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A survey evaluating hematology physicians' perspectives on central nervous system prophylaxis

Ufuk Demirci[1], Meltem Kurt Yüksel[2], Hakkı Onur Kırkızlar[1], Elif Birtaş Ateşoğlu[3], Özgür Mehtap[4], Ozan Salim[5], Ahmet Muzaffer Demir[1], Olga Meltem Akay[3]

Department of Haematology, [1]Trakya University, Medical Faculty, Edirne, [2]Ankara University, Medical Faculty, Ankara, [3]Koç University, Medical Faculty, İstanbul, [4]Kocaeli University, Medical Faculty, Kocaeli, [5]Akdeniz University, Medical Faculty, Antalya, Turkey

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Correspondence to
Ufuk Demirci, M.D.
Department of Haematology, Trakya University, Medical Faculty, Edirne 22030, Turkey
E-mail: ufukdemirci3232@gmail.com

Background
Central nervous system (CNS) prophylactic options for diffuse large B-cell lymphoma (DLBCL) are administered differently in most centers. Unfortunately, there is still not a consensus on which patients, which regimen, for how many cycles, and when prophylaxis should be administered. Thus, this remains an unmet clinical need.

Methods
We administered a survey study under the Lymphoma Scientific Subcommittee of the Turkish Society of Haematology. The questions were directed to hematologists through the monkey survey system.

Results
The CNS International Prognostic Index score is a factor that clinicians frequently use when deciding on prophylaxis and is considered reliable. Although the perspective on anatomical risk factors is similar to that reported in the literature, breast involvement is still considered a critical risk factor in Turkey. Participants considered double or triple hit and double/triple expressor lymphoma as significant risk factors. Various methods have been used to demonstrate CNS relapses. Intrathecal prophylaxis is the preferred method.

Conclusion
There are diverse methodological and technical ideas. The controversial results reported in the literature on the effectiveness of CNS prophylaxis may explain this finding. Although CNS prophylactic methods for patients with DLBCL are still controversial, the effect of secondary CNS involvement on survival is inevitable. Standard practices followed by national guidelines may be effective in reducing the variety of application methods and creating homogeneous results for efficacy and survival follow-up studies.

Key Words Prophylaxis, Diffuse large B-cell lymphoma, High dosage methotrexate

INTRODUCTION

Secondary central nervous system (CNS) involvement negatively affects the survival of patients with diffuse large B-cell lymphoma (DLBCL) [1]. Thus, approaches to reduce CNS recurrence are of great importance. These controversial CNS prophylactic options are administered differently in most centers. Unfortunately, there is still a need for a broad consensus on which patients, which regimen, how many cycles should be administered, and when. However, this remains an unmet clinical need.

The occurrence of secondary CNS involvement varies depending on the type of non-Hodgkin Lymphoma (NHL). CNS relapse is more common (30%) in patients with lymphoblastic or Burkitt's lymphomas. It varies between 1% and >15% among different risk groups in DLBCL patients [2, 3]. CNS relapse in patients with DLBCL frequently occurs within the first year after diagnosis [4]. Therefore, the question arises as to whether occult CNS involvement is detected in these patients at the time of diagnosis.

Prophylactic treatment to reduce CNS relapse significantly

protects against Burkitt's and lymphoplasmacytic lymphomas. The toxicity of these strategies must be considered for certain age groups. Although there has been an increase in survival rates after the introduction of immunotherapy in patients with DLBCL, it is not clear whether this benefit reduces the occurrence of CNS relapse in these patients [5, 6]. Therefore, we aimed to survey the CNS prophylaxis used in Turkey's hematology centers and evaluate the centers' awareness and perspectives.

MATERIALS AND METHODS

We administered the survey under the guidance of the Lymphoma Scientific Subcommittee of the Turkish Society of Hematology. Our survey included seven questions on CNS prophylaxis for patients with DLBCL. The questions were directed to hematology physicians using a monkey survey system. This study was approved by Trakya University Faculty of Medicine Ethical Committee (TUTF-GOBAEK 2022/313).

Q1: If you prefer not to use CNS prophylaxis, what is the reason for your choice?
Q2: If you think CNS prophylaxis should be used, in which patient groups do you think should it be administered? Which patient group is at a high risk for CNS prophylaxis?
Q3: Which method do you use to diagnose CNS relapses?
Q4: Which CNS prophylaxis method do you prefer?
Q5: What is your method of administering high-dose methotrexate prophylaxis?
Q6: For your preferred prophylaxis method, what is your application frequency?
Q7: Is there a patient group other than those with DLBCL for whom you apply CNS prophylaxis?

RESULTS

We forwarded seven question survey to hematologists working in academic or state hospitals. The questions were answered by 480 physicians. A total of 137 hematology physicians filled out the inquiry (49% hematology specialist doctors, 22% associate professors, 13% fellowship program members, 11% assistant professors, and 5% professors), and the answers were anonymous.

Q1: We found that 136 participants preferred CNS prophylaxis as a treatment strategy. Only one physician stated that CNS prophylaxis was ineffective and they did not prefer it.

Q2: We asked clinicians who preferred prophylaxis, in which patient groups they chose to use prophylaxis, and to describe the risk factors in these patient groups. Participants answered with more than one choice. Common reasons were suggested to the participants and the question was left open-ended for the additional options they wanted to add. More than 50% believed that a high CNS International Prognostic Index (CNS-IPI) score; testis, orbit, paranasal sinus, adrenal gland, and breast involvement; and the presence of double/triple expresser and high-grade B-cell lymphoma (HGBL) with rearrangements in *MYC* and *BCL2* and/or *BCL6* were the reasons for providing prophylaxis (Fig. 1).

Q3: In suspected cases, 64% of physicians considered performing cytological sampling with lumbar puncture a priority. In contrast, only 48% believed that cytology alone was sufficient. Conversely, 36% of physicians believed that

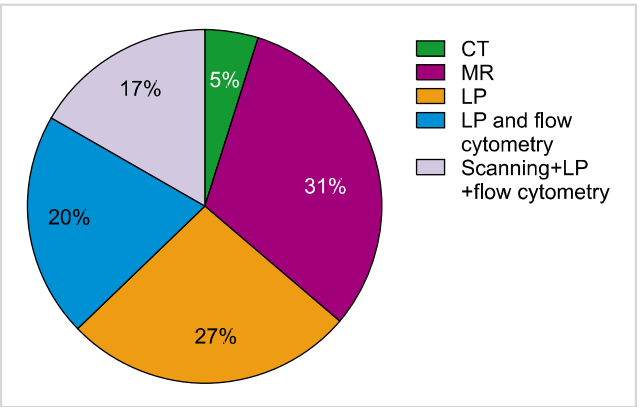

Fig. 2. Preferred methods to detect CNS relapse.

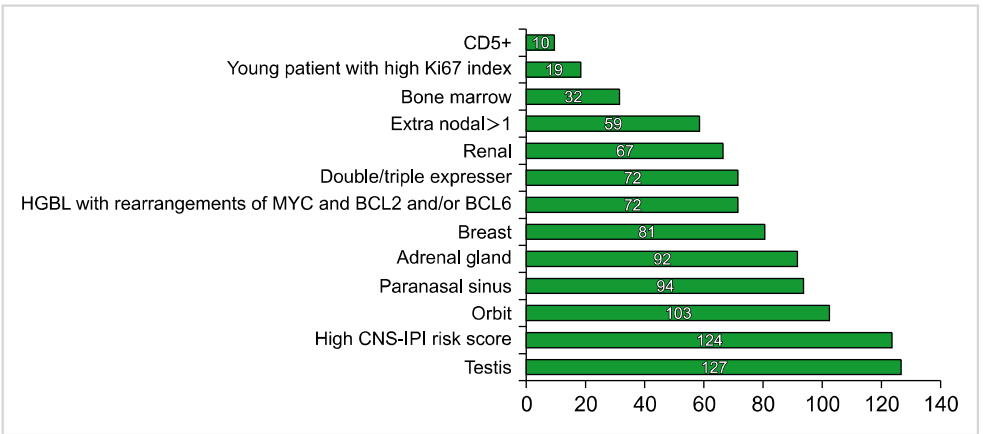

Fig. 1. Reasons that physicians preferred CNS prophylaxis.

imaging alone was sufficient to detect relapses (Fig. 2).

Q4: Physicians' choice of prophylactic method varied, and there was no standard choice. Those who preferred intrathecal prophylaxis (IT) alone constituted 74% of the participants. In addition, 26% of the physicians preferred high-dose methotrexate (HD-MTX) prophylaxis. While 8% of the participants using HD-MTX prophylaxis preferred HD-MTX only, 18% stated that they might prefer IT prophylaxis over HD-MTX depending on the patient's condition and comorbidities. One-third of the physicians who preferred IT prophylaxis used methotrexate (MTX; 12 or 15 mg) alone, while the other two-thirds preferred to add cytarabine (50 mg) or hydrocortisone/dexamethasone (15 mg/m^2/4 mg) in combination. One-third of the physicians who preferred IT prophylaxis used MTX alone. In contrast, the remaining physicians preferred the addition of cytarabine and/or hydrocortisone/dexamethasone in combination (Fig. 3).

Q5: Physicians who frequently administered HD-MTX (63%) used the intercalated HD-MTX (i-HD-MTX) approach (Fig. 4).

Q6: The frequency of prophylaxis use varies. The responses showed that to 2–4 courses were administered most frequently (Fig. 5).

Q7: Physicians stated that they considered CNS prophylaxis most frequently for patients with Burkitt's lymphoma, mantle cell lymphoma (especially the blastoid variant), lymphoblastic lymphoma, primary mediastinal B-cell lymphoma, T-cell lymphoma, HIV-associated lymphoma, HGBL, or leg type DLBCL along with DLBCL.

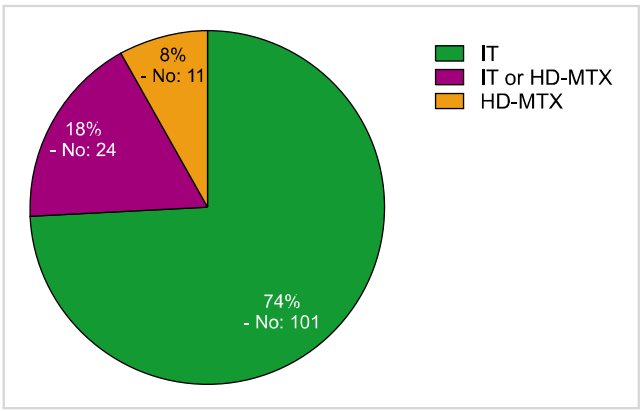

Fig. 3. Physicians' choices for prophylaxis methods.

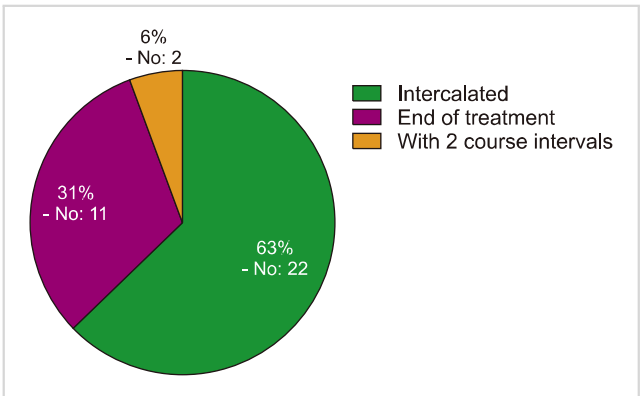

Fig. 4. Physicians' HD-MTX protocol options.

DISCUSSION

There are several theoretical considerations regarding the occurrence of lymphoma with CNS recurrence. It can spread hematogenously, directly from adjacent bones, and undergo retrograde growth through neurovascular structures. After CNS relapse, survival in patients with DLBCL is markedly reduced, with a median of 2.2 months [7]. Therefore, various risk factors have been established to predict and prevent CNS relapse, which is less common in DLBCL patients than in Burkitt's disease and lymphoplasmacytic lymphoma patients, and prophylactic methods for these patients are discussed. Clinical, anatomical, and biological risk factors have been previously evaluated.

Clinical risk factors

The CNS-IPI is the most commonly used risk-scoring system for predicting CNS relapse in clinical practice. For example, Schmitz *et al.* [8] observed that in patients in the low-, intermediate-, and high-risk CNS-IPI risk categories, the 2-year CNS relapse rates were 0.6%, 3.4%, and 10.2%, respectively. In line with these data, although the relapse rate increased as the risk factors increased, prophylaxis was found to be unnecessary in 90% of the patients who received prophylaxis based on their CNS-IPI risk category.

Elevated lactate dehydrogenase, especially a >3-fold increase, is a clinical finding that should be considered in CNS relapse risk assessment. Monocytosis is also a clinical risk factor [9].

The British Society for Hematology (BSH) recommendations published in 2020 recommend prophylaxis for high-risk CNS-IPI risk categories [10].

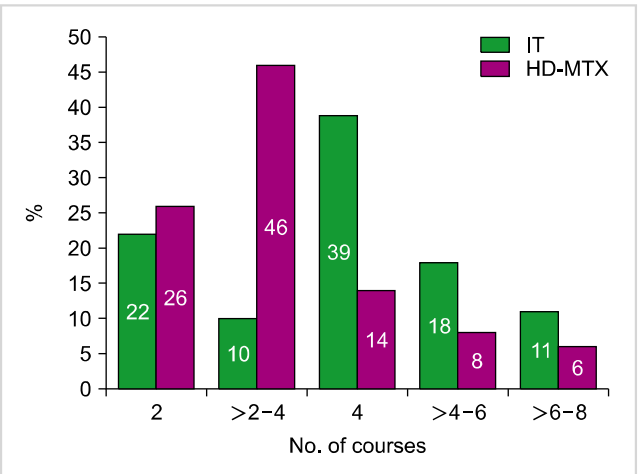

Fig. 5. Number of courses for prophylaxis treatments.

In Turkey, the CNS-IPI score is a factor that clinicians frequently use when deciding on prophylaxis and find it a reliable option.

Anatomical risk factors

Regardless of the patient's stage, kidney, testis, and adrenal gland involvement were important extra nodal sites. In the pre-rituximab area, CNS relapse is 15–21% in these patients [11]. Another factor that increased relapse in these patients was disease stage (CNS relapse in 5 years: 10% in limited stage, and 24% in advanced stage) [12]. The cumulative CNS relapse rate in adrenal gland or kidney involvement appears to be very high, at 35% [13]. Uterine involvement (except ovarian involvement) is another extra nodal site hat poses a risk of CNS relapse [14]. Although less common in patients with DLBCL, breast involvement has also been shown to be a risk factor in retrospective studies [15]. There are also articles suggesting that it should be considered for prophylaxis in bilateral involvement or lesions >5 cm [16]. Intravascular large B-cell lymphoma is also an important risk factor [17].

Adjacent structures may also be risk factors for direct invasion. Although DLBCL in the nasal and paranasal areas may be a risk factor for CNS recurrence before rituximab treatment, the recurrence rate after rituximab administration is low. Therefore, patients with ocular non-Hodgkin's lymphoma should be treated similar to those with primary CNS lymphoma [18]. There is no clear prophylactic recommendation for CNS recurrence in patients with bone or bone marrow involvement.

In the 2020 BSH recommendations, prophylaxis was recommended regardless of CNS-IPI score in the testis, adrenal gland, kidney, intravascular lymphoma, or more than three sites of extra nodal involvement [10].

The anatomical risk factors considered for CNS prophylaxis in Turkey are similar to those recommended in the literature. However, breast involvement, as evidenced by biopsy sampling, is still considered a critical risk factor for CNS relapse in Turkey.

Histological and molecular risk factors

With the increase in molecular studies in DLBCL, which has a heterogeneous structure, the diagnosis and management of patients with double or triple hit lymphoma have gained importance. Studies have reported that CNS relapses may occur in 50% of these patients [19]. In a Japanese study, the presence of CD5 was found to be a risk factor for CNS relapse (2-year relapse, 12.7%) [20]. The identification of *MYD88* and *CD79B* mutations is also essential [7, 21].

In both Turkey and the literature, CNS prophylaxis is preferred for patients with double or triple hit lymphoma. However, contrary to this recommendation, CNS prophylaxis is preferred in patients with double or triple expressor lymphoma.

Diagnostic approach

Multi-modality imaging-incorporating methods are preferred for detecting CNS relapse in lymphoma. Fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) and contrast-enhanced magnetic resonance imaging are the most essential methods for detecting CNS relapse. There is also a possibility for systematic evaluation using FDG-PET-CT [22].

Lumbar puncture should be performed in all patients with suspected CNS lymphoma relapse, if it is safe. Cytological and flow cytometric assessments are routinely recommended. As initially suggested by Hegde *et al.* [23] and later developed by Alvarez *et al.* [24], a storage buffer allows for the long-term use of flow cytometric analysis. Storage buffers that prolong the survival of lymphoma cells in vitro are easily available. This approach may become standard practice in the future [18]. In addition, if molecular analysis is possible, it is recommended to examine immunoglobulin heavy-chain rearrangements and *MYD88* L265P mutations. A CNS biopsy is recommended if there is a diagnostic doubt or if there is isolated CNS involvement >2 years after the primary diagnosis.

Physicians make various choices during the diagnostic process in Turkey. Imaging, lumbar puncture, cytology, and flow cytometry (multicolor flow cytometry, which is accessible at some centers) are the preferred methods.

CNS prophylaxis strategies

CNS prophylaxis in patients with DLBCL is still controversial, with methodological and efficacy limitations.

Historically, IT CNS prophylaxis has been the most frequently used method. In studies using IT, data on its effectiveness vary. This was a retrospective study with heterogeneous patient groups. In addition, most of the data were from the pre-rituximab area. The GELA study observed CNS relapse in 2.2% of patients receiving IT MTX [25]. Similarly, Tomita *et al.* [26] observed no CNS relapses with IT MTX and hydrocortisone. However, data regarding its effectiveness are contradictory. In a study by Tai *et al.* [27] only high-risk patients who received IT MTX showed no advantage in CNS relapse. Similarly, the benefit of IT MTX prophylaxis (CNS relapse: 2.5% in IT MTX vs. 4.4% in non-IT MTX) was not observed in the RICOVER-60 study [5]. In addition, in the GOYA study, the CNS relapse rates were similar (2.8% for IT MTX vs. 2.6% without prophylaxis) [28]. However, these studies included heterogeneous patient groups, with most patients having high-risk disease [29].

No prospective randomized studies have demonstrated the efficacy of the IT MTX prophylactic strategy, and data on its effectiveness are conflicting. Nevertheless, there are no studies with strong evidence showing that IT prophylaxis has less toxicity and fewer systemic side effects than systemic prophylaxis. Therefore, the BSH recommends that IT MTX prophylaxis be given 3–6 doses (12–15 mg, at least once per cycle, as early as practical during treatment) to all patients with a high relapse risk [10].

Another prophylactic strategy involves administration of HD-MTX. The HD-MTX prophylaxis method hypothesizes that drugs with deep penetration capabilities may be needed because recurrence is more common in the brain parenchyma

tissue. Ferreri *et al.* [30] showed that applying a dose of 3 g/m^2 with a 4–6-hour infusion was the ideal dose according to the area under the curve in primary CNS lymphomas. In a retrospective analysis, 2.5% of CNS relapses were observed in 40 patients who received HD-MTX, compared to 12% in patients who did not receive HD-MTX [31]. Similarly, in a study by Ong *et al.* [32] of a cohort including 85% high-risk patients, CNS relapse was 3.1% in the HD-MTX group compared with 14.6% in patients not receiving HD-MTX.

In a study comparing HD-MTX and IT MTX, CNS recurrence was observed in 5.4% of the IT MTX group (894 patients) and 6.8% of the HD-MTX group (236 patients). However, only 30% of the patients in this study had a high CNS-IPI score [33]. In a single-center study by Bobillo *et al.* [34] 68% of a 585-patient cohort had a high CNS-IPI score. In the Bobillo *et al.* [34] study, patients were treated with IT MTX (253 patients), HD-MTX (42 patients), or without prophylaxis (290 patients) and the 5-year CNS relapse rates were 5.5%, 5%, and 7.5%, respectively. However, patients who received prophylaxis experienced CNS relapse later than those who did not (median, 19 vs. 8 mo) [34].

Nephrotoxicity and myelosuppression are significant limiting factors of HD-MTX prophylaxis in patients with DLBCL. To reduce toxicity and increase effectiveness, HD-MTX should be administered at the end of treatment (EOT) or on the 10–14th day. In an international, retrospective cohort study by Wilson *et al.* [35] EOT-HD-MTX was found to be non-inferior to i-HD-MTX. In this study, all the patients had aggressive B-cell lymphoma and received HD-MTX along with R-CHOP (-like) treatment. CNS relapse was similar in both groups (5.7% and 5.8% for i-HD-MTX and EOT-HD-MTX, respectively). This result was similar for all the high-risk subgroups. However, in the i-HD-MTX group, 1/5 of the patients had delayed treatment due to prophylaxis-related conditions. Inferior lymphoma outcomes were observed in patients whose R-CHOP treatment was postponed at least once for seven or more days [35].

The BSH recommends the administration of HD-MTX in 2–3 courses (at least 3 g/m^2 and 2–4 hours infusion) in patients with physiological fitness and creatinine clearance $>$50 mL/min. Early application is essential, and if it is to be added to the treatment interval, it should be given before the 10th day.

The choice of HD-MTX prophylaxis by the surveyed physicians was low (26%). Similar to the recommendations in the literature, i-HD-MTX administration was found to be more frequent (63%). Although the frequency of application varies, 2–4 courses were administered most frequently.

CONCLUSION

In conclusion, most of the participants in the survey used similar CNS prophylactic approaches for patients with DLBCL, as in the literature. However, there are no standard risk factors for the prophylactic treatment options or methods. Unfortunately, the biggest reasons for this might be the controversial results regarding the effectiveness of CNS prophylaxis reported in the literature; prophylaxis methods are still controversial, and the impact of CNS involvement on surveillance is inevitable. Therefore, it is important to increase clinicians' awareness of CNS prophylaxis. Standard practices followed by national guidelines may be effective in reducing the variety of application methods and creating homogeneous results for efficacy and survival follow-up. This study aimed to evaluate the clinicians' perspectives on CNS prophylaxis and prophylaxis application methods in Turkey's hematology centers. Although the participation rate in the study was high, the most important limitation was that the long-term results of the applied methods were not known.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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