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Dose-Adjusted EPOCH-R and Mid-Cycle High Dose Methotrexate for Patients with Systemic Lymphoma and secondary CNS Involvement

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Treatment of patients with lymphoma who have **secondary** central nervous system (CNS) involvement is challenging, particularly for those who also have systemic disease. High-dose methotrexate (HD-MTX)-based regimens, often followed by radiotherapy (RT) or high dose chemotherapy with autologous stem cell transplant (ASCT) are considered standards of care for patients with primary CNS lymphoma (PCNSL) (Rubenstein, *et al* 2013); however, HD-MTX itself is not optimum treatment for disease in sites outside the CNS (systemic lymphoma) (Bokstein, *et al* 2002). Dose-adjusted EPOCH (etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone) plus rituximab (DA-EPOCH-R) has significant efficacy in the treatment of aggressive B-cell lymphoma, and is well tolerated, but drugs in this regimen are not known to effectively treat PCNSL (Wilson, *et al* 2008).

In an attempt to develop an effective, well-tolerated regimen for patients with systemic lymphoma and **secondary** CNS involvement, we began a pilot programme using DA-EPOCH-R with mid-cycle HD-MTX (DA-EPOCH-R/HD-MTX) at our centre. This retrospective analysis was performed in accordance with the declaration of Helsinki and approved by the institutional review board of MD Anderson Cancer Center.

In total, eight patients were treated with this strategy; seven patients had diffuse large B-cell lymphoma (DLBCL) and one had Burkitt lymphoma (BL, Table I). All patients except for one had two or more extranodal sites and six had a performance status 2. Patient 1 had

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Author contributions

D.C. and F.B.H. designed the study. D.C. performed the statistical analysis. N.H.F., Y.O., M.A.F., L.E.F., J.R.W., provided patient care. D.C. and F.B.H. interpreted the data and wrote the draft of the paper. All authors have read and approved the final version of the manuscript

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MYC translocation by fluorescence *in situ* hybridization and double protein expression with *MYC* and *BCL2* by immunohistochemical staining. None were seropositive for human immunodeficiency virus. CNS regions included parenchymal sites in three, spinal masses in three and cerebrospinal fluid (CSF) involvement in two. DA-EPOCH-R was administered as previously described (Wilson, *et al* 2008). Cycles were to be given every 21 days, providing that the absolute neutrophil count was at least $1 \times 10^9/l$ and the platelet count was at least $100 \times 10^9/l$. All but one patient (Patient 5) received intrathecal (IT) chemotherapy 1 or 2 times during the first week of DA-EPOCH-R (methotrexate alternating with cytarabine in four and methotrexate alone in three). IT chemotherapy was not administered coincident with HD-MTX (3.5 g/m^2), which was to be given on day 15 of DA-EPOCH-R. Urine alkalinization, hydration and leukovorin rescue were performed as described (DeAngelis, *et al* 2002). Patients received sulfamethoxazole and trimethoprim three times per week for standard prophylaxis. No patients received consolidative RT. Adverse events were assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Systemic and CNS disease responses were assessed by previously described criteria (Abrey, *et al* 2005, Cheson, *et al* 2007).

Overall, 42 cycles of HD-MTX were given in combination with 46 cycles of DA-EPOCH-R (Table I). Two patients (Patients 1, 5) started their initial treatment with HD-MTX to control CNS disease. The median numbers of days between DA-EPOCH-R cycles was 24 (range: 19–35); the median numbers of days from HD-MTX to DA-EPOCH-R was 8 (range: 3–20). Pegylated granulocyte colony-stimulating factor (G-CSF) (pegfilgrastim) was used on day 6 of DA-EPOCH-R in 28 of 46 cycles, and G-CSF (filgrastim) was used from day 6 until the day before HD-MTX in 18 of 46 cycles. There was no significant difference in the duration to next DA-EPOCH-R between these uses of pegfilgrastim and filgrastim. Three patients were able to escalate the dose of EPOCH, four patients received the same dose throughout treatment and one patient required one dose reduction from the second cycle on. Grades 3–4 neutropenia, anaemia and thrombocytopenia occurred in 55%, 62% and 12% of cycles, respectively. Infectious complications that required hospitalization occurred in 15% of cycles. Non-haematological toxicities were mostly grade 1 or 2: grades 1–2 nephrotoxicity occurred in three patients with no grade 3–4 events, and grades 3–4 hepatotoxicity with elevations in transaminases or bilirubin occurred in 14% of cycles, but all resolved spontaneously. All patients achieved complete response (CR); the one patient with BL experienced a recurrence of CSF involvement at 4.4 months following discontinuation of IT chemotherapy, but achieved a negative CSF status following reintroduction of IT chemotherapy. Four patients underwent consolidative ASCT after achieving CR, including the patient who had recurrence of disease in the CSF. With a median follow up of 11 months (range: 6.5–17.4 months), all remain alive without systemic or CNS relapse.

There is no standard of care for patients with lymphoma who have both **secondary** CNS involvement and systemic disease. Recently, Ferreri *et al* (2015) reported the final results of a high-dose chemoinmunotherapy programme followed by ASCT for 38 patients with **secondary** CNS involvement at the time of initial diagnosis or at relapse. The CR rate before

ASCT was 61% and the 5-year event-free survival for all patients was 40%. There was no significant difference in the survival outcome for patients with **secondary** CNS involvement at diagnosis compared to those treated at relapse. Importantly, four patients died of treatment-related toxicity, ten patients experienced progressive disease during treatment and only 20 (53%) underwent planned ASCT.

In the current case series, DA-EPOCH-R/HD-MTX induced 100% systemic CR: control of CNS disease was also favorable; one patient with BL developed CSF positivity during treatment following discontinuation of IT chemotherapy. Although the follow-up duration is short, all patients remain free of disease and were alive at the time of this analysis. Treatment was well tolerated without major toxicities or treatment-related mortality. Three patients who did not undergo consolidative ASCT are still free from relapse for over one year.

HD-MTX is often given every two weeks in therapy of PCNSL, a schedule in which patients maintain higher cytotoxic levels of MTX in the CSF (Rubenstein, *et al* 2013). In our treatment strategy, HD-MTX was administered every 3 weeks or more; nevertheless, this schedule appeared effective in control of CNS relapse in the seven DLBCL cases. Administration of IT chemotherapy in combination with HD-MTX for patients with PCNSL is also controversial, as it did not improve outcomes in one study (Khan, *et al* 2002). However, the one patient who had CSF relapse had BL and achieved CR with reintroduction of IT therapy; the use of IT therapy in our programme will also require further study.

Although we report results for only eight cases, DA-EPOCH-R/HD-MTX achieved CR in all; three who did not undergo consolidative ASCT are free from relapse for more than 1 year. However, only prospective trials can define the optimum scheduling of this regimen and the importance of IT chemotherapy and consolidative ASCT for these patients.

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Table 1

Patient characteristics

Patient	Age (years)	Sex	Diagnosis	Stage	PS	2	LDH >UNL	Ki67 (%)	MYC (IHC)	Extranodal sites	CNS region	IPI
1	68	M	DLBCL (non-GCB)	1	-	-	+	NA	+	CNS	parenchymal	L-I
2	58	M	DLBCL (non-GCB)	4	+	+	+	70	+	CNS, liver, BM	CSF	H
3	52	F	DLBCL (non-GCB)	4	+	+	+	95	NA	CNS, bone	Spinal	H
4	40	F	DLBCL (GCB)	4	+	+	+	95	+	CNS, bone, BM	CSF	H
5	54	F	DLBCL (unknown)	4	+	+	-	NA	NA	CNS, Lung	parenchymal	I-H
6	51	M	DLBCL (GCB)	4	+	+	+	80	+	CNS, bone, BM	Spinal	H
7	60	M	DLBCL (GCB)	4	-	-	+	85	NA	CNS, bone	parenchymal	I-H
8	30	M	Burkitt lymphoma	4	+	+	+	100	+	CNS, bone, kidney, pleura, soft tissue	Spinal	H

BM, bone marrow; CNS, central nervous system; CSF, central spinal fluid; DLBCL, Diffuse large B-cell lymphoma; F, female; GCB, germinal centre B-cell; IHC, immunohistochemical; IPI International prognostic index; L, low, I, intermediate; H, high; LDH, lactate dehydrogenase; M, male; NA, not assessed; PS, performance score; UNL, upper normal limit.

Response and outcomes

Table II

Patient	EPOCH cycle	HDMTX cycle	Response	CNS control	Consolidative ASCT	Regimen	Relapse	Death	Survival (Months)
1	6	4	CR	CR	-		-	-	+12.4
2	6	6	CR	CR	-		-	-	+17.4
3	6	6	CR	CR	-		-	-	+16.6
4	4	3	CR	CR	+	BEAM	-	-	+17.3
5	6	6	CR	CR	+	TBC	-	-	+11.4
6	6	5	CR	CR	+	GBMV	-	-	+6.7
7	6	6	CR	CR	-		-	-	+6.5
8	6	6	CR	PD	+	GBMV + at 4.4 months (CNS)	-	-	+8.4

ASCT, autologous stem cell transplantation; BEAM, carmustine, etoposide, cytarabine, melphalan; CNS, central nervous system; CR, complete response; EPOCH, etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone; GBMV, gemcitabine, busulfan, melphalan, vorinostat; HDMTX, high-dose methotrexate; PD, progressive disease; TBC, thiolepa, carmustine, cyclophosphamide.