Central nervous system-directed preventative therapy in adults with lymphoma

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Summary
All adult patients with Burkitt lymphoma or lymphoblastic lymphoma should receive central nervous system (CNS)-directed therapy with both intrathecal and high-dose systemic chemotherapy. There is no evidence to support the routine use of prophylactic CNS-directed therapy in any specific subgroup of adult patients with 'low grade' lymphomas. There are some anatomical sites where involvement by lymphoma is associated with a higher risk of CNS relapse. These probably include testis, breast, paranasal sinuses and the epidural space. Multivariate analyses strongly support a raised serum lactate dehydrogenase level and the involvement of more than one extranodal site as the strongest predictors of subsequent CNS relapse. A high International Prognostic Index score may replace the use of the above two factors in combination. There is evidence of good efficacy when intrathecal chemotherapy and high-dose systemic chemotherapy are used in combination. It is not clear how the best balance between the 'sensitivity' and 'specificity' of the choice of patients to receive CNS-directed therapy can be achieved.

Keywords: lymphoma, central nervous system-directed therapy, intrathecal chemotherapy, lymphomatous meningitis.

Greater clarity was achieved with the publication of the 'working formulation' [The Non-Hodgkin's Lymphoma Pathologic Classification Project (NHLPCP), 1982] and many of the papers referenced in this article are classified using this scheme. In particular, Burkitt lymphoma (BL) and lymphoblastic lymphoma (LBL) were separated from other 'intermediate grade' lymphomas. However, some confusion remained because of the inclusion of immunoblastic lymphoma as high grade (with BL and LBL). This histological subtype has now been recognised as part of DLBCL as this was rectified with the advent of the Revised European American Classification of non-Hodgkin Lymphoma (Harris et al, 1994) and its updating to form the current World Health Organisation (WHO) classification of lymphoma (Jaffe et al, 2001). The picture is much clearer but a full understanding of patients who require intervention to prevent CNS relapse has remained elusive.

Scope of review
This article will attempt to identify, according to the WHO classification, those groups where specific CNS-directed therapy to prevent later relapse within the CNS is justified, but it must be stated at the outset that, unfortunately, there are no randomised prospective trials available which specifically address this decision-making process. CNS relapse of lymphoma may occur rarely in a wide range of different low-grade histology's, for example the Bing–Neel syndrome reported in lympho-plasmacytoid lymphoma (Pennacchio & Orlandini, 1969; Cetto et al, 1981), however the incidence of CNS relapse of lymphoma may occur rarely in a wide range of different low-grade histology's, for example the Bing–Neel syndrome reported in lympho-plasmacytoid lymphoma (Pennacchio & Orlandini, 1969; Cetto et al, 1981), however the incidence of CNS relapse is insufficient to justify prophylactic therapeutic intervention for any of the broad range of low-grade NHL subtypes. Paediatric NHL and primary CNS lymphoma (including ocular lymphoma) will not be discussed in this annotation.

Burkitt lymphoma and lymphoblastic lymphoma
There is universal agreement that BL (e.g. Wolf et al, 1985) and LBL (e.g. MacKintosh et al, 1982) require CNS-directed therapy to prevent CNS relapse. Reports published prior to routine use of CNS-directed therapy would suggest that
without CNS-directed therapy, the observed incidence of CNS relapse is of the order of 20% (estimated from (Levitt et al., 1980).

There is very little evidence examining in detail the precise nature of the CNS-directed therapy required in BL, but the overall success of the cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide and high-dose cytarabine (CODOX-M/IVAC) schedule, initially published by Magrath et al (1996) and recently confirmed by the UK lymphoma group (Mead et al., 2002) means that when this schedule is adopted good control of the risk of CNS relapse can be reliably achieved. This schedule includes not only alternating methotrexate and cytarabine intrathecal treatment but also high-dose systemic therapy with methotrexate and cytarabine at a dose sufficient to achieve CNS penetration (see later).

The relative rarity of LBL compared with acute lymphoblastic leukaemia (ALL) means that there is little data available specific to the treatment of LBL as distinct from ALL but, as the two conditions are very closely related, it would seem reasonable to adopt the same approach to the prevention of CNS disease in LBL as is currently used in the treatment of ALL. The effect on CNS relapse in successive cohorts treated at the MD Anderson Cancer Centre with increasing CNS-directed therapy has been well documented (Cortes et al., 1995). Schedules in common usage, such as the Berlin–Frankfurt–Münster (Hoelzer & Gokbuget, 2000) and Medical Research Council United Kingdom XII (MRC-UKALL XII), normally include a combination of intrathecal methotrexate, intrathecal cytarabine, high-dose systemic methotrexate and cytarabine as well as cranial radiotherapy in some cases.

### Table I. Examples of early reports (pre-1990) of prevalence of central nervous system (CNS) disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>CNS relapse %</th>
<th>Incidence</th>
<th>Examples of terminology used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bunn et al (1976)</td>
<td>52</td>
<td>15</td>
<td>29</td>
<td>Diffuse histiocytic, undifferentiated</td>
</tr>
<tr>
<td>Litam et al (1979)</td>
<td>98</td>
<td>13</td>
<td>13.5</td>
<td>Diffuse poorly differentiated, diffuse undifferentiated</td>
</tr>
<tr>
<td>Levitt et al (1980)</td>
<td>592</td>
<td>52</td>
<td>9</td>
<td>Histiocytic, diffuse, poorly differentiated lymphocytic lymphoma</td>
</tr>
</tbody>
</table>

**Aggressive lymphomas, including DLBCL and related histologies**

**Surveillance.** There are two potential methods by which patients requiring treatment could be identified, first at the time of diagnosis a surveillance lumbar puncture might demonstrate the presence of lymphoma cells and the demonstration of these cells could be used to require CNS-directed therapy. Secondly, the identification of patients whose characteristics are indicative of a high risk of CNS disease could be treated without demonstration of the presence of CNS disease in order to try and prevent CNS relapse occurring. The sensitivity of the former strategy using cytology of a conventional cytospin cell preparation is unlikely to be sufficient to allow reliable prevention of disease but it is possible that, in the future, techniques such as flow cytometry may be able to detect currently occult disease. A minimal level of CNS disease might then be eliminated by early therapy during first-line treatment. A recent publication (Hegde et al., 2005) detected a 10-fold greater number of patients with CNS disease by flow cytometry than conventional cytology. The patients in this study with occult disease were more likely to have extranodal disease ($P = 0.006$ on univariate analysis) and, as will be observed from data presented later in this annotation, this is consistent with the hypothesis that the patients identified by flow cytometry are those who would have suffered a later CNS relapse. This technique now needs to be prospectively tested in large multicentre series but it seems likely that this may become a standard staging procedure in the future. However, at present it will be argued here that patients must be identified for prophylaxis on the basis of their level of risk of CNS relapse as assessed by other criteria.

### Table II. Examples of recent reports of prevalence of central nervous system (CNS) disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Histology</th>
<th>CNS prophylaxis</th>
<th>CNS relapse incidence (%)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keldsen et al (1996)</td>
<td>498 (consecutive)</td>
<td>BL and LBL included</td>
<td>No prophylaxis</td>
<td>5.4</td>
<td>4 months median survival</td>
</tr>
<tr>
<td>Zinzani et al (1999)</td>
<td>175 (consecutive)</td>
<td>BL and LBL excluded</td>
<td>No prophylaxis</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Feugier et al (2004)</td>
<td>399</td>
<td>DLBCL</td>
<td>No prophylaxis</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Bos et al (1998)</td>
<td>286</td>
<td>WF D to F</td>
<td>No prophylaxis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bashir et al (1991)</td>
<td>277 (consecutive)</td>
<td>Aggressive NHL (working form)</td>
<td>1:1 diagnosis</td>
<td>4.0 relapse</td>
<td>2 months median survival from relapse</td>
</tr>
</tbody>
</table>

BL, Burkitt lymphoma; LBL, lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma.
Identification of patients at risk. Case-series published after improvements in histological subtyping have reported an incidence of CNS relapse of around 5% (see Table II). Although this incidence is relatively low it is important to be aware that the outcome of those patients suffering CNS relapse is extremely poor (Bashir et al., 1991; Zinzani et al., 1999) and therefore prevention of relapse by CNS-directed therapy needs to be carefully considered.

Current practice in DLBCL. The null hypothesis with respect to the treatment of DLBCL is that there is no group with a sufficient incidence of CNS relapse for prophylactic treatment to be justified. This was the view taken, for example, by the HOVON Dutch National Study group (Bos et al., 1998) after a review of a 286 patient series with intermediate grade NHL (Working Formulation grade D–H) and it is also the approach taken by at least two large national cooperative study groups (see Table III) who have recently reported large randomised prospective trials in the first-line therapy of DLBCL in which no specific CNS-directed therapy was given. A survey of practice in Canada reported by Buckstein et al. (2003) reported that lymphomas of the testis, orbit, paranasal sinuses or epidural space were the sites most frequently perceived as requiring CNS-directed therapy. Feugier et al. (2004) confirmed the previously suggested figure of 5% as the risk of CNS relapse in the context of standard cyclophosphamide, hydroxydaunomycin, Oncovin, prednisone (CHOP) chemotherapy given in the elderly (over 60 years) with no specific CNS-directed therapy. An alternative to this minimal approach has been to try and identify patients at risk on the basis of involvement of specific-anatomical sites. For example, Hollender et al. (2000) reported a very large series spanning 16 years at the Norwegian Radium Hospital, Oslo. From 1990, a policy of administering CNS prophylaxis to patients with involvement of bone marrow, epidural space, skeleton, testis or paranasal sinuses was instituted. The evidence for increased risk in patients with involvement of lymphoma at these sites will be examined later, but it is important to note that a strategy based on only treating patients with involvement of these sites will inevitably miss a significant number of patients at risk and therefore not have an important impact on the lymphoma population as a whole. This statement is corroborated by the absence of evidence, on multivariate analysis of large case series, demonstrating a significant predilection of CNS disease in patients with lymphomatous involvement at these sites.

Risk of CNS disease in DLBCL according to anatomical sites involved

Testicular lymphoma. The evidence for a site-related predilection for CNS relapse is probably strongest for testicular lymphoma and this has been recognised for many years (MacKintosh et al., 1982) and, more recently, well documented (Zucca et al., 1999) (Fonseca et al., 2000). Although the numbers of patients in reports are often small, the consequence of not administering CNS-directed therapy is well described (e.g. Batchelor et al., 2001). In an analysis of 498 patients treated in a major centre in Denmark (Keldsen et al., 1996) the authors found testicular involvement to be significant in predicting for CNS disease on univariate but not multivariate analysis. This is likely to be because other factors that were identified on multivariate analysis such as stage 4 disease and B symptoms had greater predictive values and were linked to testicular involvement. The best assessment of the risk of CNS relapse, currently reported, comes from the International Extranodal Lymphoma Study group survey (Zucca et al., 2003), in which data of 373 patients was collected retrospectively from a large number of centres. Of
these, 255 patients received an anthracycline-based therapy and so it is reasonable to regard these patients as being those treated with curative intent. Surprisingly a much smaller number (68% or 18% of the whole group) received intrathecal chemotherapy but of these only 51/68 received four or more doses of intrathecal therapy. There were 56 relapses in the CNS but intrathecal chemotherapy was not associated with an improved outcome on multivariate analysis, possibly because of the small proportion of the patients who received it. A total of 29% of patients received high-dose intravenous methotrexate as part of their initial treatment without any apparent effect on outcome. These authors also noted that, unlike the pattern in extranodal sites from other primary sites, testicular lymphoma seemed to be associated with a higher incidence of parenchymal brain involvement as opposed to lymphomatous meningitis.

**Breast lymphoma.** The situation is similar but not as well documented for lymphoma of the breast. The largest series reported is that of Gholam et al (2003) from France who reported on 30 patients, mainly of DLBCL, observed over 25 years at a single institution and treated with CHOP. They noted two CNS relapses from complete response and two progressions from a partial response in the CNS with an overall incidence of three of 16 (18.75%) of DLBCL patients developing isolated CNS disease. All these four patients with CNS disease died and these authors recommend CNS prophylaxis for all patients with isolated breast lymphoma. Yamazaki et al (2003) also noted the high incidence of CNS relapse with breast lymphoma.

**Lymphoma involving paranasal sinuses.** This localisation is very frequently quoted but the evidence base is scanty. Liang et al (1990) reported an increased incidence of CNS disease with involvement of the nasal/paranasal sinuses (23%), though the incidence was higher with orbital disease (43%). The study was conducted at Hong Kong where the ‘biology and epidemiology of lymphoma’ may be different from Western Europe (e.g. nasal lymphoma). An association between paranasal sinus involvement and CNS risk is strikingly absent from significance in univariate and multivariate analyses in most reports but this may be masked by the strong association with >1 extranodal localisation (van-Besien et al, 1998) (Hollender et al, 2000). However, the association detected in these multivariate analyses is only with more than one extranodal site and so it is possible that localised disease of the sinuses is not associated with CNS spread.

**Lymphoma involving the epidural space.** The close anatomic association between involvement of the epidural space and the CNS has reinforced this observation and it is reported in a number of case series (e.g. MacKintosh et al, 1982; Bashir et al, 1991). A more recent report (Chahal et al, 2003) estimated this localisation to occur in 4% of all lymphomas. There may be significance to physical breaching of the dura but, because of the difficulty of establishing this radiologically, the precautionary principle would suggest that these patients should be regarded as at high risk of CNS involvement.

**Summary: significance of anatomic sites of involvement.** The significance of disease localisation would therefore appear to be that there is good evidence of CNS involvement occurring with an increased incidence at some specific-anatomic sites. However, the relative rarity of these sites compared with the generality of the sites of presentation of lymphoma makes the detection of the significance of this increased involvement difficult to detect in multivariate and even univariate analyses. It is likely that most physicians will continue to wish to give CNS-directed therapy to these patients, most importantly, those with testicular disease.

The other anatomic localisation that has been frequently associated with an increased risk of CNS relapse is the bone marrow (Getto et al, 1981) (Keldsen et al, 1996) (Wolf et al, 1985) (Levitt et al, 1980). However, this was probably initially exaggerated by the inclusion of patients with BL or LBL where bone marrow involvement is very common, but this continued identification even in series including only DLBCL is most likely be due to the association with advanced disease (Keldsen et al, 1996). In those reports where bone marrow involvement is not associated with CNS relapse in multivariate analysis this is frequently due to the identification of a closely associated parameter such as a raised serum lactate dehydrogenase (LDH) level or the presence of ‘B’ symptoms. Therefore, it can be argued that bone marrow involvement should not be recorded as a specific site of anatomic risk but rather part of a more general assessment of advanced disease.

**Risk of CNS disease according to histology.** Aside from BL and LBL, DLBCL represents most of the cases at risk of CNS relapse and most case series have not identified histological subtypes at increased risk, although few of the case series have been sufficiently recent to include all the subtypes recognised by the WHO classification. An exception to this is the report by Feugier et al (2004) of patients treated with CHOP or CHOP-R. They reported that three of the 20 cases of CNS relapse identified were reclassified as the blastoid variant of mantle cell lymphoma. It seems likely that, with greater recognition, this very aggressive histological subtype may become associated with increased CNS relapse risk.

Other subtypes that have been associated with CNS relapse risk include:

1. **Nasal (NK cell) lymphoma.** For example, Shikama et al (2001) reported four of 43 patients to have CNS involvement. However, all CNS relapse occurred in patients with stage 3 or 4 disease so the predictive value of this histology cannot be considered proven;
Primary mediastinal B-cell lymphoma (PMBCL) has also been identified in at least one report as predisposing to CNS relapse (Bishop et al., 1999). This study included four of 23 cases of CNS relapse in PMBCL but all of these had extranodal disease so would have been at higher risk, regardless of histological subtype. Once again, therefore, the predictive value of the histology as distinct from the disease status is open to question.

Effect of introduction of rituximab into primary therapy. Coiffier et al. (2002) reported a markedly improved outcome of therapy in DLBCL with the addition of rituximab to standard CHOP chemotherapy. If it is postulated that CNS disease occurs partly as a reflection of failure to control systemic disease then it is at least possible that the inclusion of rituximab will alter the pattern and/or frequency of CNS relapse in DLBCL. It is therefore valuable that the occurrence of CNS relapse in the original patient group has recently been examined and published (Feugier et al., 2004). CNS relapses occurred in 20 of 399 patients treated with either CHOP or rituximab-CHOP representing a similar incidence of around 5% to many of the previous reports. They did not detect any difference between patients receiving Rituximab or not with respect to CNS relapse. The outcome of patients with CNS relapse was poor, with only three out of 20 remaining alive at the time of publication, again in line with previously reported outcomes in many other case series.

Strategies to identify patients appropriate for CNS-directed therapy. It is therefore clear that many patients with DLBCL who are destined to relapse in the CNS cannot be identified on the basis of involvement of a particular anatomical site or histological subtype. To identify these patients requires the identification of patients at risk within the population as a whole and multivariate analysis of large patient groups is probably the best way of achieving this. It is clear from many of the reported case-series that advanced disease is a major component of CNS relapse risk. Four papers in the literature, in particular, have sought to address this question and the results of the univariate and multivariate analyses are presented in Tables IV and V.

It can be seen from these data that the figure of 5% risk without CNS-directed therapy is robust and multivariate

### Table IV. Significant factors for central nervous system (CNS) relapse from Hollender et al. (2000), van-Besien et al. (1998) and Feugier et al. (2004) – publications in case series without universal prophylaxis.

<table>
<thead>
<tr>
<th>Publication</th>
<th>No. of patients</th>
<th>CNS relapse risk</th>
<th>Significant factors identified on univariate analysis (5 most significant)</th>
<th>Significant factors on multivariate analysis with P-value (not including IPI)</th>
<th>Significant factors on multivariate analysis with P-value including IPI if available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hollender et al</td>
<td>5214</td>
<td>5%</td>
<td>&gt;1 E/N, sites Age &gt;60 Alb &lt;35 Retroperitoneal LN LDH &gt;450 U/l</td>
<td>&gt;1 E/N, &lt;0.001 sites Age &gt;60, 0.002 Alb &lt;35, 0.005 Retroperitoneal LN 0.037 LDH &gt;450 U/l 0.049</td>
<td>N/A</td>
</tr>
<tr>
<td>van-Besien et al</td>
<td>605</td>
<td>4.5%</td>
<td>&gt;1 E/N, sites High LDH Poor PS Advanced stage Skin/subcutaneous/muscle</td>
<td>&gt;1 E/N 0.0005 site High LDH 0.0008</td>
<td>N/A</td>
</tr>
<tr>
<td>Feugier et al</td>
<td>399</td>
<td>5%</td>
<td>High aaIPI (HI or H) Advanced stage High LDH Poor PS</td>
<td>Poor PS High LDH</td>
<td></td>
</tr>
</tbody>
</table>

PS, performance status; aaIPI, age-adjusted International Prognostic Index (H, high; HI, high-intermediate); LDH, lactate dehydrogenase; E/N, extranodal; N/A, not available.

### Table V. Significant factors for CNS relapse from Haioun et al. (2000a) – publication in a case series with universal prophylaxis.

<table>
<thead>
<tr>
<th>Publication</th>
<th>No. of patients</th>
<th>CNS relapse risk</th>
<th>Significant factors on multivariate analysis with P-value (not including IPI)</th>
<th>Significant factors on multivariate analysis with P-value if IPI included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haioun et al (2000a)</td>
<td>974</td>
<td>1.6%</td>
<td>High LDH 0.05 &gt;1 E/N site 0.05</td>
<td>High IPI 0.002</td>
</tr>
</tbody>
</table>

E/N, extranodal.
analyses strongly support a raised LDH level and more than one extranodal site as the strongest predictors of CNS relapse. CNS-directed therapy is complicated and expensive to deliver, so a balanced decision has to be made between treating a large number of patients, only a few of whom would have developed CNS disease, or targeting a smaller number of patients with the risk of missing some cases who might develop CNS disease. This dilemma is well illustrated by van-Besien et al (1998) using the model from their analyses – 20% of patients had more than one extranodal site and 50% had a raised LDH. A total of 15.4% of patients had both risk factors and had a cumulative risk of CNS relapse close to 20% and this group and could clearly be recommended CNS-directed therapy. However, this group included only 11 of the 24 patients who developed CNS disease so half the patients at risk would not be recommended CNS treatment. By contrast, if the 50% of patients with a raised LDH level all received CNS-directed therapy then 21 of 24 patients who suffered a CNS relapse would have received treatment to prevent it but this would have been achieved at the cost of treating 50% of all patients with CNS-directed therapy.

**Modalities of CNS therapy**

The delivery of CNS-directed therapy can be based on up to four strategies:

1. Direct introduction of chemotherapy agents via a lumbar puncture or a centrally placed Omaya Reservoir. A PubMed search revealed that this was reported in the Literature as early as 1964.(Spevak, 1964) and has been in common usage ever since. It represents the cornerstone of CNS-directed therapy. Chemotherapy agents that can be safely delivered include methotrexate and cytarabine as well as the steroid, hydrocortisone. Extreme care and secure institutional protocols are required to prevent untoward consequences arising from inadvertent delivery of other inappropriate chemotherapy agents to the cerebro-spinal fluid. A number of authors have questioned whether delivery of chemotherapy by this method is sufficient to achieve disease control (e.g. Chua et al, 2002). Most recently, early experiments in animal models would suggest that immunotherapy with intrathecal rituximab may have a role to play in future CNS-directed therapy (Rubenstein et al, 2003).

2. High-dose systemic chemotherapy with diffusible agents that can penetrate to the CSF, e.g. methotrexate and cytarabine. This strategy was first published in trials in the mid-1980s (e.g. Balis et al, 1985) and the mechanism of action has been extensively discussed (e.g. Jolivet, 1987). The level of high-dose methotrexate which achieves plasma levels sufficient to penetrate the CSF will always require the use of folinic acid rescue after 24–36 h to prevent unacceptable toxicity to mucosal surfaces.

3. Some chemotherapy agents are able to penetrate the CSF at standard doses either as the native drug (Ifosphamide) or as an active metabolite (Idarubicin/Idarubicinol). This strategy has been less well developed because of the relative novelty of these agents but would appear to have significant potential on the basis of the outcome of the treatment of active disease with schedules such as idarubicin, dexamethasone, cytosine arabinoside and methotrexate (Idarubicin/Idarubicinol) (Moreton et al, 2004). A detailed further discussion of the rationale and principles of these modalities of therapy will not be made as they have been well reviewed by Pinkel and Woo (1994).

4. Cranial or cranio-spinal radiotherapy is a highly effective modality of therapy of overt CNS disease but is not routinely applicable to CNS-directed therapy given as prophylaxis in adult lymphoma, except possibly in rare cases to reduce the risk of direct extension/invasion of the CSF.

The delivery of effective CNS-directed therapy, in cases where the argument for prophylaxis is accepted, should utilise both of the first two strategies and in future may need to incorporate more of the third as new protocols are developed. The analogy with treatment strategies in ALL (Cortes et al, 1995) is very close and the requirement for both intrathecal and high-dose systemic therapy has already been made for BL above (Magrath et al, 1996).

**Effective implementation of strategies for control of CNS disease**

The effectiveness of implementing CNS-directed therapies in NHL has been relatively poorly documented but two recent publications from the French Groupe d’Etudes des Lymphomes de l’Adulte would appear to provide good evidence on which to base future strategies.

In the first study (Haïoun et al, 2000a), 974 patients with aggressive lymphoma in complete remission all received a standard chemotherapy programme (ACVBP), which included CNS prophylaxis consisting of intrathecal injections of methotrexate combined with two cycles of high-dose methotrexate (3 g/m²). The incidence of CNS relapse reported in this group of patients was only 1.6%, which contrasts with many of the papers discussed earlier in this review where an incidence of around 5% was repeatedly reported. In multivariate analysis, as previously recognised in earlier studies, a raised level of serum LDH (P = 0.05) and the presence of disease at more than one extranodal site (P = 0.05) were once again identified as independent risk factors in predicting CNS relapse. However, in this analysis, when the multivariate analysis was repeated with the inclusion of either a high or a high intermediate International Prognostic Index (IPI) as a unique parameter, it replaced both (raised serum LDH) and (more than one extranodal site) as the only factor independently associated with a high risk of CNS relapse (data in Table V). This paper would appear to demonstrate robust efficacy of a programme of CNS prophylaxis using both intrathecal and high-dose systemic chemotherapy. It is interesting to note that this was achieved with a relatively well-tolerated dose of high-dose methotrexate (3 g/m²) as other reports include dose levels two times or more above this dose.
Recently, the same group has published the results of a randomised trial of 708 patients between the ages of 61 and 69 years (Tilly et al, 2003). In this second report the patients were randomised to receive the same ACVBP schedule with intrathecal methotrexate and high-dose systemic chemotherapy and this group was compared with the outcome of patients receiving standard CHOP chemotherapy without any CNS-directed therapy. All patients in this study were poor risk according to the non age-adjusted IPI. CNS progression or relapse occurred more frequently in the CHOP group (P = 0.004) and in terms of overall survival there was a superior outcome using the ACVBP schedule (P = 0.036). This study would appear to further demonstrate the efficacy of the use of the ACVBP schedule incorporating CNS-directed therapy. It can be argued that at least some of the reduced CNS relapse might be due to more intensive systemic therapy rather than the CNS-directed therapy itself, but this is probably not an important distinction if control of CNS relapse is achieved in either way.

Conclusions

All adult patients with Burkitt or LBL should receive CNS-directed therapy with both intrathecal and high-dose systemic chemotherapy. There is no evidence to support the routine use of prophylactic CNS-directed therapy in adult patients with low grade lymphomas.

The most important outstanding problem is to decide which adult patients with DLBCL should receive CNS-directed therapy. It would appear reasonable that patients with involvement of specific-anatomical sites, where a high risk of CNS relapse has been identified, should receive treatment. This should probably also be with both intrathecal and high-dose systemic chemotherapy. Treatment of these patients, because of their rarity, will only impact on a small proportion of DLBCL patients at risk of CNS relapse. Reduction of the overall incidence of CNS relapse will involve targeting patients with aggressive disease and there would be appear to be three possible ways of defining the population who should receive CNS-directed therapy.

These are those patients with:

1. raised serum LDH and involvement of more than one extranodal site (15% of all DLBCL);
2. a high IPI score (high or high intermediate) (38% of all DLBCL);
3. a raised serum LDH (50% of all DLBCL).

This would involve treating approximately 15%, 38% or 50%, respectively, of all patients with DLBCL and will help to prevent CNS relapse in an increasing proportion of the patients at risk.

The decision as to which of these strategies should be followed will depend on the perception of the balance between the ‘over treatment’ of a wider group of patients that includes a high proportion of patients who may be at risk (greater ‘sensitivity’ of therapy) compared with treatment of a smaller number of more accurately targeted patients and ‘missing’ some patients who will still suffer a CNS relapse (greater ‘specificity’ of therapy).

References


