Primary central nervous system lymphoma (PCNSL) is an extranodal non-Hodgkin lymphoma (NHL) confined to the central nervous system (CNS) at the time of diagnosis [1,2]. The incidence of PCNSL has increased threefold from 1973 to 1984 [3]. Most PCNSL are diffuse large B-cell lymphomas, according to the World Health Organization (WHO) lymphoma classification [4]. The pathogenesis of PCNSL remains unknown. In immunosuppressed patients, PCNSL is almost invariably associated with a latent infection of the B-cells by the Epstein-Barr virus [5-7]. Furthermore, PCNSL occurs much more frequently among AIDS patients than in immunocompetent individuals [8]. Chemokines, substances involved in the chemotaxis of leukocytes during inflammatory processes, could play a role in PCNSL pathogenesis [9-11]. One study investigated the expression pattern of CXCR4, CXCR5 and CCR7 in PCNSL using immunohistochemistry, and compared it with that in systemic B-cell lymphoma. CXCR4, CXCR5 and CCR7 expression was observed in the neoplastic cells in all 31 PCNSL. Positivity for all chemokine receptors was restricted to the cytoplasm and, in some cases, to the nucleus (CXCR4); no membranous staining was observed. CXCR4 and CCR7 cytoplasmic location was confirmed by immunofluorescence microscopy. In contrast, membranous expression of CXCR4, CXCR5 and/or CCR7 was observed in 11, 11, and 14, respectively, of the 29 peripheral B-cell lymphoma specimens [11]. Occult systemic disease has been reported in patients initially thought to have isolated CNS involvement [12-15]. Thus, a complete systemic staging is warranted in every patient, including CT scans of the chest, abdomen and pelvis and bone marrow aspirate and biopsy. Recently, up to 17% of PCNSL patients were found to have subclinical systemic disease in peripheral blood and/or bone marrow detectable by polymerase chain reaction (PCR) of the immunoglobulin heavy chain genes. Furthermore, follow-up PCR showed a persistent monoclonal amplificate in blood in one of these patients 27 months after diagnosis. [15]. However, the impact of this finding on staging, treatment and prognosis of PCNSL remains to be defined and is currently being investigated.

The optimal treatment of PCNSL is controversial and is yet to be defined, mainly due to treatment data being limited to small studies. Therapies effective for extra-CNS NHL have not been successful in PCNSL due to the inability of most chemotherapeutic agents to sufficiently cross the blood-brain barrier [16-18]. Until the early 1990s, whole-brain radiation therapy (WBRT) was considered the standard treatment of PCNSL. With WBRT alone using doses between 40 and 60 Gy, remission of PCNSL can be induced in about 80% of patients. However, WBRT is not curative and disease relapse almost invariably occurs, resulting in a median overall survival of only 12-18 months. Moreover, WBRT is associated with an increased likelihood of delayed neurotoxicity, especially in those older than 60 years [12,19]. Because of its limited efficacy and considerable risk of delayed neurotoxicity, WBRT is often deferred until relapse or reserved for patients refractory to primary chemotherapy, especially in elderly subjects [20,21]. Today, it is generally believed that high-dose methotrexate-based chemotherapy should be part of the first-line treatment for the vast majority of patients. In the treatment of PCNSL, doses of 1 to 8 g/m² are commonly administered as a single agent or
in combination with other cytostatic drugs. High-dose methotrexate is a safe treatment for PCNSL patients regardless of age, provided that supportive care and dose reduction determined by calculating the glomerular filtration rate before each treatment cycle are performed properly. In one study, 154 patients (median age 61 years, 89 patients >60 years old) were evaluated prospectively for high-dose methotrexate (4 g/m², up to six treatment cycles) toxicity. Toxicity was generally mild, and the differences in the incidence and severity of toxicity were not statistically significant between patients >60 and ≤60 years of age. The same was true for therapy termination due to methotrexate toxicity and for delayed serum methotrexate clearance. However, dose reduction significantly differed between patients ≤60 years and those >60 years (18% versus 44%, p = 0.001) [22]. Methotrexate-based intensive multi-agent chemotherapy with high-dose methotrexate and cytarabine, along with vinca alkaloids, ifosfamide, cyclophosphamide, and intraventricular methotrexate, cytarabine, and prednisolone was assessed in a phase II study with 65 patients and yielded a response rate of 71%, a median overall survival of 50 months, and a five-year overall survival of 43%. However, this regimen was associated with six treatment-related deaths (9%) and 12 occurrences of Ommaya reservoir infection (19%) [23]. In a study on 56 patients treated with the carmustine, methotrexate, procarbazine, and dexamethasone (BMPD) protocol, responders to chemotherapy had a significantly longer median overall survival than non-responders (18.2 vs. 9.9 months, p = 0.02). Median survival was significantly longer at institutions accruing at least four patients than at those with fewer patients (31.5 vs. 9.5 months, p = 0.03), indicating that institutional experience with chemotherapeutic regimens for PCNSL may be crucial for treatment success [24]. Combined modality therapy with high-dose methotrexate-based chemotherapy followed by WBRT yields five-year overall survival rates up to 32% [25], but is associated with rates of neurotoxicity as high as 100% in patients over 60 years [26]. Other protocols focused on chemotherapy without WBRT in order to decrease the rate of delayed neurotoxicity in patients >60 years [27,28]. In an effort to clarify the role of adjuvant WBRT in primary treatment of PCNSL, a multicenter phase III/IV study was initiated in 2000 (German Primary CNS Lymphoma Study Group 1). The study has been closed since April 2009 and data are currently being analyzed. Initial treatment consisted of high-dose methotrexate in all patients. Patients were then randomized according to remission status. Those with complete remission either received immediate WBRT, or WBRT was deferred until relapse. Patients without complete remission were randomized to either receive immediate WBRT or high-dose cytarabine [22]. High-dose chemotherapy with autologous stem cell transplantation followed by WBRT has also been investigated as first-line treatment in a study with 30 PCNSL patients <65 years old. Induction chemotherapy included high-dose methotrexate, cytarabine, and thiopeta, followed by stem-cell harvest. High-dose chemotherapy comprised carmustine (400 mg/m²) and thiopeta (two doses of 5 mg/kg body weight), followed by autologous stem cell transplantation. WBRT (45 Gy) was administered thereafter. Twenty-three patients received high-dose chemotherapy plus autologous stem cell support, resulting in 15 complete and eight partial remissions. After WBRT, 21 of 21 evaluable patients had a complete response. High-dose chemotherapy was well tolerated apart from WHO grade 3/4 cytopenia. Median follow-up was 63 months. The five-year overall survival probability was 69% for all patients and 87% for patients receiving high-dose chemotherapy with autologous stem cell transplantation [29].

Relapse of PCNSL occurs within 1-2 years in 30-60% of patients who achieve complete remission after primary chemo- and radiotherapy [30-34]. Prognosis of relapsed PCNSL is poor, a survival of only 2-4 months has been reported [35]. The role of salvage therapy has been mainly evaluated in small patient populations. As a consequence, standard therapies for relapsed PCNSL have not yet been established, and many patients do not receive any treatment [33,36]. It has been shown that relapsed PCNSL patients benefit from PCNSL-specific salvage therapy independently of age. Performance status, site of relapse and salvage treatment significantly affect survival [37]. Several treatment options have been evaluated for relapsed and refractory PCNSL. In patients experiencing relapse after first-line treatment with high-dose methotrexate, a second response to methotrexate at relapse can be obtained. In one study with 22 relapsed patients who had achieved prior complete response to methotrexate, the overall remission rate after methotrexate treatment at relapse was 91%. Median survival after first relapse was 61.9 months, and median overall survival was 91.9 months [38]. Temozolomide monotherapy has led to an overall response rate of 31% and an overall
survival of 3.9 months [39]; the respective numbers for temozolomide administered in combination with rituximab were 53% and 14 months, respectively [40]. Topotecan has been investigated in a phase II trial. In one study with 27 patients with a median age of 51 years and a median ECOG performance status of 2, patients were pretreated with up to four regimens. The response rate to topotecan was 33% with five complete and four partial remissions. The median follow-up was 37.7 months. All complete responders had sustained remissions lasting for 9 to 28 months. The median event-free survival was 2 months for all patients and 9.1 months in responders, the median overall survival was 8.4 months. Toxicity was manageable. [41]. Radioimmunotherapy has emerged as a novel treatment option for relapsed or refractory systemic NHL over the past years [42]. Recently, in a phase II study, radioimmunotherapy with $^{90}$Y ibritumomab tiuxetan has been investigated in 10 heavily pretreated, relapsed or refractory PCNSL. Four patients responded: one patient had a complete response lasting 30+ months, and three patients had short-lived responses of only ≤4 weeks. Five patients progressed, and one patient did not receive treatment due to infectious complications. Relapses typically occurred distant to the target tumor, indicating poor penetration of $^{90}$Y ibritumomab tiuxetan into the brain around and distant to the tumor which has also been reported by others [43]. Accumulation of the antibody in the tumor was demonstrated in 4 of the 6 patients examined by single photon emission computed tomography imaging with $^{111}$Indium ibritumomab tiuxetan. All patients experienced grade III/IV hematotoxicity, and no acute neurotoxicity was observed [44].

A variety of treatment regimens have been used to treat CNS relapse of systemic NHL, but a systematic review of the literature indicated that treatment strategies using conventional therapies, including high-dose and intrathecal methotrexate, were generally little effective in improving survival [45,46]. Most previous investigations on CNS involvement of NHL are based on retrospective data on heterogeneously treated patient collectives. Furthermore, many studies included patients treated in the 1970s and 1980s, i.e. before the widespread use of current treatment approaches (e.g., rituximab plus chemotherapy and high-dose chemotherapy with stem cell rescue) and modern diagnostic tools. In the majority of these patients, only local treatment modalities (WBRT, intrathecal therapy or both) were used, and only a minority received CNS-directed systemic chemotherapy. More data from prospective trials are needed to define which patients could benefit from CNS prophylaxis. According to available data, treatment of CNS relapse should include high-dose methotrexate. Use of methotrexate can result in long-term survival in a minority of patients with CNS recurrence [47,48]. However, more effective regimens are needed in order to improve survival after CNS relapse. Treatment intensity at relapse has to be adapted to the patient’s age and performance status. For patients ≤65 years, salvage therapy with regimens containing high-dose methotrexate followed by autologous stem cell support seems promising and will be further investigated.

References


