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Outcomes After Allogeneic Stem Cell Transplantation in Patients with Double-Hit and Double-Expressor Lymphoma

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Abstract

Double-hit lymphomas (DHL) and double-expressor lymphomas (DEL) are associated with resistance to frontline and salvage immunochemotherapy, as well as autologous stem cell transplantation (SCT). We hypothesized that allogeneic SCT (alloSCT) could overcome the chemoresistance associated with DEL/DHL. We retrospectively studied the impact of DEL/DHL status in a multicenter cohort of patients who underwent alloSCT for relapsed/refractory (rel/ref) aggressive B-cell non-Hodgkin lymphoma (B-NHL). 78 patients transplanted at 3 centers in whom tumor tissue was available for immunohistochemistry and FISH were enrolled; 47% had DEL and 13% had DHL. There were no significant differences in 4-year progression-free (PFS) or overall survival (OS) between patients with DEL compared to patients without DEL (PFS 30% v 39%, p=0.24; OS 31% v 49%, p=0.17) or between patients with DHL compared to patients without DHL (PFS 40% v 34%, p=0.62; OS 50% v 38%, p=0.46). The lack of association between DEL or

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DHL and outcome was confirmed in multivariable models, though limited sample size may have limited our ability to detect significant differences. In our cohort, alloSCT produced durable remissions in patients with rel/ref aggressive B-NHL irrespective of DEL and DHL status, justifying its consideration in the treatment of patients with rel/ref DEL/DHL.

Keywords

Double-hit lymphoma; double-expressor lymphoma; diffuse large B-cell lymphoma; MYC; allogeneic

Introduction

Double-hit lymphomas (DHL) with rearrangement of *MYC* and *BCL2* and/or *BCL6*, and double-expressor lymphomas (DEL) with co-expression of MYC and BCL2 by immunohistochemistry, are subsets of aggressive B-cell non-Hodgkin lymphoma (B-NHL) associated with chemoresistance. Patients with DEL or DHL have poor outcomes after standard chemoimmunotherapy.[1-18] Patients with relapsed or refractory (rel/ref) DEL or DHL have poor outcomes after salvage chemoimmunotherapy,[12, 19, 20] and even patients with chemosensitive rel/ref DEL or DHL have inferior outcomes after autologous stem cell transplantation (autoSCT) compared to patients without either abnormality.[21] Allogeneic stem cell transplantation (alloSCT) is an immune-based therapy that produces durable remissions in a subset of patients with rel/ref aggressive B-NHL even after failure of autoSCT.[22, 23] We hypothesized that alloSCT, through its reliance on a graft-versus-lymphoma effect, could potentially abrogate the negative prognostic impact of DEL and DHL.

Methods

We performed a retrospective, multicenter study of adult patients with rel/ref aggressive B-NHL including diffuse large B-cell lymphoma (DLBCL), transformed indolent lymphoma (TIL), or high-grade B-cell lymphoma unclassified (BCLU, based on the 2008 WHO Classification) with available tumor tissue who underwent alloSCT at the Dana-Farber Cancer Institute/Brigham and Women's Hospital, Massachusetts General Hospital, and City of Hope. Patients were transplanted between 1/2000 and 5/2014. Patients with Richter transformation of chronic lymphocytic leukemia or primary mediastinal B-cell lymphoma were excluded. Patients with a history of secondary central nervous system (CNS) involvement by lymphoma were eligible, but patients with primary CNS lymphoma were excluded. Patients who underwent a planned tandem transplantation or consolidative alloSCT in 1st response were excluded. Patients underwent alloSCT according to institutional practices.

Confirmation of the histologic diagnosis and review of immunohistochemistry was performed by two hematopathologists from the institutions (J.Y.S, Y.K., S.J.R, G.K.G); discrepancies were resolved at a multi-headed microscope. In all cases, even if previously evaluated in the course of a patient's care, immunohistochemistry for MYC and BCL2 and fluorescence *in situ* hybridization (FISH) for *MYC, BCL2*, and *BCL6* were performed as

detailed previously.[21] DEL was defined as MYC expression in ≥ 40% of tumor cells and BCL2 expression in ≥ 50% of tumor cells. DHL was defined as concurrent rearrangements of *MYC* and *BCL2* and/or *BCL6*. "Atypical DHL" was defined as *MYC* without rearrangement but with at least 3+ copy gain (CG) along with one or more of the following: *BCL2* 3+CG, *BCL6* 3+CG, *BCL2* or *BCL6* rearrangement; or *MYC* rearrangement without *BCL2* or *BCL6* rearrangement, but with *BCL2* 3+ CG and/or *BCL6* 3+ CG. In all cases, the most recent available tumor specimen prior to alloSCT was analyzed.

Baseline characteristics were treated descriptively, and groups were compared as previously described.[21] Survival analyses, incidences of non-relapse mortality (NRM), relapse/progression (CIR), and acute and chronic graft-versus-host disease (GVHD) as well as univariable and multivariable modeling were performed as described previously.[24] In patients with TIL, relapse was considered a PFS event regardless of aggressive or indolent relapse histology. P-values were two-sided with a significance level of 0.05. All data was analyzed using SAS version 9.3 (Cary, NC) and R 3.1.2 (R Foundation for Statistical Computing, Vienna Austria). The study was approved by the Institutional Review Boards at all centers.

Results

At the participating centers, 318 patients with aggressive B-NHL underwent alloSCT during the study period and 220 patients met the eligibility criteria. Tumor tissue was available in 103 patients and complete immunohistochemistry, FISH, and clinical data were available in 78 patients, who comprised the study cohort. Immunohistochemistry, FISH, and baseline characteristics in the cohort are summarized in Table 1. There were 50 patients with de novo DLBCL, 25 patients with TIL, and 3 patients with BCLU. The median number of lines of prior therapy was 4 (range, 2-9), 58% of patients had prior autologous stem cell transplantation, and 49% of patients had primary refractory disease with initial therapy. Reduced intensity conditioning was utilized in 77% of patients, 36% of patients had a matched sibling donor, 42% a had fully HLA-matched (8/8) unrelated donor, and 22% had HLA-mismatched, haploidentical or umbilical cord donors. Most patients (58%) had tacrolimus and sirolimus based GVHD prophylaxis, and the use of peri-transplantation rituximab or anti-thymocyte globulin and other T-cell depleting strategies was infrequent (< 15% of the cohort) with no statistically significant imbalance in their use among the study groups (Supplemental Table 1). In order to evaluate for a possible selection bias, we compared the outcomes of these 78 patients with those of 142 patients with available relapse and survival information who were not included due to lack of tissue or incomplete data. The outcomes of the 2 groups were similar: 3-year PFS was 39% (95CI, 28-50%) in the cohort versus 38% (95CI, 30-47%) in the other patients (p=0.5), and 3-year OS was 44% (95CI, 32-55%) compared to 47% (95CI, 38-56%, p=0.7).

In the study cohort, the median follow-up for survivors was 46 months (range, 18-147). The overall cumulative incidences of GVHD were 22% grade II-IV acute GVHD at day +100, 10% grade III-IV acute GVHD at day +100, and 37% chronic GVHD at 1 year. The PFS, OS, CIR, and NRM at 4 years were 35% (95CI, 24-46%), 40% (95CI, 29-51%), 43% (95CI, 32-54%) and 22% (95CI, 13-32%), respectively.

Among the 78 patients, 47% had DEL and 13% had DHL. There were no significant differences in clinical characteristics (Table 1) or outcome when patients with DHL or DEL were compared to patients with neither DHL nor DEL. The 4-year PFS in patients with DEL compared to patients without MYC/BCL2 coexpression was 30% (95CI, 18-51%) versus 39% (95CI, 26-58%, p=0.24); the corresponding 4-year OS was 31% (95CI, 18-52%) versus 49% (95CI, 35-68%, p=0.17); 4-year CIR was 50% (95CI, 35-70%) versus 38% (95CI, 25-57%, p=0.20); and 4-year NRM was 20% (95CI, 10-40%) versus 23% (95CI, 13-42%, p=0.75, Figure 1A and 1B). The 4-year PFS in patients with DHL compared to patients who did not have DHL was 40% (95CI, 19-85%) versus 34% (95CI, 24-48%, p=0.62); 4-year OS 50% (95CI, 27-93%) versus 38% (95CI, 27-53%, p=0.46); 4-year CIR 40% (95CI, 18-91%) versus 44% (95CI, 33-58%, p=0.90); and 4-year NRM 20% (95CI, 5-77%) versus 22% (95CI, 14-36%, p=0.81, Figure 2A and 2B) As DHL and DEL status can overlap, we also compared mutually exclusive subgroups: no significant differences in PFS were observed when patients with DHL were compared to patients with DEL/non-DHL, and to patients with neither DEL nor DHL (4-year PFS 40% versus 29%, versus 38%, respectively, p=0.56, Figure 2C). Among 45 patients who had previously undergone autoSCT, there was no significant difference in PFS between patients with DHL, DEL/non-DHL, and neither DEL nor DHL (data not shown, p=0.4). Of note, there was no imbalance in cause of death among these subgroups (Supplemental Table 3). When the analyses were limited to patients with DLBCL/BCLU or separately to patients with TIL, there were no significant differences in PFS between patients with DHL, DEL/non-DHL, and neither DEL nor DHL (data not shown, DLBCL/BCLU subgroup, p=0.4; TIL subgroup, p=0.6). Lastly, 22% of patients had atypical DHL, which was not associated with a significant difference in outcome: 4-year PFS of 34% compared to 36% in patients who did not have atypical DHL (p=0.9), 4-year OS of 46% compared to 38% (p=0.9).

We confirmed our findings in multivariable Cox models stratified by conditioning regimen. In those models, factors associated with a lower incidence of relapse and improved PFS and OS were age > 55, CR/PR prior to alloSCT, and TIL histology (for PFS only). No variable was significantly associated with NRM. DEL and DHL were not significantly associated with PFS, OS, CIR or NRM in the models (Tables 2 and 3). Due to the unexpected association between older age and improved PFS and OS, we assessed whether there were differences in the HCT-CI scores of older versus younger patients, as well as between the DHL, DEL, and non-DEL/non-DHL subgroups, but no differences in HCT-CI were observed (Supplemental Table 2). In addition, older age remained associated with favorable PFS and OS when only patients who underwent RIC alloSCT (n = 60) were analyzed (data not shown). Patients with DEL appeared to have a lower incidence of chronic GVHD (24% versus 49%, p=0.039) as compared with patients who did not have DEL but no difference in acute GVHD was observed.

Discussion

In our multicenter cohort study evaluating the prognostic impact of DEL and DHL in a real-world population of patients with rel/ref aggressive B-NHL who underwent alloSCT, patients with DEL or DHL did not have a significantly inferior outcome compared to patients without either abnormality. In addition, patients with cytogenetic abnormalities of

MYC and *BCL2* and/or *BCL6* other than concurrent rearrangement did not have a significantly different outcome than patients who did not have atypical DHL. Because of the small number of patients included, our ability to detect meaningful differences between the groups may have been hampered.

As a retrospective study, our analysis is subject to inherent limitations and biases. For example, although the incidence of chronic GVHD in our cohort is consistent with what was observed in prior studies of allo SCT for DLBCL, the incidence of grade 2-4 acute GVHD was lower than expected in our cohort. This was not explained by the use of peri-transplantation rituximab, ATG, or other T-cell depleting strategies, which occurred in < 15% of patients. We attempted to minimize these potential biases by including all patients who had tissue available for testing among consecutively transplanted patients during the specified period. In addition, there was no significant difference in outcome between patients included in the study and patients who were not included due to lack of tissue or incomplete data. Our study only evaluated patients who were able to undergo alloSCT, and thus does not answer the question of whether patients with rel/ref DHL or DEL are less likely to eventually receive alloSCT, which is plausible given the difficulty of obtaining remission with salvage therapy. It is possible that there was a selection bias in the choice of transplant strategy for these patients. However, there were virtually no patients in whom DEL or DHL status was considered in the transplant decision-making, as most of the time the testing to identify DEL/DHL was performed only for this study, after the alloHSCT.

There are limitations in multivariable modeling of cohorts with small sample sizes. Here we performed multivariable analyses only to exclude a strong confounding effect by other known prognostic variables. As expected, refractory disease at alloSCT was associated with poorer outcome. A history of prior indolent lymphoma was associated with favorable outcome, a finding which has been previously reported[25] and requires validation in a larger cohort. The result that older patients had a favorable outcome is unexpected. That older patients had improved outcomes was not explained by an unexpected imbalance in HCT-CI scores, nor could it be explained by differences in conditioning regimen intensity, since older patients had more favorable outcome even in the subgroup of patients who underwent RIC alloSCT. The implication of this finding is unclear, and we feel that they are likely an artifact of our small study cohort. The observed association between DEL and a lower incidence of chronic GVHD may have been explained by the relatively higher proportion of patients in the DEL group (19%) who received ATG or other T-cell depleting strategies (post-transplant cyclophosphamide) compared to other groups (3% in non-DEL/non-DHL patients and 0% in DHL patients) though the difference in strategies among groups was not quite significant (p=0.052).

In conclusion, our results confirm that alloSCT produces durable remissions in a subset of patients with rel/ref aggressive B-NHL. More importantly, the outcome of alloSCT did not appear to differ based on either DEL or DHL status. This stands in contrast to previous studies showing that DHL and DEL are associated with adverse outcome after standard front-line chemoimmunotherapy,[5, 8-14, 17] salvage therapy,[19, 20] and autoSCT.[21] Biologically, this suggests that while DEL and DHL confer chemoresistance, they are not necessarily associated with immune resistance, and thus can potentially be targeted with the evolving

weaponry of immunotherapy. Nevertheless, the high incidence of post-alloSCT disease progression we observed across the disease subgroups demonstrates that improvement of alloSCT outcomes in patients with aggressive B-NHL remains a tremendous unmet need. Novel approaches to decreasing post-alloSCT disease relapse are desperately needed and the incorporation of targeted agents (e.g. ibrutinib in activated B-cell subtype DLBCL) or immunotherapies (e.g. PD-1 inhibitors or chimeric antigen receptor modified T-cells) prior to, during, and following conditioning (e.g. maintenance) should be studied. Clinically, the main implication of our study is for patients with rel/ref DEL or DHL who are able to attain remission. Since salvage treatment is often ineffective in these patients and autoSCT yields poor outcomes, alloSCT should be considered when remission can be achieved. Our intriguing findings merit further study of this question in a larger cohort and ideally should be confirmed in a prospective study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosure of Conflicts of Interest

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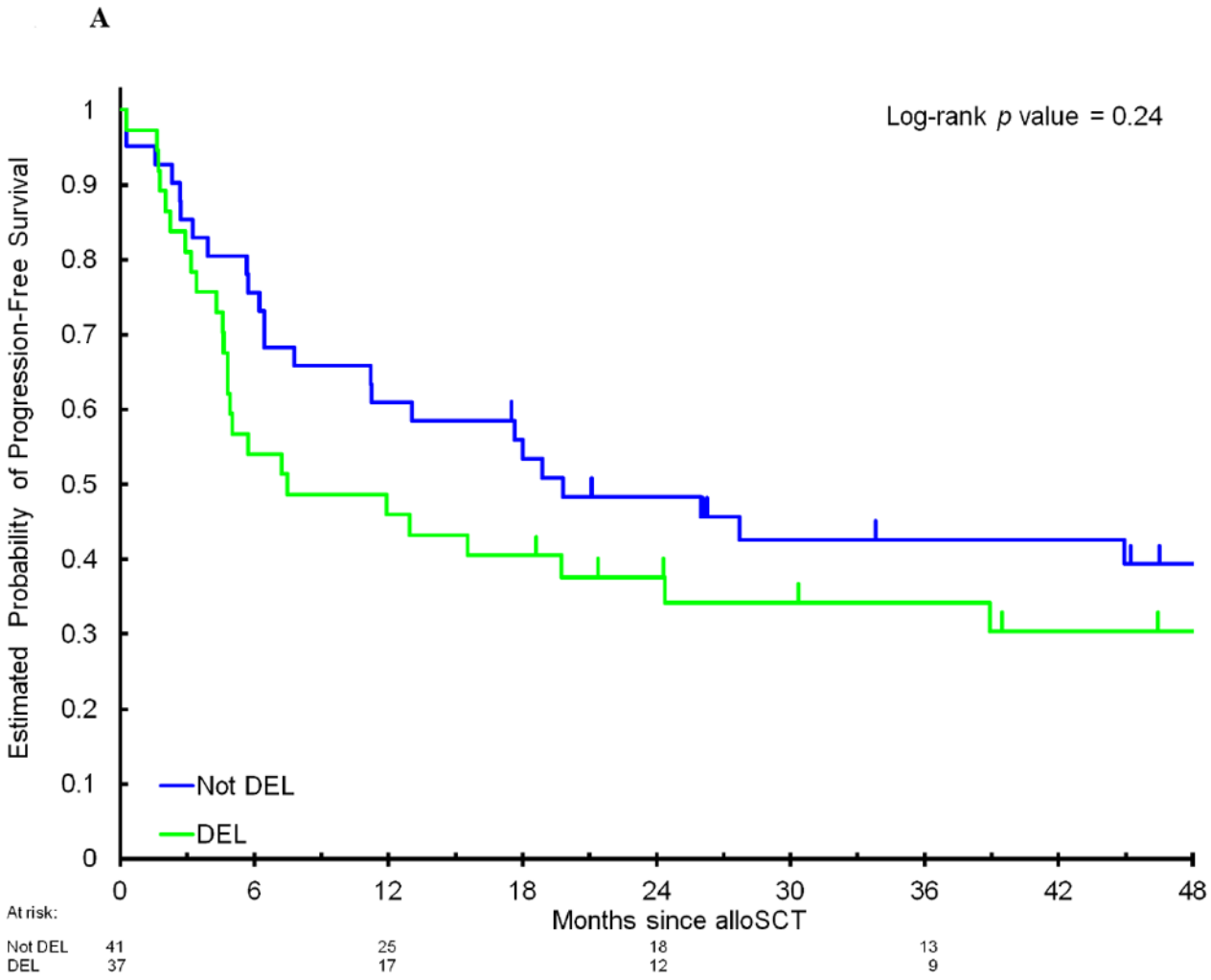
Highlights

- We retrospectively studied the prognostic impact of double-expressor (DEL) and double-hit lymphoma (DHL) in a multicenter alloSCT cohort.
- In patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma, DEL and DHL status did not impact alloSCT outcome.
- The study findings were confirmed in multivariable analyses



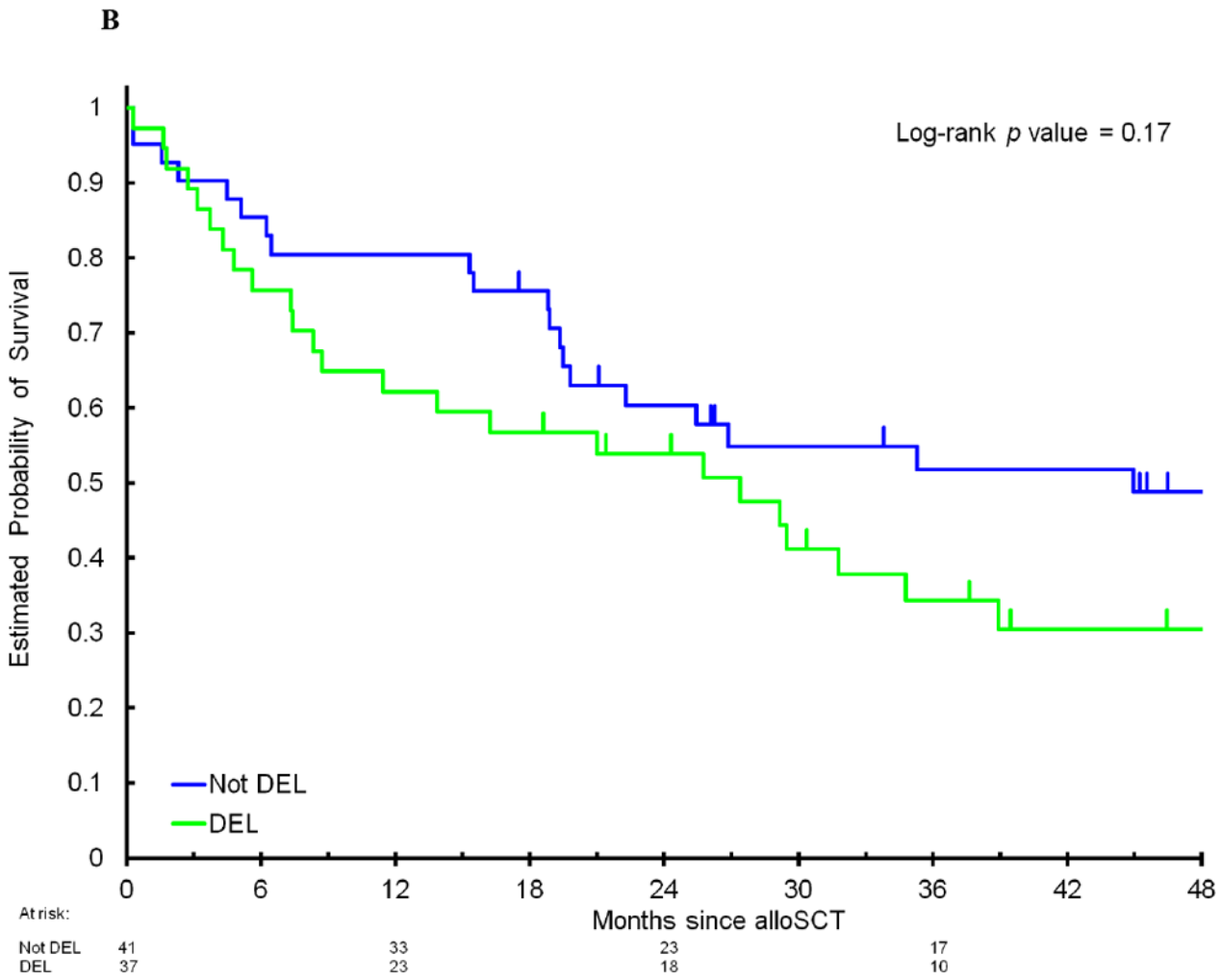
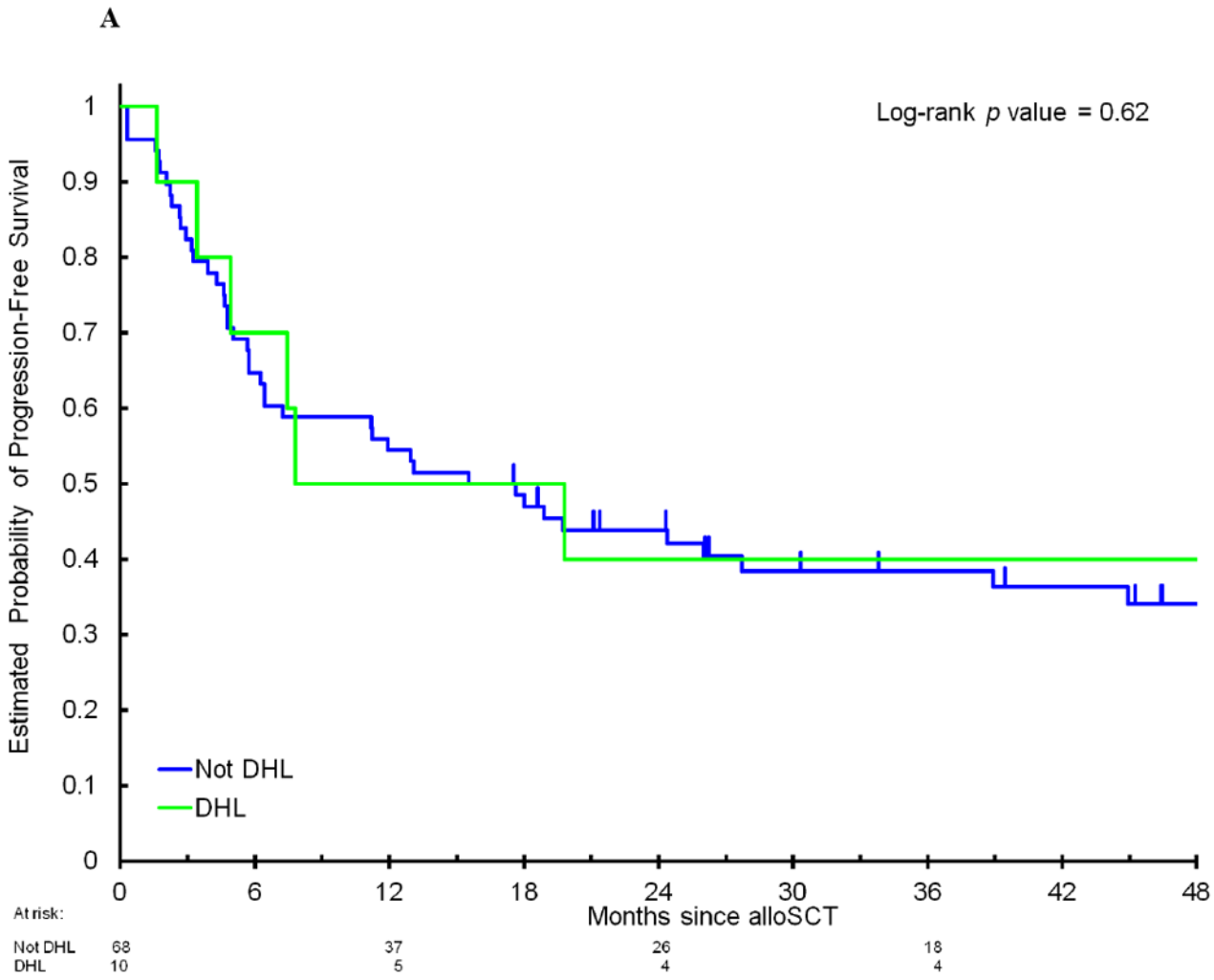
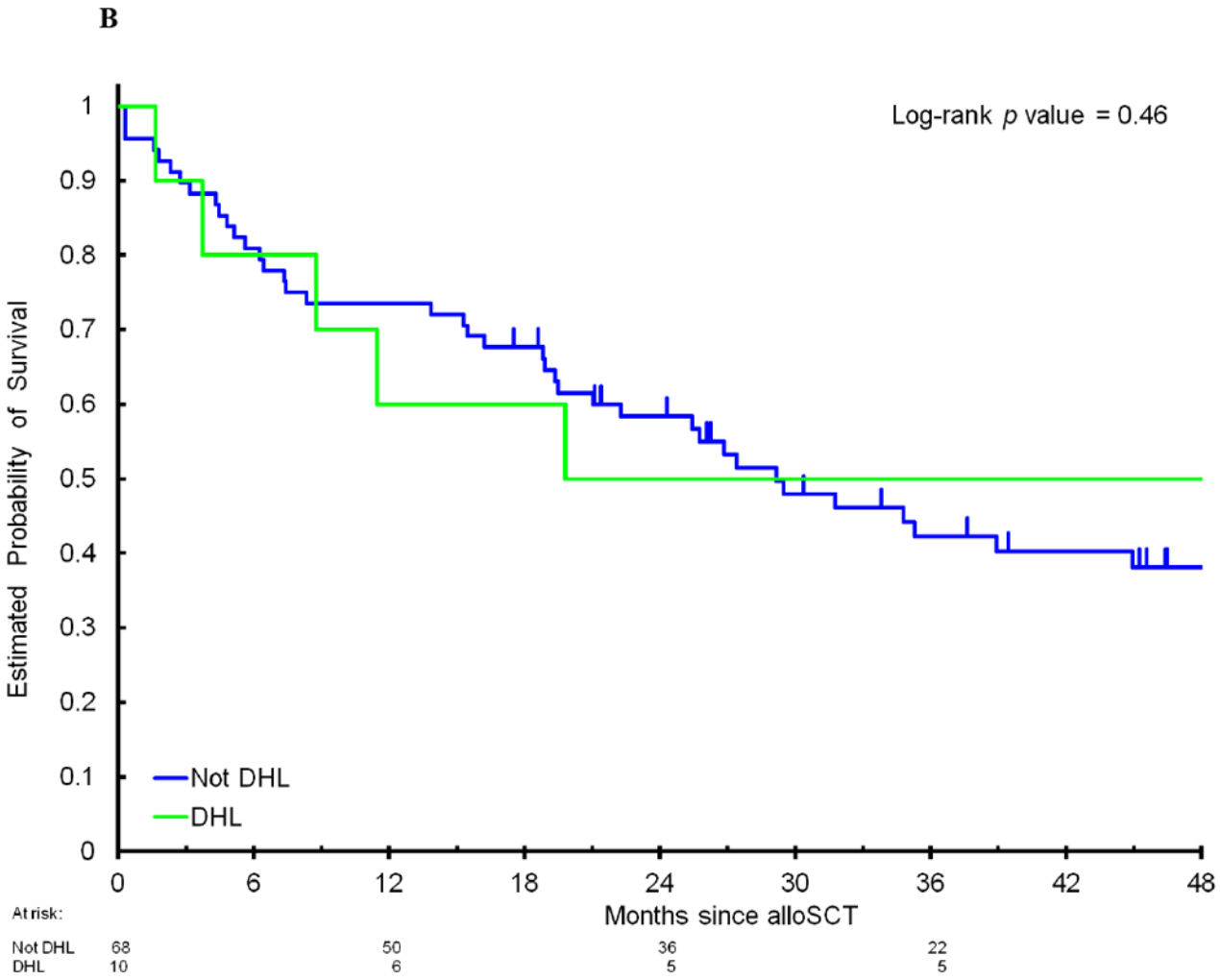


Figure 1.

Progression-free survival (A) and overall survival (B) after allogeneic stem cell transplantation in patients with DEL compared to non-DEL patients.





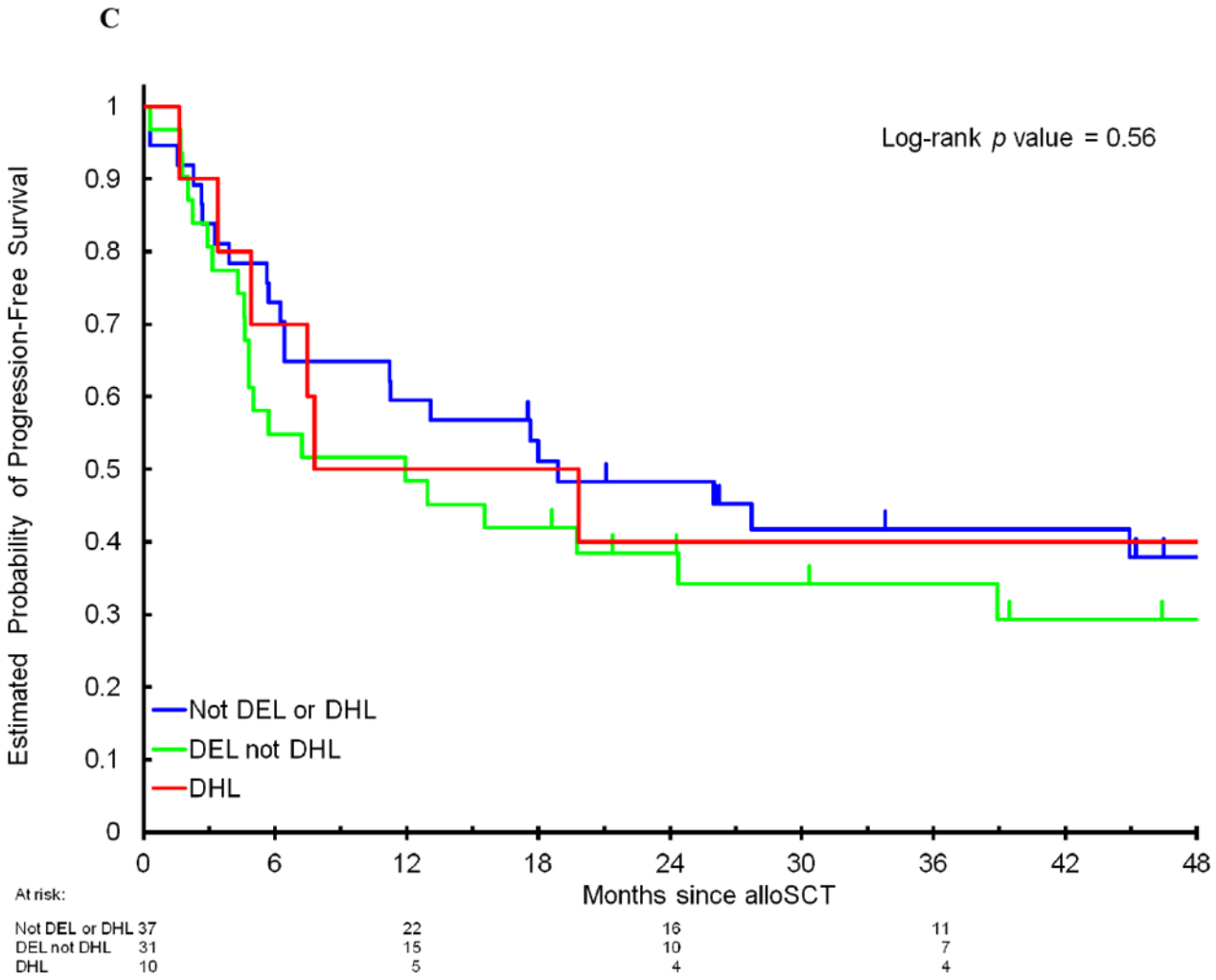


Figure 2.

Progression-free survival (A) and overall survival (B) after allogeneic stem cell transplantation in patients with DHL compared to non-DHL patients. (C) Progression-free survival in patients with DHL compared to patients with DEL without DHL and patients with neither DEL nor DHL. DEL indicates double-expressor lymphoma. DHL indicates double-hit lymphoma.

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Table 1

Summary of Immunohistochemistry and FISH Results and Comparison of Clinical Characteristics Between Patients with DEL, DHL, and Neither DEL nor DHL

Variable	All N (%)a	Non-DHL/Non-DEL N (%)a	DEL (non-DHL) N (%)a	DHL N (%)a	p valueb
Total	78	37	31	10	
IHC					
MYC median (range)	40% (0-90)				
BCL2 median (range)	90% (0-100)				
DEL	37 (47)				
FISH					
MYC not rearranged	57 (73)	33 (89)	24 (77)	0 (0)	
MYC rearranged	21 (27)	4 (11)	7 (23)	10 (100)	
MYC only	11 (14)	4 (11)	7 (23)	0 (0)	
DHL	10 (13)	0 (0)	0 (0)	10 (100)	
Atypical DHL	17 (22)	9 (24)	8 (26)	0 (0)	
Age median (range)	54 (24-69)	55 (24-69)	54 (32-69)	47 (34-62)	0.4
Gender					
Male	53 (68)	28 (76)	21 (68)	4 (40)	
Female	25 (32)	9 (24)	10 (32)	6 (60)	
Histology					0.089
DLBCL/BCLU	53 (68)	25 (68)	24 (77)	4 (40)	
TIL	25 (32)	12 (32)	7 (23)	6 (60)	
Prior lines of therapy (median, range)	4 (2-9)	4 (2-8)	4 (2-6)	5 (2-9)	0.16
Prior autoSCT	45 (58)	21 (57)	17 (55)	7 (70)	0.8
Disease status at SCT					0.8
Remission	58 (74)	27 (73)	23 (74)	8 (80)	
CR	33 (42)	18 (49)	11 (35)	4 (40)	

Variable	All N (%)a	Non-DHL/Non-DEL N (%)a	DEL (non-DHL) N (%)a	DHL N (%)a	p valueb
PR	25 (32)	9 (24)	12 (39)	4 (40)	
Not in remission	19 (24)	10 (27)	7 (23)	2 (20)	
SD	10 (13)	5 (14)	4 (13)	1 (10)	
PD	9 (12)	5 (14)	3 (10)	1 (10)	
Unknown	1 (1)	0 (0)	1 (3)	0 (0)	
Primary refractory disease	38 (49)	15 (41)	17 (55)	6 (60)	0.4
GVHD prophylaxis					0.3
CNI/MTX	13 (18)	7 (19)	6 (19)	0 (0)	
CNI/MMF +/- MTX	10 (13)	4 (11)	3 (10)	3 (30)	
CNI/SIRO +/- MTX	45 (58)	22 (60)	16 (52)	7 (70)	
Other	10 (13)	4 (11)	6 (19)	0 (0)	
Donor					0.2
MSD	28 (36)	17 (46)	10 (32)	1 (10)	
MUD	33 (42)	14 (38)	13 (42)	6 (60)	
MMUD	8 (10)	4 (11)	3 (10)	1 (10)	
Haplo	3 (4)	0 (0)	3 (10)	0 (0)	
Cord	6 (8)	2 (5)	2 (6)	2 (20)	
Graft source					0.14
PBSC	69 (88)	35 (95)	26 (84)	8 (80)	
BM	3 (4)	0 (0)	3 (10)	0 (0)	
UCB	6 (8)	2 (5)	2 (6)	2 (20)	
Conditioning					1.0
MAC	18 (23)	9 (24)	7 (23)	2 (20)	
RIC	60 (77)	28 (76)	24 (77)	8 (80)	
Months from Dx to AlloSCT					0.220
Median	33.2	30.4	30.5	63.5 41.3, 92.2	
Interquartile range	12.4, 58.3	10.7, 55.7	13.3, 45.8		
Range	(0.2-161.9)	(1.8-153.0)	(4.3-161.9)	(0.2-128.6)	

IHC indicates immunohistochemistry, DEL indicates double-expressor lymphoma, FISH indicates fluorescence in situ hybridization, DHL indicates double-hit lymphoma, DLBCL indicates diffuse large B-cell lymphoma, BCLU indicates B-cell lymphoma unclassified, TIL indicates transformed indolent lymphoma, autoSCT indicates autologous stem cell transplantation, SCT indicates stem cell transplantation, CR indicates complete response, PR indicates partial response, SD indicates stable disease, PD indicates progressive disease, GVHD indicates graft-versus-host disease, CNI indicates calcineurin inhibitor, MTX indicates methotrexate, MMF indicates mycophenolate mofetil, SIRO indicates sirolimus, MSD indicates matched sibling donor, MUD indicates matched unrelated donor, MMUD indicates mismatched unrelated donor, Haplo indicates haploidentical donor, Cord indicates umbilical cord blood donor, PBSC indicates peripheral blood stem cells, BM indicates bone marrow, UCB indicates umbilical cord blood, MAC indicates myeloablative conditioning, RIC indicates reduced intensity conditioning, Dx indicates diagnosis

Table 2

Multivariable Cox regression model for Progression-Free and Overall Survival

		PFS		OS	
Variable	**N**	**HR (95%CI)**	**Wald test P value***	**HR (95%CI)**	**Wald test P value***
Age, years					
≤55	41	Reference		Reference	
>55	37	0.43 (0.24 to 0.78)*	0.005*	0.46 (0.25 to 0.85)*	0.013*
Disease status at transplant					
Remission (CR or PR)	58	Reference		Reference	
Not in remission or unknown	20	2.46 (1.28 to 4.70)*	0.007*	2.52 (1.28 to 4.97)*	0.007*
Histology					
DLBCL/BCL-u	53	Reference		Reference	
Transformed indolent B-NHL	25	0.48 (0.25 to 0.91)*	0.024*	0.48 (0.24 to 0.93)*	0.030*
DEL					
No	41	Reference		Reference	
Yes	37	1.24 (0.71 to 2.17)§	0.45§	1.52 (0.85 to 2.73)§	0.16§
DHL					
No	68	Reference		Reference	
Yes	10	0.88 (0.37 to 2.11) §	0.78§	0.86 (0.32 to 2.27)§	0.76§

*Based on the Cox proportional hazards regression model including only three top variables in the table and stratified by conditioning regimen.

§Based on the Cox proportional hazards regression model adjusting three top variables in the table and stratified by conditioning regimen.

Table 3

Multivariable Cox regression model with competing risks for Relapse and Non-Relapse Mortality

	Relapse		NRM	
Variable	**HR (95%CI)**	**Wald test P value***	**HR (95%CI)**	**Wald test P value***
Age, years				
≤55	Reference			
>55	0.37 (0.18 to 0.78)	0.008	0.87 (0.33 to 2.25)	0.77
Disease status at transplant				
Remission (CR or PR)				
Not in remission or unknown	3.99 (1.83 to 8.71)	<0.001	0.41 (0.13 to 1.34)	0.14
Histology				
DLBCL/BCL-u	Reference			
Transformed indolent B-NHL	0.34 (0.15 to 0.80)	0.013	1.51 (0.68 to 3.37)	0.32
DEL				
No	Reference			
Yes	1.28 (0.63 to 2.61)	0.50	0.75 (0.31 to 1.84)	0.53
DHL				
No	Reference			
Yes	1.17 (0.39 to 3.50)	0.79	0.85 (0.27 to 2.65)	0.77

*Based on the proportional subdistribution hazards model for competing risks including only three top variables in the table and stratified by conditioning regimen.

§Based on the Cox proportional hazards regression model with competing risks adjusting three top variables in the table and stratified by conditioning regimen.