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New treatment approaches in relapsing/refractory primary central nervous system lymphomas

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Abstract

Aim: Primary central nervous system lymphoma (PCNSL) is a rare disease that affects the brain, leptomeninges, spinal cord, cerebrospinal fluid, or vitreoretinal compartment without evidence of systemic disease. Although some treatment success is achieved with high dose methotrexate-based regimens, the prognosis is still poor. In this respect, new therapeutic approaches are required.

Materials and Methods: The clinical data of 6 patients diagnosed with primary central nervous system lymphoma in a hematology center of a university hospital were analyzed for 3 years. Ibrutinib monotherapy was applied to these 6 refractory patients as the last-stage treatment. The results were evaluated.

Results: Six patients (5 women, 1 man) with relapsed and refractory PCNSL received ibrutinib as monotherapy. As initial treatment, 3 patients received high-dose methotrexate + rituximab, 1 patient received MATRix (Rituximab, Methotrexate, Cytarabine, Thiotepa), 1 patient received high-dose methotrexate. Only one patient received radiotherapy (RT), following the initial treatment. Two patients were consolidated with autologous transplantation and one patient with RT. All patients received treatment at a dose of 560 mg. No serious side effects have been detected. Three patients who received ibrutinib monotherapy for the shortest 1 month and the longest 24 months died. The patient, who has been on ibrutinib monotherapy for 11 months, is being followed up stably.

Conclusion: We have demonstrated the therapeutic benefit of ibrutinib as monotherapy in our refractory patients. However, we believe that using ibrutinib as part of combination therapy at the initial stage of the disease would yield better results.

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare cerebral malignancy with an aggressive clinical course and poor outcome [1]. Bruton tyrosine kinase (BTK) inhibitor ibrutinib is the first FDA-approved drug in it is class and has shown a single agent activity in PCNSL. Phase I and Phase II studies of ibrutinib monotherapy in relapsed/refractory PCNSL revealed promising outcomes with response rates as high as 81% but clinical responses are usually incomplete or transient, suggesting the need for a novel combination therapy approach. The combination of ibrutinib with other systemic therapeutic agents (i.e., rituximab and methotrexate) has proven successful in Phase I studies [2]. Combination with intensive multidrug chemotherapy regimens has also shown potential, but these combinations have exhibited potential dose-limiting toxicity profiles including opportunistic fungal infections [3]. The number of clinical trials for ibrutinib in PCNSL is small. In this study, we want to share our experience on following up on 6 cases with relapsed/refractory PCNSL treated with a single agent ibrutinib.

Materials and Methods

Six adult patients diagnosed with PCNSL in our clinic between 01.06.2018 and 15.06.2021 were evaluated. All patients underwent positron emission tomography or whole body-computed tomography and bone marrow biopsy to exclude systemic lymphoma. HIV-related cases were also excluded. Each patient was evaluated by brain magnetic resonance (MRI). The results of the treatment were evaluated according to the mass of the tumor; if the mass detected in the brain completely disappeared, it was accepted as complete remission (CR), if the mass size was reduced

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by more than 50 percent, as partial remission (PR). If less than 50 percent reduction was observed in the mass size, it was considered as stable disease (SD). Ethics committee approval was obtained with the decision dated 09.06.2021 and numbered 2021/18-05.

Results

The median age of the patients at the initial of ibrutinib therapy was 59. Five of the six patients were women. 4 patients had an ECOG performance score of 2 and above, and 2 patients had an ECOG performance score of less than 2. Only one patient had B symptoms at presentation. Three patients had GC subtype and three patients had non-GC subtype diffuse large B-cell lymphoma. For first-line therapy, three patients received high-dose methotrexate (HD-MTX) plus rituximab (R), one patient received high-dose methotrexate and one patient received radiotherapy alone. One patient received the MATRix regimen (high dose methotrexate, high dose cytarabine, rituximab, thiotepa). After the first treatment, partial remission (PR) was achieved in two patients and was evaluated as stable disease (SD) in the other patients. Two patients who achieved PR with HD-MTX+R were consolidated with autologous stem cell transplantation (ASCT). Patient 1 achieved PR after HD-MTX + Rituximab treatment. Despite being consolidated with ASCT, it progressed clinically and radiologically. In this regard, ibrutinib was started, however patient died within the first month of treatment. Patient 4 had PR on imaging after HD-MTX + Rituximab treatment. Patient 4, consolidated by ASCT, showed a stable course on the control MRI. This patient, with no change in the size of the existing mass, is currently being followed up with ibrutinib therapy, which was started 11 months ago. Patient 3 was evaluated as having SD after HD MTX primary therapy. Because of the advanced age of the patient and her inability to tolerate RT, ibrutinib treatment was initiated and she was followed up steadily for 14 months. Patient 2, who initially received the MATRIx regimen and was evaluated as having SD, refused ASCT and was therefore started on ibrutinib. He was followed stable for 24 months under ibrutinib treatment. Patient 5 was 75 years old, and her general condition was poor. She took one session of RT and then got worse. Control MR indicated SD. Therefore, ibrutinib treatment was started. He died 3 months after starting treatment. Patient 6 was evaluated as having SD after the first treatment. Because of his poor general condition, he was not considered suitable for autologous transplantation. Therefore, ibrutinib treatment was started. He died 2 months after starting ibrutinib therapy. Patients 2, 3, 4 achieved long-term survival with ibrutinib therapy. These patients were evaluated by MRI while under ibrutinib therapy. Patients 3 and 4 were considered SD. However, there was a significant decrease in the mass of patient 2 and it was evaluated as PR. All patients received 560-mg ibrutinib daily. No serious adverse events were observed. Mild lymphopenia due to ibrutinib alone developed in one of our patients. Concomitant corticosteroid treatment was administered to 3 patients because of symptomatic cerebral edema. Five patients died while on ibrutinib and one patient is still in the follow-up.

Discussion

Primary central nervous system lymphoma (PCNSL) is a rare form of aggressive non-Hodgkin lymphoma without evidence of systemic disease. Diffuse large B-cell Lymphoma (DLBCL), Germinal center B-cell-like (GCB) and Activated B-cell-like (ABC) subtypes have been defined according to cell origin. It was determined that the Non-GC (ABC) subtype had a worse prognosis than the Germinal center B cell-like subtype. The vast majority (>85%) of PCNSL belong to its non-germinal center subgroup [4–5]. It was determined that 3 of our patients were of the GC type and 3 of our patients were non-GC type. We found that 2 of our 3 patients, who had a long-term and successful clinical response with Ibrutinib treatment, were of non-GC origin and one was of GC origin.

For treating DLBCL, cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) is the chemotherapy regimen generally used. This regimen is ineffective for PCNSL [6]. Instead, high- dose intravenous methotrexate is used, which crosses the blood-brain barrier. However, high doses of MTX alone are insufficient. In this respect, the ability of ibrutinib, which is a small molecule, to cross the blood-brain barrier has suggested its use for treating PCNSL [7]. Ibrutinib's recommended dose is 420 mg/day for CLL and 560 mg for lymphomas. C. Soussain et al. demonstrated an effective clinical activity of 560 mg dose in relapsed/refractory PCNSLs. Generally, the most common side effects are neutropenia and lymphocytopenia [8]. In our study, all 6 patients used ibrutinib at a dose of 560 mg. Our patients tolerated the dose very well, and only one of our patients had mild neutropenia.

Two of the six patients who were followed up with partial response and stable disease, received autologous stem cell transplant as consolidation. Both patients were later started on ibrutinib due to disease progression. Autologous transplantation was not performed because the fifth patient was old. The second patient did not accept autologous transplantation. Due to the poor clinical condition of our 3rd and 6th patients, they were not considered suitable for autologous transplantation.

Ibrutinib can be combined with chemotherapy as initial therapy. The use of ibrutinib in combination with high-dose methotrexate has been tried in the treatment of PCNSL. According to Feili Chen et al. gave 8 courses of methotrexate at a dose of 3.5.gr/m^2 per cycle to 11 participants. Ibrutinib maintenance therapy was administered to a total of 9 patients who completed this treatment. According to Feili Chen et al. in this study, complete remission (CR) was found to be 64%, and partial remission (PR) was 18% [9]. In our study, methotrexate was given to 4 patients at a dose of 5 g/m^2 per cycle, while methotrexate was given to 1 patient at a dose of 8 g/m^2 (Table 1).

Combination treatments appear more effective than monotherapy. Ibrutinib therapy with a high dose chemotherapy is recommended as the initial therapy. However, possible side effects need to be considered. Leonakis et al. conducted a phase Ib study of ibrutinib plus chemotherapy (DA-TEDDi-R) following ibrutinib monotherapy. Among the 18 PCNSL patients, 94% showed tumor reduction with ibrutinib alone, 86% of

Table 1. Clinical characteristics of the patients and results of ibrutinib treatment.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	56	39	69	56	75	58
Sex (M/F)	F	M	F	F	F	F
ECOG performance score	1	4	2	0	4	4
B symptoms (Yes/No)	No	No	No	Yes	No	No
Type	Germinal Center (GC)	GC	Non-GC	Non-GC	GC	Non-GC
Initial Therapy	HD-MTX + Rituximab	MATRix regimen	HD-MTX	HD-MTX + Rituximab	RT	HD-MTX + Rituximab
Number of methotrexate cycles	7	6	4	9	-	6
Best response to the most recent prior therapy	PR	SD	SD	PR	SD	SD
Consolidation treatment	Autologous SCT	-	RT	Autologous SCT	-	-
İbrutinib total daily dose	560 mg	560 mg	560 mg	560 mg	560 mg	560 mg
Dexamethasone therapy within the first 28 days of ibrutinib (Yes/No)	Yes	Yes	No	No	Yes	Yes
Ibrutinib treatment duration (Months)	1	24	14	11	3	2
Survival	Dead	Dead	Dead	In life	Dead	Dead

Abbreviations: ECOG: Eastern Cooperative Oncology Group, HD-MTX: High dose methotrexate, RT: Radiotherapy, PR: Partial Response, SD: Stable Disease SCT: Stem cell transplant.

evaluable patients achieved complete remission with DA-TEDDi-R. However, combination treatments have a higher risk of side effects. In this respect, fungal infections are seen as an important problem. In the study of Leonakis et al., aspergillosis infection occurred in seven of 18 patients [10]. No fungal infection was detected during the follow-up of our cases. It was noteworthy that 3 patients who received long-term treatment did not develop a fungal infection. We thought this was because we were using ibrutinib as the sole agent.

We believe that ibrutinib therapy can be used for consolidation such as autologous stem cell transplantation and RT, in patients who have a complete response with high dose chemotherapy. However, since we did not have such a patient, no comment was made on this subject. Resistance to ibrutinib monotherapy is another important problem during ibrutinib use. This problem can be overcome with combination therapy. Especially, the use of biological agents has increased recently. In this respect, the use of Anti-CD20 antibody seems appropriate [11]. The major challenge here is the ability of ibrutinib to antagonize the therapeutic effect of rituximab. However, it has been observed in clinical studies that this situation does not pose a problem [12]. Skarzynski et al. showed that CD55, which regulates the complement cascade, was inhibited by ibrutinib. This suggests that the effect of ibrutinib on rituximab therapy is both inhibitory (CD20 antagonism) and stimulatory (CD55 antagonism) [13]. In another study by Jaglowski SM et al., it was observed that using ibrutinib along with the anti-CD20 agent ofatumumab was more effective than using ibrutinib alone [14]. Four of our patients received rituximab as first-line therapy. Three of our patients who received rituximab received it in along with MTX. Our remaining patient received Rituximab within the MATRix protocol.

Despite improvements in methotrexate and rituximab-based regimens, relapse is common and long-term survival is low. Many centers have worked on different combination therapies. Radiotherapy is still a valid treatment approach today. In this study, we applied radiotherapy to one of our patients. We believe that radiotherapy will help us choose the right patient. However, these studies did not find a significant difference in the benefits of the treatment regimens. Therefore, different centers apply different treatment regimens to their patients [15– 17]. Additionally, treatment options for recurrent disease are limited and there is no consensus on optimal treatments. Therefore, there remains a critical need for new, effective therapeutics for relapsed/refractory PCNSL.

The prognosis for patients with PCNSL is poor. Additionally, survival in Relapsed/Refractory patients is very short. Despite the poor prognosis, ibrutinib was used as monotherapy for 24 months, 14 months and 11 months in 3 patients without any problem. We have determined that our patients who have been using ibrutinib for a long time benefit a lot clinically. We noticed that the lesions regressed on MRI. Additionally, our patient, who has been taking ibrutinib for 11 months, continues to live stably. Rituximab was included among the initial treatments of our 4 cases. We believe that the addition of rituximab to the initial chemotherapy of patients has clinical value. In conclusion, we believe in the benefit of ibrutinib monotherapy in Relapsed/Refractory patients. Additionally, we believe that ibrutinib treatment together with high-dose MTX and Rituximab as initial treatment will be effective.

Limitations

PCNSL is a rare disease. The limitations of the study are that it is retrospective, and the number of patients is small.

Ethics approval

Ethics committee approval was obtained with the decision dated 09.06.2021 and numbered 2021/18-05.

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