



BACKGROUND

Secondary central nervous system lymphoma (SCNSL) in diffuse large B-cell lymphoma (DLBCL) remains a highly aggressive complication associated with poor outcomes and limited therapeutic options. Conventional systemic regimens provide inadequate CNS penetration, while optimal induction and consolidation strategies remain undefined. R-MIADD, a CNS-directed regimen with reported activity in SCNSL, may achieve meaningful responses; however, durability of disease control without subsequent transplantation remains uncertain. We describe our institutional experience with R-MIADD and highlight circumstances in which transplantation remained necessary despite use of a non-transplant regimen.

METHODS

We retrospectively reviewed four adult patients with histologically confirmed DLBCL and SCNSL treated at a tertiary referral center using R-MIADD consisting of rituximab 375 mg/m² (day 0), high-dose methotrexate 3.5 g/m² (day 1), ifosfamide 1.2 g/m²/day (days 2), cytarabine 1 g/m² every 12 hours (days 3), liposomal doxorubicin 20–25 mg/m² (day 4), and dexamethasone. Clinical characteristics, CNS disease sites, treatment delivery, toxicities, responses, transplant utilization, and outcomes were reviewed descriptively.

RESULTS

The cohort included two men and two women aged 19–61 years. Three patients developed SCNSL following prior R-CHOP–based therapy, while one presented with CNS involvement at diagnosis. CNS disease involved brain parenchymal/brainstem and spinal canal sites. All patients exhibited high-risk disease features and received R-MIADD as CNS-directed therapy. Treatment was deliverable in all patients with no treatment-related mortality. Three patients completed six cycles, while one discontinued treatment after three cycles due to reversible ifosfamide-associated neurotoxicity. Grade 3–4 hematologic toxicity occurred but was manageable with supportive care.

Three patients achieved complete CNS response and one achieved partial response with marked neurologic improvement. Despite clinically meaningful activity, two of four patients subsequently underwent autologous stem cell transplantation (ASCT): one following treatment intolerance related to reversible ifosfamide-associated neurotoxicity after three cycles and another after developing isolated CNS relapse with decreased sensorium during admission for cycle 6. The latter completed the final R-MIADD cycle, subsequently received whole-brain radiotherapy (WBRT), and proceeded to ASCT. At last follow-up, three patients remained alive with ongoing disease control.

Table 1. Treatment response and subsequent transplant utilization following R-MIADD in secondary CNS DLBCL

Case	CNS site	Best response	Cycles	Reason for HSCT	Current status
1	Brain parenchyma	CR	6	None	Alive, remission
2	Brain	CR → isolated CNS relapse	6	Relapse during cycle 6 → WBRT	Alive, remission
3	Spinal canal	PR	3	Ifosfamide neurotoxicity/intolerance	Alive, disease control
4	Brainstem	CR	6	None	Alive, remission

CONCLUSION

R-MIADD demonstrated feasibility and clinically meaningful CNS activity in SCNSL. However, our experience suggests that active CNS-directed chemotherapy does not eliminate the need for transplant-based strategies. Selected patients may still require multimodal approaches including radiotherapy and HSCT because of treatment intolerance or inadequate durability of response.

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