Hematological Oncology
Hematol Oncol 2015; **33**: 25–28
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hon.2211

Supplement Article

III. Current concepts in primary central nervous lymphoma

Gerald Illerhaus*

Clinic for Hematology, Oncology and Palliative Care, Stuttgart Cancer Center/Tumour Centre Eva Mayr-Stihl, 70174 Stuttgart, Germany

**Correspondence to: Prof. Dr. Gerald Illerhaus, Medical Director, Clinic for Hematology, Oncology and Palliative Care, Stuttgart Cancer Center/Tumour Centre Eva Mayr-Stihl, Klinikum Stuttgart, Kriegsbergstr.60, 70174 Stuttgart, Germany.*
E-mail: G.Illerhaus@klinikum-stuttgart.de

Primary CNS lymphoma

Primary CNS lymphoma (PCNSL) is a rare disorder defined by involvement of the cerebral parenchyma, leptomeninges, eyes or spinal cord without evidence of systemic disease. PCNSL accounts for approximately 3% of all primary brain tumors and 2–3% of all Non-Hodgkin's lymphomas. The incidence of PCNSL rose nearly threefold between 1973 and 1984 with a slight stabilization over the last years. The median age at diagnosis is 61 years rising in patients over 60 years. Approximately 95% of PCNSL is B-cell Non-Hodgkin's lymphomas classified as diffuse large B-cell lymphomas, whereas indolent B-cell lymphomas and T-cell lymphomas occur rarely. The pathogenesis of PCNSL is controversial. Some concepts indicate that clonal proliferation might occur among normal B lymphocytes drawn to the CNS, a theory supported by the occurrence of white matter brain lesions that herald brain lymphoma. Alternatively, a clone of malignant systemic lymphocytes displaying specific adhesion molecules might travel and penetrate the brain.

The International Extranodal Lymphoma Study Group (IELSG) identified the following parameters as independent factors for a poorer outcome: age over 60 years, ECOG performance status greater than 1, elevated serum LDH, high CSF protein concentration, and tumour location within the deep regions of the brain (periventricular regions, basal ganglia, brainstem and/or cerebellum). Patients with 0 to 1, 2 to 3, or 4 to 5 of these adverse risk factors had 2-year overall survival (OS) rates of 80%, 48% or 15%, respectively. A study at the Memorial Sloan-Kettering Cancer Center identified three distinct prognostic classes based on age and performance status only: class 1 (patients < 50 years), class 2 (patients ≥ 50, Karnofsky performance score ≥ 70) and class 3 (patients ≥ 50, Karnofsky performance score < 70).

For diagnostic evaluation, patients should undergo contrast-enhanced brain magnetic resonance imaging and if a lumbar puncture can be performed safely, cytologic evaluation and flow cytometry of CSF. All patients should be subjected to a slit lamp examination as well as CT scans of the chest, abdomen and pelvis to exclude systemic disease. The impact of bone marrow biopsy is currently under discussion as in the case of exclusion of systemic disease by CT scan, a bone marrow involvement has never been observed. For histological diagnosis of PCNSL, the procedure of choice is a stereotactic needle biopsy because patients derive no clinical benefit from surgical resection. The deep-seated location of most lesions bears a high risk of surgical complications. Patients with PCNSL usually present with a brief disease history of often only a few weeks. Most patients have focal neurologic deficits and neuropsychiatric symptoms; symptoms of increased intracranial pressure and seizures are less frequently. In case of leptomeningeal involvement at the time of PCNSL diagnosis, most patients show no clinical obvious signs. Approximately 20% of patients have ocular involvement at the time of PCNSL diagnosis, with both eyes affected in most patients. Patients with intraocular lymphoma generally complain of floaters, blurred vision, diminished visual acuity and painful red eyes. About a third of patients present with disseminated disease that is characterized by highly diverse deficits.

Untreated, median survival of PCNSL patients is limited to a few months. Historically, radiotherapy (RT) has been the standard treatment for PCNSL. Despite the high complete remission rate, almost all patients relapse after a few months after RT with a median survival of 12 months [1]. High-dose MTX (MTX $> 1.5\ g/m^2$) is considered the single most effective substance for treating PCNSL. Several studies have demonstrated response rates between 70% and 100% and a prolongation of median survival to as many as 55 months. The addition of chemotherapy to RT has been recommended to improve survival of PCNSL patients [2,3]. The impact of high-dose cytarabine (HD-AraC) was determined within the IELSG20 trial [4]. In this trial, 79 patients with untreated PCNSL were randomly assigned to receive four cycles of HD-MTX ($3.5\ g/m^2$) alone or in combination with HD-AraC ($2\ g/m^2$) twice a day on days 2–3 followed by WBRT in both arms. The addition of HD-AraC resulted in a significantly improved outcome, with CR rates of 18% and 46% ($P = 0.006$) and

a 3-year OS of 32% and 46% ($P = 0.07$), respectively. Hematological toxicity was higher in the combination arm, whereas non-hematological toxicities were uncommon. The authors concluded to regard the HD-MTX/HD-AraC as the current standard treatment [4]. Several studies attempted to improve outcome by HD-MTX with other drugs [5]. However, those drugs known to be most effective in NHL like doxorubicin and cyclophosphamide are associated with unsatisfactory results in PCNSL, which is at least partially due to their poor blood–brain barrier penetration [6–8]. The combination of MTX-based chemotherapy with whole brain RT has shown very high response rates, but is associated with a considerable risk of neurotoxicity (30% of all patients and 40–50% of those over 60 years) [9]. In a large randomized trial, 551 patients treated with HD-MTX-based chemotherapy were randomized to receive WBRT 45 Gy versus observation in the case of CR after chemotherapy or versus HD-AraC in the case of partial or no response [10]. The results showed that consolidation WBRT is associated with a significantly better median PFS of 18 vs. 12 months, but does not change median OS. Because of some execution flaws of the trial's design, interpretation of results should be taken with caution.

The most common symptoms of post-therapeutic leukoencephalopathy are cognitive deficits as serious as dementia, gait disturbances and incontinence, which are as disabling as the lymphoma itself. Post-therapeutic leukoencephalopathy is associated with 30% of treatment-related mortality. The main risk factors for leukoencephalopathy are RT, age over 60 years, intrathecal therapy and chemotherapy after WBRT.

There is some preliminary evidence in PCNSL literature supporting a role for rituximab, an anti-CD20 hybrid monoclonal antibody that has been shown to be effective in the treatment of different types of B-cell lymphomas. In fact, the addition of rituximab to CHOP has significantly improved therapeutic results in patients with diffuse large B-cell lymphoma [11]. However, there are doubts about the capability of this antibody to cross the blood–brain barrier and the large French randomized trial comparing CHOP with R-CHOP that did not show any role for this drug to prevent CNS dissemination [12]. A prospective experience suggests that rituximab is active against relapsed PCNSL, while a prospective phase II trial from the Memorial Sloan-Kettering Cancer Center demonstrates that the rituximab–methotrexate combination is feasible and active[13], but the precise role of rituximab in PCNSL remains to be defined, preferably in a randomized study. Two trials will be presented at ICML 2015 that highly suggests that rituximab added to chemotherapy improves remission duration.

Consolidation after induction chemotherapy probably represents the best role for RT [3,14]. Because PCNSL is often multifocal, the target for RT is the whole brain, whereas the added value of the 'tumour-bed boost' is questionable [15]. Combined chemoradiation therapy is associated with a relevant risk of severe neurotoxicity. With the intention to reduce the risk of severe leukoencephalopathy, some investigators propose to replace WBRT with other strategies for consolidation treatment.

High-dose chemotherapy (HDT) supported by autologous stem cell transplantation (ASCT) represents one of these strategies. In a multicenter French trial, patients with PCNSL who relapsed after first-line treatment with an HD-MTX-containing regimen have been treated with intensive chemotherapy followed by ASCT. Twenty-six of 27 patients who completed the planned treatment achieved a CR. Clearly, patients benefited from HDT followed by ASCT with a median survival of 58.6 months among transplanted patients and 18.3 months in the overall population (median follow-up 36 months) [16]. Similar strategies have been used as part of front-line treatment in PCNSL patients with encouraging results, mostly when thiotepa-based conditioning regimens have been used [17]. After a median follow-up of 63 months, the 5-year survival rate for all patients was 69%, and 87% for those who completed HDT. Over time, 5/30 patients developed leukoencephalopathy. In a consecutive pilot study, cytostatic chemotherapy (HD-MTX followed by cytarabine and thiotepa) was intensified, and consolidating RT was restricted to patients *not* responding completely to chemotherapy [18]. Seven out of 11 patients were in complete remission following ASCT, and three in partial remission received RT as consolidation treatment. After a median follow-up of 25 months, 3-year disease-free survival as well as OS was 77%. None of the patients suffered from severe neurotoxicity during the follow-up period. Both trials demonstrated a curative effect of in young patients. This new approach has been implemented in a multicenter phase II trial with 79 included patients in Germany [19]. Preliminary results showed an overall remission rate (ORR) for the intend-to-treat population of 91% (77% CR and 14% PR), for patients treated with HDT and ASCT ($n = 73$), overall remission rate was 91%. After a median follow-up of 35 months, the 3 year OS was 77.6% for all patients and 87.1% for patients after HDT and ASCT. In another recently published phase II trial, 32 patients were treated with rituximab, HD-MTX, procarbazine and vincristine for induction [20]. Patients responding to induction were consolidated with HDT containing thiotepa, cyclophosphamide and busulfan followed by ASCT. Following rituximab, HD-MTX, procarbazine and vincristine, objective response rate was 97%, and 26 (81%) patients proceeded with HDC-ASCT. Two-year PFS and OS were 79% and 81%, respectively.

Benefit and side effects of these consolidative strategies, that is, conventional WBRT and HDT supported by ASCT, deserve to be compared in a randomized trial so as to draw definitive conclusions on the role of consolidation

DOI: 10.1002/hon

regarding both efficacy and neurotoxicity in patients with newly diagnosed PCNSL. The multinational IELSG32-trial (NCT01011920) and the French PRECIS-trial (NCT00863460) compared HDT and ASCT with consolidation WBRT for patients with untreated PCNSL. Both trials completed accrual recently. In the ongoing MATRIX/IELSG43, initiated by the German cooperative PCNSL group and the IELSG high-dose consolidation, chemotherapy and ASCT will be compared with conventional consolidating chemotherapy following the DeVIC-Protocol (Dexamtehasone, VP-16, ifosfamide and carboplatine).

MTX-based therapy should also play a role in the treatment of older patients with PCNSL. Contrary to the widely held opinion that MTX is overly toxic in older patients, we have observed that, provided their kidney function is not impaired, MTX is *not* excessively toxic. Combinations with the oral alkylating agents CCNU and procarbazine raise response rates and survival: median survival of 15 months and 30% cures have been reported with such therapy [21,22]. Whole brain radiation should only be considered as a last resort in older patients with refractory disease due to its highly neurotoxic properties. However, formal studies confirming the value of this strategy have not been reported.

Conclusion

In summary, PCNSL is a rare form of extranodal non-Hodgkin's lymphoma. Initial diagnosis is supported by MRI. Definitive confirmation should be based on stereotactic biopsy findings. Clinical presentation depends on the location of the tumour. Methotrexate-based, multi-agent chemotherapy is currently the treatment of choice leading to high remission rates, although most patients relapse. Consolidation therapy may improve survival. Whole brain RT as commonly employed is associated with a high risk of treatment-related neurotoxicity, especially in older patients. Consolidating HDT with autologous stem cell transplantation has highly curative potential in patients younger than 65 years. Benefit and side effects of these consolidative strategies, that is, conventional WBRT and HDT supported by ASCT, are currently compared in randomized trials to draw definitive conclusions on the role of consolidation regarding both efficacy and neurotoxicity in patients with newly diagnosed PCNSL.

Conflict of interest

The authors have no competing interest.

References

1. Reni M, Ferreri AJ, Garancini MP, Villa E. Therapeutic management of primary central nervous system lymphoma in immunocompetent patients: results of a critical review of the literature. *Ann Oncol* 1997; **8**: 227–234.
2. Ferreri AJ, Blay JY, Reni M, *et al.* Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. *J Clin Oncol* 2003; **21**: 266–272.
3. Ferreri AJ, Reni M, Villa E. Therapeutic management of primary central nervous system lymphoma: lessons from prospective trials. *Ann Oncol* 2000; **11**: 927–937.
4. Ferreri AJ, Reni M, Foppoli M, *et al.* High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. *Lancet* 2009; **374**: 1512–1520.
5. Ferreri AJ, Reni M. Primary central nervous system lymphoma. *Crit Rev Oncol Hematol* 2007; **63**: 257–268.
6. Mead GM, Bleehen NM, Gregor A, *et al.* A medical research council randomized trial in patients with primary cerebral non-Hodgkin lymphoma: cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. *Cancer* 2000; **89**: 1359–1370.
7. O'Neill BP, Wang CH, O'Fallon JR, *et al.* Primary central nervous system non-Hodgkin's lymphoma (PCNSL): survival advantages with combined initial therapy? A final report of the North Central Cancer Treatment Group (NCCTG) Study 86-72-52. *Int J Radiat Oncol Biol Phys* 1999; **43**: 559–563.
8. Schultz C, Scott C, Sherman W, *et al.* Preirradiation chemotherapy with cyclophosphamide, doxorubicin, vincristine, and dexamethasone for primary CNS lymphomas: initial report of radiation therapy oncology group protocol 88-06. *J Clin Oncol* 1996; **14**: 556–564.
9. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. *J Clin Oncol* 1998; **16**: 859–863.
10. Thiel E, Korfel A, Martus P, *et al.* High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *Lancet Oncol* 2010; **11**: 1036–1047.
11. Coiffier B, Lepage E, Briere J, *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; **346**: 235–242.
12. Feugier P, Virion JM, Tilly H, *et al.* Incidence and risk factors for central nervous system occurrence in elderly patients with diffuse large-B-cell lymphoma: influence of rituximab. *Ann Oncol* 2004; **15**: 129–133.
13. Shah GD, Yahalom J, Correa DD, *et al.* Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. *J Clin Oncol* 2007; **25**: 4730–4735.
14. Ferreri AJ, Abrey LE, Blay JY, *et al.* Summary statement on primary central nervous system lymphomas from the Eighth International Conference on Malignant Lymphoma, Lugano, Switzerland, June 12 to 15, 2002. *J Clin Oncol* 2003; **21**: 2407–2414.
15. Nelsaon DF. Radiotherapy in the treatment of primary central nervous system lymphoma (PCNSL). *J Neurooncol* 1999; **43**: 241–247.
16. Soussain C, Hoang-Xuan K, Taillandier L, *et al.* Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Societe Francaise de Greffe de Moelle Osseuse-Therapie Cellulaire. *J Clin Oncol* 2008; **26**: 2512–2518.
17. Illerhaus G, Marks R, Ihorst G, *et al.* High-dose chemotherapy with autologous stem-cell transplantation and hyperfractionated radiotherapy as first-line treatment of primary CNS lymphoma. *J Clin Oncol* 2006; **24**: 3865–3870.

DOI: 10.1002/hon

18. Illerhaus G, Muller F, Feuerhake F, *et al.* High-dose chemotherapy and autologous stem-cell transplantation without consolidating radiotherapy as first-line treatment for primary lymphoma of the central nervous system. *Haematologica* 2008; **93**: 147–148.
19. Illerhaus G, Fritsch K, Egerer G, *et al.* Sequential high dose immuno-chemotherapy followed by autologous peripheral blood stem cell transplantation for patients with untreated primary central nervous system lymphoma - a multicentre study by the collaborative PCNSL study group Freiburg. *Blood* 2012; **120**.
20. Omuro A, Correa DD, DeAngelis LM, *et al.* R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. *Blood* 2015; **125**: 1403–1410.
21. Hoang-Xuan K, Taillandier L, Chinot O, *et al.* Chemotherapy alone as initial treatment for primary CNS lymphoma in patients older than 60 years: a multicenter phase II study (26952) of the European Organization for Research and Treatment of Cancer Brain Tumor Group. *J Clin Oncol* 2003; **21**: 2726–2731.
22. Illerhaus G, Marks R, Muller F, *et al.* High-dose methotrexate combined with procarbazine and CCNU for primary CNS lymphoma in the elderly: results of a prospective pilot and phase II study. *Ann Oncol* 2009; **20**: 319–325.

DOI: 10.1002/hon