

Outcomes of high-dose methotrexate for CNS prophylaxis in diffuse large B-cell lymphoma with an intermediate or high CNS-International Prognostic Index: A single-center retrospective cohort study

MUBARAK AL-MANSOUR¹⁻³, AHMED ABSI²⁻⁴, ROULA AL-MUFTI^{1,3}, MAJED ALAHMADI²⁻⁴, IHAB EL-HEMAIDI²⁻⁴, SAMEER ALAMOUDI²⁻⁴, SALEEM ELDADAH^{2,3}, SYED SAMEER AGA^{2,3}, MUHAMMED A. KHAN^{2,3} and AHMED ALSAEED²⁻⁴

¹Department of Adult Medical Oncology, Princess Noorah Oncology Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs-Western Region; ²College of Medicine, King Saud Bin Abdulaziz University for Health Sciences; ³King Abdullah International Medical Research Center, Ministry of National Guard Health Affairs-Western Region; ⁴Department of Adult Hematology and Stem Cell Transplantation, Princess Noorah Oncology Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs-Western Region, Jeddah 21423, Saudi Arabia

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Abstract. Central nervous system (CNS) relapse in patients with diffuse large B-cell lymphoma (DLBCL) is rare (2-5% of cases), but is a devastating complication with a poor survival rate. The administration of high-dose methotrexate (HDMTX) for CNS prophylaxis in patients with DLBCL is controversial and variable in the literature. The present study aimed to evaluate the clinical outcomes of HDMTX CNS prophylaxis in patients with intermediate and high CNS-International Prognostic Index (IPI) DLBCL using real-world data. An observational retrospective cohort study was conducted of all patients with intermediate and high CNS-IPI DLBCL treated at Princess Noorah Oncology Center (King Abdulaziz Medical City, Jeddah, Saudi Arabia) between January 2010 and December 2020. Patients were treated with HDMTX either intravenously or intrathecally, according to the physician's evaluation of the patient. Data on patient clinical characteristics, CNS relapses,

risk factors and survival rates were obtained from hospital records. Data were analyzed using Student's unpaired t-test and the χ^2 test to compare the two subgroups, the Kaplan-Meier survival method with log-rank test to calculate and compare the survival rates, and regression analysis to determine the risk factors for CNS relapse and death. The study included 358 patients (n=32 with HDMTX CNS prophylaxis and n=326 without CNS prophylaxis). Patients in the CNS prophylaxis group had a significantly higher CNS relapse rate than those in the non-CNS prophylaxis group (12.5% vs. 1.8%; P=0.008). Patients who received CNS prophylaxis were younger and had an advanced stage of disease, with extranodal involvement and a high serum lactate dehydrogenase level at presentation. CNS prophylaxis was significantly associated with CNS relapse, while relapsed disease was associated with the risk of death (all P<0.05). In conclusion, the present study found that patients with intermediate and high CNS-IPI who received HDMTX CNS prophylaxis did not have fewer CNS relapses; however, those without CNS relapse had higher survival rates. In addition to CNS prophylaxis, Stage of DLBCL and IPI were significantly associated with CNS relapse. Future randomized control trials are needed to evaluate the efficacy of HDMTX CNS prophylaxis in patients with DLBCL.

Correspondence to: Dr Mubarak Al-Mansour, Department of Adult Medical Oncology, Princess Noorah Oncology Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs-Western Region, Jeddah 21423, Saudi Arabia
E-mail: mansourmu@ksau-hs.edu.sa; drmubarak55@hotmail.com

Dr Syed Sameer Aga, College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs-Western Region, Jeddah 21423, Saudi Arabia
E-mail: agas@ksau-hs.edu.sa

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Introduction

Over the last decade, the treatments and outcomes of diffuse large B-cell lymphoma (DLBCL) have significantly improved owing to recent therapeutic advances (such as rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone treatments) (1). However, ~5% of patients still suffer from the undesirable devastating complication of central nervous system (CNS) relapse (2,3). CNS relapse usually occurs 12 months after completion of systemic chemotherapy (4-11)

and is associated with poor outcomes and a median survival time of 6 months after relapse. El-Galaly *et al* (12) conducted an international cohort study to evaluate the prognostic factors and treatment-related differences in the outcome of CNS involvement in patients with DLBCL, and found that those patients treated with first-line immune-chemotherapy had poor outcomes following CNS involvement, but that a moderate proportion of patients with isolated CNS involvement, who received intensive therapies, achieved durable remission. Therefore, additional CNS prophylaxis is recommended for patients with high-risk DLBCL. However, owing to the relatively low rate of CNS relapse, administering CNS prophylaxis to all patients might expose a number of them to unnecessary toxicities, as only high-risk patients might benefit from this prophylaxis (3).

The definition of high-risk DLBCL has been poorly described in the literature. Commonly reported risk factors for CNS involvement are a high IPI score, increased serum lactate dehydrogenase (LDH) levels, an advanced stage of lymphoma, >1 site of extranodal involvement, and involvement of specific anatomical sites such as the kidneys, testes, uterus and breasts (13-15). The CNS-International Prognostic Index (CNS-IPI) score is commonly used for risk stratification of patients with DLBCL into risk groups of <1% (low-risk group) and >10% (high-risk group). This prognostic model was validated using combined data from the Germen High-Grade Lymphoma Study Group and the British Columbia Cancer Agency, and became the most widely used model (15).

For CNS prophylaxis, intrathecal chemotherapy was first proposed, but was found to be ineffective, since CNS involvement in DLBCL affects the brain parenchyma in 60-80% of patients (16,17). Unlike intrathecal prophylaxis, systematic prophylaxis with high-dose intravenous methotrexate (HDMTX) has the advantage of reaching the brain parenchyma owing to its ability to cross the blood-brain barrier at high concentrations. Although the addition of CNS prophylaxis with HDMTX to the standard rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone or prednisolone (R-CHOP) chemotherapy has been advocated in the literature, evidence on the clinical benefits of this prophylaxis is unclear owing to limited and conflicting data (16).

Abramson *et al* (18) retrospectively evaluated the outcomes of 65 patients with DLBCL and different CNS risk factors who received intravenous MTX as CNS prophylaxis in addition to the standard R-CHOP chemotherapy. The study found that the addition of CNS prophylaxis with intravenous MTX was safe and was associated with a low risk of CNS relapse in high-risk patients. In a multicenter phase II trial of patients with breast DLBCL, first-line immunochemotherapy and intrathecal MTX led to meaningful survival outcomes, but were not optimal for CNS prophylaxis (19). Another study by Garwood *et al* (20) showed that among 205 patients with DLBCL, of whom 28 were selected for two doses of HDMTX, no significant differences in CNS relapse rate or CNS-IPI distribution were identified in the propensity-matched analysis.

As there is no consensus on the methods and criteria for CNS prophylaxis among patients with DLBCL, the clinical practice in these patients varies across different locations. Therefore, the present observational retrospective study was conducted to determine the outcomes of HDMTX CNS

prophylaxis in patients with intermediate and high-risk DLBCL using real-world data from a single center.

Patients and methods

Ethics. The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines as the standard reporting guidelines for observational cohort studies (21). The study was approved by the Ethics Committee of the King Abdullah International Medical Research Center (KAIMRC) (approval no. #SP19/196/J).

Study design, setting, and duration. This observational retrospective cohort study was conducted at the Princess Noorah Oncology Center (King Abdulaziz Medical City, Jeddah, Saudi Arabia; under the jurisdiction of KAIMRC) between January 2010 and December 2020.

Study participants and variables. Patients who met the following inclusion criteria were included in the study: i) A diagnosis of DLBCL; ii) age >15 years; iii) biopsy-proven DLBCL; and iv) available CNS evaluation data. CNS evaluation included clinical examination, brain imaging, cerebral spinal fluid (CSF) flow cytometry or biopsy if required. Patients with were excluded if they had double/triple-hit lymphoma or Burkitt's lymphoma.

Baseline characteristics, including IPI, number and type of extranodal sites, frontline chemotherapy and type of CNS prophylaxis, were recorded for all patients. Clinical data and follow-up outcomes were retrospectively retrieved from the hospital records.

CNS prophylaxis. For patients in the high-risk group (those with testicular lymphoma, epidural disease, sinus involvement, bone marrow involvement, or renal and adrenal involvement), intravenous HDMTX (3.5 g/m²) was administered on days 10-15 post-R-CHOP or following the completion of chemotherapy for 4-6 cycles. R-CHOP chemotherapy alternating with intravenous HDMTX (8 g/m²) was administered as the frontline regimen for patients with synchronous CNS involvement. Occasionally, intrathecal MTX (12 mg) was administered for synchronous and early CNS relapses at the physician's discretion.

Sampling method and sample size calculation. A convenience sampling method was employed to collect the data. Sample size was calculated using the Raosoft® software using its associated website (www.raosoft.com/samplesize.html). The total number of patients having CNS involvement among patients with DLBCL between January 2010 and December 2020 was 358. The required sample size was estimated at the 95% confidence level with an estimated 5% prevalence of CNS involvement in the DLBCL among intermediate- and high-risk patients, and a margin of error of ±5%. The required minimum sample size was determined to be 61. As the population was small, all the population in the specified time was included to make the results representative.

Statistical analysis. Categorical data are described as frequency and percentage, while continuous data are

Table I. Demographic and clinical characteristics of the study population.

Characteristic	CNS prophylaxis group (n=32)	Non-CNS prophylaxis group (n=326)	P-value ^a
Mean age (SD), years	48.1 (17.3)	57.5 (16.5)	0.003
Age group, n (%)			
<60 years	25 (78.1)	162 (49.7)	0.002
Sex, n (%)			
Male	22 (68.8)	185 (56.7)	0.190
Female	10 (31.3)	141 (43.3)	
Origin of cell, n (%)			
GCB	15 (46.9)	110 (33.7)	0.188
Non-GCB	12 (37.5)	121 (37.1)	
Not specified	5 (15.6)	95 (29.1)	
Extranodal sites, n (%)			
≥1	30 (93.8)	209 (64.1)	0.001
Stage of cancer, n (%)			
1-2	3 (9.4)	88 (27.0)	0.029
3-4	29 (90.6)	238 (73.0)	
Abnormal high serum LDH level, n (%)	29 (90.6)	235 (72.1)	0.018
CNS-IPI, n (%)			
2-3	16 (50.0)	201 (61.7)	0.198
4-6	16 (50.0)	125 (38.3)	

^aCalculated using χ^2 test for categorical variables and unpaired Student's t-test for mean age. GCB, germinal centre B cell; CNS, central nervous system; LDH, lactate dehydrogenase; IPI, International Prognostic Index; SD, standard deviation.

described as mean and standard deviation. The association between categorical variables was analyzed using the χ^2 test and an unpaired Student's t-test. An α level <0.05 was considered for statistical significance. The overall survival (OS) time was calculated from the date of confirmed diagnosis to the date of the last follow-up date or death. Similarly, the progression-free survival (PFS) time was calculated from the date of confirmed diagnosis to the date of disease progression, death or the last follow-up. The Kaplan-Meier survival method was used to calculate OS and PFS rates, with the lo-rank test applied for the analysis. A stepwise forward Cox proportional hazard's model, including all the significant factors from the univariate analysis, was used to determine the risk factors of CNS relapse. Factors with a two-sided P-value of ≤ 0.1 were then studied in the multivariate analysis. $P \leq 0.05$ was considered to indicate a statistically significant difference. All analyses were performed using SPSS version 26 (IBM Corp.).

Results

Characteristics of the study population. A total of 358 patients were included in the present study. The overall median age of the study participants was 58.5 ± 16 years (range, 15-93 years). The male-to-female ratio was 1.37. Most of the patients had an advanced stage of cancer (75%). The cell of origin was a non-germinal center in 37% of patients, a germinal center in

35% of patients and not reported in 28% of patients. In total, 67% of patients had at least one site of extranodal involvement, 61% had an IPI of 2-3 and 39% had a CNS-IPI of 4-6. Overall, 74% of patients had an elevated LDH level. The median follow-up time was 35 months for the CNS prophylaxis group and 49 months for the non-CNS prophylaxis group. The baseline characteristics of all 358 patients are shown in Table I.

CNS prophylaxis vs. no CNS prophylaxis. In total, 32 patients (9%) received prophylactic HDMTX. The main differences between the CNS prophylaxis and the non-CNS prophylaxis groups were the following characteristics: Younger age ($P=0.003$), extranodal site involvement ($P=0.001$), advanced stage ($P=0.029$) and a high LDH level at presentation ($P=0.018$). There were no significant differences in the cell of origin or the CNS-IPI between the patients receiving prophylaxis or not. The differences between the CNS prophylaxis and the non-CNS prophylaxis groups are shown in Table I.

CNS relapse rates, characteristics and risk factors. A total of 10 CNS relapses were detected in the study population (4/32 patients in the CNS prophylaxis group vs. 6/326 patients in the non-CNS prophylaxis group). The difference in the relapse rate between the two groups was statistically significant (12.5% vs. 1.8%; $P=0.008$). The 5-year CNS relapse rates were 15 and 2% in the CNS prophylaxis and non-CNS prophylaxis groups, respectively ($P<0.0001$) (Fig. 1).

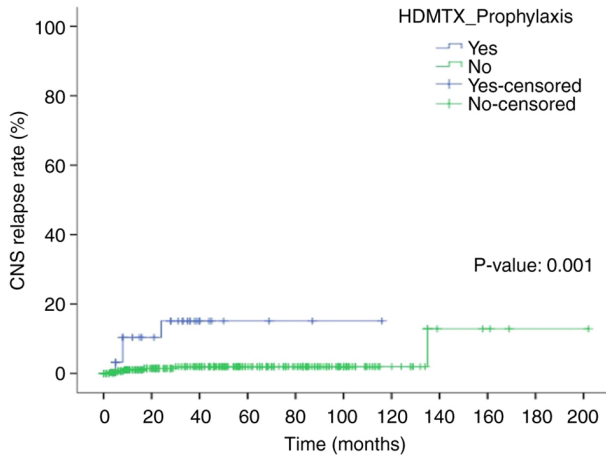


Figure 1. Kaplan-Meier survival curves for the CNS relapses in patients with and without HDMTX CNS prophylaxis. CNS, central nervous system; HDMTX, high-dose methotrexate.

Out of the 10 patients, 9 had isolated CNS relapses. For the CNS prophylaxis group, the median follow-up time was 35 months, the median time to CNS relapse was 8.5 months, the median overall survival after CNS relapse was 8 months, and the 2-year and 5-year OS rates were 20 and 0%, respectively (Fig. 2).

Clinical characteristics of CNS relapses. The predominant clinical characteristics of patients with CNS relapse were advanced disease at initial presentation, a non-germinal center phenotype and high CNS-IPI. The frequencies and percentages of these characteristics are shown in Table II.

Risk factors of CNS relapses. Results of the regression analysis showed that CNS-IPI, CNS-relapse, relapsed disease, IPI (all $P < 0.001$) and stage of DLBCL ($P = 0.006$) were significantly associated with the risk of death. In the multivariate analysis, only relapsed disease retained significance as an independent variable ($P < 0.001$) (Table III).

Systemic relapse, survival rates and factors associated with death. In total, 59 patients (16%) experienced a systemic relapse. The median time to the systemic relapse was 18 months. The median survival time after the relapse was 12 months, and the 5-year OS rate for patients with systemic relapses was 10%. The median OS time was 27 months (95% CI, 13.7-40.2) for the CNS relapsed group, but was not reached for the non-CNS relapsed patients ($P = 0.004$). The 5-year OS rate for the non-CNS relapsed group was 84% (Fig. 3). The median PFS time was not reached and the 5-year PFS rate was 79% for the entire population (Fig. 4).

Discussion

The present study aimed to evaluate the outcomes of CNS prophylaxis with HDMTX among patients with intermediate and high CNS-IPI DLBCL. This study reflects real-world data from experience in a single center and consisted of 358 patients who were treated either with or without HDMTX for CNS prophylaxis. The study expands the literature by providing

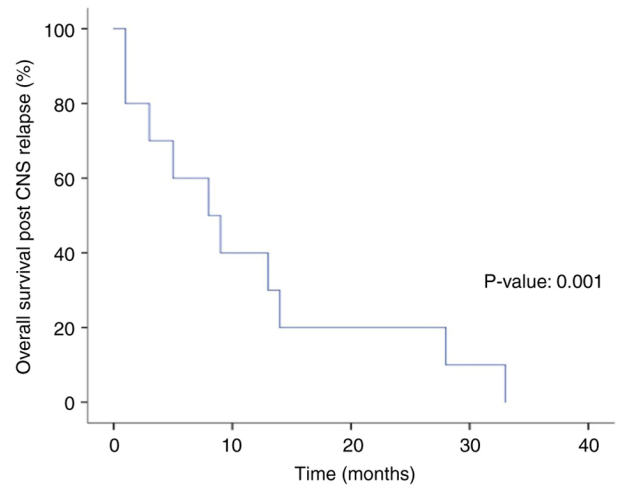


Figure 2. Kaplan-Meier survival curves for overall survival in patients with post-CNS relapse. CNS, central nervous system.

information about the clinical outcomes of HDMTX CNS prophylaxis in patients with intermediate and high CNS-IPI DLBCL. CNS prophylaxis using HDMTX is a prophylactic treatment strategy that has been debated in the literature for a long time due to the limited evidence, conflicting data from observational studies and the lack of clear class evidence on its benefits or futility of use in this population.

The present results showed that among patients who received CNS prophylaxis, the proportions of patients with an age of < 60 years, ≥ 1 extranodal site, an advanced stage of cancer (3,12) and abnormally high serum LDH values were significantly higher than those in the non-CNS prophylaxis group. Furthermore, patients with HDMTX CNS prophylaxis had a higher CNS relapse rate and a lower survival rate, in comparison with the non-CNS prophylaxis group (12.5% vs. 1.8%; $P = 0.008$). These results were consistent with the data from the UK National Cancer Research Institute (NCRI) R-CHOP-14 vs. 21 trial where the non-CNS group had a 1.9% CNS relapse rate in contrast to the CNS prophylaxis group which had a higher CNS relapse rate of 2.8% (17); however, the rate was much lower than the 12.5% reported in the present study population. In a single-center cohort study by Lee *et al* (22), 130 patients were evaluated, and it was reported that the 64 patients receiving HDMTX had a higher risk of CNS relapse in comparison to the other 66 patients not receiving prophylaxis (8.1% vs. 6.9%).

By contrast, in a retrospective analysis of 95 high-risk DLBCL patients treated with R-CHOP with ($n = 57$) or without ($n = 38$) CNS prophylaxis using systemic HDMTX, Kuitunen *et al* (23) reported that the 5-year isolated CNS relapse rate was 5% in the CNS-prophylaxis group and 26% in the non-CNS prophylaxis group, which suggested that HDMTX decreased the risk of CNS failure.

The timing of systemic HDMTX was assessed in the study by Wilson *et al* (24), which found no differences in the survival or CNS relapse rates between intercalated HDMTX (between R-CHOP-21) and end of treatment HDMTX (at the end of R-CHOP-21). Furthermore, intercalated HDMTX was associated with increased toxicity and delays of the R-CHOP (24). Therefore, individualizing the timing of HDMTX CNS

Table II. Clinical characteristics of patients with CNS relapse (n=10).

Variable	Prevalence ratio (among patients with CNS relapse)	Percentage
Advanced disease at initial presentation	10/10	100
Non-GC phenotype	7/10	70
High CNS-IPI	7/10	70
Extranodal involvement	6/10	60
Leptomeningeal involvement	6/10	60
Currently, alive	5/10	50
Currently, with a progressive disease	2/10	20
Testicular lymphoma	1/10	10

CNS, central nervous system; GC, germinal center; IPI, International Prognostic Index.

Table III. Univariate and multivariate analyses of the risk factors for death.

Variable	Univariate			Multivariate		
	HR	CI	P-value	HR	CI	P-value
Sex	1.181	0.70-1.98	0.522			
Cell of origin	0.810	0.58-1.12	0.204			
HDMTX	1.138	0.41-3.15	0.804			
Extranodal involvement	0.730	0.39-1.25	0.231			
CNS-IPI	2.910	1.71-4.95	<0.001 ^a	1.837	0.83-5.28	0.259
CNS-relapse	6.280	6.28-13.90	<0.001 ^a	0.738	0.32-2.23	0.738
Relapsed disease	0.220	0.13-0.36	<0.001 ^a	0.239	0.13-0.41	<0.001 ^a
IPI	2.065	1.41-2.29	<0.001 ^a	1.241	0.67-2.29	0.491
Stage of DLBCL	3.300	1.41-7.68	0.006 ^a	1.303	0.46-3.65	0.608

^aP<0.05. HR, hazard ratio; CI, confidence interval; HDMTX, high-dose methotrexate; CNS, central nervous system; IPI, International Prognostic Index; DLBCL, diffuse large B-cell lymphoma.

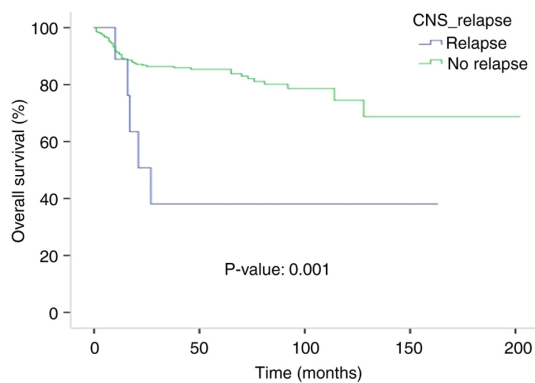


Figure 3. Kaplan-Meier survival curves for overall survival in the study population subgrouped as those with and without CNS relapse. CNS, central nervous system.

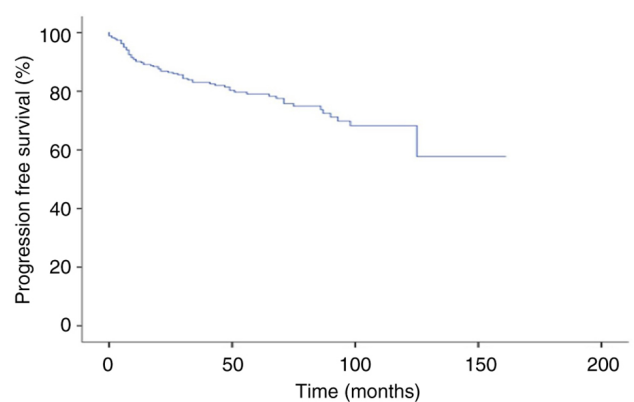


Figure 4. Kaplan-Meier survival curves for progression-free survival in the study population.

prophylaxis was recommended, as well as scheduling the intercalated HDMTX before day 10 of the R-CHOP cycles to avoid increased toxicity.

Intrathecal MTX has also been studied extensively in the literature, but is considered to be ineffective due to its inability to cross the blood-brain barrier. Intrathecal

administration of MTX has become the standard of care for patients with leptomeningeal involvement. MTX penetrates the BBB poorly when used in low doses. However, high doses of intravenous (IV) MTX reach the CNS and are effective against leptomeningeal metastasis. There are several possible reasons why patients with CNS involvement who are treated with high doses of IV MTX experience better outcomes than those treated with intrathecal therapy. Two important ones are i) the inability of intrathecal MTX to get absorbed beyond the subarachnoid space and ii) the fact that most CNS relapses frequently involve the brain parenchyma (14,18,23-26).

Intrathecal therapy must diffuse into the tumor from the interface between the CSF and the tumor. Tumor cells in areas of bulk disease, common in non-leukemic meningeal malignancies, and cells that have spread deep into the cerebral sulci, are not likely to be fully exposed to drugs administered into the CSF (27). The international phase II trial (International Extranodal Lymphoma Study Group 10) showed that combined treatment with R-CHOP21, intrathecal MTX and testicular radiotherapy was associated with a good outcome in patients with primary testicular lymphoma, but did not prevent CNS relapses. It was concluded that further research into CNS prophylaxis is still needed (28).

Eyre *et al* (29) analyzed data on 690 patients aged ≥ 70 years with DLBCL who were consecutively treated with R-CHOP across 8 UK centers (2009-2018). It was found that stand-alone intrathecal CNS prophylaxis was not associated with any benefits in terms of CNS relapse rates. In a multicentre phase II clinical trial, 33 patients with primary breast DLBCL were treated with an R-CHOP regimen and four doses of intrathecal MTX (12 mg) (10). The study found that intrathecal MTX was not optimal for CNS prophylaxis, since CNS relapses occurred in 4 patients, with a 2-year cumulative incidence rate of CNS relapse of 12.5%. In another single-center retrospective study of 21 patients with DLBCL who received CNS prophylaxis by intrathecal and intravenous MTX, half of the patients had CNS relapses, with a poor prognosis and a median survival time of 54 days (30).

In terms of the risk factors for CNS relapses, the present study showed that CNS prophylaxis, stage of DLBCL and IPI were significantly associated with CNS relapse were significantly associated with CNS relapses, while factors associated with the risk of death were CNS relapse and systemic relapse. Similar risk factors were reported by the UK NCRI R-CHOP-14 vs. 21 trial, where a performance status of 2, elevated lactate dehydrogenase level, IPI, >1 extranodal site of disease and the presence of a 'high-risk' extranodal site were significant risk factors for CNS relapses (17). In the study by Nazir *et al* (30), an advanced stage, high LDH level and extranodal involvement at the first presentation were significant risk factors for CNS relapse.

In the study, the 5-year OS rate was 84 and 83% for the CNS prophylaxis and non-CNS prophylaxis groups, respectively, while the 5-year PFS rate was 84 and 79% for the CNS prophylaxis and non-CNS prophylaxis groups, respectively. In the study by Lee *et al* (12), the PFS and OS rates were 66.3 and 77.5%, respectively, for the CNS prophylaxis group, and 67.4 and 71.4%, respectively, for the non-CNS prophylaxis group. Data from the phase II Nordic Lymphoma Group study showed that among the 156 patients treated with

R-CHOP with the addition of etoposide followed by a course of high-dose cytarabine and a course of HDMTX, the 3-year OS and failure-free survival rates were 81 and 65%, respectively (31).

It is evident that the literature data on the clinical benefits or futility of using HDMTX CNS prophylaxis are conflicting and controversial. However, it should not escape notice that most of these studies have observational designs. Therefore, these studies are susceptible to confounding bias, which means that patients with several CNS relapse risk factors are more likely to receive CNS prophylaxis in the clinical setting than those with a low risk of CNS relapses. When studying this population in an observational design, the unbalanced CNS relapse risk factors in the study groups likely influence the relapse rates. Therefore, the differences in the relapse rates between the CNS prophylaxis and non-CNS prophylaxis groups cannot be attributed to CNS prophylaxis alone. However, one study used propensity score matching analysis to compare the study groups, and found no significant difference in the CNS relapse rates between HDMTX CNS prophylaxis patients and non-CNS prophylaxis patients (10). Siegal and Goldschmidt (32) proposed that CNS relapse in some patients with DLBCL might be related to occult lymphoma cells that are present in the CNS at the time of diagnosis, while in others, it is due to a later penetration of the CNS by some malignant clones; therefore, as long as evidence on occult CNS involvement does not exist, there will be no strong indication that any strategy of CNS prophylaxis will be beneficial.

The present study has several strong points, including i) the relatively large sample size of the study ($n=358$ patients); and ii) the inclusion of patients with intermediate and high CNS-IPI in the study population. The limitation of the study is that it was an observational study; therefore, it will be difficult to establish a causative relationship between patient outcomes and CNS prophylaxis due to the lack of control over risk assignment and the lack of random allocation of the study participants to the treatment groups. Another limitation is that CNS assessment was not uniformly performed in all patients, thus occult CNS involvement in some patients would have a bias in the overall results. Additionally, the small number of CNS prophylaxis patients in the study limits the strength of the study. Furthermore, this study did not involve age-, stage- or extranodal-matched patients in both groups. In summary, the study is susceptible to confounding bias, and the results should be confirmed by conducting large randomized controlled trials to establish whether CNS prophylaxis provides benefits to patients with intermediate and high CNS-IPI DLBCL. Additional biomarkers and a larger sample size from a variety of centres should be assessed in future studies to establish the association more conclusively.

In conclusion, the present results highlight the fact that among patients with intermediate and high CNS-IPI DLBCL, those who received HDMTX CNS prophylaxis had worse survival rates compared with those without CNS prophylaxis. CNS relapse was found to be associated with other key parameters such as stage of DLBCL and IPI. The study also demonstrated that not all intermediate and high-risk patients require prophylaxis and highlighted the importance of extranodal involvement. Moreover, in the present study, the risk of CNS relapse was higher in high CNS-IPI patients despite the

use of CNS prophylaxis. The study data help fill the gap that exists in the literature from the Middle East and North Africa region. Future studies with a larger cohort and multiple centres are needed to evaluate the efficacy of HDMTX CNS prophylaxis in patients with DLBCL in the context of randomized controlled trials to mitigate the limitation of a small sample of CNS prophylaxis patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors have critically reviewed and approved the final draft, and are responsible for the content and similarity index of the manuscript. MAM conceptualized and designed the study, and wrote the initial draft of the manuscript. AA, RAM, MA, IEH, SA, SE and AA contributed in the data collection and analysis. SSA conceptualized the study, analyzed the data, and edited and revised the manuscript in the final form. MAK statistically analyzed the collected data.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of King Abdullah International Medical Research Centre (KAIMRC), a research wing of King Saud Bin Abdulaziz University for Health Sciences (Jeddah, Kingdom of Saudi Arabia). Every participant provided informed consent during the execution of the end-of-course evaluation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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