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CNS Prophylaxis in Diffuse Large B cell Lymphoma

Abstract

The outcome of patients with Diffuse Large B Cell Lymphoma (DLBCL) has significantly improved in the rituximab era. But CNS relapse remains a major complication with very poor prognosis. Systemic chemotherapy with prophylactic CNS directed therapy has been advocated for some patients, but evidence in favour of such treatment suffers from the lack of randomized clinical trials and controversy on the usefulness and type of prophylactic strategy. Since CNS directed therapies also result in chemotherapy related side-effects, judicious use of such regimen is warranted. Identifying occult CNS disease at the time of diagnosis of DLBCL is also an important aspect which is slowly evolving. Accurate detection of occult CNS disease can help narrow down the population most at need of specific CNS directed therapies. In this systematic review, we underwent an extensive search of literature and systematically reviewed the role of CNS prophylaxis in both the post-rituximab compared to the pre-rituximab era. We also reviewed the current modalities of CNS prophylaxis and attempted to identify the best strategy for high-risk patients- who would benefit most, by risk-stratification at the time of diagnosis. Lastly, we present a treatment algorithm that defines the role of CNS prophylaxis in the management of patients with DLBCL.

Research Article

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Clinical Question

A 60 year old gentleman presented with weight loss of 20 pounds in 6 months, low grade fever, night sweats and abdominal pain. Further investigation suggested normal CBC, high LDH of 802 mg/dl, mediastinal and retroperitoneallymphadenopathy, that was biopsy proven to be DLBCL. The tumor expressed CD19, CD20, CD22, CD79a and BCL2. Should he receive CNS prophylaxis in addition to rituximab based chemotherapy? If yes, what is the best strategy for prophylaxis?

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL) accounting for 25-58% of cases [1]. The addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) during the last decade has significantly improved the 4 year event free survival from 20-67% to approximately 47-80% [2].Involvement of central nervous system (CNS) including cerebrospinal fluid (CSF), meninges or brain parenchyma is one of the most serious complications for DLBCL patients. The rates of CNS involvement in DLBCL can vary from as low as 1% at the time of initial diagnosis to as high as 25% in high risk patients [3-5]. The exact set of risk factors which can most reliably identify this high risk population is controversial. Preventing this grave complication with CNS directed therapy is an important component of the treatment strategy for a few patients, but exposing all patients to it may lead to unwarranted toxicities without significant benefits. To add to this problem, since no randomized controlled trials has been performed regarding this issue, there is a lack of consensus regarding not only which patients should receive CNS prophylaxis, but also the standard prophylactic regimen. In light of this uncertainty, a focused review of literature was performed to examine risk factors and prophylaxis strategies against CNS relapse in DLBCL.

Materials and Methods

The goals of this systematic review of published literature were to: (1) identify salient risk factors for CNS relapse in DLBCL (2) evaluate the effectiveness of CNS prophylaxis both before and in the era of rituximab-based therapy and (3) analyze the different modalities of CNS prophylaxis and make appropriate recommendations. Literature search was conducted from its inception to January, 2016. Medline, The Cochrane Library and EMBASE were utilized for the purposes of this review. Keywords/ MeSH topics utilized included: Diffuse Large B Cell Lymphoma, Central Nervous System AND prevention, prophylaxis, control OR Recurrence OR Relapse. Only manuscripts written in English were considered in our search. All published full text research articles (randomized controlled trials, prospective trials, retrospective analyses) were allowed, provided they met the pre-specified inclusion and exclusion criteria identified in Table 1. After screening of the title and abstract, the full texts of eligible articles were screened, and data were extracted for case definitions, characteristics of patients and outcomes. Any work in progress such as abstracts and oral presentations from different hematological and oncological conferences were not included in this systematic review owing to the conflicting nature of their outcomes. In order to curtail publication bias, publications that were not peer reviewed were also excluded. Article selection and data abstraction were blinded. Post-doctoral research fellow and Internal Medicine resident individually screened the articles. In case of dispute or discrepancy regarding the inclusion or exclusion of the articles, the final decision was taken by senior Hematology/ Oncology fellow and Hematology/Oncology attending physician. Study quality and strength of recommendation grading was made according to Oxford Centre for Evidence-based Medicine and scoring of every individual study included in this systematic review has been delineated in Table 2 [6]. Grade of recommendation was

labelled where applicable. A guideline for the recommendation grading can also be found in Table 2.

Table 1: Properly powered and conducted randomized clinical trial; systematic review with meta-analysis.

Inclusion Criteria
All patients 18 years or older newly diagnosed with DLBCL
Exclusion Criteria
Patients with Primary Central Nervous System Lymphoma or Other aggressive form of Non-Hodgkin Lymphoma like Burkitt's Lymphoma.
Case series and Case reports with less than 10 patients
Abstracts of clinical studies where follow-up results about CNS relapse were not properly documented
Immuno-compromised patients like HIV, Hepatitis B and Hepatitis C

Table 2: Well-designed controlled trial without randomization; prospective comparative cohort trial.

Author	Quality Rating Scheme for Studies and Other Evidence
Kumar	2
Bernstein SWOG	2
Boehme RICOVER-60	2
Tilly	2
Holte	2
Vitolo	2
Haioun C	3
Villa D	3
Abramson JS	3
Arkenau H-T	3
Guirguis HR	3
Zucca E	3
Shimazu Y	3
Yamamoto W	3
Tai WM	3
Krawczyk K	3
Mitrovic Z	3
Tomita N	3
Vitolo U	3
Cheah CY	3

Risk factors of CNS Relapse

Conventional risk factors

Most retrospectives studies done so far have identified testicular involvement by DLBCL to constantly correlate with high-risk for CNS involvement. Since the involvement of testes has traditionally been associated with high-risk of CNS relapse and subsequent complete remission of around 15% despite IT prophylaxis, these patients have been traditionally considered to be high-risk candidates of CNS relapse [7]. Breast, kidney, adrenal glands, and bone have also been conventionally labelled as high-risk sites, but breast has been more consistently associated while involvement of bone marrow as a high risk extranodal site remains controversial [8-15]. Elevated Lactate Dehydrogenase (LDH) and >1 extra-nodal site have also been identified as additional risk factors [16,17]. These findings are not consistent too as other studies have shown no significant increase in CNS relapse risk with these factors [18-20]. Hegde et al. [5] showed that>1 extra-nodal site was the only parameter which can be correlated with CNS involvement [5].The RICOVER-60 trial showed that increased LDH, >1 extra-nodal site of involvement, and presence of B symptoms had a 2 year cumulative risk of 23.8% for CNS relapse [3]. The IPI (International Prognostic Index) or age-adjusted (aa)-IPI has been inconsistently associated with increased risk in many of these retrospective studies [16,19-22]. On a multivariate analysis, Hollender et al. [16] identified 5 primary independent risk factors for CNS relapse including increased LDH, serum albumin <35 g/l, age > 60 years, retroperitoneal lymph node involvement and>1 extra-nodal sites [16]. For the above reasons, except for testicular and breast DLBCL, we prefer to use combination of risk factors like elevated LDH, B symptoms and >1 extranodal sites as reason to give CNS prophylaxis. A new risk-based classification of DLBCL proposed by Fletcher et al. where the risk categories were divided into High-risk, Intermediate-Risk and Low-Risk can be envisaged for future treatment guidance and recommendations for CNS prophylaxis at the time of diagnosis [23]. The high-risk group comprise of patients having either MYC rearrangement/double hit lymphoma or >1 extranodal site accompanied by rise in LDH or solitary extranodal involvement of kidney or breast accompanied by elevated LDH or testicular involvement regardless of LDH status or a combination of either of these factors. Intermediate risk- group consists of >1 extranodal site (excluding kidney or breast) without elevation of LDH or solitary extranodal involvement of kidney or breast without elevation of LDH or elevated LDH alone. Finally the low-risk group features include 0 or 1 extranodal site (excluding kidney or breast) without elevation of LDH. Similar risk stratification of DLBCL patients into standard risk group and high risk group has been proposed by Ghose et al. using conventional risk factors like testicular, breast, paranasal, parameningeal, bone marrow kidney , adrenal glands and retroperitoneal lymph nodes involvement, elevated LDH, >1 extranodal sites, IPI score >=4. They further proposed the employment of CNS staging with cytology and flow cytometry to tailor appropriate therapies in the high risk group of DLBCL patients [24].

Biological risk factors

Patients who harbor myconcogene rearrangements (5-10% of DLBCL), including the double hit variant of DLBCL (having

both bcl2 and myc translocations) have a significantly higher risk of CNS relapse which does not decrease even with the addition of rituximab [25,26]. Whether cells of origin play an important role in CNS relapse in DLBCL is still unknown. Recent studies have concluded that the poor prognostic activated B-cell subtype of DLBCL, classified by gene expression profiling had no exact correlation with increased risk of CNS recurrence compared to germinal center B cell type but further studies need to be done to confirm this result [27-32].

In high risk patients, the importance of CNS staging with the help of comprehensive history, physical examination, neuro-imaging of brain and spine and examination of Cerebrospinal fluid (CSF) is paramount to diagnose occult CNS involvement. With the evolving landscape of biomarker detection, the use of conventional cytology of CSF alone to look for malignant cells as a diagnostic tool has fallen out of favour due to its low specificity and high false negative rates [33]. Flow Cytometry has been shown to be comparatively better than cytology in detecting occult CNS diseases and when combined with conventional cytology, the sensitivity of it increases to around 50% [5,34-38]. Identifying monoclonality by immunoglobulin H gene rearrangement analysis and detection of CSF micro RNAs are potential diagnostic tools too but they are still in experimental stages [39,40].

CNS staging which includes a comprehensive history and physical exam, neuroimaging including MRI of brain and spine as indicated and both conventional cytology and flow cytometry of CSF can be deemed helpful to identify occult CNS involvement in high-risk patients [27,28,33-37]. Occult CNS involvement warrants treatment with CNS directed therapy [41,42].

Modalities of CNS Prophylaxis

Among the drugs used for prophylaxis, methotrexate (MTX) is considered leading component of CNS directed therapy which can be given intravenously or intrathecally. National Comprehensive Cancer Network recommends 4-8 doses of intrathecal (IT) MTX, and/or cytarabine (Ara-C) or systemic MTX (3-3.5 gm/m^2) during the course of treatment [43]. The optimal dose of intrathecal MTX is 12 mg which achieves therapeutic CSF levels (>1 mol/l) for 24-48 h, and is concomitantly given with each cycle of chemotherapy for prophylaxis [44,45]. Use of high dose MTX by intravenous route for CNS prophylaxis has been evaluated in many recent studies. Vassal et al. [46], studying Non-Hodgkin's Lymphoma (NHL)where systemic MTX was given as a 3-h IV infusion of 3 g found no correlation between plasma and CSF MTX levels [46]. Another study on 25 children with lymphoid malignancies which evaluated CSF concentration at different times during 24 h intravenous infusion of MTX at 3 g/m^{2}concluded that plasma concentration of MTX is not predictive of CSF concentration. They also studied that at least 8 h of infusion is needed to achieve steady state concentration in CSF and the minimum intravenous dose of MTX to reach minimum therapeutic concentration of 5 × 10^{-7}mol/Lin CSF is of 3 g/m^2 [47]. Pre-treatment alkalization of urine and post-treatment use of leucovorin to rescue bone-marrow has been the standard practice to counter the serious adverse effects of MTX. Potential side-effects of MTX include mucositis, myelo-suppression, neurotoxicity and nephrotoxicity. Intrathecal Ara-C can serve as an alternative or an add-on to intrathecal MTX. A single 30 mg intra-ventricular dose of Ara-C has the potential to maintain a cytotoxic drug concentration between 0.4 and 1 mol/L for at least 24 h in patients [48]. Sustained release intrathecal liposomal Ara-C can also play a role in prophylaxis because when administered its level is high enough to cause cytotoxicity in the CSF for ≥14 days [49]. High dose systemic Ara-C, at a dose of 3 g/m^2 twice daily, can also be used to obtain comparable concentrations in the CSF, but is frequently shown to be associated with neurotoxicity [45]. Krawczyk et al. [50] studied 79 high risk DLBCL patients treated with intrathecal liposomal Ara-C [50]. None of the patients developed any CNS involvement during the follow-up of 28 months. In 58 (70.9%) patients the Karnofsky score improved. This study strongly encourages use of intrathecal liposomal Ara-C for CNS prophylaxis. Tomita et al conducted a study on 322 patients to evaluate the efficacy of CNS prophylaxis using four doses of IT-MTX (15 mg) with hydrocortisone (25 mg) after CR was achieved in patients with DLBCL and concluded that IT-MTX administration was insufficient to prevent CNS relapse [51]. Prophylactic intracranial irradiation has fallen out of favour nowadays owing to its toxicities. Finally, rituximab administration intravenously results in CSF levels approximately 0.1% of serum levels owing to its poor CNS penetration- a poor choice for CNS prophylaxis. In the pre-rituximab era, CNS relapse was more common in the leptomeningeal areas and in the post-rituximab era the CNS relapse has been documented more in the brain parenchyma (approximately 65-76%) [17,52,53]. The RICOVER-60 trial contradicted this view as patients receiving R-CHOP in their study were found to have more leptomeningeal recurrence than parenchymal involvement. A summarized version of all included clinical trials for intrathecal prophylaxis ANS systemic chemo-prophylaxis can be found in Tables 3 & 4 respectively.

Does CNS prophylaxis help in Diffuse Large B cell Lymphoma?

Pre Rituximab era: In the pre-rituximab era, there have been several inconsistencies in data to support the effectiveness of CNS prophylaxis in high-risk DLBCL patients. The Southwest Oncology Group conducted a prospective study (SWOG 8516) on 899 patients with aggressive B-cell lymphoma and followed them for 20 years [54]. The patients were randomly assigned to the following regimens: CHOP; MTX, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B); prednisone, MTX, doxorubicin, cyclophosphamide, etoposide- Ara-C, bleomycin, vincristine, MTX (ProMACE-CytaBOM); or MTX, bleomycin, cyclophosphamide, etoposide (m-BACOD). Patients with bone marrow involvement at diagnosis who received ProMACE-CytaBOM and m-BACOD received 24Gy of whole-brain irradiation and intrathecal MTX/ Ara-C respectively if they achieved bone marrow remission. Patients receiving either CHOP or MACOP-B received no CNS prophylaxis. The CNS relapse rate of 2.8% for the patients who received CNS prophylaxis was not statistically different from 3.6% for those who did not (P=0.74). Obvious problem with this study being the patients being compared received different chemotherapies, and also the criteria to give CNS prophylaxis was based just on bone marrow involvement. A large retrospective study by the German High Grade Non-Hodgkin Lymphoma study group (DSHNHL) on 2999 patients with aggressive lymphoma which included 2196 DLBCL patients, showed that intrathecal MTX, etoposide did not reduce

the time to CNS recurrence in patients regardless of whether they received rituximab or not [55]. In another small retrospective study comprising of 26 high risk patients with intermediate grade NHL receiving CNS prophylaxis with IT MTX ± Ara-C, 23% of patients had CNS recurrence, depicting the inadequacy of IT prophylaxis [56]. A prospective study by Tilly et al. [57] studied induction courses of doxorubicin, cyclophosphamide, vindesin, bleomycin, prednisone (ACVBP) and intrathecal MTX, followed by consolidation with intravenous MTX, etoposide, ifosfamide and Ara-C versus CHOP regimens in aggressive lymphomas in 65 elderly patients [57]. There was a lower (2.8%) rate of CNS relapse in the ACVBP group versus a higher (8.3%) rate in the CHOP group.

Rituximab era

Prospective Studies: Feugier et al. [18] analyzed a cohort of 399 elderly patients with lymphoma prospectively treated with CHOP, with or without rituximab and concluded that rituximab did not influence the risk of CNS relapse(18). A Swedish group Adde et al. [31] examined the use of dose dense R-CHOP with etoposide (R-CHOEP-14) in 38 patients with DLBCL, aged <65 years and aaIPI scores of 2 or 3 [30]. LDH was elevated in 35 patients and 60% of the patients enrolled had extra-nodal disease. CNS relapse occurred in all the patients who received intravenous prophylaxis with Ara-C (6 gm/m^2) which emphasizes the fact that systemic Ara-C did not have a beneficial role in that study. RICOVER-60 was a large randomized clinical trial in which 1222 patients with aggressive B-cell lymphomas, aged 61-80 years were studied to assess the effectiveness of rituximab by comparing R-CHOP14 versus CHOP14 [3]. In their analysis of the 58 DLBCL patients who had CNS relapse after 2 years, the group of patients receiving R-CHOP 14 had lesser incidence of CNS relapse (4.1%) compared to the group that received CHOP-14 (6.9%, p=0.043). They went afar in concluding that there was no difference in the incidence of CNS relapse between patients treated with or without intrathecal MTX in the R-CHOP group. Of the 210 patients expected to receive prophylaxis, only 120 (57.1%) actually received CNS prophylaxis with intrathecal MTX as these patients were at highest risk for spread of DLBCL to extra nodal sites like testes, bone marrow involvement or head/neck lymphomas. There was a trend toward protective effect of intrathecal MTX in the CHOP group. Another large prospective study by Kumar et al studied 989 high-risk patients identified by involvement of bone marrow, testes and other high risk sites, >1 extranodal sites, higher IPI score, elevated LDH and stages III/IV with a median follow up of 2.5 years [58]. Of the 117 patients who received CNS prophylaxis, 71.8% received intrathecal MTX and/or Ara-C, and 28.2% received systemic MTX. Only 2% of patients experienced CNS recurrences; there was a significantly higher incidence of relapse in those who received (10.9%) compared to those who did not receive chemoprophylaxis (2.1%). This shows that the study was actually able to identify patients at high risk of CNS relapse, but maybe the chemoprophylaxis strategy needs to be improvised on. But, among patients with ≥2 high risk factors, the rate of relapse was 2.5%. In hindsight CNS prophylaxis might have been beneficial in very high risk patients. In a phase 2 study on 53 primary testicular DLBCL patients, intrathecal methotrexate with RCHOP and contralateral testis irradiation resulted in 5 year CNS relapse in 6% of patients. The study concluded that the outcome was good with this approach with 5 year OS of 85%, but CNS prophylaxis needs further investigation (59).The Nordic Lymphoma Group introduced a new regimen in a phase II study of R-CHOEP-14 in 143 patients with DLBCL, all aged within 65 years and having an aaIPI score of 2-3 [60].IT MTX was only given once after diagnostic LP. The R-CHOEP regimen was given for six cycles in these patients, followed by a course of high dose Ara-C (3 g/m^2 twice daily for 2 days for four doses total), and 3 weeks later a dose of MTX (3 g/m^2 as a 24 h infusion with folate rescue at 36 h). Also dose adjustment was allowed for patients aged 60-65 years (2 g/m^2 and 1.5 g/m^2, respectively). The reported overall CNS relapse rate in this trial was 4.5%, occurring within 6 months of study registration, suggesting that the Nordic Group's prophylaxis strategy was effective in a high risk group. In another study by Deng et al on 599 patients, rituximab did not significantly reduce the risk of CNS involvement [61]. Systemic disease prior to or coincident with CNS occurrence was more common in the CHOP group than in the R-CHOP group. Isolated relapse in the rituximab era CNS events were more common in the R-CHOP group. A few case reports and case series have demonstrated that intrathecal rituximab alone in doses ranging from 10 mg to 40 mg can cause cytologic response and improvement in symptoms in patients with CNS involvement [32,62,63]. Intra-ventricular administration of rituximab via Ommaya reservoir along with intra-ventricular MTX was also shown to cause significant improvement in patients with CNS relapse in a phase I trial [64]. Intrathecal rituximab also has been reported to have resulted in serious infusion related side-effects like grade 3 hypertension, chest pain, tachypnea, diplopia and nausea/vomiting which makes the decision regarding their routine intrathecal use a matter of concern [65]. Likewise further studies are necessary before intrathecal or intra-ventricular rituximab can be routinely used. A summary of included prospective clinical trials has been included as Table 5.

Retrospective /Observational Studies: The GELA group studied 974 patients with aggressive lymphoma in complete remission who received CNS prophylaxis consisting of intrathecal MTX as well as two courses of intravenous MTX [15]. The incidence of isolated CNS relapse was 1.6%, compared to the historic control of 5%.For primary testicular lymphoma, we recommend intrathecal chemoprophylaxis with systemic MTX and irradiation of the contralateral testis after orchiectomy [41,52,66]. In testicular lymphoma, two small studies have shown no benefit from intrathecal prophylaxis alone [7,67]. In a retrospective study from Royal Marsden Hospital Sutton, among 51 out of 259 consecutive DLBCL patients who received intrathecal MTX prophylaxis based on lymphoma involvement at the following sites: testis, bone marrow, orbits, bone/vertebrae, nasal/paranasal sinuses and peripheral blood, only 3 patients (1.1%) showed CNS relapse [65]. Shimazu et al. [17] studied 403 DLBCL patients without CNS involvement among which 42 patients experienced CNS relapse [17]. They showed that rituximab may actually prevent CNS relapse by reducing the recurrence of DLBCL at all sites. This view was refuted by Yamamoto et al who studied 375 newly diagnosedDLBCL patients [20]. They came to the conclusion that rituximab did not have any impact on CNS involvement. A retrospective study by Abramson et al showed that among 65 patients with DLBCL and CNS risk factors who were given intravenous MTX with R-CHOP, 3% had CNS relapse after median follow up of 33 months suggesting a role for systemic chemoprophylaxis [41]. Villa et al. [52] performed a large-scale analysis of extranodal involvement of the kidney and its risk of

CNS relapse in a cohort of 2656 patients where 55 patients had renal involvement [21]. Half of the patients with IT prophylaxis relapsed rendering this regimen inadequate. The overall rate of CNS relapse in the R-CHOP group was also lower than the CHOP group. The literature regarding the role of rituximab in preventing CNS relapse is debatable with some studies showing no effect and others showing a protective effect [17,19,55,68-73]. In a systematic review of prospective studies no prophylactic effect of systemic rituximab was seen in rates of CNS relapse [74].

Cheah et al. [75] conducted a multicentre, retrospective analysis of 217 patients with a median follow-up of 3.4 years where three different strategies of CNS-directed therapy namely intrathecal MTX with R-CHOP 'group 1', R-CHOP with IT MTX and two cycles of high-dose intravenous (IV) MTX 'group 2', dose-intensive chemotherapy (Hyper-Cyclophosphamide, Vincristine Sulfate, Adriamycin, Dexamethasone or Cyclophosphamide, Vincristine, Doxorubicin, high-dose Methotrexate (CODOX-M)/ ifosfamide, etoposide and high-dose Ara-C) with IT/IV MTX 'group 3' were compared [74]. With median follow-up of 3.4 years, 23 CNS relapses occurred in total (12, 10 and 1 in groups 1-3 respectively). The 3-year actuarial rates of CNS relapse were 18.4% (9.5-33.1%), 6.9% (3.5-13.4%) and 2.3% (0.4-15.4%) in groups 1-3 respectively (P= 0.009).They concluded that the addition of high-dose IV MTX and/or Ara-C was associated with lower incidence of CNS relapse compared with IT chemotherapy alone. In their analysis, they also concluded that use of rituximab did not influence the risk of CNS relapse either in the cohort as a whole or when subgroup analyses were performed within groups 1 and 3, which corroborates with our systematic review.

Table 3: Case-control studies; retrospective cohort study.

Study	Systemic regimen	CNS PPx	PPx criteria	CNS relapse rate	OS	PFS/DFS/EFS
Bernstein [54]	225 CHOP, 218 MACOP-B, 233 ProMACECytaBOM, 223 m-BACOD	None for CHOP, m-BACOD, ProMACE-CytaBOM 24 Gy of WBI after cycle 4 if BM remission, MACOP-B 12 mg IT MTX and 30 mg Ara-C 2 ×/ week ×6 doses if BM remission	See CNS PPx	4.4% CHOP, 1.4% MACOP-B, 3% ProMACE-CytaBOM, 2.2% m-BACOD. By strategy (p =0.74), PPx 2.8%, no PPx 3.6%	p =0.81, 10-year OS (%) 34, 32, 37, 35	p =0.22, 10-year PFS (%) 25, 26, 27, 31
Arkenau [66]	CHOP, R-CHOP, PmitCEBO, R-PmitCEBO (177 w/o R, 62 w/ R)	IT MTX 12.5 mg Q week 39, IT MTX 12.5 mg/ cycle 5, IT MTX 12.5 mg +Ara-C 50 mg Q week 7	BM, testis, sinuses, orbits, bone/vertebrae, blood	3 year entire cohort 2.7%, prophylaxed 1.9%	3-year OS 65–70% estimated	NR
Sancho [37]	Not specified	All IT: triple IT 166, MTX 17, Ara-C 1, liposomal Ara-C 3, WBI 2	PPx in 187: EN 89, ↑LDH 87, IPI >2 62, bulky disease 43, EN >1 33, age >60 28, HIV 13	5.8% for all	NR	NR
Shimazu [17]	CHOP-like, CHOP-like w/8 cycles R, 60% R	IT MTX ×4 in 18 cases	Sinuses, testis, vertebra	42/399 w/ response, 1/18 w/ PPx, 3%		
Boehme [3]	1222: 307 CHOP-14 ×6, 305 CHOP-14 ×8, 306 R-CHOP-14 ×6, 304 R-CHOP-14 ×8	IT MTX 15 mg +LV on D1 and D5 of C1, C2 for CHOP and R-CHOP arms. Inconsistent administration	BM, testis, head, upper neck	2-year (p =0.043), R-CHOP 4.1%, CHOP 6.9%, ~3-year rate by PPx, no R/no IT 27.5%, no R/IT +7.5%, R/ no IT 7%, R/+IT 3%	3-year 67.7% (62.0–73.5), 66.0% (60.1–71.9), 78.1% (73.2–83.0), 72.5% (67.1–77.9)	3-year PFS 56.9% (50.8–63.0), 56.9% (50.8–63.0), 73.4% (68.1–78.7), 68.8% (63.2–74.5)

Villa [21]	126 CHOP, 309 R-CHOP	IT MTX/Ara-C alternating ×6	BM, blood, epidural, advanced stage, testis, sinuses	All 7.1%, CHOP 9.5%, 3/8 w/ PPx, R-CHOP 6.1%, 0/12 w/ PPx		
Tai [19]	R-CHOP 320, CHOP 179	IT MTX 12 mg on D1 of first 4 cycles, 499 total, 203 deemed high risk, 82 received PPx		2-year (p =NS): CHOP 5.1% (2.6–9.9), R-CHOP 6.0% (3.8–9.4), p =0.981. Non-IT exact no. not given (total 5%), IT 11%	NR	NR
Kumar [58]	989 R-CHOP	Intrathecal in 71.8% (MTX and/or Ara-C), 28.2% HD MTX		2.0% (1.1–2.9%)	p =0.0626	"No difference," data not reported
Schmitz [3]	CHOP or CHOP-like ±E, 14 vs. 21, 1576 w/o R, 620 w/ R	IT MTX 15 mg D1 and D15 of first 2 cycles	NHL-B1 LBL, High-CHOEP, Mega-CHOEP, upper neck, head, BM, testes	p =0.386	NR	NR
Guirguis [67]	R-CHOP	27/214 (12.6%) total:IT MTX 10, HD MTX 2, IT and HD MTX 15	↑LDH, >1 EN, testis, epidural, sinus or skull	3.7%	5-year 63%	5-year PFS 57%
Tomita [20]	R-CHOP + 4 dose of It-MTX (15 mg) and Hydrocortisone (25 mg) vs R-CHOP	40/322 (12%)	↑LDH ,BM involvement, ,testicular involvement, nasal/paranasal sinuses, bone involvement, breast involvement, extranodal sites ≥2	8% for R-CHOP + 4 dose of It-MTX (15 mg) and Hydrocortisone (25 mg) , 3% for R-CHOP(p=0.14)	3 year 8.7% vs 2.9 (p=0.14)	NR
Krawczyk [50]	R-CHOP+ Intrathecal liposomal Cytarabrine	79	↑LDH,IPI(3-5), extranodal sites	0	4 years 90.1%	86.1%

IT: Intrathecal; CHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; MACOP-B: Methotrexate With Leucovorin Rescue, Doxorubicin, Cyclophosphamide, Vincristine, Prednisone, Bleomycin; Promace: Cytabom, Prednisone, Methotrexate, Doxorubicin, Cyclophosphamide, Etoposide, Cytarabine, Bleomycin, Vincristine, Methotrexate; M-BACOD: Methotrexate (Moderate Dose), Bleomycin, Doxorubicin, Cyclophosphamide, Vincristine, Dexamethasone; R-CHOP: CHOP With Rituximab; R-Pmitcebo: Rituximab, Prednisolone, Mitoxantrone Cyclophosphamide, Etoposide, Bleomycin, Vincristine; E: Etoposide; CNS: Central Nervous System; Ppx: Prophylaxis; WBI: Whole Brain Irradiation; BM: Bone Marrow; C1: Cycle 1; C2, Cycle 2; MTX, Methotrexate; Ara-C: Cytarabine; D: Day; LV: Leucovorin; HD: High Dose; EN: Extranodal; LDH: Lactate Dehydrogenase; IPI: International Prognostic Index; HIV: Human Immuno Deficiency Virus; NHL: Non-Hodgkin Lymphoma; LBL: Lymphoblastic Lymphoma; High-CHOEP: CHOEP With Dose Escalation Until Toxicity; Mega-CHOEP: CHOEP-14 With Dose-Escalated Sequential High Dose Therapy and Rituximab; OS: Overall Survival; NR: Not Reported; PFS: Progression-Free Survival; DFS: Disease-Free Survival; EFS: Event-Free Survival.

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Table 4: Case series with or without intervention; cross-sectional study.

Study	Systemic regimen	CNS PPx	PPx criteria	CNS relapse rate	OS	PFS/DFS/EFS
Adde [31]	R-CHOEP-14	Ara-C 3000 mg/m2 Q12 h ×2 doses once	All	7.80%	79%	EFS 60%
		(23), IT MTX (3), none (12)				
Abramson [41]	R-CHOP-21 97%	IV MTX 3.5 g/m2, median 3 (1–8) cycles			3 year OS 78	3-year PFS 76%
					(64–88)	(62–86)
Recher [27]	R-ACVBP 196,	ACVBP, IT MTX × 4 plus HD MTX	All	R-ACVBP 0,	92% vs. 84%	PFS 87% vs. 73%
	R-CHOP 183	3 g/m2×2, R-CHOP, IT MTX		R-CHOP 2%		
Holte [60]	R-CHOEP-14	IT MTX allowed after LP, Ara-C 3 g/m2	All	4.50%	3-year 81%	3-year FFS 65%
		Q12 ×2D MTX 3 g/m2×1				

Table 5: Opinion of respected authorities; case reports

Author [ref]	Number of patients/ no (%)of patients with DLBCL	Systemic therapy	CNS prophylaxis	Criteria for CNS prophylaxis	CNS relapse number (%)	Median time to CNS relapse (months)	Overall survival/PFS	Isolated CNS progression or relapse (%)
Kumar [58]	989	R-CHOP21	≥2 doses of IT MTX and/or cytarabine or ≥1 doses of systemic MTX	All conventional risk factors/if no factor or 1 risk factor present weightage given on 4 main factors: >1 extra-nodal site, elevated LDH, BM involvement, or other high risk site involvement	20 (2%; 95% CI 1.1–2.9%) 5.4% for those with prophylaxis vs. 1.4% for without (P = .08)	10% relapsed within 4–6 m 90% relapse ≥6 m	Overall survival is not affected by prophylaxis (P = 0.0626)	70% of the total CNS relapse
Bernstein [54] SWOG	899	CHOP vs. ProMACE-CytaBOM vs. mBACOD vs. MACOP-B	None vs. 24 Gy vs. IT-MTX vs. ARAC vs. none	None vs. BM at CR vs. BM at CR vs. none[a]	25 (2.8%) 4.4% with CHOP; 1.4% with MACOP-B; 3.0% with PROMACE-CytaBOM; and 2.2% with m-BACOD 2.8% in prophylaxis group vs. 3.6% (P = 0.74)	5.4	10-Year estimate OS: 34% vs. 37% vs. 35% vs. 32% (P value: 0.81) PFS: 25% vs. 27% vs. 31% vs. 26% (P = 0.22	1.2%

Boehmed [15] RICOVER-60	1222	CHOP14 × 6/8 VS. RCHOP 14 × 6/8	IT-MTX × 4	BM, testis, head, upper neck[b]	58 (4.8%). Estimated 2 yr incidence 6.9% CHOP vs. 4.1% RCHOP. (P = 0.043)	8	N/A	2.8%
Tilly [18]	618	ACVBP+ consolidation vs. CHOP × 8	IT-MTX + HDMTX, etoposide, Ara-C and ifosfamide vs. none	All vs. none[c]	2.8% with ACVBP vs. 8.3% with CHOP	NA	5yr OS 46% vs. 38% (P = 0.036) 5 yr DFS 62% vs. 44% (P = 0.0002)	77.7% of CNS recurrences vs. 69.2%
Holte [60]	156	R-CHOEP-14	HD ARA-C × 2 days + HDMTX × 1	All	7 (4.5%)	<6	3 yr EFS: 65% 3 yr OS: 81%	86% of the CNS relapses
Vitolo [59]	50	R-CHOP21	12 mg total ,four doses of IT-MTX	Testicular Involvement	3(6%)	5 year	5 year EFS: 74% OS: 85%	4%

a None with CHOP and MACOP-B; 24 Gy whole-brain irradiation (if there was bone-marrow involvement) with PROMACE-CytaBOM; and six intrathecal methotrexate and cytarabine injections (if therewas bone-marrow involvement) with m-BACOD

b None for DLBCL (but 4.2% of trial population received intrathecal prophylaxis by choice of investigator).

c None with CHOP; four intrathecal methotrexate injections during induction followed by consolidation including two courses of high-dose intravenous methotrexate with ACVBP.

d Included lymphoblastic and burkitt/burkitt like lymphoma.eIncluded follicular grade 3 lymphoma.

Recommendations

Preventing the grave complication of CNS relapse in DLBCL is an important but often overlooked component of treatment. At the same time it is vital to identify the population at risk to prevent exposing all patients to potentially toxic chemoprophylaxis. The rarity of CNS relapse in DLBCL make the prospect of randomized clinical trial comparing the different interventions a daunting task, and the absence of such trials makes recommendations of standardized treatment guidelines extremely difficult. Majority of CNS relapses in the rituximab era seem to be isolated as rituximab exerts a better control on systemic disease. We haven't focused our research on treatment post CNS relapse. Involvement of testis (Grade B) and breast (Grade C) seem to consistently associate with a higher risk. The risk-based stratification system proposed by Fletcher et al. [23] & Ghose et al. [73], as mentioned earlier can be used for guiding the treatment of CNS prophylaxis in DLBCL. Since such classifications are based on analysis of several prospective and retrospective studies and not on any randomized clinical trial, further studies need to be done to test the validity of this risk-classification system.

Options for CNS prophylaxis include IT MTX, Ara-C or liposomal Ara-C or systemic MTX/ Ara-C. Our proposed therapy is solely based on the cumulative results of all the prospective and retrospective studies till date. Whether IT, systemic or both should be used in the rituximab era is still controversial and warrants a randomized clinical trial. The role of intrathecal prophylaxis by itself is questionable. Rituximab although is very efficacious in controlling systemic disease, doesn't help in preventing CNS relapse in high risk patients. We propose a treatment guideline where once high risk patients are identified, systemic MTX or Ara-C based chemoprophylaxis with or without intrathecal MTX should be used. This has also been exemplified by the strategy from the Nordic Lymphoma group and seems to be superior in preventing CNS involvement (Grade C) [54] (Figure 1). Obviously the risk-benefit of systemic prophylaxis in the individual patient must be assessed. For low risk patients, we recommend no additional CNS prophylaxis. For intermediate risk patients, physician discretion is advised after weighing the risk-benefits to the individual patient. The algorithm in Figure 2 shows our suggested approach.

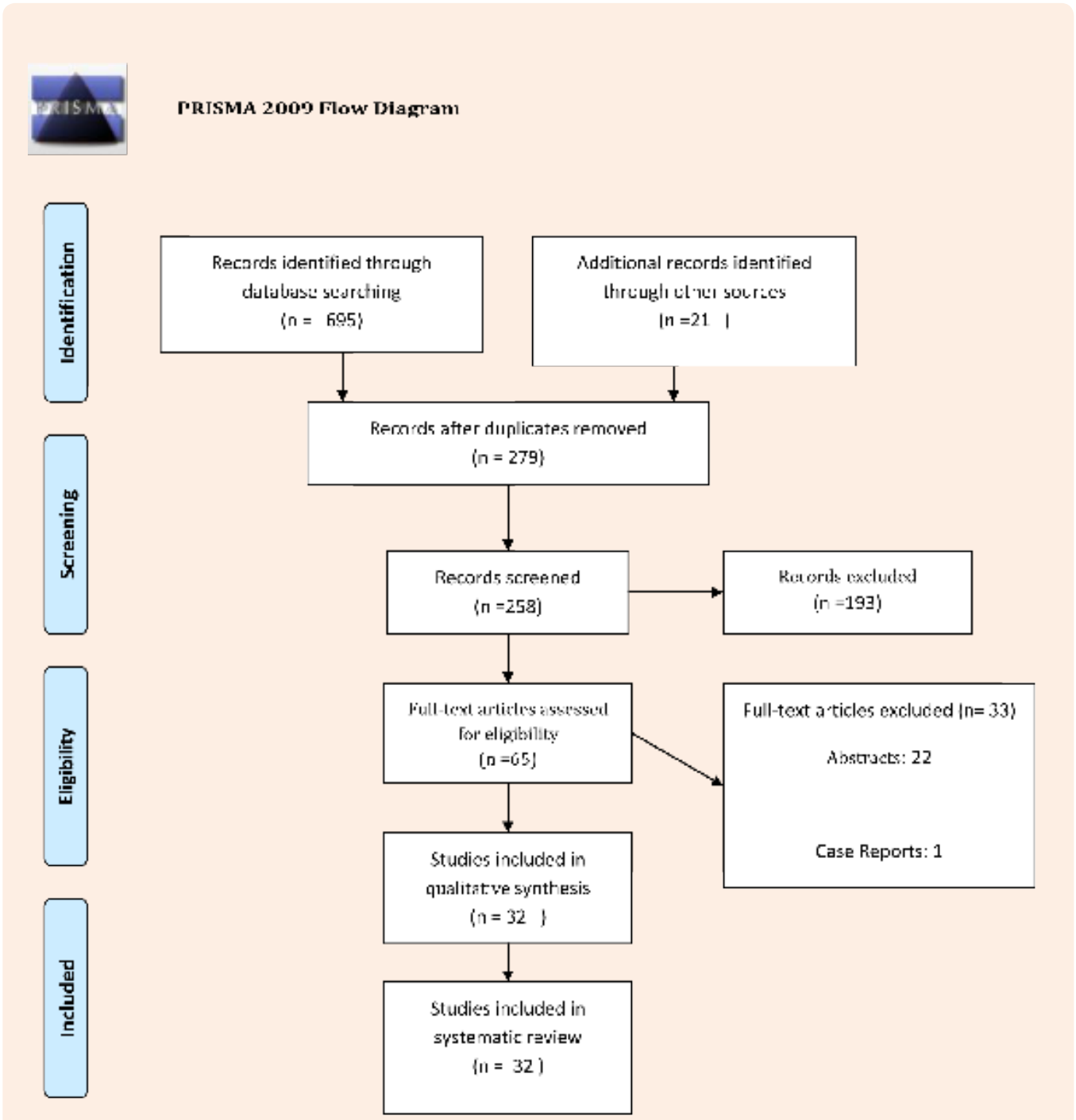

Figure 1: Flow diagram 1.

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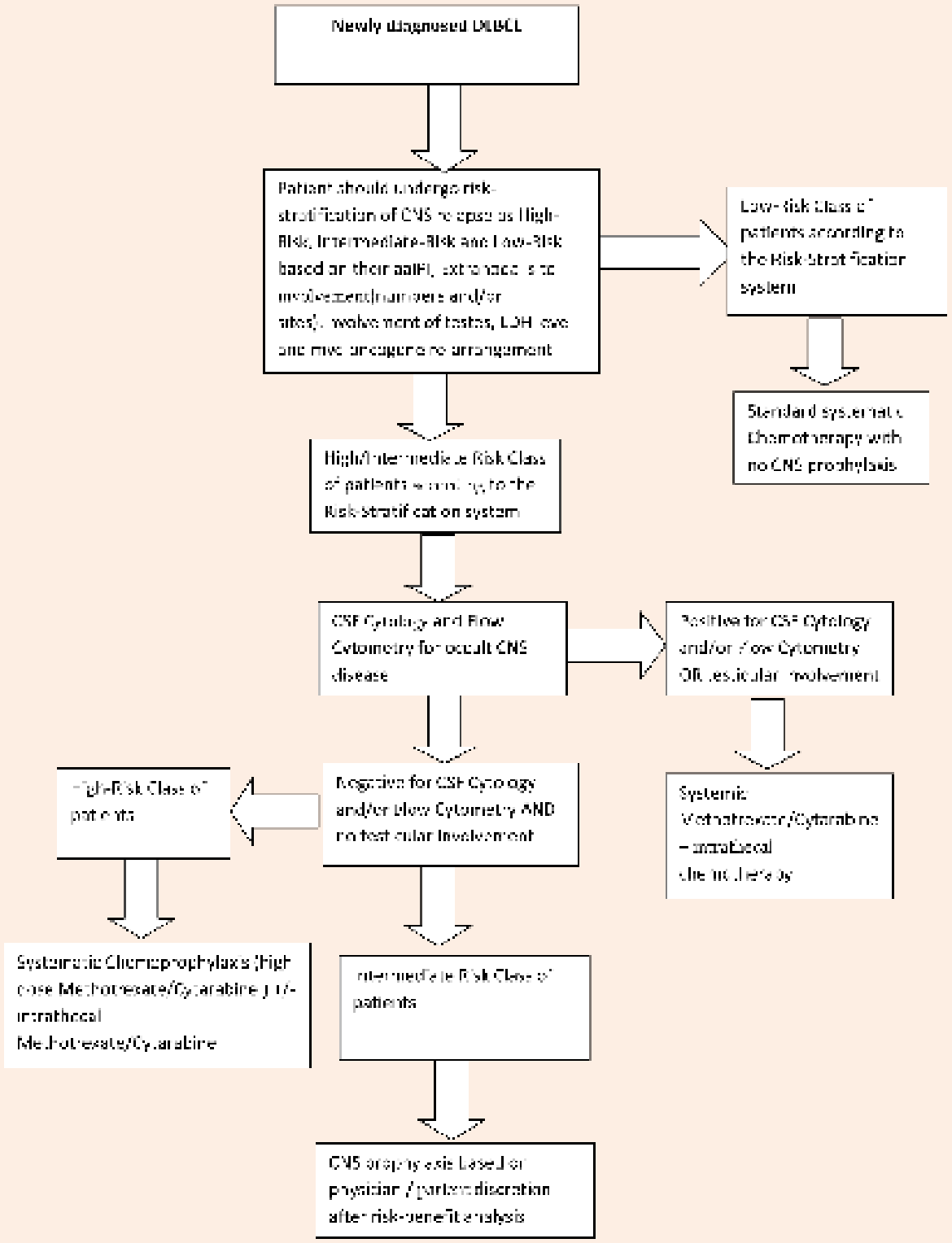

Figure 2: Flow diagram 2.

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