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Outcome of Lower-Intensity Allogeneic Transplantation in Non-Hodgkin Lymphoma after Autologous Transplantation Failure

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We studied the outcome of allogeneic hematopoietic stem cell transplantation ~~(allo-HSCT)~~ after lower-intensity conditioning regimens (reduced-intensity conditioning ~~[RIC]~~ and nonmyeloablative ~~[NST]~~) in patients with non-Hodgkin lymphoma ~~(NHL)~~ who relapsed after autologous hematopoietic stem cell transplantation ~~(auto-HSCT)~~. Non-relapse mortality ~~(NRM)~~, lymphoma progression/relapse, progression-free survival (PFS), and overall survival ~~(OS)~~ were analyzed in 263 patients with ~~NHL~~. All 263 patients had relapsed after a previous ~~auto-HSCT~~ and then had undergone ~~allo-HSCT~~ from a related (n = 26) or unrelated (n = 237) donor after ~~RIC~~ (n = 128) or ~~NST~~ (n = 135), and were reported to the Center for International Blood and Marrow Transplant Research between 1996 and 2006. The median follow-up of survivors was 68 months (range, 3-111 months). Three-year ~~NRM~~ was 44% (95% confidence interval [CI], 37%-50%). Lymphoma progression/relapse at 3 years was 35% (95% CI, 29%-41%). Three-year probabilities of PFS and ~~OS~~ were 21% (95% CI, 16%-27%) and 32% (95% CI, 27%-38%), respectively. Superior Karnofsky Performance Score, longer interval between transplantations, total body irradiation-based conditioning regimen, and lymphoma remission at transplantation were correlated with improved PFS. ~~Allo-HSCT~~ after lower-intensity conditioning is associated with significant ~~NRM~~, but can result in long-term PFS. We describe a quantitative risk model based on pretransplantation risk factors to identify those patients likely to benefit from this approach.

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INTRODUCTION

Autologous hematopoietic stem cell transplantation (auto-HSCT) is widely used to treat recurrent or refractory non-Hodgkin lymphoma (NHL) [1,2]. Unfortunately, relapse is common after auto-HSCT, and the prognosis for these patients is poor [3]. Conventional chemotherapy is noncurative after auto-HSCT failure, and a second auto-HSCT mostly benefits only a small group of patients who relapse after a long lymphoma-free interval [4,5]. The results of conventional myeloablative allogeneic hematopoietic stem cell transplantation (allo-HSCT) performed in this setting are also poor (5% progression-free survival [PFS] at 5 years), as reported previously [6]. In addition, many patients are not candidates for myeloablative conditioning because of advanced age or the presence of comorbidities.

Reduced-intensity conditioning (RIC) and nonmyeloablative conditioning (NST) regimens are increasingly used in patients with NHL. These lower-intensity conditioning regimens reportedly have lower nonrelapse mortality (NRM) and can be used in older patients with comorbidities [7]. Lower-intensity regimens for allo-HSCT use lower doses of conditioning chemotherapy and radiation, and rely on an immune-mediated graft-versus-lymphoma (GVL) effect for disease control. The magnitude of this effect in the treatment of NHL is unclear [8,9].

Previous studies reporting on RIC or NST allo-HSCT in patients with NHL who relapsed after auto-HSCT have included limited numbers of patients, with variable histologies and variable follow-up, limiting comparisons [10-14]. To analyze the wider applicability and effectiveness of this modality, we analyzed long-term outcomes of lower-intensity (RIC/NST) allo-HSCT in patients with relapsed B cell NHL (B-NHL) after a previous auto-HSCT using data from the Center for International Blood and Marrow Transplant Research (CIBMTR). To date, this represents the largest study of patients with NHL treated with lower-intensity conditioning allo-HSCT after auto-HSCT failure.

SUBJECTS AND METHODS

Data Sources

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR) and the National Marrow Donor Program (NMDP) established in 2004. It comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allo- and auto-HSCTs to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the NMDP Coordinating Center in Minneapolis. Participating centers are required to report all HSCTs consecutively, with compliance monitored by onsite audits. Patients are followed longitudinally, with yearly follow-up. Computerized checks for discrepancies, physicians' reviews of submitted data, and onsite audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with the Privacy Rule (HIPAA) as a public health authority and in compliance with all applicable federal regulations pertaining to the protection of human research participants, as determined by continuous review of the Institutional Review Boards of the NMDP and the Medical College of Wisconsin since 1985.

Subjects

Outcomes of 263 adult patients (aged >21 years) with B-NHL who relapsed after auto-HSCT and then received a lower-intensity conditioning regimen followed by allo-HSCT between 1996 and 2006 were analyzed. Follicular, diffuse large B cell (DLBCL), and mantle cell lymphoma histologies were included. Recipients of planned tandem auto-/allo-HSCT and those in first complete reposnse (CR) at the time of allo-HSCT were excluded. Donors were an HLA-matched sibling for 26 recipients and an HLA-matched unrelated donor (URD) for 237 recipients.

Only a limited number of patients who relapse after auto-HSCT subsequently undergo allo-HSCT. In the period 1990-2006, a total of 6395 patients with relapsed B-NHL after auto-HSCT registered with the CIBMTR, 373 of whom (5.8%) underwent subsequent allo-HSCT after an RIC/NST conditioning regimen. Our cohort is a subset of those patients for whom comprehensive data were available, with high-level reporting and complete case report forms. We confirmed that the global cohort and the study subset had similar outcomes.

Definitions

Lower-intensity conditioning regimens were categorized as RIC or NST using established consensus criteria [15]. Previously established validated criteria for categorizing degree of HLA matching were used [16]. Well-matched cases had either no identified HLA mismatching and informative data at 4 loci or allele matching at HLA-A, -B, and -DRB1 (6/6).

Endpoints

Primary outcomes were NRM, relapse/progression, PFS, and survival. NRM was defined as death from any cause during the first 28 days after trnasplantation or death without evidence of lymphoma progression/relapse. Progression was defined as an increase of ≥25% in the sites of lymphoma or development of new sites of lymphoma. Relapse was defined

as recurrence of lymphoma after a CR. For PFS, a patient was considered a treatment failure at the time of relapse/progression or death from any cause. Patients alive without evidence of disease relapse or progression were censored at last follow-up, and the PFS event was summarized by a survival curve. The OS interval variable was defined as the interval from the date of transplantation to the date of death or last contact and summarized by a survival curve. Other outcomes analyzed included acute and chronic graft-versus-host disease (GVHD) and cause of death. Acute GVHD was defined and graded based on the pattern and severity of organ involvement using established criteria [17]. Chronic GVHD was defined as the development of any chronic GVHD based on clinical criteria. Both of these events were summarized by the corresponding cumulative incidence estimate, with death without development of GVHD as the competing risk.

Statistical Analyses

Probabilities of PFS and OS were calculated using the Kaplan-Meier product limit estimate. Probabilities of NRM, lymphoma progression/relapse, and acute and chronic GVHD were calculated using cumulative incidence curves to accommodate competing risks [18,19]. Associations among subject-, disease-, and transplantation-related factors and outcomes of interest were evaluated using multivariate Cox proportional hazards regression. A stepwise forward selection multivariate model was built to identify covariates that influenced outcomes. Covariates with a P value $<.05$ were considered significant. The proportionality assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome [20]. All variables met the proportional hazards assumption. Results are expressed as relative risk (RR) or the relative rate of occurrence of the event.

The following variables were considered in multivariate analyses: age at allo-HSCT, sex, Karnofsky Performance Score (KPS) at allo-HSCT, time from diagnosis to auto-HSCT, time between auto-HSCT and allo-HSCT, NHL histology, disease status and sensitivity to chemotherapy at allo-HSCT, conditioning regimen intensity (RIC ~~versus~~ NST), donor type (HLA-identical related ~~versus~~ HLA well-matched URD ~~versus~~ HLA partially matched URD), donor–recipient sex match (female donor and male recipient versus all other combinations), donor–recipient cytomegalovirus (CMV) state (donor and recipient CMV-seronegative ~~versus~~ all other combinations), graft source (bone marrow ~~versus~~ peripheral blood), year of allo-HSCT (1996-2003 ~~versus~~ 2004-2006) and type of GVHD prophylaxis. Information on the interval from auto-HSCT to relapse was not available in all patients; thus, the interval between auto-HSCT and allo-HSCT was used as a surrogate variable, combining the interval from auto-HSCT to relapse and the interval from such relapse to allo-HSCT.

RESULTS

Patient- and Transplant-Related Variables

Patient-, disease-, and transplant-related characteristics are presented in Table 1. A total of 263 patients from 69 centers underwent allo-HSCT for NHL with lower-intensity conditioning after relapsing after a previous auto-HSCT. The median patient age at allo-HSCT was 52 years (range, 23-70 years). Eighty-nine patients (34%) had a KPS <90 at the time of allo-HSCT.

A total of 147 patients (56%) had DLBCL or follicular large cell NHL, 72 (27%) had mantle cell lymphoma, and 44 (17%) had follicular lymphoma. In 57 patients, DLBCL was reportedly the result of histological transformation from a lower-grade lymphoma. The median interval from diagnosis to auto-HSCT was 19 months (range, 2-278 months). Eighty-five patients (33%) underwent auto-HSCT within 1 year after diagnosis. The median interval between auto-HSCT and allo-HSCT was 25 months (range, 4-159 months). Fifty-two patients (20%) underwent allo-HSCT within 1 year after auto-HSCT, 80 patients (30%) did so between 1 and years after auto-HSCT, and 131 (50%) did so more than 2 years after auto-HSCT. Only 67 patients (27%) were in second or greater CR (CR2+) at the time of allo-HSCT. A total of 169 patients (63%) were considered to have chemotherapy-sensitive disease at allo-HSCT.

Conditioning regimens were classified as RIC in 128 patients (49%) and NST in 135 patients (51%). Sixty-six patients (25%) received total body radiation (TBI) of 2 Gy, 65 patients (25%) received lower-dose melphalan (<150 mg/m^2), and 62 patients (24%) received fludarabine and cyclophosphamide regimens. Three-fourths of the patients received rituximab at some point before allo-HSCT. A bone marrow graft source was used in 21%. One hundred forty-one patients (54%) underwent allo-HSCT between 2004 and 2006. Seventeen (6%) received donor lymphocyte infusion (DLI) for relapse or failure to achieve CR after allo-HSCT. Median follow-up of survivors was 68 months (range, 3-111 months).

Outcomes

Patient outcomes are summarized in Table 2. One hundred ninety-four of the 263 patients died (74%). Twenty-three patients (9%) were alive with lymphoma, and 46 (18%) were alive and lymphoma-free without relapse at last follow-up. The 100-day mortality rate was 30% (95% confidence interval [CI], 25%-36%). NRM rates were 39% (95% CI, 33%-45%)

Table 1. Patient-, Disease- and Transplantation-Related Characteristics

Variable	
Number of patients	263
Age at allo-HSCT, median (range), years	52 (23-70)
Age at allo-HSCT, years, n (%)	
21-30	14 (5)
31-40	34 (13)
41-50	71 (27)
51-60	107 (41)
≥61	37 (14)
Male sex, n (%)	168 (64)
KPS <90 at allo-HSCT, n (%)	89 (34)
Histology at allo-HSCT, n (%)	
Follicular large/DLBCL	147 (56)
Follicular	44 (17)
Mantle cell	72 (27)
Histological transformation after diagnosis, n (%)	57 (22)
Time from diagnosis to first auto-HSCT, months, median (range)	19 (2-278)
Time from auto- to allo-HSCT, months, median (range)	25 (4-159)
Time from auto- to allo-HSCT, months, n (%)	
<12	52 (20)
12-24	80 (30)
>24	131 (50)
Disease status at allo-HSCT, n (%)	
CR2+	67 (27)
PIF (never in CR)	22 (9)
Relapse-sensitive	90 (36)
Relapse-resistant	58 (23)
Relapse unknown/untreated	14 (6)
Chemosensitivity disease at allo-HSCT, n (%)	
Sensitive	159 (63)
Others	104 (37)
Donor type, n (%)	
Related	26 (10)
Unrelated	237 (90)
Donor-recipient sex match, n (%)	
M-M	112 (43)
M-F	54 (21)
F-M	56 (21)
F-F	41 (16)
Donor/recipient CMV status, n (%)	
+/+	50 (19)
+/−	23 (9)
−/+	90 (34)
−/−	87 (33)
Not tested/inconclusive	11 (4)
Conditioning regimen for allo-HSCT, n (%)	
Low-dose TBI-based (<500 cGy)	9 (3)
Melphalan dose ≤150 mg/m^2	65 (25)
Busulfan dose ≤9 mg/kg	54 (21)
TBI dose 200 cGy	66 (25)
Fludarabine + cyclophosphamide	62 (24)
Fludarabine only	7 (3)
Conditioning regimen at second transplantation, n (%)	
Reduced-intensity	128 (49)
Nonmyeloablative	135 (51)
Rituximab before allo-HSCT, n (%)	195 (74)
Type of donor, n (%)	
Well matched	150 (57)
Partially matched	69 (26)
Mismatched	12 (5)
Unrelated, matching unknown	6 (2)
Related	26 (10)
Graft source, n (%)	
Bone marrow	56 (21)
Peripheral blood	207 (79)
Year of allo-HSCT, n (%)	
1996-1997	2 (1)
1998-1999	8 (3)
2000-2001	41 (16)
2002-2003	71 (27)
2004-2006	141 (54)
GVHD prophylaxis at allo-HSCT, n (%)	
Methotrexate + cyclosporine ± other	35 (13)
Cyclosporine ± other	96 (37)
Methotrexate + tacrolimus ± other	72 (27)
Tacrolimus ± other	51 (19)
T-cell depletion ± other	4 (2)
Other/unspecified	5 (2)
Donor lymphocyte infusion after allo-HSCT, n (%)*	17 (6)
Follow-up of survivors, months, median (range)	68 (3-111)

*Five patients (29%) are alive and 12 (71%) are dead. Sixteen patients (95%) relapsed/progressed after second transplantation. Completeness index follow-up, 90%.

at 1 year, 44% (95% CI, 37%-50%) at 3 years, and 47% (95% CI, 40%-53%) at 5 years after allo-HSCT. The incidence of lymphoma progression/relapse was 31% (95% CI, 25%-36%) at 1 year, 35% (95% CI, 29%-41%) at 3 years, and 36% (95% CI, 30%-42%) at 5 years after allo-HSCT. Figure 1A shows cumulative incidences of NRM and lymphoma progression/relapse.

Figure 1B shows actuarial probabilities of PFS and OS. PFS rates were 30% (95% CI, 25%-36%) at 1 year, 21% (95% CI, 16%-27%) at 3 years, and 17% (95% CI, 13%-22%) at 5 years after allo-HSCT. Corresponding OS rates were 44% (95% CI, 38%-50%), 32% (95% CI, 27%-38%), and 27% (95% CI, 21%-32%).

Table 2. Univariate Outcome Probabilities

Outcome Event	Probability (95% CI)*
30-day mortality	10 (7-15)
100-day mortality	30 (25-36)
Absolute neutrophil count >0.5 × 10^9/L	
28 days	91 (87-95)
100 days	95 (92-97)
Acute GVHD at 100 days, grades II-IV	39 (34-45)
Chronic GVHD	
1 year	37 (31-43)
3 years	40 (34-46)
5 years	40 (34-46)
NRM	
1 year	39 (33-45)
3 years	44 (37-50)
5 years	47 (40-53)
Progression/relapse	
1 year	31 (25-36)
3 years	35 (29-41)
5 years	36 (30-42)
PFS	
1 year	30 (25-36)
3 years	21 (16-27)
5 years	17 (13-22)
OS	
1 year	44 (38-50)
3 years	32 (27-38)
5 years	27 (21-32)

*Probabilities of absolute neutrophil count >0.5 × 10^9/L, acute and chronic GVHD, NRM, and progression/relapse were calculated using the cumulative incidence estimate; 100-day mortality, PFS, and OS were calculated using the Kaplan-Meier product limit estimate.

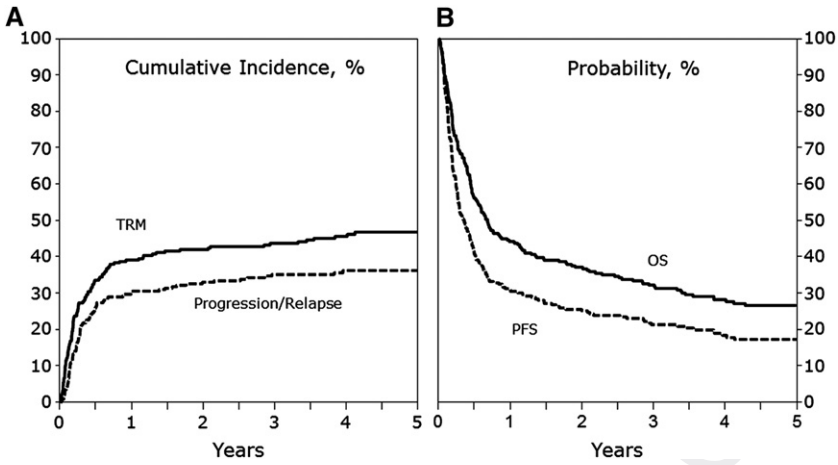

Figure 1. (A) Cumulative incidence of NRM and disease progression after RIC/NST in patients who relapsed after auto-HSCT for NHL. (B) Probabilities of PFS and OS after RIC/NST in patients who relapsed after auto-HSCT for NHL.

The incidence of grade II-IV acute GVHD within 100 days of transplantation was 39% (95% CI, 34%-45%). The incidence of chronic GVHD was 37% (95% CI, 31%-43%) at 1 year and 40% (95% CI, 34%-46%) at 5 years after allo-HSCT. PFS was not correlated with histological type of NHL (Figure 2), except for lower PFS (but not lower OS) in patients with transformed large cell lymphoma.

Seventeen patients received DLI after allo-HSCT for lymphoma progression/relapse. Survival after DLI was low: 12% (95% CI, 2%-31%) at 1 year, 6% (95% CI, 0-24%) at 3 years, and 6% (95% CI, 0-24%) at 5 years. Causes of death were lymphoma-relapse/progression in 50 patients (26%), infection in 33 (17%), organ failure in 32 (16%), and acute or chronic GVHD in 23 (12%) (Table 3).

Multivariate Analyses

NRM

KPS was significantly correlated with NRM. Patients with a KPS <90 had an increased risk of NRM (RR, 2.57; 95% CI, 1.57-3.25; $P < .001$). Figure 3 illustrates the probability of NRM based on KPS.

Lymphoma progression/relapse

The interval between auto-HSCT and allo-HSCT was significantly correlated with the risk of lymphoma progression/relapse. Recipients of allo-HSCT within 2 years after auto-HSCT were at greater risk for progression/relapse (RR, 2.09; 95% CI, 1.37-3.18; $P = .001$) (Figure 4).

PFS and treatment failure

Table 4 presents the results of multivariate analysis of PFS. Patients with a KPS <90 had nearly a 2-fold increased risk of treatment failure, and lower PFS, compared with patients with a higher KPS (RR, 1.78; 95% CI, 1.33-2.40; $P < .001$). Those undergoing allo-HSCT within 2 years after previous auto-HSCT had a lower PFS and higher risk of treatment failure (RR, 1.49; 95% CI, 1.13-1.96; $P = .004$). Recipients of non–TBI-containing conditioning regimens had a lower PFS (RR of treatment failure, 1.66; 95% CI,

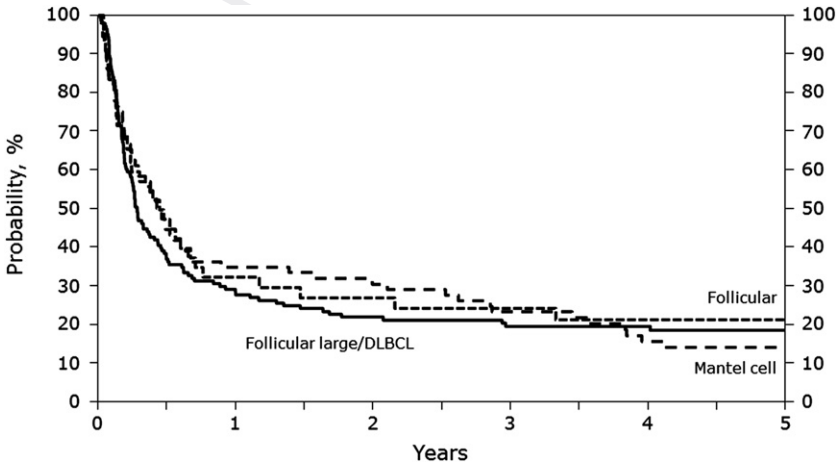

Figure 2. Probability of PFS after RIC/NST in patients who relapsed after auto-HSCT for NHL, according to histology at the time of RIC/NST.

[Q4] **Table 3. Causes of Death (n = 194 Patients Evaluated)**

Cause of Death	n (%)
Primary disease	50 (26)
GVHD	23 (12)
Pulmonary syndrome	11 (6)
Infection	33 (17)
Organ failure	32 (16)
Hemorrhage	5 (3)
New malignancy	2 (1)
Vascular	2 (1)
Unknown	36 (19)

[Q2] 1.20-2.29; $P = .002$). ~~Supplemental Table 1 compares the clinical characteristics of patients receiving TBI and those receiving a non–TBI-based conditioning regimen.~~ Patients who had never achieved CR (ie, primary induction failure [PIF]) had lower PFS (RR of treatment failure, 1.89; 95% CI, 1.12-3.18; $P = .017$). Figure 5 shows the probability of PFS according to risk factors. Figure 6 shows PFS after allo-HSCT by individual conditioning regimens. The type of conditioning regimen, RIC versus NST, did not impact PFS.

GVHD

Patients with KPS <90, those receiving a TBI-based conditioning regimen, and those receiving a graft from a female donors were at increased risk of developing grade II-IV acute GVHD. The sole variable correlated with chronic GVHD was the graft source; recipients of peripheral blood cell grafts were at greater risk than recipients of bone marrow grafts (RR, 2.45; 95% CI, 1.33-4.48; $P = .004$). Patients with grade II-IV acute GVHD were less likely to develop lymphoma progression/relapse (RR, 0.55; 95% CI, 0.34-0.90; $P = .0166$) in univariate analysis, but this difference was not statistically significant in the multivariate model. Chronic GVHD had no impact on the probability of lymphoma relapse/progression (RR, 0.71; 95% CI, 0.37-1.34; $P = .2869$).

OS

OS was significantly correlated with KPS. Patients with a KPS of < 90 had a greater risk of death (RR, 1.92; 95% CI, 1.43-2.56; $P < .001$).

Risk model

Based on the significant pretransplantation variables identified in the multivariate model, we developed a risk scoring system, outlined in Table 5. Patients with all 4 adverse risk factors (KPS <90, never in CR, non–TBI-based conditioning, and ≤24 months between auto-HSCT and allo-HSCT) had an 8.32-fold greater risk of death or relapse compared with patients with no risk factors. Similarly, patients with 3 risk factors (KPS <90, never in CR, and non–TBI-based conditioning) had a 5.58-fold greater risk of death or relapse, and those with 2 risk factors (KPS <90 and never in CR) had a 3.36-fold greater risk of death or relapse.

DISCUSSION

The aims of the present study were to define outcomes after allo-HSCT using lower-intensity conditioning regimens in patients with B-NHL who relapsed after auto-HSCT, and to identify correlations between subject-, disease-, and treatment-related variables and outcomes. This study involves a large cohort of patients from multiple centers with long follow-up, thereby providing a perspective on the feasibility and effectiveness of this treatment strategy.

Despite the lower intensity of the conditioning regimens in our cohort, 3-year NRM was high at 44% (95% CI, 38%-46%). In multivariate analysis, KPS was the sole predictor of NRM; patients with a KPS <90 had a 2-fold greater NRM compared with patients with a KPS ≥90. The NRM in this study is higher than previously reported values. In a study by

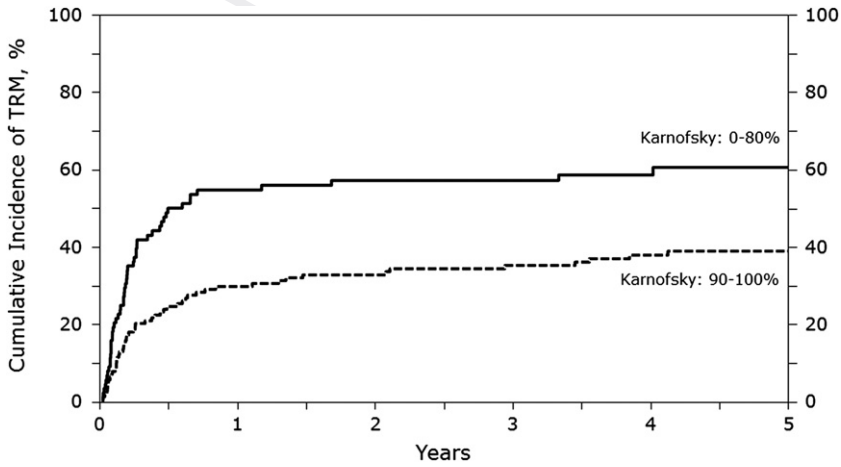

Figure 3. Probability of NRM after RIC/NST according to KPS in patients who relapsed after auto-HSCT for NHL.

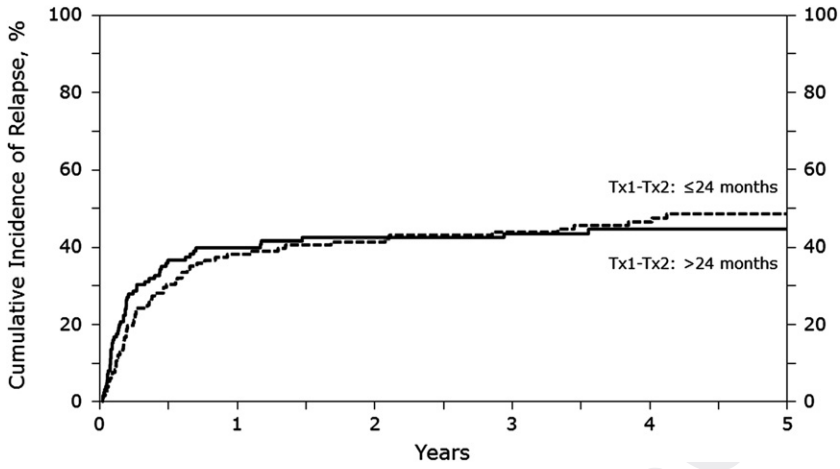

Figure 4. Probability of relapse after RIC/NST in patients who relapsed after auto-HSCT for NHL, according to the time interval between transplantations.

Branson et al. [21] using HLA-identical sibling donors, 14-month NRM was 20%. Martino et al. [7] reported a 24% NRM (95% CI, 15%-41%) at 1 year with HLA-identical sibling donors, and Escalon et al. [22] reported a 5% NRM in patients with chemosensitive lymphoma who received a transplant from an HLA-identical related donor. Baron et al. [23] reported a 28% NRM at 3 years after allo-HSCT from URDs. A recently published study by the European Group for Blood and Marrow Transplantation (EBMT) reported a 3-year NRM of 28.2% [24]. It is likely that differences in NRM between studies reflect differences in subject selection, proportion of unrelated donors, and width of CIs. Approximately 40% of the patients in our study had a KPS <90. Moreover, 90% of our patients received a URD transplant. Only ~60% of the URD transplants were well matched, lower than the proportions of well-matched URDs in other studies [22,23]. Another significant difference is that our study cohort was almost a decade older than the patients in most previous studies.

Table 4. Multivariate Analysis for PFS

Variable	n	RR of Relapse/Progression or Death (95% CI)	*P* Value
KPS			
≥90	138	1.00	
<90	119	1.78 (1.33-2.40)	<.001
Time from auto-HSCT to allo-HSCT			
>24 months	128	1.00	
≤24 months	129	1.49 (1.13-1.96)	.004
Conditioning regimen for allo-HSCT			
TBI-based	73	1.00	
Non–TBI-based	184	1.66 (1.20-2.29)	.002
[Q5] Disease status at allo-HSCT*			.043
CR2+	67	1.00	
Relapse	156	1.26 (0.90-1.75)	.177
PIF	22	1.89 (1.12-3.18)	.017
Unknown	12	0.75 (0.37-1.51)	.418

The risk for lymphoma progression/relapse was 31% (95% CI, 25%-36%) at 1 year and increased to 36% (95% CI, 30%-42%) at 5 years. These values are similar to those reported in previous studies [23,25]. The major risk factor correlated with risk of lymphoma progression/relapse was a shorter interval between auto-HSCT and allo-HSCT, which is likely a surrogate for a short time to relapse after auto-HSCT. In multivariate analyses, higher KPS, longer interval between auto-HSCT and allo-HSCT, use of TBI, and more favorable disease status at the time of transplantation were correlated with superior PFS. As in previous studies, disease status at the time of allo-HSCT was correlated with PFS. Patients with PIF (who had never achieved previous CR) were at greatest risk for treatment failure [7,23,26]. In previous studies, these patients were excluded or had worse outcomes [22,27]. Interestingly, the use of TBI in conditioning substantially improved PFS, consistent with the findings in our previous study of myeloablative allo-HSCT in this setting [6]. TBI also was found to decrease the rate of recurrence in a previous CIBMTR study of follicular lymphomas [8]. The quantitative risk model that we describe here is predictive of PFS and helps define the risks and benefits of allo-HSCT in this setting in practice.

Most previous studies had limited statistical power to detect differences in outcomes among lymphoma subtypes. Survival was similar in patients with DLBCL, follicular cell lymphoma, and mantle cell lymphoma in the present study. Although PFS was shorter in patients with histological transformation of follicular lymphoma, this did not translate into shorter OS.

The use of lower-intensity allo-HSCT is predicated on a GVL effect. Consistently detecting a GVL effect is difficult in this setting, however [8,9]. In the present study, patients with grade II-IV acute GVHD were less likely to develop lymphoma

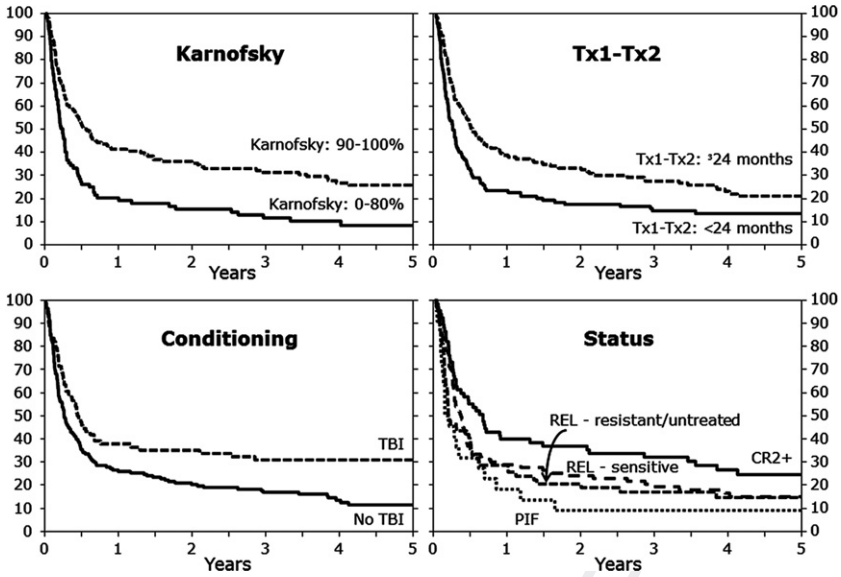

Figure 5. Probability of PFS after RIC/NST in patients who relapsed after auto-HSCT for NHL according to KPS, interval between auto-HSCT and RIC/NST, use of TBI-containing conditioning regimen, and disease status at the time of RIC/NST.

progression/relapse, but this effect was not significant in multivariate analysis. In a small study, Mohty et al. [12] reported a correlation between acute GVHD and lymphoma relapse. Others have reported a correlation between chronic GVHD lymphoma progression/relapse, whereas the EBMT study found no beneficial effect of either acute or chronic GVHD [23-25]. In aggregate, these data do not support the presence of a strong, consistent GVL effect in this population of patients with advanced relapsed NHL.

The present study has several limitations. The interval between auto-HSCT and relapse and the time to allo-HSCT after relapse are relevant disease-related variables that were not available to us. Instead, we used the interval between auto-HSCT and allo-HSCT as a surrogate incorporating both time intervals. Furthermore, our study population did not include all patients who relapsed after auto-HSCT and were eligible for RIC/NST allo-HSCT. In fact, only a minority of patients who relapse after auto-HSCT undergo allo-HSCT. The reasons for this are beyond the scope of our analysis, but might be related to the failure of salvage therapies for NHL relapse, early mortality after relapse, ineligibility for allo-HSCT, or patient/physician choice. Our results are applicable only to patients with NHL who undergo allo-HSCT.

Survival is poor in patients with NHL who relapse after auto-HSCT [28,29]. Our previous study reported only a 5% PFS at 5 years after myeloablative allo-HSCT for patients failing auto-HSCT [6]. Myeloablative conditioning in this setting has been largely abandoned in favor of lower-intensity conditioning regimens, as illustrated by the present study and the recent EBMT report [24]. Relapse or progression of NHL in this cohort of advanced, high-risk patients who underwent lower-intensity allo-HSCT was 36% at 5 years, with the vast majority of relapses occurring

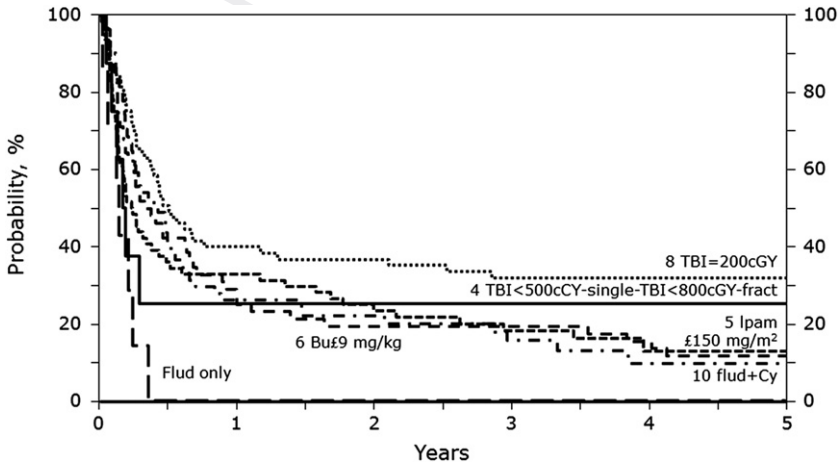

Figure 6. Probability of PFS after RIC/NST in patients who relapsed after auto-HSCT for NHL according to conditioning regimen.

Table 5. Risk Factor Model for PFS

Combination of Variables	RR of Relapse/Progression or Death (95% CI)
KPS <90 + PIF at allo-HSCT + time between HSCTs ≤24 months + non–TBI-based conditioning	8.32 (4.00-17.33)
KPS <90 + PIF at allo-HSCT + non–TBI-based conditioning	5.58 (2.82-11.04)
KPS <90 + PIF at allo-HSCT	3.36 (1.84-6.13)
Time between HSCTs ≤24 months + non–TBI-based conditioning	2.47 (1.61-3.81)

within the first year after transplantation. However, NRM was also high, contributing to the 5-year PFS of 17% and OS of 27%. More effective and less-toxic conditioning regimens, as well as posttransplantation antilymphoma therapy, are needed to improve these outcomes, considering that disease progression and NRM are the most common cause of failure.

Despite these sobering results, our risk model based on pretransplantation characteristics defines a subset of patients that can benefit from lower-intensity allo-HSCT after auto-HSCT failure. Patients with late relapse, superior KPS, and controlled disease are especially likely to benefit from this approach and should be considered for this modality.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2011.12.581.

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