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ORIGINAL RESEARCH

Outcome of Primary Mediastinal Large B Cell Lymphoma Treated with RCHOP

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Purpose: Primary mediastinal large B-cell Lymphoma (PMLBCL) is a rare aggressive lymphoma with unique clinical, pathological, and molecular features. The optimal frontline therapy is subject of ongoing debate. Our study aims to evaluate the outcomes of PMLBCL treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) at King Hussein Cancer Center.

Patients and Methods: Adult patients >18 years of age with PMLBCL treated with RCHOP from January 2011 to July 2020 were identified. All demographics, disease and treatment related variables were retrospectively collected. Correlations of clinical and laboratory variables with progression-free survival (PFS) and overall survival (OS) were determined by univariate and multivariate analyses using backward stepwise Cox regression models. The PFS and OS were plotted using Kaplan–Meier curves.

Results: 49 patients were included with a median age of 29 years. 14 (28.6%) had stage III or IV, 31 (63.3%) had mediastinal bulky disease. International prognostic index (IPI) was 0–1 in 35 (71.4%). Radiotherapy was given to 32 (65.3%) patients. End of treatment (EOT) response was complete (CR) in 32 (65.3%), partial response (PR) in 8 (16.3%) and progressive disease (PD) in 9 (18.4%). Patients who achieved CR at EOT, compared favorably with those who did not in regard to 4-year OS (92.5% vs 26.9%, p=<0.001). Overall objective response to salvage chemotherapies was 26.7%. At a median follow-up of 46 months, 4-year PFS and OS were 60% and 71% respectively. In multivariate analysis, IPI > one correlated with the EOT response (p=0.009), PFS (p=0.004) and OS (p= 0.019).

Conclusion: In PMLBCL, RCHOP chemotherapy backbone in the frontline therapy is suboptimal but can be used in patients with low IPI. Adapting more intensive chemoimmunotherapy regimens may be considered for patients with high IPI. Salvage chemotherapy has limited activity in patients with relapsed or refractory disease.

Keywords: international prognostic index, end of treatment response, radiotherapy, salvage chemotherapy

Introduction

Lymphomas are relatively common tumors in Jordan with 485 reported cases in 2017 and ranked as the third most common tumor.[1] Primary mediastinal large B-cell lymphoma (PMLBCL) is a rather infrequent aggressive lymphoma with unique clinical, pathological, and molecular features, accounts for 2–4% of all non-Hodgkin lymphomas (NHL).[2–8] The 2022 World Health Organization (WHO) classification of lymphoid neoplasms identified PMLBCL as a unique clinical and biological entity.[9] In contrast to diffuse large B cell lymphoma (DLBCL), PMLBCL typically presents at a median age of approximately 35 years and the majority of patients present with an early-stage but bulky mediastinal disease.[2,5,10]

The optimal therapeutic approach has not been defined due to the rarity of disease and absence of randomized controlled trials. In the pre-rituximab era, retrospective studies suggested that outcomes with more intensified approaches like, V/MACOP-B (etoposide or methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) are superior to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).[11,12] However, the addition of rituximab

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to CHOP might mitigate this effect.[13] Nonetheless, 20–25% of patients treated with rituximab in combination with anthracycline based chemotherapy had relapse or refractory disease.[13–15]

Recently, dose adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and rituximab (DA-EPOCH -R) regimen and a sequential administration of four doses of RCHOP followed by three cycles of rituximab, Ifosfamide, carboplatin, and etoposide (R-ICE) resulted in favorable outcomes and obviated the need for consolidative radiotherapy (RT), but with higher treatment-related toxicities.[16–19]

Our study aims to assess the outcomes of primary mediastinal large B cell lymphoma treated with RCHOP in our center.

Materials and Methods

We searched Cancer Registry of King Hussein Cancer Center (KHCC) for adults (age >18 years) with non-Hodgkin lymphoma, from January of 2011 to July 2020 (n=1156). Patients with a pathological diagnosis of PMLBCL treated with R-CHOP-21 with or without RT were identified and included. Pathological diagnosis was confirmed by the expression of B cell antigens (CD19, CD20, CD23, and CD79a) and the lack of CD15. CD30 positivity supported the diagnosis but was not required.

All demographics, laboratory, and treatment-related variables, including age, gender, date of diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, serum lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), beta-2 microglobulin (B2M), number of extranodal sites, disease stage and disease bulk were collected. Bulky disease is defined as a mediastinal mass of ≥10 centimeters.

Staging and response to treatment were determined according to Lugano criteria.[20] Initial staging was done with a computed tomography (CT) scan in 30 (61%) patients and with a CT scan and a positron emission tomography (PET)-CT scan in the remaining patients. Response to treatment was determined with PET-CT scan in 44 (89.7%) patients and with a CT scan only in 5 (10.3%) patients. International prognostic index (IPI) was calculated as previously described.[21]

Consolidative radiotherapy (RT) was given to patients with a tumor diameter >7 cm with no evidence of disease progression after finishing chemotherapy. Descriptive statistics were used to characterize patients at baseline and presented as counts and percentages. Overall survival (OS) was calculated from the date of diagnosis to the date of the last encounter or death from any cause. Progression free survival (PFS) was calculated from the date of diagnosis to the date of relapse or progression. Survival outcomes were calculated using the Kaplan Meier method. The associations between different variables with PFS and OS were analyzed using Log-rank (Mantel-Cox) test in the univariate analysis and Cox proportional hazard models in the multivariate analysis. Patients' characteristics and the end of treatment (EOT) response were compared using the Fisher's exact test. ECOG performance status was excluded from the analysis because one patient had an ECOG performance status of >1. The P-values are two-sided and considered significant when < 0.05. The waiver of the written informed consent was granted due to the retrospective nature of the review, and the data were anonymized and maintained with confidentiality. The study was approved by the King Hussein Cancer Center Institutional Review Board (IRB) complaint with the principles of the declaration of Helsinki.

Results

49 patients were included in the analysis with a median age of 29 (range:18–56) years and an almost equal gender distribution. 14 (28.6%) had stage III or IV, and 11 (22.4%) had two or more extranodal sites. CD30 was reported to be positive in 41 (83.7%) patients. About two thirds of patients had mediastinal bulky disease. IPI was 0–1 in 35 (71.4%). All patients received at least six cycles of RCHOP; 39 (79.6%) patients were given six cycles and 10 (20.4%) patients were given 7–8 cycles. Consolidative RT at doses between 30.6Gy to 39.6Gy was given to 32 (65.3%) patients, among which four (12.5%) patients were given involved site radiotherapy and 28 (87.5%) patients received involved field radiotherapy. Patients' characteristics are detailed in Table 1.

After chemotherapy completion, 39 (79.6%) had an objective response among which 30 (61.2%) had complete response (CR) and nine (18.4%) had partial response.

Consolidative RT was given to 22 (73.3%) patients while in CR, all continued to have CR at the last encounter and to 7 out of 9 patients while in PR; 2 of the moved to CR after RT, 2 PR and 3 had disease progression (DP). 3 of the 10

Table 1 Patients Characteristics and Treatment

Characteristic	Number (%)
Gender	
Male	27 (55%)
Female	22 (45%)
Median age (range)	29 (18–56) years
ECOG performance status	
0–1	48 (98%)
2 or more	1 (2%)
B symptoms	
Yes	29 (59%)
No	20 (41%)
Bulky disease (7 or more centimeters)	45 (92%)
Bulky disease (10 or more centimeters)	31 (63.3%)
Stage	
I	6 (12.2%)
II	29 (59.2%)
III	3 (6.1%)
IV	11 (22.4%)
Number of extranodal sites	
0	37 (75.5%)
1	3 (6.1%)
2 or more	9 (18.4%)
High LDH	36 (37.5%)
B2 microglobulin (2.5 mg/dl or more)	11 (22.4%)
ESR (50 mL/hour or more)	15 (30.6%)
IPI	
0–1	35 (71.4%)
More than 1	14 (18.6%)
Number of RCHOP cycles	
6	39 (79.6%)
7 or 8	10 (20.4%)
Radiotherapy consolidation	32 (65.3%)
First line salvage treatment	19 (38.8%)
DHAP	10 (52.6%)
GDP	4 (21%)
ICE	3 (15.8%)
High dose methotrexate	2 (10.5%)
Second line salvage treatment	15 (30.6%)
ICE	10 (66.6%)
GDP	2 (13.3%)
DHAP	1 (6.6%)
R-Gem-Ox	1 (6.6%)
Mini-BEAM	1 (6.6%)

(*Continued*)

Table 1 (Continued).

Characteristic	Number (%)
Third line salvage treatment	9 (18.4%)
Pembrolizumab	2 (22.2%)
Mini-BEAM	3 (33.3%)
ICE	1 (11.1%)
GDP	1 (11.1%)
DHAP	1 (11.1%)
Hyper-CVAD	1 (11.1%)

Abbreviations: ESR, Erythrocyte sedimentation rate; LDH, Lactate dehydrogenase; IPI, international prognostic index; DHAP, cisplatin, cytarabine and dexamethasone; GDP, cisplatin, gemcitabine and dexamethasone; ICE, Ifosfamide, carboplatin and etoposide; R-Gem-Ox, rituximab, gemcitabine and oxaliplatin; Mini-BEAM, carmustine, etoposide, cytarabine and melphalan; Hyper-CVAD, cyclophosphamide, vincristine, dexamethasone alternating with cytarabine and methotrexate.

patients who progressed were given salvage RT, all progressed. Based on the decision of the treating physician, four patients with a bulky disease had a CR and two patients with a PR did not receive consolidative radiotherapy.

End of treatment (EOT) response to either chemotherapy or combined modality treatment revealed CR in 32 (65.3%), no CR in 17 (34.7%) [PR in 8 (16.3%) and DP in 9 (18.4%)], Table 2.

Table 2 Response to Frontline and Salvage Treatments

Response to frontline chemotherapy	
Complete response	30 (61.2%)
Partial response	9 (18.4%)
Disease progression	10 (20.4%)
End of treatment response	
Complete response	32 (65.3%)
Partial response	8 (16.3%)
Disease progression	9 (18.4%)
Response to first line salvage chemotherapy (n=19)	
Complete response	1 (5.2%)
Partial response	1 (5.2%)
Disease progression	17 (89.6%)
Response to second line salvage chemotherapy (n=15)	
Partial response	2 (13.3%)
Disease progression or death	13 (86.7%)
Response to third line salvage chemotherapy (n=9)	
Complete response	2(22.2%)
Disease progression or death	7 (77.8)
ASCT	5 (10.2%)
Relapse post ASCT	
Yes	1 (20%)
No	4 (80%)
Status on last encounter	
Alive	35 (71.4%)
Dead	14 (28.6%)

Abbreviation: ASCT: autologous stem cell transplant.

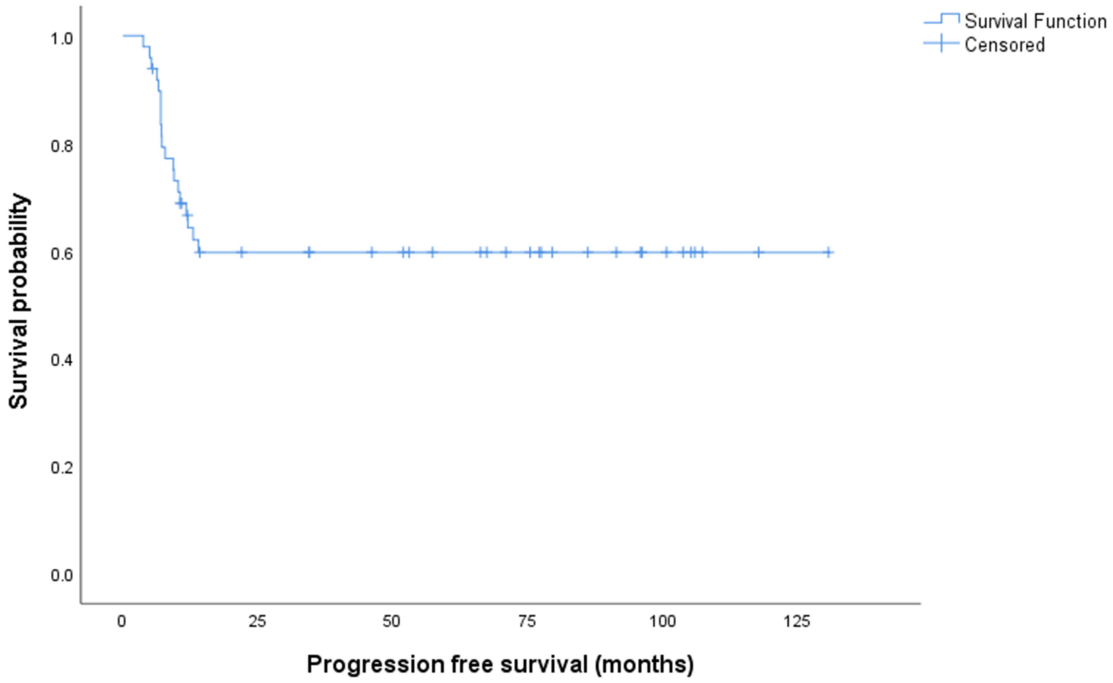

Figure 1 Progression free survival in all patients.

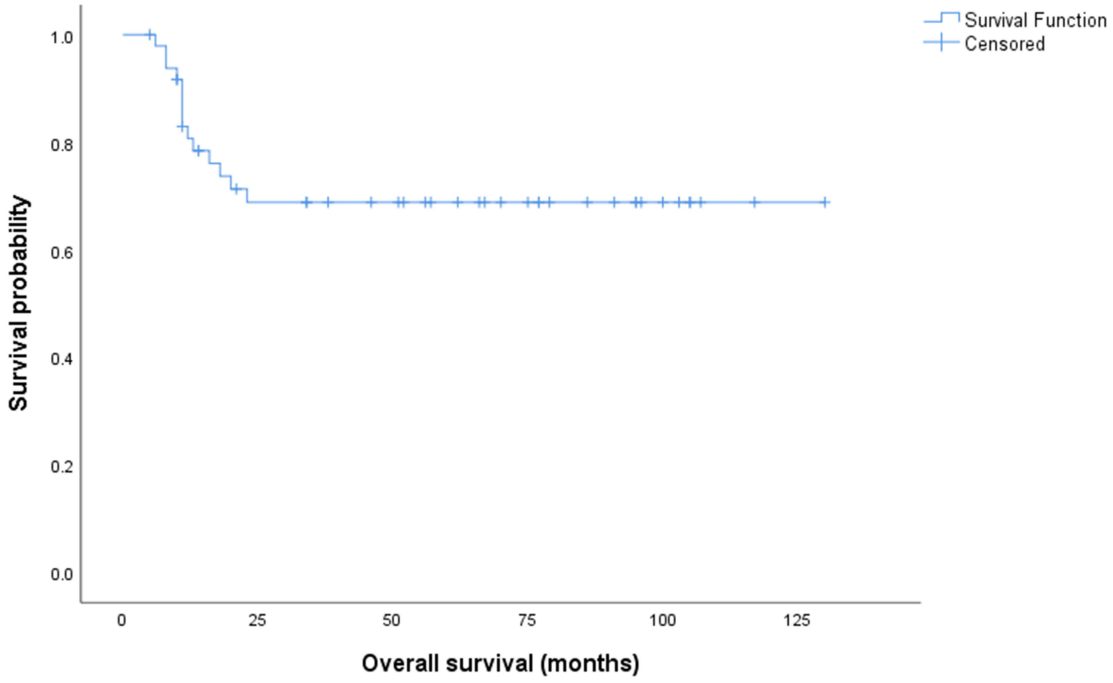

Figure 2 Overall survival in all patients.

After a median follow-up of 46 (range:5–130) months, 4-year PFS and OS were 60% and 71.4% respectively, Figures 1 and 2. The median time to relapse or progression was 7.2 (range: 3.3 −14) months.

In univariate analysis, IPI >1 (mainly driven by advanced stage and ≥ 2 extranodal sites), Figures 3 and 4, and B2M ≥2.5 correlated with PFS and OS, Table 3. In multivariate analysis, IPI>1 significantly associated with PFS (p=0.005)

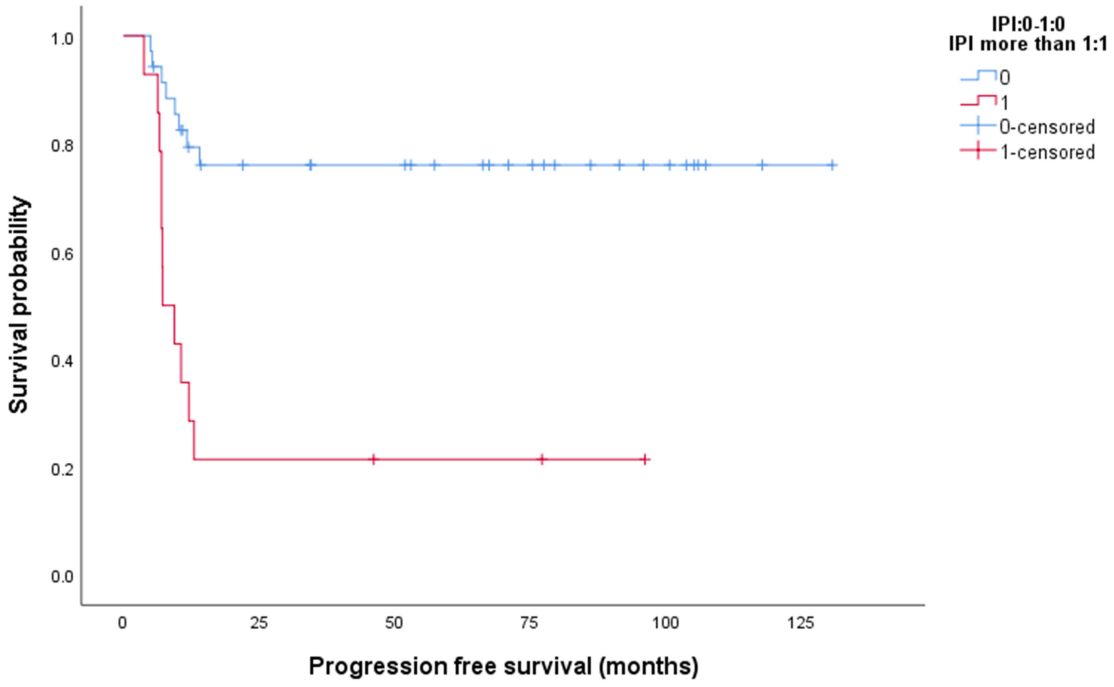

Figure 3 Progression free survival according to international prognostic index (IPI).

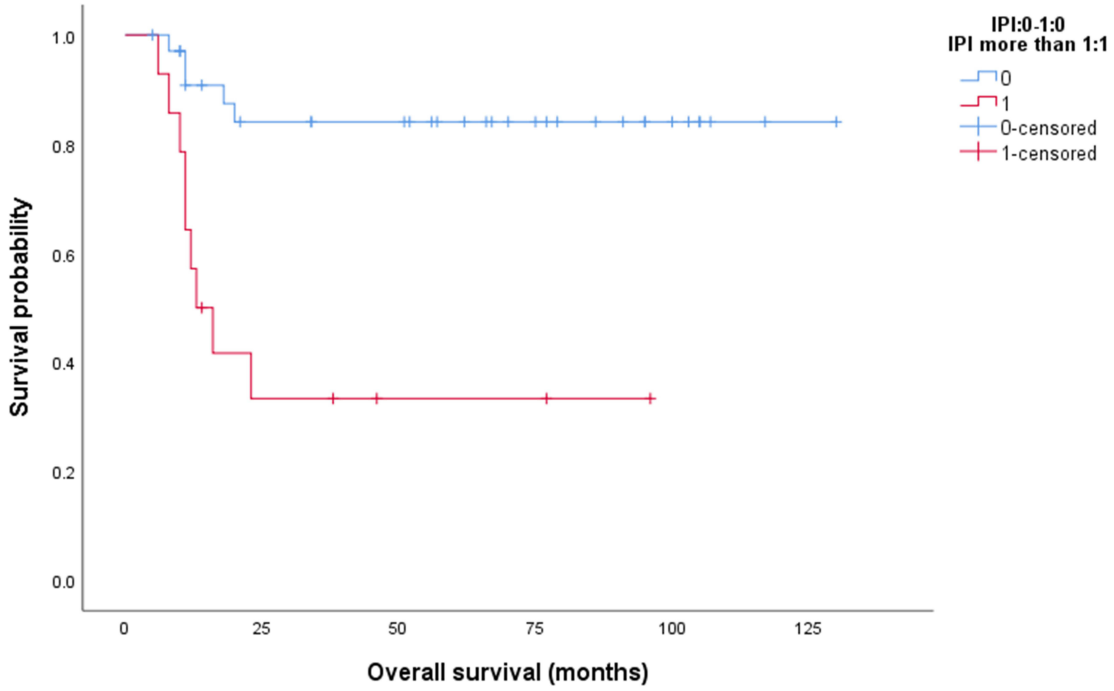

Figure 4 Overall survival according to international prognostic index (IPI).

and OS (p=0.019). In contrast, gender, the presence of B-symptoms, high ESR, and the presence of disease bulk had no statistically significant correlation with either endpoint, Table 4.

Advanced stage disease (p=0.009), ≥2 extranodal sites (p=0.005) and IPI >1 (p=0.009) correlated with EOT response, Table 5. The EOT response (CR vs no CR) correlated strongly with PFS (p=<0.001) and OS (p=<0.001), Figure 5.

Table 3 Univariate Analysis for Progression Free Survival and Overall Survival

Variable	4-year PFS %	P value	4-year OS%	P-value
Gender Male Female	 51.9% 69.7%	0.196	 65.3% 72.%	0.69
Stage I–II Stage III–IV	76% 21.4%	<0.001	84.1% 33.3%	<0.001
Bulky disease ≥7cm No bulky disease	59.8% 100%	0.13	65.8% 100%	0.197
Bulky disease ≥10 cm No bulky disease	53.1% 70.5%	0.193	64.4% 77%	0.533
B-symptoms No B symptoms	53.3% 68.9%	0.294	62.5% 78.2%	0.257
<2 extranodal sites 2 or more extranodal sites	71.4% 11.1%	<0.001	80.7% 20.2%	<0.001
ESR <50 ESR ≥50	66.3% 64.7%	0.267	70.6% 58.3%	0.335
B-2 microglobulin <2.5 B2 microglobulin ≥2.5	75% 45.5%	0.034	78.1% 43.6%	0.021
Normal LDH High LDH	83.3% 55.6%	0.273	83.3% 65.7%	0.489
IPI: 0–1 IPI >1	76% 21.4%	<0.001	84.1% 33.3%	<0.001
Response to chemotherapy Complete response Partial response Disease progression	 93.1% 22.2% 0%	<0.001	 92% 55.6% 15%	<0.001
End of treatment response Complete response No complete response	 93.1% 0%	<0.001	 92.6% 26.9%	<0.001

Abbreviations: ESR, Erythrocyte sedimentation rate; LDH, Lactate dehydrogenase; IPI, international prognostic index.

Table 4 Multivariate Analysis

Progression Free Survival				
Variable	**P value**	**HR**	**95% CI**	
			Lower	**Upper**
B2 microglobulin	0.307	1.861	0.565	6.133
IPI	0.005	6.294	1.765	22.447
Overall survival				
B2 microglobulin	0.189	2.314	0.662	8.084
IPI	0.019	4.755	1.295	17.459

Abbreviation: IPI, international prognostic index.

Table 5 Correlation Between Different Pre-Treatment Variables and End-of Treatment Response

Variable	CR (%)	No CR (%)	P-value
Gender Male Female	 50% 50%	 64.7% 35.3%	 0.378
Stage I–II Stage III–IV	84.4% 15.6%	47.1% 52.9%	0.009
Bulky disease ≥10 cm No bulky disease	59.4% 40.6%	70.6% 29.4%	0.541
B-symptoms No B symptoms	56.3% 43.7%	42.9% 35.3%	0.761
<2 extranodal sites 2 or more extranodal sites	93.7% 6.3%	58.8% 41.2%	0.005
ESR <50 ESR ≥50	68.2% 31.8%	42.9% 47.1%	0.175
B-2 microglobulin <2.5 B2 microglobulin ≥2.5	78.7% 21.3%	50% 50%	0.13
Normal LDH High LDH	18.5% 81.5%	6.7% 93.3%	0.395
IPI: 0–1 IPI >1	84.4% 15.6%	47.9% 52.1%	0.009

Abbreviations: ESR, Erythrocyte sedimentation rate; LDH, Lactate dehydrogenase; IPI, international prognostic index.

All patients with a relapsed or refractory disease (n=19) were treated with salvage chemotherapy, Table 1. 5 (26.3%) patients had a response; 3 went into CR (2 received pembrolizumab), and 2 achieved a PR. Patients with a response to salvage chemotherapy (n=5), received high dose chemotherapy and autologous stem cell transplant (ASCT), Table 2.

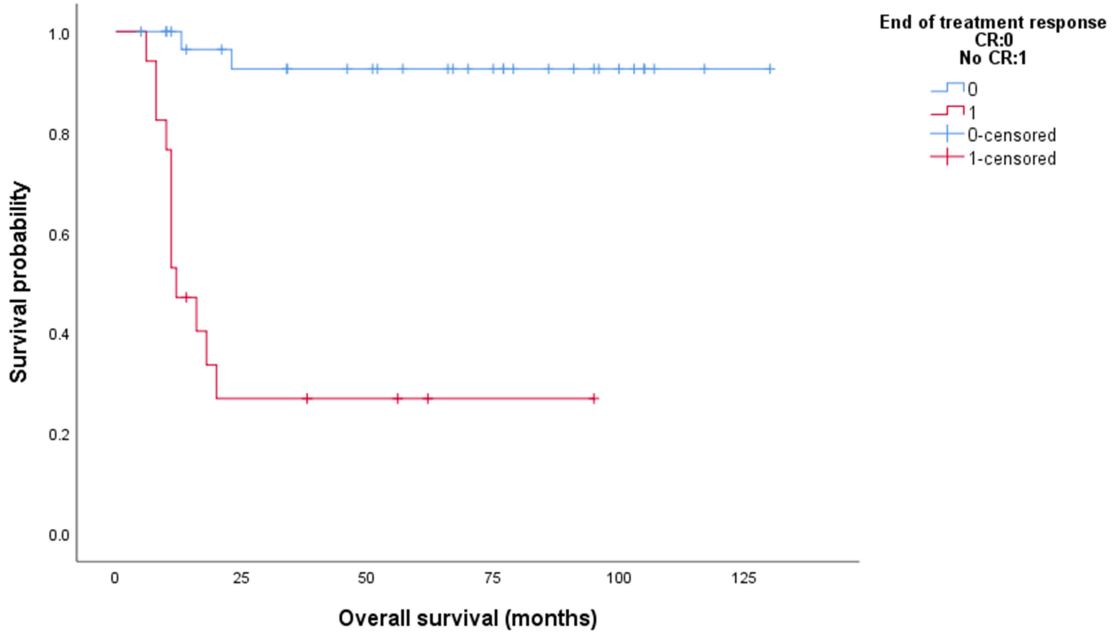

Figure 5 Overall survival according to end of treatment response.
Abbreviation: CR, complete response.

Among the patients with a relapsed or refractory disease, 4 (21.5%) were alive with no disease on the last follow-up.

Discussion

There is no standard first line therapy for PMLBCL because of the lack of prospective randomized studies and no large registry reports published. The European Society of Medical Oncology (ESMO) guidelines concluded that RCHOP-14, RCHOP-21, DA-EPOCH-R, R-VACOP-B and V-MACOP-B are reasonable first-line options.[22] RCHOP-21 with radiotherapy is the standard regimen recommended by the British Society of Haematology (BSH) guidelines and DA-EPOCH-R without radiotherapy can be used alternatively.[23] The National Comprehensive Cancer Network (NCCN) guidelines recommended either RCHOP or DA-EPOCH-R as first line therapy.[24]

The most commonly used frontline regimens, RCHOP and DA-EPOCH-R, were compared in a multicenter retrospective study and showed higher rates of CR in DA-EPOCH-R (84.4% vs 69.6%) but no difference in long-term survival outcomes.[25] However, in another recent retrospective study, the use of DA-EPOCH-R was associated with improved PFS and OS in comparison with RCHOP.[26] Toxicity is an important consideration when selecting the optimal frontline treatment. DA-EPOCH-R is associated with more acute toxicities including neutropenia, stomatitis, cardiac complications, thrombosis, the need for admission and central venous access.[27]

The PFS and OS rates in our study compare less favorably to Vassilakopoulos et al report, with 4-year PFS of 59% vs 80%, and OS of 71.4% vs 89%.[28] This can be explained by the inclusion of more patients with advanced stage disease in our study (21.4% vs 12%) and the fact that 18.4% of our patients had ≥2 extranodal sites, which was not reported by Vassilakopoulos et al, as the age-adjusted IPI was used to stratify the patients rather than the original IPI used in our study. This group had significantly worse outcomes (4-year PFS of 11% and OS of 22%). However, our results confirmed the reasonable survival outcomes of patients with low IPI (0–1) previously published in the MinT trial subgroup study.[15]

The results of our study highlight important practical points. First, patients with advanced stage disease or ≥2 extranodal sites had unsatisfactory outcomes when RCHOP was used in the frontline in accordance with the results of a recent study from British Columbia.[29] The use of DA-EPOCH-R in this high-risk group compares more favorably to our results (PFS of 60% vs 21.4%).[27] Although there are no prospective randomized studies, the use of more intensified approaches may be reasonable to improve long-term outcomes. On the other hand, for patients with limited-stage disease, RCHOP can accomplish the job.

Second, the median time to relapse or progression in our study was 7 months and none of our patients relapsed after 14 months. This observation was previously reported,[30] and may help to optimize patient's follow-up plan.

Third, the response to salvage chemotherapy in our study (26.3%), was also reported in other studies,[31,32] indicating that refractory or relapsed PMLBCL, compared to DLBCL, is less likely to respond to salvage chemotherapy. Recently, the introduction of CD19 specific chimeric antigen receptor (CAR) T cell therapy has revolutionized the treatment of relapsed DLBCL including PMLBCL. The results of two Phase 3 trials, the ZUMA-7 and the TRANSFORM trails, demonstrated a better event free survival and OS of CAR T cell therapy (axicabtagene ciloleucel in ZUMA-7 and Lisocabtagene maraleucel in TRANSFMORM) relative to salvage chemotherapy and ASCT in patients with primary refractory or early first relapse (<12 months) large B cell lymphoma including PMLBCL.[33,34]

In line with frequent expression of programmed cell death-1 (PD-1) and CD30 positivity in PMLBCL, CheckMate 436, KEYNOTE-170 and KEYNOTE-013 trails showed high efficacy of immune check point inhibitors as monotherapy or in combination with brentuximab vedotin in relapsed and refractory PMLBCL.[35,36] Two of our patients were treated with pembrolizumab as a third line salvage went into CR and received high dose chemotherapy and ASCT. Both patients are still alive and disease free at the last encounter. The use of these agents may be considered in patients not eligible or relapsing after CAR T cell therapy.

The role of consolidative radiotherapy in patients treated with RCHOP is still an area of debate. Recent reports have shown that radiotherapy can be safely omitted in patients having a complete metabolic response on PET-CT scan.[26] Due to the small number of patients who achieved a CR and did not receive consolidative radiotherapy in our study (n=8), no solid conclusions can be made. The ongoing IELSG 37 phase 3 trial is investigating the role of consolidative radiotherapy after chemoimmunotherapy in PMLBCL would hopefully help to answer this critical question.[37]

Our study has several limitations including the retrospective design, small number of patients and no comparator arm.

Conclusion

The use of frontline therapy with RCHOP in PMLBCL is suboptimal but may be reasonable in patients with low IPI score with good long-term survival outcomes. The use of more intensive approaches may be considered for patients with advanced stage disease. Patients with relapsed or refractory disease had a limited response to salvage chemotherapy and CART T cell therapy should be considered.

Disclosure

The authors report no conflicts of interest in this work.

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