How I treat patients with aggressive lymphoma at high risk of CNS relapse.

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Word count
Abstract: 124
Main body: 3898

Figures: 2
Tables: 1
Reference count: 94
Abstract

Central nervous system (CNS) relapses are an uncommon yet devastating complication of non-Hodgkin lymphomas. The identification of patients at high risk of secondary CNS relapse is therefore paramount. Retrospective data indicate prophylactic CNS-directed therapies may reduce the risk of CNS involvement; however, no consensus exists about dose, timing or route of therapy. In addition, prophylaxis is not without risk of treatment-related complications and morbidity. Here we present a series of case vignettes highlighting our approach to common dilemmas encountered in routine clinical practice. We review the method of assessing CNS relapse risk, factors that increase the likelihood of relapse including histologic subtype, MYC rearrangement, protein expression and extranodal involvement, and review our clinical practice based on available evidence in administering CNS-directed prophylaxis.
Introduction

Non-Hodgkin lymphomas (NHL) are biologically and clinically diverse hematological malignancies. Treatment is influenced by patient fitness, disease biology and tumor burden. Identifying patients at high-risk of CNS relapse is important as the outcome of secondary CNS lymphoma is poor. Risk of CNS progression is influenced by histologic subtype and subtype specific clinicopathologic features (e.g. site of involvement, protein expression or gene rearrangements). Patients with highly aggressive lymphomas (e.g. lymphoblastic, Burkitt lymphoma) are at high risk and frontline protocols include CNS-directed prophylaxis. In contrast, indolent lymphomas rarely involve the CNS and CNS prophylaxis is not required. Between these extremes fall diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma with MYC and BCL2 or BCL6 rearrangements, so-called “double hit” lymphomas (HGBL-DH) and (nodal) peripheral T-cell lymphomas (PTCL). The addition of rituximab has slightly reduced CNS relapse in DLBCL, probably through superior systemic control as there is negligible CNS penetration of the drug across the intact blood-brain barrier. However, ~4% of unselected patients with DLBCL treated with R-CHOP (prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab) experience CNS relapse and considerable efforts have been made to identify those at greatest risk. In this review, we will summarize our approach to this problem with case vignettes drawn from our practice.

How I identify patients at increased risk for CNS relapse

Many investigators have examined risk factors for CNS relapse, but studies have yielded inconsistent results, due to heterogeneity in patient populations, treatment and/or limited sample size. To address some of these limitations, Schmitz et al developed a six-point score from 2164 patients treated on prospective German studies and validated in 1597 patients with DLBCL treated with R-CHOP in the British Columbia Cancer Agency (BCCA) lymphoid malignancies database. The components of the score were the International Prognostic Index (IPI) factors: age >60, elevated serum lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) status >1, stage III/IV, >1 extranodal site, with the addition of kidney/adrenal involvement. The resulting “CNS-IPI” separates patients into low (0-1 factor), intermediate (2-3) and high (4+) risk groups with 2-year CNS relapse rates of 0.6%, 3.4% and 10.2% respectively. This provides a robust and readily calculable risk estimate in patients with DLBCL which has been externally validated in another independent cohort of 1532 patients with similar results. Despite its strengths, it remains imperfect with low positive predictive value (10-12%). Thus, if used to select patients for prophylaxis, most patients unnecessarily receive CNS prophylaxis. Other factors including the involvement of other specific anatomic sites and biologic factors have been identified in separate studies as predictive of CNS relapse and warrant specific consideration. A summary of the factors we consider when assessing CNS risk are presented in Table 1.

Case 1

Presentation

A 78 year-old retired nurse presented with hematemesis. At endoscopy a gastric tumor was biopsied and showed non-GCB (germinal centre B-cell) DLBCL (by Hans algorithm). A staging positron emission tomography with computed tomography (PET-CT) scan identified widespread lymphadenopathy and involvement of the adrenal glands, kidneys and bone. She did not have signs or symptoms suggestive of CNS involvement. Her ECOG was 2 and LDH elevated (IPI=5, CNS-IPI=6). Examination of the blood film and peripheral blood lymphocyte immunophenotyping excluded circulating lymphoma cells. Cerebrospinal fluid (CSF) cytology (CC) and flow cytometry (FCM) was negative for lymphoma.
Discussion
The decision to offer CNS prophylaxis to this patient was straightforward. Her predicted 2-
year CNS risk of 10.2% using the CNS-IPI model is likely an underestimate. In fact, for the
0.6% of patients with the maximum CNS-IPI score of 6, the 2-year risk of CNS relapse was
32.5%.6 We always send CSF for CC and FCM as the use of FCM increases the sensitivity
of detecting lymphoma in this compartment.18 Occult leptomeningeal disease (CC-/FCM+) is
associated with markedly increased risk of frank CNS progression and warrants aggressive
CNS directed therapy.19,20

Outcome
We commenced pre-phase prednisone followed by R-CHOP21 for 6 cycles with one dose of
intrathecal methotrexate (IT MTX) per cycle. In addition, two cycles of systemic MTX were
administered (with rituximab, total of 8 doses) at a reduced dose of 1g/m² due to her age.
She achieved complete metabolic response (CMR) at the end of treatment, but unfortunately
experienced nodal disease relapse with B symptoms, retroperitoneal and mediastinal
lymphadenopathy 9 months later. Her disease was refractory to second-line chemotherapy.
She was offered participation in a clinical trial and remains on study with stable disease after
4 months on the investigational agent.

Case 2
Presentation
A 45 year old female lawyer presented with a painless right breast lump and subsequently
underwent a core biopsy. Histopathology confirmed DLBCL with non-GCB phenotype (by
Hans Algorithm). The contralateral breast was normal by clinical examination and
ultrasound; PET-CT confirmed ipsilateral breast involvement only (stage IAE or primary
breast lymphoma). Her ECOG status was 0, LDH normal (IPI=0 and CNS-IPI=0).

Discussion
Certain anatomic sites of extranodal involvement of DLBCL are strongly associated with
CNS relapse, even when the CNS-IPI is low.21 While the kidney/adrenals were independent
predictors in the CNS-IPI, extranodal sites identified in other datasets (epidural, breast,
uterus and testes) were not. This is probably explained by under-representation of such
patients from prospective studies. For instance, many patients with epidural involvement
require emergent radiotherapy to treat impending spinal cord compression precluding clinical
trial participation, and patients with stage IE lymphomas are excluded from many protocols.
The propensity for primary testicular lymphoma to disseminate to the CNS is well
described;22,24 a specific treatment protocol was shown in a prospective phase II study to
result in an apparent reduction in CNS risk relative to historic controls.25 In contrast, the
association between primary breast lymphoma and CNS relapse is under appreciated,
despite data suggesting crude incidence of 12-16%.26-28 Stage IIE disease,26 stage modified
IPI ≥2,26 bilateral breast involvement29 and tumor >5cm30 have all been observed in
individual studies to be potential risk factors for CNS involvement, but the findings have not
been consistently replicated. Epidural involvement was associated with increased CNS risk
in pre-rituximab case series,31-34 however contemporary data are lacking. Sinus involvement
was associated with marginally increased CNS risk (6% in the pre-rituximab era) which was
reduced to 1.6% when rituximab is incorporated into primary therapy.35,36 El-Galaly et al
identified a strong association between uterine (but not ovarian) involvement with DLBCL
and CNS risk (hazard ratio 14.1) by multivariate analysis, independent of the CNS-IPI.37 We
offer patients with breast, uterine, testicular and epidural involvement CNS prophylaxis,
irrespective of their CNS-IPI.
Outcome
Despite the CNS-IPI of 0, we treated this patient with six cycles of R-CHOP21 with IT MTX and two cycles of high dose methotrexate (HD-MTX, 3g/m²). Consolidative radiotherapy was delivered to the ipsilateral breast and she remains in ongoing remission 4 years from initial presentation.

Case 3
Presentation
A 68-year-old retired truck driver with comorbidities including chronic obstructive pulmonary disease, ischemic cardiomyopathy (ejection fraction 35%) presented with asymptomatic lymphadenopathy. Biopsy showed both grade 3B follicular and DLBCL in the same specimen. PET-CT identified widespread lymphadenopathy with bone marrow the only apparent site of extranodal involvement. He had no antecedent history of indolent lymphoma. The ECOG was 0 and LDH normal. He therefore had stage IVA composite lymphoma (IPI=2, CNS-IPI=2). However, fluorescence in-situ hybridization (FISH) confirmed rearrangements in MYC, BCL2 and BCL6 i.e. "triple-hit" lymphoma. CSF was negative for lymphoma (CC-/FCM-).

Discussion
MYC rearranged non-Burkitt lymphomas have aggressive behavior and poor outcomes with R-CHOP.38 Aggressive lymphomas bearing rearrangements in MYC and BCL2 and/or BCL6 were previously termed “double hit” (DHL) or “triple hit” lymphomas with a spectrum in morphology from DLBCL to Burkitt lymphoma. In the WHO 2008 classification many were captured under the provisional entity of “B-cell lymphoma, unclassifiable (BCL-U), with features intermediate between DLCL and Burkitt lymphoma”.39 In the 2017 update, all aggressive lymphomas (except those with lymphoblastic or follicular lymphoma morphology) bearing rearrangements in MYC and BCL2 and/or BCL6 were reclassified as “high grade B-cell lymphoma, with MYC and/or BCL2 or BCL6 rearrangements” (HGBL-DH). While early studies of patients with DLBCL bearing MYC and/or BCL2 rearrangements indicated markedly increased risk of CNS involvement at diagnosis of up to 44%,40,41 two larger retrospective studies indicated 4-7% of patients had CNS involvement at diagnosis with a 3-year cumulative CNS risk of 13%.42,43 Both studies also suggested use of CNS prophylaxis may improve outcomes: in the first, IT MTX prophylaxis was associated with a reduction in CNS progression (3 year incidence 5% v 15%, P=0.017);42 in the second, use of CNS prophylaxis was associated with improvement in overall survival.43 We therefore consider HGBL-DH at high risk of CNS involvement and consider these patients for CNS directed prophylaxis. The 2017 WHO categories of HGBL-DH and high grade B-cell lymphoma, not otherwise specified (HGBL, NOS) have created difficulty in applying evidence from older datasets (based on the superceded BCL-U). We are unaware of specific data examining the risk of CNS progression in HGBL-NOS (i.e without MYC translocations). However, we continue to recommend CNS prophylaxis patients with HGBL-NOS based on the increased risk observed in BCL-U and Burkitt lymphoma, and that in retrospective series, many patients with BCL-U morphology presented with IPI 3-5 even in the absence of MYC translocations.44,45. However, this issue clearly warrants further studied in larger datasets with central pathology review.

Outcome
We favor dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R) for fit patients with HGBL-DH based on retrospective42,43,46 and prospective data.47 However, given substantial comorbidities including cardiac dysfunction, we used 6 cycles of R-CEOP (anthracycline substituted for etoposide). We administered IT MTX 12mg with each cycle of the first 4 cycles of chemo-immunotherapy. After the fourth cycle, he developed severe post lumbar puncture (LP) headache
unresponsive to simple analgesia and caffeine. As all CSF assessments had been negative, further IT prophylaxis was abandoned. On completion of chemo-immunotherapy, two cycles of HD-MTX (3g/m²) in addition with rituximab (to complete 8 doses), the end of treatment PET-CT demonstrated a “near” CMR (Deauville 3, with residual low grade uptake at a periportal node unsafe to rebiopsy). The node remains unchanged in size and avidity 3 months later and he remains in clinical remission at 8 months follow-up.

Case 4
Presentation
This 67-year-old male office worker presented with abdominal discomfort, night sweats and hypercalcemia. CT-guided core biopsy of retroperitoneal lymphadenopathy showed DLBCL with non-GCB phenotype (by Hans Algorithm) - cells expressed both MYC (70%) and BCL2 (60%) by immunohistochemistry. MYC-FISH was negative. PET-CT revealed extensive nodal disease and involvement of the liver, multiple bone lesions and muscle. CSF analysis was negative. His stage was IVB, ECOG 0 and serum LDH (surprisingly) not elevated (IPI=3, CNS-IPI=3).

Discussion
Although not fulfilling CNS-IPI criteria for high-risk, we assessed the patient to be at high-risk of CNS relapse for two reasons. Firstly, data from Vancouver suggest MYC and BCL2 protein dual expressers (DE) are at increased risk of CNS relapse. Savage et al examined the correlation between DE status, cell-of-origin (COO; Lymph2Cx nanostring48 and Hans algorithm) and CNS relapse in 428 patients with de novo DLBCL treated with R-CHOP (largely without CNS prophylaxis).46 DE patients were more likely to experience CNS relapse than non-DE (2-year CNS relapse risk 9.7 v 2.2%, P=0.001). Activated B-cell (ABC) COO was also associated with increased CNS relapse risk (9.4 v 2.2%, P=0.02). However, by multivariate analysis only DE status (hazard ratio 3.68) and CNS-IPI (hazard ratio 5.21) remained significant predictors of CNS relapse.49 Patients whose tumors were both DE and ABC COO had a 2-year CNS relapse risk of 15.3%. The study was important as DE account for around 30% of DLBCL (around six times more frequent than MYC/BCL2 rearranged lymphomas38,50,51 and around two-thirds of DE are ABC COO. In contrast, HGBL-DH typically arise in tumors with GCB phenotype, acknowledging that COO nomenclature is limited to pure cases of DLBCL in the revised 2017 WHO category.52-54

The second reason we would have administered CNS prophylaxis independent of DE status is the involvement of 3 extranodal sites on PET-CT. El-Galaly et al studied an independent cohort of 1532 DLBCL patients staged with PET-CT and treated with R-CHOP21 (or similar) and observed a striking correlation between the absolute number of extranodal sites and risk of CNS progression.7 Multiple areas of involvement within one organ or tissue (e.g. multifocal bone involvement) only counted for one site. Patients with ≥3 extranodal sites comprised 9.5% of the cohort and had a 2 year CNS relapse risk of 15.2% (Figure 1B). The authors explored the “≥3 extranodal sites” model further, and compared with the CNS-IPI, it identified fewer patients as high risk (9.5% vs 19.2%, P=0.005) and as a result was less sensitive (35.5% vs 55.7%, P<0.001), more specific (91.7 v 82.3%, P=0.001) and more accurate (89.4 v 81.2%, P<0.001), but had similar positive predictive value (15.3 vs 11.2%, P=0.1). Whilst both models offer an excellent negative predictive value (~97%) the ≥3 extranodal sites model has the potential advantages of being easier to remember and resulting in fewer patients being exposed to CNS prophylaxis (at the cost of decreased sensitivity). The model should be validated in an external cohort, however at present we consider patients with ≥3 extranodal sites for CNS prophylaxis even if they are not “high risk” by CNS-IPI.
Outcome
Based on DE status and involvement of ≥3 extranodal sites, we estimated his 2-year risk of CNS relapse to be ~15% despite the CNS-IPI score of 3 (intermediate). We commenced treatment with DA-EPOCH-R with one dose of IT MTX per cycle, followed by two cycles of systemic MTX following the completion of chemo-immunotherapy. End of treatment PET-CT demonstrated CMR and remains in remission 16 months after completion of therapy. We should highlight that in contrast to DHL, there are fewer data supporting DA-EPOCH-R in DE lymphoma. A small retrospective series from MD Anderson Cancer Center (MDACC) suggested a potential benefit, however, this remains to be confirmed in larger, prospective series. Further, overall results from the CALGB 50303 study (the only phase III randomized comparison of R-CHOP vs DA-EPOCH-R) was negative for cohort overall, although results from biologic subgroups including COO, DE and DHL are awaited.

Case 5
Presentation
A 32-year-old engineer presented with widespread lymphadenopathy and fevers. Biopsy showed anaplastic lymphoma kinase (ALK) positive anaplastic large cell lymphoma (ALCL). PET-CT identified involvement of the liver, spleen and multifocal bone lesions. This patient had stage IVB disease, ECOG 1, elevated LDH (IPI=3, CNS-IPI=3). Treatment with cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone (CHOEP) was commenced at another institution. He attended our institution for a second opinion after completing the first cycle of therapy.

Discussion
Applying the CNS-IPI (derived largely from patients with DLBCL) the risk would be intermediate (~3%), not warranting CNS directed prophylaxis. However, investigators have studied PTCL separate from DLBCL to better refine risk factors for CNS involvement. Ellin et al reported 28/625 (4.5%) patients with PTCL in a Swedish population-based study developed CNS relapse with >1 extranodal site, skin and gastrointestinal involvement associated with CNS risk by multivariate analysis. Yi et al identified elevated LDH and paranasal sinus involvement as associated with CNS relapse. In both studies, all PTCL subtypes were considered together to derive risk factors. Of specific relevance to this patient, Chihara et al analysed CNS risk according to PTCL subtype in 616 patients treated at MDACC - among 76 patients with ALK positive ALCL, the 5-year risk of CNS relapse was 5.3%; however among ALK positive ALCL and >1 one extranodal site the 1-year CNS relapse was 15%. Due to the rarity and heterogeneity of PTCL, interpretation of these studies presents a challenge, but the involvement of multiple extranodal sites appears a recurrent risk factor. Therefore, for this patient with ALK positive ALCL and two extranodal sites (liver and bone – we do not consider spleen to be extranodal for the purposes of determining CNS risk) we estimated the 1-year CNS risk for this patient to be 15%.

Mantle cell lymphoma (MCL) is another aggressive histologic subtype where the role of CNS prophylaxis remains controversial. Unselected patients with MCL have an estimated CNS relapse rate of 5.4%, with high risk features including Ki-67>30% associated with increased risk (HR 6.03, P=0.003). There are limited data supporting a role for CNS prophylaxis. Outside of clinical trials, in transplant-eligible patients we use high-dose cytarabine-based induction followed by autologous stem cell transplant; in elderly patients, we use bendamustine-rituximab, but we do not specifically add CNS directed prophylaxis in either setting. However, most patients with MCL at our institution are offered participation in investigational protocols incorporating Bruton’s tyrosine kinase (BTK) inhibitors; there are data suggesting the first-in-class agent, ibrutinib, penetrates the CNS and may be effective in MCL with CNS involvement. We have not observed any CNS relapses in our MCL.
patients treated with BTK inhibitors (unpublished data). However, larger datasets are required to confirm this observation.

Outcome
Although there are scarce data among patients with PTCL, by extrapolation from DLBCL we added IT MTX with each cycle of chemotherapy followed by two cycles of systemic MTX at the completion of CHOEP. This patient achieved a CMR at the completion of therapy and remains in remission at 12 months follow-up.

How I deliver CNS prophylaxis
The optimal method for administration of CNS-directed prophylaxis is unknown. Even among high-risk patients, only a minority develop CNS recurrence making adequately powered prospective randomized studies to address this question challenging. The regimen we have outlined above is adapted from an approach developed at Peter MacCallum Cancer Centre, Melbourne, Australia. IT MTX is administered once per chemo-immunotherapy cycle (total of 6). Three to four weeks after the completion of chemo-immunotherapy, two cycles of systemic MTX are administered, 2-3 weeks apart. We discontinue medications that may interfere with MTX clearance (e.g. cotrimoxazole, proton pump inhibitors) at least 3 days prior to admission for intravenous MTX. We admit patients the afternoon before scheduled MTX and alkalinate the urine with intravenous fluids containing sodium bicarbonate, with careful attention to clinical assessment of fluid status (weighing patients twice daily) and using diuretics as needed to prevent fluid overload. We administer MTX at a target dose of 3g/m² over 4 hours with leucovorin rescue commencing 24 hours later. In patients with mild to moderate renal impairment, or those aged >70 we reduce the dose of intravenous MTX to 1.5g/m².

IT MTX as CNS prophylaxis in aggressive lymphoma was extrapolated from acute lymphoblastic leukaemia, where CNS recurrence is usually leptomeningeal. In contrast, CNS relapse in DLBCL usually has a parenchymal component and the limited ability of cytotoxic drugs administered by IT injection to penetrate into deep brain tissue is problematic, with data suggesting minimal impact on CNS progression. Systemic therapy with CNS penetration is therefore paramount and an essential component for all prophylactic regimens. Systemic high-dose MTX achieves tumoricidal levels in brain parenchyma at doses ≥1g/m² and leptomeningeal penetration at doses ≥3g/m². A French randomized study (pre-rituximab) compared ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone with a consolidation phase containing etoposide, ifosfamide, cytarabine, 4 doses of IT MTX and 2 cycles of systemic MTX (3g/m²)) with CHOP (which contained no CNS prophylaxis). The CNS relapse rate was lower in the arm treated with IT and IV MTX (2.7% vs. 8%, P=0.02), acknowledging that other CNS-penetrating agents were used in the MTX arm. Several subsequent retrospective and two prospective studies also support a potential benefit for high-dose systemic MTX in this setting. However, these studies are limited by small numbers, non-randomised and retrospective study designs, with the prospective studies using other CNS penetrating agents in combination with MTX. There remains lack of consensus regarding systemic MTX dosing regimen, number of cycles and whether IT prophylaxis has any role or not. No randomised study exists to show that IT prophylaxis is effective, with only small retrospective, single-arm or non-randomised studies in combination with systemic therapy providing limited evidence for a reduction in CNS risk. Given that 20% of CNS progression occurs during primary therapy, delaying all CNS directed measures until completion of chemo-immunotherapy is too late. Accordingly, some groups are using systemic MTX either before chemo-immunotherapy or intercalated between cycles. While this is entirely rational with regard to prevention of early CNS progression, high-dose systemic MTX can be associated with toxicity, most notably renal impairment, which occurs in up to 9% of cycles. This could potentially interrupt the primary (curative intent) chemo-immunotherapy.
the quality of data supporting these approaches are suboptimal and prospective studies should guide the ideal strategy.

It is noteworthy that several groups have explored dose-intensified regimens for younger patients with DLBCL and poor prognostic features in non-randomized studies. Dunleavy et al used DA-EPOCH-R with IT MTX as the sole form of CNS prophylaxis in 52 patients with aggressive MYC rearranged B-cell lymphoma, 65% with IPI≥3. To date, no CNS progressions have occurred, though final results are awaited (personal communication, K Dunleavy). The numbers of patients treated remain relatively small, though the CNS progression rate in the phase II study using the same regimen in low risk Burkitt lymphoma appeared to prevent CNS relapse. In contrast, investigators from Chicago retrospectively examined 117 patients with DLBCL treated with DA-EPOCH-R, 62 of whom received IT MTX and 55 of whom did not. The crude incidence of CNS relapse was 7/117 (6%) and IT MTX did not appear to be associated with reduction in risk. Limitations of retrospective design notwithstanding, these data highlight CNS progression in patients receiving DA-EPOCH-R and IT MTX can occur. When we use DA-EPOCH-R, if CNS prophylaxis is indicated, we add two cycles of high-dose intravenous MTX after the last cycle of chemo-immunotherapy, as in case 4. This shares some similarities with the Nordic approach. Holte et al used dose-dense R-CHOEP14 followed by intensification with high-dose cytarabine and high-dose MTX in 156 patients with DLBCL aged 18-65 with age adjusted IPI 2-3. Apart from one dose of IT MTX on baseline LP, IT chemotherapy prophylaxis was not given. CNS relapses occurred in 7 (4.4%) patients, all within 6 months of study entry, again highlighting the need to provide some form of prophylaxis early during treatment. Finally, Phillips et al reported CNS outcomes from the United Kingdom National Cancer Research Institute phase II study of R-CODOXM-R-IVAC in intermediate-high risk DLBCL. Among the 55 patients with high-risk CNS-IPI the 2-year CNS relapse rate was lower than expected at 6.2%. This observation suggest a potential benefit from the early inclusion of high-dose MTX employed in this regimen, however confirmation of this finding in larger, randomized studies is needed.

Conclusion and future directions

Although the case vignettes detailing our approach to CNS prophylaxis have been successful, it is important to acknowledge that failures may still occur. This highlights the need to for further studies to both better identify high-risk patients and better prophylactic strategies. Novel agents such as ibrutinib and lenalidomide cross the blood-brain barrier and are active in both systemic ABC DLBCL and CNS lymphomas. In a recent pooled analysis of two prospective studies using R-CHOP + lenalidomide (R2-CHOP) in 136 patients (18% CNS-IPE≥4) with a median follow-up of 48 months, only one patient (0.7%) developed isolated CNS relapse despite minimal use of CNS prophylaxis with IT (15%) or intravenous (0%) MTX. Randomized phase III studies comparing R-CHOP ± ibrutinib (NCT01855750) and R-CHOP ± lenalidomide (NCT01856192; NCT02285062) in DLBCL will hopefully answer whether these agents can replace existing CNS prophylactic strategies. Until then, we suggest careful assessment for CNS recurrence be integrated into routine therapeutic decision making for patients with aggressive lymphomas.

Acknowledgements

CYC wishes to acknowledge the mentorship of Professor John Seymour over many years, particularly in relation to the subject of this review.

Authorship

CKC performed the literature review and wrote the first draft of the manuscript.
CYC designed the paper, reviewed and co-wrote the manuscript.

Disclosures
CKC – no conflicts of interest
CYC - Research funding: Celgene, Roche; Speakers Bureau: Roche, Janssen-Cilag, Takeda; Advisory Board member: Janssen-Cilag, Bristol Myers Squibb; Travel expenses: Bristol Myers Squibb.
Figures

**Figure 1.** Cumulative incidence of CNS relapse among 1532 patients with diffuse large B-cell lymphoma treated with R-CHOP-like regimens according to CNS-IPI (left) and number of extranodal sites determined by PET-CT (right). Reproduced from El-Galaly et al with permission.⁷
Figure 2. Specific extranodal sites associated with increased risk of CNS relapse.
<table>
<thead>
<tr>
<th>Histologic subtype</th>
<th>Histologic subtype specific risk factors</th>
<th>approximate CNS relapse risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DLBCL</strong></td>
<td>CNS-IPI ≥ 4[^1] or involvement of breast[^2], testis[^3], uterus[^7], epidural[^9,90], kidney/adrenals[^16,88]</td>
<td>10% at 2 years varies by site</td>
</tr>
<tr>
<td></td>
<td>MYC/BCL2 dual-expressing DLBCL, particularly if ABC subtype[^49]</td>
<td>10% at 2 years (15% if ABC cell of origin)</td>
</tr>
<tr>
<td></td>
<td>CD5 positive DLBCL[^91]</td>
<td>12.7% at 2 years</td>
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<tr>
<td></td>
<td>intravascular large B-cell lymphoma[^92]</td>
<td>25% at 3 years</td>
</tr>
<tr>
<td></td>
<td>IgM secreting DLBCL[^93]</td>
<td>41% cumulative incidence (7 out of 17)</td>
</tr>
<tr>
<td><strong>HGBL with MYC and BCL2 and/or BCL6 rearrangements[^42]</strong></td>
<td>-</td>
<td>13% at 3 years</td>
</tr>
<tr>
<td><strong>MCL</strong></td>
<td>blastoid histology or Ki-67 ≥ 30%[^94]</td>
<td>25.4% at 2 years</td>
</tr>
<tr>
<td><strong>PTCL (PTCL-NOS, AITL, ALCL)</strong></td>
<td>&gt;1 extranodal site, skin or gastrointestinal involvement[^97]</td>
<td>~10% at 2 years</td>
</tr>
<tr>
<td><strong>ALK positive ALCL</strong></td>
<td>&gt;1 extranodal site[^99]</td>
<td>1-year 15%</td>
</tr>
</tbody>
</table>

References


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