Questions and answers in the management of primary central nervous system and ocular lymphomas

Andrés J.M. Ferreri, Stefania Dell'oro, Michele Reni, Marco Foppoli, Nicoletta Anzalone, Silvia Govi, Piero Picozzi, Giulio Truci, Maurilio Ponzoni

Primary central nervous system lymphoma (PCNSL) is a rare form of extranodal non-Hodgkin's lymphoma (NHL) and represents 4% of all primary brain tumors.[1] PCNSL occurs in all age groups but mostly in individuals over 50 years of age, with a male:female ratio of 1.5:1.[2] The main histotype in immunocompetent patients is EBV-negative diffuse large B-cell lymphoma (Figure 1). In more than half of immunocompetent patients, PCNSL appears as a single lesion, usually localized in the periventricular regions, infiltrating the corpus callosum and the basal ganglia (Figure 2).[2] The clinical onset consists of non-specific motor and/or sensory focal deficits in about 50% of the cases; personality changes, headaches and other signs of intracranial hypertension, such as nausea, vomiting and papilledema, are also frequent. Systemic symptoms are present in 2% of cases.[2] PCNSL may arise in the cerebral, cerebellar and the brain stem parenchyma, in the eyes, the leptomeninges, and the spinal cord. Intraocular lymphoma (IOL) represents 5-20% of PCNSL, being more common among females with multifocal disease.[3] It is associated with other CNS lesions in 65% of cases,[4] and bilateral involvement of the eyes occurs in almost 80% of cases. Usually, IOL presents as a non-specific unilateral uveitis refractory to topical or systemic corticosteroids, associated with floaters or campimeter deficits, which precede cerebral symptoms by months or years.[5-7] To confirm the diagnosis of PCNSL, a staging workup completed by total-body computed tomography, bone marrow biopsy and cerebrospinal fluid cytology examination is mandatory;[8] ophthalmic ultrasonography, slit-lamp examination and indirect ophthalmoscopy are adjunctive diagnostic techniques useful for detecting an asymptomatic ocular localization in more than 5% of PCNSL patients.[9] The suspicion of infiltration of the vitreous humor should be confirmed through vitrectomy, which allows cytologic diagnosis in most cases.[10] In elderly males, staging work-up should include testicular ultrasonography[11]

Prognosis of PCNSL is poor and the median survival of untreated patients is 1.5-3.3 months.[2] Patients submitted to surgical resection alone have a median survival of 3.5-5 months. Historically, radiotherapy alone has been the standard treatment for PCNSL; however, radiotherapy is rarely a curative treatment in PCNSL patients since response is usually short-lived, with a median survival of 12-14 months.[12,13] Moreover, the positive impact of chemotherapy progressively limited the indications for radiotherapy alone. Current therapeutic knowledge in PCNSL results from a limited number of non-randomized phase-II trials,[14] meta-analyses of published series[13,15] and large retrospective, multicenter series.[2] Despite the fact that literature on PCNSL has been progressively increasing, several therapeutic questions remain unanswered, and the use of divergent study designs and entry criteria lead to incomparable results and debatable conclusions.[14] The present article summarizes the most relevant open questions in PCNSL treatment, and analyzes the related literature to identify the most reliable answers.

What is the standard therapeutic approach to PCNSL?

Patients with newly diagnosed PCNSL must be enrolled in prospective trials. A small number of patients are not eligible for clinical trials, while other patients are being treated in institutes that do not participate in multicenter prospective studies. These patients should be treated with standard combined chemo-radiotherapy, while radiotherapy alone is the rational treatment when chemotherapy is contraindicated. Even though not confirmed by results from randomized trials, there is substantial consensus regarding the superiority of combined chemo-radiotherapy with respect to radiotherapy alone.[16] Data from a large, multicenter retrospective series[2] and a large single-arm phase II trial[16] suggest that high-dose methotrexate (HD-MTX)-based chemotherapy followed by whole-brain radiotherapy (WBRT) should be preferred to radiotherapy alone. This strategy is in accordance with the treatment recommendation for the majority of localized aggressive lymphomas, for which primary chemotherapy is followed by consolidation radiotherapy. Chemo-radiotherapy produces a 5-year survival of 22-40%[14,17,18] in comparison to the 3-26% reported with radiotherapy alone,[19,20] but it is not known whether more intensive combined treatment will improve outcome. Although a survival advantage for HD-MTX-based chemotherapy followed by radiotherapy has not been fully proven, a randomized trial comparing this strategy to radiotherapy alone would likely be unacceptable to the majority of clini-

From the Departments of Radiochemotherapy, (AJMF, SDO, MR, SG), Internal Medicine (MF), Neuroradiology (NA), Neurosurgery (PP), Neurology (GT), and Pathology (MP), San Raffaele H Scientific Institute, Milan, Italy.

Correspondence: Andrés J.M. Ferreri, Department of Radiochemotherapy, San Raffaele H Scientific Institute, via Olgettina 60, 20132 Milan, Italy. E-mail: ferreri.andres@hsr.it

cians,[21] and the combined approach should be retained as the first-choice strategy.

What is the best chemotherapy regimen for newly diagnosed PCNSL?

Blood-brain barrier (BBB) penetration and efficacy against systemic non-Hodgkin's lymphomas have been retained as the determining characteristics for choosing drugs to include in primary chemotherapy against PCNSL. HD-MTX (≥1 g/m^2) is the most effective drug against PCNSL.13 HD-MTX, as monochemotherapy followed by radiotherapy, has shown a response rate of 80% - 90% and a 2-year survival of 60% - 65%.[22-25] Any regimen without HD-MTX is associated with outcomes no better than with radiotherapy alone.[26] The addition of a CHOP regimen to radiotherapy did not improve outcome, either when used as primary treatment or as post-radiation chemotherapy.[27-29]

Several studies attempted to improve survival by adding other drugs to MTX.[14] However, none of the used drugs had been previously evaluated as effective single-agents in patients with relapsed or refractory PCNSL. A recently reported survival improvement resulting from the addition of high-dose cytarabine to HD-MTX[2,15] deserves to be prospectively confirmed. Presently, primary chemotherapy against PCNSL should include HD-MTX, while there is no apparent reason to use additional drugs in ordinary clinical practice. The identification of new active drugs and combinations in phase I/II trials in relapsed or refractory PCNSL should receive high priority.

What is the best administration schedule for HD-MTX?

The efficacy of HD-MTX depends on the duration of exposure and drug concentration, which are determined by the administration schedule and pharmacokinetics. MTX enters the cells in part by an active transport mechanism and is bound as polyglutamate conjugates. During longer periods of drug exposure, a higher polyglutamate formation rate is observed and more cells enter into phase S, resulting in increased cytotoxicity. Since MTX clearance from plasma is triphasic,[30] an initial rapid administration to overcome the distribution phase of clearance, followed by a more prolonged infusion, appears the best administration schedule for this drug. The optimal duration of HD-MTX infusion is still unknown; in most trials using doses of 1–5 g/m^2, MTX has been administered in a 4-hour infusion,[31-33] while 24-hour infusions have been used for higher doses.[25,34] The use of a 3-hour infusion has been associated with a significantly higher response rate and higher cerebrospinal fluid (CSF) levels compared to those achieved with a 6-hour infusion. CSF MTX concentration seems to be strictly related to the dose administered.[35] The optimal dose and timing of MTX have not been defined, but no significant difference in efficacy or toxicity was observed when MTX at 3.5 g/m^2 was administered every 3 weeks versus every 10 days.[22]

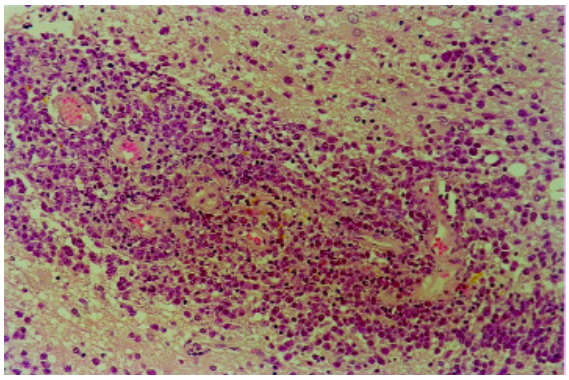

Figure 1. Diffuse large B-cell lymphoma of the brain. Diffuse perivascular proliferation with infiltration of cerebral parenchyma between the involved vessels. Neoplastic lymphocytic cuff in the perivascular space.

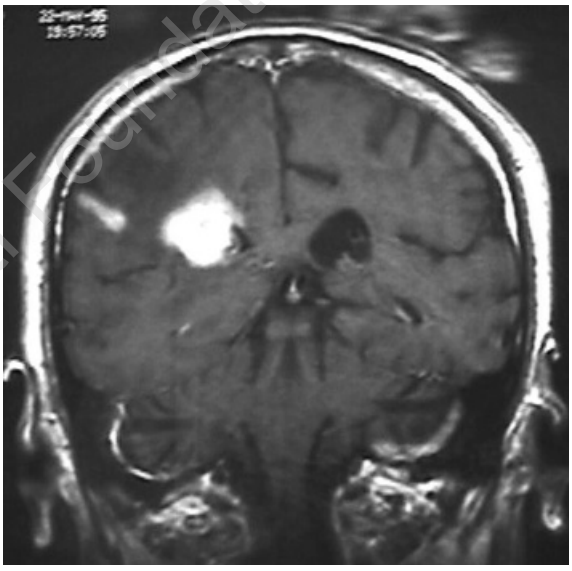

Figure 2. Magnetic resonance imaging of the brain after contrast infusion: a homogeneously enhanced lesion with polylobated limits in the deep left temporal area infiltrating the ventricular trigone, with evident perilesional edema can be seen.

Is intrathecal chemotherapy necessary for all PCNSL patients?

PCNSL infiltrates the subarachnoid space in up to 40-50% of cases,[17,36,37] thus requiring adequate meningeal treatment, which may be achieved by cranio-spinal radiation, high-dose systemic chemo-

therapy or by intrathecal chemotherapy. The first strategy is associated with relevant myelotoxicity, while the indications for and efficacy of the other two strategies are debatable. Intrathecal administration of the most commonly used drugs, such as MTX, cytarabine and steroids, is associated with an increased risk of neurotoxicity and chemical meningitis,[2,22,31] while the efficacy of this strategy has not been prospectively assessed in PCNSL patients. As the majority of meningeal relapses occur in patients with positive CSF cytology at diagnosis,[2,22,32] some authors suggested that, to minimize toxicity, intrathecal chemotherapy should be reserved for this subgroup of patients.[22,29] On the other hand, preliminary data suggest that systemic HD-MTX is associated with eradication of neoplastic cells from CSF,[25,38] and some prospective[22,23,32] and retrospective[2,39] studies suggest that intrathecal chemotherapy does not improve outcome in patients treated with HD-MTX-based chemotherapy. Finally, the potential benefit of intrathecal chemotherapy is still a matter of debate because leptomeningeal relapse is almost always associated with brain recurrence, which constitutes the cardinal prognostic event in PCNSL, obscuring the effect of concurrent leptomeningeal relapse on survival, and, consequently, the potential benefit of intrathecal chemotherapy.

Is WBRT necessary for all patients with PCNSL?

Combined chemo-radiotherapy is associated with severe neurological impairment in 40% of cases and a neurotoxicity-related mortality of 30%,[16,17] especially in patients older than 60 years of age. Thus, some authors have proposed that consolidation radiotherapy should be avoided in elderly patients who achieve a complete remission following HD-MTX-based chemotherapy to minimize iatrogenic neurotoxicity.[40] Only a few prospective trials assessing the impact of chemotherapy alone on survival and toxicity have been reported, with response rates in excess of 90%, effective salvage therapy after relapse with additional chemotherapy or radiotherapy,[41] and 69% of patients alive at 4.5 years.[40] A non-randomized study suggested that, in elderly patients, WBRT suppression markedly reduces the risk of neurotoxicity, without having a detrimental effect on survival.[42] Similar results were observed in patients achieving complete remission after HD-MTX in a retrospective series of 378 patients.[2]

Exclusive chemotherapy is feasible in PCNSL patients, but its real efficacy has not yet been defined. An ongoing, randomized study comparing combined chemo-radiotherapy versus chemotherapy alone, with HD-MTX as the induction chemotherapy regimen, will provide valuable information regarding this important clinical question in a few years (*E. Thiel, Hamburg, Germany; personal communication*). In the meantime, chemotherapy alone should be considered an experimental approach, which could, however, be used in patients with a remarkably elevated risk of severe treatment-related neurotoxicity.

What is the best treatment for intraocular lymphoma?

In the past, almost all patients with IOL treated with radiotherapy alone developed early CNS progression and died.[43-45] Promising anecdotal results in small series of patients with concurrent brain and ocular lymphoma treated with chemotherapy have been reported.[46] The efficacy of chemotherapy is strongly conditioned by intraocular pharmacokinetics, which are not well understood. Clinical data show that it is very difficult to achieve therapeutic concentrations of MTX and cytarabine in the vitreous humor after intravenous injections,[47] so that persistence of disease and recurrence in the eyes are frequent events after chemotherapy alone.[40] On the other hand, the addition of adequate radiotherapy, i.e. irradiation of two thirds of both orbits with 30-36 Gy, to HD-MTX has been associated with a higher response rate without cases of ocular recurrence.[48] Considering the positive effect of ocular irradiation and the difficulties in achieving intraocular therapeutic concentrations of cytostatics, the use of chemotherapy alone should be the subject of experimental protocols and not considered a standard approach in patients with ocular disease.

Intriguing results with new therapeutic approaches, such as high-dose chemotherapy supported by autologous peripheral blood stem cell transplantation (APBSCT)[4] and intravitreal chemotherapy,[49,50] have been reported. These experimental strategies may become valid alternatives in IOL, but their therapeutic role should be addressed in future studies.

What is the role of blood-brain barrier disruption?

Increasing drug delivery to the lymphoma-infiltrated brain could significantly enhance survival. Intra-arterial infusion of hypertonic mannitol results in reversible blood-brain barrier (BBB) disruption, which facilitates delivery of MTX- or carboplatin-based chemotherapy across the BBB, and produces high response and survival (5-year OS: 42%) rates, with excellent neurological tolerance.[51,52] BBB disruption may be an efficient strategy also in PCNSL patients who have a relapse after initial treatment with HD-MTX,[53] and may prove most useful in the delivery of agents unlikely to cross an intact BBB, such as unconjugated or radiolabeled monoclonal antibodies (*E. Neuwelt, Portland, USA; personal communication*). Despite its good efficacy and safety profiles, BBB disruption

procedures are used in a limited number of cancer centers around the world, and randomized comparison with conventional chemotherapy should be considered in PCNSL patients.

What is the role of high-dose chemotherapy supported by autologous stem cell transplantation?

High-dose chemotherapy supported by autologous peripheral blood stem cell transplantation (APBSCT) has been used as one strategy to dose intensify the dose of chemotherapy given to patients with newly diagnosed or relapsed PCNSL. Theoretically, this strategy could be used to replace consolidation WBRT in an effort to avoid treatment-related neurotoxicity. There have been two small APBSCT phase II trials in patients with newly diagnosed PCNSL the two trials yielded discordant results. In one study,[54] 28 patients received intensive MTX and cytarabine, followed by BEAM consolidation chemotherapy; only 50% of patients had chemosensitive disease and a significant proportion relapsed after transplant, only 5 (18%) patients remained in remission at a median of 26 months after transplant. In another ongoing study,[55] a combination of MTX, thiotepa and cytarabine is being used as the induction regimen followed by high-dose chemotherapy with BCNU and thiotepa and hyperfractionated radiotherapy. Nineteen of 24 patients enrolled to date have achieved a complete remission and there have not been any unexpected acute toxicities. In a study on 22 patients with recurrent or refractory PCNSL or IOL,[56] induction cytarabine and etoposide followed by high-dose chemotherapy with thiotepa, busulfan and cyclophosphamide produced a complete remission rate of 72%, with a 3-year survival of 64%. However, there was a significant incidence of neurotoxicity as well as significant treatment-related morbidity/mortality in patients over the age of 60, particularly in those who had been previously irradiated. These preliminary results suggest that high-dose chemotherapy supported by APBSCT is feasible in PCNSL patients. Further studies will need to be done to identify the optimal induction and high-dose chemotherapy regimens and to define the best role of this strategy in PCNSL patients.

What is the optimal salvage treatment for relapsed PCNSL?

Salvage therapy significantly prolongs survival in relapsed and refractory PCNSL patients.[57-59] Conclusions regarding the optimum second-line treatment cannot be made because of the extremely heterogeneous modalities used in published series; however, relapses in the brain after combined treatment oblige the use of further chemotherapy. High-dose cytarabine is the most widely used cytostatic in patients who have relapsed after HD-MTX, but re-treatment with HD-MTX has also been proposed.[25] In patients who relapse after chemotherapy alone, radiotherapy appears to be the subsequent choice, but some authors have suggested using chemotherapy again as the salvage strategy.[40,60] In some cases, re-irradiation of relapsed lesions has also been indicated.[59] Ocular recurrence, which is associated with a slightly longer survival,[58] can be treated with radiotherapy, high-dose cytarabine or high-dose chemotherapy supported by APBSCT.[56] Meningeal relapse can be treated with systemic and/or intrathecal chemotherapy or with spinal-cord irradiation. As for other aggressive lymphomas, high-dose chemotherapy supported by autologous or allogeneic PBSCT can be retained as an interesting experimental alternative.[56,61,62]

Do reliable prognostic factors exist?

The identification of reliable prognostic factors may allow PCNSL patients to be divided into risk groups, which could result in the application of risk-adjusted therapeutic strategies. Among the parameters used for the International Prognostic Index (IPI), age, ECOG performance status and serum lactate dehydrogenase level are generally correlated to survival in retrospective series.[13,28,63] However, the use of the IPI does not discriminate between low and intermediate-low risk groups in PCNSL series,[64] which could be due to the influence of more specific prognostic variables. A significant association between survival and involvement of deep structures of the brain (periventricular areas, corpus callosum, basal ganglia, brainstem, cerebellum) and elevated CSF protein concentrations has been reported.[2,65] In the IELSG series of 378 case,[2] age, ECOG performance status, serum lactate dehydrogenase level, CSF protein level, and tumor location were established as independent predictors of response and survival.[65] These variables have been used to develop a prognostic scoring system that distinguishes three different risk groups based on the presence of 0-1, 2-3 or 4-5 unfavorable features.[65] The clinical relevance of this prognostic score should be validated in further studies. Histopathologic,[66] biological and molecular[67] markers with potential prognostic value are currently under investigation.

What are the best issues for future prospective clinical trials?

An international, multidisciplinary collaboration is really needed in PCNSL. This is the only setting in which to address clinical and biological research questions and to perform randomized trials that will yield definitive conclusions. Several fundamental challenges must, however, be addressed prior to initiation of randomized studies, which require substantial financial resources as well as several years for accrual and follow-up. Among others, the

definition of fundamental questions, the more diffuse use of some specialized procedures, the chemotherapy regimen to be used as the control arm, and the role of emerging strategies against systemic NHL should be discussed and a consensus reached. An important dilemma in PCNSL treatment is the choice between strategies designed to increase dose intensity, to improve cure rate, versus strategies of treatment de-escalation, to avoid severe neurotoxicity. In fact, the evaluation of treatment impact on cognitive function and quality of life is a critical issue in these patients. Finally, international clinical trials will also be crucial to share archives of tumor tissue, which are relevant resources to explore new molecular and biological aspects of PCNSL.

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