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ORIGINAL ARTICLE

R-IDARAM treatment in central nervous system lymphomas: a single-center experience and review of the literature

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ABSTRACT

Introduction: Central nervous system lymphomas (CNSLs) require effective treatment strategies due to aggressive nature of disease. Despite therapeutic approaches having improved in the last decades, there is no standard treatment for these patients. As a CNSL targeted-therapy IDARAM protocol was developed, the outcomes were reported with a few studies. We observed the R-IDARAM protocol in our CNSL cases, and we discuss the effectiveness, tolerability, and toxicity with a review of the literature in this article. **Subjects and Methods:** We retrospectively analyzed response rates, progression-free survival, adverse events, and long-term side effects in patients who were treated by modified R-IDARAM as standard clinical care of CNSL in our hematology department. **Results:** Response was achieved in five of nine patients. Three patients (two primary CNSL and one secondary CNSL) are still being followed up without disease progression with a median duration of follow-up of 79 months (88, 79, and 17 months, respectively). Manageable hematological side effects including thrombocytopenia and neutropenia were experienced by all patients. **Conclusion:** R-IDARAM protocol may be an option with high early response rates and manageable toxicity. Hematological side effects are the main problem, and long-term neurological toxicity is not common. Eligible patients must continue with autologous stem cell transplantation due to poor long-term survival outcomes.

Key words: Aggressive lymphomas, central nervous system lymphomas, modified R-IDARAM

INTRODUCTION

Central nervous system lymphomas (CNSL) are uncommon subtype of non-Hodgkin lymphoma (NHL) with 1% of all NHL cases.[1] They show poor prognosis with the median 3 months of survival in untreated patients.[2] Owing to aggressive nature of disease, effective treatment strategies are required. The results of standard chemotherapeutics used in systemic lymphomas have been disappointing due to the poor penetration of chemotherapeutics of the intact blood–brain barrier. High-dose methotrexate (HD-MTX) plus cytarabine arabinoside (Ara-C) are known as the most effective chemotherapeutics for CNSL and associated with higher response rates.[3-5] In the last decade, Moreton *et al.*[6] developed the IDARAM protocol, which comprised idarubicin (10 mg/m^2, intravenous [IV], days 1 and 2), dexamethasone (100 mg, 12-h infusion, days 1, 2, and 3), Ara-C (1.0 g/m^2, 1-h infusion, days 1 and 2), MTX (2.0 g/m^2, 6-h infusion, day 3), and folinic acid rescue. In addition, intrathecal cytosine arabinoside (70 m) and MTX (12 mg, days 1 and 8) was administered until 3 weeks after the clearance of abnormal cells in cerebrospinal fluid. As the neutropenia is the main side effect of treatment,

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granulocyte colony-stimulating factor (GCSF) was infused during neutropenia recovery period.[6]

Yılmaz *et al.*[7] improved the protocol with additional rituximab 375 mg/m^2, an increased dose of MTX (3 g/m^2 from 2 g/m^2), and two additional courses after cranial radiotherapy (RT). In the following years, a small number of studies declared the outcomes of the protocol [Table 1].

However, more real-life data are needed to show the benefit and to clarify the management of adverse events. Hereby, we present our CNSL patient series who were treated with R-IDARAM protocol to declare the outcomes of the protocol with a literature review.

SUBJECTS AND METHODS

Patients who were treated with the modified R-IDARAM protocol in our hematology department between 2011 and 2017 were analyzed retrospectively. The patients with CNSL were histologically diagnosed according to the Revised European-American Classification of Lymphoid Neoplasms (REAL)/World Health Organization (WHO) lymphoma classification.[8] All the patients with primary central nervous system lymphoma (PCNSL) were histologically documented with the examination of mass biopsy materials or surgically resected specimens. Contrast-enhanced computed tomography (CT) of the thorax, abdomen, and pelvis was performed to confirm the absence of systemic disease. The patients with secondary central nervous system lymphomas (SCNSLs) were those with CNS relapse of diffuse large B cell lymphoma (DLBCL) and were evaluated clinically and with radiological imaging. Bone marrow biopsy was performed for the staging of all patients.

The Karnofsky Performance Status (KPS) scale was used to evaluate the performance status of patients. The risk profile and prognosis of patients were determined according to Memorial Sloan–Kettering Cancer Center (MSKCC) Prognostic Scoring system.[9]

All patients were treated with modified R-IDARAM, which is detailed in Table 2. All courses were given every 28 days. GCSF was given subcutaneously once per day (lenograstim 263 μg or filgrastim 300 μg) from day 7 until neutrophil count exceeded 1.5 × 10^9/L.

Table 1: Comparison of studies

	Moreton *et al.*		Yılmaz *et al.*	Zhao *et al.*	Maciocia *et al.*	Qian *et al.*
Patient #(M/F)	24 (11/13)		3 (3/-)	3 (2/1)	23 (13/10)	19 (9/10)
Age (range)	53 (21–73)		30 (17–48)	53 (49–57)	53 (25–69)	54 (24–75)
	PCNSL	SCNSL	PCNSL	PCNSL	SCNSL	PCNSL
	8	16	3	3	23	19
Immunophenotype						
DBLCL	8	4	3	3	23	18
Non-DBLCL	-	12	-	-	-	1
Response						
CR	7	12	3	3	6	17
PR	-		-	-	8	1
PD	1	4	-	-	7	1
TRD	-		-	-	-	-
Relapse	3	5		-	15	
Median follow-up (months)	25 (11–42)	24 (18–57)	15 (29–15)	23 (13–41)	49	39 (5–63)
MTX dose (mg/m^2)	2	2	3	2	2	2

DBLCL = diffuse large B cell lymphoma, PCNSL = primary central nervous system lymphoma, SCNSL = secondary central nervous system lymphoma, CR = complete remission, PR = partial remission, PD = progressive disease, TRD = treatment-related death, MTX = methotrexate

Table 2: R-IDARAM protocol

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Rituximab 375 mg/m^2 IV	+							
Idarubicin 10 mg/m^2 IV		+	+					
Dexamethasone 100 mg/m^2 IV		+	+	+				
Cytarabine 1 g/m^2 IV		+	+					
Methotrexate 3 g/m^2 IV				+				
GCSF*								+
IT**	+							+

GCSF = granulocyte colony-stimulating factor, IT = intrathecal treatment, IV = intravenous

*GCSF (lenograstim 263 μg or filgrastim 300 μg/day from day 7 until neutrophil count exceeded 1.5 × 10^9/L), **IT (cytosine arabinoside 40 mg, methotrexate 15 mg, and dexamethasone 8 mg)

Interim assessment was performed after two courses. Whole brain RT (WBRT) was applied at a dosage of 3600 cGy in a conventional schedule (180 cGy per day). Two additional courses of R-IDARAM (total four courses) were applied following RT.

Complete remission (CR) referred to resolution of all apparent tumors. Partial response (PR) was referred to 50% reduction in tumor size, and progressive disease (PD) was defined as increase in tumor size. The response was evaluated with cranial magnetic resonance imaging (MRI) for the patients with PCNSL, and additional thoracoabdominal CT was performed for SCNSL.

In patients where CR was achieved, follow-up was made every 3 months for 2 years and then every 6 months. At the follow-up visits, complete neurological, ophthalmological, and cranial MRI examinations were performed. The toxicity of the protocol was evaluated after all courses and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0).[10]

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

As a standard of care/action of the Ankara Dıskapı Yildirim Beyazit Research and Training Hospital, it was confirmed based on patient records that all of the study patients gave informed consent at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care.

RESULTS

Patient characteristics

Evaluation was made of two patients with SCNSL (one male and one female) and seven newly diagnosed PCNSL (four males and three females) patients. The mean age of the PCNSL patients was 55.88 ± 11.99 years (range, 45–78 years). DLBCL was the histological type for all patients. None of the patients had bone marrow involvement. Serological markers including human immunodeficiency virus (HIV), and hepatitis B and C were negative for all patients. The demographic features, KPS, and MSKCC scores of the patients are listed in Table 3.

Response assessment

CR was achieved in four of seven patients with PCNSL and one of two patients with SCNCL, following two courses of chemotherapy. The dose reduction was done in two patients with PCNSL due to poor performance status and elevation in transaminases.

Three patients (two PCNSL and one SCNCL) are still being followed up without disease progression with a median duration of follow-up of 79 months (88, 79, and 17 months, respectively). The patient with SCNCL who achieved CR was directed to autologous stem cell transplantation (ASCT). The patient remained in CR after ASCT at the time of this report.

Two of patients with PCNSL died because of progressive CNSL with 1-month survival. The treatment-related death was not experienced. The treatment and response assessment are detailed in Table 4.

Toxicity assessment

All patients had grade 3–4 hematological side effects, including thrombocytopenia and neutropenia, and intravenous antibiotherapy was required during febrile episodes. Mucosal problems (grade 1–2) were experienced in most of the patients and were managed successfully. Although peripheral neuropathy was observed in a patient, no cranial or neurological complications attributed to RT were detected in patients during following time. Rashes related to skin toxicity were observed in a patient and were treated with antihistaminics, and dose was reduced by 50%. Cardiac or renal side effects were not seen in any patient.

Table 3: Patient characteristics

Patient no.	Age/sex	Type	Histologic type	Lesion location	Biopsy	ECOG	Karnofsky%	MSKCC	IPI
1	60/F	PCNSL	DLBCL	Temporal	Steriotactical BX	4	40	3	3
2	78/F	PCNSL	DLBCL	Lateral ventricule + nasal	Nasal exicional BX	3	60	3	3
3	56/M	PCNSL	DLBCL	Frontal	Steriotactical BX	4	30	3	2
4	50/M	PCNSL	DLBCL	Occipital	Steriotactical BX	3	60	3	2
5	45/F	PCNSL	DLBCL	Parietal	Exicional BX	2	70	1	2
6	47/M	PCNSL	DLBCL	Parietal	Steriotactical BX	2	70	1	2
7	50/M	PCNSL	DLBCL	Thalamus	Exicional BX	3	50	2	2
8	72/F	SCNSL	DLBCL	Temporal	NA	4	20	3	3
9	45/M	SCNSL	DLBCL	Ocular	NA	1	80	1	2

ECOG = Eastern Cooperative Oncology Group Scale of Performance Status, MSKCC = Memorial Sloan–Kettering Cancer Center (Motzer) score, IPI = International Prognostic Index, DLBCL = diffuse large B cell lymphoma, PCNSL = primary central nervous system lymphoma, SCNSL = secondary central nervous system lymphoma

Elevation in transaminases was detected in three patients. The toxicities are listed in Table 5.

DISCUSSION

Treatment of CNSLs is a challenge due to aggressive nature with poor prognosis. Particularly, required aggressive treatment approaches must be able to pass beyond the blood–brain barrier and penetrate the CNS tissue, and have high response rates and minimum long-term side effects.

For these patients, WBRT was applied as a main treatment for many years. However, WBRT alone ensures limited benefit in survival due to relapse with short median survival and neurotoxic complications.[11-13] Therefore, targeted therapy is preferred instead of WBRT as a main therapy. Currently, it can be used for consolidation with a combined modality regimens.

The IDARAM protocol is a CNS-targeted chemotherapy protocol, which contains idarubicin, dexamethasone, cytosine arabinoside, and MTX. WBRT takes place as a consolidation as per protocol (40 Gy in 20 fractions). Although it seems to be a good combination of chemotherapeutics likely to be effective within CNS, few studies are reported in the literature. First, Moreton *et al.*[6] showed the outcomes of protocol in 24 patients with high response rates (88% and 75%). Hematological toxicity (95%) was the most common adverse event, and neurotoxicity (13%) due to radiotherapy was seen in few patients. However, a short median duration of follow-up time outcomes was declared.[6]

The protocol was improved with additional anti-CD20 monoclonal antibody, increased dose of MTX, and two additional courses after cranial radiotherapy, and was named R-IDARAM by Yılmaz *et al.*[7] In a case series of three patients, CR was achieved in all, and more than a year survival rate was obtained. Severe myelosuppression and infection were the main complications due to usage of high-dose MTX.

In our case series, results and outcomes of modified protocol were analyzed with more patients and longer median follow-up time. We speculate that early CR was ensured in most patients after two courses of therapy due to administered higher MTX dose. Similarly, hematological toxicities, which were observed in all patients, were related with MTX dosage. Moreover, all patients experienced febrile neutropenic episode, despite starting GCSF treatment on the seventh day.

Skin toxicities and mucositis were manageable frequently.

Although renal and cardiac toxicities were not observed in any patients, mild–moderate elevation in liver enzymes was observed in three patients. Dose reduction was used in patients, and elevation was not observed in the following

Table 4: Treatment and responses

Patientno.	Dose reduction	Received cycle	Response after 2 cycles	RT	IT	Survival (months)	Treatment-related death
1	50%	3 + RT	CR	+	-	7	-
2	50%	2	CR	-	-	4	-
3	Not	1	-	-	-	1*	-
4	Not	1 + RT	-	+	+	6	-
5	Not	4 + RT	CR	+	+	79 (alive)	-
6	Not	4 + RT	CR	+	+	88 (alive)	-
7	Not	1	-	-	-	1*	-
8	Not	1	-	-	-	1	-
9	Not	3	CR	-	+	17 (alive)	-

RT = radiation therapy, CR = complete remission, IT = intrathecal treatment

*Early death due to severe disease

Table 5: Assessment of side effects

Patientno.	Hematologic grade	Mucositis grade	Neurologic grade	Nausea/vomitting	Skin grade	Cardiac grade	Liver grade	Renal grade	Febrile neutropenia
1	3–4	2	2	3/2	2	-	-	-	+
2	3–4	2	-	1/1	-	-	3	-	+
3	3–4	1	-	1/1	-	-	2	-	+
4	3–4	1	-	1/1	-	-	-	-	+
5	3–4	1	-	1/1	-	-	-	-	+
6	3–4	2	-	3/1	-	-	1	-	+
7	3–4	2	-	2/1	-	-	-	-	+
8	3–4	2	-	3/2	-	-	-	-	+
9	3–4	1	-	1/1	-	-	-	-	+

course. Treatment-related death was not seen in any patients similar with other reports.

In the literature, survival rates of patients with CNSL are reported as 20%–30% at 5-year and 10%–20% at 10 years.[14-17] Certain groups have modified the R-IDARAM protocol to improve the response rates.[18,19] Qian *et al.*[20] used R-IDARAM protocol with additional intraventricular immunochemotherapy to provide therapeutic concentrations in the CNS and declared high rates of OS and PFS in a 3-year follow-up (84.2% and 63.2%, respectively). In this report, two patients of PCNSL and a patient of SCNSL have survived for 88, 79, and17 months, respectively, without disease progression in a median of 79-month follow-up. Early death (in 30 day) during therapy was seen in two patients due to severe disease.

This report had limitation because of including a small sample size. More studies are required with large number of patients to observe side effects and to study the efficacy of protocol.

CONCLUSION

R-IDARAM protocol may be an option with high early response rates and manageable toxicity. Hematological side effects are the main problem, and long-term neurological toxicity is not common. Eligible patients must continue with ASCT as long-term survival outcomes are poor. More clinical trials are still needed to develop new therapeutic methods for both primary and secondary CNSL.

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Conflicts of interest

There are no conflicts of interest.

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