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The outcome of primary mediastinal B-cell lymphoma in a single center experience

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ABSTRACT

Introduction: Primary mediastinal B-cell lymphoma (PMBCL) is an aggressive distinct subtype of diffuse large B-cell lymphoma (DLBCL). There is no standard treatment for PMBCL and the value of mediastinal radiotherapy and autologous hematopoietic stem cell transplantation (AHSCT) remains to be elucidated. **Material and methods:** A retrospective analysis of 12 patients with PMBCL (8 male and 4 female) at median age of 36 years has been performed. Induction chemotherapy consisted of R-DA-EPOCH ($n = 7$), R-CHOP ($n = 4$) and R-CVP ($n = 1$). Second and third line treatments were administered in 6 and 2 patients, respectively. Nine patients were given involved field mediastinal radiotherapy. Finally, 8 patients were proceeded to AHSCT. **Results:** Four patients achieved CR and 4 PR after induction therapy with an overall response rate of 66%. In total, after completion all lines of the combined chemotherapy, the following disease responses have been observed: complete response (CR) in 4 patients, partial response (PR) in 6 and no response/disease progression (NR/PD) in 2. The overall response rate was 83%. Eight patients were proceeded to AHSCT (4 in CR and 4 in PR). The transplant-related mortality was 0% at day 100. Median follow-ups from diagnosis and from AHSCT were 39.5 months (range 8–106) and 32 months (range 3–95), respectively. All transplanted patients are alive with CR confirmed in PET scans. **Conclusions:** The vast majority of PMBCL patients are susceptible to immunochemotherapy with a high response rate achieved after R-DA-EPOCH/R-CHOP regimens. AHSCT seems to be an option for fit patients with disease chemosensitivity.

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Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is an aggressive distinct subtype of diffuse large B-cell lymphoma (DLBCL) that arises in the thymus, and presents as a bulky mediastinal mass, often with pleural and pericardial effusions. The disease occasionally disseminates to extranodal sites including kidneys, brain, lungs or gastrointestinal organs. PMBCL affects females more frequently than men and median age at diagnosis is 30–40 years [1, 2]. A large proportion of patients have mutations in the B-cell lymphoma 6 gene (BCL6). PMBCL is also characterized by an amplification of the *REL* proto-oncogene and the *JAK2* tyrosine kinase gene which are normally observed in patients with Hodgkin's lymphoma, suggesting their common origin [3, 4]. An optimal chemotherapy schema as well as the role of radiotherapy in the management of PMBCL are to be elucidated. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen with or without radiotherapy was found to be effective in 50–60% of patients [5, 6]. The results of CHOP plus rituximab followed by radiotherapy were also found not to be fully satisfactory. In addition, the long-term side effects of mediastinal radiation especially in young adult patients might be devastating [7, 8]. A recently published study has suggested that more dose-intense regimen consisting of dose-adjusted etoposide, doxorubicin, cyclophosphamide with vincristine and prednisone plus rituximab (R-DA-EPOCH) without consolidation radiotherapy may improve outcome in patients with PMBCL [9].

Herein we report on the clinical outcome of our 12 patients with PMBCL treated in our center between 2005 and 2013.

Material and methods

Patients selection and characteristics

Between February 2005 and December 2013, twelve patients (8 male and 4 female) at median age at diagnosis of 36 years (range 22–58 years), with PMBCL were admitted to our institution. There were following complaints at admission: chest pain ($n = 7$), dyspnea ($n = 6$), fatigue ($n = 5$) and cough ($n = 8$). At diagnosis 3 patients demonstrated vena cava superior syndrome. Five patients presented with B symptoms. The disease stage was evaluated according to the Ann Arbor staging system and 8 patients had stage IV (pericardial and/or pleural effusion). The diagnostic work-up included a complete physical examination, routine hematology and biochemistry studies, chest X-ray, computed tomography of the neck, chest, abdomen, and pelvic and/or positron emission tomography (PET) scans and bone marrow biopsy. The final diagnosis was based on histological examination of the excised lymph node obtained during mediastinoscopy and performed by a local pathologist. Due to the fact that some patients were referred from other centers, not all data were available for all our patients. The clinical characteristics of study patients were presented in Table I.

Table I – Baseline patients characteristics

Parameter	$n = 12$ (%)
Gender male/female	8/4
Median age, year (range)	36 (22–58)
Bulky tumor ≥10 cm	5 (42)
Enlargement of subclavicular lymph nodes	4 (33)
Superior vena cava syndrome	3 (25)
Bone marrow involvement	0 (0)
B symptoms	5 (42)
Stage IV disease	8 (67)
Median hemoglobin concentration, g/dL (range)	12.5 (10–14.3)
Median WBC count, 10^9/L (range)	8.7 (5–11.2)
Median PLT count, 10^9/L (range)	354 (97–637)
Elevated LDH level	9 (75)
Elevated β_2 microglobulin	1 (8)

LDH: lactate dehydrogenase, WBC: white blood cells, PLT: platelets.

Treatment before AHSCT

Chemotherapy was not uniform in all studied patients and depended on the patient's overall condition (co-morbidities), year of diagnosis and physician's discretion. Induction therapy consisted of R-DA-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; $n = 7$), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; $n = 4$) and R-CVP (rituximab, cyclophosphamide, vincristine, prednisone; $n = 1$). Due to the insufficient response/early relapse after induction, 6 patients were given a second-line treatment consisting of R-ESHAP (rituximab, cisplatin, methylprednisolone, etoposide, cytarabine; $n = 4$) and R-CHOP ($n = 2$). Two patients received third-line schema: R-CHOP ($n = 1$) and IVAC (ifosfamide, etoposide, cytarabine; $n = 1$). In addition, 9 patients received involved field radiotherapy at a dose of 36 Grey (Gy). Finally, 8 patients were proceeded to AHSCT.

Response criteria

Complete remission (CR) was defined as a disappearance of all measurable lesions and symptoms for at least 4 weeks. Partial remission (PR) was defined as 50% reduction. Progressive disease (PD) was defined by any increase >25% in the sum of the diameter of any measurable lesions, or the appearance of a new lesion. CT was performed in all patients before treatment and after each line of therapy. The further evaluation using CT supported by PET was performed 3 and 6 months after AHSCT [10].

Transplant procedure

Mobilized peripheral blood was the source of stem cells for AHSCT in all transplanted patients. The regimen used for mobilization was IVE (ifosfamide, etoposide, epirubicine) in all 8 patients. The preparative regimens included CBV (cyclophosphamide, BCNU, etoposide; $n = 5$) and BEAM (BCNU, cytarabine, etoposide, melphalan; $n = 3$). Six patients required granulocyte colony stimulating factor (G-CSF) to expedite post-transplant regeneration.

Results

Therapy before AHSCT

Four patients achieved CR and 4 PR after induction therapy with an overall response rate of 66%. Four patients had stable disease after induction: R-DA-EPOCH ($n = 2$), R-CHOP ($n = 1$) and R-CVP ($n = 1$). Second-line therapy was administered in 6 patients: 4 with SD after induction, 1 with PR and 1 with early relapse from CR. Among these 6 patients, one patient achieved CR, 4-PR and 1 remained in SD. Third-line treatment received 2 patients, all with PR after the second-line. One of them remained in PR and one developed disease progression. In total, after completion the 3 lines of the combined chemotherapy, the following disease responses have been observed: CR in 4 patients, PR in 6 and NR/PD in 2. The overall response rate was 83%. Eight patients were proceeded to AHSCT (4 in CR and 4 in PR). Two patients remained in PR without AHSCT whereas 2 remaining patients died from disease progression and subsequent chemoresistance. The treatment details were listed in Table II.

Cell dose and engraftment in transplanted patients

The median number of transplanted nucleated cells was 3×10^8/kg (range 0,8–8.4) and the median number of CD34-positive cells was 6.8×10^6/kg (range 3–19). All patients engrafted. The median time to neutrophil recovery for our four patients was 13 days (range 7–19) and platelet count $>50 \times 10^9$/L was noted after a median of 14 days (range 10–19). No patient died within 100 days after the transplant.

Adverse events of AHSCT

Six transplanted patients demonstrated complications in the post-transplant period. Grade 3 or 4 non-hematological adverse events were not observed. One patient developed fever with positive fungal cultures. The other complications included proctitis ($n = 2$), gastritis ($n = 1$) and pharyngitis ($n = 2$). One patient suffered from cardiac failure, but probably due to prior radiotherapy.

AHSCT outcome

The transplant-related mortality was 0% at day 100. Median follow-ups from diagnosis and from AHSCT were 39.5 months (range 8–106) and 32 months (range 3–95), respectively. All transplanted patients are alive with CR confirmed in PET scans.

Discussion

There were only single prospective studies in PMBCL, however no consensus in terms of therapeutic standard has been established [5, 11, 12]. The value of mediastinal radiotherapy was raised in several studies, but one should realize its long-term effects [5, 11]. It was demonstrated that aggressive combined chemotherapy resulted in higher rate of CR and fewer relapses if compared with standard CHOP/CHOP-like regimen [5]. The results of treatment with R-DA-EPOCH in PMBCL seem to be the most encouraging. The event-free (EFS) and overall survival (OS) rates at 5 years were 93% and 97%, respectively. Three patients had active disease after R-DA-EPOCH completion and 2 out of them received mediastinal radiotherapy being disease-free at the last contact. One patient developed acute myeloid leukemia and died while in remission of his PMBCL. To verify the outcomes, the results were then compared with those presented in a retrospective analysis from another center. The outcome was also highly satisfactory with EFS rate was 100% after median of 3 of follow-up. The radiotherapy was omitted in this study [9]. The EFS and OS rates at 16 years using the same regimen but without rituximab were 67%

Table II – Therapy for primary mediastinal B-cell lymhoma

Patient	Age at diagnosis (years)	First-line treatment	Response	Second-line treatment	Response	Third-line therapy	Disease status after completion of therapy	AHSCT	Status at last contact
1.	39	R-DA-EPOCH	PR	R-ESHAP	PR	R-CHOP	PR	YES	CR
2.	33	R-DA-EPOCH	CR				CR	YES	CR
3.	37	R-DA-EPOCH	SD	R-ESHAP	NR		NR/PD	NO	DEATH
4.	26	R-DA-EPOCH	CR				CR	YES	CR
5	32	R-DA-EPOCH	PR				PR	YES	CR
6.	34	R-DA-EPOCH	SD	R-ESHAP	PR	IVAC	PD	NO	DEATH
7.	40	R-DA-EPOCH	PR				PR	NO	PR
8.	33	R-CHOP	SD	ESHAP	PR		PR	YES	CR
9.	30	R-CHOP	CR				CR	YES	CR
10.	52	R-CHOP	CR/REL	R-CHOP	CR		CR	YES	CR
11.	22	R-CHOP	CR/REL	R-CHOP	CR		CR	YES	CR
12.	58	R-CVP	SD	R-CHOP	PR		PR	NO	PR

CR: complete response, PR: partial response, SD: stable disease, NR: no response, PD: progression disease, REL: relapse; AHSCT: autologous hematopoietic stem cell transplantation.

and 78% respectively [13]. This finding seems to confirm the benefit of rituximab added to conventional chemotherapy. This combination improved EFS and OS rates if compared with chemotherapy alone [12]. However, the survival advantage of rituximab added to chemotherapy was not demonstrated by other reports [14]. Based on the results provided by Dunleavy et al. [9], the R-DA-EPOCH regimen seems to be highly effective with no further need of mediastinal radiotherapy in a vast majority of treated patients. This regimen was found to be safe with no serious late effects. It is difficult to interpret data on the efficacy of R-DA-EPOCH from our analysis due to small number of included patients. Nevertheless, after the median number of 6 cycles (range 3–8), the response rate was 71% with CR attained in merely 30% of patients. Two patients from this cohort died due to disease progression and subsequent resistance to chemotherapy, four patients are in CR, but all they underwent AHSCT. One patient remained in PR without AHSCT. It should be mentioned that toxicity of R-DA-EPOCH was manageable with no late morbidity. Keeping in mind all drawbacks of our study, the response rates were not as satisfactory as reported by Dunleavy [9]. Moreover, they were even worse if compared with those achieved by R-CHOP regimen where CR rate was 75%. However, the rapid relapse occurred in 2 patients shortly after R-CHOP completion. Nevertheless, our data are insufficient to draw any conclusions. The role of mediastinal radiotherapy after completion of the chemotherapy seemed to be crucial in the therapeutic algorithm of PMBCL at least in some reports. Namely, CR rate was 26% after intensive MACOP-B regimen and increased to 88% after local radiotherapy. The estimated 9-year relapse-free survival was 91% after median of 4 years of follow-up with all relapses occurring within the first year. This study strongly demonstrated the pivotal role of radiotherapy in the treatment of PMBCL [11]. Mediastinal radiotherapy was also used in 75% of patients included to our study with an intention to consolidate CR ($n = 3$), to convert patients from PR to CR before AHSCT ($n = 4$) or as a salvage regimen in resistant cases ($n = 2$). However, in the rituximab era, the value of radiotherapy remains unclear and one should realize the risk of long-term toxicity. In fact, one patient from our study developed cardiac failure several weeks later.

The benefit of high-dose chemotherapy with stem cell rescue as a CR consolidation in PMBCL is to be validated in clinical trials. The results of AHSCT in PMBCL are scarce and inconclusive. The largest study published to date, came from the GEL-TAMO registry and included 71 patients with high-risk clinical features. Nearly 50% of patients were in CR at transplant and received prior radiotherapy. After the median follow-up of 4 years the OS and PFS rate were 80% for patients transplanted in CR and less than 50% for those in PR or less [15]. The high rates of OS and PFS in patients transplanted in CR were also demonstrated by others [5, 16]. Our study has reported the high efficacy of AHSCT with 100% of CR maintained nearly 3 years after transplantation. However, one should be aware that only randomized study could demonstrate the value of AHSCT in this study population. The vast majority of reports were performed before the addition of rituximab to conventional chemotherapy. Based on the excellent results of R-DA-EPOCH study [9], the frontline AHSCT as well as radiotherapy could be redundant. Nevertheless, our small series has demonstrated the high efficacy of AHSCT in patients with relapsed chemo-sensitive disease. It was demonstrated that disease status before transplant may influence its outcome and the incorporation of PET imaging allowed for better response evaluation. However, one should keep in mind the high proportion of false positive results of PET after chemotherapy completion for PMBCL. In fact, 18 patients out of 36 from Dunleavy study had an excellent outcome without further therapy despite the presence of positive PET scan after therapy [9]. It turned out that PMBLC patients transplanted in PR fared worse than those in CR, but significantly better than patients with refractory disease [15]. Relapsed and refractory PMBCL patients had an inferior response rate and survival if compared with diffuse large B-cell lymphoma (DLBCL), but the post-AHSCT outcome is similar for chemo-sensitive PMBCL and DLBCL patients [17].

Conclusions

The vast majority of PMBCL patients are susceptible to immunochemotherapy with high response rate achieved after R-DA-EPOCH/R-CHOP regimen. The role of radiotherapy should be limited to patients with residual tumor mass in mediastinum, but one should keep on mind its long-term toxic effects. AHSCT seems to be an option for fit patients with disease chemo-sensitivity.

Authors' contributions/Wkład autorów

AA – study design, manuscript preparation, literature search. MS – data collection, literature search, manuscript preparation. GH – study design, data collection and interpretation, manuscript preparation, literature search. KW and AWK – data collection. SKK – study design, data interpretation. JP – histological examination and data interpretation. AK – data collection. MKK – data interpretation.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES/PIŚMIENNICTWO

[1] Savage KJ. Primary mediastinal large B-cell lymphoma. Oncologist 2006;11:488–495.
[2] Gaulard P, Harris NL, Pileri SA, et al. Primary mediastinal (thymic) B-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed., Lyon, France: International Agency for Research on Cancer; 2008.
[3] Guiter C, Dusanter-Fourt I, Copie-Bergman C, et al. Constitutive STAT6 activation in primary mediastinal large B-cell lymphoma. Blood 2004;104:543–549.
[4] Weniger MA, Gesk S, Ehrlich S, et al. Gains of REL in primary mediastinal B-cell lymphoma coincide with nuclear accumulation of REL protein. Genes Chromosomes Cancer 2007;46:406–415.
[5] Zinzani PL, Martelli M, Bertini M, et al. Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients. Haematologica 2002;87:1258–1264.
[6] Hamlin PA, Portlock CS, Straus DJ, et al. Primary mediastinal large B-cell lymphoma: optimal therapy and prognostic factor analysis in 141 consecutive patients treated at Memorial Sloan Kettering from 1980 to 1999. Br J Haematol 2005;130:691–699.
[7] Abramson J, Hellmann M, Feng Y, et al. High rate of initial treatment failure in patients with primary mediastinal B-cell lymphoma treated with R-CHOP. Blood ASH Annu Meet Abstr 2011;118:1601.
[8] Aviles A, Neri N, Fernandez R, et al. Randomized clinical trial to assess the efficacy of radiotherapy in primary mediastinal large B-lymphoma. Int J Radiat Oncol Biol Phys 2012;83:1227–1231.
[9] Dunleavy K, Pittaluga S, Maeda LS, et al. Dose adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013;368:1408–1416.
[10] Cheson BD. New response criteria for lymphomas in clinical trials. Ann Oncol 2008;19(Suppl. 4):iv35–iv38.
[11] Zinzani PL, Martelli M, Bendandi M, et al. Primary mediastinal large B-cell lymphoma with sclerosis: a clinical study of 89 patients treated with MACOP-B chemotherapy and radiation therapy. Haematologica 2001;86:187–191.
[12] Rieger M, Osterborg A, Pettengell R, et al. Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: results of the Mabthera International Trial Group study. Ann Oncol 2011;22:664–670.
[13] Wilson WH, Grossbard ML, Pittaluga A, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamics approach with high efficacy. Blood 2002;99:2685–2693.
[14] Savage KJ, Al-Rajhi N, Voss N, et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. Ann Oncol 2006;17:123–130.
[15] Rodriguez J, Conde E, Gutierrez A, et al. Primary mediastinal large cell lymphoma (PMBL): frontline treatment with autologous stem cell transplantation (ASCT). The GEL-TAMO experience. Hematol Oncol 2008;26:171–178.
[16] Cairoli R, Grillo G, Tedeschi A, et al. Efficacy of an early intensification treatment integrating chemotherapy, autologous stem cell transplantation and radiotherapy for poor risk primary mediastinal large B cell lymphoma with sclerosis. Bone Marrow Transplant 2002;29:473–477.
[17] Kuruvilla J, Pintilie M, Tsang R, et al. Salvage chemotherapy and autologous stem cell transplantation are inferior for relapsed or refractory primary mediastinal large B-cell lymphoma compared with diffuse large B-cell lymphoma. Leuk Lymphoma 2008;49:1329–1336.