Autologous stem cell transplant in fit patients with refractory or early relapsed diffuse large B-cell lymphoma that responded to salvage chemotherapy

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Abstract

Chimeric antigen receptor T-cell therapy is the new standard of care in fit patients with refractory or early relapsed diffuse large B-cell lymphoma (DLBCL). However, there may still be a role for salvage chemotherapy (ST) and autologous stem cell transplant (ASCT) in certain circumstances (e.g., lack of resources for chimeric antigen receptor T-cell therapy, chemosensitive relapses). We retrospectively studied 230 patients with refractory or early relapsed DLBCL who underwent ST and ASCT. The median line of ST was one (range, 1-3). Best response before ASCT was complete response in 106 (46%) and partial response in 124 (54%) patients. The median follow-up after ASCT was 89.4 months. The median progression-free (PFS) and overall survival (OS) were 16.1 and 43.3 months, respectively. Patients relapsing between 6 to 12 months after frontline therapy had a numerically better median PFS (29.6 months) and OS (88.5 months). Patients who required one line of ST, compared to those requiring more than one line, had a better median PFS (37.9 *vs*. 3.9 months; *P*=0.0005) and OS (68.3 *vs*. 12.0 months; *P*=0.0005). Patients who achieved complete response had a better median PFS (71.1 *vs*. 6.3 months; *P*<0.0001) and OS (110.3 *vs*. 18.9 months; *P*<0.0001) than those in partial response. Patients who achieved complete response after one line of ST had the most favorable median PFS (88.5 months) and OS (117.2 months). Post-ASCT survival outcomes of patients with refractory or early relapsed DLBCL appeared reasonable and were particularly favorable in those who required only one line of ST to achieve complete response before ASCT, highlighting the role of this procedure in select patients with chemosensitive disease.

Introduction

Diffuse large B-cell lymphoma (DLBCL), the most common type of aggressive non-Hodgkin lymphoma, constitutes approximately 30% of newly diagnosed cases of non-Hodgkin lymphoma each year in the United States.[1,2] Approximately 30-40% of patients encounter relapsed or refractory disease after frontline immunochemotherapy, and their survival outcomes are generally unfavorable – particularly in those with refractory disease or an early relapse occurring within 12 months of initial diagnosis (or frontline treatment), as reported by multiple studies including those by the Center for International Blood and Marrow Transplant Research (CIBMTR), the Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence, as well as the CORAL study.[3-14] To improve outcomes of such patients, three phase III randomized clinical trials were conducted in patients with refractory disease or an early relapse within 12 months of treatment completion, comparing chimeric antigen receptor T-cell (CAR-T) products (axicabtagene ciloleucel in ZUMA-7, tisagenlecleucel in BELINDA, lisocabtagene maraleucel in TRANSFORM) to the then standard-of-care salvage chemotherapy (ST) followed by high-dose chemotherapy (HDT) and autologous stem cell transplant (ASCT), which established axicabtagene ciloleucel and lisocabtagene maraleucel as the

new standard of care in the second-line setting.[15-17]
However, there are still significant challenges and barriers to timely delivery of CAR-T therapy in routine clinical practice. CAR-T therapy, to date, is mainly offered in major referral centers, and patients often need to travel long distances for evaluation for such therapy. Patients also need to spend weeks to months for eligibility and fitness assessment, insurance approval, CAR-T manufacturing, and other logistical planning.[18,19] A substantial number of patients experience symptomatic, life-threatening progressive disease before receiving CAR-T therapy and often require urgent systemic chemotherapy in the form of a salvage or bridging therapy.[19] Moreover, clinical activities of CAR-T therapy remain modest in the second-line setting, with the median event-free survival being only 8.3 months with axicabtagene ciloleucel in ZUMA-7 and 10.1 months with lisocabtagene maraleucel in TRANSFORM; the majority of patients treated with CAR-T in both studies experienced a relapse.[15,17] Furthermore, CAR-T therapy is associated with significant morbidities such as cytokine release syndrome, neurotoxicity, and cytopenia, and its long-term complications remain a major concern.[19] Given the challenges and barriers as well as the modest clinical activities of CAR-T therapy, there is a need to explore alternative strategies and identify patients who can truly benefit from HDT and ASCT. It is well understood that ASCT (or rescue) enables the use of HDT, in patients with proven chemosensitive disease, to eradicate residual lymphoma cells that have evaded ST.[20] Autologous CAR-T therapy utilizes genetically modified patient's T cells, directed against CD19 antigen on lymphoma cells, for its therapeutic effect.[15,17] Accordingly, fit patients with chemosensitive disease can benefit from consolidation with HDT and ASCT, unlike those with chemoresistant disease.[11,21] We, therefore, hypothesized that HDT and ASCT would be beneficial and preferable in patients with proven chemosensitive disease after one line of ST, and those with a later relapse 6-12 months after completing frontline immunochemotherapy. To verify this hypothesis, we conducted a retrospective study of patients with refractory disease or relapse within 12 months of completing frontline immunochemotherapy, using information from the Mayo Clinic and the University of Iowa lymphoma and transplant databases.

Methods

Patients

The institutional review boards at the Mayo Clinic and the University of Iowa approved this study. Data were abstracted on consecutive adult patients who underwent ASCT for DLBCL between July 2000 and December 2017 at the Mayo Clinic or between April 2003 and April 2020 at the University of Iowa. Clinical, pathological, molecular characteristics, cell of origin by Hans algorithm, as well as treatment course, clinical response to treatment (as determined by the treating physician), and clinical outcome data were extracted by chart reviews.
For this study, eligible patients were those who were treated with frontline R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone) or R-CHOP-like immunochemotherapy, had refractory disease (i.e., disease progression during frontline immunochemotherapy or persistent disease after completion of frontline therapy) or an early relapse occurring within 12 months of completing frontline immunochemotherapy, and underwent ST and ASCT. Patients whose response to ST was assessed by positron emission tomography and computed tomography scan and achieved a complete response (CR) or partial response (PR), as determined by treating physicians, were included. DLBCL was classified as per hematopathologists in the Mayo Clinic and the University of Iowa. Patients with *MYC* and *BCL2* and/or *BCL6* rearrangements (i.e., double-hit or triple-hit lymphoma) and transformed indolent lymphoma at diagnosis were also included, unless previously treated with immunochemotherapy. Patients who did not receive frontline rituximab and those who underwent hematopoietic stem cell transplant in the frontline (after achieving complete remission to frontline immunochemotherapy) were excluded.

Statistical analysis

Descriptive statistics are used to report baseline characteristics, treatment information, and response status. The reverse Kaplan-Meier method was used to estimate median follow-up time.[22,23] Duration of response (DOR) was defined as time from initial response after ASCT to disease progression, relapse, or death. Post-ASCT progression-free survival (PFS) was defined as time from ASCT until progression, relapse, or death from any cause. Post-ASCT overall survival (OS) was defined as time from ASCT to death from any cause. Post-ASCT PFS and OS were plotted using the Kaplan-Meier method. Log-rank tests and Cox proportional hazards models were used to evaluate the impact of clinico-pathological characteristics, treatment variables, and response status on PFS and OS. *P* values <0.05 were considered statistically significant. Cumulative incidences of relapse and non-relapse mortality as well as causes of death were analyzed with competing risk models.[24] Causes of death were categorized as a result of lymphoma progression, as a result of treatment-related toxicities, non-lymphoma-related causes (other causes), and unknown causes. Statistical analyses were performed in JMP v16 and XLSTAT v2021.2.

Results

Clinicopathological characteristics of the study population and treatment

A total of 230 eligible patients were included in the study (*Online Supplementary Figure S1*). The baseline charac-

teristics of patients at initial diagnosis are summarized in *Online Supplementary Table S1*. Clinical characteristics at relapse are described in Table 1. Of the total 230 patients, 157 (68%) had refractory disease or relapsed within 6 months of completing frontline therapy and 73 (32%) had a relapse between 6 to 12 months after frontline therapy. The median age at relapse/ST was 60 years (range, 19-78), and 107 (47%) patients were aged >60 years. The Eastern Cooperative Oncology Group performance status was ≤1 in 181 (97%) patients. Fifty-six patients (39%) had an elevated level of lactate dehydrogenase, 21 (12%) had involvement of more than one extranodal site, and 109 (61%) had advanced stage disease. Treatment patterns and responses to therapy are presented in *Online Supplementary Table S2*. First-line ST consisted of platinum or high-dose cytarabine-containing chemotherapy in 201 (87%) cases. A median of one line (range, 1-3) of ST was required. The number of lines of ST was one in 178 (77%) and more than one in 52 (23%) patients. Response before ASCT was CR in 106 (46%) and PR in 124 (54%) patients. The median age at ASCT was 60 years (range, 19-78). A BEAM (carmustine, etoposide, cytarabine, and melphalan) conditioning regimen was used in 213 (93%) patients. Following ASCT, 123 (56%) patients achieved CR, and 18 (8%) patients received post-ASCT consolidative radiation therapy.

Outcomes following autologous stem cell transplantation

The median follow-up after ASCT was 89.4 months (95% confidence interval [95% CI]: 73.5-99.2), and post-ASCT outcomes at 12 months, 24 months, and 60 months are summarized in *Online Supplementary Table S3*. The median PFS and OS after ASCT were 16.1 months (95% CI: 9.3-43.3) and 43.3 months (95% CI: 24.2-75.5), respectively. The 24-month PFS and OS rates were 47% and 57%, respectively (Figure 1A, B). The median DOR in patients who achieved CR or PR after ASCT was 96.4 months (95% CI: 61.6-160.6), with a 24-month DOR rate of 72%. The cumulative incidences of post-ASCT relapse and non-relapse mortality rate were 43.4% and 3.9%, respectively, at 12 months (Figure 1C). One hundred eighteen patients had a relapse (see *Online Supplementary Table S4* for their subsequent management), with a median post-relapse OS of 6.0 months (95% CI: 3.8-8.3) (*Online Supplementary Figure S2*), and 136 died during the follow-up (see *Online Supplementary Table S5* for causes of death). Lymphoma was the primary cause of death after ASCT, with a 12-month estimated death rate of 28.5% due to lymphoma, 2.1% due to therapies, 1.3% due to other causes, and 0.9% of unknown causes (Figure 1D).

Outcomes according to clinicopathological characteristics

No statistically significant differences in PFS and OS were seen based on age at relapse, sex, Eastern Cooperative Oncology Group performance status, serum lactate dehydrogenase level, extranodal site involvement, and stage at relapse (Table 2). Time to first relapse/refractory status (relapse between 6-12 months *vs*. refractory or relapse <6 months after frontline therapy) was not associated with a significant difference in PFS (median PFS 29.6 *vs*. 10.1 months; *P*=0.47) (Figure 2A, Table 2), but there was a trend for improvement in OS (median OS 88.5 *vs*. 28.0 months; *P*=0.07) (Figure 2B, Table 2). Patients who required one line of ST, compared to those who required more than one line of ST, had significantly better PFS (median PFS 37.9 *vs*. 3.9 months; *P*=0.0005) (Figure 2C, Table 2) and OS (median OS 68.3 *vs*. 12.0 months; *P*=0.0005) (Figure 2D, Table 2). In addition, patients who achieved a CR prior to ASCT, compared to those who achieved a PR, had significantly better PFS (median PFS 71.1 *vs*. 6.3 months; *P*<0.0001) (Figure 3A, Table 2) and OS (median OS 110.3 *vs*. 18.9 months; *P*<0.0001) (Figure 3B, Table 2). Patients who achieved CR after one line of ST had the most favorable PFS and OS, with median PFS of 88.5 *vs*. 9.1 *vs*. 12.0 *vs*. 3.2 months (*P*<0.0001) and median OS of 117.2 *vs*. 28.8 *vs*. 32.5 *vs*. 7.1 months (*P*<0.0001) in cases with CR after one line of ST *vs*. PR after one line of ST *vs*. CR after more than one line of ST *vs*. PR after more than one line of ST (Figure 3C,

Table 1. Characteristics of patients with relapsed or refractory diffuse large B-cell lymphoma at relapse/salvage therapy.

	N=230	%
Time to relapse (from completion of frontline therapy)		
Refractory/relapse <6 months†	157	68
Relapse between 6 and 12 months	73	32
Age at relapse in years		
≤60	123	53
>60	107	47
Age at ASCT in years		
≤60	117	51
>60	113	49
ECOG PS scale		
≤1	181	97
>1	5	3
Missing	44	-
Lactate dehydrogenase		
Normal	87	61
Elevated	56	39
Missing	87	-
Extranodal sites		
≤1	161	88
>1	21	12
Missing	48	-
Ann Arbor stage		
I-II	70	39
III-IV	109	61
Missing	51	-

†Primary refractory diffuse large B-cell lymphoma (N=106) and relapsed in <6 months (N=51). ASCT: autologous stem cell transplant; ECOG PS: Eastern Cooperative Oncology Group performance status.

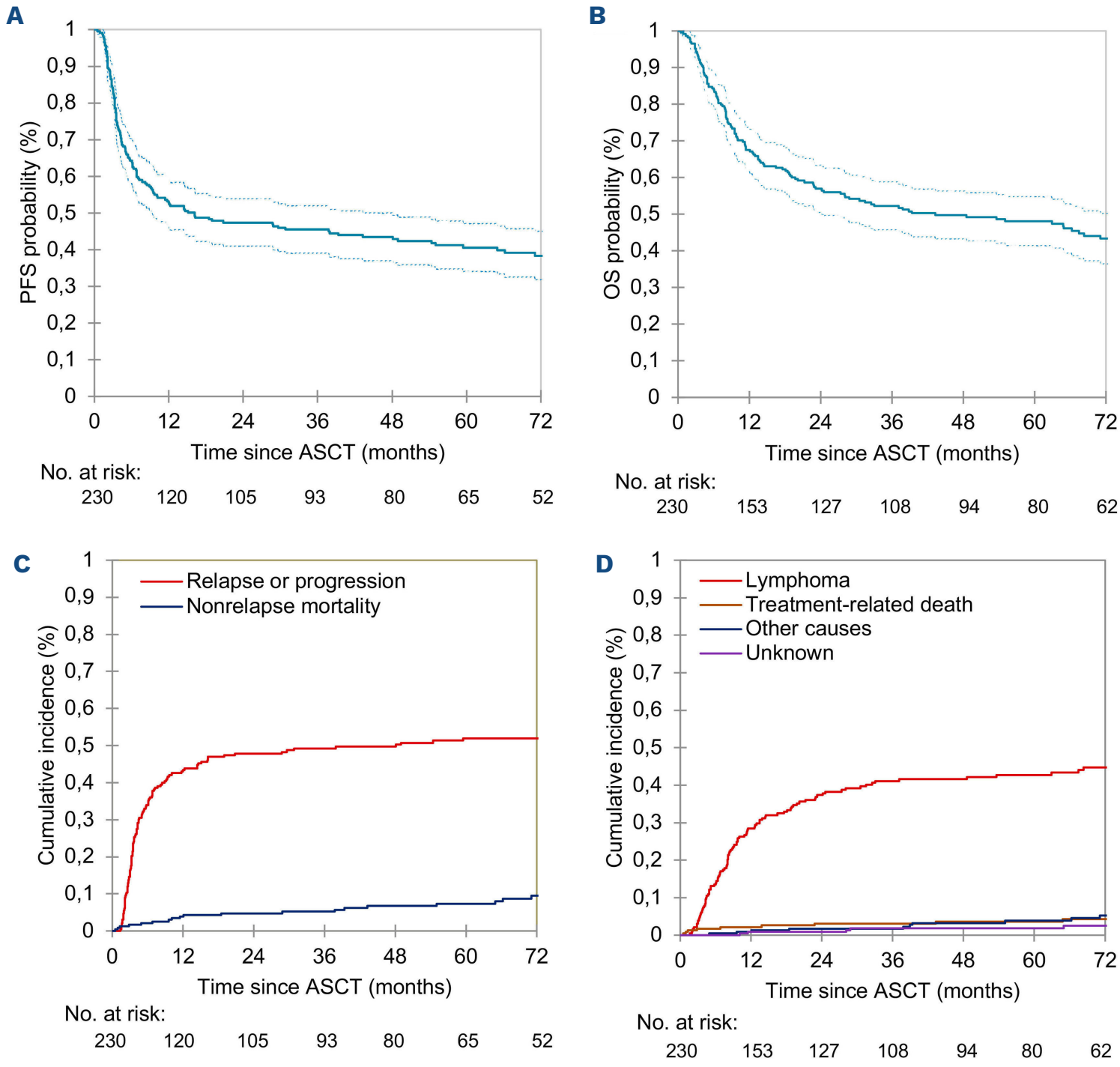

Figure 1. Outcomes after autologous stem cell transplantation in patients with refractory or early relapsed diffuse large B-cell lymphoma. (A) Progression-free survival. (B) Overall survival. (C) Cumulative incidence of relapse and non-relapse mortality. (D) Cumulative incidence of deaths divided by cause. PFS: progression-free survival; ASCT: autologous stem cell transplant; OS: overall survival.

D, Table 2). In multivariate Cox regression models adjusted for age at ASCT and sex, lines of ST and response to ST before ASCT remained prognostic for PFS (1 line of ST: hazard ratio [HR]=0.53, 95% CI: 0.36-0.77; *P*=0.0008 and CR: HR=0.49, 95% CI: 0.35-0.69; *P*<0.0001) and OS (1 line of ST: HR=0.51, 95% CI: 0.35-0.74; *P*=0.0005 and CR: HR=0.46, 95% CI: 0.32-0.66; *P*<0.0001). Additionally, in this multivariate model, time to first relapse/refractory status (relapse between 6-12 months *vs*. refractory or relapse <6 months after frontline therapy) showed a trend for improvement in PFS (HR=0.83, 95% CI: 0.59-1.18; *P*=0.31) and a statistically significant improvement in OS (HR=0.67, 95% CI: 0.46-0.98; *P*=0.04) (*Online Supplementary Table S6*).

Note that patients with a *MYC* rearrangement, compared to those without, had significantly inferior PFS (median PFS 3.1 *vs*. 43.3 months; *P*=0.0001) and OS (median OS 6.2 *vs*. 67.4 months; *P*<0.0001) (Table 2, *Online Supplementary Figure S3*).

Discussion

The new standard of care in fit patients with primary refractory or early relapsed DLBCL occurring within 12 months of completing frontline immunochemotherapy is CAR-T therapy with axicabtagene ciloleucel or lisocabtagene maraleucel according to the results of the contemporary ZUMA-7 and TRANSFORM studies.[15,17] Our study of such patients, treated with ST and ASCT, documented reasonable survival outcomes with a median PFS of 16.1 months and the 24-month PFS of 47%. The results from our study are in keeping with those of the CIBMTR that

Table 2. Survival after autologous stem cell transplantation by clinicopathological characteristics and response status.

	Median PFS in months (95% CI)	24-month PFS, % (95% CI)	*P*	Median OS in months (95% CI)	24-month OS, % (95% CI)	*P*
Time to relapse[†]			0.47			0.07
<6 months[‡], N=157	10.1 (5.8-43.3)	45 (38-53)		28.0 (14.5-67.4)	48 (40-55)	
6–12 months, N=73	29.6 (12.1-64.9)	52 (40-63)		88.5 (37.8-134.8)	67 (56-78)	
Age at relapse in years			0.33			0.37
≤60, N=123	12.2 (6.7-110.3)	47 (38-56)		48.5 (18.9-143.0)	57 (48-66)	
>60, N=107	16.2 (8.4-48.1)	47 (38-57)		39.4 (21.2-71.1)	57 (47-66)	
Sex			0.08			0.34
Male, N=149	14.6 (8.9-37.9)	46 (38-54)		43.3 (27.3-71.1)	59 (51-67)	
Female, N=81	16.2 (6.1-NR)	49 (38-60)		55.0 (14.5-NR)	53 (42-64)	
ECOG PS score			0.80			0.52
≤1, N=181	18.5 (10.1-54.4)	49 (41-56)		62.9 (28.1-88.5)	59 (52-66)	
>1, N=5	6.3 (1.6-NR)	40 (0-83)		8.1 (2.1-NR)	40 (0-83)	
Lactate dehydrogenase			0.17			0.07
Normal, N=87	48.9 (10.1-71.1)	55 (45-66)		68.3 (55.0-110.3)	70 (60-80)	
Elevated, N=56	7.7 (3.7-37.8)	41 (28-54)		20.5 (9.1-43.3)	48 (35-61)	
Extranodal sites			0.50			0.32
≤1, N=161	28.7 (11.7-59.5)	50 (43-58)		64.8 (28.8-95.5)	60 (53-68)	
>1, N=21	8.2 (3.1-NR)	38 (17-59)		32.5 (7.9-110.3)	52 (31-74)	
Stage at relapse			0.17			0.15
I-II, N=70	55.0 (14.4-95.5)	57 (45-69)		71.1 (31.5-145.2)	70 (59-81)	
III-IV, N=109	12.0 (5.4-48.1)	43 (34-52)		37.1 (13.9-75.5)	52 (43-62)	
MYC rearrangement			0.0001			<0.0001
Present, N=9	3.1 (1.9-7.7)	13 (0-35)		6.2 (3.4-13.8)	13 (0-35)	
Absent, N=53	43.3 (8.9-NR)	54 (41-68)		67.4 (22.9-NR)	64 (50-77)	
Lines of ST			0.0005			0.0005
1, N=178	37.9 (14.4-84.0)	52 (45-60)		68.3 (33.0-117.2)	63 (56-70)	
>1, N=52	3.9 (3.0-9.3)	31 (18-43)		12.0 (6.8-23.2)	37 (23-50)	
Response to ST			<0.0001			<0.0001
CR, N=106	71.1 (29.6-118.6)	62 (53-71)		110.3 (64.9-NR)	68 (59-77)	
PR, N=124	6.3 (4.2-9.7)	35 (27-43)		18.9 (9.1-31.5)	47 (38-56)	
Lines of ST and response status			<0.0001			<0.0001
CR after 1 line of ST, N=90	88.5 (43.3-NR)	65 (55-75)		117.2 (75.5-NR)	70 (61-80)	
PR after 1 line of ST, N=88	9.1 (5.4-16.2)	39 (29-49)		28.8 (13.4-64.8)	55 (45-66)	
CR after >1 line of ST, N=16	12.0 (3.5-163.8)	44 (19-68)		32.5 (19.1-163.8)	56 (32-81)	
PR after >1 line of ST, N=36	3.2 (2.8-5.4)	25 (11-39)		7.1 (4.7-14.4)	28 (13-43)	

[†]Time to relapse from completion of first-line therapy. [‡]This category included patients with primary refractory disease. PFS: progression-free survival; OS: overall survival; 95% CI: 95% confidence interval; NR: not reached; ECOG PS: Eastern Cooperative Oncology Group performance status; ST: salvage chemotherapy; CR: complete response; PR: partial response.

reported a 3-year post-ASCT PFS rate of 44% despite early immunochemotherapy failure within 12 months of initial diagnosis and another study from the CIBMTR, in patients with primary refractory DLBCL, which reported a 3-year post-ASCT PFS rate of 46.8%.[10,25] The median DOR in our patients who achieved CR or PR after ASCT was 96.4 months (24-month DOR, 72%). These results indicate that patients with chemosensitive relapsed or refractory disease, despite having primary refractory disease to frontline immunochemotherapy or an early relapse, can expect durable disease control with ASCT consolidation. These findings are further supported by durable responses seen in patients assigned to the standard-of-care group of the ZUMA-7 and TRANSFORM studies, with the former resulting in a median DOR of 8.9 months in patients who had a response (i.e., CR or PR) and the latter reporting a median DOR of 14.5 months (12-month DOR rate, 54.7%) in patients achieving CR.[15,17] More favorable survival outcomes were observed in our patients who required only one line of ST and those who achieved CR, with a median PFS of 37.9 months (24-month

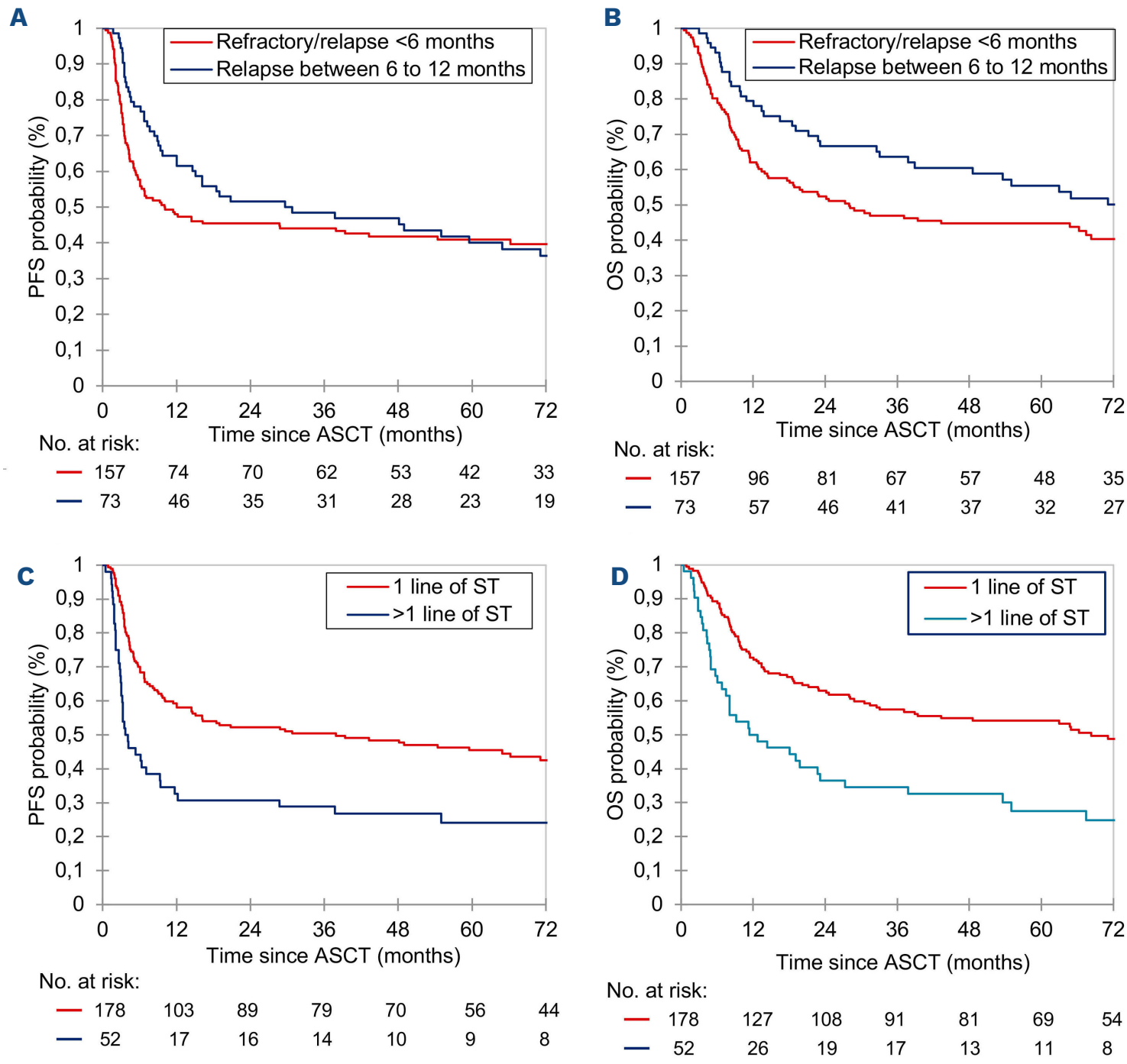

Figure 2. Post-autologous stem cell transplant outcomes according to refractory and/or time to relapse status and line of salvage chemotherapy. (A) Progression-free survival and (B) overall survival by refractory and/or time to relapse status. (C) Progression-free survival and (D) overall survival by line of salvage chemotherapy. PFS: progression-free survival; ASCT: autologous stem cell transplant; ST: salvage chemotherapy; OS: overall survival.

PFS, 52%) and 71.1 months (24-month PFS, 62%), respectively. Most importantly, survival outcomes were excellent in patients who had only one line of ST and resulted in CR, with their median PFS being 88.5 months (24-month PFS, 65%). These findings imply that HDT, followed by ASCT rescue, confers complete eradication of lymphoma cells that are biologically sensitive to chemotherapy.

In patients who achieved PR after one line of ST, our study showed that the median PFS was 9.1 months, with the 24-month PFS rate being 39%. The CIBMTR study found a 5-year post-ASCT PFS rate of 41% in patients with failure of early frontline immunochemotherapy (i.e. primary refractory disease or relapse within 12 months of diagnosis).[12] A similar result was documented in the MD Anderson Cancer Center with a 5-year post-ASCT PFS rate of 40% in patients with relapsed or refractory DLBCL who had residual disease before ASCT.[26] Variations in survival rates among these studies are due, in part, to different study populations, study eras, patterns of relapse, and management approaches.[12,26] In addition, the definition of PR by treating physicians is subjective, and varies depending on imaging modality (i.e., computed tomography alone or with positron emission tomography).[27] Nevertheless, despite achieving only PR, their survival outcomes after ASCT are reasonable, with a long-term remission rate of ~40%, supporting the role of ASCT consolidation.[12,26] In the CAR-T therapy era, the role of ASCT consolidation in patients achieving PR to ST was reported by the CIBMTR.[28] In this study, the efficacy of ASCT was compared with that of axicabtagene ciloleucel in a total of 411 patients of whom 266 undergoing ASCT consolidation and 145 receiving axicabtagene ciloleucel.[28] The study found that ASCT consolidation, compared to

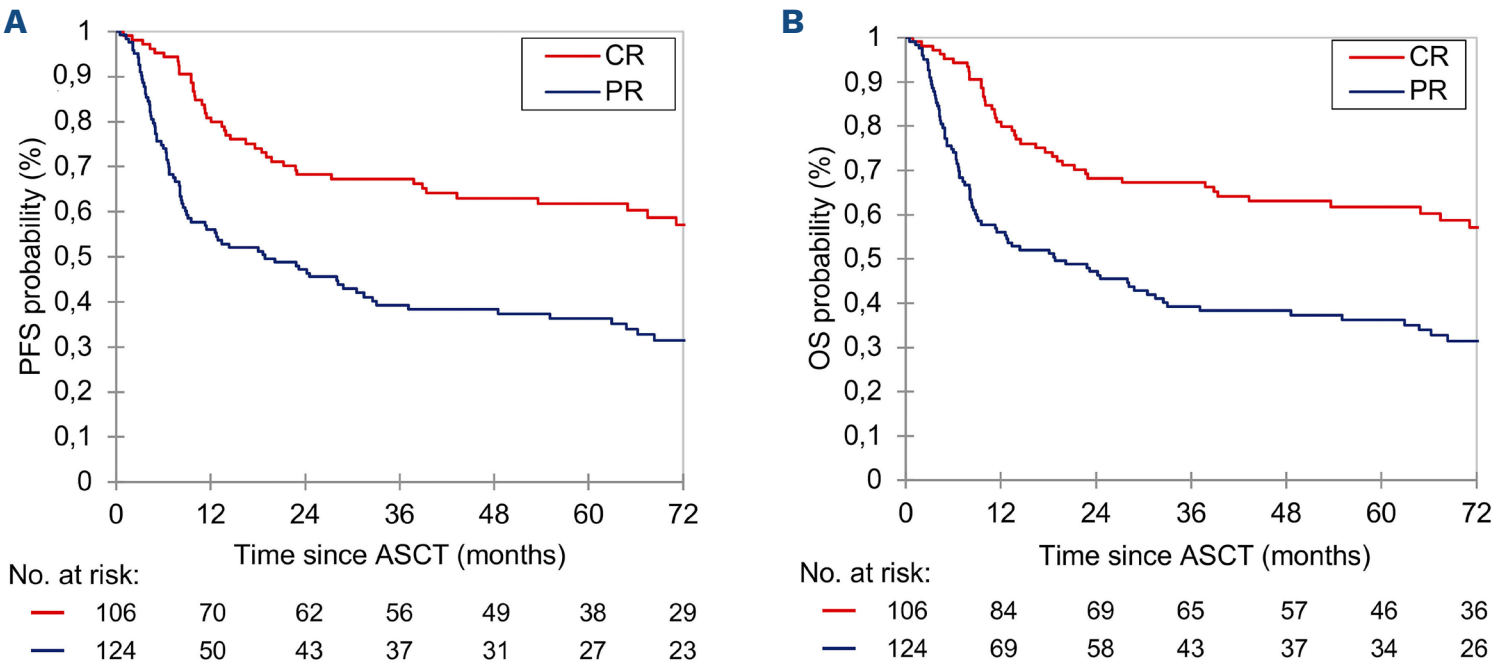

Figure 3. Post-autologous stem cell transplant outcomes according to line of slavage chemotherapy and response status. (A) Progression-free survival and (B) overall survival by response status. (C) Progression-free survival and (D) overall survival by line of salvage therapy and response status. PFS: progression-free survival; OS: overall survival; ASCT: autologous stem cell transplant; CR: complete response; PR: partial response; ST: salvage chemotherapy.

axicabtagene ciloleucel, was associated with a lower rate of relapse/progression (2-year rate, 40% *vs*. 53%; *P*=0.05), a trend for superior PFS (2-year rate, 52% *vs*. 42%; *P*=0.1), and a superior OS rate (2-year rate, 69% *vs*. 47%; *P*=0.004).[28] The caveat regarding this study was that the median line of therapy was higher in patients receiving axicabtagene ciloleucel, and the difference was no longer seen when the analysis was done in patients who received two or fewer lines of therapy (1-year PFS, 59% in the ASCT group *vs*. 65% in the axicabtagene ciloleucel group; *P*=0.5).[28]

There is no consensus among lymphoma clinicians when defining early treatment failure. Most historical studies, such as the CIBMTR, Molecular Epidemiology Resource, and CORAL studies, identified patients with refractory disease or relapse within 12 months of initial diagnosis as having an unfavorable risk.[7,10,12,13] In contrast, the three randomized clinical trials (ZUMA-7, TRANSFORM, and BELINDA) and the NCIC-CTG LY.12 study defined patients with refractory disease or relapse within 12 months of completing frontline therapy as high risk.[15–17,29] Consequently, selection of the optimal treatment strategy becomes challenging for patients who relapse between 6 to 12 months after completing frontline therapy.[19] It is noteworthy that these patients achieve a remission lasting at least 6 months after completing frontline immunochemotherapy, indicating chemosensitive biology, and are more likely to respond to ST and be able to proceed with HDT and ASCT.[7] In our study, patients who relapsed between 6 to 12 months

after frontline therapy, compared to those with refractory or relapse within 6 months, did not have a statistically significant improvement in PFS after ASCT (*P*=0.47), although PFS was numerically better in the former (median PFS 29.6 *vs*. 10.1 months). Additionally, there was a trend for improvement in OS in the univariate analysis (*P*=0.07), and a statistically significant improvement in OS, after adjustment for age at ASCT and sex, in the multivariate model (*P*=0.04). Therefore, after establishing the chemosensitivity of the disease, careful consideration between HDT followed by ASCT and CAR-T is warranted in such patients due to their favorable survival rate after ASCT (24-month PFS, 52%), although the findings from our study population, receiving care at the Mayo Clinic and the University of Iowa, may not be broadly generalizable. There remain logistical and financial barriers that prevent timely access to CAR-T therapy.[30] Patients often need to wait weeks to months for frailty and fitness assessments, overcoming logistical and financial barriers, as well as CAR-T manufacturing (although a significantly shorter wait time is anticipated with the use of allogeneic CAR-T products).[16,30,31] Moreover, patients with relapsed or progressive disease are often symptomatic requiring immediate intervention. Thus, it is reasonable to initiate ST, especially in resource-limited settings. Those who achieve PR can consider proceeding with ASCT based on reasonable survival outcomes, and this practice is supported by the report from the CIBMTR favoring ASCT consolidation, as discussed earlier.[12,28] For those achieving CR, ASCT consolidation seems favored over CAR-T in patients with early treatment failure, as per the recent study from the CIBMTR that reported a lower 2-year relapse rate (22.8% *vs*. 45.9%; *P*<0.001) and a superior 2-year PFS rate (70.9% *vs*. 48.3%; *P*<0.001), although it is difficult to draw definitive conclusions due to its retrospective study design.[32] Similar survival outcomes were reported for patients who received CAR-T therapy while in CR, with a 2-year PFS rate of 44% in the MD Anderson Cancer Center cohort and a 1-year PFS rate of 59.6% in a study from eight academic centers in the USA.[33,34] Notably, patients relapsing or progressing after CAR-T therapy have unfavorable outcomes due to the limited availability and efficacy of subsequent ST.[19] After CAR-T therapy, cytopenias and patients' intolerance of intensified therapy and the potential of stem cell mobilization failure make ASCT less feasible.[19,35] Although ASCT consolidation is generally favored in patients with established chemosensitive disease, post-ASCT outcomes of those with a *MYC* rearrangement are poor, despite them having chemosensitive disease, with a median PFS of only 3.1 months; CAR-T therapy may be preferred in such patients.[36,37]

It is, however, worth noting that only about half of patients with relapsed or refractory DLBCL treated with intensified therapy are able to proceed with ASCT consolidation, although higher response rates can be expected with the incorporation of novel therapeutic agents.[7,13,15,17,29,38,39] In the CORAL study, ~63% of patients achieved CR or PR to ST, namely RICE (rituximab, ifosfamide, carboplatin, and etoposide) and R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin), and ~53% of patients subsequently proceeded with ASCT. In NCIC-CTG LY.12, ~45% of patients had responses to the ST regimens GDP (gemcitabine, dexamethasone, and cisplatin) and DHAP.[7,29] The real-world analysis of the Molecular Epidemiology Resource database found that 40% of patients treated aggressively with second-line ST for relapsed or refractory DLBCL were able to proceed with ASCT.[13] In participants of the ZUMA-7 and TRANSFORM trials, who were then randomized to the ST group, ASCT consolidation was done in 38% and 46% of patients, respectively.[15,17] However, response to ST can be improved with the incorporation of novel therapy; notably, polatuzumab vedotin added to RICE produced an overall response rate (i.e., CR or PR) of 92%, with an acceptable toxicity profile, in a multicenter phase II study.[39] Response rates could also improve with incorporation of bispecific CD20xCD3 monoclonal antibodies to ST,[40,41] and these strategies are being evaluated by currently ongoing clinical studies such as those investigating glofitamab plus RICE (NCT05364424) and epcoritamab plus GDP (NCT05852717). The strengths of our study include systematic review of a large number of patients with relapsed or refractory DLBCL following failure of frontline R-CHOP or R-CHOP-like immunochemotherapy who then underwent ASCT after the first, early relapse or in a refractory state, with the availability of long-term follow-up data. However, our study has limitations due to its retrospective study design with potential selection bias, geographical bias with limited generalizability, and lack of centralized histopathology review, as well as some missing information and a long study period that spans over two decades with potential heterogeneity in management approaches.

In conclusion, survival outcomes after ASCT are favorable in at least a subset of patients with primary refractory or early relapsed DLBCL. Post-ASCT survival outcomes are more favorable in patients who require only one line of ST and those who achieved CR to ST. Furthermore, survival outcomes after ASCT are excellent in patients achieving CR after one line of ST. In patients who relapse between 6 to 12 months after completing frontline therapy, the choice between CAR-T therapy and ST followed by HDT and ASCT should be considered carefully. These data support the role of ST and ASCT consolidation as a second-line treatment strategy in select patients with primary refractory or early relapsed DLBCL in an appropriate clinical context.

Disclosures

No conflicts of interest to disclose.

Contributions

AMT, YW, and PBJ conceived and designed the study and

prepared the first draft of the manuscript. AMT and SM collected and assembled data. All authors analyzed and interpreted data, reviewed and revised the manuscript, and approved the final version.

Data-sharing statement

This article includes the data supporting the findings and interpretation of the results. Please contact the corresponding authors for additional data.

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