Autologous stem cell transplantation in first-line treatment of high-risk aggressive non-Hodgkin's lymphoma

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A single center, retrospective analysis evaluating the outcome of patients with poor-risk aggressive non-Hodgkin's lymphoma (NHL) treated with high-dose chemotherapy and autologous stem cell transplantation (ASCT) as a part of first-line therapy. Forty-seven patients younger than 65 years with diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL) or alk-negative anaplastic large cell lymphoma (ALCL) underwent ASCT between July 1997 and November 2005. Patients with DLBCL and alk-negative ALCL had 2 or 3 age-adjusted International Prognostic Index risk factors. All patients were transplanted after MACOP-B induction therapy followed by 2 courses of DHAP and myeloablative chemotherapy BEM or CBV. The complete response rate to the high-dose therapy was 79% with an estimated 5-year progression-free survival of 66%. At a median follow-up of 35 months (range, 16 to 112 months) the estimated overall survival at five years was 59%. There were 4 treatment-related deaths. Twenty-nine of 47 patients remain in complete remission. Our results confirm the efficacy of high-dose therapy with ASCT during first-line treatment of patients with poor-prognosis aggressive lymphoma, with substantial number of patients cured by using this treatment approach.

Keywords: high-dose chemotherapy; autologous transplantation, aggressive non-Hodgkin's lymphoma

Combination chemotherapy has been the mainstay in the treatment of patients with aggressive NHL. Despite potential curability of many patients with aggressive lymphoma, a significant number of patients die due to resistant or relapsed lymphoma. Prognosis of patients is influenced by several clinical and biological factors. Peripheral T-cell lymphoma and mantle cell lymphoma belong to the group of NHL with the most unfavorable prognosis, with 5-year survival rate of only 20-30% [1]. Patients with DLBCL are stratified according to the International Prognostic Index (IPI), which is based on evaluation of age, tumor stage, performance status, serum lactic dehydrogenase (LDH) concentration and number of extra nodal sites [2]. For patients younger than 60 years of age, the simplified age-adjusted IPI is used (aaIPI), which identifies four risk groups. Patients with an aaIPI score of 2 or 3 had less than 50% chance of long-term survival in the prerituximab era, therefore the use of intensive myeloablative therapy with ASCT represents one of attempts to improve the results achieved with conventional chemotherapy. The role of ASCT as a part of first-line therapy of aggressive NHL has been studied extensively during the last decade, but data from numerous uncontrolled as well as controlled trials are conflicting. Results of some studies suggest the beneficial role of ASCT for patients with high-risk disease whereas other trials have not confirmed prolonged survival of patients treated with ASCT. The primary reasons of discrepant results achieved in these trials are heterogeneity of patient population and different treatment schemes used, with some using only short induction and others prolonged or intensified induction therapy.

In 1997, we included consolidation high-dose therapy with ASCT to the treatment protocol of patients with aggressive lymphoma who had less than a 50% chance of long-term disease-free survival. This is a report of the results of 47 patients with high-risk aggressive NHL, who underwent ASCT as a part of their initial treatment.

Patients and Methods

This retrospective analysis was conducted in patients with aggressive Non-Hodgkin's lymphoma treated with ASCT as a part of their first-line therapy at the National Cancer Insti-

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tute, Bratislava (Slovakia). Between July 1997 and November 2005, 47 patients with high-risk aggressive lymphoma received myeloablative chemotherapy and autologous peripheral blood hematopoietic stem cell transplantation.

Inclusion Criteria. Patients with the following criteria were eligible: age between 18 and 65 years with previously untreated, aggressive lymphoma according to the World Health Organization (WHO) classification (diffuse large B-cell lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma or alk-negative anaplastic large-cell lymphoma)[3]; patients with DLBCL and alk-negative ALCL were included only if they had either high or high-intermediate risk disease defined by the age-adjusted International Prognostic Index. Patients with transformed indolent lymphoma were excluded. Adequate organ function was required, with left ventricular ejection fraction of >50%, DLCO >50% predicted, creatinine ≤150 μmol/l, no evidence of active hepatitis infection, negative HIV testing and no evidence of central nervous system lymphoma. All patients provided signed informed consent prior to transplantation.

Initial evaluation included computed tomography scanning of thorax, abdomen and pelvis, bone marrow biopsy and other investigational procedures according to clinical symptoms. All subjects were staged according to the Cotswolds modification of the Ann Arbor staging system [4].

Treatment. The protocol included three phases: induction with 10 weeks of MACOP-B; consolidation with 2 cycles of either DHAP (34 patients) or mini-BEAM (13 patients) regimens followed by intensification with myeloablative chemotherapy BEM (37 patients) or CBV (10 patients) and autologous peripheral stem cell transplantation.

The MACOP-B regimen was given according to the original scheme reported by Klimo & Connors [5]. DHAP consisted of 40 mg of dexamethasone administered intravenously (IV) on days 1 to 4, cytarabine (2 g/m^2 as a 4-hour infusion) was repeated after 12 hours on day 2 and cisplatin (100 mg/m^2) was given in a continous infusion for 24 hours on day 1. Therapy was repeated after 4 weeks. mini-Beam was administered in following scheme: carmustine 60 mg/m^2 IV on day 1, etoposide 75 mg/m^2 IV on days 2 to 5, cytarabine 100 mg/m^2 IV twice daily on days 2 to 5 and melphalan 30 mg/m^2 IV on day 6. Peripheral stem cells were collected and cryopreserved after prior mobilization with G-CSF in a dosage of 10μg/kg after second cycle of consolidation chemotherapy. A median number of CD34+ cells were 3.0 x 10^6/kg (range, 1.8-10.2). No purging procedures were performed. Patients who obtained complete remission (CR), complete remission unconfirmed (CRu) or partial remission (PR) after 2 courses of consolidation chemotherapy proceeded to transplant; patients with stable or progressive disease received further 2 courses of non-cross resistant salvage regimen.

Our institutional policy was to use CBV (cyclophosphamide 1600 mg/m^2 on day -5 to -3, carmustine 300 mg/m^2 on day -6, etoposide 200 mg/m^2 twice daily on days -5 to -3) as a myeloablative regimen. From September 1999 forward we started to use the BEM protocol (carmustine 300 mg/m^2 on day -7, etoposide 100 mg/m^2 twice daily on days -6 to -3 and melphalan 140 mg/m^2 on day -3). Starting on day 0, all patients received recombinant human G-CSF at 5μg/kg subcutaneously until their absolute neutrophil count (ANC) was ≥ 500 for 3 consecutive days. All patients received prophylactic antibiotics (ofloxacin, fluconazole, acyclovir). Broad spectrum antibiotics were started on the first febrile episode. Platelets or red blood cell transfusions were administered when the platelet count was less than 20,000/μl or hemoglobin less than 90 g/l. All blood products were irradiated before infusion. Post-transplant involved field irradiation was given to 9 patients with residual disease (mostly in the mediastinum). Doses ranged from 36 to 40Gy with usual fractionation 1.5 to 2Gy. Follow-up restaging with bone marrow studies (if initially involved), CT scans and gallium or PET scan were performed at 30-60 days post-transplant to determine the response. Response evaluation was based on the International Working Group criteria [6]. Complete response (CR) was defined as complete disappearance of disease and its symptoms for at least one month. Patients were considered to be in partial remission (PR) if they had resolution of all disease-related symptoms and at least 50% reduction in the sum of the products of the greatest perpendicular diameters (SPD) of measurable lymphoma manifestations. Stable disease (SD) was defined as no or less than 50% reduction of all evaluable disease sites; progressive disease (PD) was defined as appearance of any new lesion or a more than 25% increase from nadir in the SPD of measurable disease.

Neutrophil engraftment was defined as an absolute neutrophil count (ANC) ≥ 500/μl on 2 consecutive days. Time to neutrophil engraftment was calculated from day 0 to the first of the 2 required consecutive days. Platelet engraftment was defined as the first of 2 consecutive days with platelet count ≥ 20,000/μl followed by 30 days without a platelet transfusion.

Statistical Analysis. Primary endpoints were overall survival (OS) and progression-free survival (PFS). OS was measured from the day of stem cell infusion until death from any cause. PFS was measured from the day of stem cell infusion until documentation of disease progression, relapse, or death of any cause except early toxic deaths. In the absence of relapse or death, patients were censored at the time of last follow-up. Grading of symptoms and adverse events was assessed by using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC).

Basic description of the set of patients was made using frequency tables and descriptive statistics: mean, median, minimum and maximum. Kaplan-Meier survival curves were used for visualization of patients survival, both general and stratified by considered parameters [7]. Statistical significance of the considered parameters was evaluated via univariate Cox proportional hazards model using pre-defined alpha level equal to 0.05. All computations and graphs were done in statistical software SPSS 12.0.1 and Statistica 7.0.

Results

Patient Characteristics. The patient initial characteristics are shown in Table 1. The median age of this patient population at the time of transplant was 44 years (range, 20-60). Thirty-five (74%) of the 47 patients had a B-cell phenotype. Thirty-two patients had DLBCL, seven patients had PTCL-NOS, three had mantle cell lymphoma and five patients had alk-negative ALCL. Ninety-eight percent of the patients had advanced disease (stage III and IV). Eighty-nine percent of the patients had high-intermediate or high-risk disease defined by an aaIPI score of 2 or 3. All patients received MACOP-B as initial treatment. Six patients achieved CR, thirty-four patients had PR and 7 patients had either stable or progressive disease after the MACOP-B regimen (response rate of 88%).

Status at ASCT. Table 2 depicts clinical characteristics of the patients at the time of transplantation. Following consolidation chemotherapy consisting of either DHAP (72% of patients) or mini-Beam (28%), forty-five patients (96%) were chemosensitive and two patients had progressive disease. None of the patients had received radiation therapy before transplant.

The myeloablative regimens used were BEM in 37 patients and CBV (10 patients). All patients received only peripheral blood progenitor cells; bone marrow cells were not used.

Treatment Outcome. The median time to neutrophil engraftment was 13 days (range, 9-47). There was no association between number of infused cells and time to WBC engraftment (data not shown). The median time to platelet engraftment was 20 days (range, 9-402).

Thirty-seven patients (79%) achieved a CR with ASCT, three patients (6%) achieved a PR and three (6%) had progressive disease. Four patients died prior to day 28. Nine patients received involved-field radiation therapy due to residual disease (3 patients) or initial bulky mediastinal mass (6 patients). With a median follow-up of 35 months (range, 16 to 112) 29 of 47 patients remain in continuous CR without any further therapy. Fourteen patients have progressed or relapsed post-ASCT and all but one of them died because of disease progression. Four of the 14 relapsed patients underwent allogeneic stem cell transplantation and three of them subsequently died due to post-transplant complication or progression of lymphoma, one patient is in complete remission 26 months after reduced intensity allo-SCT. The estimated 5-year OS and PFS for the 47 patients is 59% (95% confidence interval [CI], 42 to 76%) and 66% (95% CI, 49 to 81%), respectively (Figure 1 and 2).

In a univariate analysis using Cox regression model, we identified two variables which remained predictive of PFS or OS (Table 3). Performance status ≥ 2 was associated with poor overall survival (relative risk [RR] of 3.0, 95% CI 1.10-8.18, p=0.031) and diagnosis of MCL was predictor for poor PFS (RR of 5.70, 95% CI 1.42-22.89, p=0.014).

Acute and chronic toxicity. There were four early deaths resulting from transplant-related toxicities with 100-day mor-

Table 1. Patient characteristics at diagnosis (n=47)

Characteristic	N	(%)
Age, years		
Range	20-60	
Median	44	
Sex		
Male	31	66
Female	16	34
Histology		
DLBCL	32	68
MCL	3	6
PTCL	7	15
ALCL, alk-	5	11
Stage		
I	0	0
II	1	2
III	6	13
IV	40	85
„B“ Symptoms		
Yes	38	81
No	9	19
BM Involvement		
Yes	21	45
No	26	55
Bulky mass (>10cm)		
Yes	11	23
No	36	77
LDH		
Elevated	42	89
Normal	5	11
Performance status (ECOG)		
0-1	26	55
2-4	21	45
Age-adjusted IPI		
aaIPI 1 (only MCL+PTCL)	5	11
aaIPI 2	20	42
aaIPI 3	22	47

BM indicates bone marrow; LDH, lactic dehydrogenase

Table 2. Patient characteristics at transplant (n=47)

Characteristic	N	%
Response to initial therapy		
CR	6	13
PR	34	72
SD/PD	7	15
Consolidation therapy		
DHAP	34	72
mini-Beam	13	28
Status before transplant		
CR	7	15
PR	38	81
PD	2	4
Conditioning regimen		
BEM	37	79
CBV	10	21

CR indicates complete remission; PR, partial remission; SD, stable disease; PD, progressive disease

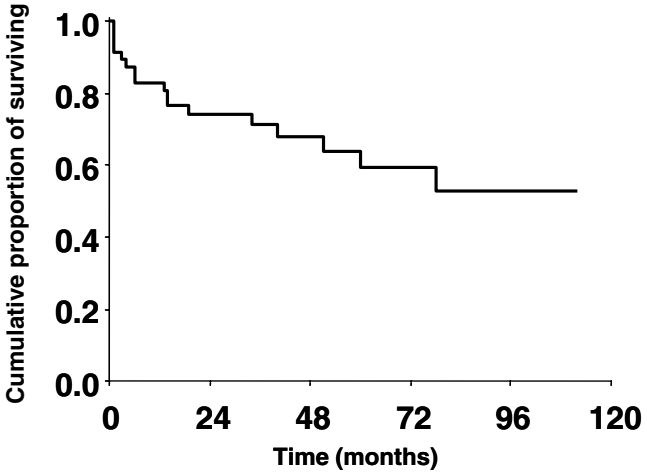

Figure 1. Overall survival from ASCT.

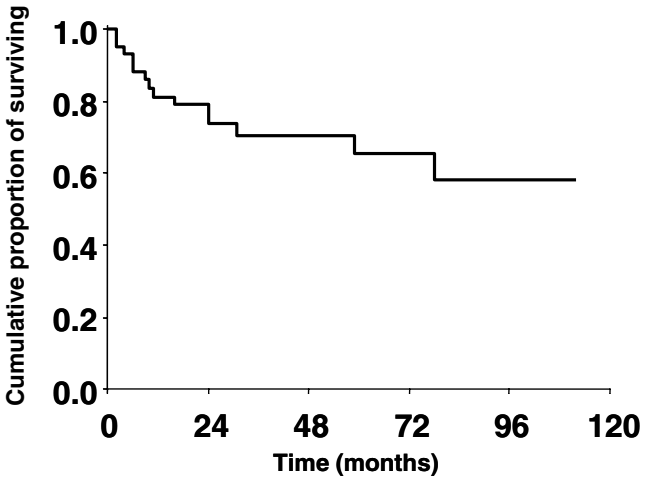

Figure 2. Progression-free survival from ASCT.

tality rate of 8.5%. Three patients died at 5, 34 and 37 days post-ASCT due to septic shock and one patient died at day 14 due to cardiac arrest. One patient died at day 21 post-transplant because of early lymphoma progression.

All 47 patients experienced grade 4 neutropenia and thrombocytopenia. The major acute toxicity was neutropenic fever, with 94% of patients requiring use of intravenous antibiotics. Thirteen patients (28%) developed grade 3-4 mucositis. There was one case of non-fatal hepatic sinusoidal obstruction syndrome.

One patient has been diagnosed with B-cell chronic lymphocytic leukemia 24 months post-transplant while in complete remission of NHL. We have not observed any other case of secondary malignancy. There has been to date no case of myelodysplasia (MDS)/acute myeloblastic leukemia (AML).

Table 3. Potential risk factors and associated relative risk for OS and PFS in univariate proportional hazards Cox model (n=47).

Prognostic factor	Relative risk	95% CI	p-value
OS			
Age (<50 yrs/>50 yrs)	1.93	0.74-5.08	0.180
aaIPI (2-3/0-1)	2.55	0.34-19.28	0.366
BM involvement	1.89	0.72-4.98	0.197
Bulky disease	2.03	0.75-5.51	0.165
PS (≥2/ 0-1)	3.00	1.10-8.18	0.031
Chemosensitivity at SCT	1.45	0.19-11.13	0.720
Post-transplant RT	0.22	0.03-1.69	0.146
PFS			
Sex (man/woman)	3.28	0.73-14.67	0.120
Age (<50 yrs/>50 yrs)	1.77	0.61-5.10	0.290
Histology (MCL/DLBCL)	5.70	1.42-22.89	0.014
aaIPI (2-3/0-1)	1.02	0.23-4.57	0.982
BM involvement	2.56	0.86-7.66	0.093
PS (≥2/ 0-1)	1.82	0.63-5.22	0.266
Post-transplant RT	0.25	0.03-1.91	0.182

Yrs indicates years; BM, bone marrow; PS, performance status; RT, radiotherapy;

Discussion

We have treated 47 patients with poor-prognosis aggressive NHL with ASCT in first-line therapy. The estimated 5-year PFS and OS rates are 66% and 59%, respectively. There were 4 transplantation-related deaths (TRM rate of 8.5%). According to data from a recently published meta-analysis of randomized trials studying the role of ASCT in first-line treatment of aggressive NHL, TRM rate was 5.7% in total [8]. Other adverse events were tolerable, with no case of BCNU-induced pulmonary toxicity and only 1 patient had grade 3/4 sinusoidal obstruction syndrome of the liver. Despite the relatively short follow-up of 35 months there has been no case of MDS/AML to date.

Most of our patients were chemosensitive before transplant, only 2 patients had chemo-resistant disease before ASCT. Seven patients (15%) entered ASCT while in CR, but the CR rate increased to 79% (37 patients) after the transplantation. The low CR rate achieved with the pre-transplant chemotherapy could be associated with the poor prognosis of this cohort of patients.

One of the major limitations in interpretation of our results is that we do not know exact number of patients who were eligible for this protocol but had not been transplanted because of refusal of high-dose therapy, early death or progression during the initial conventional chemotherapy, i.e. a dropout rate in our study is unknown. Other trials where intent-to-treat analysis was performed showed that approximately 60-70% of initially eligible patients underwent transplant.

Our data did not show worse outcome of patients with PTCL compared to DLBCL. This can be explained by the

impact of ASCT which may prolong long-term survival of patients with PTCL. Despite the very low number of patients with MCL, our results do not support data from other groups suggesting prolongation of progression-free survival with cytarabine-containing regimens and ASCT during first-line therapy [9]. All of our patients with MCL have relapsed early post-ASCT and only one of them attained second CR after non-myeloablative allogeneic SCT.

Since its introduction, high-dose therapy and autologous bone marrow or peripheral stem cell transplantation has become the treatment of choice for patients with chemosensitive relapse of aggressive lymphoma. Recommendation of ASCT as a part of first-line therapy is less clear. However, analysis of the results from the prospective randomized trials addressing this question implies two principal facts: there was no evidence for ASCT to improve OS, EFS or PFS in the group of standard risk patients [10-15] and positive results were achieved in the studies utilizing full course of conventional induction chemotherapy with ASCT used in the consolidation setting [16-19]. Our results attained with the treatment protocol consisting of 10 cycles of the MACOP-B regimen plus 2 courses of DHAP or mini-Beam plus high-dose therapy with ASCT were therefore in accordance with the results published by Gianni et al. [17], Haioun et al. [16] and Milpied et al. [19] showing improved survival of patients treated with high-dose therapy in the consolidation setting.

The situation in the treatment of aggressive lymphomas has substantially changed during last decade. All current studies and protocols for the treatment of DLBCL incorporate rituximab (anti-CD20 monoclonal antibody) into their treatment schemes. Adding rituximab to CHOP or similar chemotherapy combination improved outcome of patients with DLBCL [20-22]. One population-based study performed in British Columbia showed, that adding rituximab to CHOP increased survival for diffuse large B-cell lymphoma by approximately 20% [23]. As was published by the same authors in another study even the poor-risk group of patients with the IPI score of 3-5 has a 4-year OS of 55% [24]. Therefore the role of high-dose therapy with ASCT has to be re-defined with respect to improved outcome of patients with DLBCL treated with chemoimmunotherapy. Combining the use of clinical factors with molecular markers it will be necessary to identify patients who may still profit by the high-dose therapy with ASCT.

In conclusion, the results of our study suggest that adding high-dose therapy with ASCT to full-course induction chemotherapy improve the outcome of patients with poor-risk aggressive NHL.

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