An Update on Therapy of Primary Central Nervous System Lymphoma

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The most important advance in primary central nervous system (CNS) lymphoma treatment has been the convincing data that high-dose methotrexate-based chemotherapy regimens improve survival compared to historical controls treated with radiotherapy alone. However, the optimal treatment approach is still unclear and therapy can be associated with long-term neurotoxicity. Current research focuses on maximizing survival while minimizing neurologic sequelae.

Primary central nervous system lymphoma (PCNSL) is an extranodal non-Hodgkin lymphoma (NHL) that arises from the brain parenchyma, eyes, meninges or spinal cord in the absence of systemic disease. Recent clinical trials have focused increased interest on this cancer, particularly because of its chemosensitivity compared to other primary brain tumors.

Prognostic Factors
Baseline prognostic factors have a strong influence on the outcome of patients with PCNSL. The most consistent prognostic factors among several studies are age and performance status. Ferreri and colleagues analyzed 378 patients retrospectively from a multicenter series and identified five prognostic factors that were associated with worse survival: 1) age more than 60 years; 2) ECOG performance status more than 1; 3) elevated serum lactate dehydrogenase level; 4) high CSF protein; and 5) involvement of deep regions of the brain. An analysis of 338 patients from Memorial Sloan-Kettering Cancer Center could identify age and Karnofsky performance status (KPS) as the only significant prognostic factors; the other three failed to reach significance.

Molecular markers have been identified as a prognostic factor for lymphomas. Rosenwald and colleagues identified three molecularly distinct forms of systemic diffuse large B-cell lymphoma (DLCL) based on gene expression patterns: germinal center-like, the activated B-cell–like (ABC) and the so-called type III. Patients with germinal center B-cell–like DLCL have a significantly better overall survival that is independent from clinical prognostic factors; the other three failed to reach significance.

Radiotherapy
Extranodal NHL outside the CNS is generally a highly radiosensitive disease. When treated with RT alone with doses of 40-50 Gy, systemic stage I, NHL has local control of 90%, low incidence of local relapse and prolonged survival. In contrast, PCNSL, which is also a stage I, NHL, relapses frequently and has a much lower survival rate. Historically, whole-brain RT (WBRT) resulted in a median survival of only 12 to 18 months and a 5-year survival rate of less than 5%. A more recent retrospective analysis of 132 patients treated with RT alone in the 1990s showed a median survival time of 18 months but a higher 5-year survival rate of 18%. Most authors agree that focal RT is not indicated for PCNSL due to the multicentric and infiltrating nature of the disease, but WBRT has never been compared to focal...
RT in a randomized controlled study. Shibamoto and colleagues14 reported a retrospective analysis of patients who underwent focal RT with margins < 4 cm or ≥ 4 cm. Patients with smaller margins had an out-of-field recurrence rate of 83% compared to 22% in the group with wider margins. Median survival was longer in the group that received larger margins (28.5 months vs. 15 months, \( P = 0.057 \)). These data should be interpreted with caution, but it is clear that focal RT with narrow margins is inadequate treatment for PCNSL. Whether focal RT with wider margins is as effective as WBRT and would have less neurotoxicity for patients with single lesion PCNSL is unclear and could only be answered by a randomized controlled trial.

The RTOG15 conducted a phase II study that evaluated the efficacy of WBRT as first-line treatment for PCNSL. Forty-one patients were enrolled and underwent WBRT with 40 Gy plus a 20 Gy boost to the gross tumor with a 2 cm margin. The median survival was only 12 months. Response was measured in 26 patients by head CT and 16 patients had a complete response (CR). Recurrence of disease in the brain occurred in 61% of patients, and most relapses occurred within the region that received 60 Gy. These data suggest that there is no clear dose-response over 40 Gy.

More recent data regarding the dose of RT came from studies that combined chemotherapy with WBRT. In two sequential studies, Bessell and colleagues13 studied the effect of a reduced dose of RT in patients with PCNSL after achieving a complete response (CR) with chemotherapy. After chemotherapy,31 patients from the first study received 45 Gy WBRT. In the second study, the RT dose was reduced to 30.6 Gy in 26 patients who had a CR after chemotherapy. Among 25 patients younger than 60 years who achieved a CR after chemotherapy, the 3-year relapse risk was higher in the group that received the lower dose of RT (25% vs. 83%, \( P = 0.01 \)). Moreover, RT dose was also the only predictor of overall survival in this group (92% vs. 60% for patients receiving 45 or 30.6 Gy, respectively). During the RTOG study 93-10,14 there was growing evidence that long-term survivors of combined MTX-based chemotherapy and WBRT were developing severe permanent neurotoxicity. The study was modified so patients who achieved CR after chemotherapy would receive 36 Gy hyperfractionated RT instead of 45 Gy standard WBRT. There was no difference in progression-free survival, overall survival or late neurotoxicity between those \((n = 27)\) who received 45 Gy and those \((n = 13)\) who received 36 Gy hyperfractionated RT. However, patients in the hyperfractionated RT group developed neurotoxicity later than those who received conventional RT.15 Therefore, the data conflict whether reducing disease burden with chemotherapy can safely permit a reduction of the RT dose without compromising tumor control.

### Combined Chemotherapy and Radiotherapy

Chemotherapy with high-dose MTX-based regimens followed by WBRT has been shown in multiple phase II trials to increase survival (medians from 32-60 mo) compared to RT alone (Table 1).1,14,16-18 Although high-dose MTX is an established chemotherapy agent for PCNSL, the optimal dose and the best combination regimen remain unclear. Omuro et al reported on 17 patients treated with 1 g/m² MTX plus thiopeta, procarbazine and IT MTX followed by WBRT achieving a CR in 76%, PR in 12% and progression of disease in 12%. Median overall survival was 32 months and median disease-free survival was 18 months. Two patients were alive and disease free at 12 years of follow-up. Twenty-nine percent of patients had developed and died from delayed neurotoxicity.16

Abrey and colleagues1 used 3.5 g/m² of intravenous MTX in combination with IT MTX, procarbazine and vincristine, followed by WBRT and two cycles of high-dose cytarabine. The response rate to pre-RT chemotherapy was 90% and median survival was 60 months.

The results from these and other trials led to the multicenter RTOG study 93-10 that enrolled 102 patients with newly diagnosed PCNSL.14 This protocol consisted of high-dose MTX (2.5 g/m²), vincristine, procarbazine, and IT MTX followed by 45 Gy WBRT and high-dose cytarabine. Fifty-eight percent achieved a CR and 36% had a PR after pre-irradiation chemotherapy. Progression-free survival was 24 months and overall survival was 37 months. There was no prospective neuropsychological testing and the 15% incidence of neurotoxicity reported was a minimum.

Poortmans and colleagues18 reported a multicenter European study with 52 patients treated with high-dose MTX (3 g/m²), teniposide, carmustine, IT MTX, IT cytarabine and IT hydrocortisone preceding 40 Gy of WBRT. The overall response rate was 81% and median survival was 46 months. However, these good results were associated with significant acute chemotherapy-related toxicity and a 10% toxic death rate. Moreover, patients older than 65 years, who are known to have a worse prognosis, were excluded from the protocol.

### Treatment-Related Neurotoxicity

Neurotoxicity related to the combination of WBRT and high-dose MTX presents as a progressive subcortical dementia characterized by psychomotor slowing, executive and memory dysfunction, behavioral changes, gait ataxia, and incontinence. Imaging findings reveal diffuse white matter disease and cortical-subcortical atrophy.19 Autopsy data show white matter damage with gliosis, thickening of small vessels, and demyelination.20 In a retrospective cohort of 185 patients treated for PCNSL, the 5-year cumulative incidence of neurotoxicity was 24%.19 However, the incidence is much higher in patients older than 65 years treated with high-dose MTX and WBRT.1

### Chemotherapy Alone

Due to the high-risk of delayed neurotoxicity in patients who receive high-dose MTX and WBRT, avoiding RT, particularly in older patients, has been the current therapeutic
strategy. However, withholding WBRT in younger patients is more controversial because it can compromise disease control, although in a retrospective analysis of 378 patients, Ferreri and colleagues observed that WBRT did not improve survival in patients achieving CR after high-dose MTX. Many studies have reported excellent responses with high-dose MTX-based regimens, but overall survival is not as robust as in studies using combined modality therapy with more rapid relapses occurring a median of 6-16 months following diagnosis. For example, Abrey and colleagues compared 22 patients over age 60 treated with high-dose MTX (3.5 g/m²), procarbazine, vincristine, high-dose cytarabine, IT MTX and deferred RT to 12 patients older than 60 treated with the same chemotherapy regimen plus 45 Gy WBRT. The median overall survival was the same in both groups (33 and 32 months, respectively), but those patients who received upfront WBRT died primarily of neurotoxicity and those in the deferred RT group died mostly of lymphoma progression. The incidence of dementia in the group who received chemotherapy and WBRT was 83% compared to 5% in the group with chemotherapy alone.

The European Organization for the Research and Treatment of Cancer (EORTC) Brain Tumor Group reported a multicenter phase II study with 50 patients older than 60 years treated with chemotherapy alone as initial treatment. The protocol consisted of high-dose MTX (1 g/m²), lomustine, procarbazine, methylprednisolone, IT MTX and IT cytarabine. Only 42% achieved a CR and 6% a partial response (PR). Overall median survival was 14 months, but this still compared favorably with a median survival of only 7 months after WBRT alone for older patients. Delayed treatment neurotoxicity was reported in 12% of patients.

Pels and colleagues reported the results of a pilot and phase II study with a complex chemotherapy regimen including high-dose MTX (5 g/m²), cytarabine, vincristine, ifosfamide, cyclophosphamide, vindesine, dexamethasone, IT MTX, IT cytarabine, IT prednisolone, and deferred RT. Sixty-five patients with newly diagnosed PCNSL were enrolled, including 35 patients older than 60 years. Sixty-one patients were assessable for response and 61% had a

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Regimen</th>
<th>Response Rate (%)</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
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<tr>
<td>Nelson et al 1992†</td>
<td>41</td>
<td>40 Gy WBRT with 20 Gy boost</td>
<td>NA*</td>
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<td>Ferreri et al 2001</td>
<td>17</td>
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<td>DeAngelis et al 2002</td>
<td>102</td>
<td>MPV (MTX 2.5 g/m²) + IT MTX + 36-45 Gy WBRT</td>
<td>94</td>
<td>24</td>
<td>36.9</td>
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<td>52</td>
<td>MTX (3 g/m²)/thiotepa/carmustine + IT MTX + IT cytarabine + 30 Gy WBRT with 10 Gy boost</td>
<td>81</td>
<td>NA</td>
<td>46</td>
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<tr>
<td>Omuro et al 2005</td>
<td>17</td>
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<td>88</td>
<td>18</td>
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<td>Abrey et al 2000†</td>
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<td>MTX (8 g/m²)</td>
<td>35.1</td>
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Abbreviations: PFS, progression-free survival; OS, overall survival; IT, intra-thecal; MPV, methotrexate, procarbazine, vincristine; MTX, methotrexate; NA, not available; PFS, progression-free survival; WBRT, whole-brain radiotherapy.

*After excluding patients with disease progression during radiotherapy, 26 patients were assessed by CT: 62% had a complete response (CR), 19% an almost CR and 19% a partial response.
†patients over age 60
Complications of IT chemotherapy include neurotoxicity, chemical meningitis and infection of the Ommaya reservoir. Infection of the Ommaya occurred in up to 19% of patients in one trial. This represents a serious complication for some patients and can lead to interruption of treatment. Currently, the authors add IT drug only to the treatment regimen of patients who have a positive CSF cytologic examination.

**Intrathecal Chemotherapy**

The need for IT chemotherapy for patients with PCNSL is controversial because systemic high-dose MTX and cytarabine produce tumoricidal levels in the CSF. Two retrospective studies suggest that patients with PCNSL do not benefit from additional IT chemotherapy through an Ommaya reservoir if they receive high-dose intravenous MTX. Complications of IT chemotherapy include neurotoxicity, chemical meningitis and infection of the Ommaya reservoir. Infection of the Ommaya occurred in up to 19% of patients in one trial. This represents a serious complication for some patients and can lead to interruption of treatment. Currently, the authors add IT drug only to the treatment regimen of patients who have a positive CSF cytologic examination.

**Ocular Lymphoma**

Ocular RT is often the standard treatment for primary ocular lymphoma or ocular involvement in PCNSL. A total dose of 35 to 40 Gy should be fractionated over 5 weeks and most patients require binocular treatment. Patients exhibit vitreal clearing and most experience improvement in vision. The efficacy of chemotherapy alone is controversial because it depends on penetration of the drug into the vitreous and intraocular pharmacokinetics are not well understood. One series of patients showed that therapeutic micromolar MTX concentrations can be achieved in the aqueous and vitreous humor after high-dose intravenous MTX (8 g/m²). An alternative is intra-ocular MTX which can clear tumor cells from the ocular compartment but requires multiple injections into each involved eye.

**Autologous Stem-Cell Transplant**

High-dose myeloablative chemotherapy followed by autologous stem-cell transplant (ASCT) is an effective salvage treatment for relapsed or primary refractory systemic NHL. There have been limited data on ASCT for PCNSL, and this approach should be considered experimental and restricted to clinical trials. Abrey and colleagues reported 14 patients with newly diagnosed PCNSL who had either PR or CR after high-dose MTX and high-dose cytarabine and underwent consolidation with myeloablative chemotherapy and ASCT using the carmustine, etoposide, cytarabine and melphalan (BEAM) regimen without WBRT. The overall median event-free survival was only 9.3 months and all but 1 patient experienced relapse within 7 months of the transplantation. A small study of 6 patients with newly diagnosed PCNSL treated with a high-dose MTX-based regimen followed by BEAM chemotherapy, ASCT and 20-30 Gy WBRT showed that 2 patients relapsed 19 and 23 months after remission and both died due to recurrent disease. The other 4 patients were alive without relapse or neurotoxicity, but the study had a small number of patients and relatively short follow-up.

Cheng and colleagues evaluated 7 patients with PCNSL with at least one poor prognostic factor (poor performance status, age > 60 years or relapsed disease). These patients were treated with high-dose MTX-based chemotherapy followed by consolidation with thiopeta-busulfan-cyclophosphamide and ASCT, without WBRT. Five patients were relapse-free for 5 to 42 months from diagnosis. Myeloablative chemotherapy with thiopeta-busulfan-cyclophosphamide may be more effective than BEAM for PCNSL due to the excellent CNS penetration of thiopeta and busulfan. Soussain and colleagues reported 20 patients with relapsed or refractory PCNSL or ocular lymphoma responsive to salvage cytarabine and etoposide who were treated with thiopeta-busulfan-cyclophosphamide and ASCT. Sixteen patients achieved CR and the 3-year overall survival rate was 60% and the 3-year event-free survival was 53%. However, there was significant neurotoxicity and treatment-related morbidity and mortality in patients over the age of 60 years.
Salvage Therapy
Failure after first-line therapy has been reported in 35-60% of patients with PCNSL. Patients who are refractory to primary therapy or relapse after an initial response have a poor prognosis, with median survival of 2 months without further treatment. There is no standardized approach for refractory or relapsed PCNSL. For patients who had received chemotherapy only, WBRT can be an effective salvage therapy. Nguyen and colleagues reported a cohort of 27 patients who failed high-dose MTX and were treated with WBRT. Thirty-seven percent had a CR and 37% had a PR. Median survival from initiation of WBRT was 11 months. Patients who initially responded to MTX can be successfully treated with MTX again at relapse. Plotkin and colleagues reported 22 patients who were retreated with high-dose MTX and obtained a 90% response rate and median survival of 62 months. This is corroborated by the fact that recurrences can be due to clonal evolution of a persisting precursor cell and not necessarily subclonal selection or development of resistance. Other reported regimens for salvage therapy include temozolomide and rituximab, single-agent temozolomide, etoposide-ifosfamide-cytarabine, topotecan and procarbazine-lomustine-vincristine.

Survival Trends after the Introduction of Chemotherapy
Despite advances in the therapy of PCNSL in the past few decades, two population-based studies failed to show any improvement in the survival of patients with PCNSL. A study of 122 patients from the British Columbia Cancer Agency showed no difference in median overall survival among patients treated with WBRT only, combined chemotherapy and WBRT or high-dose MTX with deferred RT. A survival analysis of a cohort of 2462 patients from the SEER registry also did not show any trend of improvement in survival from PCNSL from 1975 to 1999. Even after excluding individuals who died of HIV/AIDS, the median survival from the time of diagnosis was only 9 months. This outcome is poorer than survival observed in clinical trials and hospital-based cohort studies. A cohort of patients from Japanese hospitals showed increased use of systemic therapy between the periods of 1985-1994 and 1995-1999. The group treated in the more recent period had a better median survival time (30 vs. 13 months) and better 5-year survival rate (31% vs. 15%). The absence of survival improvement in populational studies with PCNSL can be attributed in part to selection bias of patients with better prognosis in clinical trials and tertiary hospitals. The other possibility is that treatment with high-dose MTX has not achieved widespread use in the community.

References


