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Original Article

Retrospective evaluation of patients with primary mediastinal large B-Cell lymphoma: Real life experience

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Abstract

Aim: Primary mediastinal large B-cell lymphoma (PMBCL) is a type of lymphoma that forms approximately 3 % of non-Hodgkin lymphomas that often encounter with mass. The aim of this study was to present the epidemiological characteristics, response rates of the treatment and the survival of PMBCL patients in our single center.

Materials and Methods: Patient demographics, treatment regimens, survival rates of PMBCL patients were retrospectively analyzed.

Results: There are 15 patients in our study. Most of the patients were female (n:9, 60%). The median age at the time of diagnosis was 35.4. Nine patients applied with a bulky lesion in the mediastinum. Most of the patients have been treated with DA-EPOCH-R (dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine and prednisone with rituximab) (n:13, 87%) and 2 (n:2, 13%) patients have been treated with R-CHOP (doxorubicin, cyclophosphamide, vincristine and prednisone with rituximab) regimens for 6 cycles. Eight patients (53.3%) received involved-field radiotherapy on the mediastinum. After the first-row chemotherapy, total remission rate was 93.3%. Thirteen (87%) of the patients were still in remission and alive. The median follow-up time in our study was 43 months (13 -81). Mean disease-free survival was 67.43 months and overall survival was 72.87 months. The overall and disease-free survival rate was 86.7 % and 80%.

Conclusions: In our study, most patients responded to the treatment and are still being followed in remission.

Keywords: B-cell lymphoma; chemotherapy; Non-Hodgkin's lymphoma

INTRODUCTION

Primary mediastinal B cell lymphoma (PMBCL) is a type of non-Hodgkin lymphoma. It is believed to originate from thymus. It is categorized in the World Health Organization (WHO) classification because of its unique clinical, pathological and genetic features (1,2). PMBCL constitutes nearly 3% of all non-Hodgkin lymphomas (3). This type of lymphoma usually affects adults in their 30s and mostly occurs in female (4). Patients present typically with an anterior mediastinal mass. Depending on the mass effect in the mediastinum, symptoms such as cough, shortness of breath, chest pain and swelling of the face are common. Superior vena cava (SVC) may occur in approximately 50% of patients (5). At the time of diagnosis, patients are usually in stages 1 and 2 (6).

Histologically, PMBCL shows a large spectrum of possible morphologic appearances. Neoplastic cells have several nuclear characteristics like round to oval and may be irregular forms. In these infiltrative cells, markers such as CD20, CD79a, CD23, BCL2, BCL6 and MUM1 can be seen as positive (7). Disease-specific PD-L1 and JAK2 increases resulting from amplification of the 9p24.1 region were accused in PMBCL development (8).

There is no consensus on the optimal management of PMBCL. There are few prospective trials about optimal therapy. The initial therapy varies according to the stage of the disease and the performance status of the patient. But most preferred is a regimen containing rituximab and anthracycline (9). The use of radiation therapy is questionable and depends on the choice of induction chemotherapy and disease spread.

In our study, we aimed to investigate the epidemiological features, response rates and survival of PMBCL patients admitted to our center and to share our experiences on long-term results.

MATERIALS and METHODS

In our study, files of 15 PMBCL patients diagnosed in our center between 2010-2019 were analyzed retrospectively. These data were obtained from hospital records.

Parameters such as age, gender, stage, B symptoms, mediastinal mass size, serum lactate dehydrogenase

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levels (LDH), presence of extra nodal disease, bone marrow involvement, performance at the time of diagnosis and International Prognostic Index (IPI) score were evaluated. Patient's performances at the time of diagnosis were evaluated according to ECOG performance scoring (10). Ann Arbor Classification was used for staging the disease (11). Bulky disease was defined as a mass of ≥ 10 cm at the time of diagnosis. Patients were scored with the International Prognostic Index (IPI) as a prognostic marker (12). Lugano Classification was used to evaluate the response of the patients (13). Histopathological diagnosis was evaluated according to the morphological appearance and immunophenotyping of the tumor. All patients we included in the study were immunohistochemically CD20 positive. Response to treatment was evaluated after end of the induction chemotherapy by computerized tomographic scans according to the response criteria and bone marrow biopsy was done if initially involved.

Statistical Analysis

Overall survival time was calculated from the date of diagnosis to death or last follow-up and the disease-free survival time was calculated from the diagnosis date to the disease progression date. Survival curves were created by the Kaplan-Meier method. The median follow-up period was evaluated from the date of diagnosis until April 2020, the last updated.

Written informed consent was obtained from all patients that they allow their medical information to be used in clinical trials. Our study has the approval of Erciyes University Ethics Committee (approve number 2020/17).

RESULTS

The median age of 15 patients in our study was 35.4 (range, 20-60). Nine (%60) of the 15 patients included in the study were female. Eight (53 %) of the patients had B symptoms and 26.6% had superior vena cava syndrome. Of the PMBCL patients, 13% had bone marrow involvement. According to IPI scores, 66.6% of the patients were in the low-risk group and 6.6% were in the high-risk group. Most patients were in stage I–II (10 out of 15: 66.7%); stage III–IV patients were 5 out of 15 (33.3%). Bulky lesion in the mediastinum was present in 9 out of 15 (60%) cases. The mean larger diameter of the lesion is 110 mm, it is ranged from 60 mm to 167 mm. Pleural or pericardial effusions occurred at presentation in 9 (60%) cases. LDH levels were high in 13 cases. (1.76 times higher than normal range) The mean hemoglobin (g/dL), leucocyte (x109/L), and platelet (x109/L) levels of the patients at the time of diagnosis were 12.32, 10.6, 308.

Chemotherapy regimens combined with rituximab were preferred in all patients. A total of 13 patients have been treated with DA-EPOCH-R (dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine and prednisone with rituximab) and 2 patients have been treated with R-CHOP (doxorubicin, cyclophosphamide, vincristine and prednisone with rituximab) regimens for 6 cycles as the first line treatment. After the first-row chemotherapy; total remission rate was 93.3%, complete response was observed in 60 % and partial response was observed in 33,3% of the patients. Only 1 patient failed induction chemotherapy and died due to pneumosepsis. Eight patients (53.3%) received involved-field radiotherapy on the mediastinum.

Relapse occurred in two patients in the first year after the response. In one of the two patients, complete remission was seen with second-line chemotherapy and autologous bone marrow transplantation was performed after remission. Autologous transplantation was performed in two patients who had relapses after DA- EPOCH-R. One patient died after transplantation due to the disease progression.

Thirteen (86.7%) of the patients were still in remission and alive. The median follow-up time of the patients was calculated as 43 months (13-81.3 months). Mean disease-free survival was 67.43±7.16 (95%CI, 53.38 to 81.48) months and overall survival was 72.87±5.57 (95%CI, 61.93 to 83.80) months. The overall and disease-free survival rate was 86.7 % and 80%. (Figure 1 and 2) The clinical characters of the patients are shown in Table 1 and Table 2.

Table 1. Patients characteristics

	PMBCL (n:15)
Median age	35.4
Gender	
Female	9
Male	6
B symptoms	8
Mediastinal mass	
10 cm	6
≥10 cm	9
LDH	
Normal	2
Elevated	13
Stage	
I/II	10
III/IV	5
IPI score	
Low	10
Intermediate	4
High	1
Initial treatment regimen	
R-CHOP	2
R-DA EPOCH	13

Table 2. Patients characteristics

Patient	Chemotherapy Regimen	Response	Maximal diameter of mediastinal mass	Radiotherapy	ASCT	Follow-up time (month)
1	DA-EPOCH-R	CR	12	YES	NO	61.34
2	DA-EPOCH-R	PR	10	NO	NO	67.29
3	DA-EPOCH-R	CR	7	NO	NO	52.30
4	DA-EPOCH-R	CR	16.4	YES	YES	25.63
5	DA-EPOCH-R	PR	17	YES	NO	65.28
6	R-CHOP	CR	8	YES	NO	81.31
7	R-CHOP	CR	7	YES	NO	46.29
8	DA-EPOCH-R	PD	6	NO	YES	22.90
9	DA-EPOCH-R	CR	13	NO	NO	24.31
10	DA-EPOCH-R	CR	15.5	YES	NO	31.28
11	DA-EPOCH-R	PR	10.8	YES	NO	38.24
12	DA-EPOCH-R	CR	8	NO	NO	34.30
13	DA-EPOCH-R	CR	6.3	NO	NO	49.31
14	DA-EPOCH-R	PR	16.7	YES	NO	32.30
15	DA-EPOCH-R	PR	11	NO	NO	13.08

ASCT: Autologous Stem Cell Transplantation, DA-EPOCH-R: dose-adjusted etoposide, doxorubicin and cyclophosphamide with vincristine, prednisone and rituximab, R-CHOP: doxorubicin, cyclophosphamide, vincristine and prednisone with rituximab

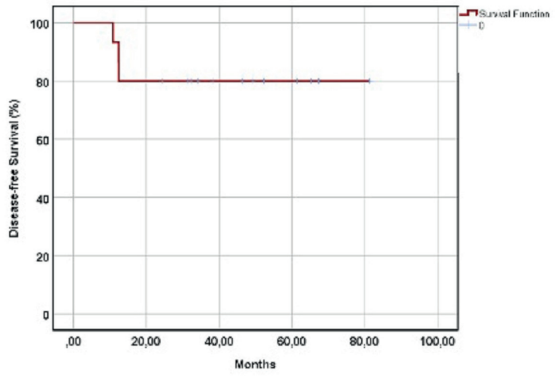

Figure 1. Disease-free Survival

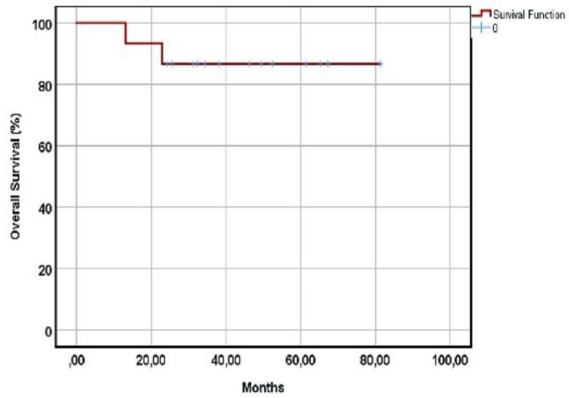

Figure 2. Overall Survival

DISCUSSION

The clinical characteristics of the patients in our study were similar to the literature (14). There are several discussions about first line induction therapy to be applied in PMBCL. Many different chemotherapy regimens have been tried in the treatment of PMBCL. Previously, CHOP-like treatments have been used frequently and responses have increased significantly with the addition of rituximab to the treatment (15, 16). In their study, Rieger et al. showed that when adding rituximab to CHOP-like chemotherapy, full remission rates improved (from 54% to 80%). In their studies, the 3-year disease-free survival rate was 78%, while 73% of the patients received radiotherapy (15). In another retrospective study involving 58 patients, R-CHOP was used as an induction therapy and 5-year progression-free survival was 68% (17). Treatments such as R-VACOP-B (rituximab, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin) and R-MACOP-B (rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) have been used in various studies and positive results have been obtained (18). In our study, R-CHOP chemotherapy was used in 2 patients who had no bulky lesion and then the involved-field radiotherapy was applied. Both patients are in remission and still alive.

Dunleavy et al. showed that DA-EPOCH-R (dose-adjusted etoposide, doxorubicin and cyclophosphamide with vincristine, prednisone and rituximab) regimen was very effective in PMBCL treatment in their phase 2 study.

In the prospective study of 51 patients, 5-year disease-free survival was reported as 93% and the overall survival was 97%. In this study, only 2 patients required consolidation radiation, consolidative radiotherapy is significantly reduced (19). In our study, 87% of the patients received the DA-EPOCH-R regimen. A total of 8 patients received radiotherapy, two of whom were patients receiving R-CHOP regimen. Six of 13 patients who received DA-EPOCH-R regimen had radiotherapy. In patients undergoing DA-EPOCH-R, there was a significant decrease in the need for radiotherapy.

Due to the excellent results after chemo-radiotherapy, the number of studies showing the efficiency of transplantation in the first line treatment is limited. It is reported to be preferred for relapse and refractory disease (20-22). Therefore, autologous transplantation was not used as the first line treatment in any of our patients. In our study, autologous transplantation was performed to 2 patients who were relapsed and refractory.

Relapses in PMBCL often occur in the early period after treatment, especially in the first year and they can be seen in the mediastinum as well as in extra nodal regions (23). Relapse occurred in two of our patients. One of them originated from the mediastinum and the other was from the central nervous system. In a study, the response rate after recovery therapy (25% vs 48%, p = 0.01) in PMLCL patients and 2-year survival after RR disease (15% vs. 34%, p = 0.018) were found to be lower (24). Unfortunately, our patient with central nervous system spread died despite salvage chemotherapy and autologous transplantation.

Currently, nivolumab and pembrolizumab, which are PD-1 blockers, are also used in the treatment of this disease. They stand out with their high response rates and safety profiles (25-27).

CONCLUSION

In conclusion, PMBCL is lymphoma type that occurs with mediastinal mass in young female. There is no consensus on treatment. There are various protocols in the literature about disease management. In a large part of our patients, we preferred an intensive regimen such as DA-EPOCH-R and combined some of these patients with radiotherapy. We think that our results are very promising. However, since our study is a single center experience, it has limitations and further large scale multi center studies are needed.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: The study was approved by the Erciyes University Ethics Committee (No:2020/17).

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