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Allogeneic Stem Cell Transplantation in Treatment of Aggressive Lymphomas: Case Series

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Aim. To assess the outcome of allogeneic stem cell transplantation in patients with aggressive lymphoma.

Methods. Between 1991 and 2002, 22 patients with aggressive lymphoma in advanced phase of the disease underwent allogeneic stem cell transplantation at the Division of Hematology, Zagreb University Hospital Center. Seventeen patients received stem cells from the bone marrow. Eighteen patients underwent total body irradiation and received cyclophosphamide for conditioning, whereas the rest of the patients received busulfan and cyclophosphamide (n = 2) or chemotherapeutic protocol combining carmustine, melphalan, etoposide, and cytarabine (BEAM regimen) (n = 2). All patients received cyclosporin and short methotrexate for the prophylaxis of graft-versus-host disease (GVHD).

Results. Three months after allotransplantation, 17 patients had complete remission, 3 patients had active disease, and the outcome in 2 patients was early death. Nine patients were alive and in complete remission for 4 to 124 months, whereas 13 patients died (8 because of disease progression and 3 because of GVHD and infection). The probability of overall survival at 4 years was 47%.

Conclusion. Allogeneic transplantation is an effective therapy for advanced aggressive lymphoma. Because of high treatment-related toxicity and mortality, prospective trials are needed to asses the best time when to apply this treatment.

Keywords: *antineoplastic combined chemotherapy protocols; busulfan; carmustine; cyclophosphamide; cytarabine; etoposide; hematopoietic stem cell transplantation; Hodgkin disease; lymphoma; melphalan; transplantation conditioning; whole-body irradiation*

In patients with relapsed or advanced aggressive lymphoma the principal curative approach involves supralethal doses of chemotherapy, often in combination with radiation therapy (1). The major life-threatening toxicity of these treatment regimens is irreversible myelosuppression. To circumvent the accompanying myelosuppression, bone marrow support from either syngeneic, allogeneic, or autologous bone marrow or peripheral blood stem cells has been used as a source of hematopoietic repopulation (2).

Allogeneic stem cell transplantation has been increasingly used as a treatment modality in patients with relapsed and refractory aggressive lymphoma (3-7). Allogeneic transplantation may be a very effective therapy because of two potential benefits: transplant of tumor-free bone marrow and possible graft-versus-lymphoma effect of transplanted immunocompetent cells (7).

We report the outcome of allogeneic stem cell transplantation in a series of patients with aggressive lymphoma.

Patients and Methods

Patients

Between February 1991 and March 2002, 22 patients with aggressive lymphoma underwent allogeneic transplantation. Most allografted patients were young and treated for anaplastic large cell lymphoma (Table 1). They received three or more treatment cycles before allotransplantation; six of them were autografted before allotransplantation. Protocol and forms were approved by the Ethical Committee of the Zagreb University Hospital Center, Zagreb.

Conditioning and Source of Stem Cells

In 18 patients, the source of stem cells was the bone marrow. Three patients received stem cells from peripheral blood, and one patient received them from the cord blood.

Most patients (n = 18) were conditioned with cyclophosphamide 120 mg/kg and total body irradiation (TBI). Total dose was 12 Gy delivered at a dose rate of 4.4-6.9 cGy/min in three 4-Gy fractions daily over three days (8). Busulfan 16 mg/kg followed by cyclophosphamide 120 mg/kg (9) was given to 2 patients for conditioning, and chemotherapeutic protocol combining carmustine, melphalan, etoposide, and cytarabine (BEAM regimen) (10) was used as a preoperative regimen in the remaining 2 patients.

Table 1. Clinical characteristics of 22 patients with aggressive lymphoma, who underwent allogeneic stem cell transplantation at the Zagreb University Hospital Center between 1991 and 2002

Patient characteristics[a]	No. of patients[b]
Men/women	12/10
Median age (years, range)	21 (4-43)
Morbus Hodgkin/NHL	4/18
Histology of NHL:	
ALCL	11
follicular grade III	2
lymphoblastic	2
T-peripheral lymphoma	3
Line of therapy (median, range)	3 (1-5)
ABMT yes/no	6/16
Disease status at transplantation:	
persistent lymphoma	4
remission	4
relapse	14
sensitive	12
refractory	2
Stem cell source:	
marrow	18
blood	3
cord blood	1
Conditioning:	
TBI/Cy	18
BU/Cy	2
BEAM	2
Median follow-up (months, range)	50 (1-124)

[a]Abbreviations: NHL – non-Hodgkin's lymphoma; ALCL – anaplasic large cell lymphoma; ABMT – autologous bone marrow transplantation; TBI – total body irradiation; Cy – cyclophosphamide; BU – busulfan; BEAM – chemotherapeutic protocol combining carmustine, melphalan, etoposide, and cytarabine.
[b]Unless stated otherwise.

Matching and GVHD Prophylaxis

In all allografted patients, the donors were HLA-A, B, and DR genotypically identical; MLC non-reactive siblings. For prophylaxis of graft-versus-host disease (GVHD), the patients received cyclosporine and short methotrexate therapy (11). Methylprednisolone 2-5 mg/kg or antilymphocyte globulin was given to treat acute GVHD (12).

Supportive Care

All patients had central venous catheter and were nursed in laminar airflow units or reverse isolations from days –7 to at least +30 after transplantation. For gut decontamination and prophylaxis of bacterial infection, patients received oral ciprofloxacin (13) and were put on a sterile diet. Cotrimoxazole was given for prophylaxis of *Pneumocystis carinii* infection (14). Transfusions of red blood cells from random donors were given to maintain hemoglobin levels above 70 g/L and platelets above $20x10^9$/L.

Statistical Analysis

We analyzed data obtained by August 2002. Continuous variables were analyzed using Mann-Whitney test, and categorical variables using chi-square test. The probability of event-free survival and overall survival was calculated by a method described in a BioMeDical (BMDP) package program (15).

Results

Three months after allotransplantation, complete remission was documented in 17 (74%) patients and active disease in 3 (15%) patients (Table 2). Two patients with refractory disease died because of serious fungal and bacterial infection early after allotransplantation. The incidence of GVHD was 50%. In 5 out of 11 patients GVHD grade II-IV was documented. Seven out of 14 patients at risk developed chronic GVHD.

The probability of event-free survival (Fig. 1) and the probability of overall survival (Fig. 2) at 4 years were 43% and 47%, respectively.

The main causes of death in 13 patients were lymphoma (n = 8), GVHD with or without infection (n = 3), heart failure (n = 1), and serious fungal lung infection (n = 1). Nine patients were alive and in complete remission for 4 to 124 months (Table 2).

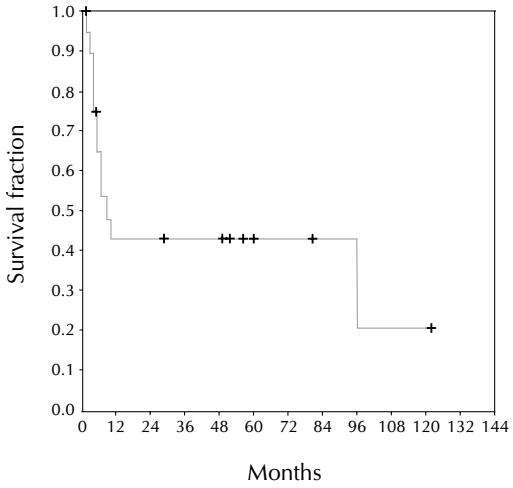

Figure 1. Probability of event free survival for patients with aggressive lymphoma who underwent transplantation of allogeneic bone marrow. Pluses indicate censored cases.

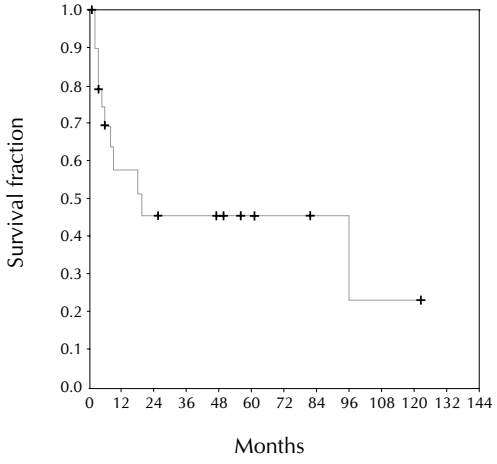

Figure 2. Probability of overall survival for patients with aggressive lymphoma who underwent transplatantion of allogeneic bone marrow. Pluses indicate censored cases.

Table 2. Outcome of allogeneic stem cell transplantation for aggressive lymphoma in 22 patients, who underwent allogeneic stem cell transplantation at the Zagreb University Hospital Center between 1991 and 2002

Parameter[a]	No. of patients
Disease status 3 months after TX:	
complete remission	17
active disease	3
early death	2
GVHD:	
acute	11
acute grade II-IV	5/11
chronic	7/14[b]
Main cause of death:	
disease progression	8
GVHD ± infection	3
other	2
Survived	9

[a]Abbreviations: TX – transplantation; GVHD – graft-versus-host disease.
[b]Patients at risk of developing chronic GVHD.

Discussion

Our study showed that allogeneic transplantation was an effective treatment for about 30-45% patients with aggressive lymphoma in advanced phase of the disease. Serious toxicity of the procedure with high mortality rate was the major problem of the therapy. According to International Bone Marrow Transplant Registry (16), the 3-year survival rates in 326 patients with diffuse large cell lymphoma allografted between 1994 and 1999 from HLA-identical siblings were 46±23% in 25 patients in the 1st remission, 32±9% for 177 patients in relapse, and 24±9% for 124 patients with persistent disease. In relapsed lymphoma, some clinical trials prospectively compared allogeneic and autologous transplantation (17-19). In these series, half of the patients had diffuse large cell lymphoma. Progression-free survival at 2 years for allogeneic and autologous transplantation was 47% and 24%, respectively. The relapse rate was lower in the allotransplant group. European Blood and Marrow Transplant Group also showed a lower relapse rate after allogeneic transplantation, but the transplant-related mortality was significantly higher than in the autotransplant group (18,19). Treatment-related mortality in this group of patients ranged between 20-50%, usually due to GVHD, opportunistic infections, and pneumonitis; in our group of patients, it was about 25-30%. Due to increased treatment-related mortality, there was no survival advantage in allotransplant patients compared with autologous transplant group.

In an effort to reduce the morbidity and mortality associated with GVHD, several groups used the technique of T-cell depletion (19,20). The incidence of GVHD grade 2-4 in these studies was about 20% (mostly grade 2). The treatment-related mortality was less than 20%, and the disease-free and overall survival between 50% and 60%. Other approaches to improve results of allogeneic transplants, such as non-myeloablative conditioning and donor lymphocyte infusions, are also being investigated (21,22). In a recent study, 23 heavily pre-treated patients underwent matched allogeneic transplantation after low-intensity conditioning with a fludarabine-based treatment program (23). Transplant-associated mortality was 30% and estimated disease-free survival at three years 40%.

In conclusion, allogeneic stem cell transplantation in advanced aggressive lymphoma seems to be an effective therapy in about 30-40% of patients. High treatment-related toxicity and mortality may be overcome by using transplantation in earlier phase of the disease in patients at high-risk by either employing T-cell depleted graft or using non-myeloablative conditioning.

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