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Autologous stem-cell transplantation in patients with mantle cell lymphoma beyond 65 years of age: a study from the European Group for Blood and Marrow Transplantation (EBMT)

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Background: Limited experience is available on the feasibility and efficacy of autologous stem-cell transplantation (ASCT) in patients with mantle cell lymphoma (MCL) beyond 65 years.

Design and methods: We analysed 712 patients with MCL treated with ASCT from 2000 to 2007 and reported to the European Group for Blood and Marrow Transplantation registry. Patients >65 years were compared with patients <65 years for the end points non-relapse mortality (NRM), relapse incidence, progression-free survival (PFS), and overall survival (OS).

Results: Seventy-nine patients were ≥65 years old. Median time from diagnosis to ASCT was longer in the elderly patients (11 versus 9 months, $P = 0.005$); they had more commonly received at least two treatment lines (62.0% versus 47.9%, $P = 0.02$) and were less commonly in first complete remission at ASCT (35.4% versus 51.2%, $P = 0.002$). Median follow-up after ASCT was 19 and 25 months, respectively. NRM was comparable at 3 months (3.8% versus 2.5%) and at 5 years (5.6% versus 5.0%). There were no differences in relapse rate (66% versus 55% at 5 years), PFS (29% versus 40%) and OS (61% versus 67%) between both populations of patients.

Conclusion: ASCT beyond 65 years of age is feasible in selected patients with MCL and results in similar disease control and survival as in younger patients.

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Key words: autologous stem-cell transplantation, elderly patients, mantle cell lymphoma, non-relapse mortality, outcome

introduction

Mantle cell lymphoma (MCL) is a specific entity of non-Hodgkin lymphoma (NHL) accounting for ~3%–10% of all cases [1, 2]. The disease is biologically characterised by overexpression of cyclin D1 and the frequently observed t(11;14)(q13;q32), with important pathophysiological implications [3]. MCL is characterised by a clear male preponderance with the median age at diagnosis of 60–65 years. The disease is usually widespread at diagnosis and carries poorer prognosis than any other type of B-cell lymphomas with a median survival of only 3–4 years. There are, however, some indications that prognosis of MCL patients has improved recently [4].

Age >60 years is a prognostic factor in MCL patients in the recently published prognostic classification (Mantle Cell Lymphoma International Prognostic Index) [5]. There are indications that addition of rituximab to chemotherapy regimens may improve progression-free survival (PFS) but without significant improvement in overall survival (OS) in MCL [6]. Promising treatment results have been observed in phase II studies using intensive chemotherapeutic regimens followed by autologous stem-cell transplantation (ASCT) [7, 8] or without a transplant [9].

ASCT has been advocated as an efficient consolidation therapy based on several phase II trials [7, 8, 10–12] or based on a registry analysis [13]. The only prospective randomised study including 122 patients showed that ASCT is superior in terms of PFS when compared with maintenance therapy with interferon [14].

Limited data are available on the feasibility and efficacy of ASCT in elderly patients with MCL. This is due to the fact that only recently the upper age limit for ASCT has shifted from 60 to 65 years or beyond. Current knowledge on the feasibility of ASCT in the elderly patients is mainly based on small series including very few patients with MCL [15–18]. A notable exception is a prospective phase II trial of the Nordic Lymphoma Group, which included 41 patients ≥60 years [12]. There are no series specifically reporting outcomes of ASCT in MCL patients >65 years. Therefore, we carried out a retrospective analysis based on data reported to the European Group for Blood and Marrow Transplantation (EBMT) addressing the feasibility and outcome of ASCT for MCL in patients beyond 65 years of age.

design and methods

The EBMT is a voluntary organisation comprising 640 transplant centres mainly from Europe. Member centres 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 EBMT centres 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 1 January 2003, all transplant centres have been required to obtain written informed consent before data registration following the Helsinki Declaration 1975.

The EBMT database was used to identify patients with MCL aged 18–75 years treated with a first ASCT from 2000 to 2007. Only fully documented transplants with MED-B forms (www.ebmt.org) were included in the analysis. Outcomes were compared by multivariate analysis between cases included and cases excluded (report with MED-A data only) to ensure that the study was not biased. Patients ≥65 years of age at ASCT were compared with younger patients transplanted during the same time period for various patient- and transplant-related variables as well as outcome parameters.

statistical methods

The main aim of this study was to investigate the risk of non-relapse mortality (NRM) and outcome after ASCT in MCL patients ≥65 years at transplant in relation to those observed in younger patients, adjusting by the potential differences existing between the both groups. All the analyses were carried out in the entire patient cohort considering age at ASCT (<65 versus ≥65 years) as the main study variable.

Patient and transplant characteristics were compared between the age groups using chi-square test or Fisher's exact test for categorical variables and the Student's *t*-test or Mann–Whitney *U* test for continuous variables. The probabilities of PFS and OS 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 log-rank test. Neutrophil engraftment, NRM and relapse or progression after ASCT were calculated using cumulative incidences to account for competing risks. Point-wise *P* values were investigated for NRM at 3 months, 1 year and 5 years after ASCT. Adjusted probabilities for outcomes after transplantation were estimated using the Cox proportional hazards method to adjust for patient-, disease- and transplant-related variables. Some risk factors in the Cox model contained 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 were tested for a significant interaction with the main factor under study. All *P* values were two sided.

Cumulative incidences were calculated using the NCSS97 software (Number Cruncher Statistical System, Kaysville, UT). All other computations were carried out using the SPSS15.0 statistical package (SPSS Inc., Chicago, IL).

results

eligible patients

Altogether, 712 patients of 2978 patients registered with ASCT for MCL fulfilled the inclusion criteria for this retrospective study. No differences were observed between included patients and those excluded because of missing MED-B information but otherwise eligible, indicating that cases in the study were representative for the whole patient group included in the EBMT registry.

patient and transplant characteristics

There were 79 patients ≥65 years who were compared with 655 younger patients transplanted during the same time period. The median age of the elderly patients was 67 years

(range 65–73). Sixty-eight patients were 65–69 years old and only 11 patients were ≥ 70 years at the time of transplant. The median age of the younger patient group was 56 years (29–64).

The characteristics of the study population and transplants are presented in Table 1. The age groups were well balanced in regard of both disease-related and transplant-related characteristics except that fewer patients in the elderly group were in first complete remission (CR1) at the time of transplant. The median follow-up time was 19 months for patients aged ≥ 65 years and 25 months in the younger patients cohort ($P = \text{n.s.}$).

engraftment

No differences were observed in the number of CD34+ cells infused between the two age groups. Also use of granulocyte colony-stimulating factor was comparable in these groups (Table 1). No difference was observed in the cumulative incidence of neutrophil engraftment (96.2% in the elderly

versus 98.1% in younger patients). The median time to neutrophils $>0.5 \times 10^9/\text{l}$ was also comparable (12 versus 12 days) as well as the time to unsupported platelet count of $>20 \times 10^9/\text{l}$ (13 versus 13 days).

non-relapse mortality

The rate of NRM was comparable between older and younger patients at 3 months (3.8% versus 2.5%), at 1 year (3.8% versus 3.3%), and at 5 years (5.6% versus 5.0%).

In multivariate analysis, age ≥ 65 at transplant was not associated with risk of NRM. The only factor of importance in this respect was the number of treatment lines (two or more) before ASCT [relative risk (RR) 2.0, 95% confidence interval (CI) 0.99–4.2, $P = 0.052$].

relapse risk

No statistically significant differences were found in terms of risk of relapse or progression after ASCT in elderly compared with younger patients, with a cumulative incidence of relapse of 28.4% versus 24.5% at 2 years and 65.8% versus 55.1% at 5 years, respectively (Figure 1). In multivariate analyses, several factors were significant for increased relapse risk including male sex ($P = 0.023$), elevated serum lactate dehydrogenase (LDH) at diagnosis ($P = 0.001$), sensitive disease versus CR1 at the time of ASCT ($P = 0.004$), refractory disease versus CR1 at the time of transplantation ($P < 0.001$), and other high-dose regimens versus melphalan, total body irradiation and cytarabine ($P = 0.004$). After adjusting for all prognostic variables, age ≥ 65 at ASCT had no significant impact on risk of relapse (RR 1.17, 95% CI 0.79–1.72, $P = 0.435$).

survival

As expected, disease status at the time of ASCT was the most important predictive prognostic factor for the transplantation

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

	n available (n = 712)	<65 years (n = 633), (%)	≥ 65 years (n = 79), (%)	P
Age, median (range), years	712	56 (29–64)	67 (65–73)	–
Male sex, n (%)	712	487 (76.9)	64 (81.0)	n.s.
Stage III–IV	671	89.8	93.2	n.s.
B-symptoms	471	36.8	32.7	n.s.
Elevated LDH	511	25.8	22.4	n.s.
Bulky disease (>10 cm)	538	16.9	12.7	n.s.
Two or more previous treatment lines	712	47.9	62.0	0.02
Time from dx to transplant, median (range), months	712	9 (3–191)	11 (5–101)	0.005
Disease status at transplant	712			
CR1		51.2	35.4	0.002
PR1		24.2	26.6	
Other		24.6	38	
Poor performance status ^a	456	1.0	7.1	0.01
BEAM regimen	712	57.3	72.2	0.01
TBI in conditioning	712	31.8	15.2	0.002
Stem-cell source PB	712	97.5	98.7	n.s.
No. of CD34+ cells infused, median (range), $\times 10^6/\text{kg}$	564	4.6 (1.2–54.0)	4.6 (2.0–26.5)	n.s.
G-CSF after stem-cell infusion	643	62.9	62.2	n.s.

^aKarnofsky < 80 .

n.s., not significant; LDH, serum lactate dehydrogenase; CR1, first complete remission; PR1, first partial remission; BEAM, carmustine–etoposide–cytarabine–melphalan; TBI, total body irradiation; PB, peripheral blood; G-CSF, granulocyte colony-stimulating factor; dx, diagnosis.

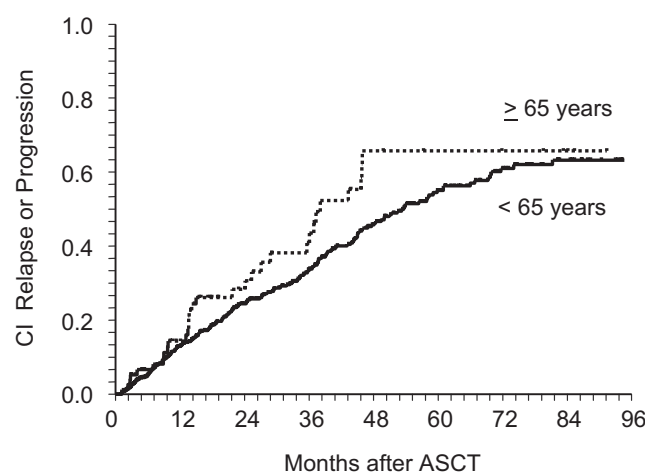


Figure 1. Cumulative incidence of relapse or progression after transplantation according to age at the time of ASCT. Dotted line: patients ≥ 65 years old; solid line: < 65 years old. Univariate $P = 0.1$; P value from multivariate Cox model $P = 0.4$. ASCT, autologous stem-cell transplantation.

outcome (49.4%, 24.4% and 26.1%, respectively, for those patients being autografted in CR1, first partial remission and in patients in more advanced phases). Nevertheless, there were no statistically significant differences in PFS between older and younger patients with a probability of PFS at 5 years of 28.6% compared with 39.9%, respectively (Figure 2). Several factors predictive for a poor PFS were identified in multivariate analyses, including male sex ($P = 0.008$), elevated LDH ($P < 0.001$), two or more treatment lines ($P = 0.016$), sensitive disease versus CR1 at transplant ($P = 0.001$), refractory disease versus CR1 at transplant ($P < 0.001$) and other conditioning than melphalan, total body irradiation and cytarabine ($P = 0.006$). After adjusting for all these variables, age ≥ 65 years at ASCT had no significant impact on PFS after ASCT (RR 1.18, 95% CI 0.82–1.69, $P = 0.383$).

The OS was not significantly different between the elderly and younger patients (Figure 3). OS at 5 years was 60.7% in patients >65 years at transplant and 67.4% in younger patients ($P = 0.15$). Factors identified as adverse prognostic variables for OS in multivariate analyses were B-symptoms at diagnosis ($P = 0.004$), elevated LDH at diagnosis ($P = 0.007$), time from diagnosis to ASCT >12 months ($P = 0.006$) and refractory disease versus CR1 at transplant ($P < 0.001$). After adjusting for these variables, age ≥ 65 years at ASCT had no significant impact on OS after transplant (RR 1.4, 95% CI 0.84–2.25, $P = 0.198$).

discussion

This retrospective study is based on data collected within the EBMT registry from >700 transplanted MCL patients with MED-B reports available. Interestingly, there were 79 patients (11%) who were at least 65 years old at the time of ASCT. The main observations were comparable early NRM also in elderly patients (median age 67 years) and also comparable risks of relapse, PFS and OS. These observations are of importance considering that about half of the patients with MCL are

>60 – 65 years old at the time of diagnosis and that older age is considered a poor prognostic factor also in this lymphoma type. In analogy with the situation with diffuse large B-cell lymphoma [19], the number of transplants in the very elderly patients with MCL has increased during the last decade.

In our series of MCL patients >65 years, NRM was acceptable (3.8% at 1 year). This figure seems to be lower than in an earlier series including 88 ASCT-treated patients aged ≥ 60 (27 had MCL) where early NRM was as high as 10% [15]. In a recent single-centre series including 95 NHL patients >65 years at transplant (median 68 years; 15 had MCL), NRM at 100 days was only 4% [16], suggesting that ASCT could also be afforded in patients up to ~ 70 years of age if they are otherwise fit. Low NRM observed in this registry series is most likely due to careful patient selection by the treating physicians. Unfortunately, we do not have data considering co-morbid conditions.

The follow-up of this registry series is relatively short taking into account current outcome of MCL treated with intensive therapies. The median follow-up time was, however, comparable in younger and elderly patients. The baseline characteristics were comparable between the age cohorts except that more patients were in CR1 in the younger cohort of patients. Remission status at transplant is known to be an important prognostic factor for outcome [20, 21]. Both risk of relapse as well as PFS were comparable in younger and elderly patients in our analysis.

No plateau was observed in survival curves either in the younger patients or in the elderly patients. These observations are skewed by the fact that about half of the patients had received at least two treatment lines before ASCT and by the fact that in long-term studies a 'plateau' appeared only after an observation time of ≥ 6 years [11, 12]. Although it is at present unclear whether first-line ASCT following intensive induction is curative in patients with MCL [22, 23], this approach results in promising long-term survival [11, 12, 24] with a hope that a fraction of these patients might be cured. Nevertheless, ASCT

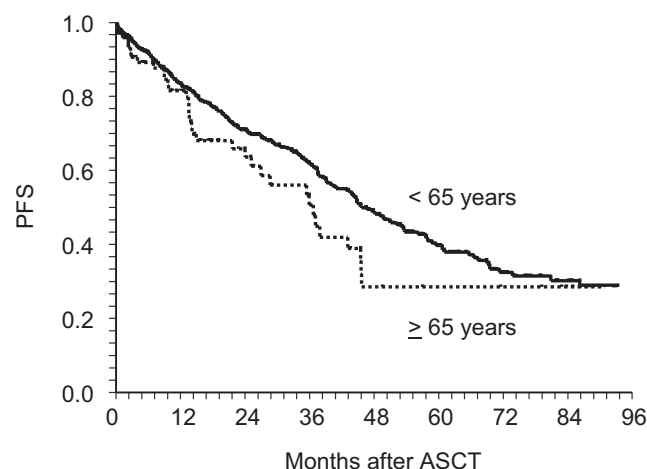


Figure 2. Probability of progression-free survival after transplantation according to age at the time of ASCT. Dotted line: patients ≥ 65 years old; solid line: <65 years old. Univariate $P = 0.1$; P value from multivariate Cox model $P = 0.4$. ASCT, autologous stem-cell transplantation.

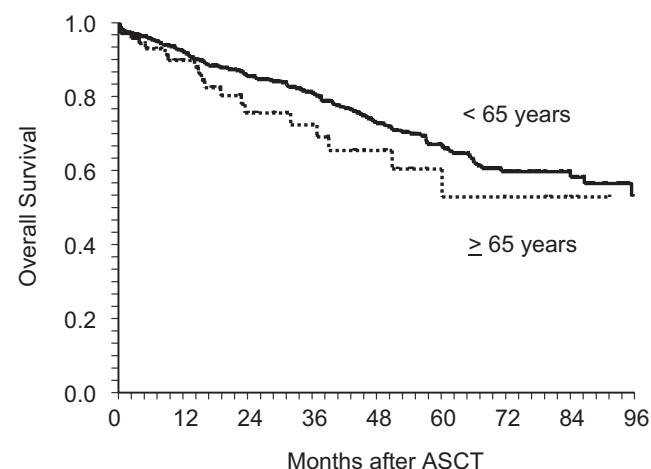


Figure 3. Probability of overall survival after transplantation according to age at the time of ASCT. Dotted line: patients ≥ 65 years old; solid line: <65 years old. Univariate $P = 0.15$; P value from multivariate Cox model $P = 0.2$. ASCT, autologous stem-cell transplantation.

seems to form an important backbone to the treatment strategy in an important proportion of patients with MCL and has been shown to be of benefit over non-transplant first-line treatment in an exploratory analysis of three prospective randomised studies involving ASCT for MCL [25].

Due to age-related co-morbidity, toxic effects associated with high-dose therapy might be more critical in elderly patients and optimal supportive care during the transplant phase appears to be important to minimise early toxicity in this patient group. Moreover, patient selection becomes an even more important issue in elderly patients. Co-morbidity indexes applied in allogeneic setting [26, 27] might also be useful in elderly patients before ASCT and should be evaluated prospectively. Unfortunately, co-morbidity scores were not covered by the EBMT MED-B forms during the study period and were thus not available for analysis.

In summary, NRM and disease control in selected patients with MCL beyond 65 years of age seem to be acceptable and not significantly different from that in younger patients. Also the long-term outcome seems to be comparable. Taking into account these observations and efficacy of ASCT given after intensive induction therapy, this strategy is worth considering in selected patients with MCL up to 70 years age. Improvements in pre- and post-transplant strategies are, however, needed irrespective of age in order to improve long-term outcome.

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disclosure

The authors declare no conflict of interest.

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