Recent advances in the management of primary central nervous system lymphoma

Yoon Seok Choi

Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, Korea

Abstract

Primary central nervous system lymphoma (PCNSL) is a rare subtype of extranodal lymphoma primarily involving the brain, spinal cord, or leptomeninges. PCNSL is associated with a relatively poor prognosis compared to other extranodal diffuse large B-cell lymphomas. However, methotrexate-based induction chemotherapy followed by consolidative chemotherapy or high-dose therapy and autologous stem cell transplantation has improved the survival outcome, together with reduced neurotoxicity. Recent studies found that aberrant activation of the B-cell receptor-signaling pathway and activation of the NF-κB are frequent genetic alterations and could be good targets for the treatment of PCNSL. Herein, we have reviewed the current status and recent advances in the biology and management of PCNSL.

Key Words Primary central nervous system lymphoma, Chemotherapy, Rituximab, Autologous stem cell transplantation, Ibrutinib

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an extranodal non-Hodgkin lymphoma (NHL) that is confined to the brain, leptomeninges, eyes, or spinal cord. PCNSL accounts for approximately 2% of all primary central nervous system tumors with a median age of 65 years at diagnosis [1]. PCNSL shows a fair response to chemotherapy or radiation therapy, but the survival outcome is inferior compared to lymphomas located outside of the CNS. Although novel approaches have been incorporated into the management of PCNSL recently, the treatment of this entity remains a challenge in the field of hematology.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

PCNSL represents only 4% to 6% of all extranodal lymphomas [1]; approximately 1,500 new patients are diagnosed each year in the United States. In recent years, an increasing incidence of PCNSL has been recognized in patients older than 60 years, for whom the annual incidence rate is 0.5 per 100,000 [2]. The median age at diagnosis is 65 years [3].

Clinical presentations of PCNSL vary according to the involved components. Focal neurologic deficits, which result from the involvement of the parenchyma or leptomeninges, lead to prompt imaging but are only seen in 70% patients [4]. Up to 43% of individuals have behavioral or neuropsychiatric changes that are nonspecific, which can lead to a delay in medical evaluation. Signs of elevated intracranial pressure, such as headache, nausea, and vomiting, are also common (33%). Because the cortex is relatively spared with PCNSL, few patients (14%) present with seizures. Patients with ocular involvement may complain of blurred vision, decreased acuity, or floaters, but visual symptoms at the presentation of PCNSL are rare, (4%) despite the frequency of ocular involvement (20% to 25%) [5]. However, these symptoms are often subtle, and asymptomatic ocular involvement is common. Ocular lymphoma resembles uveitis and may be misdiagnosed if visual complaints are the only clinical manifestation. The classic B symptoms seen in patients with non-CNS lymphoma are uncommon in PCNSL.

DIAGNOSIS AND PROGNOSIS

Patients with symptoms analogous to PCNSL should undergo brain imaging. Contrast-enhanced MRI is the modality of choice. PCNSL can appear as a solitary lesion or as a multifocal disease. Lesions are often periventricular and involve the deep white matter, basal ganglia, or the corpus callosum. Classically, the lesions appear as isointense to hyperintense on the T2 MRI. Lesions are homogeneously enhanced with a mild amount of edema and are often associated with a diffusion-weighted imaging restriction [6]. To assess the extent of the disease, the International PCNSL Collaborative Group recommends baseline staging of the neuroaxis with a brain MRI, spine MRI (if spinal symptoms are present), and ophthalmologic and cerebrospinal fluid (CSF) evaluation [7]. Definitive diagnosis requires pathologic confirmation, which often necessitates a brain biopsy. The procedure of choice to establish a diagnosis of PCNSL is a stereotactic biopsy; if ocular or CSF involvement is evident, vitrectomy or CSF cytology may be diagnostic. Corticosteroids should always be deferred until tissue is obtained, except in cases of life-threatening mass effect and edema, as corticosteroids can obscure pathology results [8]. To detect the presence of a non-CNS disease, a body PET/CT scan and a bone marrow biopsy, could be performed.

Prognostic scoring systems have been developed specifically for PCNSL [9, 10]. In a retrospective review of 105 PCNSL patients, the International Extranodal Lymphoma Study Group (IELSG) identified an age greater than 60 years, an Eastern Cooperative Oncology Group (ECOG) performance status greater than 1, an elevated serum lactate dehydrogenase (LDH) level, an elevated CSF protein concentration, and an involvement of the deep regions of the brain as independent predictors of poor prognosis [9]. In patients with 0 and 1 factors, 2 and 3 factors, and 4 and 5 factors, the 2-year survival proportions were 80%, 48%, and 15%, respectively. In another prognostic model, PCNSL patients were divided into three groups based on age and performance status: 1) less than 50 years old; 2) greater than or equal to 50 years old with a Karnofsky Performance Score (KPS) ≥70; 3) greater than or equal to 50 years old with a KPS <70 [10]. Based on these three divisions, significant differences in overall and failure-free survival were observed.

The median OS of patients with PCNSL in the United States (according to the Surveillance, Epidemiology, and End Results database) doubled from 12.5 months in the 1970s to 26 months in the 2010s. Unfortunately, this survival time was limited to patients younger than 70 years of age. More importantly, the survival of the elderly population has not changed in 40 years and remains poor, at 6 months [3]. Disease recurrence is commonly observed in patients with PCNSL and rarely occurs outside the CNS. Despite advances in initial treatment, up to half of patients experience relapse, and 10% to 15% have primary refractory disease [11]. Patients with primary refractory or relapsed PCNSL have a poor prognosis and a median survival of 2 months, without additional treatment [12]. The median time to relapse is 10 to 18 months, and most relapses occur within the first 2 years of the initial diagnosis [11]. However, the relapsed disease has been observed more than 5 years after the initial diagnosis [13].

PATHOBIOLOGY

Approximately 90% of PCNSL cases are diffuse large B-cell lymphomas (DLBCL), with the remainder consisting of T-cell lymphomas, poorly characterized low-grade lymphomas, or Burkitt's lymphomas. Over 90% of primary CNS DLBCL cases consist of the activated B-cell-like (ABC) subtype. The B-cell receptor (BCR) signaling axis with its downstream target, NFκB, is affected by frequent recurrent mutations, mainly in *MYD88*, *CD79B*, and less frequently, in *CARD11*. In recent studies, it was found that PCNSL tumor cells harbor mutations in the BCR subunit, *CD79B*, and the Toll-like receptor adaptor molecule, *MYD88* [14, 15]. These mutations can potentiate chronic active BCR signaling and promote the survival of tumor cells [16], suggesting that PCNSL may be dependent on BCR signaling.

TREATMENT

Surgical resection is not part of the standard treatment approach for PCNSL, given the multifocal nature of this tumor, and the potential long-term morbidities [17]. The role of neurosurgery in PCNSL is to establish a diagnosis via stereotactic biopsy.

Standardized induction and consolidation treatment for PCNSL has yet to be defined. Historically, PCNSL was treated only with whole brain radiation (WBRT) at doses ranging from 36 to 45 Gy, which resulted in a high proportion of radiographic responses but an early relapse. In a multicenter phase 2 trial, 41 patients were treated with WBRT at doses of 40 Gy plus a 20-Gy tumor boost and achieved a median overall survival (OS) of only 12 months [18]. Given the lack of durable responses to radiation and the risk of neurotoxicity associated with this therapeutic modality, WBRT alone, is no longer a recommended initial treatment for patients with PCNSL.

An effective treatment for PCNSL is intravenous, high-dose methotrexate (HD-MTX) at variable doses ($1–8$ g/m^2), which is typically utilized in combination with other chemotherapeutic agents and/or WBRT. However, there is no consensus on the optimal dose of HD-MTX or on the role of radiation in combination with methotrexate in the management of PCNSL. Doses of methotrexate greater than or equal to 3 g/m^2, result in therapeutic concentrations in the brain parenchyma and CSF, and when combined with WBRT, lead to more durable treatment responses [19-21]. In a phase 2 trial, 79 PCNSL patients were randomized to receive either 1) HD-MTX (3.5 g/m^2, day 1) or 2) HD-MTX (3.5 g/m^2, day 1)+cytarabine (2 g/m^2 BID, days 2 and 3). Each chemo-

therapy cycle was 21 days, and all patients underwent a consolidative WBRT after induction chemotherapy. The HD-MTX+cytarabine arm had a higher proportion of complete radiographic responses and a superior 3-year OS [21]. A subsequent randomized trial was compared with three different arms of induction chemotherapy: HD-MTX+cytarabine versus HD-MTX+cytarabine and thiotepa versus HD-MTX+cytarabine, thiotepa, and rituximab, with all arms followed by consolidative therapy. The four-drug MATRix induction was associated with the best overall response rates [22]. However, it is now widely recognized that there is a high incidence of neurotoxicity associated with combined modality treatments, such as WBRT, especially in elderly patients. The latter observation prompted studies utilizing lower doses of WBRT. In a multicenter phase 2 study, no significant neurocognitive decline was observed after consolidative reduced-dose WBRT (23.4 Gy) and cytarabine administration in patients who had achieved a complete response to induction chemotherapy, including HD-MTX [23]. However, a longer neuropsychological follow-up of these patients is necessary to definitively assess the safety of this regimen, as numerous studies have demonstrated the delayed neurotoxic effects of WBRT in the PCNSL population and the reduced risk of neurotoxicity in regimens consisting of chemotherapy alone [24, 25]. Given the risk of clinical neurotoxicity, other studies have assessed whether WBRT can be eliminated from the initial management of PCNSL. In a multicenter phase 3 trial, patients were randomized to receive HD-MTX-based chemotherapy with or without WBRT [26]. Five hundred and fifty-one patients were enrolled, of whom 318 were treated per protocol. The Intent to treat analysis revealed that patients treated in the combined modality arm (chemotherapy+WBRT) achieved a prolonged Progression-free survival (PFS) but showed no improvement in OS, demonstrating that the elimination of WBRT from the treatment regimen did not compromise OS. This has led to the deferral of WBRT and chemotherapy-only approaches for newly diagnosed PCNSL patients. These approaches are based on a foundation of HD-MTX. variable doses; schedules of HD-MTX have been utilized, but in general, a dose of greater than or equal to 3 g/m^2, is delivered as an initial bolus followed by an infusion over 3 hours; however, administration every 10 to 21 days is recommended [27]. Multiple, phase 2 studies have reported on the safety, efficacy, and relatively-preserved cognition of HD-MTX-based chemotherapy regimens [28, 29]. Moreover, a longer duration of induction chemotherapy with HD-MTX (greater than six cycles) results in higher complete response proportions [23, 28]. A first-generation chemotherapy regimen for PCNSL includes intrathecal chemotherapy. However, in nonrandomized studies that utilized intrathecal chemotherapy, there was no improvement in outcomes over regimens that did not include intrathecal injections of chemotherapy [30, 31].

Rituximab is incorporated into combination regimens for PCNSL. When rituximab is administered intravenously at doses of 375 to 800 mg/m^2, CSF levels from 0.1% to 4.4% of serum levels, are achieved. Despite limited CSF penetration, radiographic responses have been observed in relapsed PCNSL patients treated with rituximab monotherapy [32]. The addition of rituximab to a methotrexate-based chemotherapy regimen (HD-MTX, carmustine, teniposide, prednisone) in a phase 3 HOVON 105/ALLG NHL 24 study, including 200 newly diagnosed PCNSLs, did not demonstrate significant response rates and survival outcomes [29]. The future role of rituximab, in newly diagnosed PCNSL, is uncertain and should be validated in future trials.

Given the limited durability of the responses observed in many studies of PCNSL, there is an increasing interest in high-dose chemotherapy (HDT), followed by autologous stem cell transplantation (ASCT), as the first-line, consolidative therapy for PCNSL. Conditioning regimens, including thiotepa, have demonstrated encouraging results. Several randomized trials were developed to address the feasibility, safety, and efficacy of this approach versus consolidative WBRT or nonmyeloablative chemotherapy. The IELSG32 trial demonstrated that both WBRT 36 Gy and HDT/ASCT are safe and effective as a consolidation treatment after four courses of MATRix, or other regimens, whereas WBRT was associated with a significant decline of several cognitive functions [33].

RECENT ADVANCES IN TARGETED THERAPY

Insights into the pathophysiology of PCNSL have identified the BCR pathway as a key mechanism in the pathogenesis of PCNSL. The use of novel agents targeting components of the BCR pathway, namely, the Bruton Tyrosine Kinase (BTK) inhibitor, ibrutinib, and immunomodulatory drugs (IMiDs) such as lenalidomide and pomalidomide, has so far been limited to patients with recurrent and refractory PCNSL, showing promising response rates. There has been an increase in the clinical trials investigating small molecules and novel agents in the recurrent/refractory PCNSL setting, including immune checkpoint inhibitors, IMiDs, BTK, and PI3K/AKT/mTOR inhibitors.

The BTK inhibitor targets the BCR pathway at the central signaling nodule, and has produced promising results. Two distinctive studies utilized the BTK inhibitor, ibrutinib, at 560 and 840 mg, daily. In the 560 mg trial (NCT02542514), 52 patients with recurrent PCNSL or ocular lymphoma were enrolled in a French study, and the ORR was 50% after the first two cycles of ibrutinib [34]. In the 840 mg trial (NCT02315326), 20 patients with recurrent PCNSL and secondary CNS lymphoma, achieved an ORR of 75% (77% in PCNSL; 13 patients and 71% in secondary CNS lymphoma; 7 patients); additionally, the PCNSL group had a median PFS of 4.6 months [35]. Lastly, a study conducted at the National Institutes of Health showed that 15 out of 18 patients (83%) with PCNSL experienced a radiographic response after 2 weeks of ibrutinib treatment [36]. The results of this study are difficult to interpret because newly diagnosed patients with PCNSL (5 of 18) were included, multiple other drugs

were added after the initial 2-week ibrutinib monotherapy window, and a much higher frequency of infectious complications occurred, as compared with studies that used a single-agent ibrutinib. The clinical efficacy of a single-agent ibrutinib is remarkable, as the response rates are high, and the PFS is longer than that observed with conventional chemotherapy. Even patients without genomic alteration in the BCR pathway experienced a response to ibrutinib [35]. The mechanisms underlying ibrutinib resistance, that limit the duration of response, must be investigated further.

IMIDs (lenalidomide and pomalidomide) have been used in PCNSL, alone, or in combination with rituximab. IMIDs not only inhibit NF-κB activity, but also inhibit the PI3K/AKT [37] pathway; therefore, they remain promising agents. Indeed, a phase I/II trial of single agent pomalidomide in recurrent/refractory PCNSL, demonstrated an ORR of 50% at the maximally tolerated dose [38]. Recently, lenalidomide, in combination with rituximab (R^2), showed significant activity in relapsed/refractory PCNSL patients [39].

Another promising approach might be the use of immune checkpoint inhibitors. In a small retrospective study of five patients with relapsed/refractory PCNSL, a 100% response rate, with durable responses, was reported [40]. Based on this observation, a multicenter trial to investigate single agent nivolumab in PCNSL and testicular lymphoma (NCT02857426), was initiated. The susceptibility of the PCNSL tumor cells to monoclonal antibodies that program death-1 (PD-1), is attributed to the alteration in the programmed death ligand-1 (*PD-L1*) gene, resulting from the translocation or copy number gain of the 9p24.1 locus [41].

In addition, trials combining targeted inhibitors with conventional and active agents in the salvage or front-line setting, are ongoing. The TEDDi-R regimen was the first approach to combine a novel agent with chemotherapy in PCNSL [36]; it provided an impressive clinical response but also a high frequency of treatment-related adverse events. The combination of ibrutinib with HD-MTX, as well as ibrutinib with HD-MTX and rituximab, has been tested and found to be safe [42]. Furthermore, in Korea, a phase II study of ibrutinib in combination with rituximab, ifosfamide, and etoposide, is ongoing in patients with relapsed/refractory PCNSL (NCT04066920).

CONCLUSION

Recent progress in understanding the biology of PCNSL has led to various clinical trials using novel anti-lymphoma agents, during the past decade. Even with a promising clinical response, failure to obtain a durable response leading to a prolonged survival should be overcome in future clinical trials. The incorporation of novel agents into the classical chemotherapy regimen and/or maintenance therapy, especially in the earlier line, is a promising strategy, as evidenced by the NCI trials [36].

With the recent advances in the field of immunotherapy for the treatment of lymphoid malignancies, it will be of interest as to whether chimeric antigen receptor T cells will be another active option for the treatment of PCNSL.

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