

# V. Primary CNS lymphoma in immunocompetent patients

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## introduction

Primary CNS lymphoma (PCNSL) is an aggressive brain tumour, representing 3% of intracranial neoplasms and 4%–6% of extranodal lymphomas with a yearly incidence of 0.5 cases per 100 000 people and with a median survival, if untreated, of 1.5–3.3 months. The incidence of PCNSL in the past two decades has risen in immunocompetent individuals, especially in those >50 years of age. Median age at diagnosis is 60–65 years, and median survival is 10–20 months, with survival of <20%–30% at 5 years [1–2].

## clinical presentation, diagnosis and prognosis

PCNSL typically presents as an intracranial mass lesion, usually with a combination of generalized symptoms such as headache, confusion and lethargy as well as lateralizing symptoms such as hemiparesis. These symptoms usually lead to neuroimaging and either MRI (the preferred test) or CT scans demonstrate strong and homogeneous enhancing lesions that are often periventricular and lack central necrosis with variable surrounding edema. The lesion is single in 60%–70% of patients. Lesions are located in the hemispheres (38%), thalamus/basal ganglia (16%), corpus callosum (14%), periventricular region (12%) and cerebellum (9%). Gliomas, metastases, toxoplasmosis, sarcoidosis, abscesses and progressive multifocal leukoencephalopathy are the main differential diagnoses, requiring brain biopsy for definitive diagnosis. In addition to brain involvement, the eye is involved in ~20% of patients, only half of whom have any visual complaints; visual symptoms are typically floaters or blurred vision. PCNSL tends to infiltrate the subependymal tissues, disseminating through the cerebrospinal fluid (CSF) to the meninges. Concurrent meningeal involvement, often asymptomatic, is detected by conventional CSF cytology examination in 16% of patients, while isolated leptomeningeal lymphoma in the absence of a parenchymal mass represents <5% of all PCNSL.

If neuroimaging suggests a possible diagnosis of PCNSL, stereotactic guided biopsy is the method of choice in establishment of the definite diagnosis of PCNSL. Aggressive surgical resection should be avoided because it does not improve survival and may result in neurological deterioration and chemotherapy delay. Before biopsy, steroids should be administered only if osmotherapy alone cannot control life-

threatening increased brain pressure with the risk of brain herniation, since their action may interfere with or even prevent the histopathological diagnosis of PCNSL.

About 90%–95% of PCNSLs are diffuse large B-cell lymphomas (DLBCLs) [3]. Neoplastic B lymphocytes usually grow forming classical perivascular cuffings, with an almost constant expression of pan-B-cell markers (CD20, CD19, CD22, CD79a), markers of germinal center B cells (bcl-6, 60%–80% of cases) and markers of late germinal center B cells (IRF4/MUM1; 90%), while they are rarely positive for CD10 (<10%), and are negative for EBV [4]. Proliferating index is usually high. Only a small proportion of PCNSL has Burkitt (5%), lymphoblastic (5%), marginal zone (3%) or T-cell lymphoma (2%–3%) histotype.

Staging work-up to exclude systemic lymphoma includes whole-brain MRI, contrast total body CT scan, ophthalmologic evaluation (including slit-lamp examination), CSF cytology and biochemical examination, bone marrow biopsy and testicular ultrasonography (in elderly men). Suspicion of vitreal infiltration may require confirmation by vitrectomy. FDG-PET plays an investigational role.

Patient risk is usually estimated by using the International Extranodal Lymphoma Study Group (IELSG) score, which includes five independent predictors of response and survival: age, performance status, serum lactate dehydrogenase level, CSF protein concentration and involvement of deep structures of the brain. This score distinguishes three risk groups on the presence of 0–1 (low), 2–3 (intermediate) or 4–5 (high risk) of these predictors [5].

## treatment

Diverse therapeutic strategies for PCNSL are now available; however, some of these strategies are associated with an increased risk of disabling neurotoxicity, especially among elderly patients. Therefore, a dilemma in PCNSL treatment is the choice between strategies designed to intensify therapy to improve the cure rate and strategies of treatment de-escalation to avoid severe neurotoxicity. Even though not confirmed in a randomized trial, there is a consensus that combined chemoradiotherapy is superior to radiotherapy alone. Upfront chemoradiotherapy, with variable regimens and radiation doses, has been addressed in several prospective trials, obtaining complete remission rates (CRRs) of 30%–87% and 5-year overall survival (OS) rates of 30%–50%.

## chemotherapy

Chemotherapy plays a central role in the management of PCNSL. However, its efficacy is limited by several factors including the biology and microenvironment of this malignancy, which is protected by the blood–brain barrier (BBB), resulting in the establishment of chemotherapy sanctuaries, like CSF, meninges and eyes, where tumor cells grow undisturbed. Thus, the capability of crossing the BBB should be taken into account with drug selection to treat patients with PCNSL. From this perspective, available drugs can be divided into three groups: (i) drugs with poor BBB penetration that cannot be administered at high doses due to dose-limiting toxicity (i.e. anthracyclines, vinca-alkaloids); (ii) drugs exhibiting low to moderate ability to cross the BBB that can be safely administered at high doses to obtain therapeutic concentrations in the CNS [i.e. methotrexate (MTX) and cytarabine (araC)]; and (iii) drugs able to cross the BBB and to reach therapeutic concentrations in the CNS even when administered at conventional doses (e.g. steroids, some alkylating agents). The combination of drugs from the first group (i.e. CHOP regimen) represents the backbone of treatment of extra-CNS DLBCL but exhibits negligible activity in PCNSL [6].

MTX is the most widely studied drug for PCNSL. Penetration of MTX into the CNS is poor when given at conventional doses. To optimize drug delivery to the brain parenchyma and CSF, both the total dose and rate of infusion of MTX are important. Patients treated with  $<3 \text{ g/m}^2$  do not reliably achieve cytotoxic concentrations of MTX in the CSF ( $1 \mu\text{mol/l}$ ). Rapid infusion of  $3 \text{ g/m}^2$  of MTX over 3 h will consistently achieve cytotoxic concentrations in the CSF, whereas this concentration is not reliably obtained with a 24-h continuous infusion of  $8 \text{ g/m}^2$ .

High doses of MTX ( $>3 \text{ g/m}^2$ ) require intensive inpatient management and might not be feasible in elderly patients or in patients with impaired renal function. Tolerability and activity of MTX dose  $3.5 \text{ g/m}^2$  suggest that this might be a good compromise between safety and efficacy for combination regimens. Non-comparative studies [7], suggesting a survival improvement with the addition of high-dose araC to high-dose MTX were the background of the first randomized trial with completed accrual in PCNSL [8]. In this trial, named IELSG#20, the addition of four doses of araC ( $2 \text{ g/m}^2$ ) to MTX ( $3.5 \text{ g/m}^2$ ) has resulted in significantly improved CRR and OS compared with MTX alone. Hematologic toxicity was higher in the MTX–araC arm, while non-hematologic toxicities were uncommon. A recently reported study showed that araC doses  $<2 \text{ g/m}^2$  result in a less beneficial effect. This MTX–araC combination is the current standard chemotherapeutic approach for *de novo* PCNSL since it is supported by the only randomized study this far.

Temozolomide is an oral alkylating agent that displayed excellent tolerability and a 31% CRR and 1-year OS of 31% in patients with PCNSL relapsed or refractory to high-dose MTX. As upfront monotherapy, temozolomide has been associated with a CRR of 47%, and median OS of 21 months in elderly patients. This drug can be safely combined with MTX in elderly patients, and the

combination of high-dose MTX, rituximab and temozolomide is associated with a 63% CRR, and a 3-year progression-free survival (PFS) of 50% [9].

Topotecan produced an objective response in one-third of patients with refractory or relapsed PCNSL, with a 1-year PFS of 13%. The use of this drug was frequently followed by progressive disease and severe 3–4 leukopenia in 26% of patients and clinically evident neurological deterioration in two-thirds of survivors [10].

Alkylating agents are interesting drugs since they are active in systemic lymphomas, hit phase-0 (quiescent) cells, have a different antineoplastic mechanism if compared with MTX and araC, and a synergistic effect with antimetabolites. In particular, thiotepa exhibits high CNS bioavailability, is used in aggressive lymphomas and is feasible and effective in combination with antimetabolites and idarubicin (MATILDE regimen) [11]. The use of rituximab, an anti-CD20 chimeric monoclonal antibody, in patients with PCNSL is based on its positive effect when added to CHOP in patients with DLBCL, the most common lymphoma category arising in the CNS. Promising effects of rituximab, as single agent or in combination with high-dose MTX, have been reported in a few studies; however, some doubts about its capability to cross the BBB remain, and its precise role in PCNSL should be assessed in randomized trials. Preliminary results suggest that anti-CD20 radioimmunotherapy with [ $^{90}\text{Y}$ ]ibritumomab tiuxetan is feasible in PCNSL patients, and able to target brain lymphoma. However, this radioimmunoconjugate is unable to treat adequately microscopic lesions with intact BBB.

Some authors have suggested that adequate treatment of chemotherapy sanctuaries requires drug delivery by intrathecal/intraventricular and intravitreal routes. The first one has not been assessed in prospective trials, its use is supported by a low level of evidence and is associated with additional risk of infective complications, neurotoxicity and chemical meningitis. Thus, most investigators do not use intrathecal chemotherapy at all or reserve it for the minority of patients with a positive CSF cytology examination. Intraocular disease control is erratic with systemic chemotherapy; irradiation of the posterior two-thirds of both globes with 35–45 Gy has therefore been recommended. Some authors are investigating the role of intravitreal injections of MTX, thiotepa and rituximab with encouraging results, but the impact on survival of this approach remains to be defined.

## radiotherapy

PCNSL is a radiosensitive tumor, and radiotherapy had been the standard treatment for decades. In these patients, the whole brain should be irradiated because of the diffuse infiltrative nature of PCNSL. Most trials use conventional photon font and standard fractionation, hyperfractionated whole brain radiotherapy (WBRT) did not show a clear benefit in terms of disease control and reduced neurotoxicity. WBRT of 40–50 Gy can be the exclusive treatment in patients who cannot tolerate chemotherapy; unfortunately, this strategy is rarely curative in PCNSL, with median survival ranging from 10 to 18 months. Consolidation after chemotherapy represents the best role for radiotherapy.

High-dose MTX-based chemotherapy followed by WBRT is associated with disabling neurotoxicity, in particular among elderly patients. This complication has not been defined clearly in PCNSL patients because it is usually assessed in small and biased series and rarely in prospective trials. Recent important progress in this field consisted of the establishment of a panel of neuropsychological tests to assess, quantify and follow up treatment-related neurologic deterioration in patients with PCNSL. There are three main therapeutic strategies to minimize neurotoxicity risk: to avoid post-chemotherapy WBRT, to optimize radiation parameters and to replace consolidation WBRT with other treatment. The first one can be applied only to patients with CR after primary chemotherapy and was addressed in a recently reported randomized phase III trial on 551 patients, where consolidation WBRT was associated with a significantly better PFS, but did not change survival [12]. Unfortunately, this trial is fraught with design and execution flaws that have resulted in important interpretation biases and unreliable conclusions [13].

The benefit of improving radiation parameters, mostly to reduce WBRT dose, has been demonstrated by two recent pioneered studies, where WBRT doses of 23–30 Gy in patients in CR after chemotherapy have been associated with similar outcome with respect to higher doses, with better neurotolerability [14]. Finally, the enrolment of patients in randomized trials comparing consolidation WBRT with an experimental approach is advisable since these studies will furnish important information useful in minimizing neurotoxicity. In particular, high-dose chemotherapy/autologous stem cell transplantation (HDC/ASCT) deserves to be assessed in this context.

### high-dose chemotherapy supported by autologous stem cell transplantation

The rationale for the use of HDC/ASCT is multiple and includes the administration of high doses of cytostatics to overcome drug resistance and to achieve therapeutic concentrations in the lymphoma tissue and other chemotherapy sanctuaries. Initially HDC/ASCT was used in patients with relapsed or refractory PCNSL, obtaining a CRR of 60%, transplant-related mortality of 16%, severe neurotoxicity in 12% and a 2-year OS of 45%. These encouraging results prompted investigators to include HDC/ASCT as part of first-line treatment of PCNSL, but published prospective experience is limited to a few small single-arm phase II trials. Cumulative data from these few trials seem to suggest that high-dose MTX-based polychemotherapy is more active than monochemotherapy, that intensification with araC, alone or in combination with thiotepa or ifosfamide, was useful as a stem-cell mobilizing regimen, but did not further improve response rates, and that thiotepa-containing regimens are more effective than the BEAM combination. The comparison between WBRT and HDC/ASCT in two ongoing randomized trials will establish the most effective and better tolerated strategy to consolidate response obtained with primary chemotherapy [15].

### future trends

Future therapeutic progresses in PCNSL will be based on four major fields: the expansion of molecular and biological knowledge, the improvement of diagnostic sensitivity and

specificity, the conduction of well-designed prospective trials, and the prevention or reduction of iatrogenic neurotoxicity. All these endpoints will require multidisciplinary and international efforts and additional fund support from scientific institutions and societies, which is a relevant problem in this orphan malignancy. The IELSG #20 [8] and the G-PCNSL-GS1 [12] studies opened the era of randomized trials in PCNSL, which will constitute the cornerstone instrument to improve therapeutic strategies. Phase II trials addressing new potentially active drugs in relapsing patients and laboratory studies focused on the identification of new therapeutic targets should be encouraged. All these approaches should be developed in parallel with new strategies aimed at preventing and reducing iatrogenic neurotoxicity, which remains one of the main goals in the management of PCNSL.

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