Management of Primary CNS Lymphoma in Elderly Patients

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11.1 Definition of PCNSL and Epidemiology

Primary central nervous system lymphoma (PCNSL) describes a malignant extranodal non-Hodgkin's lymphoma (NHL) whose sole site of involvement is, by definition, the central nervous system. Most PCNSL cases present in the supratentorial space, most commonly in the frontal or temporo-parietal lobes, followed by the basal ganglia. Rarely, the disease may present in the cerebellum, brainstem or even the spinal cord. The disease may include the eyes and leptomeninges. PCNSL must be differentiated from systemic NHL with metastasis to the central nervous system.

It is commonly accepted that elderly patients should be defined as older than 60–65 years of age [1].

The peak age at diagnosis of PCNSL is 53–57 years in immunocompetent patients with a male/female ratio of 1.2–1.7:1 [2]. However, since 1990, the incidence has increased dramatically in those aged 60 and more [3]. The incidence of PCNSL is 28 per 10 million [4]. In immunocompromised patients, the typical age at presentation is younger with a mean age range between 31 and 35 years, consistent with the population that is most at risk of AIDS. Similarly, in this population the male/female ratio is 7.38:1 [2, 5].

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11.2 Prognosis

Certain prognostic factors have a significant impact on the outcome of patients. Multiple prognostic scales have been developed, but in all, performance status and age have been consistently identified as treatment-independent prognostic factors [6, 7]. The fact that age plays a key role is critical as the median age of diagnosis for PCNSL in immunocompetent patients is around 65 years with most patients being between 45 and 70. Two scales are widely used as they have been validated in large multicentric populations of PCNSL patients. The IELSG prognostic index included five independent variables: age (>60), performance status (ECOG >1), serum LDH level (elevated), protein levels in the CSF (elevated) and involvement of deep structures [7]. This index shows a survival rate at 2 years of 80 % for patients with up to 1 abnormal factor, 48 % for up to 3 abnormal factors and 15 % for 4 or more abnormal prognostic factors. The Memorial Sloan Kettering prognostic index identified age and performance status as sole independent prognostic factors (Fig. 11.1) [8].

11.3 Predisposing Conditions

The only characteristics shared by immunocompetent patients with PCNSL are advanced age and a slight propensity for male gender. Next to AIDS, conditions that favour the development in immunocompromised patients include iatrogenic immunosuppression for transplantation or for autoimmune diseases (such as rheumatoid arthritis and rare congenital immunodeficiency syndromes such as severe combined immunodeficiency, Wiskott-Aldrich or ataxia-telangiectasia syndromes) [9]. The risk of PCNSL directly correlates with the degree of immune suppression as illustrated in AIDS patients, where the median CD4 count in patients with PCNSL is 30 cells/mm^3 [10].

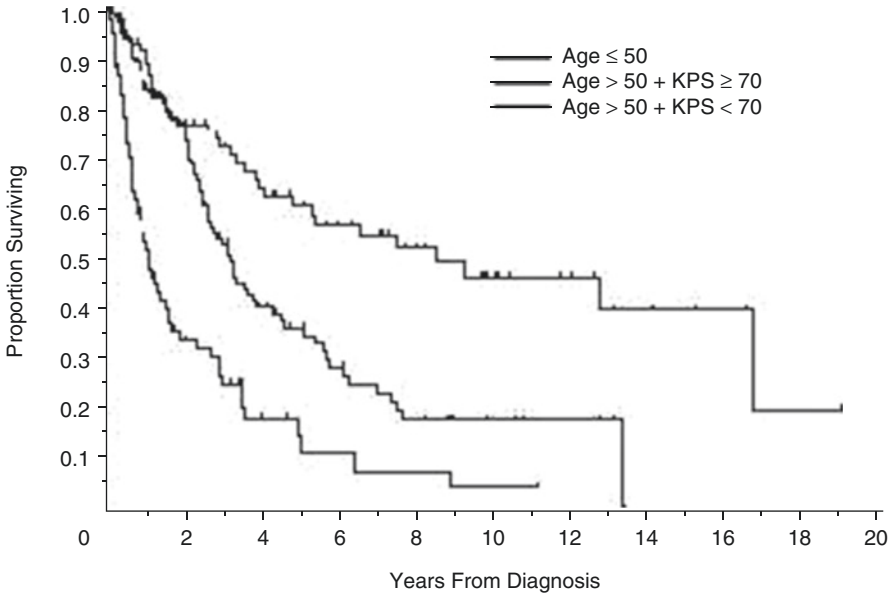

Fig. 11.1 The Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic model

11.4 Clinical Features

11.4.1 Anatomic Distribution of the Lesions

The signs and symptoms of PCNSL reflect the neuroanatomic localization of the lesions. PCNSL can be separated into four distinct anatomic distributions: (1) intracranial mass lesions that can be solitary or multiple, often in contact with the ventricular surface; (2) leptomeningeal lesions; (3) ocular lymphoma that can present either without or with associated cerebral lesions; and (4) spinal cord lesions (extremely rare).

Intracranial PCNSL lesions appear as a solitary lesion in about 70 % of immunocompetent patients, whereas AIDS-associated PCNSL is as likely to present with either multiple or solitary lesions [5, 11]. Approximately 85 % of the lesions are found in supratentorial site, whereas only 15 % will be localized in an infratentorial location [11]. Of the lesions localized supratentorially, more than 60 % are periventricular and may involve the basal ganglia, thalamus or corpus callosum, which is especially suggestive of the presence of PCNSL [12]. When considering the distribution between cerebral lobes, the frontal (20 %) parietal (18 %) and temporal (15 %) lobes are more often involved than the occipital lobe (4 %) [11].

Primary leptomeningeal lymphoma is defined as PCNSL limited to the meninges, without presence of parenchymal cerebral or systemic disease. It is rare and represents only about 7 % of all immunocompetent PCNSL [13]. In contrast, involvement of the meninges by intracranial PCNSL is much more common and can be observed in up to 41 % of cases [14].

Primary intraocular lymphoma involves the vitreous, retina, choroid or the optic nerve. It is a rare malignancy, but the exact incidence is unknown. Of note, about 10–20 % of immunocompetent patients with intracerebral PCNSL are found to have ocular involvement of the disease at time of diagnosis [15].

With less than 1 % of presenting cases, the spinal cord is rarely involved in PCNSL. In multifocal PCNSL, dissemination to the spinal cord may result from direct invasion from the caudal brainstem or through dissemination through the CSF [16].

11.5 Presenting Signs and Symptoms

The average time from presentation of symptoms to diagnosis is 2–3 months [5]. The localization of the PCNSL will determine the clinical presentation in each patient. In a large series of 248 immunocompetent patients, 70 % of patients showed focal neurological deficits; 43 % showed neuropsychiatric symptoms including apathy, depression and confusion. These symptoms have been linked to infiltration and function disruption of the white fibre tracts that surround the periventricular regions and the corpus callosum. Signs and symptoms suggestive of intracranial hypertension (headache, nausea and vomiting) were seen in 33 % of patients. Merely 14 % of patients presented with seizures. This low number reflects the deep localization of

Table 11.1 Signs and symptoms of PCNSL at presentation

Signs or symptoms	Percentage
Focal neurological deficit	70 %
Neuropsychiatric symptoms Apathy Depression Confusion	43 %
Increased intracranial pressure Headache Nausea Vomiting	33 %
Seizures	14 %
Ocular symptoms Floaters Blurred vision Decrease in acuity Painful red eye	4 %
Cranial nerve palsies	5–31 %

Adapted from Bataille et al. [11]

the tumour, away from the cortical grey matter. Four percent of patients present with ocular symptoms (Table 11.1). In contrast to immunocompetent patients, immunocompromised patients are more likely to present with mental status changes and seizures [5].

Leptomeningeal involvement is asymptomatic in the majority of cases [14]. Cranial nerve palsies have been reported in 5–31 % of patients [9, 17].

In case of ocular lymphoma, both eyes will be affected in the majority of cases, and patients will complain of floaters and blurred vision. More rarely, patient will present with loss of visual acuity or painful red eyes. Up to 20 % of patients will be asymptomatic [15].

Symptoms and signs of intramedullary spinal tumours may include limb numbness or paraesthesia, weakness (often asymmetrical) and bowel or bladder dysfunction.

11.6 Diagnosis and Staging

The diagnosis of PCNSL will usually be established based on the clinical presentation of the patient and the radiological appearance. It cannot be stressed enough that the initiation of a steroid treatment might compromise the further work-up and should only be performed after careful consideration of the situation (e.g. given the presence of important neurological deficits). There is a common belief that any cerebral lesion that shows a partial or complete response following administration of steroids will be a PCNSL by definition. Recent studies over show that merely 50 % of these lesions will be PCNSL [18].

11.6.1 Neuroimaging

The appearance of PCNSL presents some characteristic features both on CT and MRI. A solitary lesion that infiltrates the corpus callosum and shows a very intense and homogeneous enhancement and little peritumoral oedema is highly suggestive of PCNSL. On CT, masses appear most commonly iso- or hyperdense and show homogeneous enhancement following contrast injection. On MRI, lesions are typically hypointense on T1 sequences and iso- or hyperintense on T2 weighted sequences (Fig. 11.2). They will show homogeneous contrast enhancement following gadolinium contrast injection [19]. Linear enhancement at the margins of a lesion tracking along the Virchow-Robin perivascular spaces has been described as highly specific for PCNSL. Evidence of calcifications, intratumoral haemorrhages or necrosis are rarely observed in untreated PCNSL lesions.

Moreover, these lesions often show a high hyperintensity on diffusion-weighted images, based on the relative restriction of water diffusion. This is however not exclusive to PCNSL and may also be observed in acute stroke, cerebral abscess and other high-grade tumours. On perfusion sequences, PCNSL lesions typically present a low rCBV, which might be attributed to the typical angiocentric growth pattern. This also explains the important leakage of contrast media into the interstitial space and the high and homogeneous contrast enhancement observed in these lesions [20]. MR spectroscopy often shows increased choline and decreased NAA along with the presence of lipid peaks. This pattern does not allow for a clear discrimination from glioblastoma or metastases but may help in differentiating PCNSL from other lesions [20].

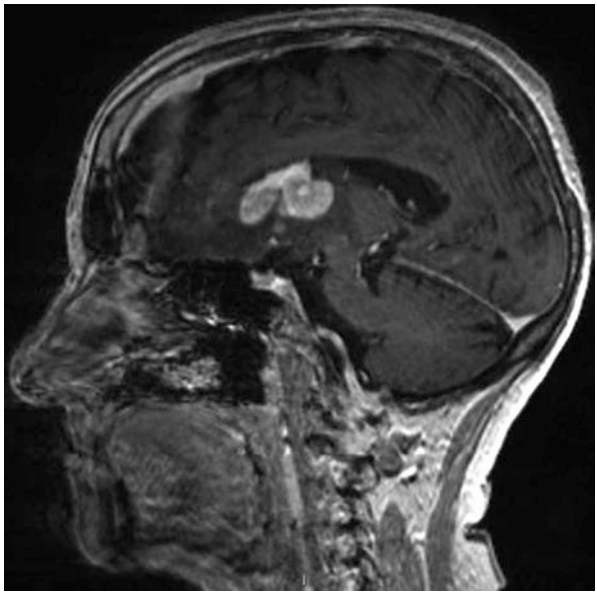

Fig. 11.2 Typical MRI T1 contrast-enhanced image of PCNSL

As spinal cord involvement is rare, enhanced MRI of the spine is not recommended routinely but should be reserved for patients where the clinical suspicion of PCNSL involvement is high [21].

11.6.2 Radiological Differential Diagnosis

In most instances the differential diagnosis will be established based on MRI findings. Many patients however present with atypical lesions that do not include all the hallmarks of PCNSL. The differential diagnosis of such a lesion on MRI includes glioma, metastatic brain tumour or focal demyelinating lesions. For immunocompromised patients, the differential diagnosis must further include toxoplasmosis cerebri, which has a similar incidence than PCNSL in AIDS patients.

11.7 Patient Work-Up

Once PCNSL is suspected, because of the clinical history of the patient and based on findings on the MRI, a definitive diagnosis must be established through other diagnostic modalities before initiation of treatment (Table 11.2). The work-up must be performed not only to establish the diagnosis of PCNSL but also to exclude the possibility of a systemic lymphoma, to tailor the optimal treatment and to ensure that the patient will not present exclusion criteria for the planned treatment. A spinal tap, if not contraindicated, and ophthalmologic evaluation in all patients are recommended, including those without ocular symptoms [1]. In the presence of a high clinical and radiological suspicion of PCNSL, identification of lymphoma cells in the vitreous fluid or the CSF might obviate the need for a stereotactic biopsy to confirm the diagnosis. In a prospective study of 96 immunocompetent patients with

Table 11.2 Diagnostic studies and work-up

Diagnostic studies	Evaluation
Radiological studies	Contrast-enhanced cranial CT Contrast-enhanced cranial MRI Body CT of the chest, abdomen and pelvis FDG-PET
Biopsy	Stereotactic brain biopsy Bone marrow biopsy
CSF lumbar puncture	Cell count, total protein Cytology, flow cytometry Search for clonal rearrangement EBV PCR (immunocompromised patients)
Blood	Lactate dehydrogenase (LDH) levels HIV serology Electrolytes Kidney and hepatic functions
Ocular evaluation	Slit-lamp examination

PCNSL, 15 % could be diagnosed by CSF cytology alone; in contrast 5 % were diagnosed by vitrectomy and 78 % by operative means [14].

The blood work-up should include determination of complete blood counts (CBC), serum lactate and dehydrogenase (LDH) levels, HIV testing and determination that electrolytes and kidney and liver functions are within normal limits.

At diagnosis, evidence of systemic lymphoma will be found in 2–3 % of "PCNSL" cases. This might however represent an underestimation of the true rate as many cases will not be included in PCNSL case series. Over the course of the disease, 7–10 % of cases will develop systemic involvement, usually late in the course of the disease [22, 23]. Systemic staging should include at least a physical examination, bone marrow biopsy, testicular ultrasonography and CT scan of the chest, abdomen and pelvis. Whole-body fluorodeoxyglucose PET might be an alternative to testicular sonography and the body CT [1].

11.7.1 Cerebrospinal Fluid

Analysis of cerebrospinal fluid (CSF) is an important part of the work-up. As a note of caution, as with any other patient presenting an intracerebral mass lesion, a lumbar puncture should however only be performed on PCNSL patients once the risk of herniation could be reasonably excluded. The CSF examination should include (1) basic studies including white blood cell count, protein and glucose levels (the glucose level will have to be compared to the serum glucose level); (2) cytology and/or (flow cytometry); and (3) determination of the presence of clonal immunoglobulin gene rearrangements or, in AIDS patients, PCR for Epstein-Barr virus DNA [24]. Most neuropathologists will rely on CSF cytology. In many immunocompetent patients, basic CSF parameters may be within normal limits or only slightly abnormal: in a study of 96 patients, a mild pleocytosis was present in only slightly more than half the patients (54 %), with a median WBC count of 8 cells/mm^3 (normal, $\leq$7 cells/mm^3). In the same study proteins were elevated in 67 % of patients, and low glucose was found in 10 % [14]. CSF cytology can be sufficient to establish the diagnosis in a significant percentage of cases: positive CSF cytology will be positive in 26–31 % of cases [5]. Serial samples of CSF might increase the probability of establishing the diagnosis through CSF cytology; this approach must however be balanced against the possibility to quickly perform a cerebral biopsy. Given the relatively low yield of cytology, the search for clonal rearrangements of the immunoglobulin heavy chains by PCR can establish monoclonality of a lymphocyte population in the CSF and thus confirm the diagnosis of PCNSL [25–27].

11.7.2 Neurosurgical Approach: Biopsy

Biopsy remains the standard procedure to obtain tissue that is adequate for pathologic diagnosis of PCNSL [1]. As administration of steroids may prevent to establish a histopathological diagnosis, its use should be avoided prior to the biopsy. In

the case when, following administration of steroids, the neuropathologist is unable to establish a diagnosis due to remission or the presence of an aspecific inflammation, the patient should be carefully followed clinically and radiologically with serial MRIs and be rebiopsied once the lesion recurs [1].

The immunohistochemical markers should include pan-B-cell markers (CD19, CD20, PAX5) BCL6, MUM1/IRF4 and CD10). In difficult cases PCR analysis of immunoglobulin gene families might help to establish the diagnosis by demonstrating monoclonal rearrangement.

In immunocompromised patient, both the morbidity and mortality are higher compared to non-immunocompromised patients as these patients present both a higher risk of haemorrhages and of infections [28]. The diagnostic accuracy of a biopsy in AIDS patients ranges from 88 to 96 % [29]. In this patient population, the most common differential diagnosis includes toxoplasmosis. As all HIV-associated PCNSL are associated with EBV, PCR detection of EBV DNA in the CSF has become an established tool for the diagnosis and can obviate the need for a biopsy. It has a high sensitivity (83–100 %) and a high specificity (>90 %) [30–32].

11.7.3 Surgery Versus Biopsy?

Of note, traditionally, surgery has been deemed to have no role in the treatment of PCNSL. This view is based on small retrospective series, which suggest that there is no clear benefit of outcome for patients when compared with supportive care and to patients who underwent biopsy [33]. Similarly, patients who undergo maximal treatment with chemo- and radiotherapy have the same outcome regardless whether they had undergone prior resection or biopsy [11, 34]. This lack of efficacy of surgical resection might be attributed to a number of reasons, including the possibility that, due to its infiltrative nature, there is microscopic disease localized at distance from the visible site of disease [35]. Moreover, any potential benefit of a larger resection might be mitigated as PCNSL is highly sensitive to chemotherapy and radiation therapy. Given the usually deep localization of the disease, a neurosurgical approach is often also linked with a significant risk of postoperative morbidity. The recommendation to discourage neurosurgical resection is however not based on any randomized trial data. Interestingly a retrospective analysis of the German PCNSL study group-1 phase III trial evaluated the association between outcome and surgery. Interestingly, patients with subtotal or total resections had significantly longer progression-free survival and overall survival than did patients who received biopsies [36]. This was independent of age and of postoperative performance status. There is a possibility that this difference in outcome might have been influenced by the fact that the resected lesions were localized more frequently in more superficial localizations. It must also be noted that once adjusted for the number of lesions present, the outcome difference remained statistically significant for PFS but not for OS. Presently, an aggressive resection approach can therefore not be recommended as a standard approach. It might however be considered in patients with large lesions and symptoms of acute herniation to rapidly reduce intracranial pressure and potentially in unifocal and resectable lesions [1].

11.7.4 Ocular Evaluation

As part of the assessment of any PCNSL patient, an ocular evaluation including visualization of the fundus and a slit lamp should be performed. Typically, a cellular infiltration can be observed in the vitreous, and subretinal infiltrates may be seen. If indicated, vitrectomy may establish the diagnosis of PCNSL. It should be performed in the eye with the worst vision and most severe vitritis [1]. The specimen can also be analyzed by immunohistochemistry or flow cytometry to establish monoclonality.

11.8 Treatment

In general, PCNSL is an extremely radio- and chemosensitive tumour. Relapse is however common, and the ideal combination of chemotherapy and radiotherapy has not yet been established. Moreover, balancing the efficacy of treatment with the risk of serious, permanent long-term neurological deficits must be considered.

11.9 Steroids

Administration of steroids can delay or confound the diagnosis as steroids induce cytolysis of lymphoma cells, by way of cytoplasmic steroid receptors that are translocated to the nucleus [37]. This effect is independent from wild-type p53 activity but attenuated by the Bcl-2 proto-oncogene product [38]. Initial treatment of PCNSL with steroids may result in complete and partial remissions of 15 % and 25 %, respectively [39, 40]. This remission may outlast steroid administration, but the effect is usually temporary and recurrence is common. At that point the tumour is most often resistant to re-exposure to steroids. Because of this direct cytotoxic effect of steroids, they should, whenever possible, be avoided before biopsy to avoid false-negative results. Optimally, they should be withheld during the initial clinical evaluation, especially before CSF and ocular examination are performed. Steroids will have a rapid and important impact on peritumoral oedema and will decrease the mass effect induced by the PCNSL. If needed, they may therefore represent a key tool to improve neurological deficits in patients [39, 40]. To date, it remains however unclear whether steroids are an essential component of chemotherapy regimen against PCNSL, comparable to their use in systemic NHL. In summary, corticosteroids are useful to control increased intracranial pressure. The dose should be tapered off as quickly as possible to the lowest dose possible allowing to control neurological symptoms and can usually be tapered off once definitive treatment has been started.

The most common secondary complication of steroids include glucose intolerance, weight gain, myopathy, insomnia, adrenal insufficiency and increased rate of *Pneumocystis jiroveci* pneumonia. Steroids should be, whenever possible, avoided in immunocompromised patients because of the high risks of reactivated tuberculosis, *Pneumocystis jiroveci* infection and other life-threatening infections.

11.10 Radiation Therapy Alone

When used alone, whole brain radiation therapy targeting the whole brain and eyes achieves response rates of 60 %, but recurrences are usually rapid and median overall survival remains limited to 12–18 months and the 5-year survival rate is 4 % [41, 42]. This poor outcome might be attributed to several factors, including the microscopically diffuse and multifocal nature of PCNSL. A phase II radiation therapy oncology group (RTOG) trial delivered a total dose of 40 Gy with a 20 Gy boost to the contrast enhancing lesions. The results were disappointing with a median overall survival of 11.6 months and most recurrences occurring within the areas that had received the highest doses of RT [41]. These results strongly suggest that WBRT does not have any significant role in the management of PCNSL.

In various trials, the combination of high-dose methotrexate with WBRT has been suggested to result in better outcomes than WBRT alone with longer median overall survivals of 30–72 months and by increasing the percentage of long-term survivors (20–50 % of patients alive at 5 years) [43–50]. The optimum dose and fractionation schema have never been evaluated prospectively in PCNSL. Most protocols use a total dose of 40–45 Gy without a boost with 1.8–2 Gy delivered per fraction. A randomized phase III trial (G-PCNSL-SG1 trial) has evaluated RT following chemotherapy versus watch and wait. This non-inferiority trial randomized patient that had achieved a complete response following high-dose methotrexate chemotherapy to receive either consolidation RT (45 Gy in 30 fractions of 2 Gy) vs no further treatment. 318 patients were treated per protocol, and the overall survival was similar in both groups. In the protocol population, there was a slight but statistically non-significant outcome advantage in progression-free survival but not for OS for patients that had received WBRT [51]. The results of this trial have been hotly debated as the trial did not meet its primary endpoint and as there were a high number of patients that violated the protocol. Nevertheless, many experts estimate that these results contribute strongly to the accumulating retrospective evidence that suggest that omission of WBRT results in shorter progression-free survival but does not compromise overall survival [1].

11.11 Chemotherapy

Methotrexate-based regimens are the only that have demonstrated a significant advantage in outcome. Standard therapies for systemic NHL, such as cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP), have not resulted in any sustained responses in PCNSL, probably linked to the poor CNS penetration of these agents due to the BBB [52–55]. Rapid infusion of high-dose MTX over 3 h greatly increases the drug level in the CSF [56]. As the efficacy of methotrexate can likewise depend on duration of exposure, MTX administration interval should range between 10 and 21 days [57]. High-dose administration of MTX however requires expertise for its administration, as attention to proper supportive care after administration must be scrupulous. All patients must have adequate creatinine clearance of ≥50 ml/min. The patient must be able to support important hydration and alkalinization of the urine and

leucovorin rescue to reduce any morbidity associated with MTX. Leucovorin is a folate antagonist that is unable to cross the BBB, which will reverse the effect of MTX at the systemic level and will prevent hematologic and gastrointestinal toxicities. MTX is usually combined with a number of other agents that have demonstrated activity in PCNSL. In most protocols, a minimum of 4–6 injections are delivered, especially if no consolidation treatment (radiotherapy or intensive chemotherapy) is planned. Additional rounds of treatment might improve the complete remission rate in patients who achieve only a partial response [58]. Currently, most protocols combine high-dose MTX with various other agents to improve the response rate and duration of the remission. The best illustration comes from the IELSG phase II trial that compared high-dose MTX (3 g/m^2 every 21 days) alone versus high-dose MTX combined with cytarabine (2 g/m^2 twice per day on days 2 and 3 of every cycle). The patients receiving the combination treatment showed improved outcome in terms of response rate, percentage of complete remission and PFS [59].

The value of intrathecal chemotherapy as prophylaxis remains unclear. Intrathecal chemotherapy (intralumbar or preferably intraventricular through an Ommaya reservoir) can be proposed whenever meningeal involvement is documented [1].

11.12 Specific Considerations for the Treatment of Elderly Patients

For PCNSL patients, older age has been correlated with poorer outcome. The definition of older is however variable from study to study and may in some instances include patients as young as 50 years old. Moreover, older age (usually defined as >60 years) is associated with an increased risk of suffering from neurotoxic effects of treatments. The cut-off for elderly is therefore 60 years of age in most studies. A RTOG phase II trial demonstrated that WBRT alone in patients over 60 years of age resulted in a median overall survival of only 7.8 months [41]. Following MTX-based therapy of at least 1 g/m^2, median PFS and OS were between 6 and 16 months and 14–37 months respectively [50, 60–71]. Formal comparisons between the different high-dose methotrexate-based regimens have not been performed. However, a recent phase II study of elderly patients compared methotrexate, procarbazine, vincristine and cytarabine (MPV-A) and methotrexate-temozolomide. Side effects were similar in both arms, and there was a slight although not statistically significant better outcome in the MPV-A arm in regard to response rate, percentage of patients with complete responses, PFS and OS [64].

It must be noted that in most studies, administration of high-dose MTX up to doses of 3.5 g/m^2 was usually well tolerated by elderly patients [61, 62, 72, 73]. In the different trials, less than 10 % of elderly patients developed grade 3–4 nephrotoxic effects, and 7–10 % of patients needed to discontinue treatment related to adverse toxic events. It is however essential to adequately monitor renal function [74]. The risk of developing delayed leucoencephalopathy with neurocognitive deficits is also of great concern in elderly PCNSL patients [75, 76].

Because of this, it is recommended that patient with a KPS $\geq$ 70 be treated with high-dose MTX with deferral or omission of WBRT. In patients with a poor

performance status and those older than 80 years, the treatment strategies must be weighted individually, based on co-morbidities and the poorer prognosis of any survival benefit as those patients have a worse prognosis and increased risk of treatment-related toxicities [1].

11.13 Rare Forms of PCNSL

11.13.1 Primary Leptomeningeal PCNSL

Primary leptomeningeal lymphoma is defined as PCNSL limited to the meninges, without presence of parenchymal cerebral or systemic disease. It is rare and represents only about 7 % of all immunocompetent PCNSL [13]. In contrast, involvement of the meninges by intracranial PCNSL is much more common and can be observed in up to 41 % of cases [14].

11.13.2 T-Cell Primary CNS Lymphoma

The clinical characteristics of T-cell PCNSL appear similar to the presentation of classical NHL PCNSL with similar median age of onset, performance status and location of lesions. There might be a male preponderance in T-cell lymphoma, and patients may present more commonly with B symptoms. Ocular involvement is uncommon [77]. The pathology is heterogeneous: one subtype shows CD30-positive anaplastic large cell lymphoma [78, 79]. Another subtype is a small cell variant [80, 81]. In most reported cases, the treatment consisted in combined modality therapy with systemic chemotherapy with either high-dose MTX alone or combined with other agents. The 2-year overall survival rate is around 37 % and the median disease-free interval 25 months [82].

11.13.3 Neurolymphomatosis

Neurolymphomatosis is a very rare syndrome, defined as a neuropathy of the peripheral nerves, nerve root, plexus or cranial nerve infiltration by NHL [83]. The clinical presentation mimics paraneoplastic or autoimmune neuropathies and may present as painful polyneuropathy or polyradiculopathy, cranial neuropathy or a painless neuropathy. In most cases, many months to years elapse between symptom presentation and diagnosis. In most cases, the diagnosis is made by biopsy of a mass lesion or through CSF analysis.

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