High-dose therapy and autologous stem cell transplantation in patients with diffuse large B-cell lymphoma in first complete or partial remission

T. PAPAJIK[1*], L. RAIDA[1], E. FABER[1], J. VONDRAKOVA[1], V. PROCHAZKA[1], Z. KUBOVA[1], I. SKOUMALOVA[1], M. JAROSOVA[1], L. KUCEROVA[2], M. TICHY[2], B. PAUCEK[3], M. MYSLIVECEK[4], C. NEORAL[5], I. ORAL[6], J. JARKOVSKY[7], L. DUSEK[7] K. INDRAK[1]

[1]Department of Hemato-oncology, [2]Department of Pathology, [3]Department of Radiology, [4]Department of Nuclear Medicine and [5]Department of Surgery, University Hospital, Olomouc, I. P. Pavlova 6, 775 20 Olomouc, Czech Republic, e-mail: tomas.papajik@fnol.cz; [6]Hranice Hospital, Czech Republic; [7]Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic

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Improved survival has been observed in poor-risk diffuse large B-cell lymphoma (DLBCL) patients treated with high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) in first complete remission. Retrospective studies have suggested that HDT with ASCT can improve survival also in partial responders but some doubts about the advantage of intensive therapy in such patients still remain. We evaluated retrospectively the results of HDT and ASCT in 55 patients with confirmed DLBCL treated between May 1999 and July 2006. Thirty-six patients (65%) showed partial remission (PR) and 19 patients (35%) reached complete remission (CR) after induction treatment with (44%) or without (56%) concomitant rituximab (R) immunotherapy. After HDT and ASCT, 69% of patients fulfilled the criteria of CR, 22% had unconfirmed CR (CRu), 7% remained in PR and 1 patient (2%) relapsed. Twenty patients in PR after the induction treatment reached CR after ASCT, 12 other PR patients achieved CRu. The 5-year event-free survival (EFS) of the 55 transplanted patients was 76% (95% confidence interval /CI/, 63% to 89%) and the 5-year overall survival (OS) was 85% (95% CI, 73% to 97%). The EFS and OS rates differed significantly only between patients younger than 40 years and older groups (p=0.022 and p=0.046, respectively). On univariate analysis of prognostic factors, EFS and OS were not affected by any of the following: age, sex, stage, subtype of DLBCL, initial lactate dehydrogenase, beta-2-microglobulin and serum thymidine kinase levels, International Prognostic Index (IPI) and age-adjusted IPI scores, induction treatment with or without rituximab and type of primary therapeutic response (CR vs PR). These results show that first-line HDT and ASCT for adults up to the age of 65 years with poor-risk DLBCL is a feasible and effective treatment option even in the era of R-chemotherapy in CR as well as for patrients in PR.

Key words: diffuse large B-cell lymphoma, autologous transplantation, rituximab, survival

Diffuse large B-cell lymphoma (DLBCL) is the most frequent lymphoma subtype in industrialized countries of Europe and North America, accounting for 30-40% of all new non-Hodgkin's lymphoma (NHL) cases. DLBCL represents a heterogeneous group of tumors with poor histopathological reproducibility of its major subtypes and variants. However, the essentially similar treatment approach to all DLBCL patients has led the International Lymphoma Study Group to create a separate category of DLBCL in the revised European-American (REAL) and World Health Organization (WHO) classifications of lymphoid neoplasms [1, 2]. DLBCLs are highly chemotherapy-sensitive malignancies. The probability of being cured depends on the presence or absence of adverse prognostic factors such as the tumor stage, patient's age and performance status, lactate dehydrogenase (LDH) level, number of extranodal organs involved (included in the International Prognostic Index – IPI) [3], beta-2-microglobulin (B2M) level [4], chromosomal changes [5] or expression of important cell regulatory genes and proteins [6, 7]. Achieving complete remission (CR) with first-line therapy is another very important prognostic indicator as patients who fail to achieve it have a notably worse prognosis irrespective of subsequent conventional salvage therapy [8, 9]. High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) has been established as the best treatment for DLBCL

* Corresponding author
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patients with relapsed disease still responding to salvage therapy [10] and should also be early proposed to patients who achieve partial remission (PR) after induction treatment [11]. The final results of randomized multicenter trials compared HDT and ASCT with standard or sequential chemotherapy confirmed that HDT is superior to conventional treatment in young, poor-risk DLBCL patients in first CR [12, 13].

Recently reported results of rituximab (chimeric anti-CD20 monoclonal antibody) added to standard induction chemotherapy in DLBCL have documented improved remission and survival rates [14, 15] and have also showed that the addition of rituximab (R) to HDT means no unexpected toxicity, allows the harvesting of sufficient numbers of stem cells and safe performance of AT in high-risk patients [16, 17, 18].

We retrospectively analyzed results of 55 patients with DLBCL who were treated with HDT and ASCT in first CR or PR at the Department of Hemato-oncology, University Hospital Olomouc between 1999 and 2006. The purpose of the analysis was to determine progression-free and overall survival of this population and to identify variables correlated with the outcomes.

Patients and methods

Patients. From May 1999 to July 2006, 55 ASCTs in confirmed histopathological diagnosis of DLBCL (classified according to the REAL/WHO system) were performed in the group poor-risk patients younger than 65 years who achieved CR and or in patients who achieved only PR after induction chemotherapy or R-chemotherapy. The study population consisted of 29 females and 26 males with the median age of 41 years (range, 19-62). The cohort included 29 patients with centroblastic or immunoblastic DLBCL (53%), 7 patients with T-cell or histiocyte-rich DLBCL (13%), 2 patients with plasmablastic DLBCL (3%) and 17 patients with mediastinal (thymic) DLBCL (31%). Eleven of the 29 patients with centroblastic or immunoblastic DLBCL (20% of all DLBCL) had a small proportion of the follicular component in their lymph node samples. None of them had a previously known history of follicular lymphoma. All pathological specimens were reviewed by two independent hematopathologists and a panel of monoclonal antibodies including anti-CD20, CD79a, CD5, CD3, bcl-2 and Ki-67 was used.

The treatment protocols were reviewed and approved by our institutional review board, the Independent Ethical Committee of University Hospital Olomouc, and written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Staging and treatment. All patients were initially staged according to the Ann Arbor system [19]. Physical examination, laboratory tests, bone marrow biopsy, thoracic and abdominal computed tomography were performed in all of them. The lymphoma biopsy specimens were reviewed by an expert pathologist and a panel of necessary immunohistochemical staining was done in each patient. The baseline characteristics of the patients at the time of diagnosis are summarized in Table 1. The indication criteria for ASCT were defined as IPI 3 - 5 or age-adjusted IPI (aaIPI) 2 – 3 (for patients younger than 60 years), IPI 1 – 2 or aaIPI 1 with one or more additional adverse prognostic parameters (bulky disease more than 10 cm in largest diameter, B2M more than 3.0 mg/l, bcl-2 protein expression in immunohistochemical staining), and failure to achieve CR in stage II with bulky disease or III – IV irrespective of the patient's initial IPI/aaIPI.

Three patients were primarily treated with 6 courses of the ProMACE-CytaBOM regimen, and 2 patients with 6 courses of PACEBO regimen. All other patients received intensive sequential chemotherapy consisting of 3 courses of PACEBO, 1 course of IVAM (ifosfamide 1500 mg/m^2 on days 1 to 5 with mesna support, etoposide 150 mg/m^2 on days 1 to 3, cytosine arabinoside 100 mg/m^2 on days 1 to 3, methotrexate 3 g/m^2 by 24-hour continuous infusion on day 5 with subsequent leucovorin rescue), and 1 course of HAM (cytosine arabinoside 2 g/m^2 twice daily on days 1 to 2, mitoxantrone 10 mg/m^2 on days 2 to 3) that was utilized as peripheral stem cells (PSC) mobilization regimen. An intrathecal injection of methotrexate (15 mg) and dexamethasone (4 mg) was routinely given before each chemotherapy course as prophylaxis for patients in the risk of central nervous lymphoma dissemination. Rituximab 375 mg/m^2 was administered on day 1 of the chemotherapy regimens in patients receiving chemotherapy with concomitant rituximab. PSC were mobilized after CE (cyclophosphamide 4 g/m^2 on day 1, etoposide 200 mg/m^2 on days 1 to 3) in 5 cases or after HAM in 50 cases followed by 5 μg/kg body weight of rhG-CSF from day 8. The PSC were collected by leukapheresis with a targeted minimum cell count > 2x10^6/kg body weight of CD 34+ cells and then cryopreserved without purging or CD34+ selection.

Preparative regimen and stem cell transplantation. The BEAM conditioning regimen (BCNU 300 mg/m^2, etoposide 200 mg/m^2, cytosine arabinoside 200 mg/m^2, and melphalan 140 mg/m^2) was given to all 55 patients. The cryopreserved CD34+ cells were reinfused on day 0. Broad-spectrum antibiotics and antifungal therapy were initiated in case of proven infection or fever above 38°C in the neutropenic phase. Leukocyte-filtered and irradiated blood products (25 Gy) were given for red cell and platelet support. Radiotherapy of 40 Gy was given to the sites of primary bulky disease at the physician's decision only when the patient did not reach CR by day 100 after transplantation.

Response and follow-up. The response was evaluated after 6 cycles of ProMACE-CytaBOM or PACEBO, and at the time of HAM chemotherapy in patients treated with intensive sequential chemotherapy. Only patients with at least partial response were indicated for mobilization of stem cells. The final evaluation of response was performed on day 100 after stem cell transplantation. Lymphoma response was classified according to the International Workshop Criteria [20].

CR was defined as complete disappearance of any detectable clinical and radiological evidence of disease. All lymph nodes and nodal masses had to regress to their normal sizes (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment had to decrease to ≤ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD). Also normalization of biological abnormalities assignable to lymphoma seen at diagnosis and no new lesion were required. The spleen, if considered to be enlarged before therapy on the basis of a computed tomography scan, had to regress in size and could not be palpable by physical examination. If the bone marrow was involved before treatment, the infiltrate had to be cleared in repeated biopsy. Unconfirmed CR (CRu) was defined as CR with one or more of the following features: a residual lymph node mass greater than 1.5 cm in the greatest transverse diameter that had to regress by more than 75% in the SPD and/or indeterminate bone marrow with normalization of all biological abnormalities. This category was used only in the final evaluation of response. If persistent lymphoma cells were demonstrated in any puncture or biopsy analysis, the patients were classified as partial remission (PR). PR was defined as regression of more than 50% (in the SPD) of all measurable lesions and disappearance of non-measurable lesions and no new lesions on physical and radiological examinations. Progressive disease was characterized as the appearance of a new lesion or growth of any previously identified abnormal lymph node by more than 50% of the SPD.

The follow-up procedures included physical and laboratory examinations every three months for at least the first 2 years, every six months for the next 2 years, and annually thereafter. Thoracic and abdominal tomography was performed 1 year after transplantation and then at the physician's discretion.

Statistical methods. For basic description of continuous parameters, the mean as well as the range of observed values were used, for description of categorized parameters, frequency tables were used. Survival curves were constructed based on the Kaplan-Meier methodology [21]; differences in survival between categories of analyzed parameters were evaluated using the log-rank test. The relative risk estimates together with 95% confidence intervals and also the statistical significance of relationship between disease-free survival and considered risk factors were obtained via the Cox proportional-hazards model [22]. The critical level of statistical significance for all analyses was set at α=0.05. The analyses were performed using Statistica for Windows 7.1 (StatSoft Inc., 2005) and SPSS 12.0.1 (SPSS Inc., 2003).

Results

The main base-line characteristics of the study group are shown in Table 1. Treatment characteristics are shown in Table 2. Fifty-six percent of the patients received only chemotherapy, 44 percent were treated initially with R-chemotherapy. Of the 55 patients transplanted, 36 (65%) had PR and 19 (35%) reached CR after induction treatment. The median interval between the date of diagnosis and ASCT was 7 months (range, 5 - 18 months). The median number of reinfused CD34+ cells was 6.43x10^6/kg. Only 4 patients were transplanted with less than 4x10^6/kg of CD34+ cells. No differences in the number of collected CD34+ cells were noticed between patients who were treated initially with rituximab and those who were not and a history of rituximab treatment did not affect stem cell engraftment.

Response to Autologous Stem Cell Transplantation, Toxicities and Follow-up. The tumor response was assessed on day 100 after ASCT. Thirty-eight patients (69%) fulfilled the criteria of CR, 12 patients (22%) had CRu, 4 patients (7%) remained in PR and 1 patient (2%) relapsed (from CR after

Table 1. Base-Line Characteristics of the Patients

Characteristic		No.
Age at diagnosis	Median (yr) yr	41
	Range (yr)	19-62
	<40 yr	26 (47%)
	≥40	29 (53%)
Ann Arbor stage	II	12 (22%)
	III or IV	43 (78%)
Bone marrow involvement		10 (18%)
Serum lactate dehydrogenase	Normal	22 (40%)
	Elevated	33 (60%)
Serum beta-2-microglobulin	<3,0 mg/l	31 (56%)
	≥3,0 mg/l	24 (44%)
Serum thymidin kinase	<13,5 U/l	16 (29%)
	≥13,5 U/l	39 (71%)
International prognostic index	0 or 1	15 (28%)
	2	20 (36%)
	3 or 4 or 5	20 (36%)
Age-adjusted prognostic index	0	8 (16%)
(only for patients <60 yr)	1	17 (33%)
	2 or 3	26 (51%)
Tumor diameter	≥10 cm	30 (55%)
Nodal involvement	>one site	44 (80%)
Extranodal involvement	>one site	32 (58%)

Table 2. Treatment Characteristics of the Study Population

Characteristic		No.
Induction therapy	ProMace-CytaBOM	3 (5%)
	PACEBO	2 (4%)
	Sequential therapy	50 (91%)
Rituximab with chemotherapy	Yes	24 (44%)
	No	31 (56%)
Disease status after induction	CR	19 (35%)
chemotherapy	PR	36 (65%)
Mobilization chemotherapy	CFA+ETO	5 (9%)
	HAM	50 (91%)
Reinfused CD34+ stem cells	Median	6,43x10^6/kg
	Interval	2,76 – 37,3x10^6/kg

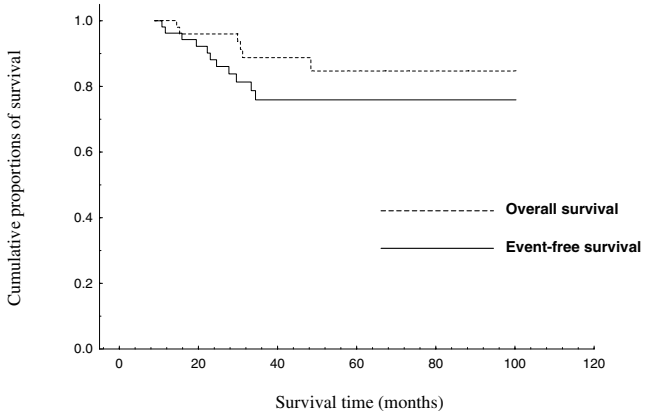
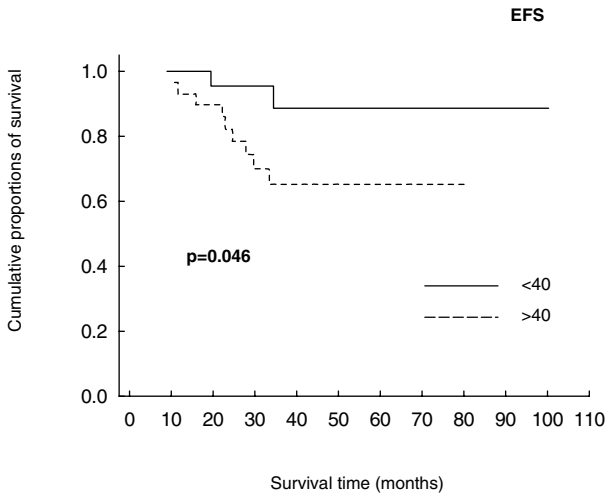


Figure 1. Event-free and overall survival of patients



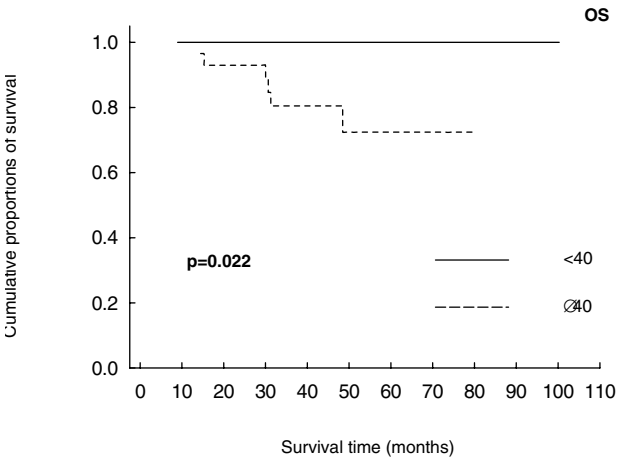


Figure 2. Event-free (EFS) and overall survival (OS) of patients according to age

induction treatment). Twenty patients in PR after initial treatment reached CR after ASCT, 12 other PR patients reached CRu. Radiotherapy after ASCT was given to 9 patients, 6 were in CRu and 3 were in PR on day 100. All of them had tumor bulk greater than 10 cm at diagnosis. The median follow-up of the patients from the time of diagnosis was 42 months (range, 9 – 100 months). No toxic or transplant-related death was reported after ASCT. No patient developed a second malignancy or myelodysplastic syndrome to the date of analysis.

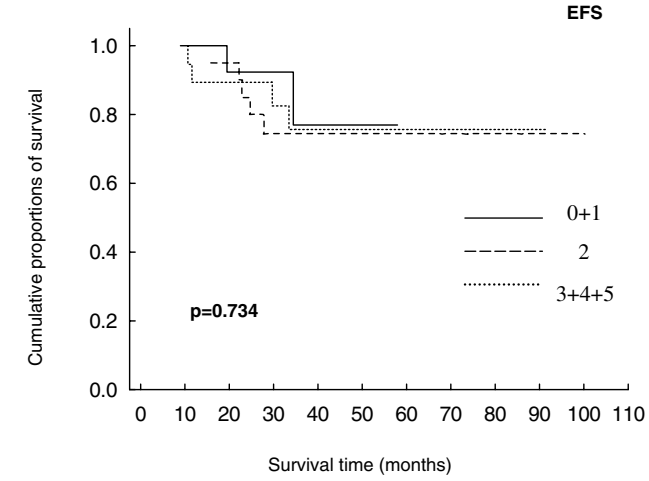
Event-Free Survival. The 5-year event-free survival of the 55 transplanted patients was 76% (95% confidence interval / CI/, 63% to 89%) (Fig.1). The event-free survival rates differed significantly only between patients younger than 40 years and older groups (p=0.046) (Fig. 2). On univariate analysis of prognostic factors, event-free survival was not affected by any of the following: age, sex, stage, subtype of DLBCL, LDH, B2M and s-TK levels, IPI (Fig. 3) and aaIPI scores, initial treatment with or without rituximab and type of primary therapeutic response (CR vs PR) (Fig. 4).

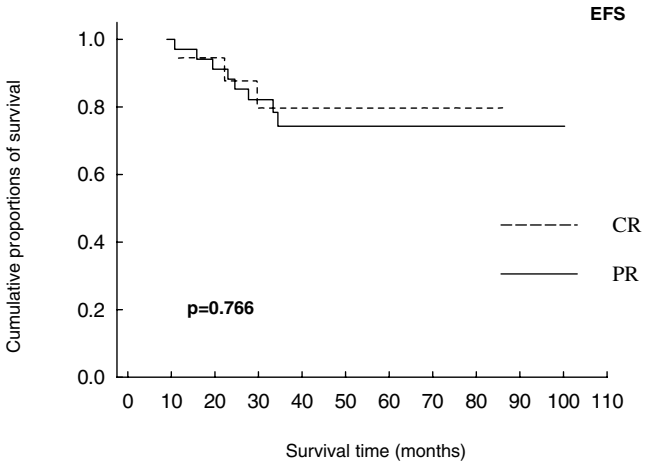
Overall Survival. The 5-year overall survival of the 55 patients was 85% (95% CI, 73% to 97%) (Fig. 1). The overall survival rates differed significantly only between patients younger than 40 years and older groups (p=0.022) (Fig. 2). There were 14 patients (54%) with the mediastinal subtype of DLBCL in the group of patients younger than 40 years, but only 3 (10%) mediastinal DLBCLs in older patients. The patients with mediastinal DLBCL had excellent outcome and all are alive with a median follow-up of 44 months (range, 9 – 100 months) Despite of that, the univariate analysis of prognostic factors showed that the overall survival was not affected by any of the following: age, sex, stage, subtype of DLBCL, LDH, B2M and s-TK levels, IPI (Fig. 3) and aaIPI scores, initial treatment with or without rituximab and type of primary therapeutic response (CR vs PR) (Fig. 4).

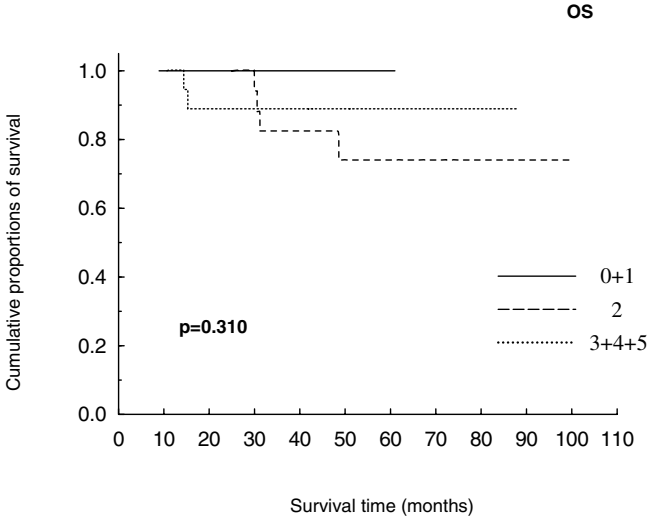
Relapses. Eleven patients (20%) relapsed/progressed within the median time of 23 months from the time of diagnosis (range, 11 – 34 months) and 11 months from ASCT (range, 3 – 27 months). Seven patients relapsed from CR after ASCT, 2 from CRu, 1 progressed from PR and in 1 patient relapse was detected before the final response evaluation (she was in CR before ASCT). Six of the relapsed patients died (11%); in all cases, lymphoma was the main cause of death.

Discussion

Treatment of DLBCL with conventional combination chemotherapy produces CR rates of 40% to 60%, EFS rates of approximately 40% to 50% and OS of 50% [8, 23]. Intensive chemotherapy in poor-prognosis patients compared with conventional treatment (CHOP) improves EFS (39% vs 29%, p=0.005) and OS (46% vs 38%, p=0.036) despite its higher toxicity [24] and sequential intensive chemotherapy is also superior to CHOP plus radiotherapy in low-risk patients with







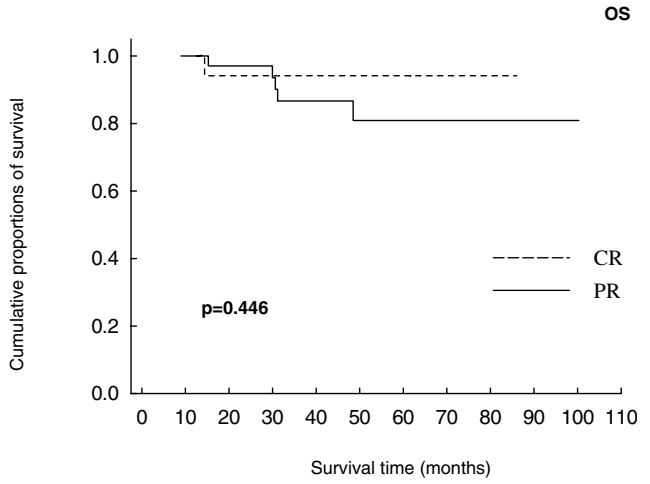


Figure 3. Event-free (EFS) and overall survival (OS) of patients according to international prognostic index (IPI) at diagnosis

Figure 4. Event-free (EFS) and overall survival (OS) of patients according to response to initial therapy

localized DLBCL (EFS 82% vs 74%, p=0.001; OS 90% vs 81%, p=0.001) [25]. Addition of rituximab to standard initial chemotherapy in DLBCL documented improved remission and survival rates in older patients [14] and in younger patients with low-risk DLBCL [15]. The survival benefit of up-front high-dose therapy and autologous peripheral blood stem cell (PBSC) transplantation was described in several randomized studies in high-risk CR or PR patients [11, 12, 13]. Other studies demonstrated that full-course conventional induction chemotherapy before ASCT led to better outcome than abbreviated induction with early ASCT [26, 27, 28] and that substantial tumor reduction before transplantation could positively affect relapse and survival rates.

We retrospectively report the results of ASCT in a series of 55 poor-risk patients with DLBCL in first CR or PR. The definition of poor-risk patient was not based only on IPI or aaIPI scores but other prognostic characteristics were also taken into account, such as bulky disease, levels of B2M and s-TK and failure to achieve CR after intensive induction therapy [29]. Some authors showed that IPI and aaIPI had no or small prognostic value in distinct DLBCL populations or that the prognostic factors were not the same throughout dirrerent phase of the disease [30, 31]. A relatively high-proportion of our patients were transplanted in PR, but most of them had tumor reduction of more than 2/3. We decided not to use CRu categories in response evaluation after initial therapy because a majority of patients had initial bulky disease and tumor residuals after induction therapy remained clinically significant. Positron emission tomography integrated with computer tomography should be the diagnostic method of choice in such a situation, but only a small proportion of patients were examined in this manner. All patients were trans-

planted after the BEAM preparative regimen and with sufficient amount of collected PSCs. Together with up-front indication of ASCT and using BEAM as a preparative regimen instead of total body irradiation and cyclophosphamid, these seem to be the main factors for zero transplant-related mortality and no occurrence of myelodysplastic syndrome and second malignancies. Initial treatment with rituximab did not affect stem cell collection and engraftment.

We found that younger patients with DLCBL had better EFS and OS than patients aged 40 or more. But age was not a significant prognostic factor for survival in the univariate Cox proportional hazards model. One possible explanation is disproportional incidence of the mediastinal DLBCL subtype in these age groups (54% in patients younger than 40 years, but only 10% of mediastinal DLBCL in the older patient group). From another point of view, histological variants and subtypes had no predictive value for EFS and OS. Together with other authors, we confirmed that follicularity in DLBCL does not adversely affect outcome after ASCT [32]. The Cox model also established that the adverse effect of IPI and aaIPI can be overcome by ASCT when given to chemotherapy-sensitive patients as consolidation treatment. The same results were observed in French NHL studies [30]. Our analysis also confirmed the identical probability of long-term survival for patients transplanted both in PR and CR, but it must be underlined that the quality of remission before ASCT and the intensity of initial chemotherapy still play a crucial prognostic role. The overwhelmig majority of our patients were treated with dose-dense chemotherapy containing high doses of methotrexate and cytosine arabinoside. This induction approach very probably led to a lower rate of relapse after ASCT in our study group.

From this point of view, there are very interesting results of adding rituximab to chemotherapy in DLBCL. R-chemotherapy improved response and survival rates in patients older than 60 years and in low-risk younger patients. No large phase III study comparing R-chemotherapy with chemotherapy alone was published in high-risk DLBCL patients younger than 60 years of age. But ASCT after R-chemotherapy induction could be an exciting approach to improve long-term survival of poor-risk DLBCL. Promising preliminary results of several studies with R-chemotherapy and subsequent ASCT showed a survival advantage for patients treated with immunochemotherapy combination [17, 18, 33]. The EFS curves between the R-chemotherapy and chemotherapy groups were not significantly distinct, but there was a trend to better EFS and lower relapse rate in R-chemotherapy in our study group (not shown). More patients and a longer follow-up will help to clarify this observation.

In conclusion, first-line HDT with ASCT for adults up to the age of 65 years with poor-risk DLBCL group in CR or PR is a feasible and effective treatment option both from short-term and long-term point of view. The quality of remission before ASCT and the intensity of initial chemotherapy still play a crucial prognostic role in high-risk patients and adding rituximab to induction chemotherapy can further improve remission and survival rates after ASCT.

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