CNS disease in younger patients with aggressive B-cell lymphoma: an analysis of patients treated on the Mabthera International Trial and trials of the German High-Grade Non-Hodgkin Lymphoma Study Group


1Department of Hematology, Oncology and Stem Cell Transplantation, Asklepios Hospital St. Georg, Hamburg; 2Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Leipzig; 3Internal Medicine II—Oncology Center, Hematology, Immunology, Internal Oncology, Palliative Medicine, St. Bernward Hospital, Hildesheim, Germany; 4Department of Oncology, University of Lund, Lund, Sweden; 5Peter MacCallum Cancer Institute, Division of Haematology, East Melbourne, Australia; 6Internal Medicine III, Department of Hematology, Oncology, Stem Cell Transplantation, Klinikum Chemnitz, Chemnitz; 7Department of Hematology and Oncology, University of Gottingen, Gottingen; 8Department of Internal Medicine I, Saarland University, Homburg/Saar, Germany

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Background: To describe incidence, risk factors, and influence of treatment on occurrence of central nervous system (CNS) relapse/progression in younger patients with aggressive B-cell lymphoma.

Patients and methods: We analyzed 2210 patients with aggressive B-cell lymphoma treated on various studies for CNS relapse/progression. Treatment consisted of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) ± etoposide. Six hundred and twenty patients also received rituximab. CNS prophylaxis was intrathecal methotrexate on High-CHOEP and MegaCHOEP phase III studies if upper neck, head, bone marrow, or testes were involved.

Results: Fifty-six of 2196 patients (2.6%) developed CNS disease. It occurred early (median 7.0 months), median survival was 5.0 months. Patients with age-adjusted International Prognostic Index (aaIPI) 0 or 1 treated with rituximab showed a low risk for CNS disease (2-year rates: 0% or 0.5%), and rituximab decreased the risk (relative risk 0.3, 95% confidence interval 0.1–0.9, \( P = 0.029 \)). Patients with aaIPI 2 or 3 showed a moderate risk (4.2%–9.7%) and no significant reduction of CNS disease with rituximab. CNS prophylaxis was of no significant benefit.

Conclusions: In younger patients with aaIPI 0 or 1, CNS relapse/progression is very rare; in patients with aaIPI 2 or 3, the risk is higher (up to 10%) and requires new diagnostic strategies and treatment.

Key words: aggressive lymphoma, central nervous system relapse, DLBCL, rituximab

introduction

Relapse or progression in the central nervous system (CNS) is a rare but mostly fatal event for patients with aggressive B-cell lymphoma. We and others reported that the incidence of CNS disease was between 2% and 7% for patients treated with state-of-the-art chemotherapy [1–3]. Part of the variations in incidences of CNS disease may reflect inclusion of patients with different histologic subtypes. If the addition of etoposide [2] or rituximab [4–6] to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) reduces the risk of CNS relapse remains controversial.

More sensitive diagnostic tools [7, 8], the identification of risk factors for CNS relapse [2, 3, 6, 9], and the use of prophylactic measures like cranial irradiation [3] and intrathecal (IT) or CNS-directed systemic chemotherapy [10] have all been claimed to help avoid the occurrence of CNS events in patients with newly diagnosed aggressive lymphoma.

Here, we report on \( > 2200 \) patients <61 years with aggressive B-cell lymphoma treated on the Mabthera International Trial (MInT) and various DSHNHL (German High-Grade Non-Hodgkin Lymphoma Study Group) protocols in order to describe the incidence, outcome, and risk factors for CNS disease and challenge the efficacy of prophylactic IT MTX (methotrexate) to prevent CNS disease in younger patients treated with modern chemoimmunotherapy including rituximab.

patients and methods

patients and treatments

From September 1993 to July 2007, 2210 patients with aggressive B-cell lymphoma <61 years were enrolled on the Mabthera International Trial
(MinT) [11] and five DSHNHL studies: the NHL-B1 study [12], the High-CHOEP phase II [13] and phase III [14] studies, and the MegaCHOEP phase II [15, 16] and phase III [17] studies. A complete list of cooperative groups and participating centers is given in the Appendix (available as supplementary data on *Annals of Oncology* online). Thousand eight hundred and nine (82.4%) of these patients had been diagnosed with diffuse large B-cell lymphoma (DLBCL), 387 (17.6%) patients with other aggressive B-cell histologies: follicular lymphoma grade III (n = 97), follicular lymphoma grade III + DLBCL (n = 76), lymphoblastic precursor B-cell lymphoma (n = 3), Burkitt lymphoma (n = 4), Burkitt-like lymphoma (n = 29), primary effusion lymphoma (n = 1), blastic mantle cell lymphoma (n = 19), and aggressive marginal zone lymphoma (n = 22). Sixty-five patients suffered from aggressive B-cell lymphoma, which could not be further classified due to technical or other reasons.

All studies used six or eight courses of CHOP or CHOP-like chemotherapy with or without etoposide (E) given at 2- or 3-week intervals for systemic chemotherapy. The doses of C, H, E, and P varied according to the study protocol with the highest doses necessitating transplantation of autologous hematopoietic stem cells [15, 16].

Rituximab (six infusions at 375 mg/m²) was added to chemotherapy in the randomized MinT [11] and the MegaCHOEP phase II and III trials [16, 17]. For further details of these studies see supplementary Table S2 (available at *Annals of Oncology* online) and the respective publications [11–17].

### CNS disease and prophylaxis

Involvement of the CNS with parenchymal brain lesions, spinal cord involvement, lymphomatous meningitis, or combinations thereof was defined as relapse or as progression if patients had not achieved a complete remission after first-line therapy. Patients with lymphoblastic lymphoma treated on the NHL-B1 study [12] and patients with lymphoma manifestations in the upper neck, head (including sinuses, orbita, oral cavity, tongue, and salivary glands), bone marrow (BM), or tests treated on the High-CHOEP [14] and MegaCHOEP [17, 18] phase III studies were to have a lumbar puncture with subsequent injection of MTX (15 mg each on days 1 and 15 of the first two courses) and cytocentrifuge preparations of cerebrospinal fluid (CSF) were evaluated for the presence of lymphoma cells. Of the 65 patients with an extranodal involvement, lymphomatous meningitis, or combinations thereof was pathology confirmed the histology to represent aggressive B-cell lymphoma but could not be further classified due to technical or other reasons. Brain imaging was done only when clinical symptoms suggested involvement; no routine imaging was carried out.

### Statistical analysis

The primary end point was time to CNS disease defined as time from randomization to disease progression in the CNS, treatment failure with CNS involvement at the end of therapy, or CNS relapse after a complete response (CR)/complete response with remaining uncertainty had been reached. The secondary end point was survival after CNS disease. Survival was defined as time from diagnosis of CNS disease until death from any cause. Time to CNS disease and survival were estimated according to the method of Kaplan and Meier. Estimators at 2 years are given with 95% confidence limits. For univariate analyses, log-rank tests were carried out; P values <0.05 were considered significant. All factors with P <0.10 were included in the multivariate analyses. To identify prognostic factors for CNS disease, we used the proportional hazard model. We proceeded in a stepwise approach including single factors as described by Collet [19]. Only patients with complete data (2190 patients) were included in the multivariate analyses. The strength of prognostic factors was estimated by determining relative risks (RR) and the corresponding 95% confidence intervals (CIs). All calculations were made in PASW (SPSS) Version 18.0.

### Results

After exclusion of 14 patients (13 patients with DLBCL and 1 patient with follicular lymphoma grade III and DLBCL) found to have CNS involvement at diagnosis 2196 patients with aggressive, mostly DLBCL and <61 years remained eligible for this analysis. Major patient and disease characteristics of 2140 patients without and 56 patients with CNS disease are given in Table 1. The median age of all patients studied was 48 years with almost 60% of patients being male. Overall, 309 patients were treated on the MegaCHOEP phase II or III protocols [16, 17] and 256 patients on the High-CHOEP protocols.

**Table 1.** Clinical characteristics of 2196 younger patients with aggressive B-cell lymphoma

<table>
<thead>
<tr>
<th></th>
<th>With CNS event (n = 56)</th>
<th>Without CNS event (n = 2140)</th>
<th>All patients (n = 2196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>30 (53.6)</td>
<td>1267 (59.2)</td>
<td>1297 (59.1)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>50.5 (22–60)</td>
<td>48 (18–60)</td>
<td>48 (18–60)</td>
</tr>
<tr>
<td>LDH &gt; N, n (%)</td>
<td>33 (58.9)</td>
<td>739 (34.5)</td>
<td>772 (35.2)</td>
</tr>
<tr>
<td>ECOC &gt; 1, n (%)</td>
<td>12 (21.4)</td>
<td>171 (80)</td>
<td>183 (83.3)</td>
</tr>
<tr>
<td>Stage III/IV, n (%)</td>
<td>34 (60.7)</td>
<td>809 (37.8)</td>
<td>843 (38.4)</td>
</tr>
<tr>
<td>Extranodal involvement &gt; 1, n (%)</td>
<td>24 (42.9)</td>
<td>342 (16.0)</td>
<td>366 (16.7)</td>
</tr>
<tr>
<td>aIPI, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13 (23.2)</td>
<td>907 (42.4)</td>
<td>920 (41.9)</td>
</tr>
<tr>
<td>1</td>
<td>18 (32.1)</td>
<td>840 (39.3)</td>
<td>858 (39.1)</td>
</tr>
<tr>
<td>2</td>
<td>14 (25.0)</td>
<td>299 (14.0)</td>
<td>313 (14.3)</td>
</tr>
<tr>
<td>3</td>
<td>11 (19.6)</td>
<td>93 (4.3)</td>
<td>104 (4.7)</td>
</tr>
<tr>
<td>Bulky disease¹, n (%)</td>
<td>31 (55.4)</td>
<td>959 (44.8)</td>
<td>990 (45.1)</td>
</tr>
<tr>
<td>B-symptoms², n (%)</td>
<td>25 (44.6)</td>
<td>631 (29.5)</td>
<td>656 (29.9)</td>
</tr>
<tr>
<td>DLBCL, n (%)</td>
<td>42 (75)</td>
<td>1767 (82.6)</td>
<td>1809 (82.4)</td>
</tr>
<tr>
<td>Other aggressive B-NHL³, n (%)</td>
<td>14 (25)</td>
<td>373 (17.4)</td>
<td>387 (17.6)</td>
</tr>
</tbody>
</table>

¹One patient in MegaCHOEP phase II without data on ECOC status.
²Two patients in MegaCHOEP phase II without data on extranodal involvement >1.
³One patient in MegaCHOEP phase II without data on aIPI.
⁴One patient in MegaCHOEP phase II without data on bulk.
⁵One patient in MegaCHOEP phase III, one patient in MegaCHOEP phase II, and one patient in MinT study without data on B-symptoms.
⁶Follicular lymphoma III (97), follicular lymphoma III⁺ + DLBCL (76), lymphoblastic precursor B-cell lymphoma (3), Burkitt’s lymphoma (4), Burkitt-like (29), primary effusion lymphoma (1), mantle cell lymphoma (19), aggressive marginal zone lymphoma (22), not otherwise specified (65), and B unclassified -tech. insufficient mat. (71). These were patients whose diagnostic material did not allow further subclassification which means that reference pathology confirmed the histology to represent aggressive B-cell lymphoma but not exact subclassification was possible because material was insufficient.

aaIPI, age-adjusted International Prognostic Index; CHOE, cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOC, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.
used escalated doses of cyclophosphamide, adriamycin, etoposide, and prednisolone; dose escalation did not improve treatment results [14, 17]. Table 1 also shows the percentages of single factors of the International Prognostic Index (IPI) [20] present in patients with or without CNS disease as well as the frequencies of other clinical features (B-symptoms, bulky disease) reported to influence the risk of CNS involvement.

Overall, 56 of the 2196 patients (2.6%) developed CNS disease. The estimated 2-year incidences of CNS disease for patients with DLBCL and patients with other aggressive B-cell lymphomas were 2.2% and 2.5%, respectively ($P = 0.261$). The median time from diagnosis to CNS disease was 7.0 months (lower quartile: 4.9 months; upper quartile: 16.4 months; range: 0.2–85.2 months); median survival after the occurrence of CNS relapse or progression was 5.0 months (Figure 1). Interestingly, no relapse occurred between 12.9 and 46.6 months after diagnosis in patients treated with rituximab and chemotherapy, while patients given only chemotherapy relapsed continuously during the observation period.

The majority of patients (58.9%) with CNS disease progressed during systemic therapy or until 2 months thereafter. Only 23 patients (41.1%) had achieved a complete remission but relapsed after a CR had been attained. More than two-thirds (69.6%) of patients with CNS involvement developed lymphoma in the CNS and other site(s) simultaneously.

Because the case report forms of the MInT study did not differentiate between meningeal and brain involvement, we are unable to calculate the overall number and percentage of patients with leptomeningeal or brain involvement. In the MegaCHOEP phase III trial, 7 of the 12 patients (58.3%) developed parenchymal disease and the other 5 patients presented with leptomeningeal involvement.

**risk factors for CNS disease**

The age-adjusted International Prognostic Index (aaIPI) [20] especially if used to prognosticate the risk of CNS disease for patients treated with state-of-the-art immunochemotherapy clearly separated two risk groups: patients with an aaIPI of 0 or 1 showed a cumulative risk for CNS disease of 0.0% and 0.5% (95% CI 0.0%–1.5%), respectively, and form a low-risk group, while patients with an aaIPI of 2 or 3 showed cumulative risks of 4.2% (95% CI 0.9%–7.5%) and 9.7% (95% CI 1.7%–17.7%) at 2 years, respectively (Table 2).

Because even in patients with aaIPI 3 the incidence of CNS disease was not deemed high enough to justify CNS prophylaxis in every single patient, we searched for other variables potentially able to more precisely characterize a ‘high-risk’ group for CNS events.

By univariate analysis, each of the IPI factors (except age) as well as each of the aaIPI factors increased the risk for CNS disease in all 2190 patients with complete datasets as well as in the 606 patients treated with rituximab and chemotherapy.

Consequently, both higher aaIPI and IPI (data not shown) significantly increased the risk for CNS disease in all patients and in patients treated with chemotherapy plus rituximab (Figure 2A and B). In addition, the presence of B-symptoms at diagnosis increased the risk for CNS involvement, while age (by decade), sex, histology (DLBCL versus other histologies), or bulky disease did not significantly influence the risk to acquire CNS disease. The optimal risk model found by multivariate Cox regression analysis identified two IPI factors, namely ‘involvement of more than one extranodal site’ (RR 3.2, 95% CI 1.9–5.5) and ‘elevated lactate dehydrogenase (LDH)’ (RR 2.9, 95% CI 1.6–5.1) as highly significant risk factors ($P < 0.001$ for both factors) if all 2190 patients with complete data were considered (see supplementary Table S1, available at Annals of Oncology online). Using this model, 8.9% of all patients would have belonged to the high-risk group.

Figure 1. Survival of 56 patients with aggressive B-cell lymphoma after relapse or progression in central nervous system.

**Table 2. Cumulative risk of central nervous system disease in younger patients with aggressive B-cell lymphoma according to the aaIPI**

<table>
<thead>
<tr>
<th>aaIPI</th>
<th>All patients ($n = 2196$)</th>
<th>With rituximab ($n = 620$)</th>
<th>Without rituximab ($n = 1576$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Incidence$^a$</td>
<td>No. Incidence$^a$</td>
<td>No. Incidence$^a$</td>
</tr>
<tr>
<td>0</td>
<td>920 0.8% (0.2%–1.4%)</td>
<td>166 0.0%</td>
<td>754 1.0% (0.2%–1.8%)</td>
</tr>
<tr>
<td>1</td>
<td>858 2.0% (1.0%–3.0%)</td>
<td>243 0.5% (0.0%–1.5%)</td>
<td>615 2.6% (1.2%–4.0%)</td>
</tr>
<tr>
<td>2</td>
<td>313 4.4% (1.9%–6.9%)</td>
<td>157 4.2% (0.9%–7.5%)</td>
<td>156 4.6% (0.9%–8.3%)</td>
</tr>
<tr>
<td>3</td>
<td>104 11.4% (5.1%–17.7%)</td>
<td>53 9.7% (1.7%–17.7%)</td>
<td>51 13.2% (3.4%–23.0%)</td>
</tr>
</tbody>
</table>

$^a$Estimated cumulative incidence (95% confidence interval) of relapse at 2 years after randomization.

aaIPI, age-adjusted International Prognostic Index.
Disappointingly, only 28.6% of patients who actually developed CNS disease would have been captured by this definition and only 8.2% of this high-risk group actually developed a CNS event. Restricting the multivariate analysis to 616 patients treated with rituximab and chemotherapy, the optimal risk factor model included the IPI factor ‘advanced stage (III, IV)’ (RR 5.4, 95% CI 1.2–24.1, \( P = 0.029 \)) and again ‘elevated LDH’ (RR 3.8, 95% CI 0.8–17.2, \( P = 0.081 \)) as most important factors for experiencing CNS disease (supplementary Table S1, available at Annals of Oncology online). One hundred and ninety-five of the 620 patients (31.5%) would have belonged to this high-risk group and 78.6% of patients who actually developed CNS disease would have been included. However, only 11 patients (5.6%) of this high-risk group actually developed CNS disease.

**treatment and CNS disease**

etoposide. The NHL-B1 study had randomized patients to CHOP or CHOEP [12]. As reported previously [2], the addition of etoposide to CHOP significantly reduced the incidence of CNS events in this cohort [2-year rate of CNS disease 2.4% (95% CI 0.6%–4.2%) versus 1.0% (95% CI 0.0%–2.2%), \( P = 0.05 \)]. In the MinT study, patients were stratified according to the chemotherapy regimens used in different countries and were randomly assigned to receive rituximab or not [11]. No significant differences in time to CNS disease were seen between CHOP without and with etoposide (CHOEP) regardless if rituximab had been administered or not. The estimated 2-year incidences of CNS disease were 0.8% (95% CI 0.0%–1.8%) versus 1.8% (95% CI 0.4%–3.2%) when CHOP was compared with CHOEP in the total MinT population (\( P = 0.368 \)) and 0.0% versus 0.6% (95% CI 0.0%–1.8%, \( P = 0.877 \)) for patients treated with rituximab.

rituximab. Of the 610 patients treated with rituximab and chemotherapy, 14 patients (2.3%) developed relapse or progression in the CNS. In the MinT study, which included only patients with IPI 0 and 1, three patients (0.7%) treated with rituximab and chemotherapy experienced a CNS event. Figure 3A shows the Kaplan–Meier estimates for time to CNS disease with a significant difference in favor of rituximab (\( P = 0.035 \)). In a multivariate analysis including all 1570 patients treated with CHO(E)P-14 or -21 with or without rituximab and adjusting for IPI factors (except age), rituximab also significantly decreased the RR for CNS disease to 0.3

**Figure 2.** Time to central nervous system events according to age-adjusted International Prognostic Index (aaIPI) in all 2196 patients analyzed (A) and in rituximab-treated patients only (B) (\( n = 620 \)).

**Figure 3.** Time to central nervous system events in low-risk patients [age-adjusted International Prognostic Index (aaIPI) 0 or 1] on the MinT study (A) and in high-risk patients [aaIPI 2 or 3] on the MegaCHOEP phase III study (B) who received MegaCHOEP therapy with and without rituximab.
(CI 0.1–0.9, P = 0.029). In contrast, of the 210 high-risk patients (aaIPI 2 or 3) treated on the MegaCHOEP studies, 11 patients (5.2%) developed CNS disease. The addition of rituximab to MegaCHOEP chemotherapy did not significantly reduce the risk for CNS events (P = 0.733) (Figure 3B). There was also no difference when the model was adjusted for IPI factors (RR 0.8, 95% CI 0.3–1.8, P = 0.565).

CNS prophylaxis

Prophylaxis of CNS events with IT MTX was mandatory in the High-CHOEP [14] and MegaCHOEP [17, 18] phase III studies for patients with risk factors as specified in the ‘Patients and Methods’ section. Patients on other studies were not intended to receive CNS prophylaxis. Because case report forms failed to exactly show which lymph nodes in the upper or lower neck were involved, we cannot precisely tell how many protocol violations occurred. However, we were able to compare CNS events occurring in patients who actually did or did not receive MTX prophylactically. No significant differences in cumulative risks of CNS disease were seen (Figure 4).

We also analyzed the incidence of CNS events in patients traditionally deemed to be at high risk for CNS relapse. There were 141 patients (6.4%) with BM involvement at the time of diagnosis; 4 of these patients (2.8%) experienced a CNS relapse. Two patients had no complete information on prophylaxis, one patient each had received or not received prophylaxis. Twenty-five patients (1.1%) had involvement of testes at diagnosis; four of them (16.0%) experienced a CNS relapse later on. Of note, these four patients had received chemotherapy only; no patient with initial involvement of the testes and treated with chemotherapy and rituximab experienced CNS disease regardless if IT MTX had been given or not. There was also no indication that patients with involvement of orbita, paranasal sinuses, nasal and oral cavity, tongue, salivary glands, testes, or BM had less CNS events after prophylaxis (P = 0.295).

Figure 4. Cumulative risk of central nervous system disease in patients who received or did not receive IT MTX (patients receiving MACOP-B as systemic therapy were excluded to avoid bias caused by i.v. administration of MTX).

discussion

Relapse or progression in the CNS is an uncommon event in patients with aggressive B-cell lymphoma with incidences between 2% and 7% depending on the median age of the patient cohort, the presence of other risk factors like elevated LDH, advanced stage, more than one extranodal lesion, poor performance status, B-symptoms, and the treatment chosen. Most recent reports found the IPI or the aaIPI significant [1, 3, 4], although not each of the individual factors contributing to the (aa)IPI increased the risk of CNS disease [5, 21].

We found a cumulative incidence of 2.6% for CNS disease in a large cohort of younger patients (<61 years) with aggressive B-cell lymphoma. No significant difference (P = 0.142) was found between 1809 patients with DLBCL (2.3%) and 387 patients with other aggressive B-cell lymphomas (3.6%).

The overall incidence was reduced to 2.3% if only patients treated with state-of-the-art chemoimmunotherapy were considered. Other groups reported that rituximab did [5, 6, 21] or did not decrease [4] CNS events. Probably, the percentage of patients with higher IPI scores represented in the various studies made the difference. In our study, only patients with aaIPI 0 or 1 benefited from the addition of rituximab, while patients with aaIPI 2 or 3 showed a higher incidence of CNS disease regardless if rituximab was administered or not. In all studies reporting a positive effect of rituximab, the decrease of CNS events was modest and investigators agreed that the reduction of CNS disease was more likely to follow the general decrease in relapse rates seen with rituximab rather than reflect a specific effect directed to the CNS. This is supported by the fact that close to 70% of CNS events (69.6%) in our rituximab-treated patients were isolated relapses. Penetration of rituximab to the CNS obviously is not good enough [22] to prevent lymphoma emanating from CNS sanctuaries. Interestingly, some studies [5, 21] including ours show that patients treated with rituximab experience almost exclusively early CNS disease, whereas later relapses (>1 year) seem exceedingly rare. This supports the notion that late relapses reflect failure to control systemic disease and seem more amenable to prevention by rituximab.

With the current study, we confirm that etoposide can prevent CNS disease; however, its prophylactic effect was no longer detectable if given together with rituximab. This is reminiscent of a finding from the MInT study that patients treated with CHOEP experience less relapses in total if compared with patients given CHOP. This effect was also lost when rituximab was added to CHOEP and CHOP [11].

Importantly, the incidence of CNS relapse or progression was very low (0.7%) in patients with aaIPI 0 or 1 treated with chemotherapy and rituximab. Taking into account the low incidences of CNS disease reported for such patients also by other groups, the toxicity of prophylactic IT MTX [22], and the uncertainties pertinent to its efficacy, we suggest to change from faith- to evidence-based medicine [23] and abandon CNS prophylaxis at least in younger patients with aaIPI 0 or 1.

Our attempts to more precisely characterize a group of younger patients deserving CNS prophylaxis were less successful than in the elderly [6]. While in patients between 60 and 80 years, we were able to separate a small group of
patients (4.8%) with involvement of >1 extranodal site, elevated LDH, and poor performance status who ran a 33.5% risk for CNS disease, even the best models selecting younger patients with elevated LDH and involvement of more than one extranodal site (for all patients studied) or advanced stage (for patients treated with rituximab and chemotherapy) failed to catch the vast majority of patients prone to develop CNS disease and the risk for R-CHOEP-treated high-risk patients to actually experienced CNS disease was such low (5.6%) that staying with the (aa)IPI and restricting prophylaxis to patients with aIPI 2 and 3 appears adequate and more practical. We acknowledge the limitation that the (aa)IPI was used to select patients for specific studies and the differing systemic treatment might have affected the incidences of CNS disease. Clinical risk factors making up the IPI seem unsuited tools to predict the propensity of lymphoma cells to travel to lymph nodes to the CNS. Recent investigations revealed major differences in the genetic background of DLBCL with and without CNS involvement [24]; homing factors for tumor cells may also play an important role [25]. Such biological characteristics may be more promising in order to predict spread to the CNS.

Of note, several recent studies from the pre-rituximab era [3] and in patients treated with rituximab [5, 6, 21] found no evidence that prophylaxis (whole brain irradiation but mostly IT MTX) protected against CNS relapse or progression. Although we still cannot formally exclude that patients with certain extranodal lymphoma manifestations (e.g. testes) might benefit from prophylaxis—patient numbers even in large studies become rather small if specific sites are analyzed separately—our findings support recommendations to stop current practice of IT prophylaxis in patients with DLBCL and search for other strategies [26]. One promising alternative might be the use of i.v. MTX, although the high doses necessary to reach effective doses in the CNS will cause additional toxicity and effectiveness has not been formally demonstrated. The low incidence of CNS disease reported by the GELA [10] after implementation of consolidative therapy with high-dose MTX, etoposide, ifosfamide, and cytosine–arabinoside, however, is remarkable and lends some attraction to this approach. Because CNS disease tends to occur early in most patients with DLBCL and is frequently is associated with other lymphoma manifestations, we believe that systemic MTX should be administered as early as possible after diagnosis. The DSHNHL will adopt such strategy in future studies for elderly high-risk patients. For younger patients with aIPI 0 or 1, diagnostic and prophylactic measures to the CNS will no longer be mandatory, while in patients with aIPI 2 or 3, we opted to improve diagnostic measures. These patients will have routine CNS imaging and fluorescence-activated cell sorter analyses of CSF to diagnose CNS manifestations with higher sensitivity [8]. CNS-positive patients will be treated on a separate protocol including agents with high penetration to the CNS.

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