Autologous stem cell transplantation in elderly patients (≥60 years) with diffuse large B-cell lymphoma: an analysis based on data in the European Blood and Marrow Transplantation registry

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ABSTRACT

Background
There is currently limited experience on the feasibility and efficacy of autologous stem cell transplantation in elderly patients with diffuse large B-cell lymphoma.

Design and Methods
We analyzed the outcome of 2612 patients with diffuse large B-cell lymphoma treated with autologous stem cell transplantation between 2000 and 2005 and reported to the European Blood and Marrow Transplantation registry. Four hundred and sixty-three patients (18%) were ≥60 years old at the time of the transplant (median, 63 years). When compared to 2149 patients <60 years old at the time of transplantation, the elderly patients had more frequently received at least two treatment lines (76% *vs.* 57%, $p<0.001$), were less commonly in first complete remission at the time of transplantation (23 % *vs.* 30 %, $p=0.005$) and received their transplants later after diagnosis (median time 14 months *vs.* 7.5 months, $p<0.001$).

Results
Non-relapse mortality was higher in elderly patients at 100 days (4.4 % *vs.* 2.8 %), at 1 year (8.7% *vs.* 4.7%) and at 3 years (10.8% *vs.* 6.5%) ($p=0.002$). With a median follow-up of 12 months for the surviving patients for the elderly group and 15 months for the younger group, the risk of relapse was 38% and 32%, respectively ($p=0.006$). The progression-free survival was 51% and 62%, respectively, at 3 years ($p<0.001$). The overall survival rate was 60% *vs.* 70%, respectively, at 3 years ($p<0.001$).

Conclusions
Autologous stem cell transplantation is feasible in selected elderly patients with diffuse large B-cell lymphoma, although non-relapse mortality is somewhat higher than in younger patients. Both progression-free and overall survival rates are promising taking into account the generally poorer outcome of elderly patients with diffuse large B-cell lymphoma.

Key words: autologous stem cell transplantation, diffuse large B-cell lymphoma, elderly patients, non-relapse mortality, outcome.

Citation: Jantunen E, Canals C, Rambaldi A, Ossenkoppele G, Allione B, Blaise D, Conde E, Tilly H, Cook G, Clark F, Gallamini A, Haynes A, Mounier N, Dreger P, Pfreundschuh M, and Sureda A for the EBMT Lymphoma Working Party. Autologous stem cell transplantation in elderly patients (≥60 years) with diffuse large B-cell lymphoma: an analysis based on data in the European Blood and Marrow Transplantation Registry. Haematologica 2008; 93:1837-1842. doi: 10.3324/haematol.13273

Manuscript received April 28, 2008.
Revised version arrived July 1, 2008.
Manuscript accepted July 16, 2008.

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma, accounting for 30-40% of all new cases. The median age of the patients at diagnosis is more than 60 years. The proportion of elderly patients is increasing in most societies and consequently the number of DLBCL patients over 60 years of age is also continuously increasing.

Age over 60 years is a poor prognostic factor in the International Prognostic Index. Recent improvements in the management of DLBCL in elderly patients, including addition of rituximab to CHOP[1] and the use of CHOP-14,[2] have improved outcome in this most common type of non-Hodgkin's lymphoma. However, a significant proportion of elderly patients with DLBCL fail to achieve a complete remission or experience a relapse associated with poor outcome.

High-dose chemotherapy supported by autologous stem cell transplantation (ASCT) is a standard of care in patients with relapsed chemosensitive aggressive lymphomas.[3] The issue is more controversial in patients receiving ASCT after the first-line treatment. Some studies performed in the pre-rituximab era suggested that ASCT is more beneficial than conventional therapy in patients with high-risk disease[4-6] but most randomized studies have not confirmed these observations.[7-11]

Limited data are available on the feasibility and efficacy of ASCT in elderly patients with DLBCL. This is due to the fact that the upper age limit in studies including ASCT has been about 60 years and has only recently been increased to 65 years. A general assumption has been that ASCT is associated with higher toxicity and hence less clinical utility in elderly patients.

Current knowledge on the feasibility and efficacy of ASCT in DLBCL patients 60 years or over is based on several small reports.[12-18] Only four series including at least 20 transplanted DLBCL patients over 60 years of age have been published.[19-22] Although these reports give some hints on early non-relapse mortality and outcome, they are too small to facilitate proper analysis of risk factors for non-relapse mortality or prognostic factors for long-term outcome. Therefore, a retrospective analysis based on data in the European Blood and Marrow Transplant (EBMT) registry was undertaken by the Lymphoma Working Party.

Design and Methods

The EBMT is a voluntary organization comprising 525 transplant centers mainly from Europe. Member centers are required to submit minimal essential data (Med-A form) from consecutive patients to a central lymphoma registry in which patients may be identified by subtype of lymphoma and type of transplantation. Participating transplant centers are subject to on-site audits to assess data accuracy and consecutive reporting. Informed consent was obtained locally according to regulations applicable at the time of transplantation. Since January 1, 2003 all EBMT centers have been required to obtain written informed consent prior to data registration following the Helsinki Declaration of 1975.

The EBMT database was used to identify patients with DLBCL aged 18-75 years old treated with a first ASCT between 2000 and 2005. Altogether there were 6758 patients in the registry of whom 1327 (20 %) were ≥60 years old at the time of transplantation.

Only fully documented transplants with EBMT MED-B forms (*www.ebmt.org*) were finally included in the present study (n=2612). By multivariate analysis this subgroup of patients was shown to be representative of all reported patients receiving ASCT for DLBCL in the study period.

Patients ≥60 years old at the time of transplantation (n=463, 18%) were compared with younger patients (n=2149) transplanted during the same period with regards to non-relapse mortality and outcome. The number of patients ≥60 years with DLBCL reported increased from 172 in year 2000 to 265 in year 2005 (an increase of 54% during the study period). The median age of the elderly group of patients was 63 years (range, 60-74). Within this group of patients 311 (67%) were 60-64 years old, 139 patients (30%) 65-69 years old, and only 13 patients (3%) 70-74 years old at the time of ASCT. The median age of the younger group of patients was 47 years old (range, 18-59).

Patient and transplant characteristics

The characteristics of the patients and transplants of the study population are presented in Table 1. Patients transplanted at the age of 60 years or more less commonly had B-symptoms and bulky disease at the time of diagnosis than had the younger patients. On the other hand, the elderly patients received ASCT later, had more often received at least two treatment lines and were less commonly in first remission at the time of transplantation. The median follow-up for the surviving patients was 14.5 months.

Statistical methods

The main goal of this study was to investigate the risk of non-relapse mortality and outcome after ASCT in DLBCL patients 60 years or older, and compare these with the risk of non-relapse mortality and outcome in younger patients, while adjusting for significant patient, disease- and transplant-related variables. All the analyses were executed in the entire patient cohort, considering age at ASCT (<60 years *vs.* ≥60 years) the main study variable.

Patient and transplant characteristics were compared between groups using the χ^2 test or Fisher's exact test for categorical variables and the t-test or Mann-Whitney U-test for continuous variables. The probabilities of progression-free survival were calculated from the time of transplantation using the Kaplan-Meier product-limit estimate, with the variance estimated by Greenwood's formula, and compared by the log-rank test. Neutrophil engraftment, non-relapse mortality and relapse or progression after ASCT were calculated using cumulative incidences to account for competing

risks, and compared by Cox univariate analysis. Potential prognostic factors for non-relapse mortality were studied in multivariate analyses using Cox proportional hazards regression. Some risk factors in the Cox model contained a category for *unknown* to avoid loss of information. The assumption of proportional hazards for each factor in the Cox model was tested using time-dependent covariates. All variables satisfied the proportionality assumption. All variables were tested for a significant interaction with the main factor under study. All *p* values were two-sided.

Cumulative incidences were calculated using the NCSS 97 software. All other computations were performed using the SPSS 13.0 statistical package.

Results

Table 1 presents the patients' and transplant characteristics according to age group.

Hematologic engraftment

No differences were observed in the numbers of $CD34^+$ cells infused or in the use of growth factors post-transplantation between the two groups. The number of $CD34^+$ cells infused was 5.2×10^6/kg (range, 0.6-47.2) in younger patients and 5.2×10^6/kg (range, 1.7-42.1) in patients over 60 years old. Granulocyte colony-stimulating factor (G-CSF) was used in 61% and 62% of the younger and older patients, respectively. Among the elderly patients G-CSF was associated with more rapid neutrophil engraftment (11 days *vs.* 13 days, $p<0.001$).

Neutrophil recovery occurred in all but 1.1% of patients (0.9% in younger patients and 1.7% in patients over 60 years of age at ASCT), with a median time to reach an absolute neutrophil count above 0.5×10^9/L of 11 days in both groups. The cumulative incidence of neutrophil engraftment was 99% (95% CI: 98.7-99.5) in the younger patients and 98.3% (95% CI:97.1-99.5) in the elderly patients (p=n.s.).

Non-relapse mortality

The rate of non-relapse mortality was higher in the group of elderly patients at all time points analyzed (Figure 1). Non-relapse mortality in the elderly and younger groups was 4.4% *vs.* 2.8% at 100 days after ASCT, 8.7% *vs.* 4.7% at 1 year, and 10.8% *vs.* 6.5% at 3 years, respectively (p=0.002). No differences were observed in non-relapse mortality at 100 days between patients aged 60-64 and those aged 65-69 (4.4% *vs.* 4.2%). In multivariate analysis four factors were statistically significantly associated with non-relapse mortality: age ≥ 60 years (RR 1.6, 95% CI 1.1.-2.3, p=0.01), two or more lines of therapy prior to ASCT (RR 1.9,95% CI 1.3-2.8, p=0.001), poor performance status at ASCT (RR 3.8, 95% CI 2.2-6.7, p=0.001), and refractory disease at ASCT (RR 1.9, 95% CI 1.1-3.3, p=0.02).

Infections were the main cause of non-relapse mortality among the elderly patients (56%) followed by multiorgan failure (16%), second malignancy (13%), pulmonary toxicity (3%) and cardiac toxicity (3%). Causes of death did not differ between younger and elderly patients except for second malignancy, which was more common in the elderly patients (13% *vs.* 5%). The risk of developing second malignancy was 2.5% *vs.* 1.4% at 3 years and 7.5% *vs.* 2.6% at 5 years, respectively (RR 2.2, 95%CI 1.0-4.7, p=0.05).

Table 1. Patient and transplant characteristics according to age at the time of autologous stem cell transplantation.

	<60 years (n= 2149)	≥60 years (n=463)	p
Age, median (range), years	47 (18-59)	63 (60-74)	–
Male sex	58.5%	59%	n.s.
Stage III-IV	72%	71.5%	n.s.
B-symptoms	49%	43%	0.04
Elevated LDH	49%	48%	n.s.
Bulky disease	30%	19%	<0.001
Time from dx to tx, (median), months	7.5	14	<0.001
Two or more previous treatment lines	57%	76%	<0.001
Prior rituximab therapy	26%	33%	0.009
Disease status/tx			
CR1	30%	23%	0.005
CR ≥2/PR/sens rel	63%	71%	
untested/refractory	7%	6%	
Poor performance status at tx#	2.3%	3.7%	n.s.
Stem cell source PB	99%	99%	n.s.
TBI in conditioning	1.7%	1.1%	n.s.
BEAM regimen	62%	73%	<0.001

LDH: lactate dehydrogenase; n.s.: not significant; dx: diagnosis; tx: transplantation; CR: complete remission; PR: partial remission; sens: sensitive; rel: relapse; #Karnofsky score; PB: peripheral blood; TBI: total body irradiation; BEAM: carmustine-etoposide-cytarabine-melphalan.

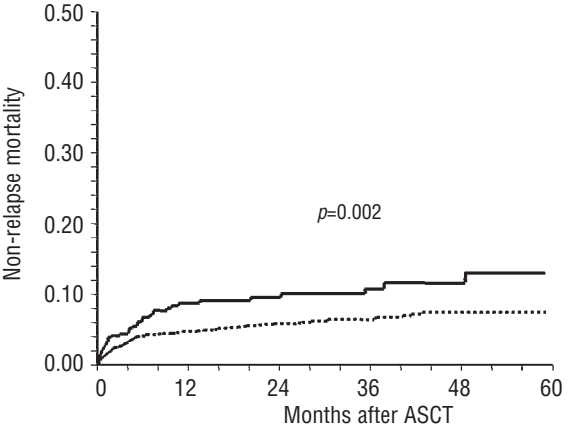

Figure 1. Non-relapse mortality according to age at the time of autologous stem cell transplantation in patients with diffuse large B-cell lymphoma. Solid line: patients ≥60 years old; dotted line: patients <60 years old; p=0.002.

Relapse risk

The cumulative risk of relapse at 3 years was 38% in the elderly patients and 32% in the younger patients (p=0.006) (Figure 2). In a multivariate analysis, four factors remained significant for the risk of relapse: no rituximab therapy prior to ASCT (RR 1.6, 95% CI 1.3-2.0), p<0.001), two or more lines of prior therapy (RR 1.7, 95% CI 1.4-2.0, p=0.001), poor performance status at ASCT (RR 1.6, 95% CI 1.1.-2.5, p=0.02) and refractory disease at ASCT (RR 2.8, 95% CI 2.1-3.7, p=0.001). On the other hand, in a multivariate analysis, the elderly patients showed only a trend towards a higher relapse risk (RR 1.2, 95% CI 0.9-1.4, p=0.06).

Survival after autologous stem cell transplantation

The elderly patients had a lower progression-free survival rate than that of the younger patients (Figure 3). The progression-free survival rate was 51% *vs.* 62% at 3 years, respectively (p<0.001). In a multivariate analysis the following factors were associated with poorer progression-free survival: age ≥60 years (RR 1.2, 95% CI 1.0-1.5, p=0.02), no rituximab therapy prior to ASCT (RR 1.5, 95% CI 1.2-1.8, p<0.001), two or more lines of therapy before ASCT (RR 1.6, 95% CI 1.4-2.0, p=0.001), poor performance status (RR 2.1, 95% CI 1.5-2.9, p=0.001), and refractory disease (RR 2.7, 95% CI 2.1-3.5, p=0.001). Elderly patients who had had two or more treatment lines prior to ASCT had a poorer progression-free survival than that of younger patients (RR 1.2, 95% CI 1.0-1.5, p=0.04). The impact of rituximab therapy prior to ASCT was specifically analyzed as a function of disease status at transplantation. Previous rituximab use did not have any impact on the progression-free survival of patients autografted in first complete remission. The absence of prior rituximab therapy was, however, associated with poorer progression-free survival in patiens transplanted in second complete remission (p=0.03).

The overall survival rate was inferior in the group of elderly patients when compared to that in younger patients (Figure 4). Overall survival was 60% *vs.* 70%, respectively, at 3 years (p<0.001). In multivariate analysis seven factors were associated with lower overall survival: male gender (RR 1.2, 95% CI 1-1.4, p=0.04), age ≥60 years (RR 1.4, 95% CI 1.2-1.7, p=0.001), no rituximab therapy prior to ASCT (RR 1.5, 95% CI 1.2-1.9, p<0.001), elevated serum lactate dehydrogenase level at diagnosis (RR 1.3, 95% CI 1.1-1.6, p=0.008), two or more lines of therapy prior to ASCT (RR 1.8, 95% CI 1.5-2.2, p=0.001), poor performance status at ASCT (RR 2.7, 95% CI 1.8-3.9, p=0.001) and refractory disease at ASCT (RR 2.9, 95% CI 2.2-3.9, p=0.001).

Discussion

This retrospective study based on data collected in the EBMT registry considered more than 2600 transplanted DLBCL patients with MED-B reports available. Notably there were 463 patients ≥60 years old at the time of transplantation, allowing some estimation of non-relapse mortality and outcome in elderly patients with

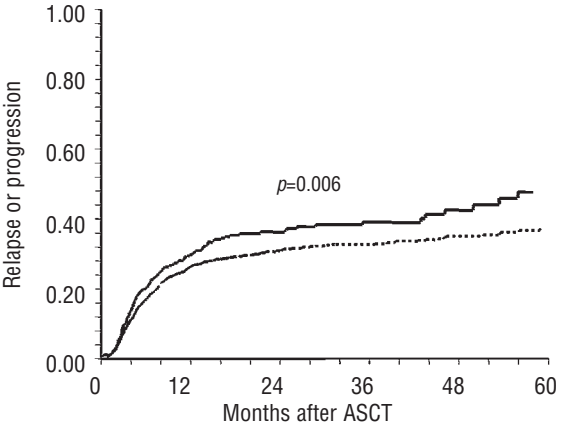

Figure 2. Relapse risk after autologous stem cell transplantation in patients with diffuse large B-cell lymphoma according to age at transplant. Solid line patients ≥60 years old; dotted line <60 years old.

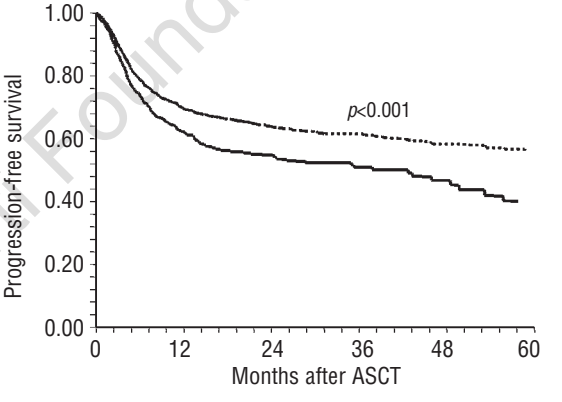

Figure 3. Progression-free survival after autologous stem cell transplantation in patients with diffuse large B-cell lymphoma according to the age at transplant. Solid line patients ≥60 years; dotted line <60 years old.

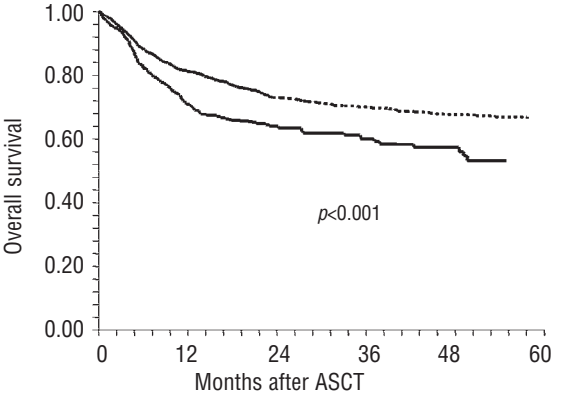

Figure 4. Overall survival after autologous stem cell transplantation in patients with diffuse large B-cell lymphoma according to the age at the time of transplant. Solid line patients ≥60 years old; dotted line: <60 years old.

DLBCL. The main observations were a somewhat higher non-relapse mortality rate among the elderly patients than among the younger ones, but a reasonable outcome after ASCT. These observations are of importance, especially with regards to a generally poorer outcome of elderly patients with DLBCL.

The proportion of elderly DLBCL patients transplanted increased during the study period. There may be several reasons for this. Increasing experience with ASCT in many centers might be one explanation as might be improvements in transplant settings including, for example, the use of blood progenitor cells and better supportive care. In addition, the proportion of elderly patients in the population is increasing and, therefore, so too is the proportion of elderly DLBCL patients in most affluent societies. Consequently, more elderly and often otherwise fit patients are considered for ASCT if they have poor initial features or relapse after first-line therapy.

The rate of early non-relapse mortality, i.e. within 100 days of ASCT, among the elderly patients in this series (4.4%) compares favorably with the rates in many earlier smaller series in which a significant proportion of the patients had DLBCL.[19,20] A probable explanation is that the present series includes only patients transplanted more recently while previous studies have included patients transplanted during a longer time period. Of note, there was no statistically significant difference in non-relapse mortality between patients aged 60-64 and those aged 65-69 in our analysis. The number of patients over 70 years old was too small for any meaningful analysis. In general the causes of non-relapse mortality were comparable in younger and older patients, with infectious complications predominating. The only major difference was in the risk of second malignancies, which was higher in elderly patients.

The follow-up of this registry analysis is relatively short. However, taking into account that the median time to relapse after ASCT in patients with DLBCL is only 4 months,[23] the observation time is sufficient to be able to estimate the risk of relapse. With regards to non-relapse mortality it is likely that the proportion of cardiovascular deaths would increase in the elderly patients and the relative proportion of infectious causes would decrease with prolonged follow-up. The same holds true with second malignancies, most of which may have nothing to do with treatment of DLBCL as such.

All transplanted patients are to some extent selected based on either patient or disease-related characteristics or both. It is likely that elderly patients are even more selected than younger patients but this is impossible to judge on the basis of a retrospective registry analysis. It would be interesting to ask transplant centers whether they have exactly the same inclusion and exclusion criteria for older and younger patients with DLBCL. The answers to this question could offer insight into the patient selection process used in various centers and give some basis for guidelines. Various co-morbidity indices have been used in the allogeneic setting.[24,25] Such instruments might be useful also in elderly patients for whom ASCT is contemplated.

In this registry series, elderly patients with DLBCL had poorer progression-free and overall survival rates than those of younger patients. This was in part due to a higher risk of relapse and limited salvage options after relapse but also due to higher non-relapse mortality. Taking into account the facts that elderly patients had more often received ASCT after at least two treatment lines and were less often in the first complete remission at the time of transplantation, the outcome of the elderly population seems to be reasonable.

Due to more common co-morbid conditions, elderly patients tend to have more toxicities associated with high-dose therapy. There may be ways to improve this.[26] In addition to patient selection, the conditioning regimen also appears to be important. Regimens based on total body irradiation have conventionally been used cautiously in elderly patients, which was also apparent in this registry analysis. BEAM was the most commonly used regimen both in elderly and younger patients. In multivariate analysis of the present study, no differences were observed in the outcomes according to the conditioning regimen used. Routine use of G-CSF after stem cell infusion might be advisable especially in elderly patients. The combined use of radioimmunotherapy together with high-dose chemotherapy and autologous stem cell support might be one possibility to increase the efficacy of the autologous procedure without increasing early treatment-related toxicities.[27]

To conclude, ASCT is feasible in selected, elderly patients with DLBCL although non-relapse mortality is higher than in younger patients. The outcome seems to be reasonable when considering the generally poorer outcome of non-Hodgkin's lymphomas in elderly patients. More studies are needed to optimize patient selection as well as to decrease early and long-term toxicity of ASCT. Age, as such, should no longer be considered a contraindication to ASCT in patients up to 70 years of age with non-Hodgkin's lymphomas.

Authorship and Disclosures

EJ conceived and designed the study and was responsible for the final interpretation of the data and the final draft of the manuscript; CC was responsible for the statistical analysis, interpretation of data and creation of the tables and figures; AR, GO, BA, DB, EC, HT, GC, FC, AH, NR, NM, PD and MP participated in patients' care, data recording and interpretation and analysis of the data; AS participated in the design of the study, interpretation of the data, critically reviewed the manuscript and gave an important intellectual contribution. All authors were involved in the final revision of the manuscript and final approval of the version to be published. The authors reported no potential conflicts of interest.

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