Clinical Outcomes of CNS Lymphoma Treated with Ibrutinib-Based Therapy: A Real-Life Multicenter Experience on Off-Label Use of Ibrutinib

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ABSTRACT

Despite recent therapeutic advances, the prognosis of patients with relapsed/refractory (RR) primary (PCNSL) and secondary central nervous system lymphoma (SCNSL) remains poor. Therefore, the need for new treatment options in CNSL continues. Ibrutinib has been used in clinical trials for CNSL in recent years. However, there is no real-life data on this subject yet. We retrospectively evaluated the efficacy of ibrutinib alone or in combination with various treatment options in 39 patients, 21 with PCNSL and 18 with SCNSL. The median age was 62 years and the overall response rate (ORR) was 59%. The median overall survival (OS) was four months for all patients and 13 months for responder patients ($p< 0.001$). Invasive aspergillosis occurred in 10.2% of the patients. Lactate dehydrogenase activity, response to treatment, and the presence of the invasive fungal infection were prognostic factors affecting OS on the ibrutinib therapy ($p= 0.04$, $p= 0.02$, and $p= 0.048$, respectively). There was no significant difference in prognosis between the IBR monotherapy and IBR combination groups. Compared to early-phase clinical studies, lower ORR, shorter OS, and a higher incidence of invasive fungal infections were observed in this real-life study of ibrutinib which was used alone or in a combination regimen in patients with RR PCNSL and SCNSL.

Keywords: Ibrutinib, Central nervous system lymphoma, Relapsed/refractory, Maintenance, Aspergillosis

INTRODUCTION

Both primary and secondary central nervous system (CNS) lymphomas are difficult to manage, especially during relapsed/refractory (RR) settings. The backbone of therapy is high-dose methotrexate, which is commonly used in combination with other drugs such as procarbazine, vincristine, cytarabine, and rituximab.[1,2] In cases where high-dose methotrexate cannot be used or is resistant, treatment options are very limited, and the survival rates are very low.[3,4] There is no standard-of-care guidance or consensus in the RR settings of CNS lymphomas due to the lack of randomized studies.

For a drug to be effective in CNS lymphomas, it must first pass through the blood-brain barrier and reach the brain parenchyma and cerebrospinal fluid.

Drugs with this feature have been evaluated for CNS lymphomas from the past to the present, but no new drug has come to the fore. Ibrutinib (IBR) is an irreversible selective inhibitor of Bruton's tyrosine kinase and is currently approved for some subtypes of B-cell lymphomas, such as mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). There are early phase studies of ibrutinib monotherapy in CNS lymphoma.[5]

Here, we retrospectively analyzed and reported the clinicopathological features, side effects, and outcomes in patients with CNS lymphoma who received IBR in the treatment process.

PATIENTS AND METHODS

Patients

We retrospectively analyzed all consecutive immunocompetent adults with PCNSL or SCNSL treated with IBR at 10 centers from March 2016 to September 2022. Demographic and clinical characteristics of the patients were recorded by reviewing the patient files and electronic medical records in the centers.

Treatment

After approval from the health authority, ibrutinib was prescribed off-label for CNS lymphoma at a dose of 420 mg or 560 mg orally once daily (28-day cycles) as monotherapy or in combination, until disease progression or unacceptable toxicity occurred.

Response

CNS response assessment was performed using magnetic resonance imaging and cerebrospinal fluid cytology according to the International Primary CNS Lymphoma Collaborative Group Response Criteria[6], and systemic responses were assessed by PET-CT. Patients' best response to treatment was recorded to calculate the ORR, which was defined as the proportion of patients with complete response (CR, no contrast-enhancing disease) or partial response (PR, 50% or more decrease in enhancement) according to the guideline.[6] Adverse events were graded using the Common Terminology Criteria for Adverse Events (AE) version 4. Invasive aspergillosis is classified according to the revised consensus definitions in the categories proven, probable or possible disease.[7]

This study was approved by the Institutional Review Board of Akdeniz University Hospital and conducted in accordance with the Good Clinical practice guidelines (16.02.2022/KAEK-24) and Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study.

Statistical Analysis

IBM SPSS Statistics (version 24) was used for statistical analysis. Descriptive statistics were used to present the data. Categorical data were presented as numbers and ratios, and numerical data were presented as median, minimum, and maximum. Overall survival (OS) was defined as the duration from the date of the first day of the treatment to the date of death or time to the survivors' last follow-up date. Kaplan–Meier survival analysis was applied for OS, and log-rank tests were used to examine the factors affecting survival. Univariate Cox Regression analysis was applied to evaluate factors affecting survival. Multivariate Cox Regression analysis was applied when there are multiple potentially interacting covariates in Univariate analysis. A two-sided p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Patients

The demographic and clinical characteristics of the patients are presented in Table 1. A total of 39 patients (21 PCNSL and 18 SCNSL) were included in the study. Two were treatment-naive, and IBR was used as first-line therapy. The remaining 37 patients had recurrent/refractory disease and received prior high-dose methotrexate-based chemotherapy. The median number of prior treatments in patients with RR CNS lymphoma was 2 (range, 1-5). The median age at treatment initiation was 62 (range, 25-80) years. The median Eastern Cooperative Oncology Group (ECOG) performance status was 2 (range, 0-4), with 14 (35.9%) patients having a performance status > 2. The lymphoma subtype was DLBCL (n= 33) in most of the patients, and the lymphoma subtypes of the other patients were fol-

Table 1. Baseline characteristics of the patients

Characteristics	
Age - years	
Median (min-max)	62 (25-80)
Gender	**n (%)**
Male	18 (46.2)
Female	21 (53.8)
ECOG PS	**n (%)**
0-2	25 (64.1)
3-4	14 (35.9)
CNS lymphoma	**n (%)**
PCNSL	21 (53.8)
SCNSL	18 (46.2)
LDH	**n (%)**
Normal	16 (41.1)
1-3 x ULN	21 (53.8)
> 3 x ULN	2 (5.1)
Ki-67	**n (%)**
< 45	1 (2.6)
45-75	7 (17.9)
> 75	16 (21)
Unknown	15 (38.4)
Histology	**n (%)**
Diffuse large B-cell lymphoma	33 (84.6)
Other	5 (12.8)
Unknown	1 (2.6)
Disease status	**n (%)**
R/R PCNSL	19 (48.7)
R/R SCNSL	18 (46.2)
Newly diagnosed SCNSL	0 (0)
Newly diagnosed PCNSL	2 (5.1)
Site of disease	**n (%)**
Brain parenchyma	30 (76.9)
Cerebrospinal fluid (CSF)	11 (28.2)
Brain parenchyma and CSF	8 (20.5)
Intraocular Lymphoma	3 (7.7)
Spinal	4 (10.2)
Presence of additional therapy to ibrutinib	**n (%)**
Ibrutinib monotherapy	12 (30.7)
RT → Ibrutinib	12 (30.7)
RT → Rituximab+Ibrutinib	1 (2.6)
RT, Temozolomide, Ibrutinib*	1 (2.6)
Rituximab+Ibrutinib	5 (12.8)
Lenalidomide+Ibrutinib	1 (2.6)
MATRix → Ibrutinib	3 (7.7)
HDMTX-based chemotherapy → auto-HSCT → Ibrutinib	2 (5.1)
Rituximab + ICE + Ibrutinib	1 (2.6)
Rituximab+Bendamustine → Ibrutinib	1 (2.6)
Number of Prior Regimens	
Median (min-max)	2 (1-5)

*CNS= central nervous system; HDMTX= high-dose methotrexate; HSCT= hematopoietic stem cell transplantation; ECOG PS= Eastern Cooperative Oncology Group performance status; LDH= lactate dehydrogenase; MATRix= methotrexate, cytarabine, thiotepa and rituximab; PCNSL= primary central nervous system lymphoma; R-Benda= rituximab and bendamustine; RR= relapsed/refractory; RT= radiotherapy; R-ICE= rituximab, ifosfamide, carboplatin and etoposide; SCNSL= secondary central nervous system lymphoma; ULN= upper limit of normal; +, simultaneously; →, sequential; *= order of use not available.*

licular lymphoma (n=2), low-grade non-Hodgkin lymphoma (n= 1), CLL (n= 1), MCL (n= 1) and unknown (n= 1). Immunohistochemical classification of the cell of origin was available for six patients (1 patient Germinal Center B-Cell-like, five patients Activated B-cell-like).

Treatment and Response

Six patients were treated with IBR at a fixed dose of 420 mg once daily, and the remaining 33 patients were treated with 560 mg. IBR was used as a single agent in 12 patients. In other patients, it was used in combination with another treatment option. Ibrutinib was administered sequentially in 19 patients, simultaneously in 7 patient and order of use was unavailable in one patient. Table 2 summarizes the treatment responses in IBR monotherapy and combination therapies containing IBR. The ORR was considerably lower with IBR monotherapy (33.3%) than with combination therapies containing IBR (70.4%) (p= 0.03). In the IBR monotherapy group there were four responder patients (3 PR, 1 CR), and long-lasting responses (> 12 months) were observed in these four patients. In the IBR combination group, there were 19 responder patients (13 CR, 6 PR), and long-lasting responses were observed in 9 of them. Five of long-lasting responder patients were still alive and in remission under IBR monotherapy.

Survival

At a median follow-up of four (range, 1-81) months, 23.1% of the patients (n= 9) were alive. Only one of 39 patients died within 30 days of starting IBR therapy. This patient was in the IBR monotherapy group and died within the second week of IBR treatment. The median OS from starting IBR for all patients was four months (95% CI: 1.37-6.62)(Figure 1a). The median follow-up period of patients with CR and PR was 13 (range, 1-81) months, with a 60.9% mortality rate, and a median OS of 13 months (95% CI: 0.47-25.52) (Figure 1b). In treatment-refractory patients at a median follow-up of 2 (range, 1-8) months, the death rate was 100%, and the median OS was two months (95% CI: 1.22-6.62). The survival of patients with fungal infection was significantly shorter than that of patients without fungal infection (2 vs. 6 months) (p= 0.013) (Figure 1c). Both univariate

Table 2. Treatment responses in ibrutinib monotherapy and ibrutinib combination therapies

Characteristic	All patients n= 39	Ibrutinib alone n= 12	Ibrutinib in combination n= 27
Response, n (%)			
ORR (CR+PR)	23 (59)	4 (33.3)	19 (70.4)
CR	14 (35.9)	1 (8.3)	13 (48.1)
PR	9 (23.1)	3 (25)	6 (22.2)
SD	4 (10.2)	4 (33.3)	0 (0)
PD	12 (30.8)	4 (33.3)	8 (29.6)

CR= complete response; ORR= overall response rate; PD= progressive disease; PR= partial response; SD, stable disease.

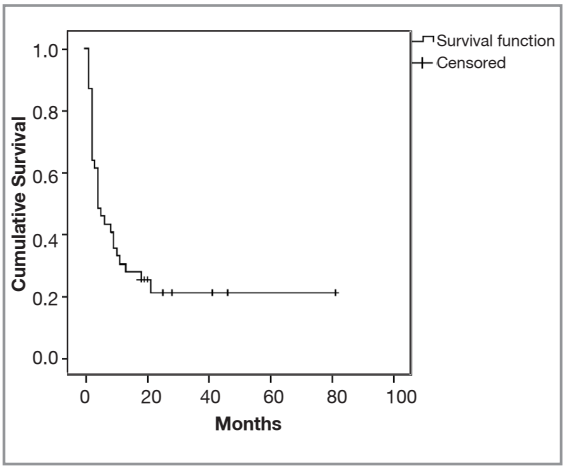

Figure 1. Survival. **a)** In all patients.

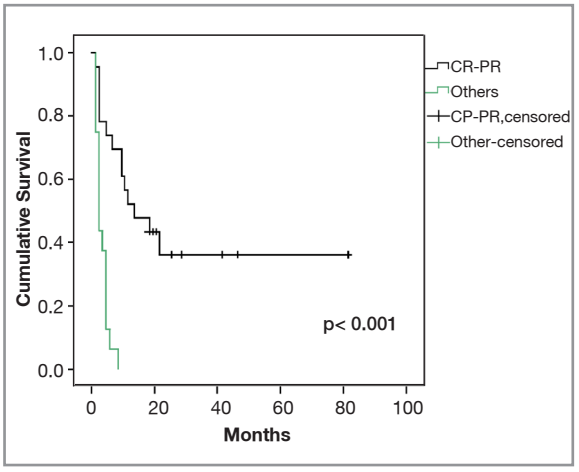

Figure 1. b) In responder and nonresponder patients

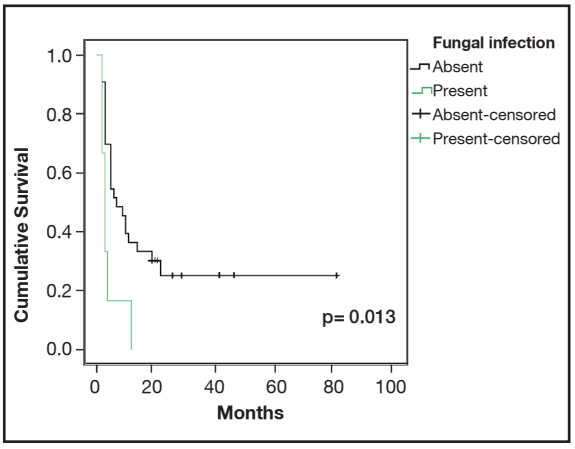

Figure 1. c) In patients with and without invasive fungal infection.

and multivariate Cox regression analyses indicate that LDH, response to treatment, and fungal infection were prognostic risk factors for the OS (Table 3). There was no significant difference in survival between the IBR monotherapy group and the IBR-containing combination therapy group (p= 0.23).

Safety

The most common adverse events were hematological toxicities (Table 4). The side effects classified as infection included brain abscess (n= 1), cellulitis (n= 1), meningitis (n= 1), onychomycosis(n= 1), candidiasis (n= 3), and aspergillosis (n= 4). Atrial fibrillation in one patient and intracranial hemorrhage in one patient were observed at grade 1.

Proven (n= 3) or possible (n= 1) invasive aspergillosis occurred in 4 patients (10.2%). One of the patients was a treatment-naive newly diagnosed PCNSL and received rituximab and IBR as first-line therapy. The other three patients, 2 PCNSL and 1 SCNSL, had recurrent disease and had previously received 2-4 lines of treatment. In these patients, IBR was used for maintenance or consolidation after cranial radiotherapy. Three of the four patients died within the second month of IBR therapy, while the other had a survival of > 24 months. Furthermore, invasive Candida infection developed in another 3 (7.7%) patients. Candida was isolated in

Table 3. Univariate and multivariate analyses of clinical parameters on OS.

Univariable models				Multivariable models			
Characteristic	**HR**	**95% CI**	**p-value**	**Characteristic**	**HR**	**95% CI**	**p**
Age	1.04	1.011-1.087	0.01	Age			0.196
Sex			0.1				
LDH	1.003	1.001-1.005	0.01	LDH	1.002	1.000-1.005	0.04
ECOG PS 0-2 or 3-4			0.94				
Primer or Sekonder CNSL			0.224				
Histology of CNSL			0.223				
Ki-67			0.507				
Dose of ibrutinib			0.417				
Response to treatment (SD/PD)	6.12	2.38-15.74	<0.001	Response to treatment (SD/PD)	4.874	1.809-13.132	0.02
Fungal infection	2.814	1.115-7.103	0.029	Fungal infection	2.853	1.012-8.044	0.048
RT before ibrutinib			0.056				
HSCT before ibrutinib			0.421				
Ibrutinib monotherapy vs combination therapy with ibrutinib		0.271					

CNSL, central nervous system lymphoma; PD, progressive disease; RT, radiotherapy; SD, stabil disease.

blood culture in these 3 patients, but specific localizations were not specified. All three patients were using IBR after cranial RT for RR CNS lymphoma. All patients died, 2 in remission and 1 in progressive disease.

DISCUSSION

In a phase 1 study of 20 patients with RR primary CNS lymphoma (PCNSL) or secondary CNS lymphoma (SCNSL), treatment with daily IBR monotherapy (860mg) resulted in an overall response rate (ORR) of 77% and a median PFS and OS of 4.6 and 15 months, respectively.[8] In a phase II clinical study involving 44 patients with RR primary CNS lymphoma using IBR monotherapy (560 mg), an ORR of 61% was reported.[9] Although a few similar publications have been included in the literature later, the data on this issue are limited.[5]

This is a real-life study of IBR in a series of PCNSL and SCNSL. The ORR to IBR monotherapy we

Table 4. Adverse events

Adverse event	**Grade 1/2 (n)**	**Grade 3/4 (n)**	**All grades n (%)**
Hematological toxicities			
Leukopenia	3	6	9 (23)
Neutropenia	2	5	7 (17.9)
Thrombocytopenia	8	2	1 (9.1)
Anemia	5	4	9 (25.6)
Nonhematological toxicities			
Neuropathy	1		1 (2.5)
Atrial fibrillation	1		1 (2.5)
Intracranial hemorrhage	1		1 (2.5)
Constipation	1		1 (2.5)
Infection	5	6	11 (28.2)
Purpura fulminans		1	1 (2.5)
Esophagitis		1	1 (2.5)
Hyponatremia	1		1 (2.5)

observed in patients with CNS lymphoma is lower than the response rate reported in the early phase clinical study to IBR monotherapy in RR PCNSL.[9] IBR alone showed clinical activity in 33% of our patients, with 75% of these patients achieving partial remission. It is remarkable that the ORR to IBR monotherapy was quite low compared to combination therapy containing IBR. However, there was no significant difference in survival between the IBR monotherapy and IBR combination groups.

Among lymphoma subtypes, DLBCL accounts for the majority of cases of both primary and secondary CNS lymphoma.[10,11] Therefore, a treatment option that is expected to be effective for CNS lymphomas should primarily have good CNS penetration, as well as good efficacy against lymphomas, especially DLBCL. In our series, there were also patients with CLL (n= 1) and MCL (n= 1) subtypes other than DLBCL, and IBR is known to be effective for these lymphoma subtypes.[12-14] The expectation of long-term remission with IBR[15,16], particularly in lymphoma subtypes, including MCL and CLL was provided in these patients. However, due to the limited number of patients with non-DLBCL lymphoma subtypes in our study cohort, this finding needs to be supported by further studies with more patients.

The risk of aspergillosis during treatment with IBR is estimated to be 10.2% in our real-life series, which is higher than the reported risk of approximately 5% in early-phase studies for RR CNS lymphoma patients treated with IBR monotherapy.[9,15] All patients who developed invasive aspergillosis in our study had used IBR in combination with another treatment option. In another study, in which IBR monotherapy was followed by IBR plus chemotherapy, seven out of 18 patients (39%) developed pulmonary and cerebral aspergillosis.[17] Two of these patients developed aspergillosis during the IBR monotherapy phase, while in the other five patients, aspergillosis was detected after the chemotherapy regimen was initiated. Furthermore, 3 (7.7%) patients developed invasive candidiasis in our study. It can be stated that there is an increased risk of invasive fungal infection with IBR, primarily when used in combination with other treatment options. It is not known whether there is any additional benefit of using antifungal agents at the same time, and this issue should be investigated in prospective studies. Improvement in the prophylaxis policy may reduce mortality in the future.

The main limitations of this study, beyond its retrospective design, are its small sample size and heterogeneity in treatment regimens. Another limitation of the study is the lack of prognostic scores and the fact that the immunohistochemical classification of the cell of origin was performed in minority of patients. However, despite the small sample size of our study, the off-label use of IBR for CNS lymphomas is quite limited in the literature, making it valuable. Heterogeneity is inevitable in the treatment of patients with CNS lymphoma due to short-duration treatment responses and frequent recurrences, as well as the lack of consensus on treatment options for CNS lymphomas.

In conclusion, lower ORR and shorter OS were observed in this real-life study of ibrutinib compared to early-phase clinical studies. IBR monotherapy provided disease control in one-third of our heavily pretreated patients but it is unlikely that IBR could be curative as monotherapy. IBR in combination with a polychemotherapy regimen was a more effective therapeutic option. However, combination regimens containing IBR resulted in a high incidence of invasive fungal infection. Therefore, the potential role of fungal prophylaxis needs to be investigated by considering drug interactions. The role of IBR maintenance, for which our study data may not be sufficient to make a comment, should also be investigated in prospective controlled studies in patients with RR CNS lymphoma who had a CR/PR to the salvage IBR either as a single agent or combined with another regimen.

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