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CORRESPONDENCE

# Long-term outcomes of older patients with relapsed/refractory NHL referred to ASCT

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## To the Editor:

Although the median age of patients is >60 years for most subtypes of lymphoma, older patients have been underrepresented in randomized clinical trials studying autologous stem cell transplantation (ASCT) and in most of these studies, only patients with aggressive lymphomas have been included [1–4]. On the other hand, retrospective studies focusing on older patients undergoing ASCT have generally neglected the population of patients included to ASCT programs who did not actually receive transplant for various reasons [5–9], therefore, the true benefit from inclusion to transplant program might be overestimated. Furthermore, these studies tend to have relatively short median follow-up.

From 2006 to 2016, 114 patients with various NHL diagnoses and relapsed/refractory (R/R) disease were referred for ASCT to the General University Hospital, Prague. Patients were identified through records of weekly transplantation group meetings. Both patients treated previously in General University Hospital (79%) and referred from other hospitals (21%) were included. This study was a part of the analysis of Czech Lymphoma Study Group Database NiHiL (NCT03199066) and was approved by the institutional review board. All patients signed an informed consent with data collection and processing. Survival data were collected up until 31st December 2019.

Staging and restaging procedures were performed according to actual versions of Cheson guidelines [10]. All patients had CT or PET-CT before salvage and at the end of treatment; transplanted patients were evaluated before ASCT as well. CR was confirmed by PET-CT in all high-grade lymphomas but one. In patients with CNS and ocular involvement, brain MRI, cerebrospinal fluid examinations and/or diagnostic vitrectomy and slit lamp examinations were done. Hematopoietic cell transplantation comorbidity index (HCT-CI) at relapse was counted and patients were grouped according to their point score as described previously [11]. Treatment regimens were given as recommended in Czech Lymphoma Study Group Guidelines [12]. Supportive care was given according to institutional standards. PBPC were collected and stored in the Institute of Haematology and Blood Transfusion, Prague. Successful collection of PBPC was defined as collection of $\geq 2 \times 10^6$/kg CD34+ cells. All survival data were counted from the date of last relapse before referral for transplantation. Overall survival (OS) was defined as the time to death or last follow-up. Progression-free survival (PFS) was defined as the time to progression of lymphoma or death from any reason. Categorical data were compared with chi-squared tests, numerical data with Mann–Whitney U test. Survival data were counted with Kaplan–Meier method and survival curves were compared by log-rank tests. Multivariate analysis was performed by logistic regression or Cox regression method. All tests were two-sided.

General characteristics of patients at referral to transplant program are in Table 1. Median age was 64 years

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**Table 1** Characteristics of patients.

| | |
|---|---|
| Number of patients | 114 |
| Median age at the last relapse (range) | 64 (60–71) |
| Age ≥ 65 years | 47 (41%) |
| Male sex | 59 (52%) |
| Median time to relapse/progression | 7.43 (0.20–167.77) |
| Time to last relapse/progression ≤12 months | 62 of 113 (55%) |
| Time to last relapse/progression >12 months | 51 of 113 (45%) |
| Lymphoma subtypes (last relapse) | |
| DLBCL | 62 (54%) |
| FL | 26 (24%) |
| T-NHL | 7 (6%) |
| MCL | 5 (4%) |
| Other low-grade[a] | 8 (7%) |
| Other high-grade[b] | 6 (5%) |
| All low-grade[c] | 34 (30%) |
| All high-grade[d] | 80 (70%) |
| B-NHL (CD20+) | 107 (94%) |
| Prognostic factors | |
| Clinical stage III-IV | 86 (77% of 112) |
| LDH > normal | 75 (66% of 113) |
| ECOG 2–4 | 12 (11% of 112) |
| >1 involved extranodal sites | 27 (24% of 113) |
| HCT-CI | |
| 0 | 49 (43% of 113) |
| 1–2 | 40 (36% of 113) |
| ≥3 | 24 (21% of 113) |
| Previous treatment | |
| >1st relapse/progression | 20 (17%) |
| Number of previous lines of treatment (median, range) | 1 (1–5) |
| Anthracyclines adminisitered | 106 (93%) |
| AntiCD20 administered in B-NHL | 100 of 107 (93%) |

*DLBCL* diffuse large B-cell lymphoma, *FL* follicular lymphoma, *B-NHL* B non-Hodgkin lymphoma, *T-NHL* T non-Hodgkin lymphoma, *MCL* mantle cell lymphoma.

[a]Other low-grade: marginal zone lymphoma (4 patients), B-NHL not otherwise specified (3 patients), CLL/SLL (1 patient).

[b]Other high-grade: primary CNS lymphoma (2 patients), primary intravitreal lymphoma (1 patient), high-grade B-NHL with intermediate features between DLBCL and Hodgkin's lymphoma (1 patient), peripheral T-cell lymphoma with features of classical Hodgkin's lymphoma (1 patient), B-NHL, high-grade, not otherwise specified (1 patient).

[c]Low-grade lymphomas: FL, other low-grade lymphomas.

[d]High-grade lymphomas: DLBCL, MCL, T-NHL, other high-grade lymphomas.

(range, 60–71), 84% of patients were in their first relapse/progression and median number of regimens before referral for ASCT was 1 (range, 1–5). In pre-salvage treatment, 93% of patients received anthracyclines, and of 107 B-cell lymphomas, 100 (92%) received anti-CD20 antibody. 80 patients (70%) had aggressive and 34 (30%) indolent lymphomas. Most frequent diagnosis was diffuse large B-cell lymphoma (DLBCL) in 62 patients (54%). Median time from last pre-salvage therapy to current relapse/progression was 7.4 months.

Flowchart of patients showing their progress through subsequent treatment stages is shown in Supplementary Fig. S1. Most frequent salvage treatment was ESHAP (47 patients, 41%), followed by DHAP (33 patients, 29%) and ICE (22 patients, 19%). 15 patients (13%) received more than 1 salvage regimen and 98% of CD20+ lymphomas received anti-CD20 treatment during salvage. The overall response rate (ORR) to salvage therapy was 71%, with 47% CR and 24% PR.

94 patients proceeded to mobilization (82%), 85% of mobilized patients successfully collected $\geq 2 \times 10^6$/kg CD34+ cells, and 62 patients (54% of the whole cohort) were finally transplanted. Main reasons for non-proceeding to transplant were: refractory disease (19 patients), complications of salvage therapy (16 patients), and mobilization failure (14 patients). Of pretreatment characteristics, only ECOG performance status (PS) 2–4 was independent predictor of non-proceeding to ASCT. Only 2 of 12 such patients achieved ASCT, while 5 of them succumbed to salvage-related mortality. When response to treatment was added to the model as time-dependent variable, it was the most powerful predictor of non-proceeding to ASCT (odds ratio = 3.4 for non-response, $p = 0.00017$), but poor PS retained its significance (OR = 3.3, $p = 0.024$). HCT-CI was neither predictive for transplant administration, nor did it correlate with ECOG PS.

Majority of transplanted patients received BEAM conditioning regimen (89%). Median $5.14 \times 10^6$/kg CD34+ cells was administered, median time to ANC $>0.5 \times 10^9$/l recovery was 11 days and to platelet $>20 \times 10^9$/l recovery was 13 days. 100-day transplant-related mortality (TRM) was 1.5%. Overall response rate for transplanted patients was 85%, with 73% CR and 12% PR.

Median follow-up of living patients was 72.6 months (5.9–170.0). 68 patients (60%) died during follow up (71% of non-transplanted and 50% of transplanted). Progression of lymphoma accounted for 68% of deaths in both transplanted and non-transplanted cohorts. Median progression-free (PFS) and overall survival (OS) were 22.6 and 50.3 months (Fig. 1a). There were no differences in PFS across different diagnoses, only trend for better PFS in patients with low-grade compared to high-grade histologies (36.7 vs. 10.3 months, $p = 0.07$). Median OS for patients with FL and other low-grade lymphomas was not reached, for MCL, T-NHL, DLBCL and other high-grade lymphomas median OS was 105.1, 58.9, 31.8 and 11 months, respectively ($p = 0.04$ at univariate analysis). In multivariate analysis for PFS, age ≥65 years (HR 2.0, $p = 0.004$),

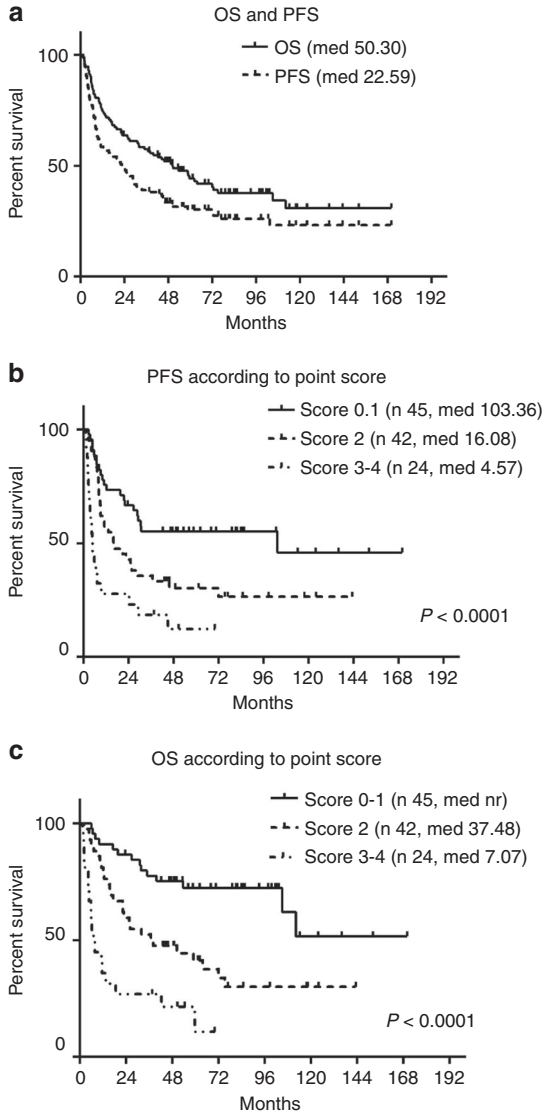


**Fig. 1 Survival curves. a** PFS and OS for all patients. **b** PFS and **c** OS according to point score (number of risk factors from multivariate analyses: age ≥65 years, high LDH, ECOG 2–4, time from last pre-salvage therapy to relapse <12 months).

ECOG ≥ 2 (HR 2.9, $p = 0.003$) and LDH above normal (HR 1.8, $p = 0.003$) were significant. In multivariate analysis for OS, besides age (HR 3.1, $p < 0.00001$), ECOG (HR 3.2, $p = 0.002$), and LDH (HR 2.3, $p = 0.006$), also interval <12 months from last pre-salvage therapy to relapse was significant (HR = 2.0, $p = 0.01$). Lymphoma histology grade lost its significance on OS on multivariate analysis and HCT-CI did not affect PFS or OS. Number of significant risk factors for PFS and OS on multivariate analysis enabled construction of predictive curves for three patient subgroups with different prognosis (Fig. 1b, c).

Despite the fact that only 54% of our patients were actually transplanted, survival data are comparable to other studies of older NHL patients, which included only those who underwent transplant [4–8], with longer follow-up. Inclusion of low-grade lymphoma patients in our analysis may suggest selection of better risk population in comparison to studies including only high-grade histologies [1–5, 7], however, our low-grade patients did not seem to have better results than high-grade ones. 85% of patients were collected successfully, but significant proportion of patients did not proceed to ASCT because of deterioration or death during salvage. This may partially explain the low treatment-related mortality and uneventful course of ASCT of those actually transplanted. HCT-CI was not predictive neither of proceeding to ASCT, nor of survival parameters which is in accordance to some [8, 9], but not other studies [6, 13]. We hypothesize that this may be due to low TRM in our cohort. Also, history of previous cancer alone puts transplant patients to poor risk group according to HCT-CI, which may not be appropriate in older lymphoma patients undergoing ASCT [9].

We conclude that the benefit of ASCT in older patients with R/R NHL was not overestimated in previous studies, though most of them focused only on those actually transplanted. Our results also show that the benefit in these patients is durable. Patients with poor PS at relapse had high salvage-related mortality and only minority of them proceeded to ASCT, however, their numbers are too small to justify strong conclusions. Comorbidity score did not affect treatment results.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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