original reports abstract

Real-World Data (RWD) on the 3-Year Follow-Up Outcomes of Different CNS Prophylaxis Strategies Across CNS-IPI Risk Groups in Patients With Diffuse Large B-Cell Non-Hodgkin Lymphoma

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PURPOSE CNS relapse in patients with diffuse large B-cell lymphoma (DLBCL) is associated with poor prognosis with a median survival of about 2.5 months. Data demonstrating best prophylactic strategy remain controversial and need further definition.

PATIENTS AND METHODS We present data of 110 patients with DLBCL treated with standard systemic therapy divided into four groups based on primary CNS prophylaxis strategy and CNS International Prognostic Index (IPI) risk categories. We compared their 3-year CNS relapse rate and overall survival in each group.

RESULTS The CNS prophylaxis strategy consisted of intrathecal (IT) methotrexate (MTX) in group 1, high-dose (HD) MTX in group 2, combination IT and HD MTX in group 3, and IT and/or HD MTX with intensive chemotherapy in group 4. At 3 years, CNS relapse rate was 8.6% (4/46), 8.3% (1/12), 4.8% (2/42), and 18% (2/11) in groups 1-4 ($P = .64$), respectively. According to CNS IPI, the CNS relapse rate was 16.6%, 10.1%, and 0% in high-, intermediate-, and low-risk groups, respectively. The 3-year overall survival rate was 69%, 75%, 80%, and 45% in groups 1-4 ($P = .71$), respectively.

CONCLUSION Our study while did not find statistical significance did indicate a lower incidence of CNS relapse with the addition of systemic HD MTX to IT MTX in the high-risk DLBCL population.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is an aggressive and most common subtype of non-Hodgkin lymphoma (NHL), constituting up to 40% of all patients of NHL globally.[1] The treatment outcomes for DLBCL have improved significantly in the rituximab era; however, relapse in the CNS remains an important mode of treatment failure in high-risk DLBCL patients with a universally poor outcome.[2] CNS relapse in DLBCL has an overall incidence of about 2%-5% and is associated with a median overall survival of about 2-5 months post relapse.[3-6] Most relapses occur within the first 2 years of completion of primary treatment, and up to one third of patients with CNS relapse had a previous complete response to the primary treatment.[7]

Because of the low rate of overall CNS relapse, not all patients with DLBCL requires a CNS prophylaxis.[8] However, the criterion for selecting patients for CNS prophylaxis varies widely among clinicians. The risk of CNS relapse is strongly correlated with the absolute number of extra-nodal sites, for example, in the large multinational study, 3-year cumulative risk of CNS relapse was about 15% in > 2 extra-nodal sites compared with 3% in < 2 extra-nodal sites.[9] Although different criteria exist, CNS International Prognostic Index (IPI) prognostication score has the National Comprehensive Cancer Network (NCCN) recommendation to use for selecting patients for CNS prophylaxis.[10] It classifies the rate of developing CNS relapse at 2 years into low- (< 1%), intermediate- (2.9%), and high-risk (> 10%) categories with the high-risk category recommended to undergo CNS prophylaxis. This tool, however, does not incorporate other important extra-nodal sites of involvement such as testicular, uterine, breast, and biomarkers such as dual expression of c-myc and BCL2 and/or BCL6 that confer additional risk of CNS relapse. This ambiguity highlights the need to accurately identify at-risk patients and develop safe and effective prophylactic strategies. Hall et al[11] proposed one such algorithm that displays a strategy for combining the CNS-IPI with additional clinical and biological risk factors to identify DLBCL patients at increased risk for CNS relapse and in need of CNS prophylaxis.

Controversy also exists regarding the optimum strategy for providing CNS prophylaxis in DLBCL. The most commonly used prophylaxis strategies consist of

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CONTEXT

Key Objective

The optimal CNS prophylaxis strategy in diffuse large B-cell lymphoma (DLBCL) is not well established. This study sought to determine the CNS relapse risk in patients who received CNS prophylaxis in the real world setting and stratified it according to their CNS IPI (International Prognostic Index) risk category. Furthermore, this study sought to determine the most optimal CNS prophylactic strategy.

Knowledge Generated

Overall CNS relapse rate in the study population was 8.1%. CNS relapse rate in the combination intrathecal (IT) and high-dose (HD) methotrexate (MTX) treatment group was 4.8% compared to 8.6% and 8.3% in the IT MTX and HD MTX alone groups respectively. Combination strategy appears to be superior to either strategy alone, however these findings did not reach statistical significance ($P = .64$).

Relevance

In the area where prospective randomized clinical trials are challenging to conduct, this study adds to the growing body of real world evidence on the optimal CNS prophylaxis strategy.

intrathecal (IT), methotrexate (MTX), and/or cytarabine (4-8 doses) or systemic MTX (3-3.5 g/m^2 for 2-4 cycles) during the course of treatment. Studies performed in patients with DLBCL who received rituximab showed no benefit of adding an IT MTX CNS prophylaxis in preventing CNS relapse.[12,13] On the other hand, there are both retrospective and prospective data suggesting the benefit of high-dose (HD) systemic MTX added to the systemic therapy in high-risk DLBCL.[14-16] These existing strategies are derived from the benefit seen with incorporating CNS prophylaxis with the treatment protocols of other high-grade lymphomas with a high risk of CNS relapse, particularly Burkitt's lymphoma and acute lymphoblastic leukemia.[17]

Shaukat Khanum Cancer Memorial Hospital and Research Center (SKMCH) is a large tertiary referral center for hematological malignancies in Pakistan. We reviewed our registry data of patients with DLBCL who had undergone primary treatment and CNS prophylaxis as deemed fit by their clinicians in the real-world setting and evaluated their CNS relapse, CNS-IPI risk category, and survival outcomes.

PATIENTS AND METHODS

Design

This is a single-center retrospective study using data from the SKMCH Cancer Registry between the periods of January 1, 2000 and December 31, 2018 following the approval by the Institutional Review Board (IRB).

Patient Population

All adult patients with confirmed histologic diagnosis of DLBCL by WHO criteria, who received CNS prophylaxis based on clinician's assessed high-risk features, were included in the study. These high-risk features included two or more of the following: elevated lactate dehydrogenase, multiple extra-nodal site involvement > 1, stage III or IV, poor performance status, and involvement of high-risk anatomical sites, that is, bone marrow, renal, adrenal glands, testes, nasopharynx, and paranasal sinus. Four patients in the study population were intermediate between DLBCL and Burkitt's lymphoma. Patients with CNS involvement at the time of diagnosis were excluded from the study.

Study Procedure

Eligible individuals based on the inclusion and exclusion criteria were chart reviewed and the following information was extracted from the medical records: demographics, variables of IPI-score and CNS-IPI score, presence of bulky disease, stage of the disease, splenic involvement, chemotherapy regimen, CNS prophylaxis regimen, number and location of extra-nodal sites of disease. CNS involvement was defined by either (1) neuroimaging findings compatible with CNS involvement and/or (2) histologically confirmed CNS involvement. In patients with CNS relapse we also identified location of relapse as either (1) leptomeningeal, (2) parenchymal, or (3) both. These patients were categorized into four treatment groups. Group 1 received systemic chemoimmunotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP] with or without rituximab) plus IT MTX, group 2 received chemoimmunotherapy (CHOP with or without rituximab) plus intravenous HD MTX, group 3 received systemic chemoimmunotherapy (CHOP with or without rituximab) plus IT and HD intravenous MTX, and group 4 received intensive chemoimmunotherapy (Hyper-CVAD [cyclophosphamide, vincristine, doxorubicin, dexamethasone]) plus IT and/or intravenous HD MTX. According to the risk assessment tool, patients were also categorized in the CNS IPI low, intermediate, and high risk.

Our CNS prophylaxis regimen consisted of either (a) 12 mg of IT MTX administered on day 2 with rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP); or (b) 3.5 mg per meter sq intravenous MTX delivered over 2 hours followed by folinic acid rescue administered on day 15 of alternate R-CHOP/CHOP chemotherapy cycles or 2-4 cycles after the completion of R-CHOP/CHOP therapy.

Wilcox in rank sum test was performed to compare continuous variables. The Fisher exact test was performed to compare categorical variables. We defined overall survival as the time from the date of diagnosis to any cause of death. Relapse-free survival was described as the time from the date of diagnosis to CNS relapse. All data were analyzed using SAS 9.4 with a significance level of a = 0.05.

Outcome

The primary outcome in this study was CNS relapse-free survival by each treatment group. The secondary outcome was overall survival by each treatment group and CNS relapse-free survival by CNS-IPI score.

RESULTS

We identified 145 patients with DLBCL who received CNS prophylaxis of whom 110 were included in the final analysis. Of these patients 35 patients were excluded either because of age < 18 years, absence of CNS prophylaxis given or presence of CNS involvement at the time of diagnosis. A total of 46 patients (41.8%) in group 1 received CHOP therapy with or without rituximab plus IT MTX alone, 12 patients (10.9%) in group 2 received CHOP therapy with or without rituximab plus HD MTX alone, 41 patients in group 3 (37.3%) received CHOP therapy with or without rituximab plus both IT and HD MTX, and 11 (10%) patients in group 4 received Hyper-CVAD chemotherapy plus IT MTX and/or HD MTX.

The baseline characteristics of the patients in these four groups are summarized in Table 1. In the overall study population mean age was 33 years with a male-to-female ratio of 1.4:1. Around 55% of the patients had stage IV disease and 56% had bulky disease. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 was seen in most patients. When stratified according to the CNS IPI risk, six patients (5.4%) were in the high-risk group, 79 patients (71.8%) were in the intermediate-risk group, and 25 patients (22.7%) were in the low-risk group. Twenty-one (45.7%) patients in group 1, four (33%) patients in group 2, 16 (39%) patients in group 3, and none in group 4 received Rituximab.

Our patient population had a high compliance rate of planned CNS prophylactic therapy. IT MTX therapy was delivered at a median of six cycles in groups 1 and 3 with a minimum of four cycles administered to 91%, 95%, and 36% of patients in groups 1, 3, and 4 respectively. Similarly, planned HD MTX was delivered at a median of three cycles in groups 2 and 3.

CNS Relapse

During the median follow-up of 39 months (3.25 years), a total of nine CNS relapses occurred in the overall study population. Group 1 had a median follow-up of 41 months with four relapses, group 2 had a median follow-up of 48 months with one relapse, group 3 had a median follow-up of 38 months with two relapses, and group 4 had a median follow-up of 25 months with two relapses. Of these nine CNS relapses, three relapses occurred concurrently with systemic disease relapse suggesting a primary disease relapse. The median time to CNS relapse was about 7 months from the time of initial diagnosis. The number and distribution of CNS relapse, CNS relapse-free survival, and overall survival by treatment group are presented in Table 2, Figures 1 and 2, respectively.

The CNS relapse rate at 3 years was numerically lowest (4.8%) in the combination of IT plus systemic HD MTX arm (group 3). In the IT MTX alone (group 1) and systemic HD MTX alone (group 2), the relapse rate was 8.6% and 8.3%, respectively. However, the comparison between the groups was not statistically significant ($P = .64$, Table 2). In terms of distribution of CNS relapse, there were four leptomeningeal (44%), three parenchymal (33%), and two (22%) both leptomeningeal and parenchymal. The pattern of localization did not differ between groups ($P = 34$). The 3-year overall survival was 69%, 75%, 80%, and 45% in groups 1, 2, 3, and 4 respectively ($P = .71$, Table 2).

CNS IPI Risk Category

When stratified for CNS IPI risk, the rate of CNS relapse in the overall population was 1/6 (16.6%) in the high-risk group, 8/79 (10.1%) in the intermediate-risk group, and 0/25 (0%) in the low-risk group ($P = .54$, Table 3). The Kaplan-Meier curve for CNS relapse-free survival was shown in Figure 3. Of the total of six patients in the CNS IPI high risk, there were three patients each in groups 1 and 3 respectively. One of the three patients in group 1 suffered a relapse, whereas none of the three patients in group 3 relapsed. Groups 2 and 4 had no CNS IPI high-risk patients. In the CNS-IPI intermediate-risk category, the isolated CNS relapse rate was 3/26 (10.3%), 1/10 (9.1%), 2/28 (6.7%), and 2/7 (22.7%) in groups 1, 2, 3, and 4 respectively. There were no relapses in the CNS IPI low-risk category across all groups.

Impact of Rituximab

In addition, the use of rituximab had no impact on CNS relapse when all groups were considered collectively (hazard ratio [HR], 0.76; 95% CI, 0.25 to 1.64; $P = .54$, data not shared).

DISCUSSION

In this study, we have presented real-world data (RWD) on 110 patients with DLBCL who received three different strategies of CNS prophylactic therapy and compared their outcomes within the limitations of a retrospective review. The median age of our study population is significantly low at 33 years and this is because of the fact that only young and fit patients are admitted to our institution for treatment because of significant capacity and resource limitations. There was a higher male to female ratio (1.4:1) noted in our cohort. Rituximab was not available to all the patients in our study population because of the financial cost burden in a

TABLE 1. Baseline Patient Characteristics

Characteristic	Group 1 n = 46 (41.8%)	Group 2 n = 12 (10.9%)	Group 3 n = 41 (37.3%)	Group 4 n = 11 (10.0%)	*P*
Age in years					.002
Mean ± SD[a]	33.06 ± 6.74	39.42 ± 9.82	30.07 ± 7.95	30.91 ± 8.13	
Sex, n (%)					.13
Male	24 (52.2)	8 (66.7)	29 (70.7)	4 (36.4)	
Female	22 (47.8)	4 (33.3)	12 (29.3)	7 (63.6)	
Ann Arbor stage, n (%)					.04
I	5 (10.9)	0 (0.0)	1 (2.4)	1 (9.1)	
II	9 (19.6)	5 (41.7)	7 (17.1)	3 (27.3)	
III	10 (21.7)	4 (33.3)	3 (7.3)	1 (9.1)	
IV	22 (47.8)	3 (25.0)	30 (73.2)	6 (54.5)	
B-symptoms, n (%)					.004
No	27 (58.7)	10 (83.3)	13 (31.7)	7 (63.6)	
Yes	19 (41.3)	2 (16.7)	28 (68.3)	4 (36.4)	
LDH, n (%)					.65
Normal	3 (6.5)	1 (8.3)	1 (2.4)	0 (0.0)	
High	43 (93.5)	11 (91.7)	40 (97.6)	11 (100.0	
ECOG performance status, n (%)					.12
0	42 (91.3)	10 (83.3)	36 (87.8)	9 (81.8)	
I	4 (8.7)	0 (0.0)	1 (2.4)	2 (19.2)	
II	0 (0.0)	2 (16.7)	2 (4.9)	0 (0.0)	
III	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	
IV	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	
Bulky disease, n (%)					.56
No	17 (37.0)	7 (58.3)	19 (46.3)	5 (45.5)	
Yes	29 (63.0)	5 (41.7)	22 (53.7)	6 (54.5)	
IPI, n (%)					.21
1	13 (28.9)	1 (8.3)	8 (19.5)	2 (18.2)	
2	19 (42.2)	9 (75.0)	14 (34.1)	7 (63.6)	
3	13 (28.9)	2 (16.7)	17 (41.5)	2 (18.2)	
4	0 (0.0)	0 (0.0)	2 (4.9)	0 (0.0)	
Spleen involvement, n (%)					.91
No	36 (78.3)	10 (83.3)	33 (80.5)	10 (90.9)	
Yes	10 (21.7)	2 (16.7)	8 (19.5)	1 (9.1)	
Extra nodal sites, n (%)					.85
Nil involvement	11 (23.9)	2 (16.7)	7 (17.1)	7 (17.1)	
Single-node involvement	21 (45.7)	4 (33.3)	16 (39.0)	16 (39.0)	
≥ 2 nodal involvement	14 (30.4)	6 (50.0)	18 (43.9)	18 (43.9)	
Specific extra-nodal sites, n (%)					
Bone marrow	0 (0)	0 (0)	3 (8.8)	2 (22.2)	.05
Breast	0 (0)	0 (0)	0 (0)	0 (0)	—
Ovary	1 (2.9)	0 (0)	1 (2.9)	0 (0)	.90
Testes	0 (0)	1 (10.0)	1 (2.9)	1 (11.1)	.24
Renal	3 (8.6)	0 (0)	2 (5.9)	0 (0)	.64

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TABLE 1. Baseline Patient Characteristics (Continued)

Characteristic	Group 1 n = 46 (41.8%)	Group 2 n = 12 (10.9%)	Group 3 n = 41 (37.3%)	Group 4 n = 11 (10.0%)	*P*
Hepatic	1 (2.9)	1 (10.0)	5 (14.7)	1 (11.1)	.39
Paranasal	1 (2.9)	0 (0)	1 (2.9)	1 (11.1)	.56
Nasopharynx	4 (11.4)	0 (0)	5 (14.7)	2 (22.2)	.49
Bowl	4 (11.4)	4 (40.0)	3 (8.8)	1 (11.1)	.10
Paraspinal	2 (5.7)	0 (0)	5 (14.7)	1 (11.1)	.42
Skeletal	13 (37.1)	0 (0)	7 (20.6)	2 (22.2)	.10
Thymus	4 (11.8)	1 (10.0)	3 (8.8)	2 (22.2)	.73
Pleura	5 (14.7)	1 (10.0)	5 (15.2)	0 (0)	.64
CNS IPI, n (%)					—
Low	14 (56)	1 (4)	8 (32)	2 (8)	
Intermediate	26 (32)	10 (12.6)	28 (35)	7 (8.8)	
High	3 (50)	0	3 (50)	0	
Chemotherapy regimen, n (%)					—
CHOP	25 (54.3)	8 (66.7)	25 (61.0)	0 (0)	
Hyper-CVAD	0 (0)	0 (0)	0 (0)	11 (100)	
R-CHOP	21 (45.7)	4 (33.3)	16 (39.0)	0 (0)	
IT MTX (4-8 doses)	42 (91.3)	N/A	36 (87.8)	4 (36.4)	—
HD MTX (2-4 cycles)	N/A	10 (83.3)	36 (87.8)	5 (45.5)	—

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; ECOG, Eastern Cooperative Oncology Group; HD, high dose; IPI, International Prognostic Index; IT, intrathecal; LDH, lactate dehydrogenase; MTX, methotrexate; N/A, not available; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

[a]Standard deviation.

largely indigent study population. Only 45.7%, 33%, 39%, and 0% patients in groups 1, 2, 3, and 4 received rituximab with chemotherapy respectively. These observations highlight the challenges associated with the treatment of DLBCL in a low- to middle-income country.

Our cohort identified six (5.5%) patients who fell into the high-risk category and therefore met the requirement to receive CNS prophylaxis as per current guidelines. Sixteen patients (14.5%) in the CNS IPI intermediate-risk group and two patients (1.18%) in the CNS IPI low-risk group also met the requirement for CNS prophylaxis after adjusting for other factors not accounted for in the CNS IPI score such as other important anatomical sites for risk of CNS recurrence, dual expression of c-myc, and BCL2 or BCL6, according to an algorithm proposed by Hall et al.[11] Other high-risk features, as assessed by the treating physician, were

TABLE 2. Three-Year Overall Survival and CNS Relapse Rate by Each Group

Variables	Group 1 n = 46 (41.8%)	Group 2 n = 12 (10.9%)	Group 3 n = 41 (37.3%)	Group 4 n = 11 (10.0%)	*P*
CNS relapse					
Number	4	1	2	2	—
Isolated CNS relapse					
Number	3	1	2	0	—
Location of relapse					.34
Leptomeningeal	2	1	0	1	
Parenchymal	2	0	1	0	
Both	0	0	0	1	
Unknown	0	0	1	0	
CNS relapse rate at 3 years, %	8.6	8.3	4.8	18	.64
Overall survival at 3 years, %	69	75	80	45	.71

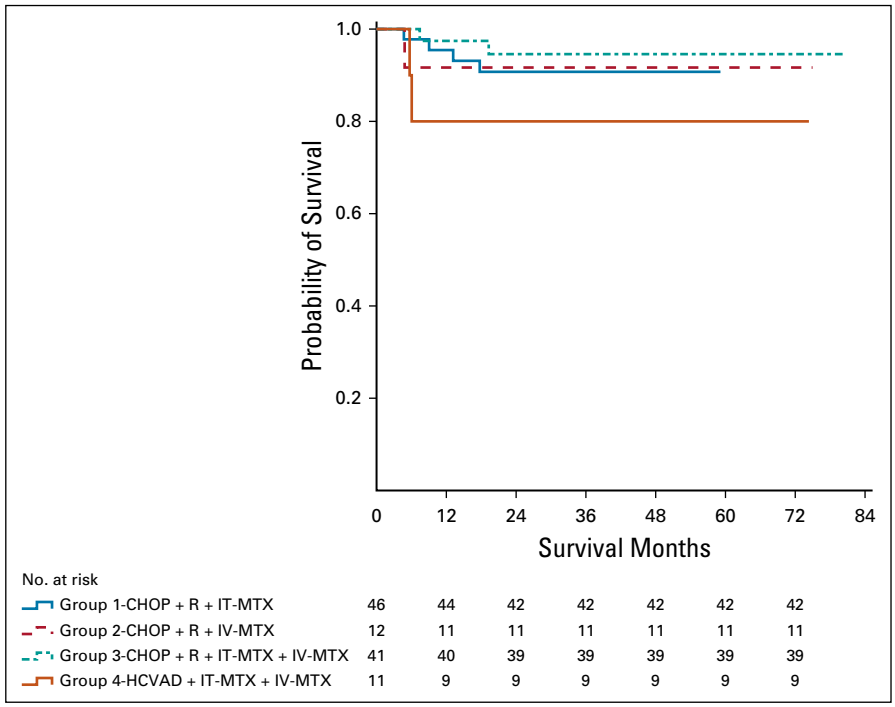

FIG 1. CNS relapse-free survival by treatment groups (log-rank $P = .48$). CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; HCVAD, hyper cyclophosphamide, vincristine, doxorubicin, dexamethasone; IT, intrathecal; MTX, methotrexate.

used to justify CNS prophylaxis in the rest of the low/intermediate-risk population constituting about 78% of our cohort. This exemplifies the typical challenge of patient selection often encountered in this patient population, especially before the validation of CNS-IPI risk score.

Our study showed that the combination strategy of IT MTX and systemic HD-MTX had the lowest incidence of overall CNS relapse rate of 5% at 3 years, compared with a relapse rate of 8% and 9% in HD MTX alone and IT MTX alone groups respectively. The comparison among these strategies could not reach statistical significance (P value .64) because of the low number of CNS events. A similar lower incidence of CNS relapse was also noted, when each group was stratified according to the CNS IPI risk category. An average relapse rate of 6.7% was noted in the combination arm (group 3) compared with a 21.8% in IT MTX alone

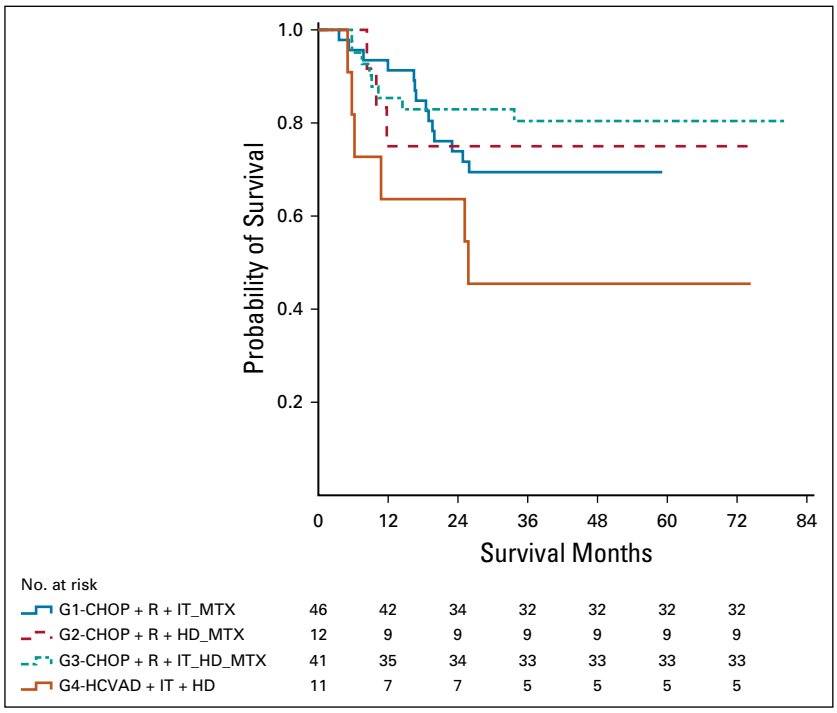

FIG 2. Overall survival by treatment groups (log-rank $P = .10$). CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; HCVAD, hyper cyclophosphamide, vincristine, doxorubicin, dexamethasone; HD, high-dose; IT, intrathecal; MTX, methotrexate.

TABLE 3. CNS Relapse Rate Stratified by CNS-IPI Risk Category in Each Group

	Groups				
CNS Relapse	**Group 1 (n = 46)**	**Group 2 (n = 12)**	**Group 3 (n = 41)**	**Group 4 (n = 11)**	***P***
CNS-IPI high (n = 6), n (%)	1/3 (33.3)	0	0/3 (0)	0	.273
CNS-IPI intermediate (n = 79), n (%)	3/26 (10.3)	1/10 (9.1)	2/28 (6.7)	2/7 (22.2)	.603
CNS-IPI low (n = 25), n (%)	0/14 (0)	0/1 (0)	0/8 (0)	0/2 (0)	.557

Abbreviation: IPI, International Prognostic Index.

(group 1) and 9.1% in the systemic HD MTX alone arm (group 2). This adds further weightage to the fact that combination strategy is superior to either strategy alone as also noted in previous studies.[16,18,19] A higher rate of CNS relapse and a lower 3-year overall survival were noted in the intensive chemoimmunotherapy group, that is, group 4. This was due to the fact that group 4 comprised of patients (4/11) with very aggressive features (intermediate between DLBCL and Burkitt's) and both relapses were accompanied by systemic relapses signifying the failure of primary therapy. A small sample size of group 4 further made comparison with other groups difficult. There were in total 3 systemic relapses concurrent with CNS relapses in the overall population. When adjusting for systemic CNS relapses in each group, the isolated CNS relapse rates were 6.5%, 8.3%, 4.3%, and 0% in groups 1, 2, 3, and 4, respectively.

Our study also showed a higher incidence of CNS relapse rate in the intermediate/high-risk CNS IPI category in the overall study population compared with the historically reported data considering that these patients had undergone CNS prophylactic therapy.[10] We report a CNS relapse rate of 16.6% in the CNS IPI high group and 10.1% in the intermediate group and 0% in the CNS IPI low-risk group. When adjusting for isolated CNS relapse, all three systemic relapses in our study belonged to the intermediate CNS IPI category and the adjusted isolated CNS relapse rate fell to about 7.7% in the intermediate-risk category. Although a small sample size (5.45% of the population) accounts for the high relapse rate seen in the high-risk group, the sample size (57.2% of the study population) does not fully account for the relatively higher rate seen in the intermediate-risk group. These high rates could be explained by other clinical and biological risk

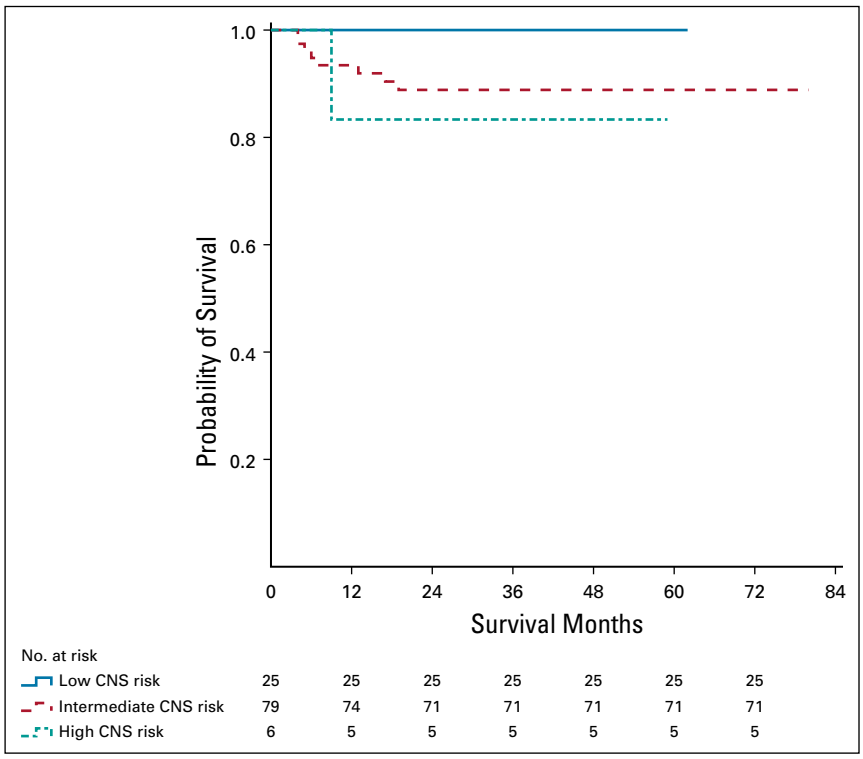

FIG 3. CNS relapse-free survival by IPI score (log-rank *P* = .18). IPI, International Prognostic Index.

factors not fully elucidated in our data in our study population.

Rituximab was not available to all the patients and this likely had an impact on the systemic relapse as was seen in three of nine patients presenting with synchronous CNS and systemic relapse. Two of these systemic relapses occurred in group 4 that did not receive rituximab. However, the addition of rituximab did not impact the overall isolated CNS relapse rate (HR, 0.76; 95% CI, 0.25 to 1.64; P = .54, data not shared). Our study also showed a 7-month median time for CNS relapse from the time of initial diagnosis raising the possibility of occult CNS involvement. Our study population had only CSF cytology as their part of workup and flow cytometric studies on CSF were not available for diagnosis.

In summary, our study adds to the earlier observations made in a similar retrospective study indicating a lower incidence of CNS relapse with the addition of systemic HD MTX to IT MTX alone. Although a cross-trial comparison is difficult because of heterogeneous population compared with Ferreri et al[19] study, our study showed a lower relapse rate in the IT MTX alone arm (9% *v* 18.4%) but a similar relapse rate in the combination arm (5% *v* 6.9%). Our overall 3-year survival was similar in the IT MTX alone arm (69% *v* 68%) compared with the combination arm (86% *v* 80%). Furthermore, our study showed a high relapse rate in the CNS IPI intermediate category suggesting the need to further refine baseline risk assessment for CNS prophylaxis as also proposed by Klanova et al[20] by the integration of cell of origin into the CNS-IPI score.

Like previously reported retrospective studies, our data are also limited because of potential for bias. However, stratification of data using the CNS IPI risk category and further characterization of high-risk population using the algorithm proposed by Hall et al[11] should help in reducing the heterogeneity in the baseline risk assessment for comparison purposes with existing and future studies.

Unarguably, a well-designed prospective study could provide robust data on deciding the best CNS prophylactic strategy; however, because of the rarity of the CNS relapses in DLBCL and accumulating retrospective data favoring combination strategy, it has become very difficult to conduct such a study in the future.

In conclusion, our study on the RWD adds to the growing body of nonrandomized data favoring the combination strategy of systemic HD MTX and IT MTX for the prophylaxis of CNS relapse in DLBCL.

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Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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REFERENCES

1. European Society for Medical Oncology: World Cancer Report 2014. https://www.esmo.org/oncology-news/World-Cancer-Report-2014
2. Pfreundschuh M, Kuhnt E, Trümper L, et al: CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) group. Lancet Oncol 12:1013-1022, 2011
3. Mead GM, Kennedy P, Smith JL, et al: Involvement of the central nervous system by non-Hodgkin's lymphoma in adults. A review of 36 cases. Q J Med 60:699-714, 1986

4. Hollender A, Kvaloy S, Lote K, et al: Prognostic factors in 140 adult patients with non-Hodgkin's lymphoma with systemic central nervous system (CNS) involvement. A single centre analysis. Eur J Cancer 36:1762-1768, 2000
5. Hoerni-Simon G, Suchaud JP, Eghbali H, et al: Secondary involvement of the central nervous system in malignant non-Hodgkin's lymphoma. A study of 30 cases in a series of 498 patients. Oncology 44:98-101, 1987
6. Boehme V, Zeynalova S, Kloess M, et al: Incidence and risk factors of central nervous system recurrence in aggressive lymphoma: A survey of 1693 patients treated in protocols of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Ann Oncol 18:149-157, 2007
7. Savage KJ: Secondary CNS relapse in diffuse large B-cell lymphoma: Defining high-risk patients and optimization of prophylaxis strategies. Hematol Am Soc Hematol Educ Program 2017:578-586, 2017
8. Ghose A, Elias HK, Guha G, et al: Influence of rituximab on central nervous system relapse in diffuse large B-cell lymphoma and role of prophylaxis: A systematic review of prospective studies. Clin Lymphoma Myeloma Leuk 15:451-457, 2015
9. El-Galaly TC, Villa D, Michaelsen TY, et al: The number of extranodal sites assessed by PET/CT scan is a powerful predictor of CNS relapse for patients with diffuse large B-cell lymphoma: An International Multicenter Study of 1532 patients treated with chemoimmunotherapy. Eur J Cancer 75:195-203, 2017
10. Schmitz N, Zeynalova S, Nickelsen M, et al: CNS International prognostic index: A risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with R-CHOP. J Clin Oncol 34:3150-3156, 2016
11. Hall KH, Panjic EH, Valla K, et al: How to decide which DLBCL patients should receive CNS prophylaxis. Oncology 32:303-309, 2018
12. Wilson WH, Bromberg JEC, Stetler-Stevenson M, et al: Detection and outcome of occult leptomeningeal disease in diffuse large B-cell lymphoma and Burkitt lymphoma. Haematologica 99:1228-1235, 2014
13. Kumar A, Vanderplas A, LaCassce M, et al: Lack of benefit of central nervous system prophylaxis for diffuse large B-cell lymphoma in the rituximab era. Cancer 118:2944-2951, 2012
14. Holte H, Leppä S, Björkholm M, et al: Dose-densified chemoimmunotherapy followed by systemic central nervous system prophylaxis for younger high-risk diffuse large B-cell/follicular grade 3 lymphoma patients: Results of a phase II nordic lymphoma group study. Ann Oncol 24:1385-1392, 2013
15. Phillips EH, Kirkwood AA, Lawrie A, et al: Low rates of CNS relapse in high risk DLBCL patients treated with R-CODOX-M and R-IVAC: Results from a phase 2 UK NCRI/Bloodwise Trial. Blood 128:1855, 2016
16. Abramson JS, Hellmann M, Barnes JA, et al: Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. Cancer 116:4283-4290, 2010
17. Cortes J, O'Brien SM, Pierce S, et al: The value of high-dose systemic chemotherapy and intrathecal therapy for central nervous system prophylaxis in different risk groups of adult acute lymphoblastic leukemia. Blood 86:2091-2097, 1995
18. Cheah CY, Herbert KE, O'Rourke K, et al: A multicentre retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. Br J Cancer 111:1072-1079, 2014
19. Ferreri AJM, Bruno-Ventre M, Donadoni G, et al: Risk-tailored CNS prophylaxis in a mono-institutional series of 200 patients with diffuse large B-cell lymphoma treated in the rituximab era. Br J Haematol 168:654-662, 2015
20. Klanova M, Sehn LH, Bence-Bruckler I, et al: Integration of cell of origin into the clinical CNS International Prognostic Index improves CNS relapse prediction in DLBCL. Blood 133:919-926, 2019

