

Outcomes of patients with diffuse large B-cell and high-grade B-cell lymphomas with synchronous CNS and systemic involvement at diagnosis treated with high-dose methotrexate and R-CHOP: a single-center retrospective study

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Abstract

Background: The optimal treatment of patients with systemic diffuse large B-cell (DLBCL) or high-grade B-cell (HGBL) lymphomas with synchronous central nervous system (CNS) involvement at diagnosis is not well defined. High-dose methotrexate administered concurrently with R-CHOP (RM-CHOP) is a commonly used regimen, but data on outcomes achieved with this regimen are limited.

Objective: To report our experience with RM-CHOP in patients with systemic DLBCL or HGBL with synchronous CNS involvement at diagnosis.

Design: A single-center retrospective analysis.

Methods: We identified consecutive patients with systemic DLBCL or HGBL with synchronous CNS involvement at diagnosis who were treated with RM-CHOP from January 2012 to January 2021.

Results: Fifty patients were included with a median age of 62 years; 82% had DLBCL ($n=41$) and 18% had HGBL ($n=9$). Treatment with RM-CHOP was followed by consolidative autologous hematopoietic cell transplantation in 14 patients (28%). The complete response (CR) rate following RM-CHOP was 62%. With a median follow-up of 40 months, the median progression-free (PFS) and overall (OS) survivals were 16 and 58 months, and the 2-year PFS and OS were 41% and 57%, respectively. The 2-year cumulative incidence of CNS progression/relapse was 29%. Outcomes were particularly poor in HGBL, with median PFS and OS of 6 and 7 months, compared with median PFS and OS of 22 months and not reached in DLBCL, respectively. The outcomes of patients with relapsed/progressive disease were poor, with only 63% of patients receiving subsequent treatments and only 21% achieving CR to next subsequent treatment. Most patients (58%) with disease relapse/progression had CNS involvement which was associated with very poor outcomes (median OS of 2 months).

Conclusion: CNS involvement in aggressive B-cell non-Hodgkin lymphoma at diagnosis dictates clinical outcomes and requires more effective treatment options.

Keywords: CNS involvement, DLBCL, high-grade B-cell lymphoma, methotrexate, RM-CHOP

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma in the United States, accounting for approximately 20% of all lymphoid malignancies.¹ High-grade B-cell lymphoma (HGBL) is a rare type of aggressive lymphoma that comprises two subtypes: lymphomas with *MYC* and *BCL2* and *BCL6* rearrangements (also known as double- or triple-hit lymphomas) and HGBL, not otherwise specified (NOS). The latter is defined by morphologic criteria in cases of large B-cell lymphomas that appear blastoid or cases intermediate between DLBCL and Burkitt's lymphoma but lack *MYC* and *BCL2* and *BCL6* rearrangements (which include cases previously classified as 'B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt's lymphoma'). HGBL is generally more aggressive than DLBCL and associated with inferior outcomes.²

Synchronous involvement of the central nervous system (CNS) in systemic DLBCL and HGBL at diagnosis is uncommon, reported in less than 5% of patients, and represents a unique therapeutic challenge.^{3–5} Because treatments should be effective against both the systemic and the CNS components, they generally incorporate strategies used in treating patients with systemic DLBCL/HGBL and primary CNS lymphoma, despite the differences in biological and clinical disease features. The optimal treatment in this setting is not well defined, given the rarity of synchronous CNS involvement at diagnosis, and as these patients are typically excluded from clinical trials.^{6–8} R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is established as the standard-of-care treatment for most patients with DLBCL whereas some retrospective studies support the use of more intensive regimens in HGBL such as dose-adjusted R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), R-CODOX-M/R-IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate alternating with rituximab, ifosfamide, cytarabine, and etoposide), or R-HyperCVAD/MA (rituximab, hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone alternating with methotrexate and cytarabine).^{5,9,10} R-CHOP and R-EPOCH have poor blood–brain barrier penetration and lack any clinically significant CNS activity.

R-CODOX-M/R-IVAC and R-HyperCVAD/MA incorporate methotrexate and cytarabine, which penetrate the blood–brain barrier and can achieve therapeutic CNS levels. Their use is limited to selected younger and fit patients given their relatively high treatment-related morbidity and mortality, however.^{11–15} As the backbone treatment for primary CNS lymphoma, high-dose methotrexate (HDMTX) is commonly combined with R-CHOP (RM-CHOP) to treat patients with systemic DLBCL and HGBL with synchronous CNS involvement, but data on the outcomes achieved with this regimen are limited. In this study, we sought to report our experience with the use of RM-CHOP in patients with DLBCL and HGBL and synchronous CNS and systemic involvement.

Methods

Study design, treatment, and patient population

We retrospectively identified consecutive patients with DLBCL or HGBL with synchronous CNS and systemic involvement at diagnosis who received treatment with RM-CHOP at the James Cancer Hospital of The Ohio State University (Columbus, OH, USA) from January 2012 through January 2021 under an institutional review board-approved protocol (protocol no. 2020C0170 approved on 20 November 2020). All patient data were de-identified in this publication. We identified patients using pharmacy treatment plan records and the OSU Lymphoma Database; the latter is a prospectively maintained database of patients with lymphoma treated at our institution. Patients who were incarcerated and those with inadequate records were excluded. Cases were classified as HGBL based on the presence of *MYC* with *BCL2* and *BCL6* rearrangements by fluorescence *in situ* hybridization (FISH) or morphology (diagnosis of HGBL, NOS, or B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt's lymphoma). Patients with a history of indolent lymphomas were allowed if they did not have a prior history of CNS involvement.

CNS involvement by lymphoma was defined as involvement of the CNS parenchyma (including spinal cord), cerebrospinal fluid (CSF), cranial nerves, meninges, and intraocular compartment (vitreous, choroid, or retina), confirmed by

biopsy, CSF cytology and flow cytometry, vitreal cytology, and/or brain/spine magnetic resonance imaging (MRI). Baseline CNS evaluation with brain and spine MRI, CSF analysis, and ophthalmic examination was at the treating physician's discretion. Patients found to have CNS involvement during treatment with R-CHOP/R-EPOCH were included if they had not received prophylactic HDMTX and did not have evidence of systemic progression when the CNS involvement was discovered. Response to treatment was determined by the treating physician following completion of RM-CHOP and prior to hematopoietic cell transplantation (HCT) according to the most recent guidelines at the time of treatment using positron emission tomography (PET) for systemic involvement and brain and/or spine MRI and/or CSF analysis for CNS involvement.

Treatment with RM-CHOP was administered inpatient every 21 days and consisted of HDMTX (3.5 g/m²) on day 1 followed by standard R-CHOP on day 2. All patients received adequate hydration, urine alkalinization aimed to maintain a urine pH ≥ 7 , and leucovorin rescue according to the institutional standards of care. Complete blood counts, chemistries, and appropriately timed methotrexate levels were obtained at least once daily and typically twice weekly following discharge. The use of intrathecal (IT) methotrexate including the number and frequency of IT treatments as well as the decision to use consolidative HCT after RM-CHOP were not standardized and were at the treating physician's discretion.

Data collection

Patient characteristics, laboratory data, and clinical outcomes were extracted from the OSU Lymphoma Database and manually from the electronic medical record (EMR). Treatment regimen details including doses of HDMTX and components of R-CHOP were collected through the pharmacy treatment plan records and the EMR. Acute kidney injury (AKI) and hepatotoxicity were evaluated for HDMTX-containing cycles only. Neutropenic fever and mucositis were collected for all cycles *via* review of clinic notes and emergency department or inpatient encounters. Severity was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

Statistical analysis

Baseline patient characteristics were summarized by descriptive statistics with median and range presented for continuous variables, and frequency count and percentage provided for categorical variables. Univariable logistic regression models were built to estimate the association between patient characteristics and outcomes. Progression-free survival (PFS) was calculated from the time of diagnosis to either progression or death, and overall survival (OS) was calculated from the time of diagnosis to death because of all causes; patients without events were censored at the time of the last follow-up. PFS and OS were estimated through the Kaplan–Meier method. Cumulative incidence of CNS relapse was calculated with non-CNS relapse or death as the competing risk, and estimated through cumulative incidence function. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.¹⁶

Results

Patients

Of 837 patients with aggressive B-cell lymphoma treated with R-CHOP at our institution from January 2012 through January 2021, 50 patients (6%) had DLBCL ($n=41$, 82%) or HGBL ($n=9$, 18%) with synchronous CNS and systemic involvement at diagnosis and received concurrent intravenous HDMTX (Table 1). FISH was available for 43 patients (86%) (35 DLBCL, 8 HGBL). Of the nine patients with HGBL, six had *MYC* with *BCL2* and/or *BCL6* rearrangements (four with *MYC* and *BCL2*, one with *MYC* and *BCL6*, and one with *MYC*, *BCL2*, and *BCL6* rearrangements). Six patients (14%) (four DLBCL; two HGBL, NOS) had *MYC* without *BCL2* rearrangements (FISH for *BCL6* rearrangement was available and negative in three patients). The median age was 62 years (range = 19–80) and 42% were female. Eastern Cooperative Oncology Group (ECOG) performance status was ≥ 2 in 16 patients (36%). Lactate dehydrogenase (LDH) was elevated in 41 patients (87%). The International Prognostic Index (IPI) score classified 40% and 56% of patients as having intermediate- or high-risk disease, respectively. Eleven patients (55%) had *MYC* and *BCL2* double expression by immunohistochemistry (IHC) (available for $n=20$). CNS involvement was leptomeningeal in 28

Table 1. Baseline characteristics.

Variable ^a	Overall (n=50)	DLBCL (n=41)	HGBL (n=9)
Age (years), median (range)	62 (19–80)	62 (19–80)	64 (56–75)
Female sex	21 (42)	15 (37)	6 (67)
ECOG performance status			
• 0–1	29 (64)	24 (65)	5 (63)
• 2	12 (27)	10 (27)	2 (25)
• 3	4 (9)	3 (8)	1 (13)
• Unknown	5	4	1
Elevated LDH			
• Unknown	41 (87)	33 (85)	8 (100)
Site of CNS involvement			
• Parenchymal	14 (28)	12 (29)	2 (22)
• Leptomeningeal	28 (56)	23 (56)	5 (56)
• Both	8 (16)	6 (15)	2 (22)
Number of extranodal sites outside of CNS, median (range)			
• ≥ 2 extranodal sites	24 (48)	17 (41)	7 (78)
• ≥ 3 extranodal sites	16 (32)	13 (32)	3 (33)
Extranodal sites outside of CNS			
• Renal/adrenal	6 (12)	3 (7)	3 (33)
• Paraspinal	5 (10)	5 (12)	0
• Paranasal sinus	2 (4)	1 (2)	1 (11)
• Testicular (% of males)	4 (14)	4 (15)	0
• Breast (% of females)	2 (10)	0	2 (33)
IPI score			
• Low risk (0–1)	2 (5)	2 (6)	0
• Intermediate risk (2–3)	17 (40)	15 (43)	2 (25)
• High risk (4–5)	24 (56)	18 (51)	6 (75)
• Unknown	7	6	1
MYC/BCL2 double expression by IHC			
• Present	9 (45)	8 (47)	1 (33)
• Absent	11 (55)	9 (53)	2 (67)
• Unknown	30	24	6

(Continued)

Table 1. (Continued)

Variable ^a	Overall (n=50)	DLBCL (n=41)	HGBL (n=9)
Laboratory parameters (cycle 1, day 1)			
• Albumin <3.5g/dl, unknown	27 (73), 13	20 (69), 12	7 (88), 1
• Hemoglobin <10.0g/dl, unknown	15 (34), 6	10 (28), 5	5 (63), 1
• Platelets <150K/ μ l, unknown	11 (25), 6	9 (25), 5	2 (25), 1
• ANC <1500 cells/ μ l, unknown	2 (5), 6	2 (6), 5	0, 1
• Creatinine clearance (ml/min), median (range)	106 (31–366)	113 (31–217)	86 (44–366)
ANC, antenatal care; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HGBL, high-grade B-cell lymphoma; IHC, immunohistochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase. ^a n (%) unless stated otherwise.			

patients (56%), parenchymal in 14 (28%), or both in 8 (16%). One patient had vitreoretinal in addition to brain parenchymal involvement. A diagnostic lumbar puncture with CSF examination by cytology and flow cytometry was done in 38 patients (76%). The median number of extranodal sites outside of the CNS was 1 (range=0–6) with 48% of patients having ≥ 2 extranodal sites outside of the CNS. The most common extranodal sites outside the CNS were testicular ($n=4$, 14% of males), renal/adrenal ($n=6$, 12%), paraspinal ($n=5$, 10%), and breast ($n=2$, 10% of females).

Treatment

Of the 249 R-CHOP cycles received by 50 patients, most cycles (89%, $n=222$) included HDMTX with a median of 5 HDMTX-containing R-CHOP cycles administered per patient (range=1–6) (Supplemental Table 1). HDMTX was administered on day 1 of R-CHOP in all HDMTX-containing cycles but three cycles (two cycles on day 2 and one on day 8). HDMTX starting dose was 3.5 g/m² in all but three patients (1.5, 1.75, and 2 g/m²). Four patients started treatment with R-EPOCH before RM-CHOP: three patients with DLBCL received R-EPOCH for one cycle with concurrent IT methotrexate for known leptomeningeal involvement (one patient while awaiting FISH result, two patients transferred from other institutions) and one patient with HGBL was found to have leptomeningeal involvement after the second cycle of R-EPOCH. Twenty-one patients (42%) received additional

treatment with IT methotrexate (17 patients with leptomeningeal involvement, 2 with parenchymal involvement, and 2 with leptomeningeal and parenchymal involvement) with a median number of total IT methotrexate treatments per patient of 1 (range=1–8, 4 patients received ≥ 4 IT methotrexate treatments). Granulocyte colony-stimulating factor (G-CSF) was administered in 95% of the cycles.

Treatment with RM-CHOP was followed by high-dose chemotherapy and consolidative autologous hematopoietic cell transplantation (AHCT) in 14 patients (28%) (13 patients with DLBCL and 1 with HGBL; Supplemental Table 1). Twelve patients were in complete response (CR) and two in partial response (PR) following RM-CHOP and before AHCT. The preparative high-dose chemotherapy regimen in all patients was thiopeta and carmustine with or without cyclophosphamide. The median time from DLBCL/HGBL diagnosis to AHCT was 7 months (range=5–14 months). One patient with a history of heavily pretreated marginal zone lymphoma and transformation to DLBCL achieved CR following RM-CHOP and underwent allogeneic HCT.

Toxicities

Treatment delay of ≥ 7 days because of toxicity occurred in 15% of patients (11% had delays in 1 cycle and 4% in ≥ 2 cycles). Six patients (12%) had ≥ 1 HDMTX dose reduction in ≥ 1 cycle and three patients (6%) had dose reductions in

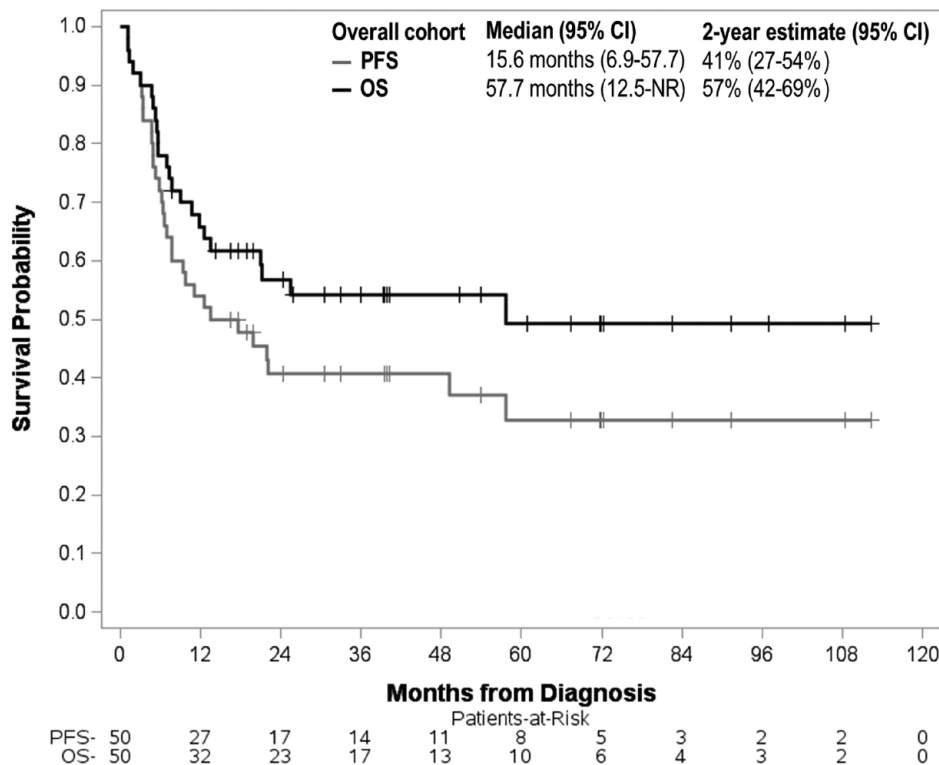


Figure 1. PFS and OS for the overall cohort.

doxorubicin and cyclophosphamide. Thirteen patients (26%) discontinued RM-CHOP prematurely because of disease progression/death ($n=9$), alternate therapy ($n=2$), toxicity ($n=1$), or other ($n=1$). HDMTX was discontinued because of toxicity, without or before R-CHOP discontinuation, in four patients (8%) [three patients had leptomeningeal involvement and one had parenchymal; all patients had AKI grade 2 ($n=1$) or 3 ($n=3$) with delayed methotrexate clearance (7–24 days) and three required glucarpidase]. Twenty-seven patients (54%) developed AKI including grades 2 and 3–4 in 19 (38%) and 8 patients (16%), respectively. Four patients (8%) received glucarpidase. Eleven patients (22%) developed neutropenic fever, five patients (10%) grade ≥ 3 mucositis, four patients (8%) grade ≥ 3 elevation in hepatic transaminases, and one patient (2%) grade ≥ 3 hyperbilirubinemia.

Outcomes

Three patients with DLBCL and one with HGBL died after one to two cycles of treatment and before response assessment. Overall, 31 patients

achieved CR (62%), 3 patients (6%) achieved PR, and 12 patients (24%) had stable or progressive disease. With a median follow-up of 40 months, the median PFS and OS were 16 months [95% confidence interval (CI)=7–58 months] and 58 months (95% CI=13 months – not reached), respectively (Figure 1). The 2-year PFS and OS were 41% (95% CI=27–54%) and 57% (95% CI=42–69%), respectively. The 2-year cumulative incidence of CNS progression/relapse was 29% (95% CI, 17–42%). Eleven patients (22%) died within 6 months of diagnosis (eight with DLBCL and three with HGBL). For the 31 patients with DLBCL or HGBL who achieved CR following RM-CHOP, the 2-year PFS and OS were 62% (95% CI=42–77%) and 79% (95% CI=59–90%) compared with 5% (95% CI=0–21%) and 20% (95% CI=6–40%) for those who did not achieve CR, respectively (Figure 2). PFS and OS were not significantly different among patients who had leptomeningeal involvement only versus parenchymal with or without leptomeningeal involvement (2-year PFS 40% versus 41%, $p=0.50$; 2-year OS 68% versus 43%, $p=0.13$, respectively) (Figure 2).

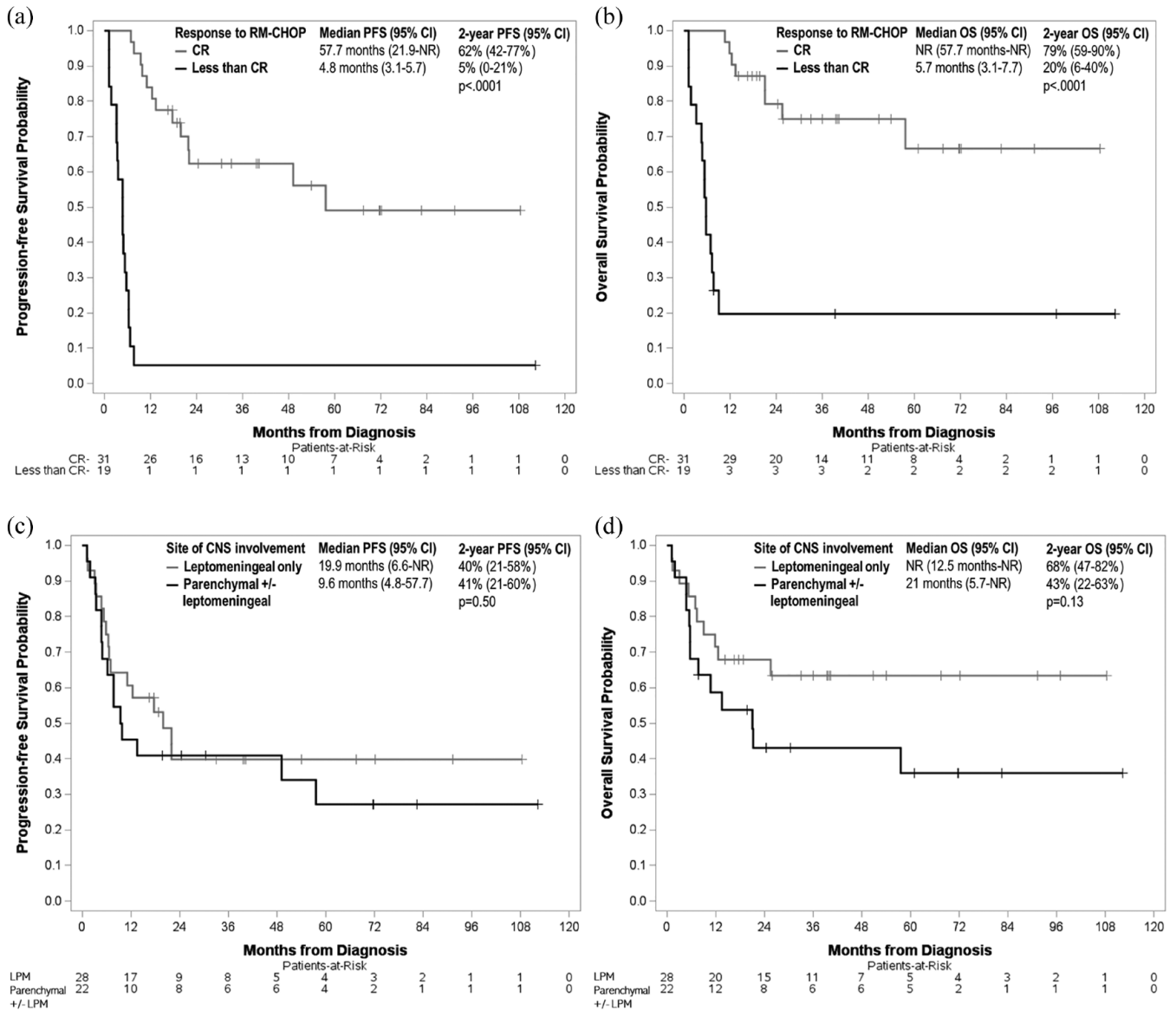


Figure 2. PFS and OS according to response to RM-CHOP (a and b) and site of CNS involvement (c and d).

Outcomes were particularly poor for patients with HGBL (Figure 3). Only two patients achieved CR (22%). The median PFS and OS were 6 months (95% CI=1–10 months) and 7 months (95% CI=1–13 months), and the 1-year PFS and OS were 11% (95% CI=1–39%) and 33% (95% CI=8–62%), respectively. For patients with DLBCL, 29 patients (71%) achieved CR. The median PFS and OS were 22 months (95% CI=10 months – not reached) and not reached (95% CI, 26 months – not reached), and the 2-year PFS and OS were 50% (95% CI=33–64%) and 68% (95% CI=51–80%), respectively.

In univariable analyses to identify prognostic factors for survival outcomes, only age and lymphoma type (DLBCL *versus* HGBL) were significantly associated with PFS and OS whereas ECOG performance status, MYC/BCL2 double expression by IHC, IPI score, number of extranodal sites, and site of CNS involvement at diagnosis were not (Supplemental Table 2).

Outcomes based on receipt of HCT

We sought to evaluate the impact of consolidative AHCT in patients who achieved CR following

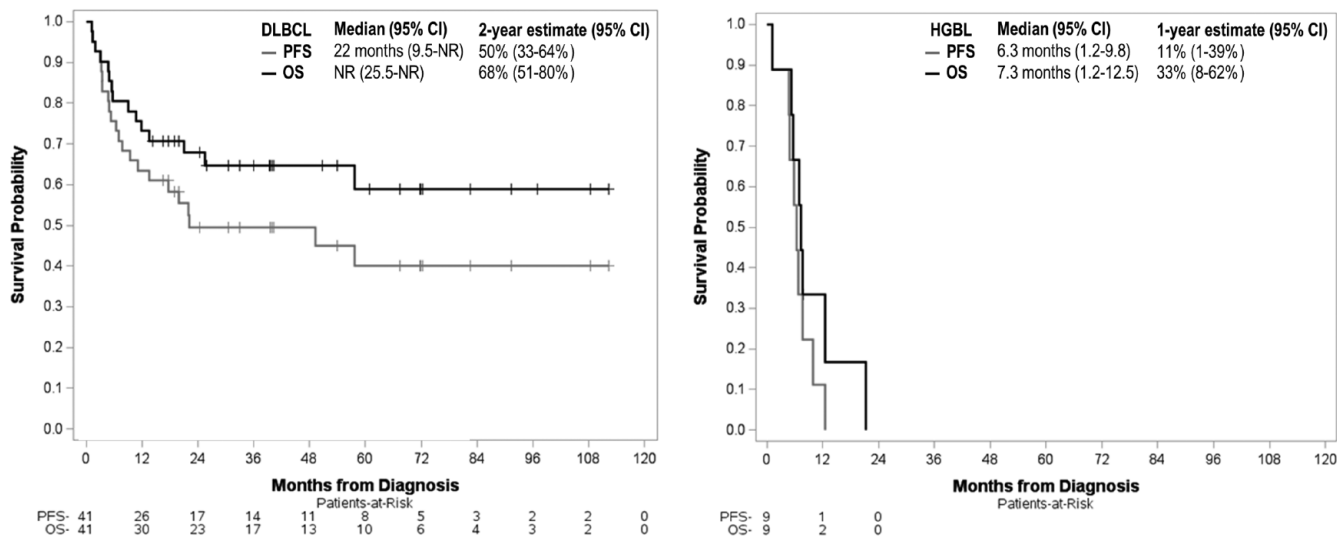


Figure 3. PFS and OS for patients with DLBCL or HGBL.

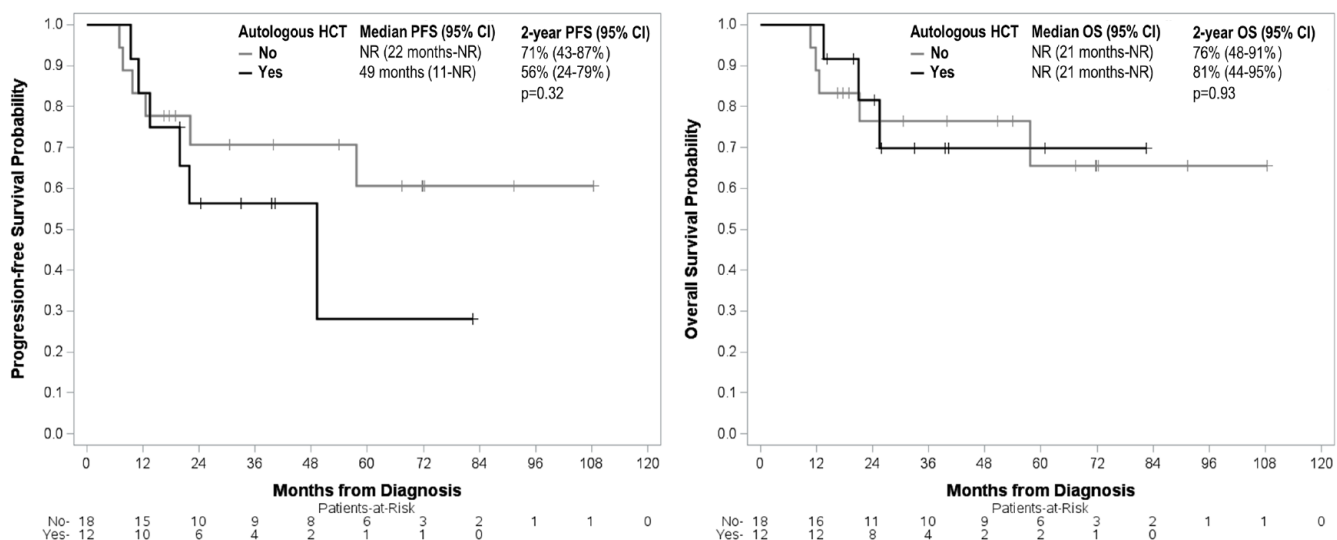


Figure 4. PFS and OS in patients with CR after RM-CHOP who did or did not undergo consolidative AHCT.

RM-CHOP. Supplemental Table 3 shows the baseline characteristics of patients who achieved CR following RM-CHOP and did ($n=12$) or did not ($n=18$) undergo consolidative AHCT (one patient who received allogeneic HCT was not included in either group). The AHCT cohort was slightly older (median age 63 *versus* 58 years) and had a lower proportion of patients with HGBL (0% *versus* 11%), elevated LDH (73% *versus* 88%), leptomeningeal involvement only (50% *versus* 67%), high-risk IPI (36% *versus* 53%), and serum albumin level less than 3.5 g/dl (38% *versus*

77%). AHCT was not associated with significant improvement in PFS or OS with 2-year PFS of 56% (95% CI=24–79%) *versus* 71% (43–87%) ($p=0.32$) and 2-year OS of 81% (44–95%) *versus* 76% (48–91%) ($p=0.93$; Figure 4).

Outcomes of patients with relapsed/progressive disease

Figure 5 illustrates the outcomes of the 24 patients who had progressive or relapsed disease following RM-CHOP grouped based on lymphoma type

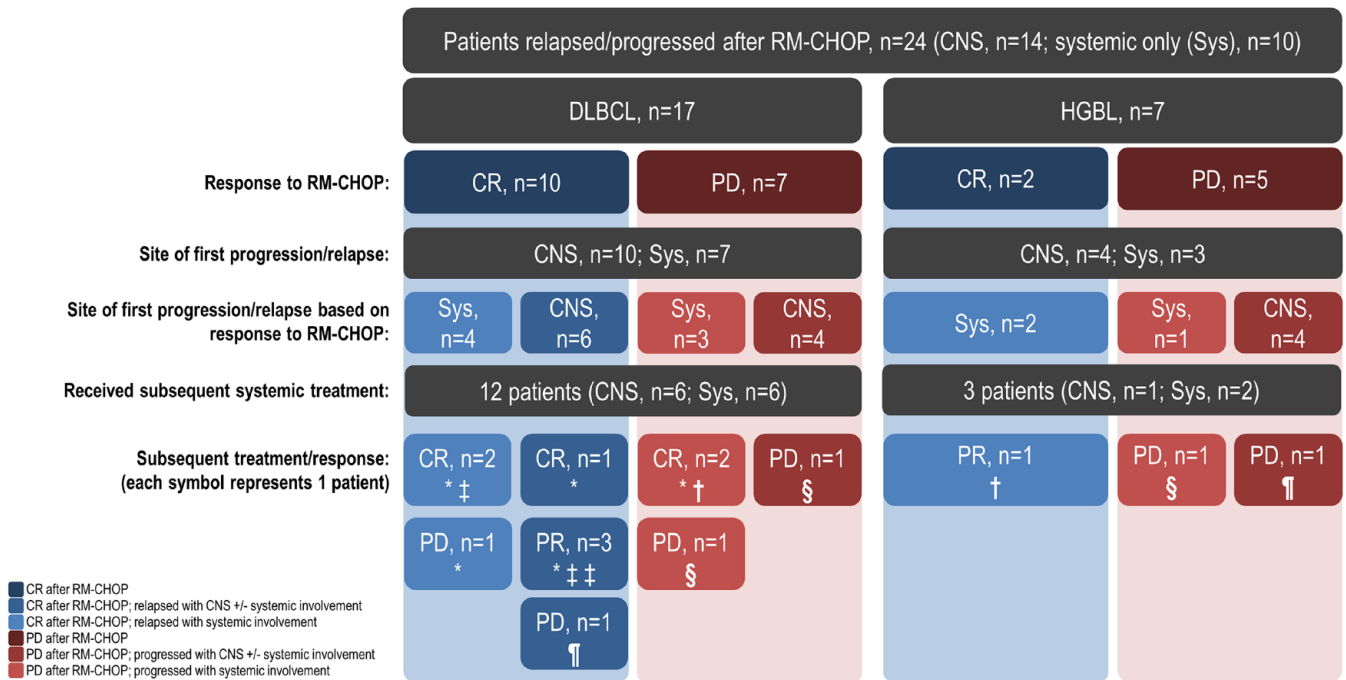


Figure 5. Outcomes of patients with relapsed or progressive disease.

*CART with or without bridging therapy.

†Platinum-based chemotherapy followed by AHCT.

‡Platinum-based chemotherapy alone.

§Lenalidomide +/- rituximab.

¶Other, bendamustine + obinutuzumab (n=1), HyperCVAD (n=1), R-HDMTX and donor-lymphocyte infusion (n=1).

[DLBCL (n=17) versus HGBL (n=7)], response to RM-CHOP [CR (n=12) versus not (n=12)], and site of first relapse/progression [CNS with or without systemic involvement (n=14) versus isolated systemic involvement (n=10)]. Seventeen patients with DLBCL relapsed or progressed with 10 patients having CNS involvement (4 parenchymal, 4 leptomeningeal, 2 both, 1 with systemic involvement) at their first relapse/progression event. Twelve patients (six with CNS involvement and six with systemic involvement only) received subsequent systemic treatments and eight responded (four with CNS involvement and four with systemic only) including five CRs and three PRs. Five patients (two with CNS involvement and three with systemic only) received chimeric antigen receptor (CAR) T cells of whom four responded (three CR and one PR): one patient who had leptomeningeal involvement only at relapse achieved CR and remains in remission for 3 months after CAR T cells, two patients who had systemic involvement only at relapse achieved CR and remain in remission for 1 and 3 years after CAR T cells, and one patient who had

leptomeningeal and systemic involvement at relapse achieved PR but relapsed with leptomeningeal and systemic involvement 3 months after CAR T cells. One patient with systemic involvement at relapse underwent AHCT and remains in remission after more than 7 years from AHCT. Seven patients with HGBL relapsed or progressed with four patients having CNS involvement (two parenchymal, two leptomeningeal, one with systemic involvement) at their first relapse or progression event. Three patients received subsequent systemic treatments (none received CAR T cells) and only one patient responded (PR after AHCT). Overall, of the 24 patients who relapsed/progressed after RM-CHOP, 15 patients (63%) received subsequent treatments and 5 (21%) achieved CR to the next subsequent treatment. Compared with patients with systemic involvement only at the time of first relapse/progression, those with CNS involvement at first relapse/progression had inferior OS (calculated from the date of first relapse/progression): median of 2 months (95% CI=0.7–5) versus 11 months (95% CI=0 to not reached), $p=0.04$, respectively (Supplemental Figure 1).

Discussion

Despite its relatively small size, this study is the largest to our knowledge to report on the outcomes of RM-CHOP in patients with systemic DLBCL or HGBL with synchronous CNS involvement at diagnosis. We report median and 2-year PFS of 16 months and 41% and median and 2-year OS of 58 months and 57% for the overall cohort. The outcomes of the 31 patients who achieved CR after RM-CHOP were encouraging with median and 2-year PFS of 58 months and 62% and median and 2-year OS of not reached and 79%. The outcomes of patients with HGBL were poor, with a CR rate of 22% and median PFS and OS of 6 and 7 months, respectively, and suggest that RM-CHOP is a suboptimal treatment for these patients, although we acknowledge the very small sample size of this cohort ($n=9$). In contrast, the more favorable outcomes in DLBCL with CR rate of 71%, median and 2-year PFS of 22 months and 50%, and median and 2-year OS of not reached and 68% support the use of RM-CHOP in this group. Notably, 22% of patients died within 6 months of diagnosis, highlighting the aggressive clinical course of DLBCL and HGBL with CNS involvement. AKI occurred in more than half of the patients (54%) treated with RM-CHOP including grades 2 in 38% and 3–4 in 16%. Neutropenic fever occurred in 22% and grade ≥ 3 mucositis in 10%. Only four patients (8%) discontinued HDMTX because of toxicity (AKI in four patients), however. We have previously reported in more detail on our experience with administering HDMTX on day 1 of R-CHOP.¹⁷ Similar to two other studies, we did not find significant

differences in outcomes among patients who had leptomeningeal involvement only *versus* parenchymal with or without leptomeningeal involvement.^{18,19}

Our results are in line with those of other studies of RM-CHOP or similar regimens with CR rates of 51–68% and 2- to 3-year PFS and OS of 37–45% and 44–56%, respectively. Table 2 shows the results of clinical trials and retrospective studies that included patients with systemic DLBCL or HGBL with synchronous CNS involvement at diagnosis (studies with ≤ 15 patients with synchronous CNS involvement at diagnosis were not included).^{14,20–24} The table highlights the paucity of published data and considerable heterogeneity in patients' characteristics and types of treatments received. Furthermore, none of these studies reported on the outcomes of patients with HGBL specifically. Perry *et al.*¹⁹ reported on 44 patients with DLBCL with synchronous CNS and systemic involvement at diagnosis including 23 patients treated with RM-CHOP and 12 treated with similar regimens (R-CHOP/HDMTX-based regimens). Nineteen patients underwent AHCT. The CR rate for the overall cohort was 66% and the 3-year PFS and OS were 42% and 56%, respectively. An international multicenter retrospective study by Wight *et al.*²⁵ included 80 patients with DLBCL or HGBL treated with intensive [$n=38$, most commonly R-HyperCVAD ($n=25$) or R-CODOX-M/IVAC ($n=9$)] or less-intensive chemotherapy regimens [$n=42$, RM-CHOP ($n=18$)]. The 2-year PFS and OS for the 18 patients treated with RM-CHOP were 37% and 53%, respectively.

Table 2. Clinical trials and retrospective studies of patients with systemic DLBCL/HGBL with synchronous CNS involvement.^a

Study type, reference	Phase II trial, MARIETTA ²⁶	Phase II trial, SCNSL1 ²⁷	Retrospective, multicenter ²⁵	Retrospective, multicenter ¹⁹	Retrospective, multicenter ²⁸	Retrospective, multicenter ²⁹	This study; retrospective, single-center
Number of patients	75	38	80	44	21	60	50
Number of DLBCLs or HGBLs with CNS inv at diagnosis	32	16	80	44	21	54	50
Number of HGBLs	NR	NR	12	NR	NR	NR	9
Median age (range)	58 years ^b	59 years ^b	64 years	54 years	54 years	61 years	62 years
Performance status ≥ 2	37% ^b	29% ^b	55%	≥ 3 , 27%	66%	≥ 1 , 52%	36%

(Continued)

Table 2. (Continued)

Study type, reference	Phase II trial, MARIETTA ²⁶	Phase II trial, SCNSL1 ²⁷	Retrospective, multicenter ²⁵	Retrospective, multicenter ¹⁹	Retrospective, multicenter ²⁸	Retrospective, multicenter ²⁹	This study; retrospective, single-center
High-risk IPI	23% ^b	NR	68% (NCCN IPI)	R-IPI ≥ 3 80%	24%	72%	56%
LPM involvement only	11% ^b	13% ^b	49%	43%	0%	NR	56%
Treatment	MATRix, R-ICE	MTX+Ara-C R-HDS	Intensive, <i>n</i> =38: R-HCVAD 66%, R-CODOX-M/IVAC 24% Less-intensive, <i>n</i> =42: RM-CHOP, <i>n</i> =18	RM-CHOP, <i>n</i> =23; RM-CHOP + others, <i>n</i> =12	MBVP/R-CHOP, <i>n</i> =10; alternating MTX/R-CHOP, <i>n</i> =10	RM-CHOP <i>n</i> =5; CHOP-like, HDMTX and Ara-C <i>n</i> =31; CHOP alone <i>n</i> =8	RM-CHOP
AHCT, <i>n</i> (%)	42 (56%) ^b	20 (53%) ^b	13 (16%)	19 (43%)	0	19 (32%)	14 (28%)
Objective response rate, CR rate	84%, 53%	63%, 63% ^b	Intensive: 80%, 69% Less-intensive: 63%, 51%	81%, 66%	62%, 57%	76%, 68% ^b	68%, 62%
Median follow-up, months	29 ^b	48 ^b	NR	27	44	15 ^b	40
Progression-free survival (PFS)	2-year 71%	5-year EFS 40% ^b	Intensive: 2-year 50% Conservative: 2-year 31%	3-year 42%	3-year 45%	3-year 42% ^b	2-year 41%
Overall survival (OS)	NR	5-year 41% ^b 5-year 36%	2-year: intensive: 54%; less-intensive: 44%	3-year 56%	3-year 49%	3-year 44%	2-year 57%
Outcomes with RM-CHOP	–	–	2-year PFS 37% 2-year OS 53%	NR	NR	NR	–

AHCT, autologous hematopoietic cell transplantation; Ara-C, cytarabine; CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; HDMTX, high-dose methotrexate; HGBL, high-grade B-cell lymphoma; Inv, involvement; IPI, International Prognostic Index; LPM, leptomeningeal involvement; MATRix, rituximab, methotrexate, cytarabine, and thiotepea; MBVP, methotrexate, carmustine, teniposide, and prednisolone; MTX, methotrexate; NCCN-IPI, National Comprehensive Cancer Network IPI; NR, not reported; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CODOX-M/IVAC, rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate alternating with rituximab, ifosfamide, cytarabine, etoposide; R-HCVAD, rituximab, hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone alternating with methotrexate and cytarabine; R-HDS, rituximab, cyclophosphamide, cytarabine, and etoposide; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; R-IPI, revised IPI.

^aStudies with ≤ 15 patients with synchronous CNS involvement at diagnosis were not included.

^bReported for the whole study population and includes patients with relapsed/refractory DLBCL/HGBL with CNS involvement.

Limited data suggest benefit from using more intensive frontline treatments in systemic DLBCL/HGBL with synchronous CNS involvement. These, however, need to be interpreted cautiously as they are based on small retrospective studies or single-arm phase II trials and confounded by the use of consolidative AHCT in a subset of patients. In the above-mentioned retrospective study by Wight *et al.*, the use of intensive treatments (mainly R-HyperCVAD and R-CODOX-M/R-IVAC) improved the 2-year PFS (50% versus 31%, $p=0.006$) and OS (54% versus 44%, $p=0.037$) compared with less-intensive treatments. The SCNSL1 phase II trial included 38 patients of whom 16 had DLBCL with synchronous CNS

involvement at diagnosis.²⁷ Patients received treatment with high doses of methotrexate and cytarabine followed by R-HDS (rituximab, cyclophosphamide, cytarabine, and etoposide). Twenty patients (53%) underwent AHCT. The 5-year OS for the 16 patients with CNS involvement at diagnosis was 36% (CR rate and event-free survival were not reported for this subgroup).²⁷ In the MARIETTA phase II clinical trial, 75 patients were treated including 32 patients with DLBCL or HGBL with synchronous CNS involvement at diagnosis.²⁶ Patients received treatment with three courses of MATRix (HDMTX, cytarabine, thiotepea, rituximab) followed by three courses of R-ICE (rituximab, ifosfamide, carboplatin, and

etoposide). Forty-two patients (56%) underwent AHCT. Focusing on the 32 patients with CNS involvement at diagnosis, the CR rate after MATRix-R-ICE and 2-year PFS were 53% and 71%, respectively (the OS was not reported for this subgroup).²⁶ In the phase II UK Neurological Clinical Research Institute (NCRI) trial of patients with high-risk DLBCL/HGBL, R-CODOX-M/R-IVAC showed favorable outcomes in the 10 patients with CNS involvement at diagnosis with 2-year PFS of 70% without any patient undergoing consolidative AHCT.¹⁴

The role of consolidative AHCT in patients with DLBCL or HGBL with CNS involvement at diagnosis is also unclear. This approach has an established role as a consolidation strategy in eligible patients with primary CNS lymphoma,^{30,31} and there is convincing evidence against its use in the initial treatment of patients with systemic DLBCL or HGBL,^{9,10,32-36} but data on its role in DLBCL/HGBL with CNS involvement at diagnosis are limited. Although this study did not show significant improvement in PFS or OS with the use of consolidative AHCT in patients who achieved CR following RM-CHOP, it lacked the power to answer this question. This study, however, shows favorable outcomes for the 18 patients who achieved CR following RM-CHOP and did not undergo consolidative AHCT as indicated by the 2-year PFS and OS of 71% and 76%, respectively. The limited available data show contradicting results for the role of consolidative AHCT in this setting. In a retrospective study of 60 patients with aggressive systemic non-Hodgkin lymphomas with synchronous CNS involvement at diagnosis of whom 54 had DLBCL, Damaj *et al.*²⁹ reported improvement in PFS and OS for the 19 patients who underwent consolidative AHCT. In contrast, the above-mentioned retrospective studies by Wight *et al.* and Perry *et al.* did not find significant improvement in PFS and OS with the use of AHCT in the small number of patients who underwent AHCT (19 and 13 patients, respectively).^{19,25} The SCNSL1 and MARIETTA trials included patients with DLBCL/HGBL with synchronous CNS involvement at diagnosis treated with intensive induction regimens followed by AHCT and reported outcomes better than historical controls.^{26,27}

The outcomes of patients with relapsed/progressive disease were poor, with only 63% of patients receiving subsequent treatments and only 21% achieving CR to next subsequent treatment. Most

patients (58%) had CNS involvement at relapse/progression which was associated with worse outcomes (median OS of 2 months). Retrospective studies and small single-arm phase II trials support the use of AHCT in patients with relapsed/refractory DLBCL or HGBL with CNS involvement; however, many patients are ineligible because of age, comorbidities, poor performance status, or having a chemorefractory disease.^{18,26,37-39} Lenalidomide and the Bruton tyrosine kinase inhibitors have limited activity as monotherapies for CNS involvement by aggressive B-cell lymphoma but are being evaluated in combination with chemotherapy and novel agents.⁴⁰⁻⁴² Despite the recent approvals of several new agents in relapsed/refractory DLBCL and HGBL, treatment of CNS involvement remains an unmet need as these agents have largely not been tested in patients with CNS involvement and likely have limited efficacy in this setting.⁴³⁻⁴⁶ One important exception might be CAR T cells with emerging data showing feasibility and efficacy, although the majority of patients still need effective bridging therapies.^{38,47-49} Of the five patients in this study who received CAR T cells, two had CNS involvement and responded but one relapsed within 3 months. CAR T cells might play an important role in this setting given recent data showing superiority of certain CAR T cell products over AHCT in patients with high-risk relapsed or refractory systemic DLBCL or HGBL.^{50,51}

In addition to its single-center retrospective design, this study has several limitations. This study did not collect data on patients with systemic DLBCL or HGBL with synchronous CNS involvement treated with other regimens. We did not include a comparator arm of patients who received more intensive treatments which might have been preferentially used in younger and fit patients. We also did not include patients treated with R-CHOP and IT chemotherapy which might have been used in older or unfit patients. Whereas limited data suggest that HDMTX achieves prolonged CSF cytotoxic concentrations compared with IT methotrexate,⁵² IT methotrexate might be preferred in selected older or unfit patients with leptomeningeal involvement who might not tolerate HDMTX. Furthermore, we could not evaluate the impact of concurrent treatment with IT methotrexate, given the small number of patients who received it and heterogeneity in the number and schedule of treatments received. Retrospective studies in primary CNS lymphoma

did not demonstrate a benefit from additional IT chemotherapy, however.^{52–54}

In conclusion, this study shows that RM-CHOP results in favorable outcomes in patients with DLBCL with synchronous CNS and systemic involvement and supports its use in this setting. RM-CHOP can also serve as a platform that permits the incorporation of novel agents. The outcomes in the small number of patients with HGBL were poor, however. Limited data suggest benefit from the use of more intensive approaches which may be favored in young and fit patients and those with HGBL.^{14,25,26} Most patients who had relapsed or progressive disease had CNS involvement which was associated with very poor outcomes. Synchronous CNS involvement in systemic DLBCL and HGBL at diagnosis remains a major therapeutic challenge, dictates clinical outcomes, and requires more effective and novel treatment options.

Declarations

Ethics approval and consent to participate

This study was conducted under an institutional review board-approved protocol at The Ohio State University. Irrespective of this analysis, all patients provided informed consent before receiving treatment.

Consent for publication

Not applicable.

Author contribution(s)

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Availability of data and materials

Requests for data sharing may be submitted to Yazeed Sawalha (yazeed.sawalha@osumc.edu).

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Supplemental material

Supplemental material for this article is available online.

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