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Clinical relevance of MYC/BCL2 expression and cell of origin in patients with diffuse large b-cell lymphoma treated with autologous transplant.

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Abstract

Dual expression of MYC and BCL2 proteins (double-expressor lymphoma [DEL]) as well as cell of origin (COO) are important prognostic factors in patients with diffuse large B-cell lymphoma (DLBCL) after conventional chemotherapy. We studied the prognostic impact of DEL and COO in patients with relapsed DLBCL treated with autologous stem cell transplant (ASCT). Three-hundred and three patients with stored tissue samples were identified. Classification was successful in 267 patients: 161 (60%) were DEL/non-double hit (DHL), 98 (37%) were non-DEL/non-DHL, and 8 (3%) were DEL/DHL. Compared to non-DEL/non-DHL, DEL/DHL had worse overall survival while DEL/non-DHL did not significantly differ in overall survival. On multivariable analysis, DEL/DHL, age >60 years, and >2 prior therapies, but not COO, were important prognostic factors for overall survival. When we explored the interaction of COO and

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BCL2 expression, patients with germinal center B-cell (GCB)/BCL2 (+) had inferior progression-free survival (PFS) compared to GCB/BCL2 (−) patients (HR, 4.97; $P = .027$). We conclude that the DEL/non-DHL and non-DEL/non-DHL subtypes of DLBCL have similar survival after ASCT. The negative impact of GCB/BCL2 (+) on PFS warrants future trials targeting BCL2 after ASCT. The inferior outcomes in DEL/DHL need to be verified in a larger number of patients.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma worldwide, representing approximately 30%−40% of all cases in different geographic regions.[1,2] It is characterized by significant heterogeneity,[3] in part due to differences in cell of origin (COO) and the presence of *MYC* and *BCL2/BCL6* translocation (double-/triple-hit lymphoma [DHL/THL]) or C-MYC and BCL2 protein expression (double-expressor lymphoma [DEL]).[4] These differences in molecular makeup imply differences in clinical behavior and response to conventional therapy.[2,5–8]

Multiple studies have suggested that COO has an impact on overall prognosis in DLBCL, with the non-GCB (germinal center B-cell) by immunohistochemistry subgroup experiencing worse outcomes when treated with standard chemoimmunotherapy. Some investigators have suggested that this poor outcome of patients with non-GCB DLBCL may in part be attributed to the higher incidence of dual expression of C-MYC and BCL2.[6–8] In the relapsed setting, the role of the COO remains controversial. In a CORAL study, the GCB subtype was associated with better response to salvage therapy in preparation for autologous stem cell transplantation (ASCT).[9] We have previously shown that immunohistochemistry (IHC)-based COO classification did not retain prognostic survival significance in patients with relapsed DLBCL treated with ASCT in four prospective trials.[10] Similar results were reported in another study in the pre-rituximab era.[11]

While the majority of DLBCL can be cured with frontline chemoimmunotherapy, high-dose chemotherapy and ASCT remain the standard of care for patients with chemosensitive relapse.[9–13] However, the impact of these molecular profiles of DLBCL and their interactions in the ASCT setting are underreported.

In this report, we aimed to study the prognostic impact of C-MYC and BCL2 and their possible interaction with COO and clinical features in patients with relapsed DLBCL who received ASCT at our center.

METHODS

Study design and eligibility criteria

This was a single-center retrospective study of adult patients with de novo DLBCL who underwent treatment with high-dose chemotherapy and ASCT at The University of Texas MD Anderson Cancer Center (Houston, TX) during January 2000 through December 2018. All cases were diagnosed according to World Health Organization classification criteria. We excluded patients with a history of DLBCL transforming from low-grade lymphoma and those with primary mediastinal large B-cell lymphoma, primary cutaneous lymphoma,

or infection by HIV. Patients were also required to have formalin-fixed, paraffin-embedded biopsy samples with viable tumor available for analysis.

Patients with relapsed DLBCL that was chemosensitive to salvage treatments were included. Additional inclusion criteria were age 18–70 years, bone marrow with less than 5% involvement by lymphoma at the time of study entry as defined by marrow biopsies, adequate performance status (Eastern Cooperative Oncology Group score of 0–2), adequate liver function (bilirubin level of ≤1.5 mg/dL and liver enzyme concentrations up to 2 times the upper limit of normal), adequate renal function (creatinine level of <1.6 mg/dL), adequate cardiac function (ejection fraction higher than 50%), and adequate pulmonary function (higher than 50% of predictive value).

Data regarding patients' baseline demographic and clinical characteristics, lymphoma treatments, and transplants were collected from a protected database in the Department of Stem Cell Transplantation and Cellular Therapy at MD Anderson. The study was approved by our Institutional Review Board committee and all patients had a consent form signed for their treatment.

COO classification

The histologic diagnoses and other relevant molecular studies were reviewed by expert hematopathologists for confirmation. COO was classified using IHC methodologies as described by the algorithms of Hans, Visco-Young, and Choi.[14,15]

Tissue microarray immunohistochemical studies

Hematoxylin-eosin–stained slides from all DLBCL cases were reviewed, and representative areas with the highest percentage of tumor cells were selected for tissue microarray construction. IHC studies for a variety of markers were performed using a streptavidin-biotin complex technique on 2-mm tissue microarray sections. MYC expression (detected by clone Y69; Epitomics) showed a distinct nuclear pattern, and BCL2 expression (clone 124; DAKO) exhibited a cytoplasmic pattern. A cutoff value for each marker was established from analysis of receiver operating characteristic curves to achieve maximum specificity and sensitivity as described previously.[15] Cutoff values of 40% for MYC and 70% for BCL2 were established. These values were similar to those used by the International DLBCL Rituximab-CHOP Consortium Program.[15]

Fluorescence in situ hybridization for *MYC* and *BCL2*

Fluorescence in situ hybridization analysis was performed using formalin-fixed, paraffin-embedded tissue using *BCL2* dual-color break-apart probes (Vysis) as described previously.[15] *MYC* was assessed by fluorescence in situ hybridization using locus-specific IGH/MYC/CEP8 tricolor dual-fusion probes and locus-specific *MYC* dual-color break-apart probes (Vysis). Cases were considered for evaluation if at least 200 tumor cell nuclei per core displayed positive signals in the tissue microarray sections.

Preparative regimens for ASCT

The predominant (81%) preparative regimen for ASCT had been R-BEAM, which consisted of intravenous rituximab, carmustine, etoposide, cytarabine, and melphalan as previously described. [11,16] Rituximab was also administered during chemomobilization at a dose of 375 mg/m^2 1 day before chemotherapy, which consisted of ifosfamide at 3.33 g/m^2 daily for 3 days and etoposide at 150 mg/m^2 twice per day for 3 days, and then another dose 7 days later. Rituximab was also administered on days +1 and +8 after transplant as previously described.[16] Twenty-six patients (10%) had received gemcitabine, busulfan, and melphalan with or without vorinostat (n=7) or SAHA (n=3),[17] or BEAM alone (8%), per physician choice. Patients with a history of lymphoma involving the central nervous system (n=19; 7%) had received a thiotepa and carmustine regimen with rituximab.[18]

Clinical evaluation

Lymphoma staging was performed using Ann Arbor staging criteria, and each patient was assigned an International Prognostic Index (IPI) score at the time of study entry.[19] Positron emission tomography (PET) scanning of the whole body was routinely performed for all patients at our center starting in December 2002. Treatment response was assessed using computed tomography of the neck, chest, abdomen, and pelvis or whole-body PET-CT imaging at 1, 3, 6, and 12 months after ASCT, then every 6 months for 5 years, then yearly afterwards using the criteria of Cheson and colleagues.[19,20]

Statistical analysis

The primary objective of this study was to determine the effects of the interaction of MYC/BCL2 and COO on overall survival (OS) and progression-free survival (PFS) in patients with relapsed DLBCL following ASCT at our center. The secondary objectives were to determine predictors of OS and PFS, the cumulative incidences of relapse and mortality, and the prognostic impact of BCL2 expression on outcomes. Patients were divided into four DLBCL groups based on their MYC/BCL2 status: double expressor with double hit (DEL/DHL), double expressor without double hit (DEL/non-DHL), double hit without double expressor (non-DEL/DHL), or neither (non-DEL/non-DHL).

The covariates of patient and disease characteristics were compared using generalized Fisher's exact test (categorical variables) or Kruskal-Wallis test (continuous variables). OS time was computed from date of ASCT to date of death from any cause. PFS time was computed from date of ASCT to date of relapse, progression, or death from any cause, whichever came first. Patients who were alive, or alive and without relapse/progression, at last follow-up were censored for OS and PFS, respectively.

The Kaplan-Meier method was used to estimate OS and PFS, and groups were compared using the log-rank test. Cox proportional hazards regression models were used to assess associations between covariates of interest and OS or PFS. The cumulative incidences of non-relapse mortality and relapse were determined using the competing risks method. The competing risk for non-relapse mortality was relapse, and the competing risk for relapse was death. Patients who were alive and did not experience relapse by the last follow-up date were censored. Differences in cumulative incidence between groups were assessed

using Gray's test,[21] while associations between measures of interest and the cumulative incidence outcomes were determined using proportional subdistribution hazards regression models.[22] Analyses were performed using SAS 9.5 for Windows (SAS Institute Inc., Cary, NC). *P*-values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics

Three hundred and three patients with DLBCL were identified. Eight patients had atypical DHL and were excluded from this analysis. Three patients were classified as non-DEL/DHL and due to their small number were excluded as well. In addition, 25 (8%) patients did not have enough tissue material to test for DHL and DEL status, and they were considered controls. Of the remaining 267 patients, 161 (60%) were DEL/non-DHL, 98 (37%) were non-DEL/non-DHL, and 8 (3%) were DEL/DHL. Patients' demographic and clinical characteristics are summarized in Table 1. There were no statistically significant differences in baseline characteristics between the DLBCL groups except for COO classification: GCB subtype was seen in 100% of DEL/DHL and 95% of unknown subtypes but only 39% of DEL/non-DHL and 45% of non-DEL/non-DHL ($P = 0.002$). Most patients (214, 80%) received the R-BEAM conditioning regimen (Table 1).

Survival

The median follow-up time for surviving patients was 41 months in the non-DEL/non-DHL group, 60.2 months in the DEL/non-DHL group, and 63.5 months in the DEL/DHL group ($P = 0.004$). The corresponding 5-year PFS rates for these three groups were not significantly different (48% vs 49% vs 25%, respectively; $P = 0.28$) (Figure 1A). However, the 5-year OS rates were 61% in non-DEL/non-DHL, 58% in DEL/non-DHL, and 25% in DEL/DHL. The OS rate of DEL/DHL was significantly inferior to that of the other two groups ($P = 0.032$) (Figure 1b). On univariable analysis, compared to non-DEL/non-DHL, DEL/DHL had worse OS (hazard ratio [95% confidence interval], 2.97 [1.24, 7.08]; $P = 0.014$) while DEL/non-DHL did not significantly differ in OS (1.17 [0.78, 1.77]; $P = 0.44$) (Table 2). Results of univariable and multivariable analyses for both PFS and OS are shown in Tables 2 and 3, respectively. New regimens of gemcitabine, busulfan, and melphalan with or without vorinostat or SAHA had significantly inferior PFS compared to R-BEAM on univariable analysis despite non-including any cases of DEL/DHL (Figure 2).

The 5-year cumulative incidences of relapse for non-DEL/non-DHL, DEL/non-DHL, and DEL/DHL were 33%, 37%, and 25%, respectively, which were not significantly different ($P = .62$). The non-relapse mortality rates for non-DEL/non-DHL, DEL/non-DHL, and DEL/DHL were 4%, 3%, and 13%, respectively, at 100 days and 18%, 14%, and 50%, respectively, at 5 years ($P = 0.030$). Compared to non-DEL/non-DHL, DEL/DHL had worse non-relapse mortality (3.74 [1.28, 10.97]; $P = 0.016$) while DEL/non-DHL did not significantly differ (0.98 [0.52, 1.83]; $P = 0.94$). Causes of death in the DEL/DHL group was infection (n=2), cardiac (early death, n=1), psychiatric (n=1), unknown (n=2).

Interaction between COO and BCL2

We found no difference in OS and PFS between GCB and non-GCB patients (Figure 3a, b). We also found no difference in outcomes based on BCL2 expression alone (Figure 3c, d). We subsequently evaluated the effects of the interaction between BCL2 protein expression and COO on outcomes. Among GCB patients, positive BCL2 expression was associated with worse PFS (3.04 [1.23, 7.55]; $P = 0.017$) (Figure 3c, Table 2); the 5-year PFS rate was 82% in GCB-BCL2 (−) DLBCL in contrast to 47% in GCB-BCL2 (+) DLBCL. This association remained significant in the multivariable analysis (Table 3). There was no association between BCL2 expression and OS among GCB patients ($P = 0.10$) or among non-GCB patients (Figure 3e, f).

DISCUSSION

The presence of *MYC* and *BCL2/BCL6* translocation or BCL2 protein expression has been shown to impact the outcomes of DLBCL treated with chemoimmunotherapy.[2–8] In this report, we analyzed the clinical relevance of these abnormalities in patients with relapsed and refractory DLBCL who received an ASCT at our center. This was a retrospective analysis based on the presence of archived tissue material, which may explain the distribution of various histology subtypes: 60% DEL/non-DHL, 37% non-DEL/non-DHL, and 3% DEL/DHL. Most of these patients had disease that was sensitive to the last treatment they received before the transplant. Our analysis showed similar PFS and OS rates between DEL/non-DHL and non-DEL/non-DHL. However, patients who had the DEL/DHL subtype had significantly worse OS compared with the other two subtypes. These findings in DEL/DHL are based however on a small number of patients and were similar to another study by Herrera et al.[23]

In our study, BCL2 expression >70% was used as the cut-off for BCL2 positivity, instead of the. 50% cutoff that is normally used for primary de novo DLBCL patients in evaluating the impact of BCL2 expression on clinical outcomes. In the setting of relapsed/refractory disease, BCL2 positivity rates are usually higher than in DLBCL patients at their original diagnosis. For this purpose, we analyzed the dataset using X-tile program and performed a ROC (receiver operating characteristic curve) analysis to determine the most optimal cutoff, including 50% and 70%. Results were similar between them, but the impact on clinical outcomes was more distinctive when the 70% cutoff was used.

In what is the largest single-center study to address the impact of these molecular markers in patients with DLBL undertaking ASCT, patient and disease characte11ristics were similar between all three subtype groups, with the except of COO: a lower percentage of patients were of germinal center like B-cell (GCB) origin in the non-DEL/non-DHL (45%) and DEL/non-DHL (39%) groups compared to the DEL/DHL (100%) group ($P = 0.002$). However, COO profiling was not associated with OS or PFS. This finding confirms our previous report in a smaller number of patients.[10]

The role of ASCT in DEL and DHL relapsed/refractory DLBCL was evaluated by Herrera and colleagues in a multicenter retrospective study.[23] The analysis included 117 patients, of whom 47 (44%) had DEL, 12 (10%) had DHL, and 58 (50%) had the non-DEL/non-DHL

subtype. Like our study, they found patients with DEL/DHL had the worst outcomes, with a 4-year PFS of 0%. Contrary to our study, the authors showed inferior 4-year PFS for DEL vs non-DEL/non-DHL (48% vs 59%, respectively; $P = .049$). The 4-year OS rates were similar between the two groups (56% vs 67%, $P = .1$). This difference in PFS may be related to the retrospective nature of the analyses, disease status of patients at the time of transplant (patients with DEL or DHL were less likely to be in complete remission at time of transplant compared to non-DEL/non-DHL [$P = .006$]), different conditioning (cyclophosphamide, carmustine, and etoposide [CBV] was the most common conditioning regimen used in the previous study, in contrast to R-BEAM in our study). In addition, IPI and PET status were not reported in the previous study.

In a recent study by Tsuyama et al,[24] BCL2 protein expression by IHC score was a strong prognostic factor independent of the IPI and MYC protein/rearrangement status in DLBCL treated with chemoimmunotherapy. Therefore, we further explored the effects of the interaction between BCL2 expression and COO on outcomes in this study. We found that positive BCL2 expression was associated with significantly inferior PFS compared to BCL2 negativity in the GCB subtype. The 5-year PFS rates for GCB/BCL2 (+) vs GCB/BCL2 (−) subgroups were 58% vs 89%, respectively ($P = .012$) (Figure 3e, f). A similar association was not seen in the non-GCB subtype. Similar results were reported in another study,[25] where it was apparent that BCL2 positivity determines the unfavorable trend and not MYC positivity.

Our study is limited by the retrospective nature of an analysis that involves patients with archived material, and the fact that not all tests were done in all patients owing to the lack or scarcity of material available. The strengths, however, include the pathology review at a single laboratory by an expert hematopathologist, the relatively large sample of patients, the adequate follow-up time, and the comprehensive data collected for patients compared to other similar studies.

In our study, four different conditioning regimens were used. We consider the R-BEAM our standard regimen. The thiotepa-based regimen is reserved for patients with a history of central nervous system involvement. On univariable analysis, patients who received R-BEAM and R-thiotepa, carmustine regimen with rituximab had better OS and PFS than those who received BEAM alone or the gemcitabine-based regimens. However, the difference was not significant . Similarly, the study by Herrera et al involved three conditionings for ASCT without a significant difference in the outcomes. This suggests that different strategies beyond the conditioning regimens are needed to improve the outcomes.

We have previously reported that combination strategies using the checkpoint inhibitor ipilimumab, at 3 mg/kg every 3 weeks alternating with lenalidomide (10 mg orally daily for 28 days) for a total of 8 cycles, resulted in enhanced immune activity manifested by a significant increase in the numbers of $ICOS^{+}CD4^{+}FoxP3^{-}$ T cells.[26] We have used this combination to prevent relapse after ASCT in patients with high-risk lymphoma, including 8 patients with DEL/DHL.[27] This group was heavily pre-treated. The median number of prior chemotherapies excluding their ASCT was 3 (range, 1–5). Five patients did not experience a response to dose-adjusted rituximab, etoposide, prednisolone, vincristine,

cyclophosphamide, doxorubicin (DA-R-EPOCH), and one patient did not have a response to rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-Hyper-CVAD). With a median follow-up of 35 months (range, 4–78 months), all patients remained alive. One patient with DEL/DHL who underwent a transplant during second remission had a relapse at 1.6 months after initiating therapy (just after finishing the cycle 2 of maintenance). All others remained in complete remission.

In conclusion, our study shows that relapsed/refractory DLBCL patients whose disease is both DEL and DHL have inferior survival compared to the other subtypes. Interestingly, we also found that patients who have DEL and those with non-DEL/non-DHL have similar outcomes after ASCT. BCL2 expression is an important prognostic factor in GCB lymphoma. Investigational studies combining targeted therapies are warranted in this setting.

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Data availability statement

Raw data were generated at the University of Texas MD Anderson Cancer Center, Houston, TX. Derived data supporting the findings of this study are available from the corresponding author [IFK] upon request at ikhouri@mdanderson.org

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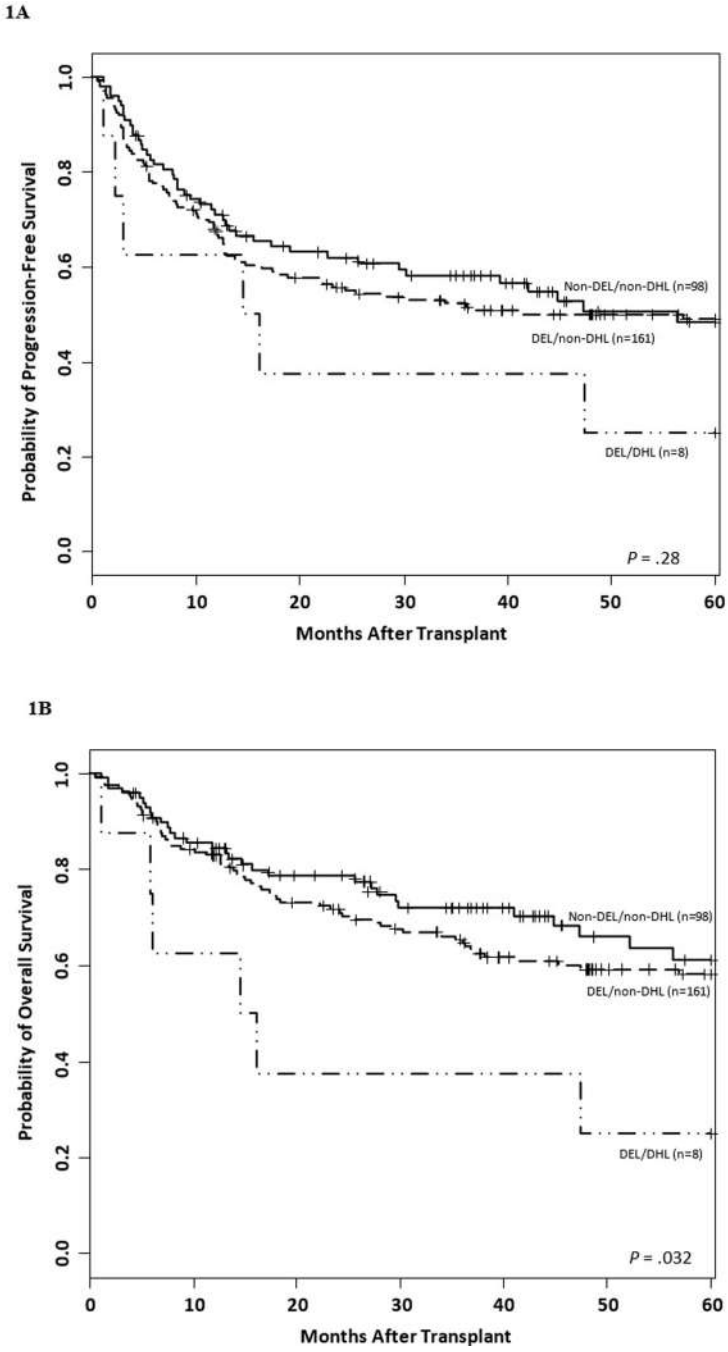

Figure 1:

Kaplan-Meier survival curves of progression-free survival (a) and overall survival (b) by diffuse large B-cell lymphoma subtype. DEL, double-expressor lymphoma; DHL, double-hit lymphoma.

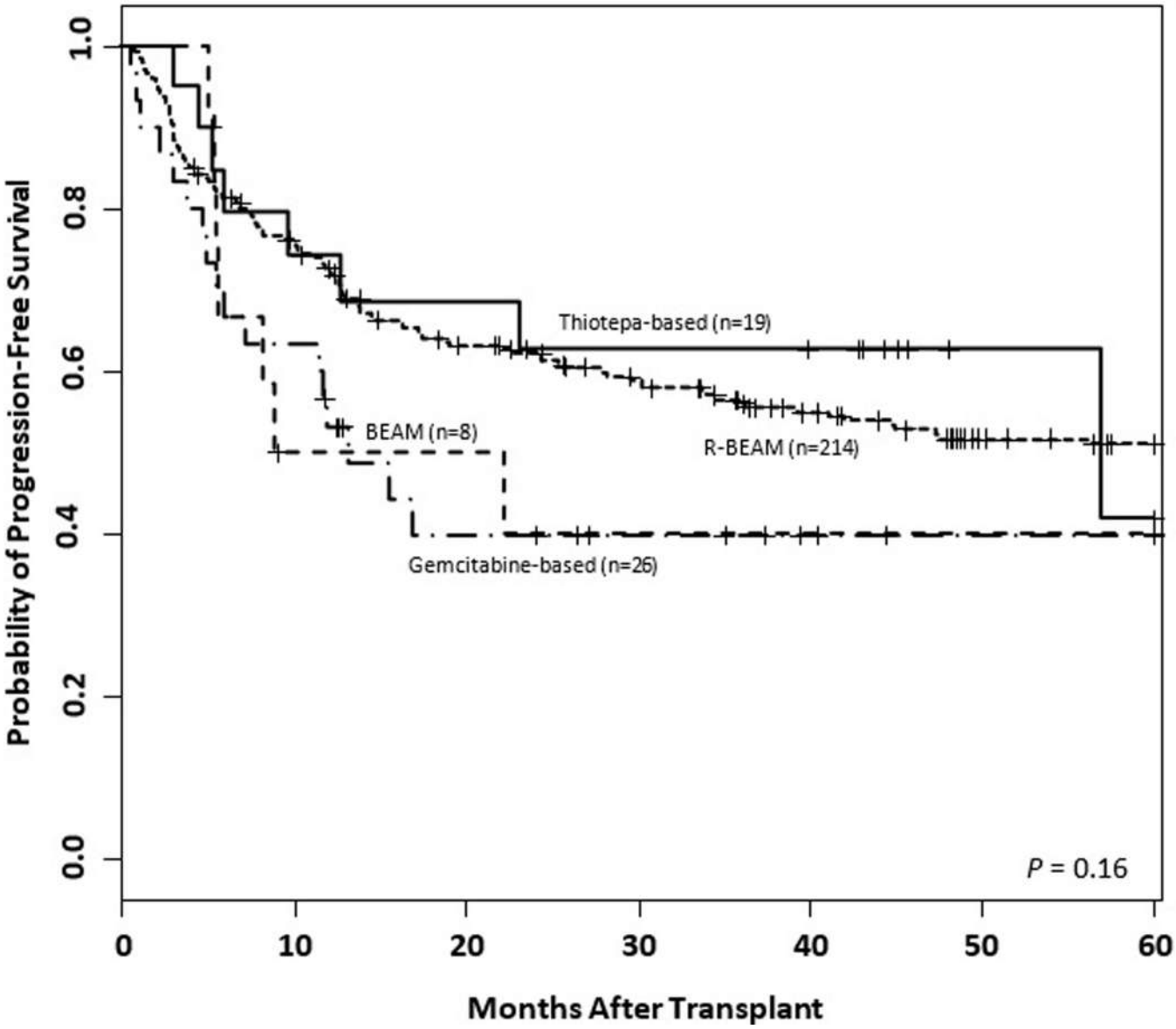

Figure 2:

Kaplan-Meier survival curves of progression-free survival stratified by conditioning regimen. R-BEAM, rituximab, carmustine, etoposide, cytarabine, and melphalan; BEAM, carmustine, etoposide, cytarabine, and melphalan.

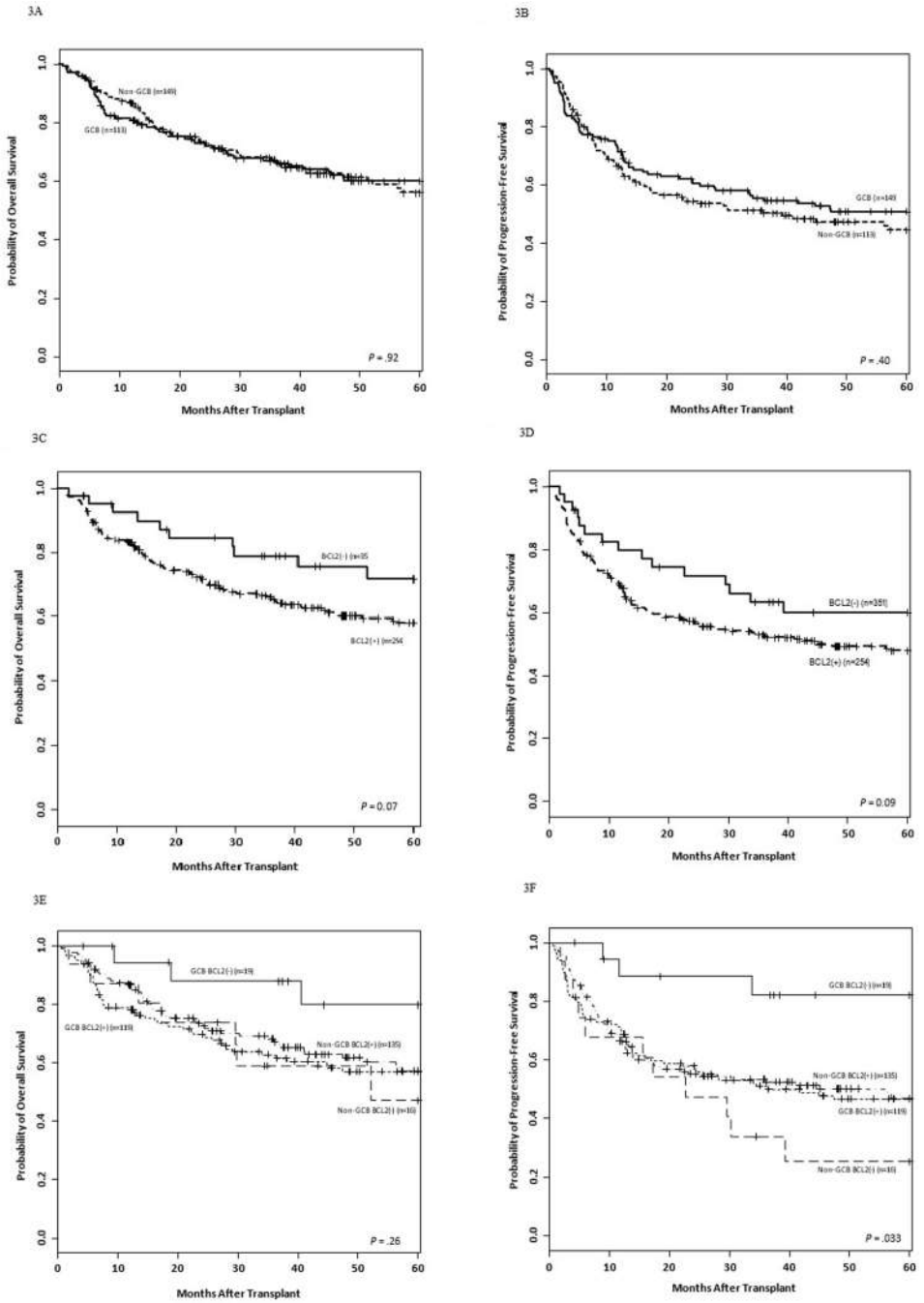

Figure 3:

Kaplan-Meier survival curves of overall survival (a) and progression-free survival (b) based on cell of origin. Kaplan-Meier survival curves of overall survival (c) and progression-free survival (d) based on BCL2- expression. Kaplan-Meier survival curves of overall survival (e) and progression-free survival (f) based on the interaction between cell of origin and BCL2 expression and GCB, germinal center–like B-cell.

Table 1:

Demographic and baseline clinical characteristics by diffuse large B-cell lymphoma subtype

Characteristic	non-DEL/non-DHL (N=98)	DEL (non-DHL) (N=161)	DEL/DHL (N=8)	*P*
Age, years				0.42
Median	60.9	59.5	66.4	
Range	32.7–76.4	18.3–79.6	45.8–72.7	
Sex, n (%)				0.76
Male	65 (66)	101 (63)	6 (75)	
Female	33 (34)	60 (37)	2 (25)	
Race/ethnicity, n (%)				0.74
White	75 (77)	119 (74)	7 (88)	
Other	23 (23)	42 (26)	1 (13)	
Cell of origin, n (%)				0.002
Non-GCB	53 (55)	96 (61)	0	
GCB	44 (45)	61 (39)	8 (100)	
Unavailable	1	4	0	
HCI-CI score				0.63
Median	2.0	2.0	3.0	
Range	0.0–7.0	0.0–9.0	0.0–4.0	
Number of prior chemotherapies				0.11
Median	2.0	2.0	1.5	
Range	1.0–4.0	1.0–6.0	1.0–5.0	
Lymphoma stage at initial diagnosis, n (%)				1.00
I-II	27 (28)	44 (28)	2 (25)	
III-IV	68 (72)	114 (72)	6 (75)	
Unavailable	3	3	0	
Lymphoma stage at transplant, n (%)				0.37
0-II	91 (94)	144 (90)	7 (88)	
III-IV	6 (6)	16 (10)	1 (13)	
Unavailable	1	1	0	
IPI score at transplant, n (%)				0.92
0	43 (45)	73 (48)	4 (50)	
≥1	52 (55)	78 (52)	4 (50)	
Unavailable	3	10	0	
LDH level at transplant, n (%)				0.97
Normal	65 (69)	106 (68)	6 (75)	
>ULN	29 (31)	51 (32)	2 (25)	
Unavailable	4	4	0	
Prior CNS involvement, n (%)				0.33
No	87 (89)	151 (94)	8 (100)	
Yes	11 (11)	10 (6)	0	
PET status at transplant, n (%)				0.80

Characteristic	non-DEL/non-DHL (N=98)	DEL (non-DHL) (N=161)	DEL/DHL (N=8)	*P*
Negative	66 (73)	107 (72)	7 (88)	
Positive	24 (27)	41 (28)	1 (13)	
Unavailable	8	13	0	
Disease status at transplant, n (%)				0.32
CR	64 (65)	101 (63)	7 (88)	
PR	27 (28)	50 (31)	0	
SD/PD	7 (7)	10 (6)	1 (13)	
Conditioning chemotherapy, n (%)				0.52
R-BEAM	72 (73)	134 (83)	8 (100)	
BEAM	4 (4)	4 (2)	0	
Gem/Bu/Mel-based	12 (12)	14 (9)	0	
R-Thiotepa/B	10 (10)	9 (6)	0	

Abbreviations: DEL, double-expressor lymphoma; DHL, double-hit lymphoma; GCB, germinal center–like B-cell; HCT-CI, hematopoietic cell transplant–specific comorbidity index; IPI, International Prognostic Index; LDH, serum lactate dehydrogenase level; CNS, central nervous system; PET, positron emission tomography; CR, complete remission; PR, partial remission; SD, stable disease; R-BEAM, rituximab, carmustine, etoposide, cytarabine, and melphalan; BEAM, carmustine, etoposide, cytarabine, and melphalan; Gem/Bu/Mel, gemcitabine, busulfan, and melphalan; ULN, upper limit of normal.

Table 2:

Univariable analysis for PFS and OS

Covariate	PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Lymphoma subtype						
Non-DEL/non-DHL	1.00			1.00		
DEL/non-DHL	1.08	0.76, 1.53	0.68	1.17	0.78, 1.77	0.44
DEL/DHL	1.91	0.82, 4.48	0.13	2.97	1.24, 7.08	0.014
Age						
Continuous	1.02	1.00, 1.03	0.011	1.03	1.01, 1.04	0.002
≤60 years	1.00			1.00		
>60 years	1.51	1.11, 2.07	0.009	1.73	1.21, 2.46	0.002
Sex						
Male	1.00			1.00		
Female	0.75	0.54, 1.05	0.09	0.58	0.39, 0.85	0.006
Cell of origin						
Non-GCB	1.00			1.00		
GCB	0.97	0.71, 1.32	0.83	1.01	0.71, 1.43	0.96
BCL2						
Negative	1.00			1.00		
Positive	1.52	0.93, 2.49	0.09	1.70	0.96, 3.02	0.07
GCB-BCL2						
Negative	1.00			1.00		
Positive	3.04	1.23, 7.55	0.017	2.14	0.86, 5.35	0.10
HCT-CI score						
Continuous	1.02	0.94, 1.11	0.60	1.07	0.97, 1.17	0.18
≤4	1.00			1.00		
>4	1.29	0.78, 2.13	0.32	1.63	0.94, 2.84	0.08
Number of prior chemotherapies						
Continuous	1.36	1.16, 1.60	<0.001	1.39	1.16, 1.67	<0.001
≤2	1.00			1.00		
>2	1.80	1.32, 2.44	<0.001	1.66	1.17, 2.34	0.004
Lymphoma stage at initial diagnosis						
I-II	1.00			1.00		
III-IV	1.30	0.91, 1.84	0.15	1.34	0.90, 1.99	0.15
Lymphoma stage at transplant						
0-II	1.00			1.00		
III-IV	2.96	1.88, 4.66	<0.001	2.60	1.57, 4.28	<0.001
IPI score at transplant						
0	1.00			1.00		
≥1	2.02	1.45, 2.81	<0.001	1.73	1.20, 2.49	0.003
LDH						

Covariate	PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Normal	1.00			1.00		
>ULN	1.50	1.07, 2.11	0.017	1.11	0.75, 1.65	0.60
Prior CNS disease						
No	1.00			1.00		
Yes	0.95	0.50, 1.80	0.87	0.82	0.36, 1.86	0.63
PET status at transplant						
Negative	1.00			1.00		
Positive	1.60	1.13, 2.27	0.008	1.66	1.13, 2.45	0.010
Disease status at transplant						
CR	1.00			1.00		
PR	1.53	1.10, 2.15	0.012	1.50	1.03, 2.19	0.035
SD/PD	1.59	0.89, 2.83	0.12	1.76	0.96, 3.25	0.07
Conditioning regimen						
R-BEAM	1.00			1.00		
BEAM	1.30	0.63, 2.66	0.48	1.20	0.56, 2.59	0.64
Gem/Bu/Mel-based	1.75	1.06, 2.88	0.028	1.75	0.97, 3.15	0.06
R-Thiotepa/B	0.98	0.50, 1.93	0.95	0.77	0.31, 1.90	0.57

Abbreviations: DEL, double-expressor lymphoma; DHL, double-hit lymphoma; GCB, germinal center–like B-cell; HCT-CI, hematopoietic cell transplant–specific comorbidity index; IPI, International Prognostic Index; LDH, serum lactate dehydrogenase level; CNS, central nervous system; PET, positron emission tomography; CR, complete remission; PR, partial remission; SD, stable disease; PFS, progression-free survival; OS, overall survival; R-BEAM, rituximab, carmustine, etoposide, cytarabine, and melphalan; BEAM, carmustine, etoposide, cytarabine, and melphalan; Gem/Bu/Mel, gemcitabine, busulfan, and melphalan; UNL, upper limit of normal.

Table 3:

Multivariable analysis for PFS and OS

Covariate	PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Lymphoma subtype						
Non-DEL/non-DHL				1.00		
DEL/non-DHL		NI		1.35	0.75, 2.42	0.31
DEL/DHL				3.35	1.12,10.02	0.031
Cell of origin						
Non-GCB	1.00			1.00		
GCB	0.68	0.15, 3.04	0.61	1.06	0.65, 1.74	0.81
Age						
≤60 years	1.00			1.00		
>60 years	1.36	0.87, 2.14	0.18	2.08	1.14, 3.82	0.017
Sex						
Male	1.00			1.00		
Female	0.67	0.45, 0.99	0.046	0.64	0.38, 1.08	0.10
Number of prior chemotherapies						
≤2	1.00			1.00		
>2	2.00	1.40, 2.85	<0.001	1.65	1.00, 2.71	0.049
Lymphoma stage at transplant						
0-II	1.00			1.00		
III-IV	3.09	1.61, 5.96	<0.001	1.60	0.68, 3.75	0.28
GCB-BCL2						
Negative	1.00					
Positive	4.97	1.20, 20.61	0.027		NI	
Other	3.62	0.46, 28.52	0.22			
IPI score at transplant						
0	1.00			1.00		
≥1	1.65	1.01, 2.71	0.046	1.31	0.74, 2.32	0.36
PET status at transplant						
Negative	1.00					
Positive	0.88	0.46, 1.70	0.70	1.77	0.68, 4.64	0.24
LDH						
Normal	1.00					
>ULN	1.21	0.80, 1.83	0.36		NI	
Disease status at transplant						
CR	1.00			1.00		
PR	1.03	0.58, 1.84	0.91	0.69	0.28, 1.67	0.41
SD	1.31	0.53, 3.23	0.56	1.19	0.36, 4.00	0.78
BCL2						
Negative		NI		1.00		

Covariate	PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Positive				1.06	0.41, 2.76	0.90
HCT-CI score						
≤4				1.00		
>4		NI		1.57	0.80, 3.08	0.19

Abbreviations: DEL, double-expressor lymphoma; DHL, double-hit lymphoma; NI, not included in the model; GCB, germinal center–like B-cell; HCT-CI, hematopoietic cell transplant–specific comorbidity index; IPI, International Prognostic Index; LDH, serum lactate dehydrogenase level; CNS, central nervous system; PET, positron emission tomography; PFS, progression-free survival; OS, overall survival; CR, complete remission; PR, partial remission; SD, stable disease; ULN, upper limit of normal.