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Reduced Intensity Conditioning Prior Autologous Stem Cell Transplantation in Elderly DLBCL Patients

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ABSTRACT

High-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) is widely used in patients with diffuse large B-cell lymphoma. HDCT/ASCT is associated with increased morbidity in elderly/unfit patients. We retrospectively evaluated the use of reduced intensity conditioning in DLBCL patients. Our study included 146 patients aged 60 years and older treated at our institution between 2005 and 2019; 86 patients received standard intensity conditioning (SI group) with BEAM or TEAM (BCNU or thiotepa, etoposide, cytarabine, melphalan). Sixty patients received reduced intensity high-dose conditioning (RI group) with BM (BCNU, melphalan, 43.3%), TM (thiotepa, melphalan, 16.7%), BCNU or busulfan thiotepa (38.4%), or bendamustine melphalan (1.7%). Median follow-up was 62.4 months. We observed comparable toxicities in the SI and RI groups. The cumulative incidence of relapse at 3 years was higher in the RI group (30.8% vs. 23.4%, $p = 0.034$). There was no difference in non-relapse mortality (NRM). In univariate analyses, SI vs. RI conditioning resulted in superior progression-free survival (PFS) (HR 1.80 CI 1.11–2.92, $p = 0.017$) but not in superior overall survival (OS) (HR 1.48 CI 0.86–2.56, $p = 0.152$). On multivariate analysis, we observed no difference in PFS (HR 0.74 CI 0.40–1.38, $p = 0.345$) and a trend toward better OS with RI conditioning (HR 0.45 CI 0.22–0.94, $p = 0.032$). Age 60–69 versus ≥ 70 years and remission prior to ASCT were the only factors predicting better PFS. Factors associated with better OS were RI conditioning, age 60–69 versus ≥ 70 years, ECOG 0 versus ≥ 1 performance status, bulky disease, and prior lines 1 versus ≥ 2 . In conclusion, RI conditioning prior to ASCT may be feasible in elderly patients and led to a comparable outcome when corrected for several significant confounders.

1 | Introduction

Despite recent advances in the treatment of relapsed diffuse large B-cell lymphoma (DLBCL), high-dose chemotherapy (HDCT) with subsequent autologous stem cell transplantation (ASCT) remains a valid treatment option for younger and fit patients. With increasing incidence of elderly lymphoma patients and advances in supportive care strategies, HDCT/ASCT is used more

frequently in elderly patients. There are limited data on the use of HDCT/ASCT in elderly patients and the optimal conditioning regimen regarding substances and dosing is not well defined [1–5]. However, age and comorbidities were reported to impact the prognosis of patients with lymphoma undergoing HDCT/ASCT [6].

The number of DLBCL cases is projected to increase in the United States and Western Europe. Especially, the elderly patients aged

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65+ will have a higher annual increase rate [7]. Thus, treatment of elderly DLBCL patients remains an urgent medical need.

In the frontline setting, age above 60 years remains an independent prognostic factor for survival, even when treated with standard regimens in the rituximab era [8]. HDCT/ASCT was considered the standard of care as second line therapy in DLBCL patients for the last decades [9]. Wherever available, CAR-T-cell treatment is considered the new standard of care as second line therapy in patients with early relapse or refractory disease [10, 11]. However, HDCT/ASCT remains the standard of care for patients with late relapse and a valid option for patients with early relapse achieving a complete remission with salvage chemotherapy [12]. The role of consolidation ASCT in first remission has been extensively investigated: A Cochrane systematic review and meta-analysis of 15 randomized trials did not report a survival benefit for ASCT in first remission compared with patients who did not undergo transplantation [13]. This has remained unchanged in the rituximab era [14]. However, there is limited evidence that high-risk DLBCL patients might benefit from HDCT/ASCT consolidation in first complete remission [15, 16]. In case of simultaneous CNS involvement, HDCT/ASCT is a preferred consolidation strategy [17]. Thus, HDCT/ASCT remains a relevant treatment option for DLBCL patients in the CAR-T-cell era. Therefore, we retrospectively investigated reduced intensity conditioning regimens with two alkylating agents as conditioning regimen prior ASCT in older and frailer patients.

2 | Material and Methods

2.1 | Patient Selection and Characteristics

We identified 146 DLBCL patients with the age of 60 years and older, undergoing HDCT/ASCT at our institution between 1 January 2005 and 31 December 2015. Patients with primary central nervous system lymphoma, primary mediastinal B-cell lymphoma and T-cell lymphoma were not included in the analysis. Patients with secondary or simultaneous central nervous system manifestation were included in the analyses. Clinical data were collected prospectively and retrospectively analyzed. Patient characteristics are described in Table 1. Adverse events of interest (febrile neutropenia [FN], sepsis, enterocolitis, mucositis, pneumonia, urinary tract infections, catheter-related infections, and atrial fibrillation) were reviewed and reported according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, for 30 days post ASCT.

2.2 | Conditioning Regimens and Institutional Standards

Patients in the standard intensity (SI) conditioning group received either BEAM or TEAM protocol (BCNU/carmustine 300 mg/m² or thiotepa 5 mg/kg bodyweight at Day -7; cytarabine, 2 × 200 mg/m² per day from Day -6 to Day -3; etoposide, 2 × 100 mg/m² per day from Day -6 to Day -3; and melphalan, 140 mg/m² at Day -2). Reduced intensity regimens were either BCNU/melphalan (BCNU/carmustine 300 mg/m² Day -4, melphalan 140 mg/m² Day -2), thiotepa/melphalan (thiotepa 5 mg/

kg bodyweight Day -4 to -3, melphalan 140 mg/m² Day -2) BCNU- or busulfan/thiotepa (BCNU/carmustine 400 mg/m² Day -6 or busulfan 3.2 mg/kg Day -7 to -6, +thiotepa 5 mg/kg Day -5 to -4), or bendamustine-melphalan (bendamustine 100 mg/m² Day -4 to -3, melphalan 140 mg/m² Day -2).

Chemotherapy- and granulocyte colony-stimulating factor-mobilized peripheral blood stem cell grafts were used in all cases.

All patient cases were discussed in the institutional lymphoma tumor board before transplantation. The guidelines of the Comprehensive Cancer Center Freiburg stipulate that reduced conditioning should be considered from a biological age of 65. Nevertheless, older patients were also treated with standard conditioning (presumably if they were fit enough), and younger patients were treated with reduced conditioning if they had relevant preexisting conditions. The final decision was made by the transplant team on the ward.

2.3 | Study End Points, Definitions, and Statistical Analysis

Univariate analyses for progression-free survival (PFS) and overall survival (OS) were performed with GraphPad Prism 8. PFS was defined as the time from ASCT until disease progression or death from any cause. OS was estimated from ASCT until death from any cause. The PFS and OS rates were estimated using the Kaplan-Meier method. For those patients not experiencing the event of interest during follow-up, time to last contact was used as a censored observation. The Cox proportional-hazards regression model was used to estimate hazard ratios (HR) with corresponding two-sided 95% confidence intervals (CIs) for OS and PFS.

Relapse was defined as detection of disease activity via histological, cytological, or radiological assessment after ASCT; death without prior relapse was considered a competing risk and denoted as nonrelapse mortality (NRM). We applied Gray's test to compare NRM and cumulative incidence rates (CIR) in the presence of competing risks [18]. Remissions prior ASCT were defined into three groups: Patients with achievement of a first remission due to initial or salvage therapy (CR/PR1), patients with second remission after lymphoma relapse (CR/PR > 1), and patients with refractory disease. Lines of therapy were defined as follows: Patients were to have one line of therapy when HDCT/ASCT was used as consolidation therapy directly after first-line therapy without disease progression or refractoriness to induction therapy. Patients were counted two or more lines prior HDCT/ASCT, when disease progression or relapse occurred with subsequent lymphoma-directed therapy.

Multivariate analyses for PFS and OS were conducted using a Cox proportional-hazards regression model and a backward-selection strategy. Covariates, including clinical characteristics and risk factors, with a univariate *p* value ≤ 0.05 and at least 75% of informative patients, were included. HR and two-sided 95% CI of prognostic factors for PFS/OS were estimated. Multivariate analyses were performed with SAS v9.2 (SAS Institute Inc., Cary, NC USA).

TABLE 1 | Patients characteristic for SI and RI groups.

Parameter	SI group (86 patients)	RI group (60 patients)	<i>p</i>
Histology			0.206
DLBCL	73 (84.9%)	48 (80%)	
HGBL with MYC- and BCL2- and/or BCL6 rearrangements	6 (7%)	8 (13.3%)	
HGBL, NOS	7 (8.1%)	4 (6.7%)	
Median age at HDCT/ASCT (range)	65.5 (60–78.2)	71.8 (60.5–77.2)	<0.001
Performance status prior ASCT			0.006
ECOG 0	47 (54.7%)	18 (30%)	
ECOG ≥ 1	38 (44.2%)	39 (65%)	
Initial stage			0.536
I + II	16 (18.6%)	14 (23.3%)	
III + IV	70 (81.4%)	46 (76.7%)	
Elevated LDH	60 (69.8%)	42 (70%)	0.354
Extranodal sites			1.0
0–1 sites	51 (59.3%)	32 (53.3%)	
≥ 2 sites	32 (37.2%)	26 (43.3%)	
Bulky disease (≥ 7.5 cm)	29 (33.7%)	17 (28.3%)	0.688
Remission status prior ASCT			0.128
PR/CR1	50 (58.1%)	25 (42.7%)	
PR/CR > 1	22 (25.6%)	21 (35%)	
Refractory disease	12 (14%)	13 (21.7%)	
Lines of therapy			0.238
1	52 (60.5%)	30 (50%)	
≥ 2	34 (39.5%)	30 (50%)	

Note: Significance values are in bold.

We used Fisher's exact test to compare categorical variables as appropriate and the Student *t* test was used to compare continuous variables, assuming a normal distribution.

3 | Results

3.1 | Baseline Characteristics

Eighty-six patients (59%) received SI conditioning (SI group) with BEAM (81 patients) or TEAM (5 patients). Sixty patients (41%) received reduced intensity high-dose conditioning (RI group) with BM (BCNU, melphalan, 43.3%), TM (Thiotepa, melphalan, 16.7%), BCNU/or busulfan-thiotepa (38.4%), or bendamustine-melphalan (1.7%).

At the time point of ASCT, patients in the RI group were significantly older (median age 71.8 vs. 65.5 years, $p < 0.001$) and less fit, resulting in a higher ECOG performance status ($p = 0.006$). We found no difference regarding remission status prior ASCT or lines of therapy. Regarding baseline characteristics, we found no difference for other prognostic variables including stage I + II

vs. III + IV, elevated LDH, extranodal site involvement, distribution of IPI scores, bone marrow involvement, remission status prior ASCT, or lines of therapy between SI and RI groups. Regarding histology subtype, we found slightly more cases of transformed DLBCL in the SI group (34.9% vs. 18.3% of patients, $p = 0.039$). Double expressor (DEL) and double hit (DHL) status was not available in most patients (no data for DEL-status in 74% and for DHL-status in 60.3% of patients). However, we observed no difference in DEL/DHL rates between RI and SI group for patients with available DEL/DHL-status. Cell-of-origin status by Hans-classifier was only available in 20.6% of patients with no difference in distribution of GCB versus non-GCB type DLBCL between SI and RI groups (Table 1).

3.2 | CD 34+ Cell Count and Leukocyte Engraftment

The median CD34+ cell count in the RI group was 6.12×10^6 CD34+ cells per kg bodyweight with a range of 1.99 – 32.89×10^6 CD34+ cells per kg bodyweight. The median time to leukocyte engraftment was 10 days (range 9–17 days) in the RI group. Only

TABLE 2 | Remission rates post ASCT.

	Whole cohort (146 patients)	SI group (86 patients)	RI group (60 patients)
ORR	120 (82.2%)	71 (82.6%)	49 (81.7%)
CR	102 (69.9%)	60 (69.8%)	42 (70%)
PR	18 (12.3%)	11 (12.8%)	7 (11.7%)
SD	1 (0.7%)	1 (1.2%)	0
PD	9 (6.2%)	4 (4.7%)	5 (8.3%)
Not available	16 (11%)	10 (11.6%)	6 (10%)

one patient who died 10 days after autologous transplantation in severe sepsis had not yet regenerated more than 500 neutrophils. In the SI group, the median CD34+ cell count was 6.05×10^6 per kg bodyweight with a range of $2.83\text{--}11.2 \times 10^6$ CD34+ cells per kg bodyweight. Median time to leukocyte engraftment was 10 days (range 9–15 days).

3.3 | Remission Rates, Survival Analyses, NRM, and Relapse Incidence

Post ASCT remission rates were as follows: Overall response rates were 82.2%, 82.6%, and 81.7%, and complete remission rates were 69.9%, 69.8%, and 70% for the whole cohort, the SI and RI groups, respectively. Briefly, 6.2%, 4.7%, and 8.3% of patients had progressive disease after ASCT (Table 2).

With a median follow-up of 62.4 month, we observed a 3-year OS of 67.1% and a 3-year PFS of 59.3%, respectively. 3-year OS was not significantly different between SI and RI groups with 69.6% and 62.9%, HR 1.48 (0.86–2.56) $p=0.152$, whereas the 3-year PFS was superior within the SI group (63.9% vs. 52.5%), with a higher risk of death and lymphoma progression in the RI group resulting in a HR of 1.80 (1.11–2.92) $p=0.017$ (Figure 1). Moreover, we found several factors associated with a superior PFS and OS: Age 60–69 versus ≥ 70 , ECOG 0 versus ≥ 1 , remission status prior ASCT (CR/PR1 vs. CR/PR >1 ; CR/PR1 vs. refractory disease) and lines of therapy (1 vs. ≥ 2) (Table 3).

When adjusted for significant confounders of the univariate analysis, the PFS benefit of SI vs. RI conditioning vanished (HR 0.74, CI 0.40–1.38, $p=0.35$). Only age 60–69 versus ≥ 70 (HR 2.20, CI 1.22–3.97, $p=0.009$) and remission status prior ASCT (CR/PR1 vs. CR/PR >1 vs. SD+PD, $p=0.0125$) remain an independent prognostic factors for PFS. Of interest, several factors were associated with a superior OS in the multivariate analyses: Age 60–69 versus ≥ 70 (HR 2.48, CI 1.27–4.84, $p=0.008$), ECOG PS 0 versus ≥ 1 (HR 2.12, CI 1.14–3.94, $p=0.017$), bulky disease (HR 2.52, CI 1.27–5.0, $p=0.008$), lines of therapy 1 versus ≥ 2 (HR 3.9, CI 1.17–12.98, $p=0.026$), and remission status prior ASCT (CR/PR1 vs. CR/PR >1 vs. SD/PD, $p=0.026$). Of note and in contrast to the univariate analysis, the multivariate analysis revealed that SI conditioning was associated with an inferior OS compared with RI conditioning (HR 0.45, CI 0.22–0.94, $p=0.032$) (Table 4). We performed a backward selection model with restriction to variables that significantly affect PFS, which attenuates the

effect of conditioning regimen on OS: SI versus RI conditioning, HR 0.71, CI 0.37–1.35, $p=0.29$. Whereas, age ($p=0.03$) and remissions status prior ASCT ($p<0.0001$) remain significant (Table S1).

Thirty-day mortality was 5.8% in the SI group and 8.3% in the RI group. We observed no difference in NRM 12.8% (SI group) versus 14.4% (RI group) at 3 years, $p=0.62$. Cumulative incidence of relapse was higher in the RI group: 30.8% versus 23.4% at 3 years, $p=0.034$ (Figure 2). Mortality reasons are summarized in Table S2. Of note, in both groups, a relevant proportion of reasons of death remained unknown (SI group: 14% and RI group: 11.7%), which might led to an overestimation of PFS as potential relapses remained unrecognized.

4 | Toxicities

In both groups, as expected with HDCT/ASCT, FN, and infections were common. In the whole cohort, FN of \geq Grade III was observed in all patients. We observed Grade III–V toxicities in our patients as follows: Enterocolitis 39.7%, sepsis 24%, mucositis 19.9%, urinary tract infection 16.4%, pneumonia 12.3%, and atrial fibrillation 10.3%, respectively. We observed no significant difference in frequency or severity of relevant toxicities between SI and RI groups (Table S3). Median time of hospitalization did not significantly differ between both groups (15 vs. 17 days, $p=0.144$). Briefly, 11.6% of all patients needed intensive care unit support at any time from transplant to discharge. During the follow-up, 7.5% of patients experienced a second malignancy, with no significant difference in frequency between SI and RI conditioning.

5 | Discussion

In the CAR-T-cell era, HDCT/ASCT remains the standard of care in late relapse DLBCL patients [9–11]. In addition, it might play a role in selected high-risk patients in first remission [15, 16, 19]. With advances in supportive care strategies, HDCT/ASCT with SI BEAM is used more frequently in older patients [5]. However, patients with an age of 65 years or older, or relevant co-morbidities might be deemed unfit for intensive conditioning. BEAM is considered the standard conditioning regimen prior ASCT in DLBCL patients. CO diffusion capacity corrected for hemoglobin (DLCOcSB), ≤ 60 , ECOG PS ≥ 1 (or comparable Karnofsky Index $\leq 80\%$), Hematopoietic Cell Transplantation Comorbidity Index

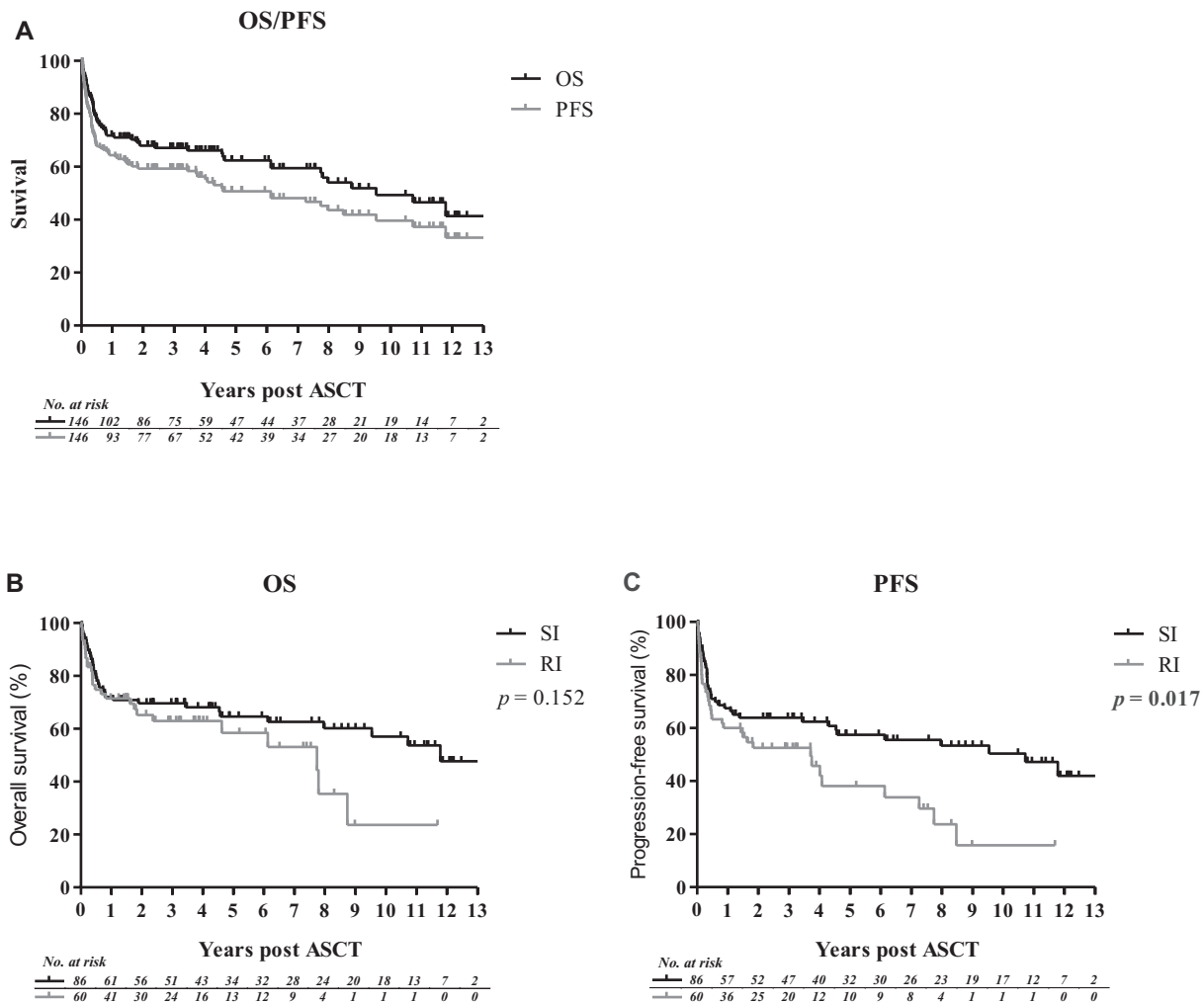


FIGURE 1 | (A) Kaplan–Meier plots: Overall and progression-free survival of the whole cohort. (B) Overall survival and (C) progression-free survival according standard intensity (SI) group and reduced intensity (RI) group (univariate analysis).

TABLE 3 | Univariate analysis for PFS and OS confounders.

Parameter	PFS hazard ratio (95% CI)	<i>p</i>	OS hazard ratio (95% CI)	<i>p</i>
SI vs. RI	1.80 (1.11–2.92)	0.017	1.48 (0.86–2.56)	0.152
Age 60–69 vs. ≥ 70	2.23 (1.34–3.70)	0.002	2.11 (1.20–3.72)	0.009
ECOG 0 vs. ≥ 1	1.80 (1.13–2.86)	0.014	1.96 (1.16–3.32)	0.012
Bulky disease	1.51 (0.86–2.63)	0.150	2.16 (1.12–4.17)	0.022
CR/PR1 vs. CR/PR > 1	3.19 (1.78–5.71)	<0.0001	4.34 (2.21–8.51)	<0.0001
CR/PR1 vs. refractory disease	10.91 (4.84–24.61)	<0.0001	16.35 (6.47–41.29)	<0.0001
Lines of prior therapy: 1 vs. ≥ 2	3.02 (1.89–4.81)	<0.0001	3.87 (2.28–6.55)	<0.0001

Note: Significance values are in bold. CR/PR1: Patients in first remission irrespective of refractoriness to initial therapy. CR/PR > 1: All patients in remission after lymphoma relapse.

(HCT-CI) score ≥ 4 and age > 70 years were associated with decreased OS in patients treated with BEAM [20]. We adopted multiple myeloma conditioning regimens like BM [21] and TM [22] for DLBCL conditioning to spare toxicity in older/unfit patients and/or patients with relevant co-morbidities. We used BNCU or

busufan/thiotepa for patients with high risk of CNS-relapse, synchronous CNS lymphoma, or DLBCL with CNS-near manifestations [23, 24]. To our knowledge, we report the largest cohort of reduced intensity conditioning prior ASCT in DLBCL with only two alkylating agents. Baseline characteristics significantly

TABLE 4 | Multivariate analysis for PFS and OS confounders.

Parameter	PFS hazard ratio (95% CI)	<i>p</i>	OS hazard ratio (95% CI)	<i>p</i>
SI vs. RI	0.74 (0.40–1.38)	0.344	0.45 (0.22–0.94)	0.032
Age 60–69 vs. ≥ 70	2.20 (1.22–3.97)	0.009	2.48 (1.70–4.84)	0.008
ECOG 0 vs. ≥ 1	1.59 (0.95–2.96)	0.080	2.12 (1.14–3.94)	0.072
Bulky disease	1.63 (0.92–2.87)	0.092	2.52 (1.27–5.0)	0.008
CR/PR1 vs. CR/PR > 1	1.10 (0.33–3.65)	0.879	1.04 (0.28–3.82)	0.958
CR/PR1 vs. refractory disease	2.49 (0.87–7.16)	0.090	2.41 (0.76–7.62)	0.135
Lines of prior therapy: 1 vs. ≥ 2	2.57 (0.86–7.69)	0.092	3.90 (1.17–12.98)	0.026

Note: Significance values are in bold. CR/PR1: Patients in first remission irrespective of refractoriness to initial therapy. CR/PR > 1: All patients in remission after lymphoma relapse.

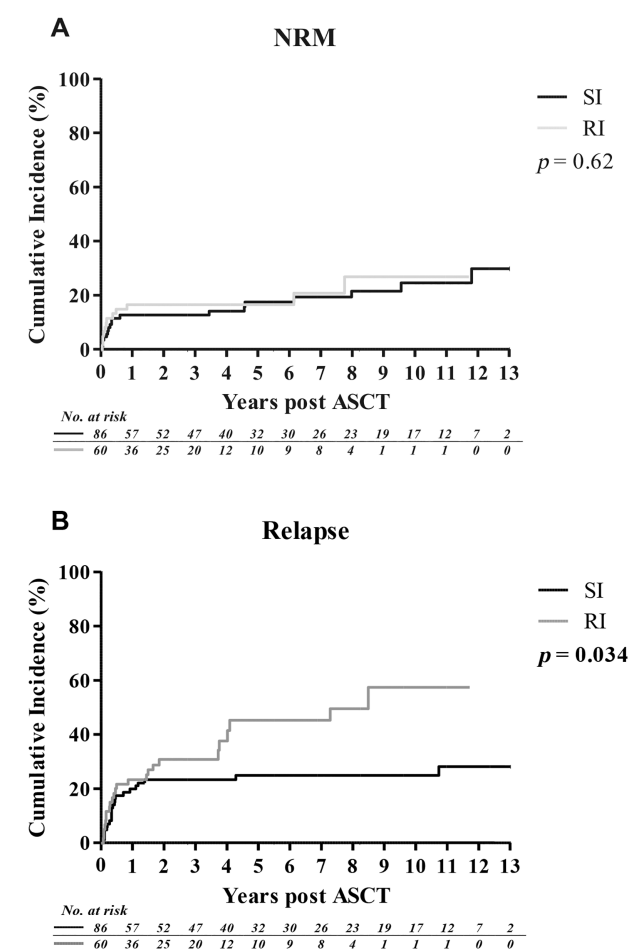


FIGURE 2 | (A) Cumulative incidence of nonrelapse mortality and (B) cumulative incidence of relapse according SI and RI groups.

differ regarding patient's age and fitness and we observed an inferior PFS for patients in the RI group. When adjusted for multiple significant confounders, this effect was no longer noticeable. Furthermore, we observed a trend for superior OS in the RI group in a multivariate analysis. We reported a 3-year OS and PFS of 67.1% and 59.3% for our whole cohort with an age above 60years. Various studies reported comparable survival rates, which are in detail discussed by Martin et al. [5]. In line with these previous

reports, we reported a comparable early mortality rate of 5.8% (SI group) and 8.3% (RI group). Patient's age and remission status prior ASCT remain robust predictors of survival in the multivariate analysis, whereas effects of conditioning regimen diminish.

A previous report from Japan, investigating dose-adjusted conditioning with MEAM (ranimustine, etoposide, cytarabine, and melphalan) in elderly DLBCL patients observed no effect of dose reduction on OS as well [4]. Other groups implemented bendamustine into conditioning regimen (BEAC) and reported a superior toxicity profile and a comparable outcome to BEAM in elderly B-NHL patients [25].

Of interest, a relevant number of our patients were transplanted in first remission, this may be one of the reasons of our favorable survival outcomes, when compared with Scholar-1 outcomes [26].

Our study inherits the limitations of a retrospective analysis, such as the heterogeneity of our patient population and the use of conditioning protocols. In addition, we report a single-center analysis with a small sample size, which may also introduce bias into the results.

In conclusion, our study can only give a hint that reduced intensity conditioning with two alkylating agents in elderly and less fit DLBCL patients is feasible. Our study was not designed to state which variables best determine the use of reduced intensity conditioning. Patients in the SI group had a younger median age, nevertheless the range of age was nearly identical in both groups. In our opinion, there are several factors to concern to proper guide decision for transplant and conditioning regimen: for example, physiological age, performance status, organ function, and co-morbidities (e.g., assessed by HCT-CI [27, 28]).

In conclusion, we provide some evidence that reduced intensity conditioning with two alkylating agents is feasible and resulted in a comparable outcome, when corrected for multiple significant confounders. Nevertheless patient selection is the most crucial step prior HDCT/ASCT. Several retrospective analyses indicate relevant factors to be considered. However, to better define the optimal predicting factors for patient outcome and the optimal conditioning regimen further studies are needed.

We advocate to conduct a prospective trial in this older patient population, as previous prospective trials regularly exclude elder patients.

Author Contributions

T.S. and R.M. conceived and designed the study. T.S., P.H., J.F., J.D.-A., M.E., and R.M. acquired data. T.S. and P.H. analyzed and interpreted data. T.S., P.H., and G.I. performed statistical analyses. J.D. gave administrative support, and T.S., P.H., G.I., J.F., J.D.-A., M.E., J.D., and R.M. critically revised the manuscript.

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Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from patients for the use of their data in clinical research. The Institutional Review Board of the University Freiburg Medical Center approved the study protocol. The study was registered in the German Clinical Trials Register (DRKS00028289). All authors had access to primary data.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.