Primary CNS lymphoma

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Abstract: Primary CNS lymphoma (PCNSL) accounts for 3% of all primary brain tumors with a median age at onset of about 62 years. In the vast majority of cases, PCNSL presents as unifocal or multifocal enhancing lesions on MRI, frequently adjacent to the ventricles. Stereotactic biopsy is the diagnostic procedure of choice revealing high-grade malignant non-Hodgkin's B-cell lymphoma in more than 90% of cases. Therapy is not evidence based. When eligible, patients should be included in clinical trials. In patients younger than 60 years cure is the aim. Polychemotherapy based on high-dose methotrexate (MTX) or alternatively high-dose chemotherapy with autologous stem cell rescue should be offered to patients eligible for this regimens. For patients over 60 years of age no curative regimen with acceptable toxicity has yet been established. An MTX-based chemotherapy, for example, in combination with temozolomide, is recommended. The role of radiotherapy as part of the initial treatment is not established; however, the combination of radiotherapy with MTX-based chemotherapy potentially leads to severe long-term neurotoxic sequelae. Therefore, radiotherapy as part of the initial therapy is not recommended by the author outside clinical trials. At relapse or in cases of refractory disease, patients will frequently benefit of salvage therapy, which depends on the initial treatment.

Keywords: CNS lymphoma, brain tumors, non-Hodgkin's lymphoma, methotrexate, temozolomide

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Introduction

Treatment of primary CNS lymphoma (PCNSL) has improved substantially within the last two decades by the implementation of high-dose systemic methotrexate (MTX)-based chemotherapy, such that a substantial fraction of patients may even be cured with this disease [Batchelor and Loeffler, 2006; Pels and Schlegel, 2006]. In this review, recent developments will be highlighted with a particular focus on chemotherapeutic and experimental approaches.

Epidemiology

The incidence of PCNSL has increased significantly in immunocompromised as well as in immunocompetent individuals and accounts for approximately 3% of primary intracranial tumors [Central Brain Tumor Registry of the United States, 2005]. It had become the most frequent brain tumor in AIDS patients; however, the introduction of highly active antiretroviral therapy (HAART) has reduced the occurrence of all non-Hodgkin's lymphomas (NHL), including primary and secondary brain lymphomas, dramatically [Antinori *et al.* 2001]. PCNSL may affect all age groups with a peak incidence in the fifth to seventh decade in non-AIDS patients [Batchelor and Loeffler, 2006].

Clinical presentation and imaging

Most commonly, PCNSL presents as diffuse and multifocal supratentorial brain masses. As a peculiarity of PCNSL, involvement of the vitreous, retina and optic nerves may be found in about 10–15% at presentation [Jahnke *et al.* 2006b]. Lymphomatous infiltration of the leptomeninges or ependymal surfaces and radicular or plexus invasion may occur as well [Pels and Schlegel, 2006]. By systemic staging, occult systemic lymphoma may be detected in up to 8% of patients initially presenting with brain lymphoma. Therefore, bone marrow biopsy, CT scan of chest and abdomen, testicular ultrasound and careful physical examination to detect occult systemic lymphoma is recommended

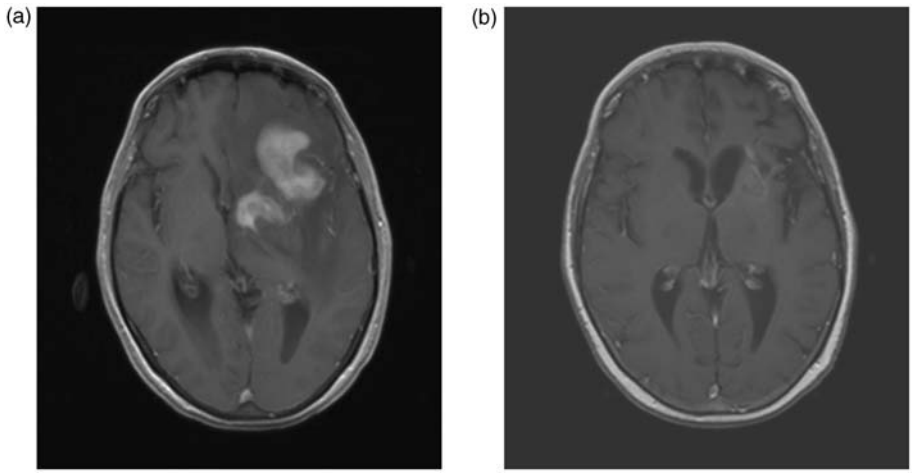

Figure 1. Contrast-enhanced T1-weighted MR image of a 64-year old lady with primary CNS lymphoma at presentation (a) and after six cycles of MTX-based polychemotherapy (b) showing complete resolution of enhancing tumor lesions. (The hyperintense areas at the initial tumor location are also visible without administration of gadolinium).

[Abrey *et al.* 2005]. In a monocentric series, whole body ^{18}F-fluorodeoxyglucose (FDG) PET has been shown to disclose systemic NHL in 7% at presentation of lymphoma primarily affecting the CNS and in 27% at relapse [Mohile *et al.* 2008]; however, its general diagnostic role is not yet established. Routine diagnostic evaluation in suspected PCNSL comprises ophthalmologic investigation including slit lamp examination, CSF analysis (see below), HIV serology, and serum lactate dehydrogenase (LDH) level [Batchelor and Loeffler, 2006]. Clinical symptoms of PCNSL comprise cognitive dysfunction, psychomotor slowing, personality changes, and disorientation in the majority of patients; raised intracranial pressure and focal symptoms affect about half of them; while brainstem, cerebellar signs and cranial nerve dysfunction and seizures are present only in a minority [Pels and Schlegel *et al.* 2006]. Magnetic resonance imaging is the most sensitive radiological procedure: the densely cellular tumor appears as single (65%) or multiple lesions on nonenhanced T1-weighted images (Figure 1), hyperintense tumor and edema on T2 or FLAIR images and densely enhancing masses after administration of gadolinium. Fifty per cent or more of the lesions are in contact with the meninges, and meningeal enhancement appears in 10–20% [Küker *et al.* 2005].

Diagnosis and pathology

Stereotactic biopsy is the diagnostic procedure of choice and can be targeted to CT or MRI-defined masses. Glucocorticoids should be withheld if possible, since steroid treated lesions may disappear within a few days and 'nondiagnostic' biopsies may result. However, a recent retrospective analysis of cases eventually confirmed as PCNSL has shown, that in this selection repeated biopsy for a nondiagnostic first procedure was infrequent irrespective of former steroid treatment (12%) or no treatment (13%) and that complete regression of a lesion under steroid treatment had been exceptional [Porter *et al.* 2008]. Steroid response is not diagnostic of PCNSL, since many types of brain infiltrates improve with steroid therapy – for example, sarcoidosis, multiple sclerosis (MS) plaques and even infectious lesions [Porter *et al.* 2008]. In a prospective series the evaluation of 116 spinal fluid specimens revealed pathologic findings in more than half of the cases analyzed and CSF cytomorphology was positive for lymphoma cells in 18% [Fischer *et al.* 2006]. Immunohistochemical studies of CSF cells using antibodies to lymphocytes (LCA) or B cells (CD20) are not specific for diagnosis of a clonal proliferate in the CSF. The detection of B-cell monoclonality by PCR amplification of immunoglobulin heavy chain gene rearrangements can be performed in specialized laboratories [Gleisner *et al.* 2002], but was found less sensitive than cytomorphology in a prospective series on 282 PCNSL patients [Fischer *et al.* 2008]. Therefore, these techniques cannot be considered established for routine diagnostics.

According to the World Health Organization (WHO) classification [Harris *et al.* 2000], the majority of PCNSL are classified as diffuse, large B-cell lymphomas (DLBCL). More than 95% of PCNSL correspond to non-Hodgkin's B-cell lymphomas as evidenced by expression of the B-cell markers CD19, CD20, and CD79a. The mitotic activity is generally high and necrosis may occur [Pels and Schlegel, 2006]. The vast majority of PCNSL are of germinal center (GC) B-cell origin: they exhibit *bcl-6* gene overexpression and ongoing mutational activity [Montesinos-Rongen *et al.* 2004] and display an activated B-cell-like phenotype: PCNSL show molecular alterations characteristic for GC B-cell (GCB)-like and for activated B-cell (ABC)-like DLBCLs [Courts *et al.* 2007]. Primary T-cell lymphomas of the CNS account for 4% of all PCNSL [Shenkier *et al.* 2005]; with respect to prognosis and response to therapy they show no obvious difference to PCNSL of the B-cell type [Shenkier *et al.* 2005]. In less than 5%, low-grade PCNSL (of B-cell or T-cell origin) are found. They may display a more indolent clinical course, frequently present with seizures and show distinct radiological features like a less intense or heterogeneous enhancement [Jahnke *et al.* 2005b].

Treatment

Surgery

The role of surgery is restricted to stereotactic biopsy of a lesion suggestive of PCNSL in order to gain material for histopathological diagnosis [Batchelor and Loeffler, 2006]. Every attempt to completely resect this diffusely infiltrating lesion is contraindicated. Surgical removal as a part of multimodal therapy has been shown to be associated with a worse prognosis [Bellinzona *et al.* 2005].

Radiotherapy

Radiotherapy has been the mainstay of treatment for many years until the early, 1990s. The only prospective phase II study on brain irradiation (Radiation Therapy Oncology Group 83-15) in HIV-negative patients with PCNSL [Nelson *et al.* 1992] evaluated 41 patients who received 40 Gy whole brain radiotherapy (WBRT) plus a focal tumor boost of 20 Gy, each dose delivered in 1.8 Gy fractions. Median survival for the whole group was 12.2 months after diagnosis and 7.6 months for patients over 60 years of age; 4 out of 41 patients (10%) died during administration of therapy. In this trial, 28 patients developed recurrent lymphoma of whom 22 were within the 'boost' fields [Nelson *et al.* 1992]. In a retrospective analysis of patients being treated with radiotherapy alone in the, 1990s, the median survival for the whole group (median age 63 years) was 18 months and the 5-year-survival fraction was 18% [Shibamoto *et al.* 2005]. Therefore, despite the lack of 'evidence-based' recommendations, there is a broad consensus, that primary provision of brain irradiation alone is insufficient to provide either durable remission or cure of PCNSL.

Chemotherapy

Concerning the role of chemotherapy, a retrospective analysis of 370 patients treated for PCNSL with different therapies has shown a significantly better outcome for patients treated with combination chemotherapy and radiotherapy in comparison with radiotherapy alone, if chemotherapy had included high-dose intravenous MTX [Ferreri *et al.* 2002]. MTX at a dosage high enough to reach therapeutic levels in plasma, CSF, brain parenchyma and eye following parenteral administration, has to be given intravenously exceeding 1 g/m^2; however, the optimal dosage or dosing schedule is not defined [Pels and Schlegel, 2006].

Two multicenter trials have evaluated high-dose MTX alone for PCNSL: in a German phase II study (NOA-03-trial) MTX was administered at a dosage of 8 g/m^2 as a 4-hour infusion every 14 days for six cycles; however, the study was terminated after including 37 of 105 projected patients, since the overall response rate was only 35%. Even with the application of salvage WBRT in 20 out of these 37 patients either for progressive disease (PD) or for relapse, median survival did not exceed 25 months [Herrlinger *et al.* 2005]. The same protocol, in a single-arm multicenter trial (NABTT 96-07), achieved a 74% overall response rate (52% complete responses, 22% partial responses); however, the median progression-free survival was only 12.8 months [Batchelor *et al.* 2003] and the median overall survival of 55 months has been the result of efficient salvage therapy at progression or relapse [Gerstner *et al.* 2008].

Combination chemotherapy is probably more efficient than high-dose MTX alone; a retrospective

analysis has identified the inclusion of high-dose cytarabine (ara-C) in MTX-based protocols as an independent positive prognostic predictor [Ferreri *et al.* 2002]. Polychemotherapy as a sole treatment has been evaluated in two prospective multicenter phase (I)/II trials. In a multidrug phase I/II trial [Pels *et al.* 2003a], 65 patients were treated with six chemotherapy cycles based on high-dose MTX, high-dose ara-C, vinca-alkaloids and alkylating agents in combination with intraventricular MTX, prednisolone and ara-C. A 61% complete response rate and a 10% partial response rate have been achieved; 9% treatment related deaths have been reported. The median event-free survival was 21 months and the median overall survival 50 months. Results have been particularly promising in 30 patients under 60 years of age included in this trial. In these patients neither median progression-free survival nor median overall survival had been reached after a median follow up of 26 months; the 5-year survival fraction was 75% [Pels *et al.* 2003a]. In patients over 60 years the overall survival was 34 months. However, the protocol resulted in an overall response rate of only 56% in patients over 60 years of age and was associated with 12% toxic deaths in this age group [Pels *et al.* 2003a]. In an EORTC trial, 52 patients 60 years and older (median age 72 years, median Karnofsky performance score 50) were treated with MTX as a 1 g/m^2 infusion on days 1, 10, and 20, combined with lomustine 40 mg/m^2 day 1, procarbazine 60 mg/m^2 days 1–7, methylprednisolone alternating days 120 g/m^2 days 1–20 and 60 mg/m^2 days 20–45, intrathecal MTX 15 mg and ara-C 40 mg days 1, 5, 10 and 15 [Hoang-Xuan *et al.* 2003]. In case of complete or partial response, documented by MRI or CT, after the first cycle, five more cycles ('maintenance therapy') were applied every 6 weeks with only one MTX infusion and only one intrathecal MTX and ara-C application on day 1 of each cycle. The overall response rate was 48%, median overall survival 14.3 months and the 1-year progression-free survival fraction 40% [Hoang-Xuan *et al.* 2003]. In a more recent French consecutive case series of 23 patients older than 60 years, MTX 3 g/m^2 on days 1, 10, and 20 was combined with temozolomide 100 mg/m^2 on days 1–5; in patients with partial or complete response to this induction chemotherapy (17 out of 20 evaluable patients) a maintenance therapy was provided with MTX 3 g/m^2 and temozolomide 100 mg/m^2 on days 1–5 every month up to five times. The median event-free survival was 8 months in this study and the overall survival 35 months, comparing favorably with results of more complicated regimens [Omuro *et al.* 2007].

Intrathecal chemotherapy The role of intrathecal/intraventricular chemotherapy in PCNSL is not defined. MTX, ara-C and steroids have been given by lumbar or ventricular (via a subgaleal reservoir) routes as part of systemic chemotherapy regimens: MTX 12 mg twice a week was given by lumbar route in two trials [Poortmans *et al.* 2003; DeAngelis *et al.* 2002], but intraventricular applications provide lower daily doses to achieve sustained CSF levels [Pels *et al.* 2003b]. In general these levels likely exceed 10 μM concentrations. Leaving the systemic polychemotherapy unchanged in comparison with the original protocol [Pels *et al.* 2003a] but omitting intraventricular therapy, a subsequent trial in patients <60 years led to significantly worse results [Pels *et al.* 2008], such that at least with this polychemotherapy protocol intraventricular chemotherapy seems indispensible. The benefits of CSF drug application have to be weighted against the risk of iatrogenic ventriculitis [Pels *et al.* 2003a], the problems of repeated access to the CSF, and the leukoencephalopathic effects of loculated drug within the neuraxis. In a small, case-controlled retrospective study, no differences in survival, disease control or neurotoxicity could be found between recipients and nonrecipients of intrathecal therapy [Khan *et al.* 2002], and a retrospective analysis of prognostic factors for 370 PCNSL did not find any influence of intrathecal therapy upon outcome [Ferreri *et al.* 2002]. However, only a small minority of patients having received intrathecal chemotherapy had not been treated with whole brain radiation chemotherapy (WBRT), an efficient treatment of the CSF compartment, such that a possible impact of intrathecal chemotherapy may have been obscured by this fact [Ferreri *et al.* 2002]. At this time prophylactic intrathecal or intraventricular chemotherapy should still be considered investigational.

Myeloablative high-dose chemotherapy This achieves therapeutic drug levels in brain, CSF and throughout the neuraxis. Autologous stem cells are provided to rescue the patients from drug-induced leukopenia and thrombocytopenia. Treatment has been provided to recurrent [Soussain *et al.* 2008] (see below) or newly diagnosed PCNSL [Abrey *et al.* 2003, Illerhaus *et al.*

2006, 2008]. 'Induction therapy' to achieve remission is provided with MTX and/or ara-C and followed by thiotepa-based regimens [Soussain *et al.* 2008; Illerhaus *et al.* 2008, 2006] or by ara-C, melphalan, carmustine and etoposide [Abrey *et al.* 2003]. While the latter has produced disappointing results [Abrey *et al.* 2003], combination of high-dose chemotherapy with WBRT (50 Gy after partial and 45 Gy after complete response to chemotherapy, respectively) within a phase II trial for patients up to 65 years has resulted in a 69% 5-year-survival fraction on an intent-to-treat analysis [Illerhaus *et al.* 2006]. First monocentric experience with an intensified regimen based on this protocol but without radiotherapy has revealed promising preliminary results [Illerhaus *et al.* 2008], and is currently subject of a multicenter, single-arm, open-label phase II trial. However, this approach should still be considered experimental as primary treatment. Response rates and event-free survival in newly diagnosed PCNSL are not better than with conventional therapy, deaths from drug toxicity or tumor progression occur in patients over 60 years, and longer follow-up of the above-mentioned trial [Illerhaus *et al.* 2006] shows late relapses [Illerhaus *et al.* 2008]. At PCNSL relapse, however, high dose chemotherapy with autologous stem cell transplantation appears to be an excellent option in younger individuals [Soussain *et al.* 2008].

Combined chemotherapy and radiotherapy Systemic 'high-dose' MTX has been included in most combination chemo- and radiotherapy protocols evaluated in phase I/II trials. Three large prospective, multicenter phase II trials have combined MTX-based chemotherapy with WBRT: Within the Trans-Tasman Radiation Oncology Group a protocol has been applied to 46 patients (median age 58 years, range 25–76) consisting of two cycles of MTX 1 g/m^2 as a 6 h infusion on days 1 and 8 followed by WBRT with 45 Gy and a 5.4 Gy tumor boost delivered in 1.8 Gy fractions starting on day 15. There was only one toxic death, and 45 patients proceeded to radiotherapy. In 39 assessable patients the complete response rate was 82% and the partial response rate 13%. Median overall survival was 33 months and the 2-year survival probability was 62% [O'Brian, 2000]. More complex protocols have been used by the Radiation Therapy Oncology Group (RTOG 93-10) and by the European EORTC (Trial, 20962). In the latter MTX 3 g/m^2 (days 1, 15) was combined with methylprednisolone 60 mg/m^2 (days 1–5), teniposide 100 mg/m^2 (days 2, 3) and carmustine 100 mg/m^2 (day 4) and with intrathecal MTX 15 mg, ara-C 40 mg and hydrocortisone 25 mg (days 1, 15) followed by radiotherapy of the brain with a total dose of 40 Gy in 1.5–1.8 Gy fractions [Poortmans *et al.* 2003]. Fifty-two patients with an upper age limit of 65 years were included; one died prior to, and five died during, treatment. In the intent-to-treat group, 69% had a complete response and 12% a partial response. Median estimated overall survival was 46 months; the 2-year survival estimate was 69% [Poortmans *et al.* 2003]. Taking into consideration that only patients up to 65 years of age have been included in this EORTC study, the data are not better than that of the trans-Tasman trial. In the RTOG study 93-10 [DeAngelis *et al.* 2002] 102 patients with a median age of 56.5 years received systemic MTX 2.5 g/m^2, vincristine 1.4 mg/m^2 and procarbazine 100 mg/m^2/day in weeks 1, 3, 5, 7 and 9, alternating with intraventricular MTX 12 mg once in weeks 2, 4, 6, 8 and 10, followed by WBRT from week 11 to 15 with 45 Gy or – for evidence of permanent neurotoxicity of this regimen – only 36 Gy in case of complete response after chemotherapy for 16 patients being accrued in the second half of the trial. Radiotherapy was followed by systemic ara-C 3 g/m^2 days 1 and 2 in week 16 and 19 [DeAngelis *et al.* 2002]. There was no treatment-related death reported; however, four patients have been excluded from the analysis. Among the 98 remaining patients, 82 proceeded to radiotherapy and 50 of these were assessed for treatment response with a 58% complete response rate, a 36% partial response rate and 6% treatment failures. The median overall survival was 37 months and the 2-year-survival fraction 64% [DeAngelis *et al.* 2002]. Since radiotherapy as part of the initial treatment is still a matter of debate, its role is currently being investigated in a large German multicenter phase IV trial (German PCNSL Study Group 1 study) comparing immediate WBRT (30 × 1.5 Gy) after complete remission (CR) to six cycles of MTX (4 g/m^2) in comparison with deferred radiotherapy *at relapse* after CR.

Immunotherapy Since PCNSL represent high-grade malignant B-cell NHL in more than 90% of cases, tumor cells express the CD20 antigen. Treatment with the anti-CD20 antibody

rituximab is effective in B-cell NHL and several reports on rituximab therapy in PCNSL refractory to established therapy have been published [Rubenstein *et al*. 2007; Enting *et al*. 2004; Pels *et al*. 2003b]. Rituximab is obviously able to clear the CSF from floating tumor cells if administered intraventricularly [Rubenstein *et al*. 2006; Pels *et al*. 2003b]; however, its efficacy to control parenchymal lesions after intravenous or intraventricular administration has been demonstrated in single cases only [Rubenstein *et al*. 2007]. As part of a multimodal protocol comprising systemic MTX, vincristine and procarbazine, rituximab has been administered at a systemic dosage of 500 mg/m^2 per cycle for five to seven cycles, followed by WBRT and by two consecutive cycles of systemic ara-C in a prospective multicenter trial; WBRT was 'prophylactic' with 23.4 Gy in case of complete response after five to seven cycles immunochemotherapy and 'standard' with 45 Gy in all other cases [Shah *et al*. 2007]. The regimen was well tolerated and the two-year progression-free and overall survival rates were 57% and 67%, respectively [Shah *et al*. 2007]. It is difficult to judge a possible therapeutic impact of rituximab within this multimodal regimen in a single-arm trial. It is of note, however, that in this trial rituximab levels in the CSF did not exceed 4.4% of the corresponding serum levels at any timepoint measured [Shah *et al*. 2007]. Including rituximab in treatment concepts directed against PCNSL might have another yet more important rationale: it has been shown that in up to 27% of relapsed PCNSL, systemic NHL is detectable [Mohile *et al*. 2008]; in 24% of another series PCNSL patients developed disease outside the CNS [Gerstner *et al*. 2008] and in an elegant study, occult NHL cells in peripheral blood samples have been detected by PCR amplification of clonally rearranged immunoglobulin heavy-chain (IgH) genes in at least 2 out of 24 PCNSL patients being in full remission of their CNS disease at the time of this analysis [Jahnke *et al*. 2006a]. Given the rather insensitive nature of this method, the real number of patients harboring occult NHL – with cells showing a tropism to CNS vasculature – may even be underestimated. Therefore, systemic administration of rituximab might well be toxic to occult systemic disease. Two case series of patients with refractory or relapsed PCNSL have shown that the application of radioconjugated CD20 antibodies like [^{90}Y] ibritumomab (Zevalin®) and [^{131}I] tositumomab (Bexxar®) is feasible and has resulted in responses in single cases [Doolittle *et al*. 2007; Iwamoto *et al*. 2007]. However, the future role of these radioconjugated CD20 antibodies in PCNSL needs to be defined [Wong *et al*. 2005].

Treatment-related late neurotoxicity

Deleterious long-term treatment related neurotoxicity after combination chemotherapy and radiotherapy has been reported in a single-center analysis in, 1998 [Abrey *et al*. 1998]. After having survived 4 years without detectable tumor, 100% of the patients being 60 years or older showed cognitive dysfunction. Younger individuals were affected less frequently and with a longer delay by this complication. Affected patients showed leukoencephalopathy and cortical/subcortical atrophy, which may leave them demented, ataxic, incontinent and dependent on custodial care [Abrey *et al*. 1998]. Pathologic investigation of the brains from patients with fatal neurotoxicity revealed no tumor cells, but myelin and axonal loss, gliosis, spongiosis and rarefication of the white matter [Lai *et al*. 2004]. In a retrospective analysis on 183 patients treated for PCNSL in a single center for the development of long-term treatment related neurotoxicity, only the administration of radiotherapy was identified as an independent risk factor [Omuro *et al*. 2005]. This finding is supported by a recent literature review suggesting that PCNSL patients having been treated with chemotherapy alone carry less risk of developing late neurotoxicity [Correa *et al*. 2007]. Therefore, formal neuropsychological testing in any prospective therapeutic trial in PCNSL is recommended and guidelines for testing have been established [Correa *et al*. 2007]. Taking into consideration the risk of long-term neurotoxicity due to 'consolidating' radiotherapy after complete response to chemotherapy, a retrospective single center analysis on 122 patients has addressed this issue. No difference in overall survival has been found between complete responders to MTX-based chemotherapy having received upfront 'consolidating' whole brain radiotherapy and those with deferred radiotherapy at relapse [Ekenel *et al*. 2008]. Therefore, and for the sake of avoidance of neurotoxicity, it is justified to withhold radiotherapy after complete response to chemotherapy for salvage at relapse (see below).

Specific situations

The impact of age

The prognosis and response to therapy in patients 60 years of age or older is significantly worse irrespective of the treatment modality applied [Pels *et al.* 2003a; DeAngelis *et al.* 2002; Nelson *et al.* 1992]. It has also been proposed that, irrespective of their Karnofsky Performance Score, patients younger than 50 years do better than older ones [Abrey *et al.* 2006]. However, the median age in PCNSL is over 60 years and a 'specific treatment situation' has to be considered for the majority of patients, since older individuals frequently show comorbidity, tolerate treatment less well and carry a high risk of neurotoxicity. Thus, specific precautions have to be undertaken. The MTX dosage is to be adjusted to the glomerular filtration rate. In 89 patients over 60 years of age treated within a German trial, 4 g/m^2 MTX have been applied as a 4 hour infusion every 2 weeks for a maximum of six cycles, together with dexamethasone 3×8 mg dexamethasone for 10 days in the first cycle. Prior to each cycle the creatinine clearance was measured and the dosage of MTX was reduced according to creatinine clearance values from 80 ml/min onwards; for example, by 20% at 80 ml/min and by 40% at 60 ml/min; a creatinine clearance value less than 50 ml/min was an exclusion criteria for high-dose MTX [Jahnke *et al.* 2005a]. Dose reduction was necessary in 44% of patients over 60 years, and termination of therapy due to nephrotoxicity in only 3%. General toxicity, a WHO score greater than 2, occurred in less than 10% of these patients; treatment results were not given [Jahnke *et al.* 2005a]. Taking these data together, it is recommended to treat older patients upfront with a high-dose MTX-based regimen; for example, 4 g/m^2 for six cycles (adjusted to the glomerular filtration rate) in combination with dexamethasone 3×8 mg dexamethasone for 10 days during the first cycle, because this has been shown to be feasible [Jahnke *et al.* 2005a]. Alternatively MTX 3 g/m^2 on days 1, 10, and 20 can be combined with temozolomide 100 mg/m^2 on days 1–5 with a maintenance therapy (MTX 3 g/m^2 and temozolomide 100 mg/m^2 on days 1–5) every month up to five times in responding patients [Omuro *et al.* 2007]. According to published results from other studies [Hoang-Xuan *et al.* 2003; Pels *et al.* 2003a], however, a response rate of less than 60% is anticipated and a salvage therapy should be initiated in refractory patients (see below).

HIV-positive patients and post-transplant lymphoproliferation (PTLD)

Prior to the era of HAART, HIV-infected patients with PCNSL usually carried a dismal prognosis: one-third of them died while receiving radiation for their brain lymphoma [Pels and Schlegel, 2006]. This situation has substantially improved: first, the incidence of PCNSL has decreased dramatically with HAART [Antinori *et al.* 2001]; and second, AIDS patients treated concomitantly with HAART and chemotherapy for NHL are more likely to respond to chemotherapy when HAART induces a reduction of HIV viral load [Hoffmann *et al.* 2001]. In a multicenter retrospective analysis, patients with PCNSL and AIDS showed the best outcome when treated with cranial radiation and HAART (median survival, 1093 days). The survival was 132 days after cranial radiation alone and 33 days without specific therapy [Hoffmann *et al.* 2001]. Selected AIDS-PCNSL patients may be candidates for aggressive chemo or chemo/radiotherapy if: (1) their performance status has a KPI greater than 50; (2) their CD4+ cell count is above 200/µl; (3) comorbidities of AIDS are limited and non-neurologic [Pels and Schlegel, 2006]. For the severely ill, comfort care only may be a therapeutic option. Non-AIDS PTLD patients tend to have EBV-induced PCNSL and demonstrate elevated loads of EBV in CSF [Pels and Schlegel, 2006]. Usually demonstrable is reactivation of latent EBV or newly acquired seroconversion. The PCNSL which emerges cannot easily be distinguished from the EBV or other infectious complications of transplant, although PCNSL may be accompanied by lymphoma invasion of the transplanted organ. Therapy is based on reduction or discontinuation of immunosuppression in favor of low-dose steroid use with chemotherapy [Pels and Schlegel, 2006].

Intraocular lymphoma

About 10–20% of PCNSL patients show ocular involvement at presentation or during the course of the disease: lymphomatous uveitis, vitrous and/or optic nerve infiltration [Batchelor and Loeffler, 2006; Pels and Schlegel, 2006]. Intraocular involvement may occur as an isolated site of relapse after successful treatment of PCNSL or in combination with CNS relapse [Jahnke *et al.* 2006b; Pels *et al.* 2003a]. Treatment with high-dose MTX-based chemotherapy, with ifosfamide or with oral trofosfamide

is efficient and frequently results in CR or PR [Jahnke *et al.* 2006b]. Alternatively, radiation to the posterior two-thirds of the eye chamber with 30–45 Gy can be applied; however, this is frequently complicated by the occurrence of cataracts and uncertain control of coincident optic nerve and brain involvement by tumor. Intraocular MTX with 400 µg in a 0.1 ml volume instillation into the vitreous achieves cytotoxic drug levels and may lead to clearance of ocular tumor as well, but is complicated by a rate of 73% cataracts, 58% corneal epitheliopathy, 42% maculopathy and other serious complications [Smith *et al.* 2002]. Therefore, this modality is considered experimental. It is recommended to treat ocular involvement at presentation of a PCNSL with high-dose MTX-based chemotherapy alone and in case of isolated ocular relapse with oral trofosfamide or intravenous ifosfamide [Jahnke *et al.* 2006b]. Ocular radiotherapy should be reserved to cases refractory to this treatment. It is of note that patients treated for intraocular lymphoma with systemic chemotherapy relapse less frequently in the CNS than patients treated with local therapy [Jahnke *et al.* 2006b].

Treatment in the refractory patient and at relapse

The optimal therapy of recurrent tumor is not established, but drug resistance is seldom documented and most patients benefit from reinduction with chemotherapeutic agents [Reni *et al.* 2007; Pels and Schlegel, 2006]. Patients with recurrent lymphoma after initial long-lasting response to chemotherapy are at least 50% likely to achieve a complete reinduction with MTX [Plotkin *et al.* 2004] suggesting that brain lymphoma may not recur as a function of drug resistance alone. In patients younger than 65 years and eligible for myeloablative therapy, intensive chemotherapy followed by hematopoietic stem-cell rescue is strongly recommended as a potentially curative salvage treatment option analogous to the situation in systemic relapsed high-grade malignant B-cell NHL. In 39 patients with relapse ($n = 21$) or refractory disease ($n = 17$) to first-line therapy, thiotepa/busulfane/cyclophosphamide-based high-dose chemotherapy was administered after two cycles of ara-C and etoposide induction. CR(PR) was achieved in 15(5) cases and median overall survival after initiation of salvage therapy was 18.3 months [Soussain *et al.* 2008]. Responses to other agents are seen in 25–40% of the cases as to temozolomide alone [Reni *et al.* 2004] or in combination with the CD20 antibody rituximab [Enting *et al.* 2004], and to topotecan 1.5 g/m^2/day, days 1–5, every 4 weeks [Fischer *et al.* 2004]. After primary or secondary failure to high-dose MTX in 27 patients, WBRT with a median dose of 36 Gy and a facultative boost to the initial tumor region has resulted in 37% long-lasting complete remissions (median duration 57.6 months) and in another 37% short-lasting partial remissions (median duration 9.7 months). A total dose of more than 36 Gy, a single fraction higher than 1.5 Gy and age over 60 were predictors of treatment-related neurotoxicity at follow up [Ngyen *et al.* 2005]. These findings have been confirmed in another retrospective single-center analysis showing a CR rate (PR rate) of 58% (21%) in 48 patients treated with a median dose of 40 Gy WBRT at relapse ($n = 24$) or progression ($n = 24$); long-term disease control was seen in 31% of the patients [Hottinger *et al.* 2007].

Follow up

MRI after successful treatment of PCNSL may reveal small enhancing lesions in regions of initial tumor or surgical manipulation. These lesions may not reflect active tumor and are classified as complete response/unconfirmed [Abrey *et al.* 2005]. Follow-up MRI in these cases may reveal a decrease in size or even a disappearance of these lesions. If PET scanning will be helpful in the future in distinguishing these 'scars' from active tumor or if it will assist in detecting relapse early, remains to be seen [Palmedo *et al.* 2006]. MRI of the brain and neurological examination should be carried out every 3 months for 2 years after treatment and every 6 months for the next 3 years [Abrey *et al.* 2005]. Examination of the CSF, ophthalmologic investigation and other tests should be carried out only in case of clinical symptoms; serial neuropsychological testing is advisable since late neurotoxicity remains an important treatment complication.

Treatment recommendations

Unfortunately, the substantial progress in PCNSL treatment has not yet translated into broad clinical practice. A recent population-based analysis of survival data in PCNSL in the US has revealed no difference in survival numbers in the late nineties in comparison with

the early seventies [Panageas *et al.* 2005]. Therefore the following is recommended:

- When eligible, patients should be included in clinical trials.
- The role of surgery is restricted to stereotactic biopsy for histopathological diagnosis.
- In patients younger than 60 years cure is the aim. Polychemotherapy based on high-dose MTX with deferred radiation [Pels *et al.* 2003a] or alternatively high-dose chemotherapy with autologous stem cell rescue [Illerhaus *et al.* 2006] should be offered to patients eligible for this regimen.
- For patients over 60 years, no curative regimen with acceptable toxicity has yet been established. An MTX-based chemotherapy; for example, in combination with temozolomide [Omuro *et al.* 2007] is recommended.
- The combination of radiotherapy with MTX-based chemotherapy potentially leads to severe long-term neurotoxic sequelae. Therefore, radiotherapy as part of the initial therapy is not recommended outside clinical trials.
- At relapse after long-lasting response, reinduction of MTX-based chemotherapy, having been effective as initial treatment, is recommended as salvage therapy in older patients. Temozolomide or topotecan may be administered in cases of short-lasting responses to initial therapy or in cases of initial failure to MTX. Radiation may be reserved for patients not responding to these regimens. In patients younger than 60 years of age intensive chemotherapy with autologous stem cell transplantation is recommended.

Conflict of interest statement

None declared.

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