 1) and overall survival (Fig. 2) of patients with relapsed HL were 72.3% and 82.8%, respectively. The 5-year disease-free survival (Fig. 1) and overall survival (Fig. 2) of patients with primary progressive HL were 63.6% for both. Five initially responder patients relapsed within the first 5 years of follow-up and underwent salvage therapy. Forty-five patient (77.6%) were alive at the term of follow-up.

Univariate analysis showed that only the presence of all three negative prognostic factors was associated with different response rate, disease-free survival and 5-year overall survival. Multivariate analysis was not possible in primary progressive disease because of the low number of patients, while in relapsed patients, it showed that short duration of first remission, III-IV stage disease at relapse but not hemoglobin levels were associated with different response rates (P <0.01, <0.01 and =0.08, respectively), and 5-year overall survival (P<0.05, <0.001 and=0.5, respectively), while all three prognostic factors were significantly associated with disease-free survival (P <0.01, <0.01 and <0.05, respectively).

Discussion

The treatment of patients with primary progressive and relapsed HL remains particularly difficult. Indeed, the prognosis of patients with primary progressive disease is poor when they are treated with conventional chemotherapy. Conventional salvage chemotherapy produces low remission rates, with short duration of response and with 8-year overall survival rates between 0% and 8%.[14] Salvage radiotherapy is of limited utility in extensive disease. In an attempt to improve the outcome of patients with primary progressive HL, high-dose chemotherapy (HDCT) followed by ASCT has been increasingly used. HDCT produces a long-term disease-free survival (DFS) rate of 32% to 50% and a 3- to 5-year overall survival (OS) of 36–55%.[15–18] Some prognostic factors, evaluated at the time of disease progression, may affect the outcome, and HDCT with ASCT may be an effective treatment for selected patients with primary progressive disease.

Josting *et al.* reported prognostic factors for OS, evaluated retrospectively at the time of progression, in 206 patients with primary progressive HL registered in the data base of the GHSG; 70 patients (34%) were treated with HDCT and ASCT. In multivariate analysis, low Karnofsky performance score at the time of progression ($P<0.0001$), age above 50 years ($P=0.019$) and failure to attain a temporary remission on first-line treatment ($P=0.0003$) were significant adverse prognostic factors for OS. Patients with none of these risk factors had a 5-year OS rate of 55%, compared with an OS rate of 0% for patients with all three unfavorable prognostic factors.[12]

The prognosis of patients relapsing after first-line chemotherapy is better than that of patients with progressive disease, but again the outcome is worse with conventional salvage chemotherapy and survival beyond 11 years from relapse for patients with late relapse and early relapse is only 24% and 11%, respectively.[19] Thus, HDCT followed by ASCT should be considered the treatment of choice for these patients. The use of HDCT is accepted in early relapsed disease, but is controversial in late relapsed disease. However, in the latter, the results have been better than those reported in most series of conventional chemotherapy, and HDCT should be offered to all relapsed patients after first-line chemotherapy.

Only two randomized studies, performed by the BNLI and the GHSG/EBMT, showed improved outcome for patients with relapsed disease treated with HDCT.[20,21] In the BNLI trial, the 3-year event-free survival rate for patients who received high dose chemotherapy (BEAM) was better than that observed in patients who received standard dose therapy (mini-BEAM): 53% versus 10%, P=0.025. However, the study failed to show any statistically significant OS advantage.[20] The German Hodgkin Lymphoma Study Group conducted a phase III trial with 161 patients who had relapsed after initial chemotherapy; the 3-year freedom from treatment failure (FFTF) for the HDCT group (2 cycles of dexa-BEAM followed by HDCT with BEAM) was 55%, compared with 34% (P=0.019) for the SDT group (4 cycles of dexa-BEAM); overall survival did not differ significantly. When patients were stratified for early relapse (relapse within the first 12 months), the FFTF was 41% for autologous transplant vs. 12% for conventional therapy. For patients with late relapse, there was also a significant difference in FFTF favoring the autologous transplant arm (75% vs. 44%).[21] Thus, these two randomized trials support the use of autologous transplant as second-line therapy by showing an improved DFS. The authors tried to explain the lack of a survival advantage. Reasons offered for no improvement in survival included the fact that almost half of the patients in the non-transplant arm received a transplant in subsequent relapses, and the observation that multiple remissions, although not sustained, could be obtained with conventional therapy. Another reason was that 40–50% of patients who undergo an autologous transplantation will subsequently relapse.

Some prognostic factors, evaluated at the time of relapse, can affect the outcome of these patients. The most relevant studies evaluating prognostic factors in relapsed HD were performed by Brice and by GHSG. In multivariate analysis, Brice *et al.*[22] identified two significant adverse prognostic factors, namely the <12 months duration of first remission (<12 months vs. >12 months; $P<0.0001$) and the III–IV stage disease at relapse (III–IV stage vs. I–II stage; P=0.0013); patients with none of these risk factors had a freedom from second failure rate of 62% and an overall survival rate of 87%, compared with a freedom from second failure rate of 32% and OS rate of 44% for patients with both the unfavorable prognostic factors. In multivariate analysis, the GHSG[13] identified three adverse prognostic factors (<12 months duration of first remission, III–IV stage disease at relapse, haemoglobin <10.5 g/dL for female or <12 g/dL for male): the 4-year rates for freedom from second failure and OS for relapsing patients with three unfavourable factors were 17% and 27%, respectively. In contrast, the 4-year rates for freedom from second failure and OS for relapsing patients with none of the unfavourable factors were 48% and 83%, respectively.

In an attempt to improve these results, we sequentially enrolled poor prognosis HL patients in a protocol of HDCT (TECA) followed by ASCT, commonly used in other diseases, such as retinoblastoma, breast cancer and germ cell tumors.[7–9]

There was no significant increase in infective and non-infective complications and no transplant-related deaths.

In conclusion, our results are better than those obtained with other conventional schedules of salvage therapy or conditioning regimens for ASCT, such as BEAM or dexa BEAM and offer a chance of cure in poor prognosis HL patients. A randomized trial may be useful to confirm the good anti-HL activity and low toxicity of these treatment schedules in poor prognosis HL patients.

Funding

This work was supported by Associazione Italiana per la Ricerca sul Cancro (AIRC), Investigator Grant and *Special Program Molecular Clinical Oncology 5 per mille n. 9965*, Milan, Italy.

Authorship disclosure

RR was the principal investigator and takes primary responsibility for the paper. FF, MDI, MC, SB, GI, AC, OM and RR recruited and treated the patients. GS and RR participated in the statistical analysis, MFM, AV, FD and RR coordinated the research. MDI, MC, SB, AR and RR wrote the paper. MDI and SB contributed equally to this manuscript.

Conflict of interest: The authors declare no conflict of interest.

Acknowledgements

This article is dedicated to the memory of Antonio Tabilio. The authors would like to thank Professor C. Perillo for English editing of the manuscript.

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