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Authors: Justyna Rybka, Bartłomiej Kuszczak, Aleksandra Bogucka-Fedorczuk

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Treatment of primary central nervous system lymphoma (PCNSL) — single center experience and literature review

Justyna Rybka, Bartłomiej Kuszczak, Aleksandra Bogucka-Fedorczuk

Clinical Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Wrocław, Poland

Abstract

Introduction: Primary central nervous system lymphoma (PCNSL) is a rare extranodal type of non-Hodgkin's lymphoma. Diffuse large B cell lymphoma (DLBCL) is most often histopathologically confirmed. Modern PCNSL therapy should include an induction and a consolidation phase. Treatment regimens are based on high doses of methotrexate, and the intensity of therapy is adapted to the age of patients and their biological condition.

Material and methods: The aim of this study was a retrospective analysis of the effectiveness and toxicity of therapy used in patients diagnosed with DLBCL of the central nervous system (CNS), treated at the Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation in Wroclaw, Poland, between 2015 and 2022. The analyzed population included 46 patients with a median age of 64.5 years (range: 27–80). Patients were treated according to the R-MATRix, R-MPV, or R-HD-MTX-ARA-C regimen.

Results: After the first-line treatment, complete remission (CR) was achieved in 11 patients, partial remission (PR) in 15, and seven did not respond to the therapy. 11 patients died and two were not qualified for chemotherapy due to their poor general condition. The effectiveness of R-MATRix and R-MPV was similar.

Conclusions: We have shown that the use of the MATRix regimen is associated with greater toxicity and prolonged neutropenia.

Key words: primary central nervous system lymphoma, diffuse large B-cell lymphoma of central nervous system, immunochemotherapy, toxicity

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare, extranodal form of non-Hodgkin's lymphoma (NHL), which accounts for c. 4% of all primary brain tumors. According to the new WHO classification (5th edition), PCNSL is included in primary large B-cell lymphoma of immune-privileged sites [1]. PCNSL is limited to the brain, spinal cord, eyeballs, meninges, cranial nerves, and cerebrospinal fluid. In 90–95% of cases, diffuse large B cell lymphoma (DLBCL) is diagnosed based on histopathological examination of the tumor. Much less common are T-cell lymphomas, Burkitt's lymphoma, lymphoblastic lymphomas and marginal zone lymphomas [2, 3]. The pathogenesis of PCNSL remains unknown in most cases, but the defined risk factors for PCNSL include HIV infection or fully developed AIDS, inborn errors of immunity, and chronic immunosuppression after organ transplantation. The median age at diagnosis in patients with PCNSL is 65 years, and the incidence of PCNSL increases with age [4].

The most common symptoms of PCNSL include deterioration of cognitive functions, personality changes,

*Address for correspondence: Justyna Rybka, Clinical Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Pasteura 1, 50-367 Wrocław, Poland; email: rybka.justyna@o2.pl

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confusion, focal neurological deficits, headaches, hydrocephalus, nausea and vomiting caused by intracranial hypertension [3, 5]. Sometimes, rapid neurological decline is observed. Convulsive incidents occur less frequently than in other brain tumors (10–20% of patients), eyeball involvement is also possible in 15–20%, and blurred vision may precede, or coexist with, neurological symptoms. General symptoms are very rare in this patient population [5]. PCNSL is an aggressive lymphoma, and although the response to chemotherapy and radiotherapy varies between 70% and 90%, relapses are frequent and are associated with a poor prognosis [4]. PCNSL therapy includes multidrug chemotherapy regimens in combination with an anti-CD20 monoclonal antibody, and autologous bone marrow stem cell transplantation in patients with at least a partial response to treatment. In patients not eligible for transplantation, radiotherapy is recommended [5].

The aim of this retrospective analysis was to assess the effectiveness and toxicity of PCNSL therapy in patients hospitalized in the Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland between 2015 and 2022.

Material and methods

Study population

This retrospective analysis included 46 patients (27 women and 19 men) diagnosed with PCNSL treated in the Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation at Wroclaw Medical University between 2015 and 2022. The median age was 64.5 years (range: 27–80). All patients underwent stereotactic brain biopsy with tumor samples taken. All cases were diagnosed with DLBCL based on histopathological examination of the tumor. In one patient, lymphoma was associated with fully-symptomatic AIDS. The clinical symptoms in patients included focal signs, aphasia, disorientation, visual disturbances, psychomotor retardation, dizziness and headaches. According to the MSKCC (Memorial Sloan Kettering Cancer Center) prognostic score, 5/46 patients were low risk, 20 were intermediate risk, and 21 were high risk [6].

Patients qualified for the MATRix and R-HD-MTX-ARA-C regimens were aged under 65, in good clinical condition, and without comorbidities. Patients qualified for the R-MPV regimen were aged 65 or over, in a worse general condition, and with additional diseases.

The clinical data of the patients is set out in Table I.

Table I. Clinical data of patients

Number of patients	46
Age	64.5 years (range: 27–80)
Sex	19 male
	27 female
Histopathological diagnosis	46 DLBCL CNS
AIDS-related PCNSL	1
Symptoms, n (%)	
Focal	21 (45%)
Aphasia	14 (31%)
Confusion	10 (22.5%)
Vision disorders	8 (17.5%)
Psychomotor retardation	8 (17.5%)
Dizziness	7 (15%)
Headaches	7 (15%)
MSKCC – risk groups, n (%)	
Low risk	5 (11%)
Intermediate risk	20 (43%)
High risk	21 (46%)
ECOG, n (%)	
0	3 (6%)
1	17 (37%)
2	12 (26%)
3	4 (9%)
4	10 (22%)

PCNSL – primary central nervous system lymphoma; DLBCL – diffuse large B-cell lymphoma; CNS – central nervous system; AIDS – Acquired Immune Deficiency Syndrome; MSKCC – Memorial Sloan Kettering Cancer Center prognostic model

Statistical analysis

We assessed overall response rate (ORR), overall survival (OS), progression free survival (PFS) and toxicity of treatment. OS was calculated from the start of treatment until death or until the date of the final follow-up, and PFS was assessed from the start of treatment until the date of disease progression, relapse, or death. Statistical analysis was performed using the R program. The Kaplan-Meier estimation method was used to evaluate OS and PFS. Differences between groups of patients were analyzed using a log rank test. The end-point estimates were given with a 95% confidence interval (CI).

Results

Treatment

26 patients with PCNSL were qualified for R-MPV chemotherapy (rituximab, methotrexate, procarbazine, vincristine), 11 patients received treatment according to the MATRix protocol (methotrexate, cytarabine, thiotepa, rituximab), six patients received R-HD-MTX-ARA-C (rituximab, methotrexate, cytarabine), and one received R-HD-MTX (rituximab, methotrexate) [7, 8].

2/46 patients were not qualified for chemotherapy due to poor general condition. In all patients who received high doses of methotrexate treatment, serum methotrexate concentrations were monitored. All patients qualified for immunochemotherapy were treated with primary

prophylaxis of neutropenia with granulocyte-colony stimulating factor (G-CSF). As part of the consolidation, nine patients who responded to the therapy underwent autologous bone marrow stem cell transplantation (autoPBSCT, peripheral blood stem cell transplantation). Six of these nine patients underwent MATRix treatment and the other three underwent R-HD-MTX-ARA-C treatment. Before transplantation, all patients achieved complete remission (CR). The conditioning regimen was based on carmustine, etoposide and thiotepa. Three months after transplantation, CR was maintained in all patients, which was confirmed by magnetic resonance imaging. Seven patients are still alive, one patient died due to SARS-COV-2 infection, and one has been lost to follow-up. Median follow-up in patients after autotransplantation was 23 months (range: 13–65). Seven patients who, due to age and biological condition, were not eligible for autotransplantation, underwent whole brain radiation therapy (WBRT). The dose of WBRT was 24 Gy or 36 Gy, depending on the response to chemotherapy.

For the whole study population, median follow-up was 13 months (range: 1–24).

Response to treatment

After first-line treatment, 11 patients achieved CR, 15 achieved partial remission (PR), seven achieved no response (NR), and 11 died before response evaluation. The assessment of the treatment was performed after three cycles of chemotherapy and the end of treatment using brain magnetic resonance imaging (MRI). The overall response rate (ORR) after the first line of treatment in the whole analyzed population was 56.5%. The median OS was 18 months, and the median PFS was 10 months. In the group of seven patients who did not respond to first-line therapy (three after MATRix and four after R-MPV), the second-line treatment was temozolomide with high doses of methotrexate and cytosine arabinoside in two patients, lenalidomide monotherapy in three, and radiotherapy only in two. CR was achieved in two patients, PR in two, and no response in three. The cause of death in five patients was disease progression, in three patients it was severe infectious complications, in two patients it was brain edema, and in one patient it was perforation of the large intestine. A comparison of the MATRix, R-MPV, and R-HD-MTX-ARA-C regimens is set out in Table II.

Therapy toxicity

Neutropenia < 0.5 10^3/ul (grade 4) occurred more often in patients receiving MATRix than R-MPV (63% vs. 23%). The median duration of neutropenia after the MATRix regimen was 12 days as opposed to two days after the R-MPV regimen. Febrile neutropenia occurred in 36% of patients receiving MATRix and in 7% of patients receiving R-MPV. Increases in transaminase levels (grades 3–4) were observed in 36% of patients after MATRix and in 26% of patients after R-MPV. Other less frequent adverse reactions included nephrotoxicity grades 2–3 in 6.5% (three patients), neurotoxicity grade 3 in 9% (four patients), septic shock grade 4 in 9% (four patients), skin lesions grades 2–3 in 2% (one patient), and pneumonia grade 3 in 4.5% (two patients).

Discussion

For years, radiotherapy has been the basis of PCNSL treatment, but only its combination with chemotherapy has significantly improved results in this patient population [9]. Currently, chemotherapy plays an essential role in the treatment of PCNSL. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) has been shown to be ineffective in the treatment of patients with PCNSL [10]. However, the addition of high doses of methotrexate (HD-MTX) to the CHOP regimen has resulted in increased toxicity without improvement in response compared to HD--MTX monotherapy [11].

The modern approach to the treatment of patients with PCNSL includes two main stages of therapy: the induction phase and the consolidation phase. Induction treatment is polychemotherapy containing high doses of methotrexate. The exact dose and duration of HD-MTX administration have not been defined, but in most analyses, a dose of ≥3 g m^2 in a 3-hour infusion seems to be optimal. The randomized International Extranodal Lymphoma Study Group — 20 (IELSG20) study showed that the addition of high doses of cytarabine to HD-MTX results in higher rates of CR, and prolongs the PFS, compared to MTX monotherapy [12].

The choice of PCNSL therapy depends primarily on the patient's age, which is one of the most important prognostic factors. Other parameters that influence the therapeutic decision regarding the use of HD-MTX-based chemotherapy include comorbidities and organ dysfunctions. In fact, there is no defined age that would constitute a boundary between younger and older patients. According to some authors, age >60 years is a contraindication to consolidation of megachemotherapy supported by autologous bone marrow stem cell transplantation (HDC/ASCT) [13]. The same treatment with ASCT was performed in 33 patients <65 years of age. In the study population, ORR was 94%, and 2-year PFS was 79% [12]. The randomized phase II study IELSG32 showed that the addition of thiotepa, rituximab to HD-MTX and cytarabine (MATRix regimen) significantly improved survival compared to the combination of HD-MTX and cytarabine. ORR was 87%, 2-year PFS 62%, and 2-year OS 67%. The IELSG32 study was conducted in 53 centers in five European countries, and the MATRix regimen has become the new standard of treatment in young patients with PCNSL [8].

Table II. Comparison of MATRix, R-MPV, R-HD-MTX-ARA-C treatment regimens

Regimen type Number of patients	MATRix 11	R-MPV 26	R-HD-MTX-ARA-C 6
Median age	60 (27–65)	67 (58–75)	61 (42–64)
Median of administered cycles	2 (1–4)	4 (1–6)	2 (1–4)
Side effects	Neutropenia grade 4 — 7 (63%) Hepatotoxicity grades 3–4 — 4 (36%) Brain edema grade 3 — 3 Septic shock grade 4 — 2 Pneumonia grade 3 — 2 Nephrotoxicity grades 2–3 — 2 Skin lesions grades 2–3 — 1	Neutropenia grade 4 — 6 (23%) Hepatotoxicity — 7 (26%) Septic shock grade 4 — 2 Brain edema grade 3 — 1 Nephrotoxicity grades 2–3 — 1	Neutropenia grade 4 — 3 (50%) Hepatotoxicity grades 3–4 — 2 (33%)
CR	2 (18%)	6 (23%)	1 (14%)
PR	4 (36%)	9 (26%)	4 (57%)
NR	3	4	–
ORR (%)	54.5	57.6	83
Death	2 (one patient progression after cycle 2, and one patient infectious complications after cycle 1)	7 (two patients infectious complications, two patients progression, two patients brain edema, and one patient intestinal perforation)	2 (progression)

CR — complete remission; PR — partial remission; NR — no response; ORR — overall response rate

The prognosis of older patients with PCNSL remains poor, with a median OS of less than two years [14]. In general, chemotherapy based on HD-MTX is quite well tolerated by older patients. However, c.7–10% of patients treated with HD-MTX require discontinuation of therapy, while 26–44% require reduction of MTX dosage due to deteriorated kidney function [14, 15]. A large meta-analysis including 783 immunocompetent patients with PCNSL over the age of 60 showed no significant difference in survival between patients who received HD-MTX with oral alkylating agents and more intensive chemotherapy [16]. The PRIMAIN study assessed elderly patients with PCNSL ≥65 years of age who received three cycles of HD MTX with an oral alkylating agent and rituximab followed by procarbazine maintenance. The complete remission rate in the study population was 36%, and the 2-year PFS was 37% [17].

In the population of PCNSL patients we analyzed, intensive treatment with the MATRix, R-HD-MTX-Ara-C regimen was administered to 17 patients. These were patients under 65, in good clinical condition, with no comorbidities. 26 patients were qualified for the less intensive R-MPV regimen due to age, poor biological condition and comorbidities. In nine patients who achieved at least a partial response, consolidation with megachemotherapy supported by autoPBSCT was performed. According to data from a large multicenter study, the CRR after PBSCT was 77%, with 3-year PFS and OS of 67% and 81% respectively. The median follow-up was 57 months, and treatment-related mortality was 5% [18]. In our center, the conditioning regimen used was thiotepa, etoposide and carmustine. No deaths related to transplant megachemotherapy were observed. Seven patients are still in remission (six after MATRix treatment and one after R-HD-MTX-ARA-C), which is 77% and is comparable to the study cited above. The median follow-up in this group of patients is 23 months.

Our data confirms that induction with HD-MTX and PBSCT consolidation is an effective therapeutic option in younger patients with PCNSL. Seven patients in remission after induction treatment, who were not treated with autoPBSCT due to age and comorbidities, were qualified for brain radiotherapy. According to the available literature, only one randomized study has compared WBRT with observation of patients after induction treatment. The use of WBRT improved PFS, but there was no difference in OS [19]. The British Journal of Haematology published a paper by Ostrowska et al. presenting the results of treatment of patients with PCNSL with the R-MIV regimen (rituximab, methotrexate, ifosfamide and vincristine). The ORR was 73%. Grade 3–4 hematological toxicity was low [20].

The response rate to therapy in our analyzed population was 56.5%. CR was confirmed in 24% of patients, and PR in 33%. These results are slightly lower compared to data from the literature [13–15]. This is probably related to the poor general condition of some patients; patients with

ECOG 3 and 4 constituted as much as 30% of our analyzed group. In patients who did not achieve remission after first-line therapy, temozozolomide with HD-MTX and cytarabine was used in two patients, lenalidomide in three and palliative therapy in two. CR was achieved in two patients receiving temozolomide, and PR was achieved in two patients receiving lenalidomide. There is no strictly defined procedure to distinguish resistant from relapsed PCNSL. If it is a late recurrence of the disease >24 months, HD--MTX-based regimens can be repeated, after which a response has been achieved. In early recurrences of the cancer process, experts prefer to use regimens based on high doses of ifosfamide (R-IE, rituximab, ifosfamide, etoposide), which, according to data, shows a response rate of 38% and 2-year survival of 25% [21]. However, this is an intensive treatment that can only be offered to patients in good clinical condition. Temozolomide (TMZ) is an alkylating drug that is well tolerated and effective in brain tumors of various etiologies.

In a prospective phase II study, TMZ was used as monotherapy in patients with refractory/relapsed PCNSL. ORR was 31% [22]. In a similar study of 17 patients with previously treated PCNSL, response to TMZ was achieved in 47% of patients [23]. However, median OS was short in both analyses [21, 22]. Immunomodulatory drugs such as lenalidomide and pomalidomide have some effectiveness in PCNSL therapy. In a phase II study, lenalidomide was used in combination with rituximab, followed by lenalidomide maintenance in 50 patients with refractory/relapsed PCNSL. ORR was achieved in 48% of patients and CR in 29%. Median PFS was 7.8 months [24]. In turn, the use of pomalidomide in combination with dexamethasone and subsequent maintenance with pomalidomide monotherapy allowed the achievement of CR in 32% of patients, with a median PFS of 5.3 months [25]. In relapsed/refractory PCNSL, the effectiveness of the class 1 Bruton's kinase inhibitor ibrutinib has been demonstrated, both as monotherapy and in combination with chemotherapy. The use of ibrutinib at a dose of 560 mg daily resulted in an ORR of 50%, while increasing the dose to 840 mg daily increased the ORR to 77%. However, the therapy was complicated by an increased rate of invasive aspergillosis in 39% of patients [26, 27]. CAR-T, anti-CD19 chimeric antigen receptor therapy, has been approved for the treatment of refractory and relapsed cases of DLBCL. Data from some trials indicates the effectiveness of CAR-T also in patients with secondary CNS involvement in the course of DLBCL. It seems that CAR-T is a therapy that will also be a beneficial therapeutic option in patients with PCNSL in refractory and recurrent cases [28].

Based on this analysis we have shown that the MATRix regimen is more toxic than R-MPV. The long duration of neutropenia and more frequent infectious complications resulted in the delay of subsequent treatment cycles, which undoubtedly affects the response. Comparing the effectiveness of MATRix and R-MPV, ORR in patients after MATRix therapy was 54.5% and after R-MPV treatment was 57.6%. These observations are preliminary, and further analyses, including those to be conducted at other hematology centers in Poland, are planned.

Article information and declarations

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Authors' contributions

JR — data analysis, writing the main text of the article, preparation of the manuscript. BK — collecting the database, data analysis. ABF — collecting the database, data analysis.

Conflicts of interest

None.

Ethics statement

Authors declare that informed consent for publication was not obtained, as published data does not allow for patient identification.

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Supplementary material

None.

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