Outcomes of patients with relapsed or refractory primary mediastinal B-cell lymphoma after frontline DA-EPOCH-R

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Abstract

Most patients diagnosed with primary mediastinal B-cell lymphoma (PMBCL) achieve cure following standard-of-care therapy with frontline DA-EPOCH-R (dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, rituximab). However, treatment strategies following relapse after DA-EPOCH-R are not well defined. We, therefore, performed a retrospective review of PMBCL patients with relapsed/refractory (R/R) disease after frontline DA-EPOCH-R to obtain better insight into outcomes with salvage therapy and autologous stem cell transplant (SCT). Our cohort consisted of 107 patients with R/R PMBCL. Ninety patients qualified for the intention-to-treat salvage therapy analysis. With a median follow up of 48.9 months in the salvage therapy analysis, the median progression-free survival was 5.4 months (95% confidence interval [95% CI]: 2.3 months-not reached) with a 5-year overall survival rate of 78% (95% CI: 69-88). Compared to relapsed patients (relapsing >6 months after frontline DA-EPOCH-R, N=23), refractory patients (relapsing <6 months after frontline DA-EPOCH-R, N=67) had an inferior overall response rate (48% *vs*. 83%), complete remission rate (19% *vs*. 44%), and 2-year progression-free survival rate (30% *vs*. 69%) with initial salvage therapy. Forty-eight patients (53%) underwent autologous SCT after salvage therapy with estimated 5-year progression-free and overall survival rates of 85% (95% CI: 75-96) and 88% (95% CI: 79-99), respectively. There were no relapses among 29 patients in complete remission prior to autologous SCT. In conclusion, this analysis is the largest review of R/R PMBCL to date and demonstrates unfavorable outcomes for patients with refractory disease after frontline DA-EPOCH-R chemotherapy. Patients able to undergo autologous SCT, especially those in complete remission prior to the transplant, had excellent outcomes.

Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is a subtype of aggressive non-Hodgkin lymphoma (NHL) accounting for 2-3% of all NHL cases.[1] Most patients with newly diagnosed PMBCL have an excellent prognosis after frontline chemoimmunotherapy consisting of dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, rituximab (DA-EPOCH-R) with several series noting 5-year progression-free survival (PFS) rates above 90% without the need for radiation therapy.[2,3] The minority of PMBCL patients who progress after or are refractory to frontline chemoimmunotherapy typically have poor responses to salvage chemotherapy followed by autologous stem cell transplant (SCT), although existing data are limited by the small numbers of patients who received DA-EPOCH-R as initial therapy.[4-7]

Novel salvage treatment strategies incorporating brentuximab vedotin (BV) in combination with checkpoint inhibitors have shown promise, but existing data are limited to early phase trials outside of the initial salvage setting.[7-9] Additionally, chimeric antigen receptor (CAR) T-cell therapy is now approved as second-line therapy for PMBCL patients who relapse within 1 year of completion of frontline chemoimmunother-

apy.[7,10,11] Thus, with the advent of novel salvage treatment and approval of CAR T-cell therapy at initial relapse, it is of paramount importance to consider real-world outcomes of these modalities when choosing an optimal treatment approach at initial relapse. Here, we aimed to evaluate the utility of salvage therapy and autologous SCT in patients with R/R PMBCL following treatment with DA-EPOCH-R.

Methods

We retrospectively analyzed data from ten US academic medical centers of patients with R/R PMBCL who received salvage therapy and/or underwent autologous SCT between 2011 and 2023. Institutional review board approval was obtained at each site. The study was conducted in accordance with the Declaration of Helsinki. Patients with a confirmed histological diagnosis of PMBCL relapsing after frontline therapy with DA-EPOCH-R were eligible for inclusion. Baseline demographic, clinical, laboratory, pathology, and outcome data were extracted by chart review and included in a study-specific data collection spreadsheet. Investigators at each center were responsible for assessing diagnostic criteria, stage, and response. Responses were assessed by individual investigators utilizing Lugano criteria and institutional standard imaging modalities.

Statistical analysis

The patients' characteristics were summarized using frequencies and percentages for categorical variables and medians and ranges for continuous variables.

Overall response rate (ORR) was defined as the percentage of patients in a particular cohort who achieved either a partial response (PR) or complete response (CR) to treatment, while CR rate was defined as the percentage of patients in a particular cohort who achieved a CR to treatment. The exact binomial method was used to construct corresponding 95% confidence intervals (95% CI).

Overall survival (OS) was defined as the time from the treatment intervention of interest (either initiation of salvage therapy or autologous SCT) to date of last follow-up or death, while PFS was defined as the time from treatment of interest to date of last follow-up or disease progression. The Kaplan-Meier method was used to estimate median OS and PFS as well as 2- and 5-year OS and PFS rates. The log-rank test was used to test for groupwise differences in survival curves. The median follow-up was calculated using the reverse Kaplan-Meier method.

Univariate Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals to assess the relationship between variables of interest at relapse such as disease stage, presence of extranodal disease, lactate dehydrogenase (LDH) levels (≥ upper limit of normal) at relapse, and time to relapse following completion of frontline therapy (before or after 6 months) and time-to-event outcomes. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals to assess the relationship between these variables and CR to the first salvage regimen. Variables returning a *P* value ≤0.05 in univariate models were eligible for inclusion in multivariate modeling. Statistical analyses were performed using R v4.3.0.

Results

The median age of the 107 patients analyzed was 32 years (range, 18-68) and the majority (57%) of the patients were female. At the time of relapse, 65% of patients had stage I/II disease, 48% had an elevated LDH, and 73% had a biopsy-proven relapse. Additional baseline characteristics are presented in Table 1. Two patients received one cycle of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or rituximab, cyclophosphamide, etoposide, vincristine, and prednisone (R-CEOP) before transitioning to DA-EPOCH-R for the remaining cycles. One patient received five cycles of DA-EPOCH-R then transitioned

Table 1. Baseline characteristics of the 107 study patients.

Characteristic	Values
Sex, N (%) Male Female	107 46 (43.0) 61 (57.0)
Age, years, median (range)	32 (18-68)
ECOG score, N 0-1 2 3+	85 83 2 0
Time to relapse, N (%) ≥6 months > 6 months	107 81 (75.7) 26 (24.3)
Frontline radiation, N (%) Yes No	107 8 (7.5) 99 (92.5)
Stage at relapse, N (%) I II III IV	93 21 (22.6) 39 (41.9) 4 (4.3) 29 (31.2)
LDH at relapse, N (%) ≥ ULN < ULN	75 36 (48.0) 39 (52.0)
IPI at relapse, N (%) 0-1 2 3 4+	73 52 (71.2) 13 (17.8) 8 (11.0) 0 (0)
Extranodal disease at relapse, N (%) Yes No	100 45 (45.0) 55 (55.0)

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ULN: upper limit of normal; IPI: International Prognostic Index.

to one cycle of R-CHOP due to intolerance. Eight patients (7.5%) received radiation therapy after frontline DA-EPOCH-R treatment as consolidation prior to relapse. After frontline treatment with DA-EPOCH-R, 62% of patients included in this analysis did not achieve a CR. In total, 76% of patients experienced relapse within 6 months of initial treatment with DA-EPOCH-R and were considered refractory. At a median follow-up of 48.9 months (interquartile range [IQR], 18.7-74.8), the median OS was not reached. Estimated 2- and 5-year OS rates were 87% (95% CI: 80-94) and 78% (95% CI: 70-88), respectively. Of the 19 deaths, 17 were due to progressive disease and two were due to graft-*versus*-host disease occurring after allogeneic SCT.

Salvage therapy analysis

Ninety (84%) patients were included in the salvage therapy analysis with 17 being excluded because of the presence of central nervous system disease on initial relapse (N=8), receipt of CAR T-cell therapy as first salvage therapy (N=6), and no receipt of salvage therapy prior to autologous SCT (N=3). After initial salvage, the ORR and CR rate were 57% (95% CI: 46-67) and 26% (95% CI: 17-36), respectively. At a median follow-up of 48.9 months (IQR, 22.6-74.8), the median PFS after initial salvage was 5.4 months (95% CI: 2.3-not reached [NR]) (Figure 1). The median OS was not reached and the estimated 5-year OS rate was 78% (95% CI: 69-88). Of the 52 patients who progressed after initial salvage, 87% (N=45) received either CAR T-cell therapy (N=30), further line(s) of salvage therapy followed by autologous SCT (N=9), or allogeneic SCT (N=6) as subsequent therapy. Eight patients in the salvage therapy analysis progressed after autologous SCT with four patients subsequently receiving CAR T cells (1 of whom subsequently underwent allogeneic SCT) and one patient has long-term remission with BV+nivolumab. Of the 25 patients who had a PR to first salvage therapy, 14 proceeded to autologous SCT, seven to a different salvage regimen, three proceeded directly to CAR T-cell therapy, and one patient died from a lymphoma-related cause without further therapy. The 14 PR patients proceeding directly to autologous SCT had 2-year PFS and OS rates of 85% (95%

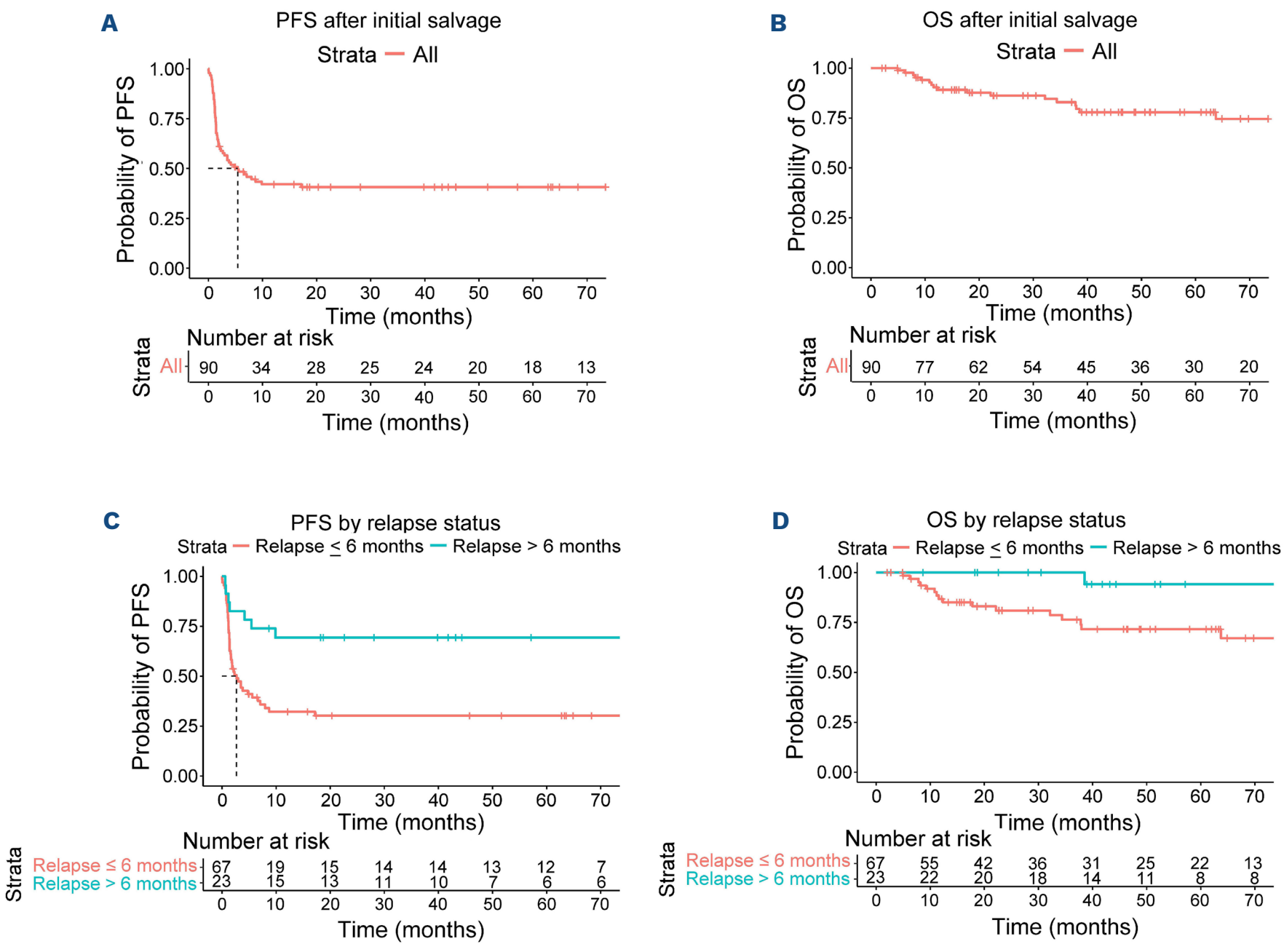

Figure 1. Survival outcomes after salvage therapy and by time of relapse. (A) Progression-free survival (PFS) of all patients in the salvage therapy cohort. (B) Overall survival (OS) of all patients in the salvage therapy cohort. (C) PFS by time to relapse. (D) OS by time to relapse.

Table 2. Univariate Cox and logistic regression models to estimate hazard of progression, death, and odds of complete response.

Variable	Progression-free survival		Overall survival		Complete response	
	HR (95% CI)	*P*	HR (95% CI)	*P*	OR (95% CI)	*P*
Relapse status Relapse ≤6 months	3.21 (1.44-7.15)	0.004	7.29 (0.96-55.0)	0.054	0.43 (0.17-1.12)	0.079
LDH at relapse LDH >ULN	5.40 (2.30-12.7)	<0.001	3.12 (0.80-12.1)	0.101	0.23 (0.07-0.70)	0.014
Stage III-IV	0.97 (0.52-1.83)	0.935	1.74 (0.58-5.27)	0.324	1.09 (0.42-2.73)	0.858
Extranodal disease Yes	1.27 (0.71-2.26)	0.410	1.77 (0.66-4.73)	0.256	0.59 (0.24-1.43)	0.251

Estimations are made relative to the following reference groups: Relapse >6 months, lactate LDH ≤ULN, stage I-II, and absence of extranodal disease. HR: hazard ratio; 95% CI: 95% confidence interval; OR: odds ratio; LDH: lactate hydrogenase; ULN: upper limit of normal.

CI: 67-100) and 100% (95% CI: 100-100), respectively, whereas the seven patients proceeding to a different salvage regimen had a 2-year OS of 71% (95% CI: 45-100).

When analyzing outcomes by refractory (primary refractory or relapse ≤6 months, N=67) or relapsed (relapse >6 months, N=23) status, patients with refractory disease had lower ORR (48%, 95% CI: 35-60) and CR rate (19%, 95% CI: 11-31) when compared to those with relapsed disease (ORR=83%, 95% CI: 61-95; CR rate=44%, 95% CI: 23-66). The 2- and 5-year PFS rate in the refractory group was 30% (95% CI: 21-44) compared to 69% (95% CI: 53-91) in the relapsed group. Estimated 5-year OS rates were 72% (95% CI: 60-85) and 94% (95% CI: 84-100) in the refractory and relapsed groups, respectively (Figure 1).

Factors associated with decreased odds of achieving CR following first salvage therapy included LDH concentration above the upper limit of normal at initial relapse (OR=0.23; 95% CI: 0.07-0.70; *P*=0.014) (Table 2). Factors associated with progression were refractory disease (HR=3.21; 95% CI: 1.44-7.15; *P*=0.004) and LDH above the upper limit of normal (HR=5.40; 95% CI: 2.30-12.7; *P*<0.001). On multivariate analysis, an increased risk of progression persisted for both those with refractory disease (HR=2.58; 95% CI: 1.05-6.32; *P*=0.04) and those with LDH above the upper limit of normal at relapse (HR=5.42; 95% CI: 2.30-12.8; *P*<0.001).

Salvage treatments

The majority (86%) of patients received traditional salvage therapy at first relapse with a median follow-up of 51.6 months (IQR, 37.1-76.4). The most common initial traditional salvage treatments were anti-CD20 (rituximab or obinutuzumab)-based chemotherapies in combination with ifosfamide, carboplatin, and etoposide (ICE) (51%) or dexamethasone, cytarabine, cisplatin, (DHAP) (12%). The ORR and CR rate to traditional salvage therapy were 53% (95% CI: 42-65) and 22% (95% CI: 13-33), respectively. The estimated 2- and 5-year PFS rate following traditional salvage was 35% (95% CI: 26-48), with estimated 2- and 5-year OS rates of 85% (95% CI: 77-93) and 76% (95% CI: 66-87), respectively. Initial salvage treatment details are presented in Table 3.

Table 3. Initial salvage treatment.

Initial salvage, N=90	N of patients
Traditional salvage	77
R/O-ICE	46
R/O-DHAP	11
R-GDP	6
R-DHAX	5
R-GemOx	5
R-IVAC	1
DHAP	1
ICE	1
R-MTX + cytarabine	1
Novel salvage	10
BV + nivolumab	9
Pembrolizumab	1
Clinical trial	3
R-ICE + ibrutinib	2
R-DHAX + epcoritamab	1

R: rituximab; O: ofatumumab; ICE: ifosfamide, carboplatin, etoposide; DHAP: dexamethasone, high dose cytarabine, cisplatin; GDP: gemcitabine, dexamethasone, cisplatin; DHAX: dexamethasone, high dose cytarabine, oxaliplatin; GemOx: gemcitabine, oxaliplatin; IVAC: ifosfamide, etoposide, high-dose cytarabine; MTX: methotrexate; BV: brentuximab vedotin.

Fifteen patients received novel salvage with BV+nivolumab with nine of those patients receiving this treatment as initial salvage. Of those nine, six were refractory to and three had relapsed disease after DA-EPOCH-R. The remaining six patients were refractory to initial salvage therapy and received BV+nivolumab at second relapse. Eleven of the 15 patients who received BV+nivolumab salvage proceeded to autologous SCT. The ORR and CR rate of the 15 patients who received BV+nivolumab were 80% (95% CI: 52-96) and 47% (95% CI: 21-73), respectively. The ORR and CR rate were 67% (95% CI: 30-93) and 33% (95% CI: 8-70), respectively, for patients who received BV+nivolumab as initial salvage. The estimated 2- and 5-year PFS rate for all patients receiv-

ing BV+nivolumab salvage was 70% (95% CI: 49-100). The estimated 2- and 5-year OS rate was 91% (95% CI: 75-100).

Autologous stem cell transplant

At a median follow-up time of 56.1 months (IQR, 25.4-74.3), 48 patients (refractory, N=30; relapsed, N=18) had undergone salvage treatment followed by autologous SCT. The median PFS and OS were not reached. Estimated 5-year PFS and OS rates were 85% (95% CI: 75-96) and 88% (95% CI: 79-99), respectively. No patients achieving CR prior to autologous SCT (N=29) relapsed after their transplant and among those patients with PR prior to autologous SCT (N=17), the estimated 2- and 5-year PFS rate was 69% (95% CI: 49-96). Twenty-two patients received radiation therapy prior to undergoing autologous SCT and 11 patients received radiation after autologous SCT.

Chimeric antigen receptor T cells as salvage therapy

At a median follow-up of 35 months (IQR, 11.9-49.9), 42 patients received autologous CD19 CAR T-cell therapy (axicabtagene ciloleucel = 29, tisagenlecleucel = 2, lisocabtagene maraleucel = 1, clinical trial = 10). Six patients received CAR T cells as second-line therapy while 36 patients received CAR T cells as third-line therapy or beyond. Four patients underwent autologous SCT prior to receiving CD19 CAR T cells. Among evaluable patients, the ORR was 74% (95% CI: 58-86) with a CR rate of 57% (95% CI: 41-72). The estimated PFS rate at 2 and 5 years was 64% (95% CI 51-81). The estimated 2- and 5-year OS rates were 80% (95% CI: 67-95) and 71% (95% CI: 56-90), respectively.

Allogeneic stem cell transplant

Nine patients underwent allogeneic SCT. These patients had received a median of two prior lines of therapy (range, 2-5) with one patient receiving prior autologous SCT and one patient receiving prior CAR T-cell therapy. At a median follow-up of 48.1 months (IQR, 22.5-49.2), the estimated 2- and 5-year PFS rate was 67% (95% CI 42-100), with a median OS of 40.2 months (95% CI: 9.8-NR) and estimated 2- and 5-year OS rates were 67% (95% CI: 42-100) and 50% (95% CI: 24-100), respectively.

Central nervous system relapse after frontline therapy

Eight patients (refractory = 6, relapsed = 2) were noted to have evidence of central nervous system involvement on relapse. With a median follow-up of 39.5 months, the 2-year OS was 80% (95% CI: 52-100). Each patient received cytotoxic chemotherapy as initial salvage with all but one receiving a high-dose methotrexate-based regimen initially. Of the seven patients who received a high-dose methotrexate-based regimen, five achieved a complete remission and each of these patients proceeded to autologous SCT. All five of these patients remain in a complete remission with a median follow up of 25.1 months (range, 0.8-93.0). One other patient proceeded to autologous SCT despite a poor response to cytotoxic salvage therapy and subsequently died of lymphoma after the transplant. One patient progressed after initial salvage chemotherapy, subsequently received CAR T-cell therapy, and was without relapse 2 months after the CAR T-cell infusion.

Discussion

While the majority of patients with PMBCL are cured with frontline therapy, the current literature is sparse regarding outcomes with salvage therapies in those that experience relapse. This publication describes the largest series of patients with R/R PMBCL, a rare subtype of NHL, in whom relapse is uncommon. This study is limited to patients receiving frontline DA-EPOCH-R, a common standard for frontline therapy for PMBCL.

This analysis describes an unfavorable response to initial salvage therapy in patients with refractory disease. Fewer than 20% of refractory patients achieved a CR to first salvage therapy and 30% (95% CI: 21-44) were estimated to be free from progression at 2 years after initial salvage. Compared to patients with relapsed disease, those with refractory disease were less likely to obtain a CR with initial salvage therapy and had an increased risk of progression after the first salvage therapy. Of patients with relapsed disease, 44% (95% CI: 23-66) achieved a CR with an estimated 2-year PFS of 69% (95% CI: 53-91) after initial salvage chemotherapy. This analysis also highlights the importance of obtaining a CR prior to autologous SCT as there were no relapses among the 29 patients who achieved CR prior to transplant. Univariate analysis noted a higher probability of obtaining a CR with initial salvage therapy in patients with a LDH concentration below the upper limit of normal. There was a trend towards refractory patients being less likely to achieve a CR with first salvage therapy in univariate analysis but this was not statistically significant. In multivariate analysis, LDH level above the upper limit of normal and refractory disease at relapse persisted in increasing the hazard ratio for progression after initial salvage therapy. The heterogeneous treatment strategies employed in patients having a PR to first salvage highlights the clinical ambiguity of PR in PMBCL patients. Despite the median PFS of only 5.4 months after initial salvage for patients in the salvage therapy analysis, the estimated 5-year OS remained high at 78% (95% CI: 69-88) for this group. This likely reflects the multiple subsequent options for curative therapy, as 87% of those progressing after initial salvage were able to receive either second/third-line salvage followed by autologous SCT, CAR T-cell therapy, or allogeneic SCT.

This analysis did not include a sufficient number of patients receiving 'novel' salvage therapy (i.e., BV+nivolumab) to make any meaningful conclusions regarding 'novel' *versus* 'traditional' salvage therapy in terms of CR rate or PFS.

Outcomes for patients receiving CD19 CAR T-cell therapy

were consistent with those in previous reports.[12] This analysis was not designed to provide a comparison of salvage chemotherapy plus autologous SCT *versus* CD19 CAR T-cell therapy as initial therapy after relapse.

This study is the largest review of R/R PMBCL patients to date and provides insight on select variables having statistically significant effects on outcomes with initial salvage therapy. Considering the outcomes described, it is reasonable to suggest salvage chemotherapy followed by autologous SCT as a viable option for patient relapsing >6 months after completion of DA-EPOCH-R. For refractory patients, long-term disease-free survival with salvage therapy and autologous SCT is unlikely, and thus CAR T-cell therapy should be strongly considered in this population of patients. Patients who achieved a CR prior to autologous SCT had an excellent prognosis. When choosing a treatment option, clinicians must consider both immediate and long-term side effects of each approach. This analysis provides a valuable resource regarding expectations of response to salvage therapy as well as providing a benchmark for outcomes in this population of patients for future studies. Further investigations regarding various salvage therapies within different subpopulations (i.e., relapsed *vs*. refractory) are warranted as well as investigation of cellular therapy *versus* salvage therapy and autologous SCT as initial therapy after relapse.

Disclosures

BH has participated in advisory boards for Bristol-Myers Squibb, Incyte and Gilead. AM has received research support from ADC Therapeutics, Beigene, Miragen, Seattle Genetics, Merck, Bristol-Myers Squibb, Incyte and SecuraBio and has received honoraria from Seagen, Affimed, AstraZeneca, Bio Ascend, Imbrium Therapeutics L.P./Purdue, Janpix Ltd., Merck, Seattle Genetics, Pfizer, Tessa Therapeutics and Takeda. JAD has acted as a consultant for Janssen Biotech, Bristol-Myers Squibb and GlaxoSmithKline and participated in a speakers' bureau for Janssen Biotech. PS receives salary support from the Leukemia Lymphoma Society Scholar in Clinical Research Career Development Program and the Kite Gilead Scholar in Clinical Research Award; has provided consultancy services for Roche-Genentech, AbbVie-Genmab, Ipsen, Kite/Gilead, AstraZeneca-Acerta, ADC Therapeutics, Sobi and Incyte; and has received research funding from Sobi, AstraZeneca-Acerta, ALX Oncology and ADC Therapeutics. YS has received research funding from BeiGene, Genmab and AbbVie and has provided consultancy services for ADC, Genmab and Genentech. BTH has received research support from and acted as a consultant for Genentech and Gilead. GLS has received research funding to the institution from Janssen, Amgen, Bristol-Myers Squibb, Beyond Spring, GPCR, and Recordati and has participated in a Data Safety Monitoring Board for ArcellX. RM has been an advisory board member for Genmab, Bristol-Myers Squibb, AbbVie, Ipsen and KITE; acted as a consultant for DG Medicine; and received honoraria from Genmab. MK has been a consultant for AbbVie, AstraZeneca, Bristol-Myers Squibb, Beigene and Genentech and has sat on a Data Monitoring Committee for Celgene and Genentech. AI has received consulting fees from AstraZeneca, Graticule and Abbvie; has received honoraria from Pfizer/Seagen, Kite/Gilead, AbbVie, MJH Life Sciences and Curio Life Sciences; has received support for attending meetings from AbbVie; has participated in an advisory board for Kite/Gilead; and holds stocks in COTA Healthcare and Outcomes Matter Innovations, Inc. NA has participated in advisory boards for Kite/Gilead, Bristol-Myers Squibb, Invivyd, and Legend Biotech and acted as a consultant for Kite/Gilead and Bristol-Myers Squibb. MH has received consulting fees and/or honoraria from ADC, Janssen, Pharmacyclics, BeiGene, Novartis, AstraZeneca, AbbVie and Kite; has received research funding from Genentech; and has received travel support from Bristol-Myers Squibb. AL has acted as a consultant for Kite Pharma, Genmab and Pierre Fabre and has participated in a speakers' bureau for Research to Practice. The other authors have no conflicts of interest to disclose.

Contributions

BH, AL and AM developed the study, including primary endpoints and data points to be collected. BH wrote the manuscript. AL, AM and JAD were primary editors of the manuscript. ACF analyzed data and edited the manuscript. All other authors performed research via data collection and provided comments regarding results and subsequent manuscript edits.

Data-sharing statement

Data corresponding to the findings in this study are available upon request to the author for correspondence.

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