Master of Medicine

The efficacy of systemic high dose methotrexate as central nervous system prophylaxis in patients with high risk diffuse large B-cell lymphoma: A propensity score-matched analysis

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The Graduate School of the University of Ulsan

Department of Medicine

Kyoungmin Lee

The efficacy of systemic high dose methotrexate as central nervous system prophylaxis in patients with high risk diffuse large B-cell lymphoma: A propensity score-matched analysis

Supervisor: Cheolwon Suh

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Kyoungmin Lee

Department of Medicine
Ulsan, Korea
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The efficacy of systemic high dose methotrexate as central nervous system prophylaxis in patients with high risk diffuse large B-cell lymphoma: A propensity score-matched analysis

This coertifies that the masters thesis of Kyoungmin Lee is approved

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Committee Chairman Professor Jae-Lyun Lee

Committee Member Professor Cheolwon Suh

Committee Member Professor Dae Ho Lee

Department of Medicine

Ulsan, Korea

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Abstract

Background: While the outcome of patients with diffuse large B-cell lymphoma (DLBCL) has been improved with the introduction of rituximab, central nervous system (CNS) relapse is still associated with poor prognosis. Although intrathecal methotrexate has been widely used for prophylaxis of such CNS relapse, its role has been questioned and systemic high dose methotrexate (HD-MTX) has been advocated as the preferred method of utilization by a few retrospective studies. With a prospectively collected cohort, we performed multiple analyses with various statistical methods including propensity score (PS)-based analysis to evaluate the efficacy of systemic HD-MTX therapy in CNS prophylaxis in high risk DLBCL patients.

Methods: The registry data set of DLBCL patients, collected from January 2010 through March 2015 at a single institute, Asan Medical Center, was retrospectively reviewed. From July 2013, all consecutive DLBCL patients who were considered at high risk for CNS recurrence received systemic HD-MTX with standard R-CHOP therapy. We analyzed the progression-free survival (PFS), CNS relapse-free survival (CNS-RFS) and overall survival

(OS) of the patients receiving CNS prophylaxis and compared them with patients who received R-CHOP only. Multivariate Cox regression and propensity score analysis were used to evaluate the treatment effect of systemic HD-MTX.

Results: A total of 197 patients with DLBCL and CNS risk factors who were treated with standard R-CHOP therapy were identified between January 2010 and March 2015. Among them, 47 patients received systemic HD-MTX as CNS prophylaxis. The actuarial 2-year risk of CNS relapse was 6.9% in patients who received R-CHOP with systemic HD-MTX, while 10.5% of patients received R-CHOP only with no other prophylactic treatment. A trend toward lower incidence of CNS relapse and longer PFS or OS (HR < 1) was seen in patients given systemic HD-MTX as CNS prophylaxis, though there was no statistical significance in multivariate nor propensity score analysis (P values > 0.05).

Conclusions: Systemic HD-MTX prophylaxis for CNS relapse show non-significant trend towards better survival outcome in high risk DLBCL patients. As these results are limited by small cohort size, short follow-up duration and by its retrospective nature, multi-center, prospective randomized studies are necessary to appropriately appraise the efficacy of

systemic HD-MTX as a method of CNS prophylaxis in high risk DLBCL patients.

Keywords: diffuse large B-cell lymphoma, central nervous system relapse, central nervous system prophylaxis, systemic methotrexate

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common, aggressive non-Hodgkin's lymphoma, constituting 30-50% of cases [1]. Through the addition of monoclonal antibody, rituximab, to systemic chemotherapy, the outcome of patient with DLBCL has significantly improved [2] and R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone) has become the standard regimen of DLBCL as ~60% of patients achieve long-term disease-free survival with current chemoimmunotherapy [3]. Despite the high efficacy of this treatment, rituximab does not help in terms of preventing CNS involvement [4]. Approximately 5% of treated patients eventually develop a secondary central nervous system (CNS) recurrence with poor survival outcomes whose median survival is only 2–6 months [5]. It is suggested that R-CHOP drugs are ineffective in penetrating the blood brain barrier and achieving therapeutic concentrations in CNS system including brain, meninges, cerebrospinal fluid (CSF) [6].

There are no uniform risk criteria for predicting CNS recurrence in DLBCL patient thus far. However, previous studies have shown that the rate of CNS recurrence was

considerably higher in patients with certain clinical features including high international prognostic index (IPI) score, high serum concentration of lactate dehydrogenase (LDH) with involvement of more than one extranodal site, and involvement of particular extranodal sites such as bone marrow, breasts, testes and paranasal sinuses [7-11]. Furthermore, the risk model consisting of IPI factors in addition to involvement of kidneys and/or adrenal glands (CNS-IPI) has also been utilized [12].

Although identification of DLBCL patients with high risk of CNS relapse is important for the application of adequate prophylactic treatment for prevention of recurrence, an appropriate measure for CNS prophylaxis has not yet been developed. While intrathecal (IT) methotrexate (MTX) has been widely used for prophylaxis, its role has been questioned as no protective effects were shown in 2 large randomized controlled trials of DLBCL [13, 14]. Systemic high dose MTX (HD-MTX) is another way of utilizing the agent which has been advocated by a few retrospective studies. However, these studies did not have a comparison group or made comparisons with imbalanced, unmatched groups [15-17].

Based on the study by Abramson *et al* which suggested CNS prophylactic benefits of systemic HD-MTX at a dose of 3.5 g/m^2 in high risk DLBCL patients [15], a CNS prophylaxis strategy for DLBCL was introduced at Asan Medical Center which consisted of administration of HD-MTX at a dose of 3.5 g/m^2 either on day 15 of alternating cycles of R-CHOP or after the completion of primary therapy. With a prospectively collected cohort, we performed multiple analyses with various statistical methods including propensity score (PS)-based analysis to evaluate the efficacy of systemic HD-MTX therapy in CNS prophylaxis in high risk DLBCL patients.

Patients and Methods

Study population

The registry data set of DLBCL patients, collected at a single institute, Asan Medical Center, was retrospectively reviewed. Patients with proven diagnosis of DLBCL according to WHO classification and considered at high risk for CNS recurrence, who were treated with at least 2 cycles of standard R-CHOP regimen in our institution from January 2010 through March 2015 (to allow a minimum of 2 years of follow-up), were included in the present study. Patients with CNS disease at presentation detected by CSF examination or neuroimaging were excluded.

Initial staging work-up including physical examination, computed tomography (CT) of the neck, thorax, abdomen and pelvis, fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET), as well as aspirate and biopsy tests of the bone marrow was performed. Baseline laboratory tests with complete blood counts (CBC), coagulation battery, serum chemistry, lactic dehydrogenase (LDH) and beta 2 microglobulin (B2M), viral serology of Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), hepatitis B

(HBV) and C (HCV), microscopic urinary analysis and pre-treatment evaluation with electrocardiogram, echocardiography or multigated acquisition (MUGA) scan, and pulmonary function tests (PFTs) were also conducted.

High risk CNS relapse was defined by the involvement of ≥2 extranodal sites and elevated LDH; or high-risk CNS international prognostic index (CNS-IPI ≥4); or involvement of specific high-risk extranodal sites including bone marrow, breasts, testes, and paranasal sinuses.

Patients provided informed consent, personal medical history, and allowed access to current and previous cancer treatment records as well as their health insurance records. This study was approved by the Institutional Review Board of the Asan Medical Center and conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

Treatment and response assessment

All patients were treated with standard R-CHOP regimen. The number of treatment cycles and consolidation therapies were decided according to stage of disease and response to initial chemoimmunotherapy. The response was evaluated after 4 cycles of treatment and at completion of treatment by repeating studies which were positive at baseline. Additional studies were performed if disease progression was suspected. Tumor response was determined according to the 2014 Lugano Classification [18]. In this study, CNS relapse was defined as appearance of a new disease in the CNS system including brain, meninges, cerebrospinal fluid (CSF), but not in cranial or peripheral nerves.

CNS prophylaxis

From July 2013, all consecutive DLBCL patients who were considered at high risk for CNS recurrence received systemic HD-MTX with standard R-CHOP therapy. Before July 2013, conforming to our institutional protocol, no DLBCL patient received CNS prophylaxis. HD-MTX was given intravenously (IV) at a dose of 3.5 g/m2 on day 15 of alternating cycles (cycle 1,3,5 or 2,4,6) of R-CHOP or delivered 2 to 5 weeks after the

completion of the primary therapy.

Statistical consideration

Clinical characteristics of the patient subgroups were compared depending on whether they received CNS prophylaxis using the student T-test or Mann-Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. Progression free survival (PFS) was calculated from the first day of chemotherapy to disease progression including any relapse or death from any cause, while CNS relapse free survival (CNS-RFS) was defined as the duration from the date of first treatment to CNS relapse, excluding other systemic recurrence and regarding deaths as censored. Overall survival (OS) was also calculated from the first day of chemotherapy to the death by any cause. PFS, CNS-RFS, OS were estimated using the Kaplan-Meier method and compared by the log-rank test.

To evaluate the efficacy of systemic HD-MTX therapy, multivariate Cox regression analysis was performed using a hazard ratio (HR) and its 95% confidence interval (95% CI). Furthermore, propensity score techniques were used to balance the distributions of

potential confounding factors between the two patient groups, including propensity score matching (PSM) and inverse probability treatment weighting (IPTW). PSM was performed using the 1:2 nearest-neighbor method. All statistical analysis was conducted using SAS 9.4 while a P-value of < 0.05 was considered statistically significant.

Results

Patient characteristics & Treatment

One hundred ninety seven patients with DLBCL that met the stated high risk CNS relapse criteria who were also treated with at least 2 cycles of standard R-CHOP therapy were identified between January 2010 and March 2015. Among them, 150 patients did not receive any CNS prophylactic therapy (R-CHOP only group) and 47 patients diagnosed after July 2013 were treated with additional systemic HD-MTX as CNS prophylaxis (HD-MTX prophylaxis group). The baseline characteristics of patients in each group are presented in Table 1.

Groups were balanced in terms of sex, age, LDH level, stage, B symptom, IPI score, as well as CNS-IPI score. The distribution of extranodal sites for each group was also similar. However, patients who received HD-MTX tended to have more extranodal involvement (median number, 2 vs 3, P=0.035) and a relatively large proportion of these patients were considered at high risk of CNS relapse as they met the above mentioned first criteria, which is the involvement of ≥2 extranodal sites and elevated LDH (98/150 [65.3%]

vs 38/47 [80.9%], P=0.045). R-CHOP was given for a median of 6 cycles and there was no statistical difference between the two groups.

CNS prophylaxis

In HD-MTX prophylaxis group, only 3 (6.4%) patients received HD-MTX twice after primary R-CHOP therapy was completed (at C6D15/D28, C6D21/D35, and C8D15/D28 each). The majority of patients (44, 93.6%) received prophylaxis during the chemoimmunotherapy period on Day 15 of alternating cycles, with 33 receiving all thrice, 8 receiving twice, and 3 receiving only once.

For HD-MTX prophylaxis, patients were admitted and leucovorin was given as rescue therapy, starting 24 hours after MTX. MTX levels were monitored daily until they reached a level of < 0.1 umol/L, while other blood works including CBC, blood urea nitrogen (BUN) and creatinine, liver panels were also monitored to evaluate toxicity of MTX.

Outcomes

The median follow-up in the entire cohort was 53.38 (range 1.34-84.3) months. During this time, a total of 22 CNS relapses occurred, 19 in the R-CHOP only group and 3 in the HD-MTX group. The number and distribution of CNS relapses of each group are displayed in Table 2.

In the R-CHOP only group, with a median follow-up of 58.88 (range 1.34-84.3) months, 61 patients (40.7%) had progressive disease, 14 patients (9.3%) experienced CNS relapse and 43 patients (28.7%) died within 2 years after diagnosis. The estimated 2-year PFS, CNS-RFS and OS rates were 58.6%, 89.5%, 71.3%, respectively. In the HD-MTX group, with a median follow-up of 27.24 (range 3.38-42.02) months, 17 patients (36.2%) had progressive disease, 3 patients (6.4%) experienced CNS relapse and 12 patients (25.5%) died within 2 years after diagnosis. The estimated 2-year PFS, CNS-RFS and OS rates were 62.3%, 93.1% and 74.5%, respectively. Kaplan-Meier survival estimates of the 2 groups are presented in Figure 1.

We performed a multivariate survival analysis that included sex, age, IPI score, CNS-IPI score, number of extranodal sites, B symptoms, LDH, stage, treatment cycles, high

risk sites, and raised serum LDH with involvement of 2 more extranodal sites (baseline characteristics presented in Table 1). Systemic HD-MTX did not significantly increase the PFS (HR 0.619, 95% CI 0.363-1.057, P=0.079), CNS-RFS (HR 0.547, 95% CI 0.156-1.924, P=0.347), or OS (HR 0.628, 95% CI 0.331-1.19, P=0.154). The results consistently showed no significant survival benefit of systemic HD-MTX, after adjustment with different propensity score methods except for PFS by weighting HR. Compared with R-CHOP only group, the hazard ratio of PFS, CNS-RFS and OS for HD-MTX prophylaxis were 0.652 (95% CI 0.36-1.18, P=0.157), 0.635 (95% CI 0.161-2.499, P=0.516), 0.625 (95% CI 0.319-1.227, P=0.172) by PSM and 0.689 (95% CI 0.503-0.945, P=0.02), 0.587 (95% CI 0.287-1.203, P=0.146), and 0.726 (95% CI 0.505-1.044, P=0.083) by IPTW, respectively (Table 3).

Toxicity (described for patient in HD-MTX prophylaxis group only)

Along with HD-MTX infusion, all 47 patients received leucovorin rescue therapy and 29 patients (61.7%) had experienced minor to severe toxicity during or after the prophylaxis. The main toxicity of HD-MTX was hepatic toxicity, defined as an increase in

serum transaminase above the upper limit of normal, which occurred in 11 patients (23.4%). Most of these events were transient involving minor elevations except for one patient whose aspartate transaminase (AST) and alanine transaminase (ALT) elevated to 627/1010 from 39/29 following C3D15 HD-MTX infusion. This patient however, was fully recovered and completed both planned chemotherapy and HD-MTX prophylaxis schedule. Renal toxicity, the most well-known complication of MTX was observed in 3 patients (6.4%). One patient who presented with grade 3 toxicity following first dose of HD-MTX had prophylaxis discontinued. Mucositis was also a complaint in patients (9, 19.1%) that received HD-MTX prophylaxis, which was ultimately discontinued in 3 patients due to severe mucositis. In addition, 10 patients (21.3%) suffered from sensory neuropathy. Nevertheless, there were no fatal side effects leading to intensive care unit (ICU) treatment or death.

Discussion

The present study evaluated the treatment effect of systemic HD-MTX on CNS relapses and survivals of high risk DLBCL patients with relevant control group using various statistical methods. We evaluated 197 patients with high risk factors for CNS relapse and 47 patients received CNS prophylaxis with 3.5 g/m^2 of intravenous HD-MTX at least once. The actuarial 2-year risk of CNS relapse was 6.9% in patients who received R-CHOP with systemic HD-MTX, while 10.5% of patients received R-CHOP only with no other prophylactic treatment. A trend toward lower incidence of CNS relapse and longer PFS or OS (HR < 1) was seen in patients given systemic HD-MTX as CNS prophylaxis, but there was no statistical significance in multivariate nor propensity score analysis (*P* values > 0.05) except for PFS by weighting HR.

Although CNS relapse was relatively rare, occurring in about 5% of DLBCL patients treated with R-CHOP regimen, it was nearly always fatal and the rate was considerably higher in patients with certain risk factors [13, 19, 20]. IT chemotherapy was the most widely used method of delivering CNS prophylaxis in the oncological setting and thus IT-MTX was the most

popular choice for high risk DLBCL patients, who usually received concurrent administration with systemic chemotherapy [6]. However, the two prospective controlled trials that contained randomized DLBCL patient groups receiving therapeutic regimens of IT MTX as CNS prophylaxis failed to prove its usefulness. The RICOVER-60 was a large clinical trials that randomized patients to CHOP or R-CHOP at 14-day intervals and included IT prophylaxis with MTX for all high risk patients (22%) having extranodal involvement of bone marrow, testes, upper neck, or head. This study showed a significantly lower incidence of CNS disease with treatment with R-CHOP-14 instead of CHOP-14 as patients treated with R-CHOP-14 did not have any benefit from IT-MTX prophylaxis [14]. In a 20-year follow-up analysis of Southwest Oncology Group protocol (SWOG) 8516, patients with bone marrow involvement randomly assigned to a 4-arm front-line therapy which included 2 arms of CNS prophylaxis including IT MTX therapy, did not shown any significant benefit of CNS prophylaxis [13].

Besides intrathecal therapy, high-dose systemic chemotherapy began to attract attention. Most of those regimens contained CNS penetrating agents and HD-MTX, which showed

superior disease control results in primary CNS lymphoma [21], emerged as an alternative. The 93-5 GELA randomized trial suggested that intravenous MTX at a dose of at least 3 g/m^2 could be an efficient option for CNS prophylaxis in DLBCL patients [22] but rituximab was not contained in their primary treatment regimen. Abramson *et al.* [15] reported the usefulness of systemic HD-MTX alone as CNS prophylaxis in combination with R-CHOP. MTX prophylaxis was administered at a dose of 3.5 g/m2 on day 15 of alternating cycles of chemoimmunotherapy to 65 patients with high risk DLBCL. The total incidence of CNS relapse was somewhat lower than expected as 3% experienced CNS relapse after median follow up of 33 months in this cohort. In light of such favorable result, our institution adopted their strategy and all consecutive high risk DLBCL patients who were diagnosed after the first half of 2013 received systemic HD-MTX prophylaxis therapy. However, this study, as well as being retrospective in nature, did not contain a comparison group. A subsequent mono-institutional study by Ferreri *et al*. [17] also supported HD-MTX prophylaxis, showing that none of the patients receiving systemic MTX experienced CNS relapse, in comparison to 12% CNS relapse rate in patients receiving no prophylaxis or only IT

prophylaxis. They compared similar groups of patients with high risk DLBCL treated in two different periods, before and after the controlled use of prophylaxis [23]. However, comparison groups were not balanced as patients who did not receive prophylaxis had worse performance status, more advanced stages, elevated serum LDH level and higher IPI or CNS-IPI score at diagnosis compared to the patient group receiving prophylaxis. Moreover, prophylaxis strategies varied according to patient's age and co-morbidities. Another retrospective study comparing inter-hospital CNS prophylaxis strategies [16] concluded that the addition of high-dose IV MTX, either at the completion of R-CHOP or as part of dose-intensive chemotherapy strategies, was associated with a reduction in CNS relapse risk in DLBCL. Nonetheless, heterogeneity in baseline risk and treatment factors still existed as major limitations. Despite such uncertainties, systemic MTX with or without IT MTX was proposed as a treatment guideline for high risk DLBCL patients by a systematic review of published literature [4].

For ethical reasons, random assignment of high-risk patients to untreated groups can be problematic. In this study, with a prospectively collected cohort of DLBCL patients who

were uniformly R-CHOP treated, we presented a considerable number of patients having identical risk criteria and the introduction of a new CNS prophylaxis strategy after a certain point divided patients into two subgroups with similar features that were managed with and without CNS prophylaxis. As a result, baseline patient characteristics were relatively balanced between two groups and our results were therefore more credible. Moreover, to overcome the natural limitation of non-randomized study, we applied propensity score methods in comparing two groups, allowing us to mimic the reporting of randomized controlled trials [24].

The most important finding of our present study was that systemic HD-MTX prophylaxis showed non-significant but consistent trend toward lower CNS relapse and better survival outcomes even after different statistical methods incorporating stringent propensity score-based analysis were applied. Besides, the CNS relapse incidence in HD-MTX prophylaxis group was higher than shown in previous results, although the median follow-up duration was shorter than those studies (Table 4). Though CSF analysis was not performed at the time of DLBCL diagnosis in whole patients in this study, we confirmed that

all 3 relapsed patients in HD-MTX prophylaxis group had negative CSF results at initial staging work-up, excluding the possibility of missed diagnosis of CNS lymphoma. Of note, in contrast to the R-CHOP only group, there was no isolated parenchymal CNS relapse in HD-MTX group, but the sample size was too small to interpret its clinical significance.

Withal, high dose MTX had some disadvantages. Patients had to be hospitalized for administration of prophylaxis which added to the financial and physical restrictions of patients, and more than half of patients in this study encountered MTX toxicities. However, most of them were controllable that grade 3+ adverse events were rare and no fatal side effects leading to intensive care unit (ICU) treatment or death occurred. Still, MTX related adverse events should always be considered as it could not only lower the patient's quality of life but also interrupt essential standard chemotherapy.

We evaluated patients in a prospectively collected cohort but this study is still limited by its retrospective nature. Although the two groups were relatively balanced and the results were consistent regardless of different statistical methods, the number of patients in HD-MTX group was much smaller than the control group (R-CHOP only) and follow-up

duration was not long enough, even though most CNS relapses occurred within a year after diagnosis. These may have affected the lack of statistical significance and indeed, the hazard ratio of PFS for HD-MTX prophylaxis was significantly lower after implementing IPTW. Moreover, the number of prophylaxis and the timing of infusion were not the same in all patients in the HD-MTX prophylaxis group. In addition, as the baseline staging work-ups or response evaluations did not include lumbar puncture unless patients had suspicious symptoms, we may have missed occult CNS lymphoma at the time of initial diagnosis and may have overestimated CNS-RFS or PFS by late identification of CNS recurrence.

So far, there is no strong evidence that supports any single approach for CNS prophylaxis [6]. Systemic HD-MTX, which has shown favorable results in several studies, has not shown statistically significant but potent efficacy in this study. Prospective, long-term, multicenter, randomized studies are necessary to appraise the efficacy of systemic HD-MTX as a method of CNS prophylaxis in high risk DLBCL patients, and further studies are needed to find an ideal prophylactic method in the prevention CNS relapse.

Conclusion

Systemic HD-MTX prophylaxis showed non-significant but consistent trend toward lower CNS relapse and better survival outcomes in high risk DLBCL patient even after different statistical methods incorporating stringent propensity score-based analysis were applied. However, these results are still limited by small cohort size, short follow-up and its retrospective nature. Prospective, long-term, multicenter, randomized studies are necessary to appraise the efficacy of systemic HD-MTX as a method of CNS prophylaxis in high risk DLBCL patients.

Table 1. Baseline Patient Characteristics

	R-CHOP only (n=150)	HD-MTX prophylaxis (n=47)	*P* value
Male sex	76 (50.7%)	30 (63.8%)	0.114
Age, y, mean (SD)	58.45 (13.814)	59.79 (11.165)	0.545
Age, y, median (range)	60.50 (16-83)	61 (25-79)	
IPI score, median (range)	3 (0-5)	3 (0-5)	0.384
Age > 60	75 (50.0%)	24 (51.1%)	0.899
LDH > normal	100 (66.7%)	37 (78.7%)	0.117
ECOG ≥ 2	22 (14.7%)	7 (14.9%)	0.969
Stage ≥ 3	142 (94.7%)	42 (89.4%)	0.201
EN site ≥ 2	126 (84.0%)	40 (85.1%)	0.856
No. of extranodal sites, median (range)	2 (0-9)	3 (1-8)	0.035
B. symptom	45 (30.0%)	17 (36.2%)	0.427
LDH, mean (SD)	569.31 (816.879)	621.51 (545.249)	0.682
Stage			0.124
Stage 1	4 (2.7%)	4 (8.5%)	
Stage 2	4 (2.7%)	1 (2.1%)	
Stage 3	2 (1.3%)	1 (2.1%)	
Stage 4	140 (93.3%)	41 (87.2%)	
Treatment cycle, median (range)	6 (2-8)	6 (3-8)	0.763
CNS-IPI, median (range)	3 (0-6)	3 (0-5)	0.417
High-risk site			
BM	72 (48.0%)	18 (38.3%)	0.244
nasal	16 (10.7%)	2 (4.3%)	0.251
breast	12 (8.0%)	5 (10.6%)	0.56
testicular	10 (6.7%)	7 (14.9%)	0.131
kidney or adrenal involvement	19 (12.7%)	6 (12.8%)	0.986
High LDH & EN site>2	98 (65.3%)	38 (80.9%)	0.045

y=year; SD=standard deviation; No.=number; EN=extranodal; LDH=lactic dehydrogenase; CNS= central nervous system; IPI= international prognostic index; R-CHOP=rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; HD-MTX=high dose methotrexate

* Data are presented as No.(%) unless otherwise indicated

Table 2. The number and distribution of CNS relapse

	R-CHOP only (n=150)	HD-MTX prophylaxis (n=47)
Number	19	3
Localization		
Parenchymal	9	0
Leptomeningeal	6	2
Both	4	1

CNS=central nervous system; R-CHOP=rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; HD-MTX=high dose methotrexate; CI=confidence interval

Table 3. Multivariate and Propensity score analysis for the efficacy of HD-MTX prophylaxis on Progression free, CNS relapse free and Overall survival

	Multivariate		PSM		IPTW	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PFS	0.619 (0.363-1.057)	0.079	0.652 (0.36-1.18)	0.157	0.689 (0.503-0.945)	0.021
CNS-RFS	0.547 (0.156-1.924)	0.347	0.635 (0.161-2.499)	0.516	0.587 (0.287-1.203)	0.146
OS	0.628 (0.331-1.19)	0.154	0.625 (0.319-1.227)	0.172	0.726 (0.505-1.044)	0.084

HD-MTX=high dose methotrexate; CNS=central nervous system; PSM=propensity score matching, IPTW=inverse probability treatment weighting; HR=hazard ratio; CI=confidence interval, PFS=progression free survival; CNS-RFS=central nervous system relapse free survival, OS=overall survival

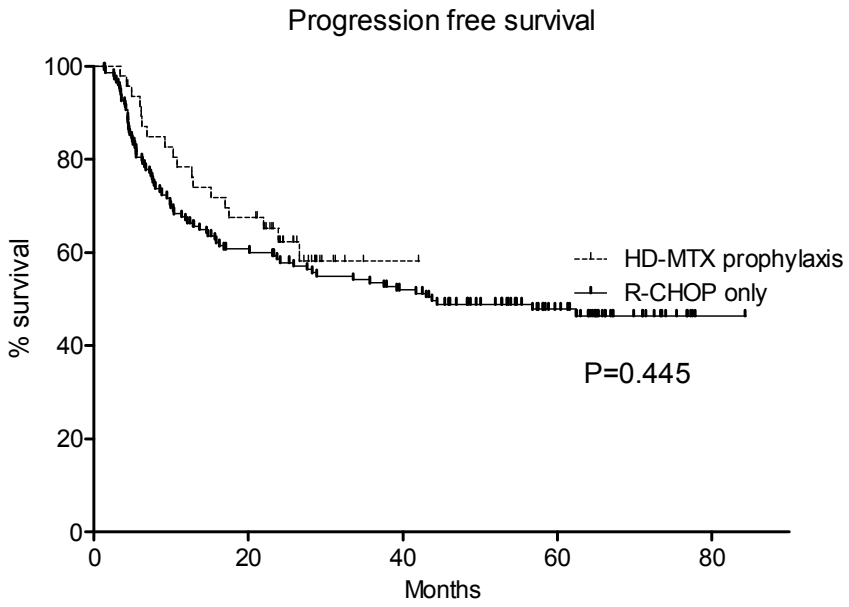
Table 4. Reported CNS relapse rate in patients with HD-MTX prophylaxis

	Present study	Abramson *et al* (2010) [15]	Guirguis *et al* (2012) [25]	Cheah *et al* (2014) [16]	Ferreri *et al* (2015) [17]
Patients with prophylaxis (n)	47	65	27	125	40
Chemotherapy	R-CHOP	CHOP ± R	R-CHOP	R ± CHOP-like chemotherapy	R-CHOP
Prophylaxis type	HD-MTX	HD-MTX	HD-MTX ± IT MTX	HD-MTX + IT MTX	HD-MTX ± IT MTX
High risk definition	(1) Involvement of ≥2 extranodal sites and elevated LDH (2) High-risk CNS international prognostic index (CNS-IPI ≥4) (3) Involvement of specific high-risk extranodal sites including bone marrow, breasts, testes, paranasal sinuses.	(1) Involvement of >2 extranodal sites plus an elevated LDH (2) Hollender 5-point criteria [20] (3) High-risk locations including bone marrow, paranasal sinuses, testes, epidural disease, liver, adrenal, renal, or orbit	(1) High risk international prognostic index (IPI) score (2) Elevated lactate dehydrogenase (LDH) and >1 extranodal site (3) human immunodeficiency virus (4) Specific extranodal sites such as invasive sinus, epidural, testicular, blood, bone marrow or orbit	(1) multiple extranodal sites (2) elevated serum LDH (3) B symptoms (4) involvement of specific high-risk anatomical sites: bone marrow (with large cell lymphoma), breast, testis, kidney, adrenal glands, paranasal sinus, nasopharynx, liver, paravertebral	(1) Involvement of the testis, spine, skull, paranasal sinuses, orbit, nasopharynx, kidney/adrenal, and/or breast (2) Simultaneous presence of advanced stage and high LDH (CNS-IPI)
Median follow-up	27.24 months	33 months	27 months	36 months	60 months
CNS relapse rate	6.9% (2-year cumulative rate)	3%	3.7%	6.9% (3-year cumulative rate)	0%

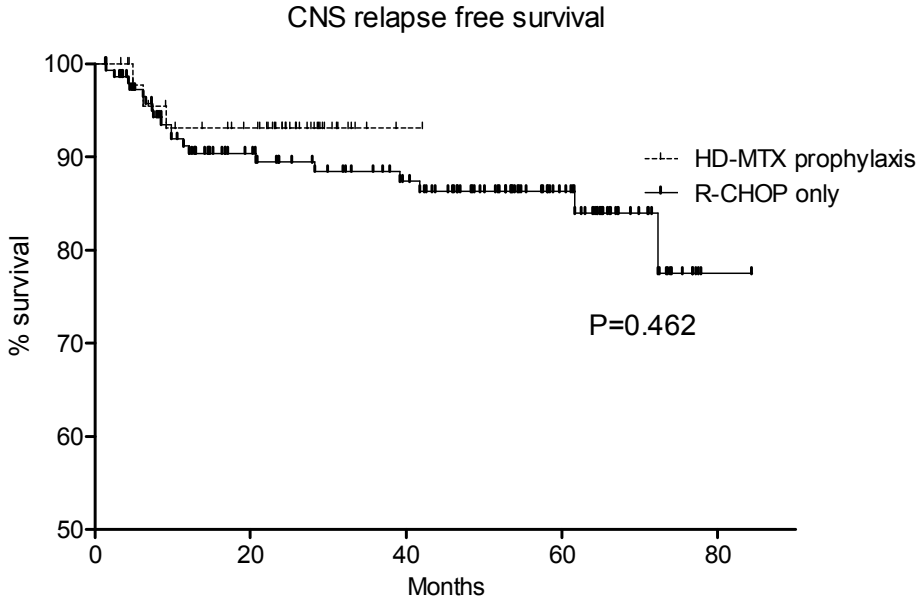
CNS=central nervous system; HD-MTX=high dose methotrexate; R=rituximab; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; IT=intrathecal; CNS-IPI=central nervous system international prognostic index

Figure 1. Kaplan-Meier curves for (A) progression free survival, (B) CNS relapse free survival, (C) Overall survival for patients in R-CHOP only group (solid line) versus HD-MTX prophylaxis group (dotted line)

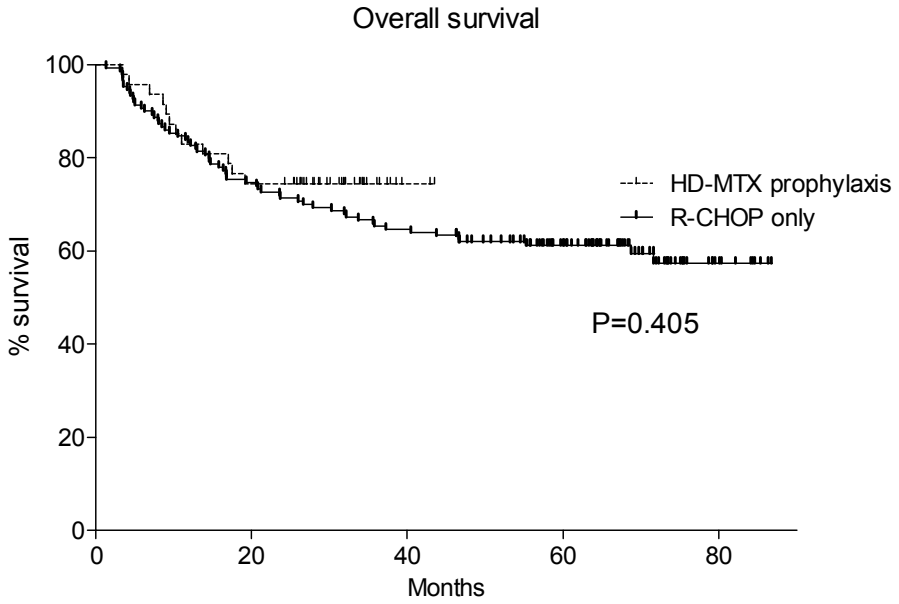
(A)



(B)



(C)


Overall survival
100
80
60
40
20
0
% survival
0
20
40
60
80
Months
HD-MTX prophylaxis
R-CHOP only
P=0.405

References

1. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v116-25.
2. Howlader N NA, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2009, National Cancer Institute, Bethesda, MD (2012). In. http://seer.cancer.gov/csr/1975_2009_pops09/ ed.
3. Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Ferme C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23(18):4117-26.
4. Ghose A. CNS Prophylaxis in Diffuse Large B cell Lymphoma. Journal of Cancer Prevention & Current Research 2016;5(5).
5. Patrij K, Reiser M, Watzel L, Pels H, Kowoll A, Herrlinger U, et al. Isolated central nervous system relapse of systemic lymphoma (SCNSL): clinical features and outcome of a retrospective analysis. Ger Med Sci 2011;9:Doc11.
6. Zahid MF, Khan N, Hashmi SK, Kizilbash SH, Barta SK. Central nervous system prophylaxis in diffuse large B-cell lymphoma. Eur J Haematol 2016;97(2):108-20.
7. Hill QA, Owen RG. CNS prophylaxis in lymphoma: who to target and what therapy to use. Blood Rev 2006;20(6):319-32.
8. Tai WM, Chung J, Tang PL, Koo YX, Hou X, Tay KW, et al. Central nervous system (CNS) relapse in diffuse large B cell lymphoma (DLBCL): pre- and post-rituximab. Ann Hematol 2011;90(7):809-18.
9. Malecek MK, Rozell S, Chu BA, Steve T, Galanina N, Nabhan C, et al. Risk Factors for CNS Relapse Among Patients with DLBCL Treated with EPOCH-R. Blood 2015;126(23):1500-.
10. Yamamoto W, Tomita N, Watanabe R, Hattori Y, Nakajima Y, Hyo R, et al. Central nervous system involvement in diffuse large B-cell lymphoma. Eur J Haematol 2010;85(1):6-10.
11. Barosi G, Carella A, Lazzarino M, Marchetti M, Martelli M, Rambaldi A, et al. Management of nodal diffuse large B-cell lymphomas: practice guidelines from the Italian Society of

Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation. Haematologica 2006;91(1):96-103.

12. Schmitz N, Zeynalova S, Nickelsen M, Kansara R, Villa D, Sehn LH, et al. CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP. Journal of Clinical Oncology 2016;34(26):3150-6.

13. Bernstein SH, Unger JM, Leblanc M, Friedberg J, Miller TP, Fisher RI. Natural history of CNS relapse in patients with aggressive non-Hodgkin's lymphoma: a 20-year follow-up analysis of SWOG 8516 -- the Southwest Oncology Group. J Clin Oncol 2009;27(1):114-9.

14. Boehme V, Schmitz N, Zeynalova S, Loeffler M, Pfreundschuh M. CNS events in elderly patients with aggressive lymphoma treated with modern chemotherapy (CHOP-14) with or without rituximab: an analysis of patients treated in the RICOVER-60 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Blood 2009;113(17):3896-902.

15. Abramson JS, Hellmann M, Barnes JA, Hammerman P, Toomey C, Takvorian T, 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 2010;116(18):4283-90.

16. Cheah CY, Herbert KE, O'Rourke K, Kennedy GA, George A, Fedele PL, 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 2014;111(6):1072-9.

17. Ferreri AJ, Bruno-Ventre M, Donadoni G, Ponzoni M, Citterio G, Foppoli M, 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 2015;168(5):654-62.

18. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059-68.

19. van Besien K, Ha CS, Murphy S, McLaughlin P, Rodriguez A, Amin K, et al. Risk factors, treatment, and outcome of central nervous system recurrence in adults with intermediate-grade and immunoblastic lymphoma. Blood 1998;91(4):1178-84.

20. Hollender A, Kvaloy S, Nome O, Skovlund E, Lote K, Holte H. Central nervous system involvement following diagnosis of non-Hodgkin's lymphoma: a risk model. Ann Oncol 2002;13(7):1099-107.

21. Batchelor T, Carson K, O'Neill A, Grossman SA, Alavi J, New P, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. J Clin Oncol 2003;21(6):1044-9.

22. Tilly H, Lepage E, Coiffier B, Blanc M, Herbrecht R, Bosly A, et al. Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. Blood 2003;102(13):4284-9.

23. Ferreri AJM. Secondary CNS lymphoma: the poisoned needle in the haystack. Ann Oncol 2017;28(10):2335-7.

24. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med 2014;33(7):1242-58.

25. Guirguis HR, Cheung MC, Mahrous M, Piliotis E, Berinstein N, Imrie KR, et al. Impact of central nervous system (CNS) prophylaxis on the incidence and risk factors for CNS relapse in patients with diffuse large B-cell lymphoma treated in the rituximab era: a single centre experience and review of the literature. British Journal of Haematology 2012;159(1):39-49.

국문요약

연구 배경: 리툭시맙의 도입으로 광범위큰 B 세포림프종 (Diffuse Large B cell lymphoma, DLBCL) 환자의 결과가 개선되었으나, 중추신경계 (Central nervous system, CNS) 재발은 여전히 나쁜 예후를 보이고 있다. 그동안 이러한 중추신경계 재발을 예방하기 위해 척수강 내 메토트렉세이트 (methotrexate, MTX) 요법이 널리 사용되었으나, 그 역할에 의문이 제기되었고 몇몇 후향연구를 통해 전신적 고농도 메토트렉세이트 (high dose MTX, HD-MTX) 주사 요법이 더 나은 방법으로 제시되었다. 이에 저자들은 전향적으로 수집한 코호트를 이용하여, 고위험군 DLBCL 환자에서 중추신경계 재발을 예방하기 위한 전신 HD-MTX 요법의 효능을 평가하기 위해 성향점수(propensity score, PS) 기반 분석을 포함한 다양한 통계 방법을 활용하여 여러 분석을 진행하였다.

연구 방법: 2010 년 1 월부터 2015 년 3 월까지 단일기관인 아산병원에서 수집된 DLBCL 한자의 등록 데이터를 후향적으로 검토하였다. 2013 년 7 월부터 CNS 재발 위험이 높은 DLBCL 환자는 모두 표준 R-CHOP 요법에 더해 전신성 HD-MTX 를 투여 받았다. 저자들은 CNS 예방 치료를 받은 환자와 R-CHOP 치료만 받은 환자들의

무진행 생존 (progression free survival, PFS), CNS 무재발 생존 (CNS relapse free survival, CNS-RFS) 및 전체 생존 (overall survival, OS) 를 분석하여 서로 비교 하였고, 다변량 콕스 회귀 분석과 성향점수 분석을 통해 전신성 HD-MTX 의 치료 효과를 평가하였다.

연구 결과: 2010 년 1 월부터 2015 년 3 월까지 표준 R-CHOP 요법으로 치료 받은 DLBCL 환자 중 CNS 재발 위험 인자를 가진 환자는 총 197 명으로 확인되었고, 그들 중 47 명이 전신성 HD-MTX 를 중추신경계 재발 예방요법으로 투여 받았다. 2 년 내 통계적 CNS 재발 위험도는 R-CHOP 치료에 더해 HD-MTX 예방 요법을 받은 환자군에서 6.9%, 예방 요법 없이 R-CHOP 치료만 받은 환자군에서는 10.5%로 계산되었다. 다변량 및 성향점수 분석에서 통계적으로 유의하지는 않았지만 (유의확률 > 0.05), CNS 재발 예방 요법으로 전신성 HD-MTX 치료를 받은 환자군에서 CNS 재발의 발생률이 낮고 PFS 및 OS 가 연장되는 경향이 확인되었다. (위험비 < 1)

연구 결론: 고위험군 DLBCL 환자에서 중추신경계 재발을 예방하기 위한 전신성 고용량 메토트렉세이트 요법은 통계적으로 유의하지는 않지만, 보다 나은 생존 결과를 보이는 경향을 나타냈다. 이러한 결과는 작은 코호트 크기, 짧은 추적 관찰 기간, 후향적 연구 특성 등에 의해 해석에 제한이 있으므로 고위험 DLBCL 환자에서

CNS 예방법으로써의 전신성 고용량 메토트렉세이트 요법의 효능을 적절히 평가하기 위해서는 다기관 전향적 무작위 연구가 필요할 것으로 생각된다.

중심 단어: 광범위큰 B 세포림프종, 중추신경계 재발, 중추신경계 예방치료, 메토트렉세이트 전신투여요법