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Long-Term Outcomes After Allogeneic Hematopoietic Stem Cell Transplantation in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma: An Italian Multicenter Collaborative Study

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A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) use in refractory/relapsed B-cell non-Hodgkin lymphoma (R/R B-NHL) has been reduced due to the efficacy of CAR-T-cell therapy as salvage treatment. However, there remains a need for data regarding the long-term outcomes following allo-HSCT, to fully characterize this procedure as a benchmark to design further studies on the role of allogeneic stem cell transplantation. The present study was lauched to assess the long-term outcomes of R/R B-NHL patients after allo-HSCT, in a multicenter study among six Italian hematology centers. Data were collected from 285 allo-HSCT procedures performed among 281 R/R B-NHL patients, in 2000 to 2020. All patients signed informed consent for sharing data with the GITMO/EBMT Registry, and the study was approved by the Institutional Review Board of the coordinating center. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), cumulative incidence function (CIF) of

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disease-related death, and non-relapse mortality (NRM). The median age at transplant was 50 yr (19 to 70), with 94 (33%) female patients. Histological subsets included indolent lymphoma (123 patients; 43.3%), aggressive lymphoma (124; 43.7%), and mantle-cell lymphoma (MCL; 37; 13%). At allo-HSCT, 135 patients (47.7%) exhibited complete remission (CR), 63 (22.3%) partial response, 30 (10.6%) stable disease, and 55 (19.4%) progressing disease. Myeloablative regimens were employed in 86 procedures (30.2%). The median follow-up for surviving patients was 8.7 yr (0.3 to 22). Three-year PFS was 43.7% (95% CI 37.9 to 49.4), 9-yr PFS 39.3% (33.4 to 45.1), 3-yr OS 50.4% (44.5 to 56.1), and 9-yr OS 46.6% (40.5 to 52.5). Positive predictors of 3-yr PFS included indolent lymphoma (55.3%) versus aggressive (37.9 %) and MCL (27.0%); and CR at allo-HSCT (51.9%) vs non-CR (30.9% to 38.9%). Similar associations were observed for OS. Among patients in CR, outcomes did not significantly differ among histological subtypes. Among patients not in CR, outcomes were significantly better for indolent lymphoma (3-yr PFS: 56.6%), compared to aggressive (26.4%), and MCL (0%). Regarding transplant procedures, the subgroup receiving post-transplant cyclophosphamide-based program for GVHD prophylaxis had a significantly improved outcome. Overall, 56 patients (19.6%) died from lymphoma progression, with 1-yr and 3-yr CIF of disease-related death of 15.9% (95% CI: 11.9 to 20.5) and 18.5 (14.2 to 23.2), respectively. The latest disease recurrence occurred at 5.4 yr post-allo-HSCT. Early NRM occurred in 75 patients (12-month CIF 26.1%), and late NRM in 25 patients (5-yr CIF 31.2%; 25.9 to 36.7). At present, 95 patients (33.3%) are long-term survivors in continuous CR at 5-22 yr since transplant. Despite pronounced toxicity, allo-HSCT is effective in high-risk, R/R B-NHL, with 5-yr PFS expectancy of ~40%, and approximately one-third of long-term survivors in CR. Patients undergoing allo-HSCT in CR exhibited the best results. Among patients not in CR, the greatest benefits were obtained in indolent lymphoma. Allo-HSCT remains a potentially curative option for R/R B-NHL patients and further investigations are warranted to define its possible use in patients unable to undergo or failing CAR-T-cell therapy and/or bispecific monoclonal antibodies.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) was long considered the last hope for lymphoma patients with recurrence after heavy pre-treatments and/or refractory disease. Despite its marked anti-lymphoma efficacy, the complexity of the procedure and the associated severe toxicities, with non-negligible fatal complications, restricted the use of allo-HSCT to cases that were not manageable with common chemo-immunotherapeutic approaches [1–4]. In recent years, allo-HSCT has been less commonly used, even in this setting, due to the emergence of CD19-directed chimeric antigen receptor (CAR) T-cell therapy. CAR-T cells, and novel antibody-conjugated therapies or bi-specific antibodies, have shown marked efficacy, without the high transplant-related mortality associated with allo-HSCT, and have progressively replaced allo-HSCT for the management of relapsed or refractory B-cell non-Hodgkin lymphoma (B-NHL), particularly aggressive diffuse large B-cell (DLBCL) subtype [5–10]. Indeed, allo-HSCT is now considered a dated therapeutic approach, and its use for B-NHL treatment is rapidly declining [11–13].

Although CAR-T cell therapy shows potent anti-lymphoma activity, its main advantage is its much higher tolerability compared to allo-HSCT. Notably, only a subset of patients shows durable responses to CAR-T cell therapy, and disease relapse remains a significant cause of treatment failure even beyond 48 months after CAR-T infusion. Indeed, large studies with prolonged follow-up are required in order to clearly define the actual curative potential of CAR-T cell therapy for high-risk B-NHL [14–16]. Additionally, novel immunotherapeutic agents, such as antibody-drug conjugates or bispecific antibodies, are quite effective although their efficacy in producing durable disease control has not been definitely proved [8,17–21]. Therefore, allo-HSCT might still have a role in treating relapsed or refractory B-NHL among patients who fail or are unable to receive CAR-T therapy or other novel

immunotherapies. Thus, there remains a need for a well-defined description of the long-term outcomes of relapsed/refractory B-NHL following allo-HSCT, in terms of response durability and occurrence of late toxicities.

Based on these premises, we have investigated outcomes following allo-HSCT among patients with refractory/relapsed lymphoma, focusing exclusively on B-NHL, including indolent, aggressive, and mantle-cell lymphoma, i.e. the main subtypes considered suitable for treatment with CAR-T cell therapy or other novel immunotherapies. This was a multicenter study, including six Italian transplant centers, with the aims of evaluating: i. the incidence of disease recurrence over time since allo-HSCT; ii. early and late non-relapse mortality; and iii. long-term outcomes and the main factors influencing both progression-free and overall survival.

PATIENTS AND METHODS

Data Source

This retrospective observational study included 285 allogeneic hematopoietic stem cell transplantation (allo-HSCT) procedures, performed between 2000 and 2020. The 281 included patients were ≥ 18 yr of age, and had a history of prior treatment for refractory or relapsed B-cell non-Hodgkin lymphoma. Six Italian hematology and transplant centers participated in the study. All included centers are part of the national and European BMT registries and are required to record and update the clinical information about all hematopoietic cell transplant recipients. This retrospective analysis was approved by the Institutional Review Board (IRB) of the coordinating center (IEO, Milan). Additional approval was obtained according to the specific policies of each participating institution. All included patients had signed an informed consent at the time of their allo-HSCT procedure, which included their consent for the routine collection of anonymized data. Data collection was completed in November of 2023.

Patients and Treatments

Patients with all subtypes of peripheral B-cell lymphoma were considered for study inclusion. This study excluded patients with Hodgkin Lymphoma or peripheral T-cell lymphoma, as well as patients with chronic lymphocytic leukemia, with the exception of few patients with unspecified small lymphocytic lymphoma. Data were collected regarding relevant prognostic variables, patient characteristics, and treatments received (Table 1). All patients had previously undergone various intensive treatments, including chemo-immunotherapy and radiotherapy if suitable. Salvage intensified therapy with an autograft was employed in 169 (61.5%) patients. In addition, a subgroup of patients received novel non-chemotherapeutic drugs including targeted therapies (Ibrutinib: 4, Idelalisib: 4, Venetoclax: 2), immunoconjugates (Zevalin: 2, Polatuzumab: 2, Loncastuximab: 1), immunomodulators (Lenalidomide: 4, Nivolumab: 2) and bi-specific Ab (blinatumumab: 1). The option of allo-HSCT as salvage therapy was offered in cases of very high-risk refractory or relapsed disease, with a suitable stem cell donor, and in the absence of other curative options. As shown in Table 1, patients who decided to undergo allo-HSCT received either myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) regimens, according to the definitions of the International Workshop Criteria [22]. MAC or RIC was selected based on the patient's clinical history and condition, and the type of donor available. Prophylaxis for graft-versus-host disease (GVHD) and for infections was administered using common protocols, in accordance with the standard policies at each center. For recipients of a haploidentical transplant, GVHD prophylaxis was often planned using the posttransplant cyclophosphamide (CY)-based program [23]. In a subset of patients, an intensified schedule was used, which included an anti-T-lymphocyte globulin, the anti-CD25 basiliximab, and mycophenolate mofetil [24].

End-Points and Outcome Definitions

All patients underwent response evaluation at 3 months after allo-HSCT, and at 6-month intervals thereafter for 5 yr, which included neck, chest, abdomen/pelvic ultrasonography and/or CT scan. FDG-PET CT and bone marrow (BM) biopsy were usually performed at the time of transplant, and thereafter, according to clinical need and the discretion of the attending physician. Complete Remission (CR) was defined as a complete regression of any palpable or visible mass to the normal size on CT scan, with negative uptakes on PET scan. Partial remission (PR) was defined as the achievement of at least a 50% reduction in masses observed on imaging scans, without new lesion development. Progressive disease (PD) was defined as either an increase in lesion size by > 25%, or the appearance of new lesions compared to the last previous assessment. Stable disease (SD) was defined as a disease status not consistent with PD or PR/CR. Relapse was defined as the appearance of new lesions in a patient with CR.

Table 1
Main Patient Characteristics and Treatment Features in 285 Allografting Procedures.

Variable	Level	n = (%)
Sex	Female	94 (33.0)
	Male	191 (67.0)
Age at diagnosis	Years, median (range)	46 (17-68)
Histological diagnosis*	Follicular lymphoma	108 (38)
	Marginal-zone lymphoma	6 (2.1)
	Other low-grade lymphomas	9 (3.2)
	Diffuse large B-cell lymphoma	91 (32.0)
	Burkitt's Lymphoma	8 (2.8)
	Primary mediastinal large B-cell lymphoma	13 (4.6)
	Unspecified high-grade lymphoma	12 (4.2)
	Mantle-cell lymphoma	37 (13.0)
Histological subsets*,†	Indolent lymphoma	123 (43.3)
	Aggressive lymphoma	124 (43.7)
	Mantle-cell lymphoma	37 (13.0)
No. of therapy lines before allo-HSCT*	1	6 (2.1)
	2	54 (19.1)
	3	91 (32.3)
	4	74 (26.2)
	5	39 (13.8)
	>5	18 (6.4)
previous intensified therapy with autograft*	NO	106 (38.5)
	YES	169 (61.5)
Salvage therapy before allo-HSCT*,‡	NO	37 (13.2)
	YES	244 (86.8)
Status at allo-HSCT*	Complete remission	135 (47.7)
	Partial remission	63 (22.3)
	Stable disease	30 (10.6)
	Progressive disease	55 (19.4)
Clinical presentation at allo-HSCT: - KPS*	> 70%	106 (100)
- HCT-CI*	0	60 (29.0)
	1-2	80 (38.6)
	≥ 3	67 (32.4)
- DRI*	Low	115 (41.4)
	Intermediate	108 (38.8)
	High	4 (1.4)
	Very high	51 (18.3)
Year of transplant	2000 – 2005	51 (17.9)
	2006 – 2010	76 (26.7)
	2011 – 2015	79 (27.7)
	2016 - 2020	79 (27.7)
Age at transplant	Years, median (range)	50 (19-70)
Type of conditioning regimen	Myeloablative (MAC)	86 (30.2)
	Reduced intensity (RIC)	199 (69.8)
Donor subtypes	Sibling HLA-id	103 (36.1)
	Sibling HLA-mis	2 (0.7)
	Haploidentical	70 (24.6)
	MUD HLA-identical	58 (20.4)
	MUD HLA-mis	42 (14.7)
	Cord blood	8 (2.8)
	Syngeneic	2 (0.7)

(*continued*)

Table 1 (*Continued*)

Variable	Level	n = (%)
Post-transplant CY[§]	NO	226 (79.3)
	YES	59 (20.7)
Center	INT, Milan	84 (29.5)
	S. Martino H., Genova[‖]	64 (22.5)
	Tor Vergata U., Rome	49 (17.2)
	Papa Giovanni XXIII H., Bergamo	39 (13.7)
	IEO, Milan[¶]	37 (12.9)
	Policlinico Gemelli, Rome	12 (4.2)

MUD, Matched Unrelated Donor; INT, Istituto Nazionale Tumori; IEO, European Institute of Oncology; H, hospital.; U, university; n =: number of patients.

[*] The following data were missing: histological diagnosis and subsets (1 case); number of therapy lines before allo-HSCT (3 cases); previous intensified therapy with autograft (10 cases); salvage therapy (4 cases); status at transplant (2 cases); clinical presentation at transplant, KPS (Karnofsky Performance Status) (179 cases), HCT-CI (Hematopoietic Cell Transplant-specific Comorbidity Index) (78 cases), DRI (Disease Risk Index) (7 cases).

[†] Three main histological subsets were defined: indolent lymphoma (including follicular lymphoma, marginal-zone lymphoma, and unspecified small lymphocyte lymphoma), aggressive lymphoma (including diffuse large B-cell lymphoma, Burkitt's lymphoma, primary mediastinal large B cell lymphoma, and unspecified high-grade lymphoma), and mantle-cell lymphoma.

[‡] Most patients received specific salvage therapy in preparation for allo-HSCT.

[§] Post-transplant CY: posttransplant cyclophosphamide-based program

[‖] *Sixty-two patients total* (2 patients underwent allo-HSCT two times)

[¶] Thirty-five *patients total* (2 patients underwent allo-HSCT two times)

The primary end-point of the study was progression-free survival (PFS), defined as the time from allo-HSCT until lymphoma relapse or progression or death from any cause. We also analyzed the following six secondary end-points. First, overall survival (OS) was defined as the time from allo-HSCT to death from any cause. Second, the cumulative incidence of disease-related death was defined as the time from allo-HSCT to death due to relapse/disease progression, considering non-disease-related death as a competing event. Third, the cumulative incidence of non-relapse mortality (NRM) was assessed in terms of death unrelated to the underlying lymphoma, accounting for disease-related death as a competing event; NRM was classified as early or late according to its occurrence within 1 yr or after 1 yr since allo-HSCT, respectively. Fourth, the cumulative incidence of recurrence was defined as the time from allo-HSCT to progression/relapse, considering death as a competing event. Fifth, the cumulative incidence of acute GVHD (aGVHD) and chronic GVHD (cGVHD) was evaluated using established clinical criteria [25–26], accounting for death as a competing event. Lastly, GVHD-free, progression-free survival (GPFS) was defined as the time from allo-HSCT until grade III–IV acute GVHD, extensive or systemic chronic GVHD requiring therapy, recurrence, or death, whichever occurred first.

Outcome parameters were evaluated according to disease status at the time of allo-HSCT. Additionally, outcomes were investigated according to histology. To this end, patients were divided into three main histological subgroups, as follows. The first group was indolent B-cell lymphoma, which was mostly represented by follicular lymphoma (FL) (108 cases), along with few cases of marginal-zone lymphoma (6 cases) and unspecified small lymphocyte lymphoma (9 cases). The second group was aggressive B-cell lymphoma, mostly represented by diffuse large B-cell lymphoma (DLBCL) (91 cases), along with few cases of Burkitt's Lymphoma (BL) (8 cases), primary mediastinal large B-cell lymphoma (PMBL) (13 cases), and high-grade lymphoma (12 cases). The third group included 37 cases of mantle-cell lymphoma (MCL).

Statistical Methods

Continuous data were reported as median and range, or interquartile range (IQR). Categorical data were reported as counts and percentages. Fisher's exact test was used to analyze the association between categorical variables. PFS, OS and GPFS functions were estimated using the Kaplan–Meier method, and the log–rank test was used to assess differences between groups. Univariable Cox proportional hazards regression models were used to evaluate associations between several factors and death or PFS events. Variables with a P value of $< .10$ in the univariable analysis were included in the multivariable analysis for both OS and PFS. Among histological subset

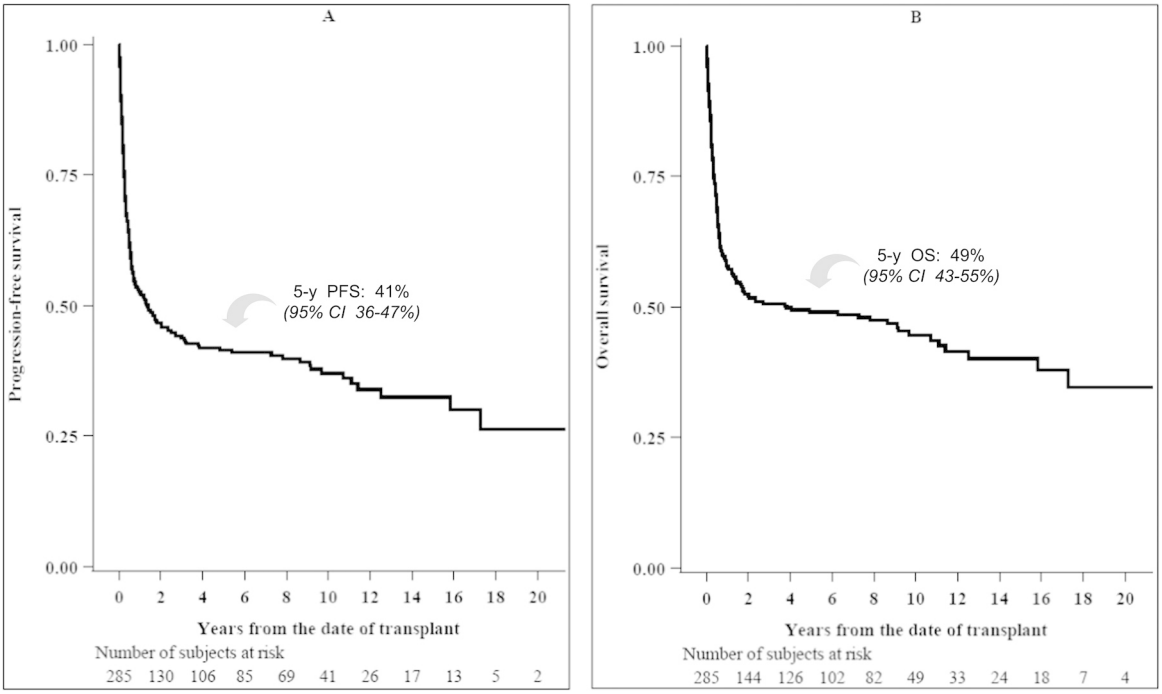

Figure 1. (A) Progression-free survival (PFS) of the whole series. (B) Overall survival (OS) of the whole series. Median follow-up of surviving patients: 8.7 years (range: 0.3 to 22).

and Disease Risk Index (DRI), only histological subset was retained in the multivariable model, and DRI was excluded to avoid collinearity. The cumulative incidence functions of recurrence, disease-related and non-disease-related death, and acute and chronic GVHD, were estimated following methods described by Kalbfleisch and Prentice [27], accounting for the competing causes of events. Gray's test was used to assess the differences between groups. Univariable Fine and Gray regression models were used to assess the associations between patient, tumor, and treatment characteristics with the development of severe aGVHD and/or cGVHD requires systemic therapy. Variables with a univariable *P* value of $< .10$ were included in the multivariable model. All reported P values were two-sided, and a P value of $< .05$ was considered statistically significant. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

The total number of patients included was 281, and four patients underwent two distinct transplant procedures, yielding a total of 285 analyzed procedures. Table 1 presents the main patient and treatment characteristics. Six Italian hematology centers participated in this study, and Table 1 presents their contributions in terms of the number of reported procedures.

PFS and OS in all Patients and Stratified by Subgroups

At a median follow-up of the survivors of 8.7 yr (range: 0.3-22), the median PFS was 1.3 yr (95% CI: 0.7 to 2.7), with a 3-yr PFS of 43.7% (37.9 to 49.4) and a 9-yr PFS of 39.3% (33.4 to 45.1), and a 20-yr projected PFS of 26.4% (17.3 to 36.3) (Figure 1A). The median OS was 3.8 yr (95% CI: 1.3 to 10.7), with a 3-yr OS of 50.6% (44.7 to 56.3), 9-yr OS of 46.8% (40.7 to 52.7), and a 20-yr projected OS of 34.6 (25.2 to 44.1) (Figure 1B).

Figure 2A and 2C present the PFS and OS curves stratified by histology (indolent B-cell lymphoma, aggressive B-cell lymphoma, and mantle-cell lymphoma). PFS was significantly better in patients with indolent lymphoma, compared to aggressive lymphoma and MCL (Figure 2A; Table 3). Similarly, indolent lymphoma seemed to be associated with a better OS, compared to the other two histological subgroups, although the differences were less pronounced (Figure 2C; Table 4). We also assessed the probability of PFS and OS according to disease status at the time of allo-HSCT. CR at allo-HSCT was associated with better outcomes in terms of both PFS and OS, compared to PD

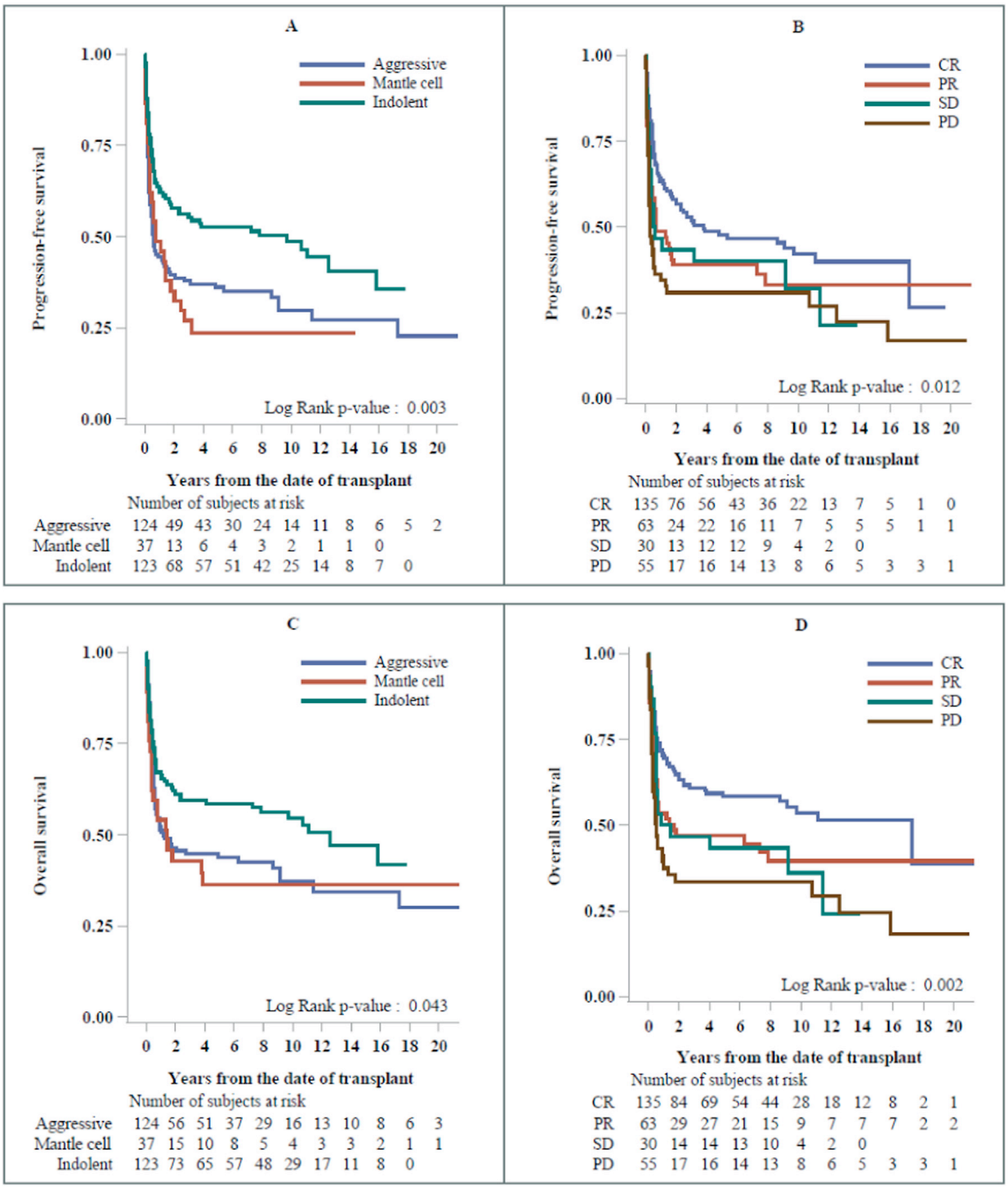

Figure 2. Progression-free survival and overall survival according to the main histological subgroups (A and C), and according to disease status at the time of allogeneic hematopoietic stem cell transplantation (B and D). CR, Complete Remission; PR, Partial Remission; SD, Stable Disease; PD, Progressive Disease.

(Figure 2 B,D; Tables 3 and 4). Patients in CR also had better outcomes than patients with PR or SD, although the differences did not always reach statistical significance (see Tables 2 and 3).

Next, both PFS and OS were assessed according to the combination of both histology and disease status at transplantation. When the analysis was restricted to patients undergoing allo-HSCT in CR, PFS and OS did not significantly differ among the three main histology groups, although MCL showed a trend toward a poorer outcome compared to aggressive and indolent lymphoma (Figure 3A,C). Aggressive and indolent lymphoma showed almost superimposable PFS and OS curves. Conversely, when considering patients undergoing allo-HSCT while not in CR, both PFS and OS were significantly different among the

Table 2
Associations of Patient and Treatment Characteristics with Progression-Free Survival.

Variable Level		n =	3-yr PFS (95% CI)	Univariate Analysis		Multivariate Analysis‖,¶	
				HR (95% CI)	*P* =	HR (95% CI)	*P* =
Sex	Female	94	44.0 (33.8-53.8)	Ref.	-		
	Male	191	43.6 (36.5-50.5)	0.92 (0.67-1.25)	*.58*		
Histological Subset*,†	Indolent	123	55.3 (45.9-63.6)	Ref.	-	Ref.	-
	Aggressive	124	37.9 (29.4-46.3)	1.61 (1.16-2.23)	*.004*	1.62 (1.16-2.25)	*.004*
	MCL	37	27.0 (14.1-41.8)	1.87 (1.20-2.92)	*.006*	2.14 (1.36-3.38)	*.001*
Previous therapy lines* (n =)	1 – 2	60	36.6 (24.6-48.6)	Ref.	-		
	> 2	222	46.3 (39.6-52.8)	0.84 (0.60-1.20)	*.35*		
Previous autograft*,‡	NO	106	42.7 (33.1-51.9)	Ref.	-		
	YES	169	44.6 (37.0-51.9)	1.01 (0.74-1.37)	*.95*		
Salvage Therapy*	NO	37	43.2 (27.2-58.3)	Ref.	-		
	YES	244	44.5 (38.2-50.7)	0.79 (0.53-1.18)	*.25*		
Status at Transplant*	CR	135	51.9 (43.1-60.0)	Ref.	-	Ref.	-
	PR	63	38.9 (26.9-50.7)	1.39 (0.95-2.04)	*.093*	1.49 (1.01-2.21)	*.046*
	SD	30	43.3 (25.6-59.9)	1.42 (0.87-2.33)	*.16*	1.54 (0.94-2.54)	*.088*
	PD	55	30.9 (19.3-43.2)	1.86 (1.27-2.73)	*.001*	1.92 (1.29-2.85)	*.001*
HCT-CI*	0	60	37.5 (25.3-49.6)	Ref.	-		
	1-2	80	46.3 (35.1-56.7)	0.84 (0.55-1.28)	*.41*		
	≥ 3	67	51.5 (38.9-62.8)	0.86 (0.55-1.34)	*.51*		
DRI*	Low	115	51.0 (41.4-59.9)	Ref.	-	ND	
	Intermediate	108	49.1 (39.4-58.1)	1.15 (0.81-1.63)	*.44*	ND	
	High/Very High	55	20.0 (10.7-31.4)	2.57 (1.75-3.78)	*<.001*	ND	
Year of transplant	2000-2005	51	38.2 (25.0-51.3)	Ref.	-		
	2006-2010	76	32.9 (22.7-43.5)	1.17 (0.77-1.77)	*.47*		
	2011-2015	79	49.1 (37.7-59.6)	0.77 (0.49-1.19)	*.24*		
	2016-2020	79	52.4 (40.8-62.8)	0.73 (0.46-1.14)	*.16*		
Age at allo-HSCT	+ 5 yr			1.03 (0.96-1.10)	*.44*		
Conditioning regimen	MAC	86	42.5 (31.9-52.7)	Ref.	-		
	RIC	199	44.3 (37.2-51.1)	0.95 (0.69-1.30)	*.73*		
Haploidentical	NO	215	41.7 (35.0-48.2)	Ref.	-		
	YES	70	50.0 (37.8-61.0)	0.88 (0.62-1.25)	*.47*		
Donor subtypes	Sibling	105	41.0 (31.5-50.1)	Ref.	-		
	Haplo	70	50.0 (37.8-61.0)	0.84 (0.57-1.23)	*.36*		
	MUD	100	44.2 (34.2-53.7)	0.86 (0.61-1.22)	*.41*		
	Others	10	24.0 (3.8-53.7)	1.47 (0.68-3.20)	*.33*		
Post-transplant CY	NO	226	40.1 (33.6-46.5)	Ref.	-	Ref.	
	YES	59	57.6 (44.1-69.0)	0.67 (0.45-1.00)	*.049*	0.67 (0.45-1.00)	*.052*

HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index; DRI: Disease Risk Index; MUD: Matched Unrelated Donor; Haplo. haploidentical donor; post-transplant CY: posttransplant cyclophosisphamide-based program; ND: not done; n =: number of patients.

* See footnote to Table 1 for information regarding missing data.

† See footnote to Table 1 for information regarding histological subset categorization.

‡ previous intensified therapy with autograft

‖ Only variables with $P < .10$ in univariable analysis were included in multivariable analysis.

¶ Among Histological subset and Disease Risk Index (DRI), only Histological subset was retained in the multivariable model, and DRI was excluded to avoid collinearity

three main histology groups (Figure 3B,D). This analysis showed significantly better outcomes for indolent lymphoma, compared to the two other histological subgroups, with the poorest outcome in MCL (3-yr PFS for non-CR patients: 56.6%, 43.5 to 67.9, for indolent lymphoma, 26.4%, 16.9 to 36.9, for aggressive lymphoma, 0% for MCL; 3-yr OS for non-CR patients: 58.2%, 45.0 to 69.3, for

Table 3
Associations of Patient and Treatment Characteristics with Overall Survival.

Variable	Level	n=	3-yr OS (95% CI)	Univariate analysis		Multivariate analysis[‖,¶]	
				HR (95% CI)	*P* =	HR (95% CI)	*P* =
Sex	Female	94	48.3 (37.8-50.0)	Ref.	-		
	Male	191	51.8 (44.4-58.7)	0.89 (064-1.24)	*.49*		
Histological subset[*,†]	Indolent	123	59.5 (50.1-67.6)	Ref.	-	Ref.	-
	Aggressive	124	44.8 (35.8-53.3)	1.46 (1.04-2.07)	*.031*	1.43 (1.01-2.03)	*.047*
	MCL	37	42.9 (26.8-58.1)	1.65 (1.01-2.68)	*.044*	1.85 (1.13-3.04)	*.014*
Previous therapy lines[*] (n=)	1 – 2	60	45.9 (32.9-58.0)	Ref.	-		
	> 2	222	52.6 (45.8-59.0)	0.86 (0.59-1.25)	*.42*		
Previous autograft[*,‡]	NO	106	53.8 (43.8-62.9)	Ref.	-		
	YES	169	49.3 (41.5-56.6)	1.26 (0.90-1.77)	*.17*		
Salvage therapy[*]	NO	37	47.6 (30.8-62.6)	Ref.	-		
	YES	244	51.9 (45.4-58.0)	0.81 (0.52-1.25)	*.33*		
Status at transplant[*]	CR	135	60.9 (52.1-68.6)	Ref.	-	Ref.	-
	PR	63	46.9 (34.2-58.7)	1.51 (1.00-2.29)	*.051*	1.55 (1.02-2.36)	*.043*
	SD	30	46.7 (28.4-63.0)	1.60 (0.95-2.68)	*.075*	1.69 (1.00-2.84)	*.049*
	PD	55	33.6 (21.5-46.2)	2.17 (1.45-3.25)	*<.001*	2.11 (1.39-3.20)	*<.001*
HCT-CI[*]	0	60	42.2 (29.5-54.4)	Ref.	-		
	1-2	80	52.0 (40.5-62.3)	0.79 (0.51-1.24)	*.31*		
	≥ 3	67	54.5 (41.8-65.6)	0.94 (0.60-1.49)	*.80*		
DRI[*]	Low	115	59.2 (49.5-67.7)	Ref.	-	ND	
	Intermediate	108	56.4 (46.5-65.2)	1.13 (0.78-1.65)	*.52*	ND	
	High/Very High	55	22.5 (12.5-34.3)	2.60 (1.74-3.90)	*<.001*	ND	
Year of transplant	2000-2005	51	50.2 (35.7-63.0)	Ref.	-		
	2006-2010	76	40.6 (29.6-51.4)	1.18 (0.75-1.85)	*.47*		
	2011-2015	79	54.1 (42.5-64.4)	0.85 (0.53-1.35)	*.48*		
	2016-2020	79	57.3 (45.4-67.4)	0.79 (0.48-1.28)	*.34*		
Age at allo-HSCT	+ 5 yr			1.05 (0.98-1.13)	*.17*		
Conditioning regimen	MAC	86	48.3 (37.3-58.4)	Ref.	-		
	RIC	199	51.7 (44.4-58.4)	0.88 (0.63-1.23)	*.45*		
Haploidentical	NO	215	47.6 (40.7-54.1)	Ref.	-		
	YES	70	60.0 (47.5-70.4)	0.77 (0.52-1.14)	*.19*		
Donor subtypes	Sibling	105	49.2 (39.3-58.3)	Ref.	-		
	Haplo	70	60.0 (47.5-70.4)	0.77 (0.50-1.18)	*.23*		
	MUD	100	48.1 (37.9-57.6)	0.95 (0.66-1.37)	*.78*		
	Others	10	24.0 (3.8-53.7)	1.85 (0.85-4.04)	*.12*		
Post-transplant CY	NO	226	45.8 (39.2-52.2)	Ref.	-	Ref.	
	YES	59	69.2 (55.6-79.3)	0.56 (0.36-0.89)	*.013*	0.60 (0.38-0.96)	*.031*
cGVHD requiring systemic therapy[§]	NO	246		Ref.	-	Ref.	-
	YES	39		2.59 (1.61-4.81)	*<.001*	2.06 (1.25-3.40)	*.005*

HCT-CI, hematopoietic cell transplantation-specific comorbidity index; DRI, disease risk index; MUD, Matched Unrelated Donor; Haplo. haploidentical donor; post-transplant CY, post-transplant cyclophosisphamide-based program; ND, not done; n =: number of patients.

[*] See footnote to Table 1 for information regarding missing data.

[†] See footnote to Table 1 for information regarding histological subset categorization.

[‡] Previous intensified therapy with autograft

[§] Time-dependent variable.

[‖] Only variables with $P < .10$ in univariable analysis were included in multivariable analysis.

[¶] Among histological subset and disease risk index (DRI), only histological subset was retained in the multivariable model, and DRI was excluded to avoid collinearity.

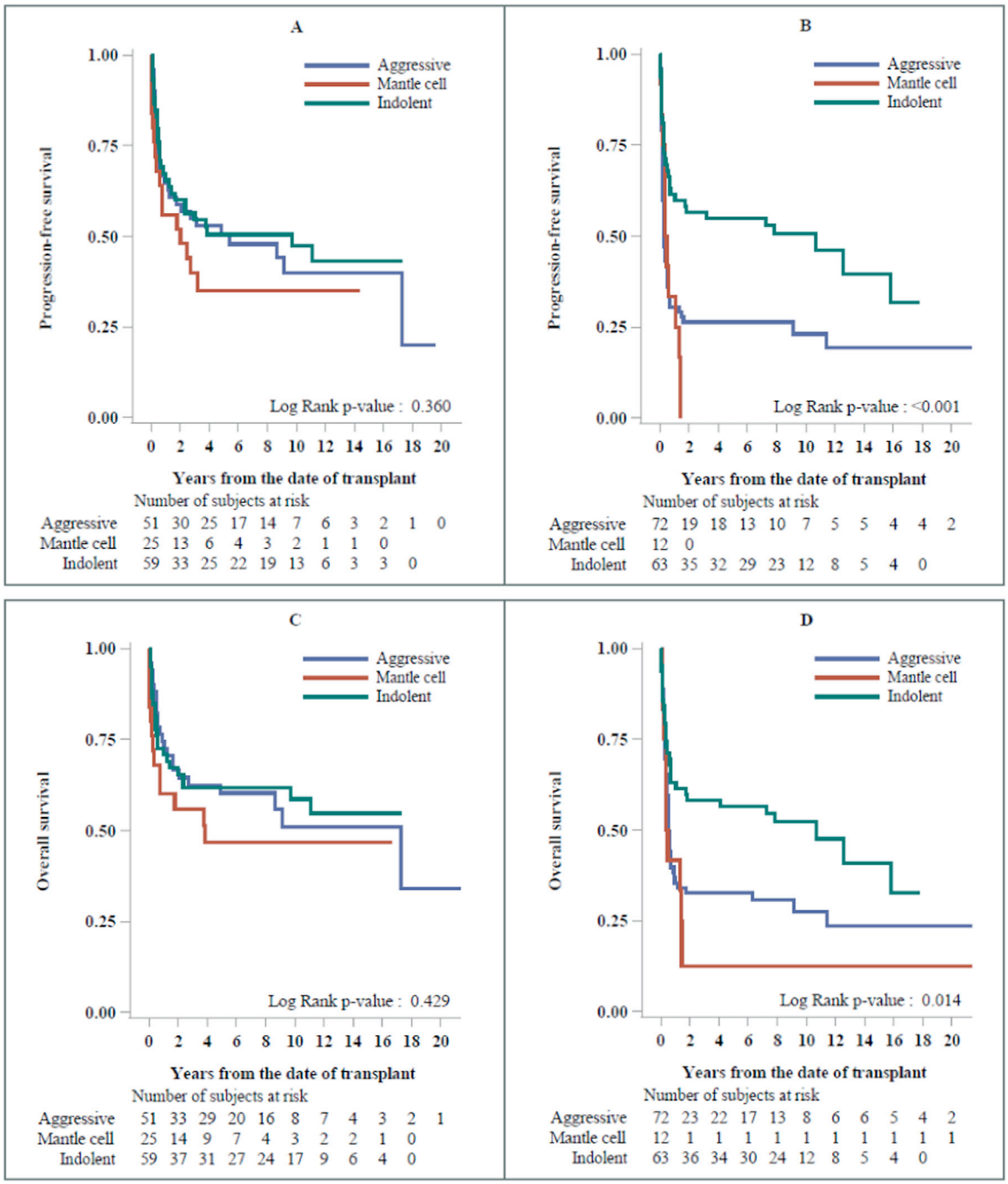

Figure 3. Progression-free survival and overall survival according to the main histological subgroups, among patients who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) in complete remission (CR) (A and C), and among patients who underwent allo-HSCT while not in CR (B and D).

indolent lymphoma, 32.6%, 22.1 to 43.6, for aggressive lymphoma, 12.5%, 0.9 to 39.9, for MCL).

Univariable and Multivariable Analysis of Factors Potentially Associated with PFS and OS

Histological diagnosis (i.e., indolent lymphoma compared to aggressive lymphoma and MCL) and disease status at allo-HSCT (i.e., CR vs. PR or PD) were the only pre-transplant variables that significantly impacted PFS and OS in both univariable and multivariable analysis, although PR and SD status did not always reach the significance threshold (see Tables 2 and 3). The remaining tested parameters - including sex, age at transplant, number of previous lines of therapy and previous autograft, planned salvage therapy

before transplant, year of transplant, type of conditioning regimen, and donor source of hematopoietic cells - did not significantly influence PFS or OS in univariate and multivariate analysis, whereas high/very high DRI was associated with a very poor outcome. Regarding transplant procedures, the subgroup receiving post-transplant CY had a significantly improved OS, with PFS very close to statistical significance. As expected, the occurrence of severe cGVHD had an unfavorable influence on OS. Lastly, outcomes did not significantly differ among Centers when PFS and OS were assessed in the main prognostic subgroups (data not shown).

Disease Recurrence, Overall Mortality Rate, and Main Causes of Death

After 285 allografting procedures, disease progression/recurrence occurred in 81 cases (28.4%). Disease progression/recurrence occurred early after transplantation, with the latest disease recurrence recorded at 5.4 yr after allograft (Figure 4). The cumulative Incidence function (CIF) of disease progression/recurrence was 21.9 % (95% CI: 17.3 to 26.9) at 1 yr, 25.8% (20.9 to 31.1) at 3 yr, and 28.5% (23.3% to 33.9%) at 5 yr. The CIF of disease progression/recurrence was significantly different in the three main histological subtypes, as shown in Supplementary Figure 1.

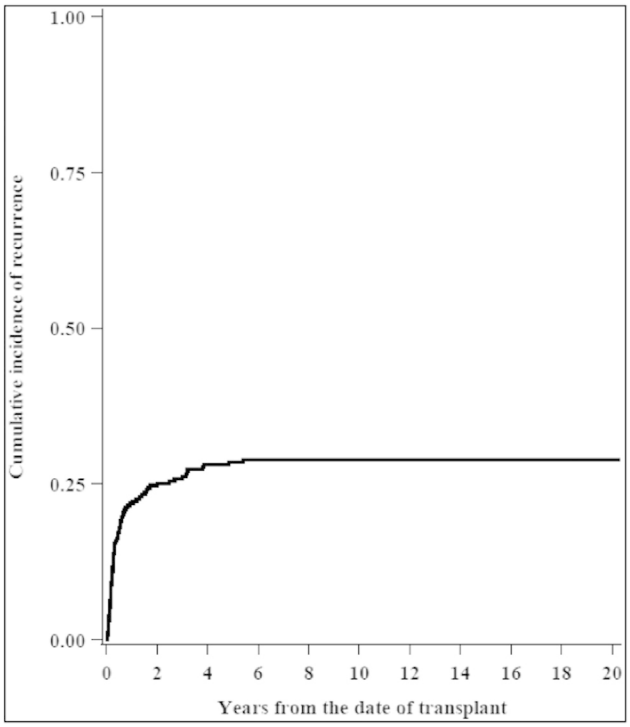

Figure 4. Cumulative incidence of disease progression/recurrence.

Overall, 156 fatal events (54.7%) occurred in the whole series, including early and late deaths, with 56 deaths due to lymphoma progression and 100 deaths due to non-disease-related causes. With regard to disease-related deaths, the 1-yr CIF was 15.9% (95% CI: 11.9 to 20.5), the 3-yr CIF was 18.5% (14.2 to 23.2), and the 20-yr projected CIF was 20.2% (15.7 to 25.2) (Figure 5A). In subgroup analysis, the 3-yr CIF for disease-related deaths was 8.3% (4.4 to 13.8) for patients in CR at allo-HSCT, 23.9% (15.7-33.1) among patients in PR/SD, and 35.1% (22.6-48.0) among patients in PD (Figure 5C).

Among progressing/relapsed patients, 46 had very rapid disease progression, and the fatal evolution occurred within a few months up to 1 yr since allo-HSCT with ineffectiveness of any control measure. Disease progression was somehow slowed down in 10 more patients who had delayed fatal disease progression at 1.5 up to 7 yr since allo-HSCT. Disease control measures included chemo-immunotherapy (5 patients), radiotherapy (1), lenalidomide combinations (2), and an Ibrutinib/Venetoclax/Rituximab combination (1). Salvage treatments were effective in 22 additional patients, who are presently alive with disease remission. Three of these patients were rescued with CAR-T cells and are presently alive and well at 6, 7, and 7 yr since allo-HSCT, respectively. The remaining relapsed/progressing patients received various and effective salvage treatments, including chemoimmunotherapy (9 patients), DLI alone or in combination with chemo or radio-immunoterapy (5), radiotherapy (2), or nonchemotherapeutic drugs (3), that is, Lenalidomide, Ibrutinib, or PD-1 inhibitor. Three more patients had complete remission from their post-allo recurrence. Unfortunately, they died of late fatal complications while in CR.

Early toxic events were the cause of death for 75 patients within the first year after allo-HSCT, showing a 1-yr CIF of 26.1 % (21.2-31.4) (Figure 5B). Additionally, there were 25 cases of late (> 1 yr) non-disease-related deaths due to infections (10 cases, including one case of COVID-19), cGVHD complications (5 cases), cardiac complications (3 cases), secondary neoplasia (3 solid tumors, and one acute leukemia), cognitive impairment and dementia (1 case), multiorgan failure (1 case), and unknown cause (1 case). Combining the early and late deaths, the overall CIF projection of non-disease-related mortality was 30.9% (25.5-36.3) at 3 yr, and 31.2% (25.9-36.7) at 5 yr, with a 20-yr projection of 45.2% (35.1-54.8) (Figure 5B). The incidence of non-disease-related

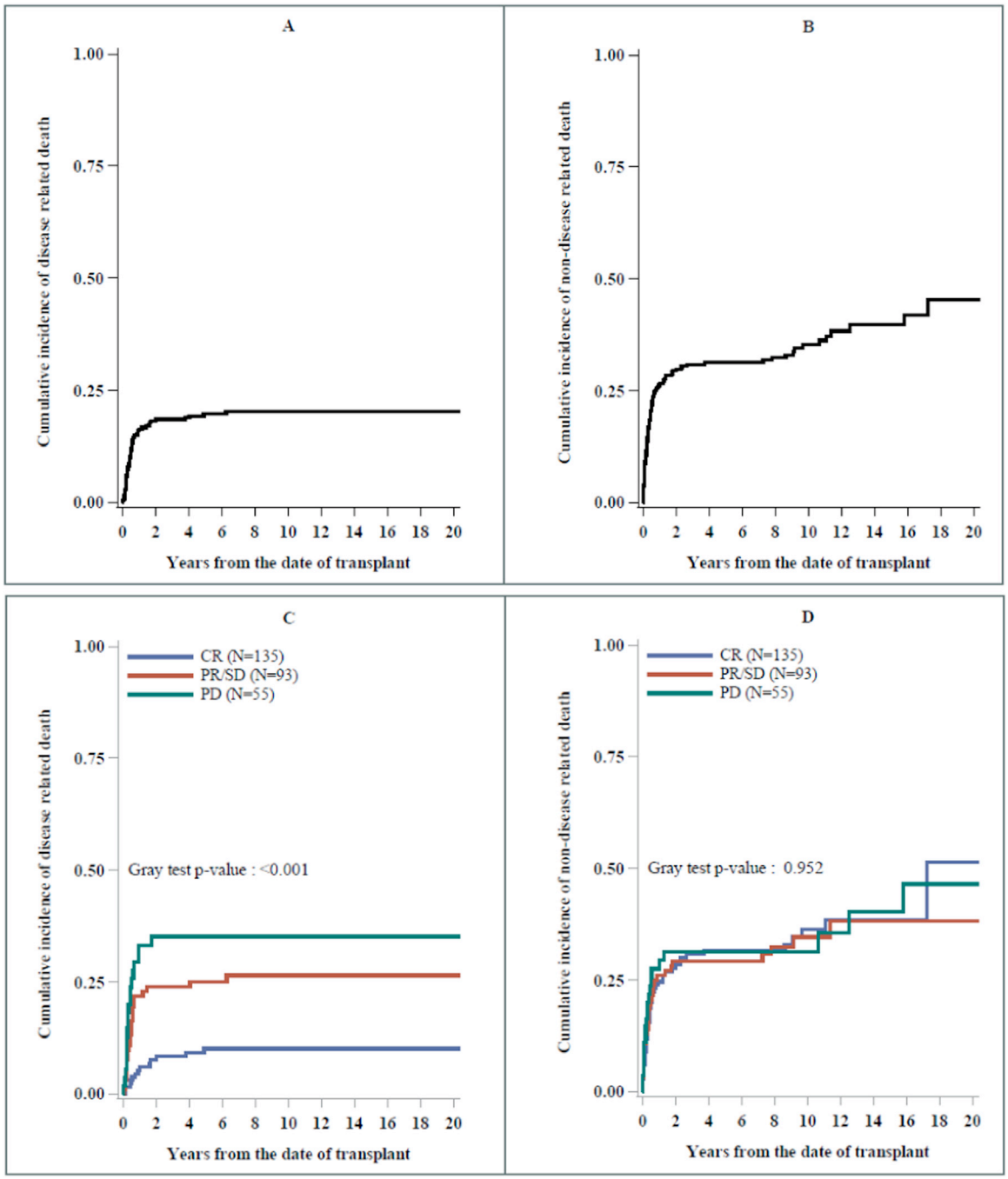

Figure 5. Cumulative incidence of disease-related death (A and C) and non-disease-related death (B and D), overall (A and B) and according to status at transplant (C and D).

deaths did not significantly differ according to the status at transplantation (Figure 5D).

aGVHD and cGVHD: Incidence, Risk Factors, and Role of Donors

Grade 3–4 aGVHD occurred in 27 patients (9.5%), with a 1-yr CIF of 9.5% (95% CI: 6.4 to 13.2) (Supplementary Figure 2A). Chronic GHVD requiring systemic therapy occurred in 39 patients (13.7%), with 2-yr and 5-yr CIF projections of 12.1% (8.6 to 16.3) and 14.0% (10.2 to 18.4), respectively (Supplementary Figure 2B). Several parameters were assessed for their association with the development of severe aGVHD and/or cGVHD. Considering the occurrence of severe aGVHD and/or For cGVHD requiring systemic therapy, the main parameters associated with significantly lower risk were the reduced-intensity

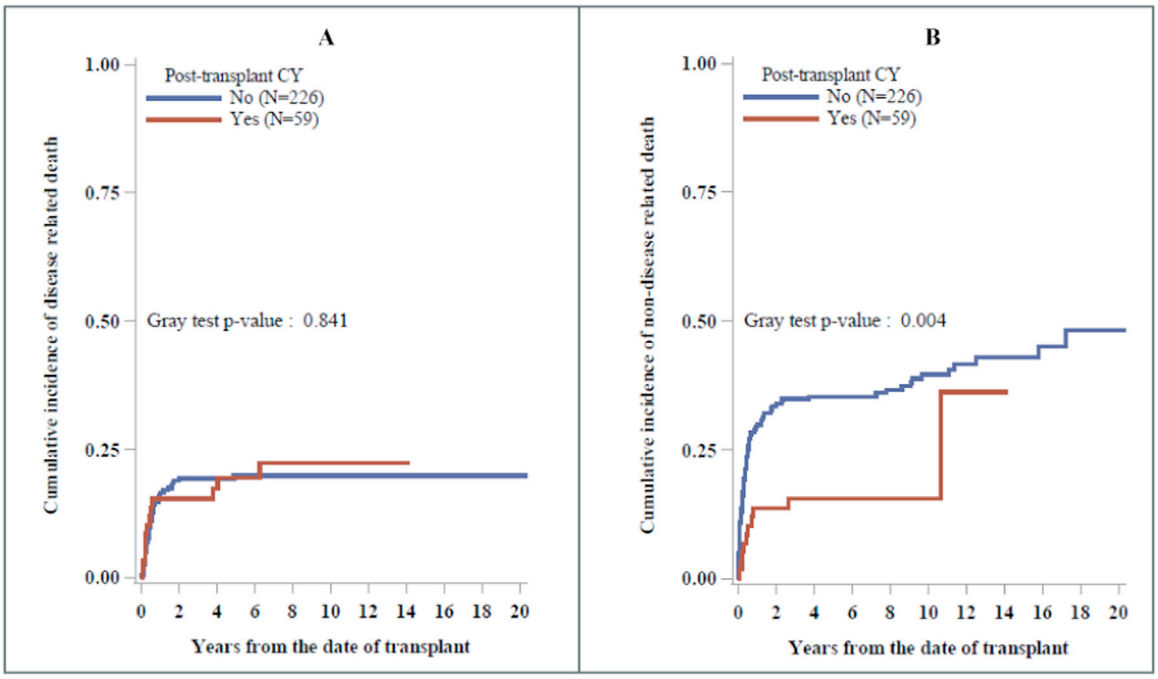

Figure 6. Cumulative incidence of disease-related death (Panel A) and non-disease-related death (Panel B) by post-transplant CY (post-transplant cyclophospamide-based program). The cumulative incidence functions (CIF) for disease-related death at 1, 3 and 5 yr were respectively of 15.4% (7.5 to 25.8), 15.4 (7.5 to 25.8) and 19.4 (10.2 to 30.7) for post-transplant CY, and 16.1% (11.6 to 21.2), 19.3 (14.4 to 24.7) and 19.8 (14.8 to 25.3) for no-CY. The CIF for non-disease-related death at 1, 3 and 5 yr were respectively of 13.7% (6.3 to 23.9), 15.5% (7.5 to 26) and 15.5% (7.5 to 26) for post-transplant CY, and 29.4% (23.6 to 35.4), 34.9 (28.7 to 41.1) and 35.3 (29.1 to 41.6) for no-CY.

conditioning (RIC) regimen, the donor subtype, and the use of the post-transplant cyclophosphamide-based program (post-transplant CY), as detailed in Supplementary Table 1. Overall, patients receiving the post-transplant CY program as GVHD prophylaxis showed an improved outcome, as previously reported in Tables 2 and 3. This is further proved by the CI curves in Figure 6 for disease-related death (Panel A) and non-disease-related death (Panel B) according to post-transplant CY.

Lastly, based on the occurrence of both severe GVHD and disease recurrence/progression, a GVHD-free, progression-free survival (GPFS) curve has been estimated and shown in Supplementary Figure 3. The 3-yr GPFS was 35.6% (30.0 to 41.2) and the 9-yr GPFS of 33.3% (27.8 to 38.8), with a 20-yr projected GPFS of 22.9% (12.9 to 34.7)

Long-Term Survivors

At present, 95 patients are alive without any sign of disease since the allograft after at least 5 yr of follow up. The main clinical features of these long-term disease-free survivors did not seem markedly different compared to the whole original series, with the exception of a significantly reduced proportion of very high-risk DRI patients among long-term survivors and an increased proportion of indolent lymphoma on borderline statistical significance (Table 4). Eight cases of cGVHD requiring prolonged treatment were recorded in this long-term survivor subgroup.

DISCUSSION

The primary aim of this study was to evaluate the long-term outcomes of patients after undergoing allo-HSCT as salvage therapy for R/R B-cell lymphoma. For this purpose, a collaborative study was performed by six Italian centers having substantial experience with allo-HSCT programs. Data were collected from 285 transplant procedures performed between 2000 and 2020. The median follow-up of survivors was 8.7 yr, which was sufficient to analyze both late toxicities and long-term disease outcomes. The results further elucidate the complexity of allo-HSCT in heavily pre-treated R/R B-NHL, which carries a high risk of transplant-related mortality due to the combination of early and late toxicities. On the other hand, a considerable proportion of patients have

Table 4
Main Patient Characteristics and Treatment Features Among 95 Long-Term Disease-Free Survivors Following Allogeneic Hematopoietic Stem Cell Transplantation (Allo-HSCT).

Variable	Level	n= (%)
Sex*	Female	29 (30.5)
	Male	66 (69.5)
Histological subsets*,†	Indolent lymphoma	52 (54.7)
	Aggressive lymphoma	36 (37.9)
	Mantle-cell lymphoma	7 (7.3)
No. of therapy lines before allo-HSCT*	1	4 (4.2)
	2	12 (12.6)
	3	35 (36.8)
	4	27 (28.4)
	5	11 (11.6)
	> 5	6 (6.3)
previous intensified therapy with autograft*	NO	33 (35.9)
	YES	59 (64.1)
Status at allo-HSCT*	Complete Remission	51 (54.6)
	Partial Remission	22 (22.7)
	Stable Disease	10 (10.3)
	Progressive Disease	12 (12.4)
Clinical presentation at allo-HSCT:		
- HCT-CI*,‡	0	18 (26.5)
	1-2	27 (39.7)
	≥ 3	23 (33.8)
- DRI§	Low.	45 (48.4)
	Intermediate	40 (43.0)
	High	0 (–)
	Very high	8 (8.6)
Age at transplant*	Years, median (range)	49 (20-67)
Type of conditioning regimen*	Myeloablative (MAC)	28 (29.5)
	Reduced intensity (RIC)	67 (70.5)
Donor subtypes*	Sibling HLA-id	28 (29.5)
	Sibling HLA-mis	1 (1.0)
	Haploidentical	29 (30.5)
	MUD HLA-identical	19 (20)
	MUD HLA-mis	16 (16.8)
	Cord Blood	1 (1.0)
	Syngeneic	1 (1.0)
Post-transplant CY*,‖	NO	68 (71.5)
	YES	27 (28.4)

Missing data: 3 cases for autograft, 27 for HCT-CI, and 2 for DRI; n =: number of patients.

* Main clinical and treatment characteristics that did not significantly differ among long-term disease-free survivors compared to the whole series (increased proportion of indolent lymphoma on borderline statistical significance, *P* 0.057).

† Histology was subgrouped into three main subsets: indolent lymphoma (including follicular lymphoma, marginal-zone lymphoma and unspecified small lymphocyte lymphoma); aggressive lymphoma (including diffuse large B-cell lymphoma, Burkitt's lymphoma, primary mediastinal large B cell lymphoma and unspecified high-grade lymphoma), and mantle-cell lymphoma.

‡ HCT-CI, hematopoitic cell transplantation-specific comorbity index.

§ DRI: Disease risk index; the proportion of very high-risk DRI was significantly lower among long-term disease-free survivors compared to the whole series, *P* 0.032.

‖ Post-transplant CY: post-transplant cyclophosphamide-based program.

survived disease-free for 5 to 20 yr after allo-HSCT. Such prolonged survival in the absence of disease recurrence has never been documented in heavily pre-treated R/R B-NHL cases with treatments other than allo-HSCT. Thus, the present results suggest that allo-HSCT may still have a role in salvage strategies for high-risk R/R B-NHL.

The present analysis was restricted to B-cell NHL, and the two main histological subtypes were FL (38%) and DLBCL (32%), which together represented approximately two-thirds of the whole series. Various other less common subtypes were included, of which mantle-cell lymphoma was the most appreciably represented, accounting for 13% of cases. As expected, all patients underwent allo-HSCT due to refractory or relapsed disease, with approximately 80% of patients having undergone at least three lines of previous treatments. Several reports demonstrate the very poor outcomes of patients with B-NHL, namely FL, DLBCL, and MCL, and with refractory or repeatedly relapsed disease [28–32]. In these settings, the therapeutic options were long limited to allo-HSCT, until the recent advent of immunotherapy-based therapies, particularly those using CAR T cells and bispecific monoclonal antibodies.

Overall, our present findings confirmed the efficacy of allo-HSCT in cases of B-NHL with very poor prognoses, showing a 3-yr PFS of >43%, which was substantiated by the 9-yr PFS of 39%. Moreover, the OS was slightly superior, with values of >50% at 3 yr, and >46% at 9 yr. Some recent reports on allo-HSCT in R/R B-NHL, including indolent and aggressive subtypes, have demonstrated results that are as good or even better than our present findings, although with smaller series and shorter follow-up compared to our study [33–35]. Somewhat different results have been reported by other previous studies, and discrepancies are likely ascribed to the prognostic heterogeneity of each series, in terms of patient age, histological subtypes, and clinical status at transplant [36–39]. Allo-HSCT has been most extensively used in R/R DLBCL, and several reports over recent years consistently show 3-yr PFS rates of around 30% to 40% [3,40–43]. These results are in keeping with the 3-yr PFS of ~38% observed in our series of 124 aggressive B-NHL cases.

Histological subtype had a major influence on outcome, with the highest PFS rates among patients with indolent lymphoma, particularly the follicular lymphoma subtype. This is in line with observations reported in several studies on allo-HSCT in NHL [41,44–45]. The poorest outcome was observed among cases of MCL, which might be related to the high frequency of TP53 mutation in progressing MCL, although this parameter was not available in our series [46]. The outcome in our small MCL cohort seems worse than in other reports; however, variability among studies may be explained by differences in clinical characteristics and time to allo-HSCT, that is, first CR or subsequent relapses [47]. Indeed, in our analysis, the most relevant prognostic parameter was disease status at the time of allo-HSCT. Despite multiple relapses, patients who underwent transplant while in CR had significantly better outcomes compared to patients not in CR. Noticeably, among patients with allo-HSCT in CR, PFS and OS did not significantly differ among histological subtypes. In contrast, among patients with allo-HSCT while not in CR, we observed marked differences among histologies, with significantly better PFS in indolent versus aggressive versus MCL, and the lowest PFS and OS features in MCL. These findings support that the achievement of CR before allo-HSCT is the most critical parameter for obtaining the highest benefit from transplantation, as previously proposed [44,48–49]. Nevertheless, among the 95 patients long-term disease-free survivors, around 45% had received transplants while not in CR, with 22 patients (23%) transplanted while having stable or progressing disease. Thus, inability to achieve CR before allo-HSCT is not an absolute exclusion criterion, and patients not in CR, including those with refractory disease, can be considered for allo-HSCT in the absence of other realistic salvage options.

The management of refractory/relapsed B-NHL has dramatically progressed with the introduction of CAR T-cell therapy into clinical practice. CAR-T cells have shown particular benefits in refractory and relapsed DLBCL, producing high response rates, even in patients with refractory disease, with manageable toxicity [5–7]. Randomized studies have shown that CAR T-cell therapy is superior to autologous transplant as salvage in R/R DLBCL, such that CAR T cells are among the first options for salvage therapy in DLBCL [50–51]. Recent reports have also demonstrated the efficacy of CAR T-cell therapy in other B-NHL subtypes, as expected [52–53]. Nevertheless, despite the rapid tumor shrinkage, a considerable proportion of patients experience disease recurrence at variable times after CAR T-cell therapy [16,54]. Indeed, in patients with refractory or heavily pretreated DLBCL, the 3-to 5-yr PFS rate remains around 30–40%, which is not significantly different from the results after allo-HSCT [55–56]. Like CAR T cells, bispecific antibodies have emerged as

a novel therapeutic option for B-cell lymphoma. However, some recent observations indicate that these promising T-cell-engaging therapies also carry a risk of disease recurrence [20,57]. Among patients with recurrently pre-treated indolent lymphoma, the duration of response following CAR T-cell or bispecific antibody therapy was slightly better compared to that observed in DLBCL, but the overall results do not appear markedly better than our results with allo-HSCT. Moreover, the studies of either CAR T-cell therapy or immunotherapy with novel MoAbs do not have prolonged follow-up, as is available for allo-HSCT.

A main concern with allo-HSCT in lymphoma is the severe toxicity of the procedure. In our series, 75 deaths occurred due to early toxicity among 285 allo-HSCT procedures (26.3%), and 25 additional late non-disease-related deaths were recorded, yielding a 5-yr cumulative incidence of non-disease-related deaths of ~31%. These numbers are extremely high and can be explained by the toxic effects of allo-HSCT in severely pretreated patients. Indeed, infections and GVHD complications were the most frequent causes of death. This further reflects the markedly immunocompromised status of the patients considered for salvage allo-HSCT. This high risk of treatment-related death favors the ongoing preferential use of salvage treatment with CAR-T cells or bispecific antibodies. In spite of similar results in terms of PFS, the novel immunotherapy-based procedures have much more manageable toxicities compared to the marked toxicities of allo-HSCT. Thus, at present, allo-HSCT can no longer be proposed prior to CAR T-cell therapy or treatment with other new monoclonal antibodies, given alone or in combination. Moreover, novel immunotherapeutic drugs may also be exploited in those patients with disease recurrence following transplantation, as here documented in three patients rescued with CAR-T cells after disease recurrence following allo-HSCT.

Despite the high rate of fatal events due to toxicity and a number of disease-related deaths, mostly occurring during the initial 3 yr after transplant, there were 95 long-term, disease-free survivors for 5 or more years after allograft. These survivors are quite representative of the original cohort of patients undergoing allo-HSCT, including both indolent and aggressive subtypes, and patients who received allo-HSCT in the presence or absence of CR. However, a significantly reduced proportion of patients with very-high DRIs was observed in this subgroup of long-survivors. Anyway, approximately one-third of high-risk patients with heavily pretreated B-cell NHL may experience long-term survival, and possibly cure of their disease, following allo-HSCT. This indicates that the allogeneic procedure has a potent and durable anti-lymphoma effect, as proved by the absence of disease recurrence in the long term, with the latest recurrence recorded at 5 and a half years after allo-HSCT. At present, none of the new treatments for refractory/relapsed B-NHL have been evaluated over a very long period of time, like in our series. In fact, the long-term response duration following salvage treatments other than allo-HSCT needs to be further outlined.

The absence of late disease recurrence is a relevant finding, supporting the belief that allo-HSCT may still have a role in the treatment strategy for R/R B-NHL [58–59]. Given its potent anti-lymphoma activity, allo-HSCT may be considered for high-risk patients who experience disease recurrence after treatment with CAR T cells and bispecific antibodies. In view of this, some recent studies with promising results have been reported [60–61]. Nevertheless, further investigations are worthwhile to prove the applicability and efficacy of allo-HSCT in patients failing novel immunotherapeutic approaches. Moreover, allo-HSCT remains an alternative option whenever novel salvage approaches are not practical. Clearly, efforts should be made to lower the detrimental toxicity of the allo-HSCT procedure. In this context, the emerging use of non-chemotherapeutic salvage programs may allow the introduction of allo-HSCT earlier in the disease course, thus avoiding its use in heavily pretreated and severely immunocompromised patients. Moreover, our observation of a significantly reduced risk of NRM in patients receiving post-transplant CY for GVHD prophylaxis, suggests expanding the use of the post-transplant cyclophosphamide-based program in order to lower the toxic complications of the transplant procedure, while maintaining adequate disease control.

In conclusion, the present study reports the long-term outcomes of a large multicenter series of patients with R/R B-NHL who received allo-HSCT following multiple relapses. The results demonstrate the substantial fatal toxicity of the procedure, along with the risk of disease recurrence. However, the long-term follow-up also allows recognition of the potent anti-lymphoma effectiveness of allo-HSCT, as a unique treatment approach that may still offer the opportunity of prolonged survival without disease recurrence, and possibly a cure for B-NHL patients with poor life expectancies.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jtct.2025.06.004.

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