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Challenges and prospects in the diagnosis and treatment of primary central nervous system lymphoma

Giovanni Citterio\textsuperscript{a}, Teresa Calimeri\textsuperscript{b} and Andrés J. M. Ferreri\textsuperscript{b}

\textsuperscript{a}Department of Oncology, IRCCS San Raffaele Scientific Institute, Milano, Italy; \textsuperscript{b}Unit of Lymphoid Malignancies, Department of Onco-Hematology, IRCCS San Raffaele Scientific Institute, Milano, Italy

\begin{abstract}
Introduction: Primary central nervous system lymphoma (PCNSL) retains peculiar biological and clinical characteristics and a worse prognosis with respect to other comparable lymphomas. The need for high doses of chemotherapy to achieve valid drug concentrations in cerebral tissues and/or radiotherapy results in severe treatment-related toxicities, mainly neurologic, which are frequently as disabling as the disease itself.

Areas covered: Several emerging combined therapies are addressed that focus on treating PCNSL. The prognosis has improved in the last years but several questions remain unanswered and the research of more effective therapies goes on. Information and data were obtained from direct authors’ experience and a PubMed search of recent peer-reviewed original articles, review articles, and clinical guidelines.

Expert commentary: The substantial progress observed in PCNSL has to be ascribed to a carefully combination of standard chemotherapeutic drugs. High-dose methotrexate-based polychemotherapy followed by maintenance therapy offers one of the best chances to control the disease. Major issues that deserve many efforts by researchers are the definition of optimal consolidation treatment and a shared management of specific conditions such as elderly population and intra-ocular localization.
\end{abstract}

1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare neoplasm, accounting for 2–3\% of all non-Hodgkin’s lymphoma cases but in increasing incidence particularly for elderly patients \cite{1}. It is an aggressive lymphoma, often categorized as diffuse large B-cell lymphoma (DLBCL), exclusively localized within the central nervous system (CNS): brain, cranial nerves, eyes, meninges, cerebrospinal fluid (CSF), and spinal cord \cite{2}. Historically, whole-brain radiotherapy (WBRT) represented the principal therapy, with significant but short-duration responses resulting in median survival of 12 months. Subsequently, a significant advance was the proven efficacy of high-dose methotrexate (HD-MTX) \cite{3}. Several recent prospective trials demonstrated markedly improved outcomes with careful combination of HD-MTX-based polychemotherapy, immunotherapy, and transplantation approaches. However, a proportion of patients are still diagnosed with relevant delay and available treatments are associated with increased risk of severe CNS damage. Accordingly, procedures for a timely diagnosis, highly effective therapies and to avoid iatrogenic neurotoxicity are the main goals of the current clinical research. Significant advances and key points in diagnostic and therapeutic management are discussed in this review.

2. Diagnosis

2.1. Clinical presentation

Disease may present (Table 1) with abrupt onset of focal neurologic defects or seizures urging to perform a brain CT scan or Nuclear Magnetic Resonance study, but more often with a sub-acute development of cognitive decline and/or personality changes (attributable to neoplastic mass effect and/or increased intracranial pressure), causing even months of diagnostic delay due to misleading hypothesis of psychiatric or degenerative neurologic disorder \cite{4}. Ocular symptoms may also occur: the involvement of retina, choroid or vitreous results in floaters and/or blurred vision, either isolated or shared with the former neurologic deficits. However, up to one-half of patients with PCNSL and ocular involvement have no visual symptoms, justifying insidious onset and delayed diagnosis \cite{5}.

2.2. Imaging

The essential diagnostic tool to define site and extension of disease is nuclear magnetic resonance imaging (MRI). Unfortunately, although suggestive, MR images are not specific enough to negate the need for brain biopsy. Common findings

\begin{table}
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Symptom} & \textbf{Clinical Presentation} \\
\hline
Focal neurologic defects & Abrupt onset of neurologic symptoms \\
Seizures & Urging to perform brain imaging \\
Cognitive decline & Sub-acute development \\
Personality changes & \textit{attributable to neoplastic mass effect} \\
Retinal involvement & Floaters and/or blurred vision \\
\hline
\end{tabular}
\caption{Clinical presentation of PCNSL}
\end{table}
Clinical presentation.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>50%</th>
<th>30%</th>
<th>55%</th>
<th>35%</th>
<th>10%</th>
<th>20%</th>
<th>5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor and sensory focal deficits</td>
<td></td>
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<tr>
<td>Personality changes</td>
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<tr>
<td>Headaches</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Uveitis</td>
<td></td>
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</tr>
<tr>
<td>Floaters or campimeter deficits</td>
<td></td>
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<tr>
<td>Seizures, brain stem, or cerebellum symptoms</td>
<td></td>
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<tr>
<td>Extrapyramidal syndrome</td>
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</table>

Disease localizations

| Multiple lesions                              | 34%     |         |         |         |         |         |        |
| Deep lesions                                  |         | 40%     |         |         |         |         |        |
| IOL (Intra-Ocular)                            |         |         | 13%     |         |         |         |        |
| CSF (Cerebro-Spinal Fluid)                    |         |         |         | 16%     |         |         |        |

Clinical presentation.

CSF analysis is also a useful complementary diagnostic tool and should be performed unless clinically contraindicated for high risk of cerebellar herniation. The information that may be obtained from CSF analysis is summarized in Table 2. In limited cases, brain biopsy might be avoided if identification of lymphoma cells in the CSF or in a vitreous biopsy occurs. Even if CSF is rarely normal, showing raised protein levels in 75% and mild pleiocytosis in 50% of patients, lymphoma cells are detected only in about 15% of samples [16]. Sensitivity may be increased by CSF cellular flow-cytometry immunophenotyping and analysis of heavy- and light-immunoglobulin chain genes, distinguishing malignant from reactive lymphocytes by the identification

Table 1. Clinical presentation.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
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<tbody>
<tr>
<td>Symptoms</td>
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<tr>
<td>Motor and sensory focal deficits</td>
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<td>Personality changes</td>
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</tbody>
</table>

Disease localizations

| Multiple lesions                              | 34%     |         |         |         |
| Deep lesions                                  |         | 40%     |         |         |
| IOL (Intra-Ocular)                            |         |         | 13%     |         |
| CSF (Cerebro-Spinal Fluid)                    |         |         |         | 16%     |

2.3. Brain biopsy

As for most neoplasms and all lymphomas, diagnosis needs to be confirmed pathologically, preferentially by stereotactic needle biopsy. In equivocal cases, particularly when biotic material is scarce, PCR testing for clonality may aid the diagnosis [13]. Even a brief exposure to corticosteroids should be carefully avoided before brain biopsy: the procedure in this setting (even after one single dose) may be non-diagnostic, showing prominent infiltration of macrophages, T lymphocytes, and reactive gliosis with lack of neoplastic cells. It is therefore mandatory, unless patients are rapidly deteriorating with suggestive radiological features of PCNSL, to defer corticosteroids until histologic confirmation has been obtained. If, nevertheless, corticosteroids have been given due to clinical need or misdiagnosis with a subsequent objective response, tapering corticosteroids within 1 or 2 weeks and delaying biopsy until tumor regrowth is recommended. Since regrowth occurs in most cases within a few weeks (and sometimes months) after corticosteroids withdrawal, a serial MRI follow-up with 1-month interval in order to identify the optimal timing for biopsy may be useful [14]. Unfortunately, there is some clinical risk with doing this as the disease often comes back more aggressively and the patient is often sicker than the initial presentation. Histologically, the vast majority of PCNSL (>95%) are DLBCL, express B-cell markers such as CD20, CD19, and CD79a, as well as monotypic surface immunoglobulin light chains, and correspond to the non-germinal center B-cell-like (non-GCB) DLBCL subtype with a CD10-BCL6+IRF4/MUM1+ pattern. Molecular investigations identified an aberrant somatic hypermutation in the VH genes and in PAX5, TTF, MYC, and PIM1 genes as well as a high frequency of somatic mutations in genes involved in important pathways such as the B-cell receptor (CD79A), the toll-like receptor (MYD88), and the NF-kB pathway (CARD11), suggesting that their deregulations are driving mechanisms in PCNSL tumorigenesis. More recently, gene-expression profiling studies suggested some genomic differences between PCNSL and non-CNS DLBCL. The most prominent genes involved are SPP1 and MAG [15]. The alteration in gene expression of SPP1 in primary CNS lymphoma is involved in biological activity, such as CNS tropism, B-cell migration, proliferation, and aggressive clinical behavior, while MAG may be an important adhesion molecule that contributes to perineural cancer invasion. These findings may serve as a genetic hallmark for PCNSL providing a genetic marker for diagnosis and potential targets for molecular therapy.

2.4. CSF analysis

CSF analysis is also a useful complementary diagnostic tool and should be performed unless clinically contraindicated for high risk of cerebellar herniation. The information that may be obtained from CSF analysis is summarized in Table 2. In limited cases, brain biopsy might be avoided if identification of lymphoma cells in the CSF or in a vitreous biopsy occurs. Even if CSF is rarely normal, showing raised protein levels in 75% and mild pleiocytosis in 50% of patients, lymphoma cells are detected only in about 15% of samples [16]. Sensitivity may be increased by CSF cellular flow-cytometry immunophenotyping and analysis of heavy- and light-immunoglobulin chain genes, distinguishing malignant from reactive lymphocytes by the identification

Table 2. Cerebral spinal fluid analysis.

<table>
<thead>
<tr>
<th>Volume</th>
<th>Timing</th>
<th>CSF studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–10 ml</td>
<td>Before or immediately after biopsy</td>
<td>Cytology examination (Pos=15%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cell count</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biochemical profile (normal glucose; increased protein level &gt;60%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flow cytometry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b2-microglobulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myd88 L265P-mutation (investigational)</td>
</tr>
</tbody>
</table>
of clonal B cells even when cytological examination is negative [17]. Moreover, CSF protein concentration may have prognostic value and may contribute to stratify patients for clinical trials [18], but its prognostic value was not shown in other studies. Potentially additional diagnostic biomarkers for PCNSL to investigate in CSF include microRNA (miR-21, miR-19b, 363, and miR-92) [19], soluble CD19 [20], interleukin-10 (IL-10), and CXCL13 [21] but they require further validation before being used in routine practice, allowing to potentially replace diagnostic brain biopsy with CSF analysis in a higher proportion of patients.

2.5. Vitreous analysis

Diagnostic workup for PCNSL should include, even in asymptomatic patients, ophthalmologic evaluation with fundoscopy and slit-lamp examination. Fluorescein angiography may be useful to put in evidence lymphomatous infiltration of the retina [5]. A vitreous biopsy has to be performed when eyes are the unique site of disease, even if positive cytology is obtained only in 50% of cases [22]. In order to increase diagnostic sensitivity, immunophenotyping and detection of IgH or T-cell receptor rearrangements by PCR analysis indicating monoclonality should be offered [23]. Furthermore, high levels of IL-10 and/or high IL-10/IL-6 ratio in ocular fluids are strongly suggestive, even if not itself diagnostic, for B-cell lymphomatous uveitis [24]. Recently, a high frequency of MYD88 mutations in vitreoretinal B-cell lymphoma was reported, thus representing a valuable tool to improve diagnostic power of vitreous aspirates [25].

2.6. Prognostic factors

With the increasing availability of effective (and toxic) treatments, it has become even more important to identify prognostic factors in order to tailor treatment for the appropriate patient, so carefully wedging efficacy/toxicity ratio. Many prognostic factors have been suggested [26–30], although only age and performance status (PS) have been consistently identified as treatment-independent prognostic factors. More recently, high Ki-67 (>90%) expression has been identified as an independent prognostic factor for a poor overall survival in a series of 45 PCNSLs [31]. The combination of five independent predictors of response and survival, i.e. age, PS, serum lactate dehydrogenase level, CSF protein concentration, and the involvement of deep structures, distinguishes three risk groups based on the presence of 0–1, 2–3, or 4–5 unfavorable features (IELSG prognostic score [30]). Currently, we include the IELSG score as a stratification criterion in randomized trials and it is strongly recommended its use in choosing individualized risk-tailored treatment. Other existing prognostic scores are the MSKCC [28] or the Nottingham–Barcelona score [29]. It may be worth noting that the MSKCC scoring system could not validate the prognostic factors included in the IELSG, other than age and PS.

3. Treatment

3.1. Surgery

As for most lymphoma patients, surgery has virtually no role in the treatment of PCNSL. This is supported by observations suggesting no benefit in outcome of surgical resection used as unique treatment compared with biopsy in patients treated with postoperative chemotherapy and/or radiotherapy [4,32]. The microscopic multifocal and infiltrative nature of PCNSL that may extend beyond the visible border of the lesion clearly explains these results but, on the other hand, the recommendation to restrict surgical interventions to biopsies is neither based on randomized data nor on contemporary data based on modern neurosurgery techniques. The German PCNSL Study Group-1 phase-III trial included a high rate of operated patients, so allowing the largest and most recent retrospective analysis of an association of surgery and outcome [33]. A significantly longer PFS and OS in patients with surgical resections compared with biopsied patients were reported, but biopsied patients more often had multiple and/or deeply seated CNS lesions than resected patients, features that may have specifically contributed to the unfavorable outcome. In fact, deep cerebral lesions retain both intrinsic unfavorable prognosis and unsuitability to surgery. Consequently, the difference in outcome may be biased by the site (other than the number) of the lesions. Anyway, there is a general agreement to consider surgery as an absolute marginal treatment in PCNSL patients. Given that other therapeutic options are far more advisable, the only rationale for surgical resection may be in much selected patients suffering from a large space occupying lesion with acute symptoms of brain herniation to reduce rapidly increased intracranial pressure, improve PS, and allow subsequent appropriate immunochemothrapy.

3.2. Front-line systemic therapy

Unlike highly effective and generally considered standard first-line treatment in most cases of extra-CNS DLBCL, it is well established that the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen has no role in PCNSL, inasmuch it determines only short-lasting responses and no survival advantage either alone or in combination to radiotherapy [34]. This has been explained by the low capability of cyclophosphamide, vincristine and doxorubicin to cross the unaltered blood–brain barrier (BBB) present in areas of microscopic disease.

Conversely, many studies proved methotrexate (MTX) given at high doses (HD) as the most important and beneficial single agent able to obtain a survival advantage and therefore became standard first-line therapy [3,35], but the optimal dose, interval, and total number of cycles have not yet been determined. MTX doses between 1 and 8 g/m² are able to cross the BBB, but lacking a clear evidence for dose–response relationship. Although comparative studies addressing different MTX administration schedules have not been performed, a wide agreement (based on studies of CSF drug levels) suggests to deliver it by a rapid i.v. infusion at a dose of ≥3 g/m² over 3 h. The interval among cycles ranges between 10 days and
3 weeks and, as far as duration of whole treatment is concerned, a minimum of 4–6 infusions was delivered in most chemotherapy regimens, especially in patients managed without consolidation treatment (radiotherapy and/or intensive chemotherapy). For patients who achieved only PR after 4–5 courses of HD-MTX, two additional courses may improve the CR rate [36]. It has to point out that HD-MTX infusion requires complex pre- and post-hyperhydration schemes, urine alkalinization, variable leucovorin rescue, and careful MTX concentration monitoring, thus requiring at least 5 days of inpatient treatment; for these reasons, it is not suitable for all centers, and this limits its wider implementation despite its proved efficacy.

HD-MTX has been combined with a variety of other chemotherapeutic agents to improve response rate and outcome. The best evidence supporting this approach came from an IELSG randomized phase-II study comparing MTX alone, administered at 3.5 g/m²/d every 21 days, to HD-MTX with cytarabine (2 g/m² twice per day on days 2–3) [37]. Both chemotherapy arms have been followed by WBRT. This study showed a significantly higher CR rate in the HD-MTX-cytarabine arm, as well as significantly improved ORR, PFS, and a trend toward better OS. Of note is the importance of cytarabine dosage: negative results have been reported in a study combining HD-MTX (3.5 g/m²), thiopeta, and cytarabine at a reduced dose of 1 g/m², suggesting that the cytarabine dose was probably suboptimal to reach cytotoxic levels in the CNS [38], as supported by pharmacokinetic studies [39]. Attempts to determine the optimal chemotherapy combination were subsequently made. Among the more representative studies, a combination of rituximab, MTX, procarbazine, and vincristine followed by low-dose whole-brain radiotherapy was assessed in 52 patients with newly diagnosed primary CNS lymphoma, with an ORR of 79% and a 2-year PFS of 57% [36]. The same combination followed by consolidative autologous stem cell transplantation was investigated in 33 patients younger than 65 years, with an ORR of 94% and a 2-year PFS of 79% [40]. A combination of MTX, temozolomide, and rituximab followed by consolidative non-myeloablative chemotherapy with HD of cytarabine and etoposide and without radiotherapy was tested in 44 patients, with an ORR of 77% and a 2-year PFS of 59% [41]. Unfortunately, no conclusions can be drawn about the effect of each drug (i.e., alkylating agent and rituximab) in these studies in view of the fact that these are small, single-arm trials and that similar results have been reported with HD-MTX monotherapy.

Finally, the results of the IELSG#32 study, a large randomized trial that enrolled 227 patients from 53 centers of five European countries, were recently published [42]. In this trial, patients were randomly assigned to receive four courses of MTX 3.5 g/m² on day 1 plus cytarabine 2 g/m² twice daily on days 2 and 3 (group A) or the same combination plus two doses of rituximab 375 mg/m² on days –5 and 0 (group B) or the same MTX–cytarabine–rituximab combination plus thiopeta 30 mg/m² on day 4 (group C—called also MATRix regimen). With the warning that the study was not designed for direct comparison of the 3 arms, at median follow-up of 30 months patients treated with rituximab and thiopeta had a significantly higher complete remission rate of 49%, compared with 23% of those treated with MTX-cytarabine alone and 30% of those treated with MTX-cytarabine plus rituximab. It has to be pointed out that the CR rate (49%) remains inferior to other regimens such as R-MVP (60%) and MT-R (66%), as well as the 5-year OS of 69% was inferior to R-MPV-HDASCT (81%) and R-MPV+RT (70%). Grade-4 hematological toxicity was more frequent in patients treated with MATRix combination, but infective complications were similar in the three groups. Patients with responsive or stable disease after the first stage were then randomly allocated between whole-brain radiotherapy and autologous stem cell transplantation (see next section). Only 61.5% of pts treated with MATRix proceeded to second randomization, moreover the outcome in arm A (HD-MTX+HD-AraC + HD-ASCT or WBRT) was very poor with a 2y PFS of 36% and 2y OS of 42% and the outcome in arm B was only slightly better (2y PFS 46%, 2y OS 65%). The very poor outcome in the comparator arms in the IELSG#32 study and its unfeasibility in every third of young and relatively fit patients are two major pitfalls for the widespread approval of the study, although a good 5-year OS was achieved. Table 3 summarizes the principal trials of front-line therapy above discussed.

Rituximab, the anti-CD20 chimeric murine monoclonal antibody, dramatically improved the prognosis of systemic DLBCL, but its large size predicts poor penetration into the CNS so its role in PCNSL would not be expected to be as determinant as in systemic lymphomas. Quite unexpectedly, a single study in which 12 patients with refractory or relapsed PCNSL were treated with a weekly i.v. dose of 375 mg/m² rituximab infusion for up to eight doses suggested a potential efficacy [43]: MRI responses were observed in 36% of patients and the median overall survival was 20.9 months. Subsequently other studies used iv rituximab in combination with an HD-MTX-based chemotherapy regimen as front-line therapy [36,41,44–46] or as salvage treatment [47,48], suggesting that the addition of rituximab to HD-MTX-based chemotherapy may improve the CR and OS rate based on retrospective comparison with historical controls. Finally, the randomized IELSG#32 trial produced the demonstration of superiority of immunochemotherapy with respect to standard HD-MTX polychemotherapy [42]. Overall, the addition of rituximab to systemic polychemotherapy is well tolerated: only one study reported a higher rate of neutropenia [49]. Targeting CD20 tumor cells for selective radioimmunotherapy is another approach whose feasibility has been demonstrated in pilot studies treating patients with relapsed or refractory CNS lymphomas [50–52] but at present it did not pass the preliminary phase. Finally, injection of rituximab into the CSF via either lumbar puncture or by intraventricular administration was evaluated in two phase-1 studies for refractory or recurrent CNS lymphoma patients [53,54]. In these studies, objective responses and good tolerability were documented but again without widespread viability.

Blood–brain barrier disruption (BBBD) by intra-arterial (IA) infusion of hypertonic mannitol followed by intra-arterial chemotherapy has been explored as a strategy to increase drug concentrations in the CNS. Front-line BBBD with IA MTX demonstrated a good safety profile and neurocognitive
tolerance and achieved comparable outcomes to those observed with HD-intravenous MTX-based chemotherapy regimens [55–57]. This approach requires careful patient selection as safety depends on the extent of intracranial mass effect. Furthermore, requiring intracranial vessels cannulation it is even more complex and it may be performed in even less centers than HD-MTX administration as it has to be managed only by teams highly trained in invasive procedures.

Intrathecal (IT) chemotherapy administration as a complement to front-line therapy is still debated. Three retrospective studies did not demonstrate benefit from the addition of intrathecal drugs (MTX, cytarabine) in patients treated with HD-MTX dosed at 3 g/m$^2$ [58–60]. In contrast, two consecutive single-arm trials using the same systemic polychemotherapy regimen suggested additional benefit when intraventricular chemotherapy was added [61,62]. In conclusion, there is no agreement on CSF prophylaxis/treatment and recently reported or ongoing PCNSL trials do not use IT/intraventricular chemotherapy. IT chemotherapy (intralumbar or preferably intraventricular through an Ommaya reservoir) could otherwise be proposed, based on clinical judgment weighted against alternative options, in the case of documented meningeal involvement with insufficient response to intravenous HD-MTX-based chemotherapy or in patients who are not able to receive an MTX dose of $\geq$3 g/m$^2$.

### 3.3. Consolidation therapy with ASCT

It is widely accepted that front-line therapies need for a consolidative treatment in order to prevent relapses that might occur in a high proportion of otherwise responding patients. Historically, this role was entrusted by radiotherapy, but more recently it seems that myeloablative high-dose chemotherapy followed by autologous stem-cell transplant (HDC/ASCT) may offer several advantages, first of all the virtual absence of neurocognitive impairment that represents a major pitfall of WBRT. HDC/ASCT is the standard treatment for relapsing systemic DLBCL, but its application on PCNSL patients is questioned by the relative advanced age and/or poor general conditions of most of them. In fact, excellent results have been obtained in highly selected series, mostly constituted by young and fit patients. Starting from its use in salvage setting, one multicenter phase-II trial evaluated HDC/ASCT, with TBC conditioning regimen (thiotepa, busulfan, and cyclophosphamide) in 43 patients relapsed/refractory after first-line treatment [63]. The CR rate was 60%, median PFS and OS were 41 and 58 months, respectively, for the 27 patients who completed the full HDC/ASCT procedure, whilst the intent-to-treat median PFS and OS times were 11 and 18 months, respectively, revealing a toxicity-related mortality in 7% and a severe neurotoxicity in 11% of patients. An update of this study to which additional cases have been included and an independent retrospective single center series confirmed the benefit of the TBC regimen followed by ASCT [64,65]. Other HDC regimens in this setting were published but limited to a few cases [47,66].

<table>
<thead>
<tr>
<th>Reference</th>
<th>Phase</th>
<th>Induction</th>
<th>Consolidation</th>
<th>No. of patients</th>
<th>Age</th>
<th>ORR</th>
<th>2-year PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris et al.</td>
<td>II, multicenter</td>
<td>R-MPV</td>
<td>rdWBRT and cytarabine</td>
<td>36</td>
<td>18-79</td>
<td>79%</td>
<td>57%</td>
</tr>
<tr>
<td>Ferreri et al.</td>
<td>II, multicenter, randomized</td>
<td>HD-MTX vs HD-MTX + HD-Cytarabine</td>
<td>WBRT</td>
<td>79</td>
<td>18-75</td>
<td>49% Not indicated (reported 3-year PFS ranging from 11 to 70% according to risk)</td>
<td></td>
</tr>
<tr>
<td>Omuro et al.</td>
<td>II, multicenter</td>
<td>R-MPV</td>
<td>TBC-ASCT</td>
<td>32</td>
<td>18-72</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>Rubenstein et al.</td>
<td>II, multicenter</td>
<td>HD-MTX vs HD-MTX + HD-Cytarabine</td>
<td>TBC-ASCT</td>
<td>44</td>
<td>12-76</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>Ferreri et al.</td>
<td>II, multicenter, randomized</td>
<td>HD-MTX + HD-Cytarabine vs MT-R vs R + HD-MTX + HD-Cytarabine vs R + HD-MTX + HD-Cytarabine + Thiotepa</td>
<td>WBRT (Arm D) vs ASCT (Arm E)</td>
<td>43</td>
<td>18-70</td>
<td>53% 24% 87%</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Principal front-line HD-MTX combinations.**

R-MPV: rituximab, methotrexate, procarbazine, and vincristine.
rdWBRT: reduced-dose whole-brain radiotherapy.
TBC: thiotepa, cyclophosphamide, and busulfan.
MT-R: methotrexate, temozolomide, and rituximab.

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An obvious evolution therefore was to shift HDC/ASCT from salvage to first-line regimens. In early studies, WBRT was administered after HDC/ASCT [67,68], but subsequently HDC/ASCT was challenged as consolidation treatment in alternative to WBRT to avoid the well-known RT-associated neurocognitive impairment. The first study with HDC/ASCT without WBRT used the BEAM conditioning regimen (BCNU, etoposide, cytarabine, and melphalan) and reported a disappointing median event-free survival of 9.3 months [69]. Subsequently, encouraging studies for which WBRT had been omitted at least in patients in CR after HDC/ASCT have been reported [70–72]. These studies used either HD thiotepa-based conditioning regimens or a combination including busulfan, cyclophosphamide and etoposide [73]. Taken together, although direct comparison between used conditioning regimens is difficult, HD thiotepa-based regimens seem more effective than BEAM-based regimens, and BCNU–thiotepa combination seems to be equally effective but less toxic that thiotepa–busulfan–cyclophosphamide combination [74].

The issue of the best choice between WBRT and HDC/ASCT as consolidation regimen has been addressed by two large multicentric randomized studies. The first one (IELSG#32, NCT01011920), randomly allocated responsive or stable patients after the first stage between WBRT and autologous stem cell transplantation: there were no significant differences in 2-year progression free survival between WBRT and ASCT: 80% (95% CI 70–90) in WBRT and 69% (59–79) in ASCT group (hazard ratio 1.50, 95% CI 0.83–2.71; p = 0.17). Both consolidation therapies were well tolerated, albeit two toxic deaths for infections were observed in ASCT group. As expected, hematological toxicity was more common in patients treated with ASCT [75]. The second one (PRECIS, NCT00863460) enrolled 140 immuno-competent patients (aged 18–60) from 23 French centers. All the patients received 2 cycles of R-MBVP (Rituximab 375 mg/m² day 1, MTX 3 g/m² days 1 and 15, VP16 100 mg/m² day 2, BCNU 100 mg/m² day 3, Prednisone 60 mg/kg/day days 1–5) followed by 2 cycles of R-cytarabine (Rituximab 375 mg/m² day 1, Cytarabine 3g/m² 2–7) as induction chemotherapy. Participants were then randomly assigned to receive either WBRT (Arm A) or HDC/ASCT (Arm B) as a consolidation treatment. HDC consisted of thiotepa, busulfan, and cyclophosphamide. Preliminary results published as abstract at 58th ASH meeting (December 2016) showed that WBRT was given to 53 patients and HDC/ASCT to 44 patients. After consolidation treatment, ORR was 71% and 67% in arm A and B respectively. Three treatment-related deaths were reported after HDC/ASCT. Relapses occurred in 16 patients who underwent WBRT but only in 5 patients treated with HDC/ASCT. The analysis of the prospective neuropsychological evaluations is pending and the full paper is awaited for better comprehension.

Meanwhile, a German phase-II study recruited 81 patients aged <65 years treated with five courses of intravenous rituximab 375 mg/m² and four courses of MTX 8 g/m² (every 10 days) followed by two courses of rituximab–cytarabine–thiotepa combination [76]. Three weeks after the last course, patients received intravenous HCT-ASCT with rituximab, carbustine, thiotepa, and infusion of stem cells, irrespective of response status after induction. Radiotherapy was restricted to patients without complete response after HCT-ASCT. All patients started induction treatment; 73 (92%) underwent HCT-ASCT, and 61 (77%) patients achieved a complete response. Four (5%) treatment-related deaths were recorded (three during induction and one 4 weeks after HCT-ASCT). The authors concluded that HCT-ASCT with thiotepa and carbustine is an effective treatment option in young patients with newly diagnosed PCNSL.

Eventually, the HDC/ASCT treatment itself is beginning to be challenged as a consolidation treatment: a multicenter phase-II trial reported promising results using cytarabine combined with etoposide as consolidation without WBRT following a HD-MTX-based front-line polychemotherapy [41]. Forty-four patients with newly diagnosed PCNSL were treated with induction MT-R (MTX, temozolomide, rituximab), and patients who achieved CR received EA (etoposide, cytarabine) consolidation. The CR rate of MT-R was 66% and the overall 2-year PFS was 0.57. The > 2-year time to progression was 0.59 and, for patients who completed consolidation, it was 0.77. Patients aged >60 years did as well as younger patients, and the most significant clinical prognostic variable was treatment delay. Given the encouraging results in terms of toxicity, response and survival achieved in the multicenter setting, the MT-R regimen is being evaluated in an ongoing intergroup, randomized phase-II trial—CALGB 51,101 (Alliance)—aimed to compare dose-intensive (non-myeloablative) EA chemotherapy with myeloablative chemotherapy with carbustine–thiotepa combination followed by ASCT.

Furthermore, as evolution of IELSG#32 trial, a multicenter, randomized phase-III trial was started [77]. Induction chemotherapy consists of four cycles of MATRix regimen; subsequently CR or PR patients will be randomized between two different consolidation treatments: (A) additional conventional-dose chemoimmunotherapy with R-DeVIC regimen (rituximab 375 mg/m² day 0, dexamethasone 40 mg/d days 1–3, etoposide 100 mg/m²/days 1–3, ifosfamide 1500 mg/m²/days 1–3 and carboplatin 300 mg/m² day 1) or (B) myeloablative chemotherapy with BCNU and thiotepa supported by ASCT. It will be interesting to know if, after HDC/ASCT undermining the WBRT supremacy, either HDC/ASCT itself would surrender in favor to non-myeloablative consolidative treatment.

### 3.4. Radiotherapy

Historically, radiotherapy was widely used in PCNSL. Due to the diffuse and multifocal nature of PCNSL, these patients are usually irradiated to the whole brain, including the eyes, and the first two segments of the cervical spine. Although lymphoma cells are highly radiosensitive, responses to WBRT are short lasting and the disease invariably relapses, with a median OS of 10–18 months and a 5-year survival rate of 5% when WBRT is used as exclusive treatment. The only phase-II trial, conducted by the RTOG, which delivered a total dose of 40 Gy with an additional 20-Gy boost to contrast-enhancing lesions, reported a disappointing 11.6 month OS [78] with the majority of relapses occurring in boosted fields. Given the superiority of front-line HD-MTX-based immunochemotherapy, primary WBRT has been abandoned, with the exception of patients in which chemotherapy is contraindicated or in patients with
unusual histologic subtypes as curative treatment (e.g. Waldenstrom macroglobulinemia) [79]. Moreover, WBRT retains its role as salvage therapy for refractory or relapsing patients when systemic chemotherapy is no longer advisable.

Currently, consolidation therapy after CR obtained with front-line chemo-immunotherapy is the most debated role for WBRT. Delayed treatment-related neurotoxicity is a dramatic occurrence in survival patients, often so disabling to frustrate the beneficial effect of treatment on the disease control. There is a general agreement that the combination of HD-MTX and WBRT is associated with disabling neurotoxicity with a cumulative 5-year incidence of 25% to 35% and related mortality of 30% [27], and this is the main feature limiting a more diffuse use of WBRT in PCNSL patients. This severe iatrogenic complication typically occurs several months to years after treatment. Neuropsychological examination may confirm impaired psychomotor speed, executive function, attention, and memory [80], while neuroimaging findings include cortical/subcortical atrophy and leukoencephalopathy [81,82], which in turn result in dementia, ataxia, and incontinence, with a median survival after onset of clinically evident neurotoxicity less than 1–2 years. Autopsy findings include myelin and axonal loss, gliosis, spongiosis, thinning of white matter, small and large vessels disease, and necrosis [83]. The most representative series addressing this issue was the retrospective analysis of 183 patients [81], in which only the administration of WBRT was identified as an independent risk factor for the development of late neurotoxicity: in this series, 2% of patients treated with chemotherapy alone developed clinically-evident neurotoxicity, in contrast with 33% of those treated with the combination of chemo-radiotherapy. The cumulative incidence of neurotoxicity for the whole group was 5% at 2 years and 24% at 5 years, with a higher risk in patients >60 years. Moreover, the prevalence of treatment-related ‘subtle’ cognitive dysfunction is probably largely underestimated, as formal psychometric evaluations have not been routinely performed in most prospective studies. Again, these results have been confirmed by three long-term evaluations [84–86]. In the most recent [86] analysis of 80 long-term survivors of PCNSL, tumor-free and having completed treatment at least two years prior to evaluation, patients who had received WBRT showed significantly lower mean scores in attention and executive function, motor skills, and neuropsychological composite score, associated with poorer quality of life items. Moreover, on brain imaging, mean areas of total T2 abnormalities in the WBRT group were more than twice the mean of any other non-WBRT group. These results justify the above depicted efforts to identify an alternative way to consolidate front-line therapy for CR patients and call for the implementation of formal neuropsychometric testing in clinical trials on PCNSL.

Of utmost importance, it remains unclear whether consolidation with WBRT provides better disease control or survival in CR patients after front-line CT. In fact, only one randomized trial comparing radiotherapy versus watch-and-wait after chemotherapy for PCNSL was published to date [87]. In this study, patients received HD-MTX 4 g/m² i.v. every 14 days for 6 cycles with or without ifosfamide. Patients who achieved CR were randomized between consolidating WBRT, 45 Gy in 30 fractions over 6 weeks vs. observation. In spite of the large population studied (551 patients), the unmet primary end point for non-inferiority, the high rate of protocol violations and several critical interpretative issues made the results questionable: OS was similar in both arms, but the WBRT arm was associated with a non-significant trend for better PFS, as compared with the no WBRT arm. Despite these inconclusive results, many physicians agree that omission of WBRT from first-line treatment does not compromise OS and spares cognitive functions. Others single-arm trials suggested that chemotherapy alone plus a deferred RT strategy may obtain comparable survivals with those reported for combined chemo-RT, but with minor cognitive deterioration [84,88,89]. On the other hand, updated results at a median follow-up of 12 years of a phase-II trial assessing first-line chemotherapy followed by WBRT showed that 9/41 patients are alive and disease-free, 8 of whom are alive at 10 years. At 10 years from diagnosis, no patient showed chronic hematologic and non-hematologic toxicities, with a Mini-Mental State Examination score of >29 in all cases but one [90]. The researchers agree that neurotoxicity appears to be related to radiation parameters, particularly to the dose, while the RTOG-9310 trial did not show a clear benefit with hyperfractionation [91]. A hypothetical alternative approach for diminishing WBRT-related neurotoxicity is to reduce the radiation doses. The optimal dose of post-chemotherapy irradiation has never been prospectively investigated in PCNSL: to date, doses of 23–50 Gy to the whole brain, with or without a tumor bed boost, are currently used, with most protocols delivering a total dose of 40–45 Gy without boost, and standard fractionation (1.8–2.0 Gy/fraction). A subset analysis from a phase-II trial that included 25 patients aged <60 years who achieved a CR after initial chemotherapy and received either 45 Gy or 30.6 Gy as consolidation treatment showed a significantly higher recurrence rate and lower OS rate in the reduced-dose RT group [92]. On the other hand, in a retrospective study of 33 CR patients consolidated with WBRT, total doses ≥40 Gy were not associated with improved disease control in comparison with a WBRT dose of 30–36 Gy [93]. In a recent phase-II trial, patients who achieved a CR after R-MPVA chemoimmunotherapy were treated with reduced-dose WBRT (23 Gy) with encouraging results both in term of survival and neurotoxicity [36]. Based on these results, a randomized study (RTOG-1114) comparing the R-MPV regimen with or without reduced-dose WBRT is currently ongoing (NCT01399372) and hopefully the results will help clarifying this issue.

### 3.5. Maintenance therapy

The role of maintenance therapy is of outmost importance in elderly patients to which consolidation strategies (WBRT or HDC/ASCT) cannot be offered. Maintenance with temozolomide was assessed in two studies. In the first one, patients were treated with MTX–temozolomide–rituximab followed by hyperfractionated WBRT and temozolomide maintenance and a 2-year OS rate of 80% was observed [94]. In the second one temozolomide was administered at the dose of 150 mg/m²/d, days 1–5 every 28 days, for one year or until progression in
patients >65 years treated with front-line age-adjusted MTX–cytarabine regimen, with a 2-year OS of 60% [95]. Procarbazine maintenance was assessed in patients >65 years responsive to rituximab–procarbazine–MTX combination, resulting in a 2-year OS of 47%. A limit of these studies is the lack of a control group so it cannot be established the specific contribution of the maintenance drug to survival. A retrospective series reported only as meeting abstract suggested a contribution of maintenance with lenalidomide in 12 patients with relapsed PCNSL. Treatment was feasible, even in elderly patients, and duration of response with lenalidomide was longer than time to progression after the first-line therapy in most patients, even after local salvage therapy (e.g. stereotactic radiotherapy, tumor resection). Taken together, these studies seem to advise a role for maintenance therapy, but more data and randomized trials are needed in order to confirm these suggestions.

4. Special issues

4.1. Elderly patients

Elderly patients represent the majority of the PCNSL patients [1,96], have been recognized as a specific subgroup and should deserve a specific consideration, inasmuch age >60 proved to be an independent prognostic factor [30,97] and generally more aggressive treatments are not advisable due to foreseeable excessive toxicity. Some prospective studies have been published on treatment of this patients’ subgroup [98–100] and others on patients of all ages but reporting specifically on older patients [91,101,102]. As in younger patients, the addition of CHOP/CHOD to radiotherapy did not improve the outcome [103]. After HD-MTX-based therapy, PFS in patients aged 60 or 65 and older is reported between 6 and 16 months, and OS between 14 and 37 months with OS in the majority of prospective studies less than 2 years [98,100,102]. Although no direct comparisons have been made in this age group, the impression is that survival after HD-MTX-based chemotherapy is equally good, and probably better, than after radiotherapy, thus allowing to spare RT-related neurotoxicity, particularly important precisely in these patients. A recent randomized phase-II study addressing MPV-A (MTX, procarbazine, vincristine, cytarabine) and MTX–temozolomide combinations [104] showed a not significant trend in CR rate and PFS in favor of the former regimen, with similar toxicity. A recent meta-analysis of first-line treatments including 783 elderly patients [105] did not show any difference in survival between patients treated with HD-MTX + oral alkylating agents and more intensive intravenous combinations. Regarding the choice of chemotherapy dosage, MTX up to 3.5 g/m² was well tolerated with 2–7% treatment-related mortality, less than 10% grade 3–4 nephrotoxicity or stomatitis, and 7–10% treatment discontinuation, though MTX dose was reduced because of decreased renal function in 26–44% of patients [98,100]. Retrospective studies substantiate this view, but more dose reductions were applied when higher MTX doses have been used [106,107]. Only one study showed that toxicity after HD-MTX was exceedingly high in old patients [101]. In conclusion, HD-MTX-based treatment may be assumed as advisable and well tolerated by older patients, providing that adequate supportive measures and careful check of renal function are met [96,108]. Risk of delayed neurotoxicity is high in patients older than 60 years managed with chemoradiotherapy, suggesting that WBRT should be deferred or avoided when possible. Management with chemotherapy alone is followed by quality of life improvement after a longer follow-up [109], suggesting that treatment in these poor prognosis patients is worthwhile. In unfit patients and in the very older (over 80) ones, both retaining worse prognosis [110], comorbidities and frequent hospital admissions therapy-related need to be carefully weighed against the even more limited survival benefit foreseeable.

4.2. Intraocular lymphoma

The optimal treatment for intraocular lymphoma (IOL) is not known, because experimental data are limited to retrospective case reports or small series with heterogeneous patient populations and treatments. The median survival of isolated IOL is about 5 years [111], but as many as 90% of patients subsequently develop brain involvement over the course of the disease [5] with dissemination to the brain being the cause of death. Generally local treatment is advisable, consisting of ocular RT at total dose of 35–40 Gy, 2 Gy per fraction using opposed lateral beams to include both globes [112] and/or intravitreal chemotherapy. Sporadic reports have shown clinical benefit with repeated intravitreal MTX [113] and more recently after rituximab injections [114]. Intravitreal MTX is highly active (remission in 100% of treated eyes) but does not affect OS and is associated with important side effects in 73% of treatments and significant deterioration of visual acuity in 27% of patients [115]. On the other side, intravitreal rituximab appears safe and active, and furthermore lasts much longer in the vitreal space than intracocular MTX which must be delivered twice a week to start. Some authors believe that this is a major reason for the reduced toxicity associated with rituximab and for the better patient acceptance, but the data are still limited. Treatment may alternatively be extensive, including systemic chemotherapy and WBRT. Intraocular responses have been reported with HD-MTX, cytarabine, ifosfamide, and trofosfamide used as single agent, with MTX-based polychemotherapy, and after HDC/ASCT [116–118]. A large retrospective multicenter study did not show any difference in IOL between focal and extensive therapy in terms of disease control and survival [111]. Unfortunately, published studies failed to provide reliable predictors of brain dissemination in IOL patients. Thus, some experts recommend local therapy for disease confined to the eyes, while others advise that initial treatment of IOL should not differ from that of PCNSL. Local treatments would remain options for refractory or recurrent disease confined to the eyes. The management decision should take into account the individual risk of treatment toxicities (including those related to ocular treatment) and local expertise [5]. When IOL is concurrent with brain lesions, it has not been identified as an independent prognostic factor and the prognosis is similar to that of the PCNSL without intraocular disease in one study [119], while in the G-PCNSL-SG1 trial IOL at diagnosis of PCNSL was an independent negative prognostic indicator for PFS and OS [120]. Accordingly, patients with concomitant intraocular
and cerebral disease should be treated no differently from PCNSL. The value of additional local ocular treatment (intravitreal chemotherapy or ocular radiotherapy if WBRT has not been delivered) to systemic chemotherapy remains matter of debate, with conflicting results in two retrospective studies [119,121]. In conclusion, considering the high risk of brain dissemination and the lacking of reliable predictors for this event, it appears reasonable to treat patients with IOL with HD-MTX-based chemotherapy (with or without WBRT depending on age) as the other PCNSL patients. Local treatment (intravitreal chemotherapy or ocular RT) is a valid approach for patients with systemic chemotherapy contraindications or for elderly patients with relapsing intraocular disease. If consolidation WBRT is proposed, it should include both eyes. Refractory and relapsed IOL should be treated according to the patients’ characteristics and prior treatments. Treatments could include MTX intravitreal injections, focal radiotherapy, WBRT, systemic chemotherapy and HDC/ASCT.

An attempt to identify the best therapeutic choice for IOL was conducted [122] with a multicentric European retrospective study on 78 patients. Therapy to prevent CNS dissemination included ocular radiotherapy and/or ocular chemotherapy (group A, 31 patients), systemic treatment (group B, 21 patients), and a combination of ocular and extensive treatment (group C, 23 patients). Overall, IOL did evolve to PCNSL in 28 patients (36%) at a median follow-up of 49 months. Specifically, PCNSL developed in 10 of 31 patients (32%) in group A, 9 of 21 (43%) in group B, and 9 of 23 (39%) in group C. This work, albeit valuable, raised some major questions [123] namely the lack of a central pathology review, the suboptimal systemic therapy and some biases in cases collection. In summary, available studies suggest that some patients with IOL can be safely treated with local treatment alone, while others should be treated with systemic chemotherapy. Unfortunately, efforts to distinguish the best candidates for each strategy remain at present ineffective due to relevant selection and interpretation biases. An international study focused on patients with IOL managed with ocular treatment alone and aimed to establish clinical and pathological predictors of CNS dissemination should be encouraged.

### 4.3. Salvage therapy

In spite of significant advances in cure rate, about one third of patients with PCNSL is refractory to first-line treatment and up to half of responders eventually experiences relapse. The prognosis of progressive or relapsed PCNSL remains poor but, while about two decades ago even first-line therapy was questioned against BSC, more recently it is worthwhile to consider second or third line treatment. Salvage options depend on age, PS, site of relapse, prior treatments, and duration of response. Sometimes, the aggressive course of relapsing PCNSL, producing a dramatic PS worsening, prevents physicians from enrolling patients in prospective trials and, finally, from recommending any treatment at all.

In patients treated with HD-MTX-based chemotherapy alone, WBRT or HDC/ASCT should be considered if permitted by age and/or PS. Two retrospective studies on WBRT delivered in relapsed PCNSL [124,125] reported a high rate of objective responses (75%) and a median survival of 11–16 months, quite similar to what is expected with front-line WBRT, with delayed neurotoxicity occurring in 15–22% of patients. Consequently, salvage WBRT (carefully weighed against neurotoxicity) is a reliable option for previously non-irradiated patients proving that it is more active than most salvage chemotherapies. HDC/ASCT is an alternative option, as previously discussed, but it could be reasonably effective only for patients aged <60–65 years and with a tumor sensitive to second-line chemotherapy capable to produce an objective response before myeloablative conditioning [64], even if attempts to treat with HDC/ASCT either a small number of patients unresponsive to conditioning chemotherapy were performed [126].

If the patient is not suitable for HDC/ASCT or it is concern about WBRT neurotoxicity, conventional chemotherapy may be proposed. Only a limited number of prospective studies are available with single-arm phase-II trials thus preventing any comparison across trials. Various non-MTX based chemotherapies have been performed, with drugs not used in first-line regimens. The most favorable results were reported with ifosfamide, etoposide and carboplatin [127], capable to obtain objective responses in 84.4% of patients. Other small studies reported valuable responses with rituximab–ifosfamide–etoposide (R-IE) [47] (ORR 41%), IA carboplatin [128] (ORR 43%), cisplatin–cytarabine according to ESHAP or DHAP schedule [129] (ORR 59%), procarbazine, CCNU, vincristine (PCV regimen) [130] (seven patients, ORR 86%). Others small studies considered rituximab–temozolomide [48] (ORR 14%), topotecan [131] (ORR 33%), pemetrexed [132] (ORR 55%), bendamustine [133] (ORR 50%), and temsirolimus [134] (ORR 54%). More recently, intriguing results were reported with lenalidomide [135] and ibrutinib [136]. The former agent has been able to determine 2/6 CRs in heavily pre-treated PCNSL patients, the latter showed a 50% ORR in 13 patients, with a favorable toxicity profile. Another retrospective series of 14 patients treated with ibrutinib [137] showed five (three CRs and two PRs) responder patients, two of which experiencing an early CR within the first 2 months of therapy. Response rates for ibrutinib in PCNSL were considerably higher than reported for DLBCL outside the CNS, suggesting a divergent molecular pathogenesis and a role for BTK inhibition, possibly in conjunction with PI3K and m-TOR inhibitors [138]. On the other hand, the risk of severe atypical infections (e.g. aspergillosis) on treatment with ibrutinib should be taken into account. Although response was short lasting in most patients, these reports, if confirmed on large series, might open the door to therapeutic agents with mechanisms of action strongly different from classic drugs currently used in PCNSL and, moreover, with particularly simple way of administration. The anti PD1/PDL1 immunotherapeutic drugs are an emerging class of agents that are changing the course of many solid tumors (i.e. malignant melanoma and lung cancer). Nivolumab, one of these agents, was tested in four relapsed/refractory PCNSL patients [139]: all four patients had clinical and radiographic responses to PD-1 blockade, and 3 patients remain progression-free at 13+ to 17+ months. These data suggest that nivolumab is active in relapsed/refractory PCNSL and support further investigation of PD-1 blockade in these diseases as a new and totally
different therapeutic strategy. Finally, a reliable option to be considered is MTX rechallenge, yielding a high rate of new objective responses (CR 75%) and durable remissions in patients who previously achieved prolonged response with front-line HD-MTX-based chemotherapy, suggesting retained chemosensitivity to MTX [140].

Extra-CNS relapses were also reported and need to be considered, accounting for 7% of failures. Some studies suggest they are associated with a better prognosis than more common CNS-involving relapses [141]. The best salvage treatment for this condition remains to be defined, but excellent results have been reported with anthracycline-based chemotherapy consolidated or not with HDC/ASCT [90].

5. Conclusion

Until two decades ago, PCNSL was considered an incurable disease, and many centers did offer patients supportive therapy only, or at most palliative radiotherapy. Since then, important advances in cure rate were made and today a good proportion of patients may achieve durable responses with multistep therapeutic options. Moreover, a significant proportion of patients fully recover from this otherwise rapidly lethal disease. These results were obtained with intense cooperation among neurosurgeons, neurologists, ophthalmologists, hematologists, medical oncologists, pathologists, and radiotherapists. Strict cooperation is needed to offer the best treatment choice for the individual patient. The fundament of treatment is HD-MTX-based chemoimmunotherapy, which still needs highly committed oncologic centers, and determinant consolidation treatments consist of myeloablative or non-myeloablative chemotherapy and radiotherapy. Further fields of specific attention are represented by salvage treatment for relapsing (often after years from first-line therapy) patients, elderly population, and isolated involvement of ocular structures. It must be outlined that the subject is still in progress: it is expected that the standard first-line therapy and the precise kind of consolidation therapy will be clarified in the coming years, in parallel with an awaited further rise in cure rate. There is a hope for reducing treatments’ complexity and/or toxicity with the aim to allow an increased number of cancer centers to treat these high-risk patients.

6. Expert commentary

Unlike other major recent advances in oncology involving innovative drugs (i.e. immune check-point inhibitors that are changing the prognosis of some NSCLC or melanoma patients), the substantial progress observed in PCNSL should be ascribed to a carefully combination of standard chemotherapeutic drugs. In fact, the shift from incurable to curable disease went from the recognition of HD-MTX to obtain durable responses in this field. Many efforts have been made in order to best clarify the dosage and the optimal combination, and at present it seems that HD-MTX-based polichemotherapy according to MATRix, R-MPV, or MTR regimens offers one of the best chances to control the disease. These combinations need in-patient treatment but proved to be feasible and manageable in specialized institutions. In particular, it has to be mentioned that the possible beneficial effect of rituximab, somewhat a-priori unpredicted, opens the way if confirmed to a wide application of immunotherapy in PCNSL like it already occurs in other B-cell lymphomas.

Another major issue that deserves many efforts by researchers is the definition of optimal consolidation treatment. In fact, even if some authors disagree, front-line therapy without a consolidation treatment proved to be unsatisfactory in order to obtain long-time remissions. Historically relied on WBRT, in recent years increasing relevance has obtained HD myeloablative CT/ASCT. Either treatment has pros and cons: ASCT is unsuitable for elderly patients and retains more hematologic toxicity; on the other hand, WBRT often determines dramatic long-term neurocognitive impairment, so the optimal consolidative treatment should be accurately wedged for the individual patient.

With the availability of effective first-line treatments it became even more relevant the issue of salvage therapy for relapse/refractory patients: many treatments have been proposed, mostly in phase-II trials or small case reports, reflecting on the one hand the vivacity of researchers on this point, but on the other the lack of a shared vision on the best choice among standard monochemotherapy, polichemotherapy, innovative drugs, radiotherapy, and immunotherapy. As for front-line and consolidation treatment, large collaborative trials are warranted to obtain reliable and widely applicable results. Furthermore, with the increase of therapeutic option, there is a need for trustworthy prognostic factors in order to tailor specific treatment for individual patient.

The elderly population is recognized as a specific subtype of PCNSL, but a widely accepted standard front-line therapy is still lacking. Although HD-MTX retains its supremacy, there is no broad agreement for the combination drugs nor for the optimal consolidative treatment, inasmuch potentially active regimens like HDC/ASCT are precluded in this subgroup. Again, there is a need for the definition of specific regimens (in terms of drugs type and/or dosages) from large studies addressing this particular subgroup.

Finally, IOL and its relationship with cerebral disease should be better investigated. First, the complexity of diagnosis is still a problem, due to safely obtain a reliable sample, often requiring the more advanced pathologic diagnostic tools to characterize the scarce cells obtained. Second, although the likelihood for IOL to extend into cerebral tissue is well documented, there is no agreement on what strategy might be more advisable between local or systemic in case of isolated ocular involvement. As for the above-mentioned issues, it is advisable to favor joint-ventures between ophthalmologists and hemato-oncologists in order to design and conduct large studies aimed to define shared guidelines.

7. Five-year view

We foresee, in the next few years, significant advances in many key points. First of all, there is a need for better understanding the specificity of PCNSL with respect to others DLBCL, and particularly to unrevealing hypothetical specific mechanisms of intracerebral growth and microenvironment interaction. This in turn might lead to more prognostic and/
or therapeutic advances. We expect also advances in understanding intra-cellular signaling with the aim to introduce either in this disease drugs proven effective in other B-cell malignancies. Again, we expect that the front-line treatment schedule will be standardized and more widely adopted, with consequently benefit in cure rate, in routine practice. Moreover, the results of some large multicenter randomized trials addressing the best consolidation treatment will be available: we foresee to better define indications for the role of HDC/ASCT in this setting and consequently to state if WBRT role might be downsized and kept for special conditions. With regard to salvage treatments, we hope for a better comprehension of which strategies among the many ones proposed may be more advisable, either for general population or even for specific subgroups identified by reliable prognostic factors. The study of blood brain barrier would also deserve a specific attention: if one might selectively disrupt it so allowing penetration of drugs usually unable to pass into CNS, than drugs active in DLBCL but not in PCNSL might potentially been used in this setting with at least two advantages: the drug equipment for this disease might largely expand and one could potentially achieve the treatment as outpatient instead of inpatient basis, with consequently social and economic benefits. Finally, we foresee a better characterization of best treatment choice for elderly population and for disease limited to ocular structures (IOL).

Key issues

- PCNSL is a rare entity, with DLBCL histologic characteristics, aggressive, and rapidly lethal course in the absence of therapy. The more trusted potentially curative treatment includes an induction and consolidation phase
- Unlike other systemic DLBCLs, front-line therapy consists of HD-MTX-based polichemotherapy (e.g. R-MPV, MTR, or MTRIx regimen). For older patients, a combination of MTX, an alkylating agent (e.g. procarbazine, temozolomide), and rituximab is more tolerable. Comorbidity, PS and prognostic factors are important characteristics in order to tailor the treatment for the individual patient
- Only elderly patients in poor neurological conditions and very old (over 80 years) patients with contraindications to chemotherapy should be treated with primary radiotherapy alone.
- There is a need for consolidation therapy to avoid relapse that may occur even years after complete responses. WBRT and HDC/ASCT are effective consolidation options, but other options (e.g. conventional chemotherapy) may be equally considered: the choice should be based on age, comorbidity, and tolerability to induction chemotherapy
- Elderly patients are often unsuitable candidates for both WBRT and HDC/ASCT; maintenance with oral alkylating agents or immunomodulators deserves to be investigated.
- For refractory or relapsing patients, several salvage treatments may be proposed, but the prognosis remains poor
- IOL requires specific treatment, but the optimal schedule is still questioned among local treatment, radiotherapy, and polichemotherapy. Intravitreous chemotherapy should be considered for presenting or recurrent disease confined to the eyes in patients with contraindications to intravenous chemotherapy.
- Lenalidomide, ibrutinib, and nivolumab are promising experimental drugs that deserve further investigation
- It is recommended to refer patients to qualified centers and to enroll them in clinical trials in order to provide reliable evidence-based conclusions on each of the main questions still open.

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