Advances in the treatment of newly diagnosed primary central nervous system lymphomas

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Abstract
Primary central nervous system lymphoma (PCNSL) is a type of highly invasive non-Hodgkin lymphoma. With a growing number of organ transplantation and immunosuppressant therapy, the incidence of PCNSL has been growing rapidly in recent years, which is attributed to the increased incidence of HIV/AIDS, a prominent risk factor for developing PCNSL. The rising rate of PCNSL incidence is the highest among the intracranial tumors. In the past 20 years, dozens of clinical trials related to PCNSL have been registered, but adequate therapeutics are still challenging. Currently, the chemotherapy regimens based on high-dose methotrexate and whole-brain radiotherapy are the two main therapeutic options; however, the toxicity associated with those is the main problem that challenges medical researchers. Novel agents and therapeutic strategies have been developed in recent years. In the current review, we describe advances in the treatment of PCNSL and discuss novel therapeutic approaches currently in development, such as the use of rituximab, disruption of the blood-brain barrier, and state-of-the-art radiotherapy.

Key Words
Primary central nervous system lymphoma, Methotrexate, Whole-brain radiotherapy, Rituximab

INTRODUCTION
Primary central nervous system (CNS) lymphoma (PCNSL), accounting for 3.3% of intracranial tumors, is a highly aggressive non-Hodgkin’s lymphoma arising in the CNS, often widely involving the brain parenchyma, spinal cord, eyes, cranial nerves, and/or meninges [1]. Diffuse large B-cell lymphoma (DLBCL) accounts for about 90% of PCNSL. Other types include Burkitt’s lymphoma, T-cell lymphoma, and low-grade malignant B-cell lymphoma [2]. Although the incidence of PCNSL is low, the rising rate of its incidence is the highest among intracranial tumors [3]. Because of its rarity and the reduced capacity of drugs to cross the blood-brain barrier (BBB), optimal treatment is limited. The overall survival (OS) rate in patients with PCNSL and long-term survival is much lower than the same histological type of lymphoma involving peripheral lymphoid organs.

A growing number of clinical trials have shown the efficacy of several treatment strategies, but high-dose methotrexate (MTX) still plays a crucial role in the chemotherapy on PCNSL, because it crosses the BBB. The key role of MTX...
is demonstrated by the fact that those patients who cannot tolerate high-dose MTX (HD-MTX) have a poor prognosis.

Radiation therapy has also been used for decades as a treatment of PCNSL, but its role has been diminishing in recent years. Standard doses of radiation can lead to serious age-related neurotoxicities, such as functional impairments including cognition and memory, brain atrophy, leukoencephalopathy, endocrine disorders, and even dementia [4, 5]. Optimal treatment approaches for patients with PCNSL remain challenging, and at present, there is no standard therapeutic approach for patients with newly diagnosed PCNSL. In this review, we will thus focus on recent progress in the management of newly diagnosed PCNSL and identify specific challenges for the future.

CHEMOTHERAPY

HD-MTX alone

Chemotherapy plays a major role in the treatment of PCNSL. MTX, the most widely used drug for PCNSL, is a folate antagonist that interrupts DNA synthesis. To achieve therapeutic concentrations of MTX in the CNS, more than 1.5 g/m² of MTX are required. Because the blood to cerebrospinal fluid (CSF) ratio is usually about 30:1 in the steady-state, doses less than 3 g/m² are too low to achieve anti-cancer effects in the CSF (1 μmol/L) [6-8]. A 3-hour infusion of 3 g/m² of MTX achieves higher CSF levels than slower infusions at higher concentration of MTX [9, 10]. However, no clinical trials clearly demonstrated advantage in the use of MTX doses of greater than 3 g/m². A phase II trial resulted in a 64% response rate before whole-brain radiotherapy by using 1 g/m² of MTX monotherapy plus six doses of intrathecal MTX (12 mg per dose) [11]. Another phase II trial resulted in a 74% response rate by using 8 g/m² of MTX monotherapy [12]. The results of the two clinical trials are comparable. Still, the clinical application of 8 g/m² MTX frequently encountered side effects such as renal impairment, bone marrow toxicity, and mucositis, requiring a dose reduction during the course of the treatment.

Although HD-MTX as a single agent is effective in induction therapy, clinical studies have shown a high rate of early relapse with median times of 12.8 months and 13.7 months [12, 13]. HD-MTX treatment is usually administered with reduced folic acid to decrease the side effects including hepatotoxicity, nephrotoxicity, myelotoxicity, and mucositis as well as various neurological symptoms. Although the purpose of HD-MTX therapy is to maintain serum MTX at high levels (10–100 μmol/L) for prolonged periods, the serum concentrations of MTX are monitored routinely to control the drug level in the patients with a high risk of toxicity. An association was found between a younger age and faster progression to the drug level in the patients with a high risk of toxicity. An association was found between a younger age and faster progression. However, the CSF level and effective cytotoxic CSF level is important.

MTX-based chemotherapy

The efficacy of HD-MTX seems to be slightly improved by using MTX-based chemotherapy regimens, which can also penetrate the BBB. Therefore, MTX-based polychemotherapy regimens are often preferred over MTX monotherapy. In the report of Sandor et al. [14], evaluating the efficacy of MTX, thiopeta, vincristine, dexamethasone, and intrathecal Ara-C and MTX in 14 PCNSL patients, the cumulative survival and progression-free survival (PFS) rates at more than 4.5 years were 68.8% and 34.3%, respectively. The median survival was not reached and the median PFS was 16.5 months. Later, Hoang-Xuan et al. [15] assessed the efficacy of chemotherapy consisted of high-dose MTX, lomustine, procarbazine, methylprednisolone, and intrathecal chemotherapy with MTX and cytarabine in patients older than 60 years with PCNSL. Twenty-four patients (48%) achieved a disease response, with a median duration of complete remission (CR) of 27 months. The overall median survival time was 14.3 months, and 1-year PFS was 40%. Pels et al. [16] reported a phase II study of systemic and intraventricular chemotherapy without radiotherapy. An HD-MTX (cycles 1, 2, 4, and 5) and cytarabine (ARA-C; cycles 3 and 6)-based systemic therapy (including dexamethasone, vinca-alkaloids, ifosfamide, and cyclophosphamide) was combined with intraventricular MTX, prednisolone, and ARA-C. Of 61 patients, 37 patients (61%) achieved complete response and six (10%) achieved partial response. Median time-to-treatment failure and median OS were 21 months and 50 months, respectively. Omuoro et al. [17] evaluated the efficacy of temozolomide and MTX in newly diagnosed PCNSL patients older than 60 years. A complete response was observed in 55% patients and the median OS and PFS were 35 months and 8 months, respectively. Gavrilovic et al. [18] evaluated the efficacy of chemotherapy consisting of HD-MTX, vincristine, and procarbazine in 26 PCNSL patients. The median OS and PFS were 26 months and 7 months, respectively. Chamberlain and Johnston [19] conducted a prospective phase II study of HD-MTX and rituximab in patients with 40 newly diagnosed PCNSL patients. A total of 28 patients (70%) had shown a radiographic response. Survival of these 28 patients ranged from 11 to 80 months, with a median of 33.5 months. Thiel et al. [20] evaluated the efficacy of HD-MTX, ifosfamide, and cytarabine in 164 newly diagnosed PCNSL patients. The OS rate was 37.1 months, which was similar to that of 32.4 months in those patients combined with whole brain radiotherapy (WBRT). However, the PFS was 11.9 months, which can be prolonged to 18.3 months by WBRT. But the increased risk of neurotoxicity in long-term survivors was not evaluated. Wieduwilt et al. [21] reported the evaluation of a combined chemotherapy regimen for 31 PCNSL patients using induction immunochemotherapy with HD-MTX, te-
mozolomide, and rituximab (MT-R) followed by intensive consolidation with infusion etoposide and high-dose cytarabine (EA). The complete response rate for MT-R induction was 52%. At a median follow-up of 79 months, the 2-year PFS and OS were 45% and 58%, respectively. For patients receiving EA consolidation, the 2-year PFS and OS were 78% and 93%, respectively. The regimen of idarubicin, dex-amethasone, cytarabine, and MTX (2 g/m²) (IDARAM) was found to be effective in 7 patients with PCNSL by Moreton et al. [22], and later, it was improved by Yilmaz et al. [23] to R-IDARAM in three patients with PCNSL, which was further improved by our team [24]. In a phase II clinical trial reported by our team [25], systemic R-IDARAM chemotherapy combined with intrathecal immunochemotherapy showed good efficacy and tolerance. The 3-year OS and PFS rates were 84.2% and 63.2%, respectively. In a phase II study reported by Omuro et al. [26], newly diagnosed 32 PCNSL patients received 5 to 7 cycles of chemotherapy with rituximab, MTX (3.5 g/m²), procarbazine, and vincristine (R-MPV). The patients with a CR or partial response proceeded with consolidation high-dose chemotherapy (HDC) (thiotepa, cyclophosphamide, and busulfan), followed by autologous stem-cell transplant (ASCT) and no radiotherapy. Following R-MPV, the objective response rate was 97%, and 81% of the patients proceeded with HDC followed by ASCT. Among all patients, the median PFS and OS were not reached (median follow-up of 45 mo) at the time of the study’s publication. Two-year PFS was 79%, with no events observed beyond 2 years. Two-year OS was 81%. In transplanted patients, 2-year PFS and OS were 81%. There were three treatment-related deaths. Prospective neuropsychological evaluations suggested a relatively stable cognitive functions post-transplant.

Weller reported the use of steroids alone producing long-term disease control [27], but response was usually short-lived, and relapse was probably inevitable during long-term period. Furthermore, given the prominent side effects of long-term glucocorticoid treatment, steroid therapy alone for PCNSL is not recommended.

**NOVEL AGENTS AND THERAPEUTIC STRATEGIES**

**Rituximab**

The addition of rituximab, an anti-CD20 monoclonal antibody, to the CHOP chemotherapy regimen prolonged OS of elderly patients with DLBCL [28]. However, rituximab has poor penetration into the CNS due to its large molecular weight. The CSF levels of rituximab are approximately 0.1% of serum levels associated with therapeutic activity in patients with CNS lymphoma [29]. Furthermore, rituximab when combined with other regimen including MTX, procarbazine, and vincristine could improve OS in PCNSL patients [30]. But the precise role of rituximab in PCNSL remains controversial and unclear [31].

**Whole brain radiotherapy**

Because PCNSL is almost always multifocal, radiotherapy is usually given to the entire brain. Until 1992, WBRT alone was considered standard primary treatment for PCNSL. Nelson et al. [32] have reported 41 patients with PCNSL treated with WBRT (36-40 Gy) as primary therapy. An overall response rate was near 90%, with nearly 50% of patients achieving CR or near CR. However, 61% of patients relapsed within the radiation field, and the median survival was only 11.6 months, with 48% surviving 1 year, and 28% surviving 2 years. Shibamoto et al. [33] have reported the effects of WBRT alone on 132 patients with histological-proven PCNSL. The median survival time was 18 months, and the 5-year survival rate was 18.0%. However, the study had some limitations such as retrospective analysis and non-standardized radiotherapy.

The main disadvantage of WBRT is its neurotoxicity. This neurotoxicity presents as dementia, ataxia, and urinary incontinence, being associated with magnetic resonance imaging (MRI) evidence of leukoencephalopathy, which tends to develop after a delay of several years. Blay et al. [34] reported that delayed neurotoxicity incidence rate was 100% in patients older than 60 years who were treated with standard dose radiotherapy, compared to 63% in those younger than 60 years [35]. WBRT alone is seldom recommended as first-line treatment of PCNSL, except as palliative therapy. Although many clinicians usually defer WBRT in patients older than 60 years, it is too simplistic to apply same age limit for all individuals.

**Chemoradiotherapy**

Because PCNSL is sensitive to both chemotherapy and radiotherapy, many of the therapeutic regimens described above involve MTX-based chemotherapy followed by WBRT. Combined modality therapy can be more effective but is also associated with more serious therapy-related toxicity.

**HD-MTX plus RT:** Glass et al. [36] have reported a study treating PCNSL with chemotherapy prior to WBRT. A total of 25 patients were treated with one to six cycles of MTX (3.5 g/m²) every 10 to 21 days prior to WBRT. Twenty-two had partial or complete responses, with a median duration of the response of 32 months. Median survival time was 33 months. O’Brien et al. [37] have reported a phase II study that assessed the long-term outcomes of a brief course of HD-MTX followed by radiotherapy for patients with PCNSL. Forty-six patients with PCNSL were treated with MTX (1 g/m² on days 1 and 8) and whole-brain irradiation (45-50.4 Gy). The 5-year survival estimate was 37%, with PFS being 36% and median survival 36 months.

**HD-MTX-based chemotherapy plus RT:** In a study reported by DeAngelis et al. [38], 98 newly diagnosed patients with PCNSL were assessed. Patients first received five cycles of MTX 2.5 g/m², vincristine, procarbazine and intraventricular MTX (12 mg). WBRT was administered to a total dose of
45 Gy, and all patients received high-dose cytarabine after RT. Among the patients with measurable disease, 58% had a complete response to pre-irradiation chemotherapy, and 36% had a partial response. Median PFS was 24.0 months, and OS was 36.9 months. The median survival was 50.4 months in patients younger than 60 years and only 21.8 months in those aged 60 years or older (P < 0.001). Grade 3 or 4 toxicity during induction chemotherapy occurred in 53% of patients, and half of these events were hematologic. However, 12 patients (15%) experienced severe delayed neurologic toxicity, eight of whom died.

In a study reported by Shah et al. [30], 30 patients were treated with five to seven cycles of 3.5 g/m² of MTX-based induction chemotherapy (R-MPV). Patients achieved CR received dose-reduced WBRT (23.4 Gy), whereas all the others received standard WBRT (45 Gy). Two cycles of high-dose cytarabine were administered after WBRT. With a median follow-up of 37 months, the 2-year overall and PFS was 67% and 57%, respectively. The overall response rate was 93%; 44% of patients achieved a CR after five or fewer cycles, and 78% after seven cycles. Of 21 CR patients, 19 received the planned 23.4 Gy WBRT. The most commonly observed grade 3 to 4 toxicities included neutropenia (43%), thrombocytopenia (36%), and leukopenia (23%). No treatment-related neurotoxicity has been observed.

In a study reported by Ferreri et al. [39], 79 patients with PCNSL were centrally randomly assigned by a computer to receive four courses of either MTX 3.5 g/m² on day 1 (N=40) or MTX 3.5 g/m² on day 1 plus cytarabine 2 g/m² twice a day on days 2–4 (N=39). Both regimens were administered every 3 weeks and were followed by WBRT. After chemotherapy, 7 patients given MTX and 18 patients given MTX plus cytarabine achieved a CR, with a CR rate of 18% and 46%, respectively. Nine patients receiving MTX plus cytarabine achieved a CR, with a CR rate of 36%, 46%, and 78% after seven cycles. Of 21 CR patients, 19 received the planned 23.4 Gy WBRT. The most commonly observed grade 3 to 4 toxicities included neutropenia (43%), thrombocytopenia (36%), and leukopenia (23%). No treatment-related neurotoxicity has been observed.

In a study reported by Ferreri et al. [40], 33 patients with PCNSL who achieved CR after MTX-containing chemotherapy were referred to consolidation WBRT. At a median follow-up of 50 months, 21 patients are relapse-free with 51% of 5-year failure-free survival (FFS). WBRT doses higher than 40 Gy were not associated with improved disease control in comparison with a WBRT dose of 30 to 36 Gy (relapse rate, 46% vs. 30%; 5-year FFS, 51% vs. 50%; P=0.26). In a multicenter phase II study reported by Morris et al. [41], among the enrolled 52 patients, Thirty-one patients (60%) achieved a CR after R-MPV and received reduced dose WBRT. The 2-year PFS for this group was 77%, median PFS was 7.7 years, and 3-year OS was 87%. The overall (N=52) median PFS was 3.3 years, and median OS was 6.6 years.

**Blood-brain barrier disruption**

Even if recent advances of basic science in understanding mechanisms of the BBB have been significant, many clinical trials are needed for bench-to-bedside transition, leading to improve the treatment of brain malignancies, including primary CNS lymphomas. The mechanisms of BBB breakdown, equivalent to the tight junction protein rearrangement, seem to involve both direct and indirect effect of stress responses and inflammatory mediators. Marchi et al. [42] have shown that S100-beta protein linked to the extent and temporal sequence of hyperosmotic BBB disruption. Thus, S100-beta can be used as a marker of BBB function, and elevated levels of this protein may indicate the presence of radiological detectable BBB leakage. It has also been described that traumatic brain injury leads to an up-regulation of the cell vascular endothelial growth factor (VEGF), VEGF receptor 1 (VEGFR1), VEGFR2 messenger RNA, and proteins in and around the lesion. The structural changes on the endothelium of primary CNS lymphomas could explain the increased permeability so frequently seen in these tumors. Endothelial cells are frequently thinned, contain fenestrations and often have no endothelial cell between the capillary lumen and the underlying basement membrane, causing frank endothelial discontinuities. These ultrastructural changes explain the dense contrast enhancement seen in many PCNSL.

Lymphoma cells are often close to the BBB, the interface between the general circulation and the CNS. The BBB, isolating the parenchyma of the brain from the general circulation and tightly regulating the movement of material into and out of the CNS, has classically been regarded as the most logical site for the immune cells to enter the CNS. The BBB is composed of microvascular endothelial cells joined together by relatively impermeable and highly developed tight and adherens junctions. Tight junctions are composed of transmembrane proteins, including occludins and claudin-5, which interact homotypically with adjacent endothelial cells and are linked to the cytoskeleton through the zonula occludens family of proteins. The transmembrane proteins of adherens junctions, VE-cadherin, and PECAM-1, also bind homotypically to adjacent endothelial cells and are linked to the cytoskeleton through beta-catenin. Together these structures form the anatomical basis of the BBB, which restrict the migratory cell pathway for circulating cells through the CNS. Tumor cells do not usually induce the inflammatory phenotype of brain microvascular endothelial cells associated with classical extravasation.

Currently, systemic DLBCL is treated with chemotherapy in conjunction with rituximab. However, this monoclonal antibody does not routinely cross the BBB and reach the malignant lymphoma cells in the CNS [29, 43, 44]. Various studies suggest that HD-MTX in a dose of at least 1 g/m², despite its modest BBB permeability of approximately 5% of plasma levels [45], combined with brain irradiation results in improved patient response and prolonged PFS and OS. Following therapy, cognitive improvement or preservation in the majority of the patients relative to pretreatment status...
at follow-up was reported between 1 to 7 years after achieving CR. Toxicity in the treated patients is generally manageable. The treatment delivery regimen is complex and should be undertaken only by trained teams at centers where neuro-oncology are available. This approach is associated with a durable tumor control, manageable toxicity, as well as a potential for deferral of radiation, despite being associated with cognitive compromise [46]. This protocol allows the enhanced delivery not only simply to areas with overly leaky BBB associated with enhancing tumor but also to the brain and corticospinal fluid globally by as much as 50- to 100-fold [47]. The long patient follow-up time suggests this is an effective first-line treatment option with a meaningful impact on OS and PFS, as well as neurocognitive status.

Evaluating the effects on the brain of different kinds of antitumor treatments is crucial. If a treatment is effective in killing tumor cells but damages normal anatomy as assessed by imaging studies or results in severe cognitive decline, the treatment has a questionable benefit as a therapeutic technique. Neurotoxicity, as determined by imaging and various cognitive changes, is associated with chemotherapy, radiation therapy, and the combination thereof for treatment of brain tumors. Even if it is difficult to make direct comparisons between different treatments applied to different tumors, many findings support previous results, which indicate chemotherapy for brain tumors does not result in a consistent pattern of cognitive decline [48]. Cognitive testing is recommended as part of standard protocols, and it has been suggested that cognitive function is a relatively sensitive measure of brain function and can sometimes predict the recurrence of the disease even before anatomic changes are evident in images [49].

Surgery
Despite scarce data on surgical treatment of PCNSL, the efforts at resection are generally discouraged. This viewpoint is based on small-scale retrospective studies, which attest that surgical resection per se holds no clear advantages over supportive care. There are a few explanations as to what shaped this outlook. First, PCNSL is an infiltrative tumor with a multifocal nature, which can expand beyond the visible margin of the macroscopic lesion and has a predilection for early wide dissemination [50]. Second, the striking responsiveness to chemotherapy and radiotherapy might have alleviated the desire of invasive procedures against this type of tumor. Another reason could be the improvement of imaging studies, making surgical resection for histologic confirmation unnecessary. Finally, the postoperative morbidity in this patient population could have played a key role in discouraging surgical resection [51].

However, this mindset is not grounded on either randomized data or contemporary reports found on modern neurosurgical techniques [52]. Henry et al. [53] described a mean survival of 3.3 months in 15 cases managed solely with supportive care, 4.6 months in 28 cases after surgery alone, and 15.2 months in 21 radiotherapy-treated cases with or without surgery. In a retrospective analysis, Bataille et al. [54] have shown that 111 patients of the total 248 patients underwent surgical resection. Of these patients, 66 had a complete surgical resection and consequently a 1-year survival rate of 56.6%, while 45 patients had a subtotal removal of the tumor, with a 1-year survival rate of 31.8%. Of the remaining 137 patients, 132 had undergone stereotactic biopsy and after treatment had a 1-year survival of 48.6%. Nevertheless, they concluded that surgery did not contribute to survival and that partial resection actually represented an unfavorable prognostic factor.

The German PCNSL Study Group I trial, which examined the role of WBRT in the treatment of newly diagnosed PCNSL patients suitable for HD-MTX chemotherapy, offered an expansive database to corroborate or contest this hypothesis on the lack of impact of surgery in PCNSL. Weller et al. [52] analyzed this database, and found that gross totally or sub-totally resected patients had some benefits of PFS and OS, compared to biopsied patients.

In contrast, Kellogg et al. [55] reported a retrospective analysis of 45 patients who underwent surgical diagnosis prior to treatment for both primary and secondary CNS lymphoma at a single institution between 2005 and 2012. Of the 45 patients, high percentage of those (17.8%, 8/45) experienced surgical complications due to diagnostic, therapeutic, or technical reasons, suggesting that there are no low risk surgical procedures for patients with CNS lymphoma.

The question remains whether surgical resection of PCNSL is safe. Shankar and Barker [50] argue that surgeons tend to resect lesions that are solitary, superficial, and have an emplacement on an eloquent area of the cortex, while patients with noticeable ocular or leptomeningeal lymphomatous involvement are generally poor candidates for surgical management. There are, however, supplementary clinical factors that may influence a neurosurgeon’s decision, such as the age, frailty, comorbidity, and performance status of the patient. None of these factors are accurate indicators of resectability. Deep-seated PCNSL tumors, which are usually unresectable, are much less likely to be MTX-responsive, having only half of the responsiveness of the superficial lesions. There have been reported differences in gene expression profiles between the deep and superficial PCNSLs [56]. Numerous molecular prognostic factors, such as the expression of BCL6, have been known to affect survival in these tumors. However, their association with resectability is uncertain. Surgery can also influence the possibility of patients that underwent resection to undergo subsequent aggressive therapy, or their chances to meet minimal performance status to enter a clinical trial enrollment. The authors also underline that the majority of the surgeons do advise a period of wound healing after craniotomy before starting chemotherapy, something that would otherwise be unnecessary after a needle biopsy. However, Rubenstein et al., in a recent multicenter phase II chemotherapy study, concluded that treatment delay was the most substantial adverse prognostic factor [57, 58]. Only the patients with...
potentially resectable tumors would be randomized to either resection or biopsy, though the diagnosis is typically undefined before the final pathology is available. This entails a repeat resection after the initial biopsy that would ultimately delay systemic therapy. Even so, the incidence of PCNSLs is relatively low, further dampening the possibility of conducting a randomized trial. The reappraisal of whether surgical resection would theoretically improve outcome in select patients should still be considered, as one of the basic principles of chemotherapy states that the fewer tumor cells are present at the time chemotherapy starts, the fewer cycles are needed to induce CR.

In a recent case report by Hsu et al. [59], a 61-year-old male patient presented with an isolated PCNSL that occupied the fourth ventricle almost entirely. The lymphoma was subtotally removed through a suboccipital craniotomy. The authors claim that its unusual location and surgical accessibility may prove a compelling indication for surgical resection. Therefore, in their opinion, the aggressive surgical cytoreduction in cases such as this is justified. In our experience, the patients with PCNSLs are recommended surgical cytoreduction before initiating chemotherapy, regardless of the tumor size and location. Because the complications such as hydrocephalus and mass effect can be prevented, the histological diagnosis is possible, and subsequent chemotherapy shows more promising results in our unpublished data.

In essence, the challenging paradigms and written-in-stone traditions are fundamental methods of progression. By questioning these surgical parameters, it is possible that these patients would not only have improved survival but also have more chance to reach CR. Nonetheless, without an adequate prospective analysis on this subject, the future of resection and its role in PCNSL remain shrouded in uncertainty.

Future directions

Since PCNSLs have low incidence and poor outcome, therapeutic approaches for PCNSL are different throughout the world. More clinical trials are still needed to develop new therapeutic methods for PCNSLs. Some studies evaluating the safety and efficacy of intraventricular rituximab for overcoming the problem of the BBB showed promises. Maybe intraventricular rituximab combined with systemic reduced-dose chemotherapy will reduce the toxicity of systemic chemotherapy but increase the efficacy [60, 61]. New pharmacologic agents are also evaluated in PCNSL, including lenalidomide, pomalidomide, agents disrupting toll-like receptor, B-cell receptor, JAK-STAT, or PIM kinases [62]. Recently, chimeric antigen receptor-modified T (CART) cells with specificity for CD19 have been used in B-cell malignant diseases [63]. In this study, CART cells were observed in the CSF, suggesting their possibility in treatment of PCNSL. But no study using CART cells for the treatment of PCNSL has been reported. Although these new methods have been developed rapidly, it is likely that the next 5 years of clinical trials will focus on optimization of interventions based on high-dose chemotherapy.

PCNSL is a rare subtype of extranodal non-Hodgkin’s lymphoma. Great progress has been made in the treatment of PCNSL in the past half century. About 40–50% of PCNSL patients may acquire long-term survival, and a significant proportion of them may be cured. Chemotherapy, radiotherapy, chemoradiotherapy, BBB disruption, and surgery are the main approaches for the treatment of PCNSL, which have been reviewed in this paper. Some new therapeutic methods have also been developed recently, but additional clinical trials are needed to evaluate their efficacy. With the development of these new therapeutic methods, we believe that PCNSL patients will acquire a better prognosis.

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REFERENCES

1. Saini M, Bellinzona M, Weichhold W, Samii M. A new xenograft model of primary central nervous system lymphoma. J Neurooncol 1999;43:153-60.
2. Miller DC, Hochberg FH, Harris NL, Gruber ML, Louis DN, Cohen H. Pathology with clinical correlations of primary central nervous system non-Hodgkin’s lymphoma. The Massachusetts General Hospital experience 1958-1989. Cancer 1994;74:1383-97.
3. Olson JE, Janney CA, Rao RD, et al. The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. Cancer 2002;95:1504-10.
4. Benković V, Knezević AH, Dikić D, et al. Radioprotective effects of quercetin and ethanolic extract of propolis in gamma-irradiated mice. Arch Hig Rada Toksikol 2009;60:129-38.
5. Valls-Belles V, Torres Mdel C, Boix L, Muñiz P, Gonzalez-Sanjose ML, Codoñer-Franch P, alpha-Tocopherol, MDA-HNE and 8-OHdG levels in liver and heart mitochondria of adriamycin-treated rats fed with alcohol-free beer. Toxicology 2008;249:97-101.
6. Lippens RJ, Winograd B. Methotrexate concentration levels in the cerebrospinal fluid during high-dose methotrexate infusions: an unreliable prediction. Pediatr Hematol Oncol 1988;5:115-24.
7. Shapiro WR, Young DF, Mehta BM. Methotrexate: distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. New Engl J Med 1975;293:161-6.
8. Ferreri AJ, Guerra E, Regazzi M, et al. Area under the curve of methotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas. Br J Cancer 2004;90:353-8.
9. Tefet ML, Margolin KA, Doroshow JH, et al. Pharmacokinetics and toxicity of high-dose intravenous methotrexate in the treatment of leptomeningeal carcinomatosis. Cancer Chemother Pharmacol 2000;46:19-26.
10. Vassal G, Valteau D, Bonnay M, Patte C, Aubier F, Lemerle J. Cerebrospinal fluid and plasma methotrexate levels following high-dose regimen given as a 3-hour intravenous infusion in children with non-Hodgkin’s lymphoma. Pediatr Hematol Oncol 1990;7:71-7.

11. DeAngelis LM, Yahalom J, Thaler HT, Kher U. Combined modality therapy for primary CNS lymphoma. J Clin Oncol 1992;10:635-43.

12. Batchelor T, Carson K, O’Neill A, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. J Clin Oncol 2003;21:1044-9.

13. Herrlinger U, Schabet M, Brugger W, et al. German Cancer Society Brain Tumor Group. J Clin Oncol 2003;21:2726-31.

14. Sandor V, Stark-Vancs V, Pearson D, et al. Phase II trial of chemotherapy alone for primary CNS and intracranial lymphoma. J Clin Oncol 1998;16:3000-6.

15. Hoang-Xuan K. Temozolomide and methotrexate for primary central nervous system lymphoma in the elderly. J Neurooncol 2007;85:207-11.

16. Pels H, Schmidt-Wolf IG, Glasmacher A, et al. Primary central nervous system lymphoma: results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. J Clin Oncol 2003;21:4489-95.

17. Omuro AM, Taillandier L, Chinot O, et al. Chemotherapy alone as initial treatment for primary CNS lymphoma in patients older than 60 years: a multicenter phase II study (26952) of the European Organization for Research and Treatment of Cancer Brain Tumor Group. J Clin Oncol 2003;21:2726-31.

18. Pels H, Schmidt-Wolf IG, Glasmaecher A, et al. Primary central nervous system lymphoma: results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. J Clin Oncol 2003;21:4489-95.

19. Chamberlain MC, Johnston SK. High-dose methotrexate and rituximab with deferred radiotherapy for newly diagnosed primary B-cell CNS lymphoma. Neuro Oncol 2010;12:736-44.

20. Thiel E, Korfel A, Marts P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncol 2010;11:1036-47.

21. Wieduwilt MJ, Valles F, Issa S, et al. Immunochemotherapy with intensive consolidation for primary CNS lymphoma: a pilot study and prognostic assessment by diffusion-weighted MRI. Clin Cancer Res 2012;18:1146-55.

22. Moreton P, Morgan GJ, Gilson D, et al. The development of targeted chemotherapy for CNS lymphoma: a pilot study of the IDARAM regimen. Cancer Chemother Pharmacol 2004;53:324-8.

23. Yilmaz M, Erkutlu I, Kiliciskiz S, et al. Modified IDARAM chemotherapy regimen for primary central nervous system lymphoma: experience of three cases. Hematologyology 2008;13:107-13.

24. Zhao D, Qian L, Shen J, et al. Combined treatment of rituximab, idarubicin, dexamethasone, cytarabine, methotrexate with radiotherapy for primary central nervous system lymphoma. J Cell Mol Med 2014;18:1081-6.

25. Qian L, Zhou C, Shen J, Cen J, Yin W. Treatment of newly diagnosed B-cell origin primary CNS lymphoma with systemic R-IDARAM chemotherapy and intrathecal immunochemotherapy. Oncotarget 2016;7:25783-90.

26. Omuro A, Correa DD, DeAngelis LM, et al. R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. Blood 2015;125:1403-10.

27. Weller M. Glucocorticoid treatment of primary CNS lymphoma. J Neurooncol 1999;43:237-9.

28. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235-42.

29. Rubenstein JL, Combs D, Rosenberg J, et al. Rituximab therapy for CNS lymphomas: targeting the leptomeningeal compartment. Blood 2003;101:466-8.

30. Shah GD, Yahalom J, Correa DD, et al. Combined immunotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. J Clin Oncol 2007;25:4730-5.

31. Feugier P, Virion JM, Tilly H, et al. Incidence and risk factors for central nervous system occurrence in elderly patients with diffuse large-B-cell lymphoma: influence of rituximab. Ann Oncol 2004;15:129-33.

32. Nelson DF, Martz KL, Bonner H, et al. Non-Hodgkin’s lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG). J Int Radiat Oncol Biol Phys 1992;23:9-17.

33. Shibamoto Y, Ogino H, Hasegawa M, et al. Results of radiation monotherapy for primary central nervous system lymphoma in the 1990s. Int J Radiat Oncol Biol Phys 2003;58:839-45.

34. Blay JY, Conroy T, Chevreaux C, et al. High-dose methotrexate for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. J Clin Oncol 1998;16:864-71.

35. Harder H, Holtel H, Bromberg JE, et al. Cognitive status and quality of life after treatment for primary CNS lymphoma. Neurology 2004;62:544-7.

36. Glass J, Gruber ML, Cher L, Hochberg FH. Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: long-term outcome. J Neurosurg 1994;81:188-95.

37. O’Brien PC, Roos DE, Pratt G, et al. Combined-modality therapy for primary central nervous system lymphoma: long-term data from a Phase II multicenter study (Trans-Tasman Radiation Oncology Group). Int J Radiat Oncol Biol Phys 2006;64:408-13.

38. DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz CJ. Radiation Therapy Oncology Group Study 93-10. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol 2002;20:4643-8.

39. Ferreri AJ, Reni M, Foppoli M, et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet 2009;374:1512-20.

40. Ferreri AJ, Verona C, Politi LS, et al. Consolidation radiotherapy in primary central nervous system lymphomas: impact on...
outcome of different fields and doses in patients in complete remission after upfront chemotherapy. Int J Radiat Oncol Biol Phys 2011;80:169-75.

41. Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. J Clin Oncol 2013;31:3971-9.

42. Marchi N, Cavaglia M, Fazio V, Bhudia S, Hallene K, Janigro D. Peripheral markers of blood-brain barrier damage. Clin Chim Acta 2004;342:1-12.

43. Doolittle ND, Abrey LE, Shenkier TN, et al. Brain parenchyma involvement as isolated central nervous system relapse of systemic non-Hodgkin lymphoma: an International Primary CNS Lymphoma Collaborative Group report. Blood 2008;111:1085-93.

44. Doolittle ND, Jahnke K, Belanger R, et al. Potential of chemoinmunotherapy and radioimmunotherapy in relapsed primary central nervous system (CNS) lymphoma. Leuk Lymphoma 2007;48:1712-20.

45. Neuwelt E, Abbott NJ, Abrey L, et al. Strategies to advance translational research into brain barriers. Lancet Neurol 2008; 7:84-96.

46. Dahlborg SA, Henner WD, Crossen JR, et al. Non-AIDS primary CNS lymphoma: first example of a durable response in a primary brain tumor using enhanced chemotherapy delivery without cognitive loss and without radiotherapy. Cancer J Sci Am 1996;2:166-74.

47. Tyson RM, Siegal T, Doolittle ND, Lacy C, Kraemer DF, Neutwelt EA. Current status and future of relapsed primary central nervous system lymphoma. Leuk Lymphoma 2003;44:627-33.

48. Butler RW, Hill JM, Steinherz PG, Meyers PA, Finlay JL. Neuropsychologic effects of cranial irradiation, intrathecal methotrexate, and systemic methotrexate in childhood cancer. J Clin Oncol 1994;12:2621-9.

49. Correa DD, DeAngelis LM, Shi W, Thaler H, Glass A, Abrey LE. Cognitive functions in survivors of primary central nervous system lymphoma. Neurology 2004;62:548-55.

50. Shankar GM, Barker FG 2nd. Primary CNS lymphoma: the role of resection. Oncology (Williston Park) 2014;28:637-8, 640-2.

51. Hoang-Xuan K, Bessell E, Bromberg J, et al. Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology. Lancet Oncol 2015;16:e322-32.

52. Weller M, Martus P, Roth P, Thiel E, Korfel A; German PCNSL Study Group. Surgery for primary CNS lymphoma? Challenging a paradigm. Neuro Oncol 2012;14:1481-4.

53. Henry JM, Heffner RR Jr, Dillard SH, Earle KM, Davis RL. Primary malignant lymphomas of the central nervous system. Cancer 1974;34:1293-302.

54. Bataille B, Delwail V, Menet E, et al. Primary intracerebral malignant lymphoma: report of 248 cases. J Neurosurg 2000; 92:261-6.

55. Kellogg RG, Straus DC, Karmali R, Munoz LF, Byrne RW. Impact of therapeutic regimen and clinical presentation on overall survival in CNS lymphoma. Acta Neurochir (Wien) 2014;156: 355-65.

56. Iwadate Y, Suganami A, Ikegami S, et al. Non-deep-seated primary CNS lymphoma: therapeutic responses and a molecular signature. J Neurooncol 2014;117:261-8.

57. Rubenstein JL, Hsi ED, Johnson JL, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol 2013;31:3061-8.

58. Holdhoff M. Role of surgical resection in primary CNS lymphoma: a resurrected discussion. Oncology (Williston Park) 2014;28: 641-2.

59. Hsu HI, Lai PH, Tseng HH, Hsu SS. Primary solitary lymphoma of the fourth ventricle. Int J Surg Case Rep 2015;14:23-5.

60. Rubenstein JL, Fridlyand J, Abrey L, et al. Phase I study of intraventricular administration of rituximab in patients with recurrent CNS and intraocular lymphoma. J Clin Oncol 2007; 25:1350-6.

61. Rubenstein JL, Li J, Chen L, et al. Multicenter phase 1 trial of intraventricular immunochemootherapy in recurrent CNS lymphoma. Blood 2013;121:745-51.

62. Ponsoni M, Isa S, Batchelor TT, Rubenstein JL. Beyond high-dose methotrexate and brain radiotherapy: novel targets and agents for primary CNS lymphoma. Ann Oncol 2014;25:316-22.

63. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med 2013;368:1509-18.