Guideline on the prevention of secondary central nervous system lymphoma: British Committee for Standards in Haematology

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Summary

The guideline group was selected to be representative of UK-based medical experts. Ovid MEDLINE, EMBASE and NCBI Pubmed were searched systematically for publications in English from 1980 to 2012 using the MeSH subheading ‘lymphoma, CNS’, ‘lymphoma, central nervous system’, ‘lymphoma, high grade’, ‘lymphoma, Burkitt’s’, ‘lymphoma, lymphoblastic’ and ‘lymphoma, diffuse large B cell’ as keywords, as well as all subheadings. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haematono-oncology Task Force of the British Committee for Standards in Haematology (BCSH). The guideline was then reviewed by a sounding board of ~50 UK haematologists, the BCSH and the British Society for Haematology (BSH) Committee and comments incorporated where appropriate. The ‘GRADE’ system was used to quote levels and grades of evidence, details of which can be found in Appendix I. The objective of this guideline is to provide healthcare professionals with clear guidance on the optimal prevention of secondary central nervous system (CNS) lymphoma. The guidance may not be appropriate to patients of all lymphoma sub-types and in all cases individual patient circumstances may dictate an alternative approach. Acronyms are defined at time of first use.

Keywords: non-Hodgkin lymphoma, central nervous system, chemotherapy, intrathecal, methotrexate.

Introduction

The outcome of secondary central nervous system (CNS) involvement by lymphoma is very poor (Mead et al, 1986; Zinzani et al, 1999; Doolittle et al, 2008), therefore the administration of preventative treatment during first line therapy to reduce the incidence of CNS relapse is a logical management strategy, if a reasonable outcome is to be achieved for those patients at risk. The most significant change in management of diffuse large B-cell lymphoma (DLBCL) in the last 20 years has been the advent of immunochemyotherapy, with the addition of rituximab to standard chemotherapy (Coiffier et al, 2002; Pfreundschuh et al, 2006) and it is necessary to consider evidence both prior to and, more importantly, subsequent to this major change. Immunochemyotherapy has significantly improved outcome, and with this the incidence of CNS relapse appears to have decreased (Boehme et al, 2009) although this has not been detected in all reports (Feugier et al, 2004). Further studies on this are discussed below. This observation supports the hypothesis that CNS relapse is more likely to occur if there is failure of control of systemic disease.

The key issue is the identification of those patients who are, with current treatment, sufficiently at risk to benefit from this CNS-directed therapy. There is, however, a paucity of good quality evidence on which to base decisions. Review articles (McMillan, 2005; Montoto & Lister, 2005) reached relatively similar conclusions about which patients were at risk. It should be noted that some authors (Bos et al, 1998) have taken the view that no patient group can be identified where CNS prophylaxis is justified. The aim of this guideline is to review the available evidence to make recommendations for the appropriate management of these patients. It is important to note that this guideline has been prepared with consideration of the service requirements that the recommendations will generate; both in terms of intrathecal (IT) therapy and also the inpatient stays required for the delivery of high dose methotrexate (HD-MTX) with folinic acid rescue.
Lymphoma subtypes

Burkitt lymphoma (BL) and lymphoblastic lymphoma (LBL)

There is universal acceptance that all patients with these two histological subtypes must be treated according to specific established protocols, which include CNS-directed therapy. In the UK in most instances this will be R-CODOX-M (rituximab, cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate)/R-IVAC (rituximab, ifosfamide, etoposide, high-dose cytarabine) for BL and either the UK acute lymphoblastic leukaemia (ALL) 2011 (<25 years) or the UKALL14 schedule (≥25 years) for LBL. No randomized studies are available with current ALL treatment schedules but the risks of omission of CNS-directed therapy would now be unethICAL as historical case series suggest the risk of CNS relapse to be in excess of 20% if CNS-directed therapy is not given (Hollender et al, 2002).

Low-grade lymphoma (follicular, mantle cell, marginal zone, small lymphocytic)

The incidence of CNS disease in these patients is so low that there is no justification for specific intervention. Although still very rare, and not common enough to require intervention, note should be made that CNS disease is occasionally seen in patients with lymphoplasmacytic lymphoma (Bing-Neel syndrome) and also the blastic subtype of mantle cell lymphoma (MCL). The BSCH Haemat-Oncology task force has produced guidelines on the management of MCL (McKay et al, 2012). It is notable that high-dose (HD) cytarabine (Ara-C) is included in the MCL2 regimen (Geisler et al, 2012), which will deliver active therapy to the CNS when utilized.

Aggressive lymphoma

Most of the following guidance is intended for patients with DLBCL, and for the purpose of this guideline this would include cases of primary mediastinal large B-cell lymphoma and high-grade transformation of follicular lymphoma (FL). There is no evidence to suggest that these subtypes require a different approach from the generality of DLBCL. In addition, aggressive T-cell non-Hodgkin lymphoma (NHL), including peripheral T-cell lymphoma not otherwise specified, anaplastic large cell lymphoma (ALCL) (whetherALK-positive or -negative), angioimmunoblastic T-cell lymphoma (AITL) and enteropathy-associated T-cell lymphoma (EATL), should be managed in the same manner although there are insufficient data to individually substantiate this strategy due to the rarity of these diagnoses (Dearden et al, 2011). There are insufficient data to determine whether patients seropositive for human immunodeficiency virus (HIV) have a higher risk of CNS relapse independent of other criteria and thus such patients should be given CNS prophylaxis according to the same criteria as HIV-negative patients.

What is the risk, and which patients are at risk of CNS relapse after first-line therapy?

Firstly, an assessment of the overall risk needs to be made; two Groupe d’Etude des Lymphomes de l’Adulte (GELA) studies that included patients not receiving any prophylaxis reported a risk of CNS relapse of 8% (Tilly et al, 2003) and 5% (Feugier et al, 2004). The latter study included 50% CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) – and 50% R-CHOP (CHOP + rituximab)-treated patients. Hollender et al (2002) reported an overall incidence of CNS relapse of 5-2%, but a proportion of high risk patients were given IT therapy in the second half of the long time period studied. The current clinical consensus is that, at these levels of risk, the application of universal CNS prophylaxis is unjustified and subgroups of patients at higher risk need to be identified.

It is acknowledged that ~50% of those patients who subsequently relapse in the CNS do not fall into pre-identified risk groups (van Besien et al, 1998) and cannot currently be separated from other patients with a predicted good outcome. If CNS-directed therapy were to be offered to a wider group of patients at diagnosis, more patients who would never go on to have a CNS relapse would become included in the group receiving potentially unnecessary CNS therapy and greater demands on service requirements would be placed on clinical teams.

Effect of inclusion of rituximab in primary therapy

As has already been described, an analysis of the pivotal GELA study comparing CHOP versus R-CHOP in elderly patients showed that the addition of rituximab had no significant impact on the risk of CNS recurrence (Feugier et al, 2004). This finding is compatible with the low levels of rituximab detected in the cerebrospinal fluid (CSF) after intravenous (IV) administration (0-1% of serum levels) (Rubenstein et al, 2003). Indeed, the majority of CNS relapses occur in the context of a systemic relapse of disease (Hollender et al, 2002). However, retrospective analysis which reviewed data from the Deutsche Studiengruppe Hochmaligne Non-Hodgkin-Lymphome (DSHNHL) RICOVER -60 protocol showed a reduction in CNS relapse in patients who received rituximab (2-year risk of CNS relapse in the CHOP-14 arm was 6-9% vs. 4-1% in the R-CHOP-14 (P = 0.046) (Boehme et al, 2009). Although two recent studies including R-CHOP-treated patients (Yamamoto et al, 2010; Tai et al, 2011) reported no difference after the introduction of rituximab, both of these studies were approximately one-third of the size of the DSHNHL study, and also the second of these included IT therapy in selected patients judged to be at high risk.
Other published studies on this issue have shown a decrease in the incidence of CNS relapse with the addition of rituximab. A single-centre study from Okayama (Shimazu et al, 2009) reported benefit of rituximab in a 403-patient study. The British Columbia Cancer Agency (BCCA) analysed the risk of CNS relapse in patients treated with R-CHOP in comparison with a historical population treated with CHOP (Villa et al, 2010). The 3-year CNS relapse risk was 6.4% and 9.7% for patients receiving R-CHOP and CHOP respectively (P = 0.085), with a significant reduction in the CNS relapse risk for patients treated with R-CHOP when only those patients that had achieved a complete remission were considered (2.2% vs. 5.85%, P = 0.009). The authors concluded that the beneficial effect of rituximab might be through eradication of the systemic disease (Villa et al, 2010). Lastly, the Nebraska group reported their experience of over one thousand patients (Mitrovic et al, 2012) together with a careful review of published papers. This report also recorded a significant reduction in CNS relapse in patients treated with rituximab-containing regimens and noted a marked reduction in leptomeningeal disease, such that virtually all CNS relapses observed in patients treated with R-CHOP were parenchymal in nature.

Thus, it can be concluded that the balance of probability favours the hypothesis that the overall risk of CNS relapse has decreased with the addition of rituximab to CHOP chemotherapy. It should be noted that any effect on CNS relapse is not discussed here as a goal of adding rituximab chemotherapy. It should be noted that any effect on CNS relapse is not discussed here as a goal of adding rituximab chemotherapy.

The use of anatomical localization will only allow a minority of patients to be identified for treatment and this will not significantly reduce the overall incidence of CNS relapse. However, there are now a number of reports showing an association between the risk of CNS relapse and advanced stage disease at diagnosis. Three studies (van Besien et al, 1998; Haioun et al, 2000; Hollender et al, 2002) clearly identified the risk of CNS relapse as being associated with advanced stage disease at diagnosis. The conclusions of these papers can be summarized in that patients at risk of CNS disease are most simply identified by various adverse factors included in the International Prognostic Index (IPI) (The International Non-Hodgkin’s Lymphoma Prognostic Factors Project’s, 1993). In practice this is most simply achieved by using the criteria identified by van Besien et al (1998), i.e. the combination of an elevated serum lactate dehydrogenase (LDH; > laboratory normal unique indicator of CNS risk may have arisen prior to the improvement in lymphoma diagnosis, which has allowed the clear separation of BL and LBL from other cases of aggressive NHL because BM involvement is over represented in BL and LBL and both are strongly linked with CNS involvement. In the unusual situation where either of these sites do occur as a solitary extra nodal localization then a precautionary decision to administer CNS therapy might be chosen by the clinician on an individual basis.

Ocular NHL (as distinct from lymphoma of ocular adnexal structures) should be regarded as equivalent to primary CNS lymphoma (PCNSL) and will not be discussed further in this review.

The strongest evidence for individual sites is for primary testicular lymphoma (Fonseca et al, 2000; Zucca et al, 2003), breast lymphoma (Gholam et al, 2003) and disease involving the epidural space (MacKintosh et al, 1982), and all patients in these categories should be regarded as in the high-risk category and offered CNS prophylaxis.

For anatomical sites that are historically perceived to lead to increased risk (i.e. those other than breast, testicle or epidural space), this risk estimate has been based on case series and clinical experience. Overall, the number of cases at these sites is modest and the evidence when balanced against the risk of the therapeutic intervention required does not justify the use of CNS therapy in these groups as has historically been common practice. However, any suspicion of physical encroachment to the CNS should trigger inclusion in the group considered at high risk of CNS relapse, and, in view of the longstanding practice of delivering CNS prophylaxis to NHL of the nasal sinuses, it would be acceptable to use prophylaxis at the treating physician’s discretion as long as the risk of toxicity is low. The level of risk for these patients is further reduced by the overall decrease in CNS relapse since the addition of rituximab to the CHOP regimen.

Defining high-risk groups

High risk of CNS relapse according to anatomical sites of involvement

Historically, many physicians have given CNS-directed chemotherapy to patients with involvement of certain anatomical extra-nodal sites perceived as being associated with a particularly high risk of CNS disease. The content of any list of such sites is rarely consistent but would mostly include: testicular (MacKintosh et al, 1982; Liang et al, 1990; Zucca et al, 1999, 2003; Fonseca et al, 2000), cranial air sinuses (including nasal) (Liang et al, 1990), bone (Cetto et al, 1981; Keldsen et al, 1996), breast (Gholam et al, 2003), renal (Villa et al, 2010) and epidural space (MacKintosh et al, 1982) Bone marrow (BM) and renal involvement rarely occur in isolation and there is insufficient evidence to suggest that involvement of either one of these areas alone as an indication for prophylaxis, though both BM and renal involvement must, necessarily, be recorded as extranodal localizations in the algorithms discussed below. The perception of the adverse significance of BM involvement as a
range) and the presence of involvement of more than one extra-nodal site (van Besien et al, 1998). Both elevated LDH and extra-nodal localization (ENL) are defined as per the IPI. For clarity, it should be noted that the spleen is not regarded as an extra-nodal site – all sites except lymph nodes and spleen are regarded as extra-nodal. Also, two lesions within the same system (e.g. bilateral lung lesions) are regarded as a single extra-nodal localization. ENL is defined by conventional staging and PET if available – there is no requirement for additional biopsy to confirm involvement of the extra-nodal site.

The second of the above studies (Haioun et al, 2000) proposed identifying patients at risk of CNS relapse as those with a poor-risk IPI (IPI 3-5). This produced very similar results to the method reported by van Besien et al (1998), as both LDH and >1 ENL are included in the calculation of IPI score (Haioun et al, 2000). The van Besien method is recommended because it selects fewer patients.

It is clear that patients with these risk factors are not only at risk of CNS relapse but are also at greater risk of systemic failure as well. Therefore these patients, particularly in the context of clinical trials, may be offered more intensive treatment schedules which already include systemic or IT CNS-directed therapy e.g. ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) plus GELA consolidation (Tilly et al, 2003; Recher et al, 2011) or (R)-CODOX M/(R)-IVAC (Mead et al, 2002). If these schedules are successful, as with ACVBP (Recher et al, 2011), then a decrease in both systemic and CNS relapse may be observed simultaneously.

Flow cytometry of CSF
An alternative strategy to attempt to identify patients with a greater risk of CNS relapse has been to use sensitive flow cytometric methods to detect levels of abnormal lymphocytes in the CSF below the usual levels of detection provided by conventional morphological examination of cytospin samples. This was initially proposed by Hegde et al (2005), with the Salamanca group (Alvarez et al, 2012) subsequently developing a storage buffer which allowed longer times to analysis to be tolerated. Storage buffers that prolong the survival of lymphoma cells in vitro are now routinely available. A recent paper (Benevolo et al, 2012) reinforced the promise of the use of flow cytometry however the study was limited by the inclusion of BL and LBL patients. In those patients with DLBCL, only 11 CNS-positive cases were reported, of whom six were CSF flow positive and CSF cytology negative (five being positive for both). Patients with CSF flow positivity appeared more at risk but the numbers are so small that they cannot be used to structure guidance. One of the logical flaws in this approach is that a significant proportion of cases record parenchymal CNS relapse without leptomeningeal disease and it is conceptually hard to understand how these cases could be predicted from CSF flow cytometry.

However, interestingly, all DLBCL CNS relapse in this study was parenchymal even though the CSF was being monitored. At present this strategy cannot be recommended to direct therapy in routine clinical practice but collection and analysis of CSF specimens for flow cytometry and subsequent audit would be highly desirable. Further research is ongoing and it is possible or even probable that this approach may become standard practice in the future.

Summary of decision to offer CNS-directed therapy
With a background incidence of around 5%, there is a wide consensus across many of the above referenced publications that universal CNS-directed therapy is not indicated.

Patients should be carefully informed of the risks and benefits of these therapies.

It is the view of the authors that in the higher risk groups, as defined above, where the risk is ~20% (or one in five as it might be expressed in a patient discussion) that therapeutic intervention is indicated. Any treatment decision is the result of an individual patient/physician discussion but we believe that these recommendations represent a logical treatment choice for patients and have also been formulated with regard to the use of resources required for the delivery of this therapy.

Recommendations
1 CNS-directed therapy should be offered to patients with high-grade NHL AND either:

- A raised [above institutional upper limit of normal (ULN)] serum LDH AND more than one extra-nodal localization (noting that the spleen is not regarded as an extra-nodal site and also, two lesions within the same system (e.g. bilateral lung lesions) are regarded as a single extra-nodal localization).

- OR

- Anatomical sites: Testicular, breast and epidural

(Level of evidence: 1B).

Timing of prophylaxis
A number of studies have suggested that many CNS events occur soon after diagnosis (3–9 months) and a substantial proportion present during therapy or shortly after completion of treatment (Haioun et al, 2000; Feugier et al, 2004; Bjorkholm et al, 2007; Bernstein et al, 2009; Boehme et al, 2009). This suggests that initial CNS involvement may have gone undetected in some cases (see above) but also supports the consensus that any planned prophylactic measures should be adopted early during the treatment course. This is discussed in further detail in Sections 6 and 7 regarding IT and systemic prophylaxis respectively.
Use of intrathecal (IT) prophylaxis

Historically, CNS prophylaxis is most commonly delivered via the IT route (Cheung et al, 2005), targeting particularly the leptomeningeal compartment. It has been suggested that this may be less appropriate in the rituximab era where parenchymal relapses are relatively more common (Shimazu et al, 2009; Villa et al, 2010), however no evidence is yet available to support a routine change in management. A number of drugs including MTX, Ara-C (including sustained release form), hydrocortisone and rituximab can be administered intrathecally. There are insufficient long-term toxicity data to support the use of sustained release Ara-C in the prophylactic setting and it should be noted that this is not a licenced indication. There are data to suggest efficacy of IT rituximab in the treatment of CNS relapse (Schul et al, 2004) but there are no data to support its use in the prophylactic setting.

IT chemotherapy is not without clinical risk and toxicity. Delivery of inappropriate chemotherapy to the CSF can have fatal consequences and strict control measures must be in place to ensure safe delivery of IT therapy. In the UK, following a number of serious incidents where vinca alkaloids were administered intrathecally, the UK Government Department of Health has issued guidance on safe procedures for the administration of IT therapy (Department of Health, 2008), which must be followed. Complications of IT therapy delivered via the lumbar route include headache, arachnoiditis and encephalitis. Technical difficulties may also occur due to obesity, anatomical variation and previous spinal surgery, which can render the lumbar approach difficult or impossible. The use of Omaya reservoirs inserted at neurosurgical procedures may solve this problem but they are rarely used and have potentially serious complications, especially if they become infected. There is no randomized study to show that IT prophylaxis is effective, except in combination with other therapies, however there are some studies which support this approach (Table I). They all have limitations, such as small numbers, no control arm (Perez-Soler et al, 1986; Tomita et al, 2002; Arkenau et al, 2007; Vitolo et al, 2011) or co-administration of systemic MTX at doses that penetrate the CNS (Haïoun et al, 2000). The Royal Marsden group (Arkenau et al, 2007) reported a low rate of CNS relapse (1.1%) in a cohort of 259 patients where three doses of IT MTX were given as prophylaxis to those deemed at high risk of CNS disease.

There is some suggestion that IT chemoprophylaxis is not effective in reducing the risk of CNS relapse when applied to whole, unselected populations of DLBCL patients (Bernstein et al, 2009; Boehme et al, 2009) (Chua et al, 2002; Hegde et al, 2005; Tai et al, 2011). These studies are summarized in Table II. Two large studies (Bernstein et al, 2009; Boehme et al, 2009) have reported high CNS relapse risk though it is important to note that the studies were not originally designed (or powered) to test the efficacy of CNS prophylaxis. In neither case was there a protective benefit of IT prophylaxis demonstrated. The first study (Bernstein et al, 2009) was an analysis of the 20-year follow-up data from the Southwestern Oncology Group (SWOG) 8516 study, which prospectively compared the outcome of four established chemotherapy regimens, two with and two without CNS prophylaxis. CNS prophylaxis was given to patients with BM infiltration at diagnosis and who achieved BM remission with chemotherapy. Of the 238 patients who had BM involvement at diagnosis, there was no statistically significant benefit of receiving IT prophylaxis. In the second study (Boehme et al, 2009), CNS events were reported in elderly patients with aggressive lymphoma treated with CHOP-14 with or without rituximab in the RICOVER-60 trial. Indication for CNS prophylaxis (four doses of IT MTX) was involvement of the following sites: BM, testes, sinuses, orbits, oral cavity, tongue and salivary glands. CNS disease occurred in 4.8%. The analysis was not pre-planned and was only possible as a result of a high number of protocol violations (42-9%). Systemic relapse of disease was more common in the group who did not receive prophylaxis, however there was no statistically significant difference between the number of CNS events in high-risk patients who did or did not receive CNS prophylaxis (2.5% vs. 4-4%, n.s.). In another retrospective study by (Tai et al, 2011), 203 patients were deemed to be at increased risk of CNS relapse. CNS prophylaxis, given to 82 of these patients at the discretion of the treating physician, did not appear to decrease the incidence of CNS relapse (11% in the group receiving IT prophylaxis compared with 8.3% in those who did not). In a study of 989 patients with DLBCL registered on the National Comprehensive Cancer Network NHL

Table I. Studies that demonstrate a benefit of IT prophylaxis for CNS lymphoma.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Type of study</th>
<th>Prophylaxis</th>
<th>Relapse rate – prophylaxis</th>
<th>Relapse rate – no prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perez-Soler et al (1986)</td>
<td>21</td>
<td>Historical control</td>
<td>IT MTX + IV MTX 1 g/m²</td>
<td>5% at 2 years</td>
<td>41% at 2 years</td>
</tr>
<tr>
<td>Tomita et al (2002)</td>
<td>68</td>
<td>Retrospective, non-randomized</td>
<td>IT MTX + hydrocortisone</td>
<td>0%</td>
<td>15%</td>
</tr>
<tr>
<td>Arkenau et al (2007)</td>
<td>259</td>
<td>Retrospective</td>
<td>IT MTX +/- IT cytarabine</td>
<td>1-1%</td>
<td>No control arm</td>
</tr>
<tr>
<td>Vitolo et al (2011)</td>
<td>53</td>
<td>Prospective</td>
<td>IT MTX x 4</td>
<td>6% at 5 year</td>
<td>No control arm</td>
</tr>
<tr>
<td>Haïoun et al (2000)</td>
<td>974</td>
<td>Non-randomized</td>
<td>IT MTX + IV MTX 3 g/m²</td>
<td>1-6%</td>
<td>No control arm</td>
</tr>
<tr>
<td>Tilly et al (2003)</td>
<td>708</td>
<td>Randomized</td>
<td>IT MTX + IV MTX 3 g/m²</td>
<td>2-8%</td>
<td>8-3%</td>
</tr>
</tbody>
</table>

IT, intrathecal; IV, intravenous; CNS, central nervous system; MTX, methotrexate.
Outcomes Database (Kumar et al, 2012), 11.8% with risk factors for CNS relapse received prophylaxis (IT in 71.8%), at the discretion of individual oncologists. For those who had ≥2 pre-defined high-risk features, the rate of CNS relapse was 2.5% with no significant difference between those who received prophylaxis versus those who did not (5.4% vs. 1.4%, P = 0.08). These studies were clearly open to physician bias in identifying patients for IT therapy and do not provide suitable data as a basis for rejecting IT prophylaxis.

In conclusion, many years of experience administering IT prophylaxis in DLBCL has, as yet, failed to provide clear evidence of its efficacy and no prospective studies exist to support its efficacy. However, there are no strong evidence-based data to support a lack of efficacy, either. There are only retrospective studies, in which CNS relapse risk is reviewed subsequent to assessment of the initial end-point, and, in some, with a high proportion of treatment violations (Boehme et al, 2009). The data from these studies should be regarded as insufficient for the time being to allow the omission of IT prophylaxis from high-risk patients, especially in the absence of an evidence-based alternative strategy. Thus, we conclude that there remain insufficient grounds for routinely advocating other therapeutic approaches in high-risk groups. This recommendation is principally based on the low rates of CNS relapse reported in some studies (see Table I) using the strategy of IT prophylaxis, even though doubt still remains as to the efficacy of this practice.

**Recommendation**

1 All patients requiring CNS-directed therapy should receive 3–6 doses of IT MTX (flat dose of 12–15 mg each dose) during primary therapy, which should be commenced as early as practical during treatment and given at least once per cycle (Level of evidence: 2C).
undertaken. The policies of adopting either systemic or IT prophylaxis are compared in Table III.

In order for systemically administered chemotherapy to be useful in preventing CNS disease, the drug concerned, or its active metabolites, must be able to penetrate an intact blood brain barrier (BBB) and achieve adequate concentrations in the CNS. The data on the potential effectiveness of systemic chemotherapy for CNS prophylaxis in patients with NHL at high risk for CNS relapse are mainly based on information extrapolated from the experience in children with ALL, data derived from studies in primary CNS lymphoma (PCNSL), and retrospective series in NHL.

HD-MTX was demonstrated to be the most effective drug in patients with PCNSL in a non-randomized study comparing different treatment modalities (Ferreri et al, 2002). A subsequent study analysed the effectiveness of different doses and schedules of HD-MTX in the same population and found that overall survival (OS) was associated with a higher area under the curve (AUCMTX) and slow plasmatic creatinine clearance (Ferreri et al, 2004). Given that AUCMTX correlated with dose intensity and infusion rate, the authors suggested a 4- or 6-h infusion of MTX >3 g/m², as schedules using this dose achieved the highest AUCMTX (Ferreri et al, 2004). In line with this, studies in children with ALL demonstrated that lower doses of MTX do not reach adequate levels in the CSF (Evans et al, 1983). This was corroborated by a study analysing the efficacy of systemic and IT MTX as prophylaxis in adults with NHL at high risk for CNS relapse (Perez-Soler et al, 1986). In this series, the CSF MTX levels were below the therapeutic level after a 4-h infusion of 1 g/m² of MTX. The results in a study of risk factors for CNS relapse (van Besien et al, 1998) supported these data, as the incidence of CNS progression was not reduced in patients receiving an intensive chemotherapy that included 1·5 g/m² Ara-C IV and 1 g/m² MTX IV. Similarly, no differences in CNS relapse were found in the SWOG 8516 study comparing CHOP (no CNS prophylaxis) versus MACOP-B (MTX, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) (MTX: 400 mg/m², no CNS prophylaxis) versus ProMACE (prednisone, MTX, doxorubicin, cyclophosphamide, etoposide) -CytabOM (cytarabine, bleomycin, vincristine, MTX) (MTX: 1·5 g/m² × 2, cranial radiotherapy if BM involvement) versus M-BACOD (MTX, bleomycin, cyclophosphamide, and etoposide) (MTX: 200 mg/m² × 2, IT MTX + Ara-C if BM involvement) (Bernstein et al, 2009). From an interpretation of the above-mentioned studies, it seems advisable to administer doses of MTX greater than 3 g/m² if systemic chemotherapy is to be used as CNS prophylaxis.

The suggestion of the importance of systemic chemotherapy to decrease the risk of CNS relapse comes, once again, from studies in children (Tubergen et al, 1993; Nathan et al, 2006). The difficulty in assessing the usefulness of IV chemotherapy as CNS prophylaxis in adults with NHL lies in the fact that it is usually given in combination with IT chemotherapy. The GELA analysed the incidence of CNS relapse in a cohort of patients with ‘aggressive’ NHL treated with the ACVBP regimen, which includes CNS prophylaxis with two courses of 3 g/m² MTX IV and IT MTX, and found that the incidence of CNS progression (2·2%) was lower than previously reported in similar populations (Haioun et al, 2000). The same group confirmed the efficacy of CNS prophylaxis in a randomized trial comparing ACVBP (including 3 g/m² MTX IV × 2 and IT MTX) with CHOP chemotherapy (no CNS prophylaxis). The incidence of CNS relapse was 3% in the group receiving ACVBP versus 8% in the group treated with CHOP (P = 0·002) (Tilly et al, 2003). In contrast, a retrospective study comparing M-BACOD dosages showed that the reduction in the MTX from 3 g/m² to 200 mg/m² × 2 was not associated with a higher risk of CNS relapse (5% vs. 4%, respectively). In this retrospective study, none of the patients received CNS prophylaxis with IT chemotherapy, suggesting that HD-MTX alone might not be sufficient to protect from CNS progression (Shipp et al, 1990).

Administration of MTX

The pharmacology and potential toxicity of MTX are complicated, and subject to large inter-individual differences, and this is summarized well in a recent review (Schmiegelow, 2009). Thus, although renal MTX clearance is a major determinant of the variation in pharmacokinetics, other confounding factors are differences in cellular influx, polyglutamation and drug metabolism. Information from pharmacogenetic studies is ongoing although the impact on patient outcome is unclear at present.

Important variables for both efficacy and toxicity are the dose of MTX, duration of infusion and the dose and timing of folinic acid rescue, as these influence peak concentrations and exposure time. Thus millimolar concentrations of MTX for minutes or hours may lead to acute renal, CNS and liver toxicity, whereas concentrations of 0·05–0·1 μmol/l for more than 24–48 h will result in haematological and gastrointestinal toxicity. Regarding efficacy, a significantly lower failure-free survival was demonstrated in ‘high-risk’ patients with B-cell neoplasms who received MTX 5 g/m² as infusion over 4 h compared with patients randomized to receive the same MTX dose over 24 h (P = 0·008) (Woessmann et al, 2005). In this study the ‘high-risk’ patient cohort were children and adolescents with raised LDH and/or CNS involvement at presentation: lymphoma (n = 145) and acute leukaemia (n = 79). The former group was predominantly patients with BL and DLBCL. The MTX serum concentrations at 24, 42, and 48 h after the start of MTX infusion were significantly higher in patients receiving MTX-24 h compared with those receiving MTX-4 h. Although severe mucositis was significantly lower in those receiving MTX-4 h, the inferior outcome in this group was an unexpected finding and resulted in premature closure of the study. Although CNS recurrences were seen exclusively in the patients with BL and acute leukaemia in this study, this highlights the impact that
duration of administration of MTX can have on the anti-disease activity, as suggested in other studies (Wolfrom et al, 1993; Mikkelsen et al, 2011).

A recent randomized study assessed the efficacy and safety of two MTX doses and administration schedules in children with ALCCL (96% ALK positive), for whom CNS prophylaxis is generally recommended (Brugieres et al, 2009). Randomization was between six courses of MTX 1 g/m² over 24 h and an IT injection followed by folic acid rescue at 42 h (MTX1 arm; n = 175) and six courses of MTX 3 g/m² over 3 h followed by folic acid rescue at 24 h without IT therapy (MTX3 arm; n = 177). The 24-h infusion arm was rescued with leucovorin (15 mg/m²) at 42, 48, and 54 h. The 3-h infusion arm used leucovorin rescue (15 mg/m² every 6 h) starting at 24 h and ending when the MTX level was <0.15 μM/l. This trial involved most European paediatric/lymphoma study groups and a Japanese group, and therapy was based on the NHL-Berlin-Frankfurt-Muenster 90 (NHL-BFM90) study protocol. Again, toxicity (grade 4 haematological toxicity, infection and grade 3–4 stomatitis) was greater in those patients receiving MTX over 24 h, even though the MTX dose was much lower. Only two CNS relapses occurred in this study meaning that impact of dosing on this could not be assessed. However, the 2-year event-free survival and OS curves were superimposed, demonstrating that a less toxic schedule of MTX 3 g/m² in a 3-h infusion without IT therapy was as effective for patients with ALCCL on this protocol. It is not clear whether this conclusion can be translated directly in to the efficacy of this schedule in DLBCL. The administration of HD-MTX in this schedule is supported by pharmacokinetic and efficacy data from studies in patients with PCNSL (Ferreri et al, 2004; Joerger et al, 2010, 2012) and such high MTX doses are supported by evidence that the ratio of CSF-plasma MTX concentration is only ~1% (Schmiegelow, 2009). It is to be noted that there is no consensus on the delivery of MTX either over 3 h, in line with treatment schedules used in the therapy of PCNSL, where better delivery of MTX to the CSF is believed to occur, or over 24 h, which historically was more common.

The use of a HD-MTX regimen has also been described in a small retrospective study involving 65 adult DLBCL patients [median age: 60 years (range 25–79)] who received HD-MTX (3.5 g/m²) as CNS prophylaxis. There was an issue regarding toxicity because 26 patients suffered ‘renal toxicity’ (creatinine >ULN) and a minority suffered acute renal failure (transient, but resulted in avoidance of further MTX in seven patients and delay in chemotherapy in eight patients). In this cohort, 16/26 with renal toxicity were more than 60 years old and so further studies regarding feasibility and safety of this approach in adults are warranted, especially in older adults. (Abramson et al, 2010). It is also notable that this study was retrospective and involved a wide variation in the number of cycles of HD-MTX delivered.

Historically the HD-MTX approach has most frequently been given following completion of R-CHOP chemotherapy but the DSHNHL group reported a significant risk of early CNS relapse during therapy (Boehme et al, 2007) so an alternative strategy could be to deliver this therapy intercalated with the R-CHOP chemotherapy on day 10–14 of each of the first 2–5 cycles, to allow safe assessment of tolerance of R-CHOP in cycle 1. This has logistic consequences in terms of in-patient bed availability but has been shown to be deliverable without causing delay to subsequent cycles of systemic therapy. Avoiding a delay in administration of R-CHOP must be considered to be an essential goal in order to avoid a decrease in systemic disease control (Kim et al, 2011).

Agents other than MTX

With regard to other drugs that are occasionally recommended for CNS prophylaxis given that they cross the BBB, such as HD Ara-C, the information is even more scarce. In a randomized study in children with ALL, the addition of HD Ara-C (1 g/m² b.d.) to a prophylactic regimen including HD-MTX and IT MTX did not decrease the risk of relapse (Millot et al, 2001). Ara-C is seldom given as initial treatment for adult NHL (other than for BL), which makes it difficult to reach any conclusion regarding its usefulness for CNS prophylaxis in this setting.

The abilities of other systemically administered drugs used in the treatment of lymphomas to penetrate the BBB are listed in Table IV. Whilst some of these drugs, e.g. idarubicin and ifosfamide, have been incorporated into chemotherapy regimens designed to treat lymphomas at high risk of CNS involvement, they are almost always used in combination with IT chemotherapy and systemic MTX or Ara-C, making it impossible to determine the particular contribution of these drugs in CNS prophylaxis e.g. CODOX-M/IVAC.

Unlike doxorubicin, whose metabolite doxorubicinol is inactive, idarubicin’s active metabolite, idarubicinol, crosses the BBB. Studies comparing CHOP and CIOP (cyclophosphamide, idarubicin, vincristine, prednisolone), which might have been in a position to determine the efficacy of idarubicin as prophylaxis, have not reported on CNS relapse rates (Zinzani et al, 1995; Burton et al, 2005).

In a recent study that analysed the risk factors for CNS relapse in a large cohort of patients with ‘aggressive’ lymphoma, treatment with etoposide (VP-16) emerged in the multivariate analysis as a protective factor for CNS progression (Boehme et al, 2007). This result is difficult to interpret, as in the original studies comparing treatment with CHOP and CHOEP (CHOP + etoposide), no analyses regarding CNS relapse were performed (Pfreundschuh et al, 2004).

Dexamethasone has been reported to have better CNS penetration and lympholytic properties than prednisolone (Balis et al, 1987; Kaspers et al, 1996). When dexamethasone was substituted for prednisolone in induction, consolidation and continuation phases of treatment in newly diagnosed children with ALL, the risk of isolated CNS relapse was halved. Similar information is not available in DLBCL and a comparison of
Table IV. Penetrance of blood-brain barrier by drugs with activity in lymphoma, when given systemically.

<table>
<thead>
<tr>
<th>Chemotherapeutic agent</th>
<th>Penetrance of blood-brain barrier</th>
<th>Micromedex Gateway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>No</td>
<td>Unable to cross intact meninges</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Yes</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Carmustine (BCNU)</td>
<td>Passes readily</td>
<td>30–97% of plasma levels</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>No information found</td>
<td>Limited information but CNS side effects only seen at higher doses</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Not readily</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Cladribine</td>
<td>25% of plasma levels</td>
<td>Minimal</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Limited</td>
<td>25% of plasma concentration</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Limited</td>
<td>~50% plasma. Alkylating (active) metabolites do not cross as easily: peak levels ~ 20% of plasma</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>No evidence it crosses BBB</td>
<td>~10% plasma levels</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>No</td>
<td>Does not appear to cross BBB</td>
</tr>
<tr>
<td>Etoposide</td>
<td>In low and variable concentration</td>
<td>CSF &lt;3% of concurrent plasma levels</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>No information found</td>
<td>Penetration into CSF not systematically evaluated but presumably crosses readily due to occurrence of neurotoxicity</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>No information found</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>Yes</td>
<td>Idarubicin and idarubicinol cross BBB</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Ifosfamide: yes (active metabolite: no)</td>
<td>Unchanged ifosfamide (but none of the active metabolites) detected in small amounts in the CSF: negligible alkylating activity</td>
</tr>
<tr>
<td>Lomustine (CCNU)</td>
<td>Passes readily ≥50% concurrent plasma concentration</td>
<td>Not listed</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Low concentration (plasma:CSF 10:1 to 100:1)</td>
<td>Not thought to cross the BBB in therapeutically useful concentrations</td>
</tr>
<tr>
<td>MTX</td>
<td>Plasma: CNS ratio 10–30:1</td>
<td>At steady state, MTX concentrations are 3% of those in plasma during a constant rate of IV infusion</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>No information</td>
<td>Autopsy and animal studies show little CNS penetration</td>
</tr>
<tr>
<td>Rituximab</td>
<td>0–1–1.7% plasma concentration</td>
<td>Not listed</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Poorly, not in therapeutic concentrations</td>
<td>Penetrates CSF but at levels unlikely to be therapeutic</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Not significant amount</td>
<td>Penetrates CSF but at levels unlikely to be therapeutic</td>
</tr>
</tbody>
</table>

BBB, blood-brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; MTX, methotrexate; IV, intravenous.
CHOP-R and CHOD-R (rituximab, cyclophosphamide, doxorubicin, vincristine, dexamethasone) may be warranted.

**Recommendation**

1. **Systemic HD-MTX**, given at a dose of 3–5 g/m², with folinic acid rescue, can also be considered as additional CNS-directed therapy in high-risk patients. This should be given strictly in line with published schedules and considered in the context of performance status and renal function. The benefit of the additional or alternative use of HD-MTX must be carefully balanced against the risk of toxicity and the resource utilization consequences of the schedule (Level of evidence: 2B).

2. There are no data to confirm that HD-MTX alone can replace IT therapy and if this strategy is followed, it is essential that the practice is carefully audited (Level of evidence: 2C).

3. For the delivery of intravenous HD-MTX, the use of rapid infusion schedules can be recommended, although the authors acknowledge lack of consensus on this issue (Level of evidence: 2B).

4. If given without IT chemotherapy, systemic prophylaxis should be commenced as early as practical during treatment without compromising delivery of R-CHOP chemotherapy (Level of evidence: 1B).

5. Further studies to determine the benefit of systemic and/or IT therapy for the prevention of secondary CNS lymphoma are warranted (Level of evidence: 2C).

6. The use of systemic agents other than HD-MTX as CNS prophylaxis in addition to, or instead of, IT chemotherapy and/or HD-MTX have not been shown to be beneficial. Their use is therefore not recommended except where they form part of an established multi-agent regimen or as part of a clinical trial (Level of evidence: 1C).

**Recommendations specific to primary testicular lymphoma**

The particularly high rate of CNS relapse seen in primary testicular lymphoma has meant that some study groups have regarded it separately for the purposes of clinical trials, and as such, some evidence exists for its management. The International Extranodal Lymphoma Study Group (IELSG) reported a low rate of CNS relapse (6% at 5 years) in patients with primary testicular lymphoma in the IELSG 10 study where patients received four doses of IT MTX for CNS prophylaxis (Vitolo et al., 2011). This compared with a rate of 20% in a previous study by this group (Zucca et al., 2003). The observation of development of CNS disease (one parenchymal) in three patients despite prophylaxis, was also reported in a recent study (Guirguis et al., 2012), and might suggest that other strategies might need to be pursued. However with an incidence of CNS disease of 6%, further intensification of CNS-directed therapy will run the risk of increasing toxicity when only a small number of patients are at risk. The IESLG group have moved on to a further study using four cycles of IT MTX and an additional two cycles of intermediate dose systemic MTX(1.5 g/m²) with folinic acid rescue (clinicaltrials.gov identifier:NCT00945724). This cannot be regarded as standard of care until this study has been reported but demonstrates a potential option for therapy. If utilized, the strategy of systemic therapy as CNS prophylaxis should be carefully audited by centres using this therapy for both efficacy and toxicity. No data are available for IV MTX alone in primary testicular lymphoma. All patients in the IELSG study had stage 1 or 2 disease however, and it is reasonable for patients with more advanced disease involving the testicle, many of whom would trigger the Van Besien criteria, to be treated in the same way.

**Recommendation**

1. Patients with primary testicular lymphoma should receive four or more doses of IT MTX during primary chemotherapy as per the IESLG protocol (Level of evidence: 2B).

**Conclusions and recommendations**

The heterogeneity of studies and lack of randomized controlled trials in this area mean that the level of evidence supporting many of these recommendations is low (see level of evidence for each recommendation). The committee is able to make the following recommendations.

**Summary of recommendations**

1. CNS-directed therapy should be offered to patients with high-grade NHL AND either:
   - A raised (above institutional ULN) serum LDH AND more than one extra-nodal localization (noting that the spleen is not regarded as an extra-nodal site and also, two lesions within the same system (e.g. bilateral lung lesions) are regarded as a single extra-nodal localization).
   - OR
   - Anatomical sites: Testicular, breast and epidural (Level of evidence: 1B).

2. All patients requiring CNS-directed therapy should receive 3–6 doses of IT MTX (flat dose of 12–15 mg each dose) during primary therapy, which should be commenced as early as practical during treatment and given at least once per cycle (Level of evidence: 2C).

3. Systemic HD-MTX, given at a dose of 3–5 g/m², with folinic acid rescue, can also be considered as additional
CNS-directed therapy in high-risk patients. This should be given strictly in line with published schedules and considered in the context of performance status and renal function. The benefit of the additional or alternative use of HD-MTX must be carefully balanced against the risk of toxicity and the resource utilization consequences of the schedule (Level of evidence: 2B).

4 There are no data to confirm that HD-MTX alone can replace IT therapy, and if this strategy is followed it is essential that the practice is carefully audited (Level of evidence: 2B).

5 For the delivery of intravenous HD-MTX, the use of rapid infusion schedules can be recommended, although the authors acknowledge lack of consensus on this issue (Level of evidence: 2B).

6 If given without IT chemotherapy, systemic prophylaxis should be commenced as early as practical during treatment without compromising delivery of R-CHOP chemotherapy (Level of evidence: 1B).

7 Further studies to determine the benefit of systemic and/or IT therapy for the prevention of secondary CNS lymphoma are warranted (Level of evidence: 2C).

8 The use of systemic agents other than HD-MTX as CNS prophylaxis in addition to, or instead of, IT chemotherapy and/or HD-MTX have not been shown to be beneficial. Their use is therefore not recommended except where they form part of an established multi-agent regimen or as part of a clinical trial (Level of evidence: 1C).

9 Patients with primary testicular lymphoma should receive four or more doses of IT MTX during primary chemotherapy as per the IESLG protocol (Level of evidence: 2B).

10 Given that the evidence supporting any single approach is less than strong, it is recommended that patients should be entered in to prospective randomized controlled trials where available, and, in all other settings, prospective audit of practice should be performed to support the approaches taken. Such audit should record not only the nature of prophylaxis administered, but also the type of CNS relapse and if there is any evidence of concurrent systemic relapsed disease (Level of evidence: 2C).

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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Appendix 1

The GRADE system

From January 2010 BCSH guidelines have used the GRADE nomenclature for assessing levels of evidence and providing recommendations in guidelines. For laboratory tests guidance is related specifically to clinical utility (that is the ability of a test to alter clinical outcome). GRADE stands for: Grading of Recommendations Assessment, Development and Evaluation (Guyatt et al, 2008).

Strength of recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as ‘recommend’.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as ‘suggest’.

Quality of evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g. inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g. lack of blinding, large losses to follow up, failure to contain appropriate numbers of patients, etc.)
adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

References


