Original Article

Treatment options in primary mediastinal B cell lymphoma patients, retrospective multicentric analysis; a Turkısh oncology group study

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ABSTRACT

Introduction and Aim: Primary mediastinal B-cell lymphomas (PMBL) are aggressive B- cell lymphomas. Although the initial treatment models vary in PMBL, appropriate treatment methods are not known. We aim to show real-life data on health outcomes in adult patients with PMBL who received various type of chemoimmunotherapies in Turkey.

Method: We analyzed the data of 61 patients who received treatments for PMBL from 2010 to 2020. The overall response rate (ORR), overall survival (OS) and progression-free survival (PFS) of the patients were evaluated.

Results: 61 patients were observed in this study. The mean age of the study group was 38.4 ± 13.5 years. From among them, 49.2% of the patients were female (n = 30). For first-line therapy, 33 of them had received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen (54%). Twenty-five patients had received rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-EPOCH-R) regimen. The ORR was 77%. The median OS and PFS were as follows: 25 months (95% CI: 20.4–29.4) and 13 months (95% CI: 8.6–17.3), respectively. The OS and PFS at 12 months were 91.3% and 50%, respectively. The OS and PFS at five years were 64.9% and 36.7%, respectively. Median follow-up time period was 20 months (IQR 8.5–38.5).

Conclusion: R-CHOP and DA-EPOCH-R showed good results in PMBL. These remain one of the best determined systemic treatment options for first-line therapy. Also, the treatment was associated with good efficacy and tolerability.

KEY WORDS: Chemoimmunotherapy, DA-EPOCH-R, primary mediastinal B-cell lymphomas, R-CHOP

INTRODUCTION

Primary mediastinal B-cell lymphoma (PMBL) is an aggressive type of B-cell lymphoma originating from thymic B-cells. It constitutes 7% of diffuse B-cell lymphomas.[1] Patients are usually presented with a local invasive anterior mediastinal mass, and it can progress aggressively. It usually causes airway obstruction and vena cava syndrome. Fifty-five percent of patients are presented with vena cava syndrome.[2]

While the initial treatment models vary in PMBL, appropriate treatment methods are not known. Treatment options may vary depending on whether the disease is in a limited or advanced stage. Although radiotherapy is part of the primary therapy, all patients are treated with induction chemo immunotherapy. In limited-stage patients, six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) plus radiotherapy (RT) or six to eight cycles of dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-EPOCH-R) are recommended in the

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first line.[3] DA-EPOCH-R is generally recommended in younger patients who do not want or cannot receive radiotherapy. In advanced stage PMBL patients, six to eight cycles of R-CHOP plus radiotherapy or six to eight cycles of DA-EPOCH- R are recommended as the first-line therapy. Treatments are chosen according to the character of the tumor. There is currently no standard or an agreed treatment method in relapsed and refractory PMBL. These patients are encouraged to go for clinical trials. Treatments such as alternative chemo immunotherapy, immune control point inhibitors, chimeric antigen receptor cell therapies, and hematopoietic stem cell transplantation are performed.

PMBL are clinicopathologically distinct from large B-cell lymphomas and show similarities to nodular sclerosing-type Hodgkin lymphoma. As immunophenotype, CD19, CD20, CD22, CD79a and CD45 are positive, CD5 and CD10 are negative, and CD30 is often weakly positive. Because of CD30 positivity, brentuximab vedotin is used in anaplastic large cell lymphoma and refractory peripheral T-cell lymphoma.[4,5] Bendamustin is also used in the treatment of relapsed and refractory T-cell lymphoma. Nivolumab, a PD-1 inhibitor, is used in the treatment of refractory classical Hodgkin lymphoma.[6] In the light of these data, agents are used all over the world in clinical studies.

We also use these treatment options for such patients in Turkey. Our hematology and medical oncology departments have experience in all kinds of lymphoma treatments. And we have good results.

We aim to demonstrate the real-life data about the treatment options in PMBL patients and show the overall response rate (ORR), progression free survival (PFS), overall survival (OS), and toxicities of treatments in the Turkish population.

MATERIAL AND METHOD

Study design and cases

The study was carried out by investigating patients with PMBL who had undergone different treatment choices in 11 Turkish medical oncology and hematology departments between October 2010 and May 2020 in diagnosis, treatment, complications, and outcomes. The study is a multi-center, retrospective study.

A retrospective case control study was carried out with 61 cases comprising cases that had been previously diagnosed and treated or those currently on different treatments for PMBL in terms of demographics, cancer-specific features including histology and stage of the cancer, previous or ongoing treatment, and previous radiotherapy.

In R-CHOP regimen, rituximab at a dose of 375 mg/m^2, cyclophosphamide at a dose of 750 mg/m^2, doxorubicine at dose of 50 mg/m^2 and vincristine 1.4 mg/m^2 (maximum dose 2 mg) at day 1 and prednisone 100 mg/day at days 1–5 were administered.[7]

In DA-EPOCH-R regimen, rituximab at a dose of 375 mg/m^2 at day 1, etoposide 50 mg/m^2 at days 1–4, doxorubicine at dose of 10 mg/m^2 at days 1–4, vincristine 0.4 mg/m^2 at days 1-4, cyclophosphamide at a dose of 750 mg/m^2 at day 5 and prednisone 60 mg/m^2 at days 1–5 were administered.[7]

We used fluorodeoxyglucose (FDG) positron emission computed tomography (PET-CT), ultrasound or computed tomography for tumor assessment.

The primary end point of this study was to assess the PFS and OS periods. Secondary end points were to identify clinical factors prognostic of disease progression after treatments, and to define the safety and the toxicity profile.

Ethical approval

The Ethics Committee of University of Health Science, Gulhane Research and Training Hospital approved the study with 2020-257 ethical committee number on June 9, 2020. All procedures were according to the Helsinki Declaration of 1975, which was revised in 2008, and all procedures were convenient to the ethical standards of the responsible committee on human experimentation (institutional and national).

Data collection and statistical analysis

Medical records admitted to the Department of Medical Oncology and Hematology in 11 Turkish hospitals and eventually diagnosed with PMBL were investigated. Medical records of suitable cases were enrolled in an Statistical Package for the Social Sciences data sheet by the registered staff at the Department of Oncology at University of Health Science.

Patients' demographics, clinical and biochemical features, and clinical and radiologic outcomes were recorded in an SPSS v 22.0 (SPSS Inc., Chicago, IL USA) data sheet, considering the patients' confidentiality. Data was accessible only by the authorized institutional staff and caregivers. Student's *t*-test was utilized for the test because of the normal distribution of data. Demographic indices were provided in mean values with the standard deviation or median values as appropriate. Frequencies were noted in numbers with percentiles. Survival analysis was conducted utilizing Kaplan-Meier tables and survival plots provided.

RESULTS

We determined that 61 patients were followed up with diagnosis of PMBL between October 2010 and May 2020. The mean and median age of the study group was 38.4 ± 13.5 (minimum to maximum: 18–69) years. From among them, 49.2% of the patients were female (n = 30). Four patients were at stage 1, 16 patients were at stage 2, and the others were at stages 3 or 4 67,2% (n = 41) at the time of diagnosis. Tumor histology revealed diffuse B-cell lymphoma (100%).

The IPI (ınternational prognostic index) scores, which calculate the estimated OS and PFS by using Ann Arbor staging, age, extranodal metastatic sites, ECOG (Eastern Cooperative Oncology Group) performance status and LDH (lactate dehidrogenase) levels, were high-medium risk and high risk in 28 patients (45.9%).[8] In high-medium risk and high risk IPI score patients, the one year and five years OS were 86.9% and 45.5%, respectively (P = 0.002 HR 12.3 [95 CI: 1.61-100]) [Table 1].

On mutational analysis of pathological specimens by using Polymerase Chain Reaction (PCR), we showed that 12 patients had double hit mutation. There was no triple hit mutation [Table 1].

Table 1: The demographic and disease-related characteristics of the patients

Features	*n* (%)	Mean±SD
Age (years)	61 (100)	38.4±13.5
Gender		
Male	31 (51.8)	
Female	30 (49.2)	
Histopathology		
Diffuse Large B Cell Lymphoma	61 (100)	
Ann Arbor Stage at the Time of Diagnosis		
3B	16 (26.2)	
4A	10 (16.4)	
4B	16 (26.2)	
IPI scores		
Low risk and low- medium risk	33 (54.1)	
High- medium risk and high risk	28 (45.1)	
Mutation analysis		
Bcl - 2	7 (11.5)	
Bcl- 6	15 (24.6)	
Myc	12 (19.7)	
Double Expressor	12 (19.7)	

The response of the patients after Therapies

Response	First line: *n* (%)	Second line: *n* (%)	Third line: *n*(%)	Fourth line: *n* (%)	Fifth line: *n* (%)
Complete Response	30 (49.1)	5 (17.2)	3 (20)	2 (20)	0
Partial Response	17 (27.9)	9 (31)	10 (66.7)	4 (40)	2 (25)
Stabil Disease	3 (5)	4 (13.8)	0	2 (20)	2 (25)
Progressive Disease	11 (18)	11 (37.9)	2 (13.3)	2 (20)	4 (50)

The treatments lines patients received

-Treatments	First line: *n* (%)	Second line: *n* (%)	Third line: *n*(%)	Fourth line: *n* (%)	Fifth line: *n* (%)
-R- CHOP	33 (54.2)	1 (3.4)	-		
-DA- EPOCH-R	25 (41)	2 (6.8)	-		3 (37.5)
-R- ICE	1 (1.6)	3 (10.4)	3 (20)		2 (25)
-R-DHAP	-	12 (41.4)	2 (13.3)	2 (20)	2 (25)
-R- CVP	1 (1.6)	1 (3.4)	1 (6.7)		
- R-ABVD	1 (1.6)	-	-		
-R- BENDAMUSTİN	-	3 (10.4)	1 (6.7)		10 (66.7)
-HDCT	-	-	2 (13.3)	8 (80)	
-RADYOTHERAPY	-	4 (13.8)	3 (20)		1 (12.5)
-R-GDP	-	3 (10.4)	3 (20)		

HDCT: High dose ChemoTherapy, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone, DA-EPOCH-R: dose adjusted, rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin, R- DHAP: Rituximab, High Dose Ara-C and Dexamethasone , R-ICE: Rituximab, Ifosfamide, Carboplatin and Etoposide, R-CVP: Rituximab, cyclophosphamide, vincristine, prednisone, R-ABVD: Rituximab, Adriamycin, Bleomycin, Vincristin and Dakarbazin, RT: Radiotherapy, , R- Bendamustin: Rituximab, bendamustin, R-GDP Rituximab, Gemcitabine, dexamethasone, cisplatin. IPI score: International Prognostic Index score

Sixty-one patients had received first-line chemotherapy. Thirty-three of them had received R-CHOP regimen (54%). Twenty-five patients received DA-EPOCH- R regimen [Table 1]. Thirty patients had complete response (49.1%), 17 patients had partial response (27.9%), and three patients had stabile disease (5%). Progression was observed in 11 patients [Table 1]. The ORR was 77%. The median OS and PFS were as follows: 25 months (95% CI: 20.4–29.4) and 13 months (95% CI: 8.6–17.3), respectively [Figures 1 and 2]. The OS and PFS at 12 months were 91.3% and 50%, respectively. The OS and PFS at five years were 64.9% and 36.7%, respectively. The median follow-up time period was 20 months (IQR 8.5–38.5). Ten patients had received high-dose chemotherapy (HDCT).

On univariate analysis of PFS for the first-line therapy, we showed that DA-EPOCH- R versus the other chemotherapy regimens was significantly different ($P = 0.037$, HR 2.28 [95% CI: 1.05–5]). Gender, age, stage at diagnosis, IPI score and MYC mutation were not different [Figure 1].

On univariate analysis of OS for the first-line therapy, we determined that IPI score and MYC mutation were significantly different ($P = 0.02$ and $P = 0.002$, respectively). Gender, age, stage at diagnosis and DA-EPOCH- R versus the other chemotherapy regimens were not different [Figure 1].

Patients underwent different combination therapies for the second, third and fourth lines [Table 1].

The numbers of side effects related to the first-line chemotherapy are demonstrated in Table 2. Leukopenia, anemia, thrombocytopenia, neurotoxicity, febrile neutropenia, diarrhea, vomiting/nausea were observed. No bleeding was observed. There was no life threatening toxicity [Table 2, Figure 3]. In the follow-up period, 10 patients were dead and no death was related to the treatment toxicities. Complete response was 30% [Figure 4].

DISCUSSION

PMBL are aggressive B-cell lymphomas that originate from the thymic medullary B-cells. They are clinicopathologically different from diffuse B-cell lymphomas and have some clinical and biological features of nodular sclerosing type Hodgkin lymphomas. The most appropriate treatment option is not known in PMBL. Various treatments are used in practice. There are no randomized controlled trials on PMBL treatments. Generally, data were obtained from retrospective or uncontrolled prospective studies. In these retrospective studies, rituximab was generally not added to chemotherapy regimens. Therefore, primary refractory or early relapse rates increased and the success rates of second-line treatments decreased.[9]

In the MabThera International (MinT) study, rituximab was added to the CHOP regimen. Three-year event-free survival and overall survival increased from 59% to 79% and from 84% to 93%, respectively.[9] Dunleavy *et al.* administered DA-R-EPOCH in 51 patients in a single-center phase 2 prospective study. Five-year event-free survival and overall survival were reported as 93% and 97%, respectively. None of them received radiotherapy.[10] We also mostly used R-CHOP and DA-EPOCH-R as first-line treatment. The OS and PFS at 12 months were 91.3% and 50%, respectively. The OS and PFS at five years were

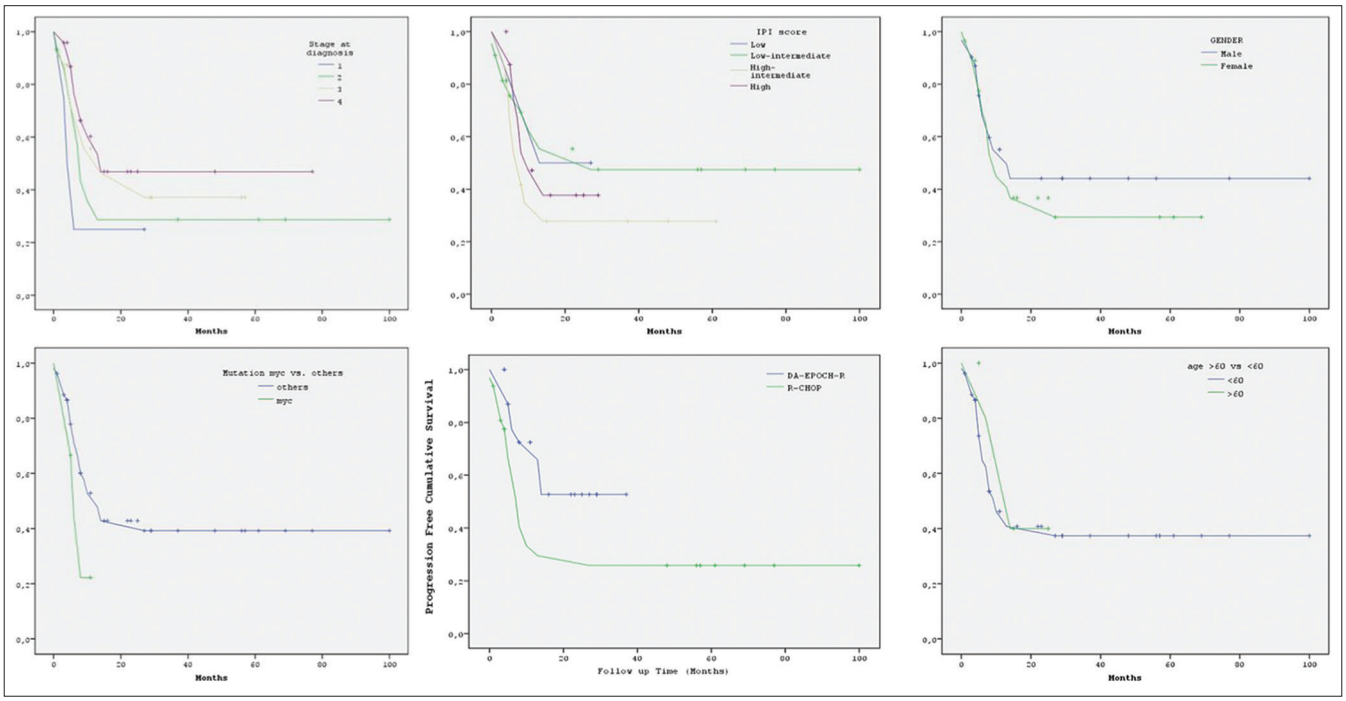

Figure 1: Progression free survival (PFS) of first line therapies (Kaplan-Meier Curve)

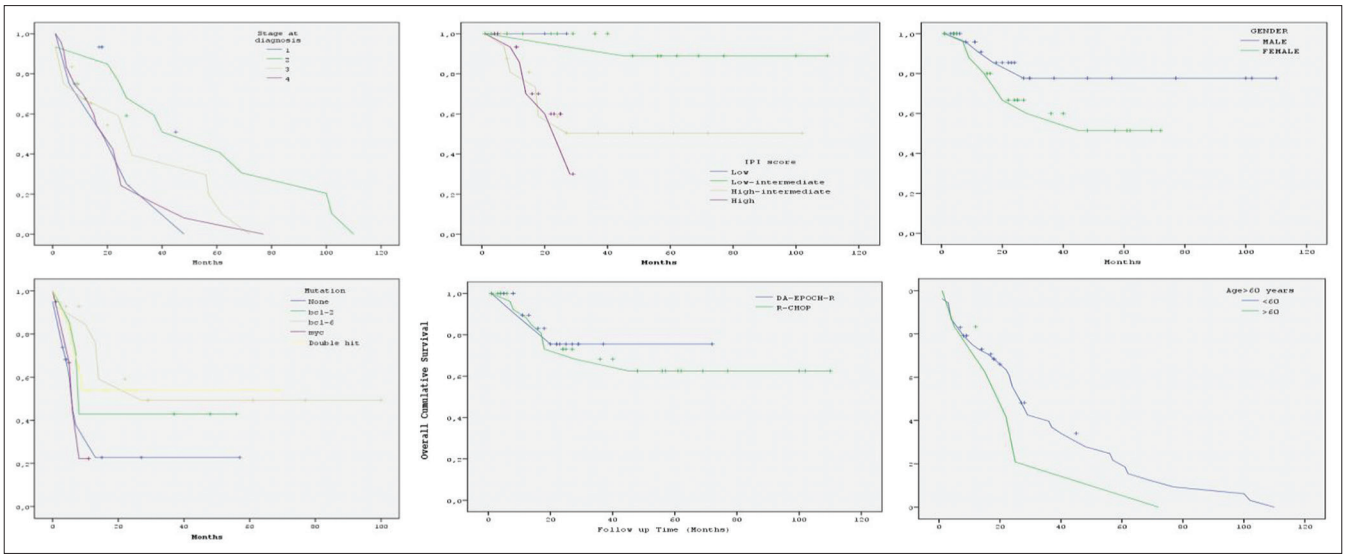

Figure 2: Overall survival (OS) of first line therapies (Kaplan-Meier Curve)

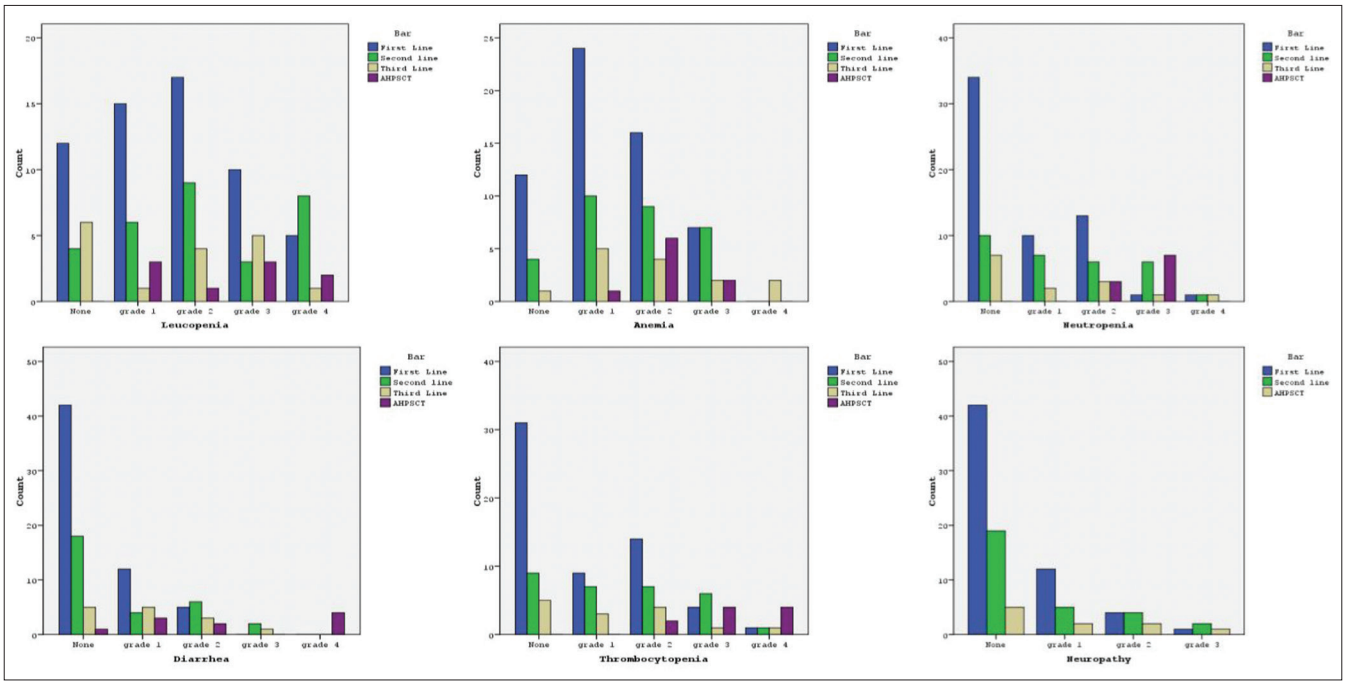

Figure 3: Toxicities of all therapy lines

64.9% and 36.7%, respectively. On univariate analysis of OS and PFS, DA-EPOCH-R regimen had better PFS than the other regimes, but OS was similar.

Treatment options in relapsed and refractory PMBL are the same as for relapse and refractory diffuse large B-cell lymphomas. The general approach is to perform HDCT in patients sensitive to chemotherapy.[11] Several retrospective studies showed that the response to second- and third-line treatments was poor in cases with relapse and refractory.[12] Armand *P et al*.[13] administered pembrolizumab in patients with PMBL expressing programmed death ligand-1 (PDL-1). They showed that ORR and CR were 50% and 30%, respectively. Zinzani PL *et al*.[14] used nivolumab plus brentuximab vedotin (anti-CD30) and showed that ORR and CR were 70% and 43%, respectively. Our patients mostly received R-DHAP, R-İCE, R-Bendamustin and HDCT for second-, third- and fourth-line treatments. Ten patients underwent HDCT.

Dunleavy *et al*.[10] showed that severe neutropenia and thrombocytopenia were detected in 50% of the patients. Febrile neutropenia developed in 13 patients. The toxicities of our treatments were similar as that in literature. Also, we observed that R-CHOP and DA-EPOCH-R had similar toxicities. No deaths were related to the treatments. Overall, the toxicities of first-lines were acceptable.

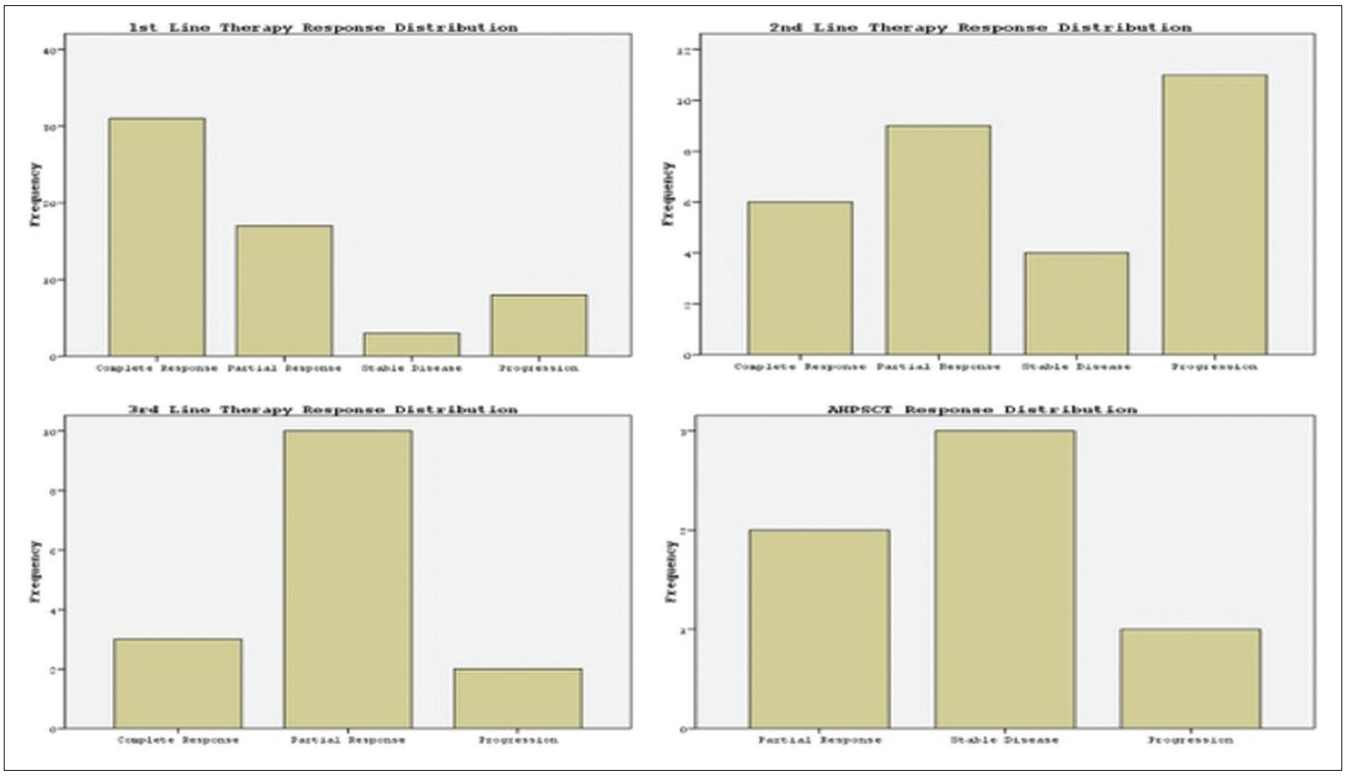

Figure 4: Responses of all therapy lines

Table 2: Toxicities of R-CHOP and R-EPOCH

Toxicities	R-CHOP *n* (%)	R-EPOCH
Leukopenia		
Grade 3-4 All grades	10 (30.3) 25 (75.7)	5 (32) 22 (88)
Anemia		
Grade 3-4 All grades	4 (12.1) 24 (72.7)	3 (12) 23 (92)
Thrombocytopenia		
Grade 3-4 All grades	2 (6) 12 (36.6)	3 (12) 12 (48)
Febril Neutropenia		
Grade 3-4 All grades	1 (3) 10 (30.3)	1 (4) 12 (48)
Neurotoxicity		
Grade 3-4 All grades	0 7 (21.2)	1 (4) 7 (28)
Vomiting/Nausea		
Grade 3-4 All grades	3 (9.1) 24 (72.7)	4 (16) 22 (88)
Diarrhea		
Grade 3-4 All grades	0 10 (30.3)	0 6 (24)

R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone, DA-EPOCH-R: dose adjusted, rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin

Vassilakopoulos *et al.*[15] detected that IPI score was not predictive for estimating prognosis of PMBL. We showed that in high-medium risk and high risk IPI scores, patients had poor prognosis.

Although this study had a small sample size of PMBL, we observed good PFS and OS. There are some limitations to the report. It is a retrospective study, and the patient population was relatively heterogeneous. The patient sample size was small. We believe that these patients need multidisciplinary expertise, and hence, should be treated at centers of stem cell transplantation excellence. The results cannot be applied to other countries with different cancer epidemiology and practice.

In conclusion, overall R-CHOP and DA-EPOUCH-R showed good results in PMBL. These remain one of the best determined systemic treatment options. Also, the treatment was associated with good efficacy and tolerability.

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Conflicts of interest

There are no conflicts of interest.

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