

Diagnosis, prognosis and treatment of primary central nervous system lymphoma in the elderly population (Review)

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Abstract. Primary central nervous system lymphoma (PCNSL) is a rare subtype of extranodal non-Hodgkin lymphoma that is unique and different from systemic diffuse large B-cell lymphomas. The median age at diagnosis of PCNSL is 65 years and its incidence is rising rapidly in the elderly population. A total of $\geq 20\%$ of all patients with PCNSL are ≥ 80 years old. Notably, age has been identified as an independent poor prognostic factor for PCNSL. Elderly patients have an inferior prognosis to that of younger patients and are more severely affected by iatrogenic toxicity; therefore, elderly patients represent a unique and vulnerable treatment subgroup. The present review summarized the available literature to provide an improved understanding of the epidemiology, clinical characteristics, diagnosis, prognosis and management of PCNSL in the elderly population. Notably, the incidence of PCNSL in immunocompetent elderly patients, predominantly in men, is increasing. For the diagnosis of CNSL, imaging-guided stereotactic biopsy is considered the gold standard. When stereotactic biopsy is not possible or conclusive, certain biomarkers have been described that can help establish a diagnosis. PCNSL has a very poor prognosis in the elderly, even though several prognostic scoring systems exist and several prognostic markers have been reported in patients with PCNSL. Furthermore, the treatment of elderly patients remains challenging; it is unlikely that a novel agent could be used as a curative monotherapy; however, a combination of novel agents with polychemotherapy or its combination with other novel drugs may have therapeutic potential.

Introduction

Primary central nervous system (CNS) lymphoma (PCNSL) is a rare subtype of extranodal non-Hodgkin lymphoma

(NHL), which is typically confined to the brain, spinal cord, eyes or leptomeninges, without evidence of systemic spread. PCNSL was first described by Bailey in 1929 as perivascular sarcoma (1). The symptoms of PCNSL often progress rapidly and are non-specific and vary depending mainly on the primary location of the lesions. Contrast-enhanced brain MRI is the preferred method of diagnosis (2), and the histological analysis of biopsy material, usually obtained by imaging-guided stereotactic biopsy, is regarded as the gold standard for the diagnosis of PCNSL (3). In total, $\sim 95\%$ of PCNSL cases worldwide are classified histologically as diffuse large B-cell lymphomas (DLBCL); however, PCNSL is unique and distinct from systemic DLBCL (4,5). Considering the recent identification of distinct genotypic and immunophenotypic features, with reference to morphological and clinical characteristics, primary DLBCL of the CNS (PCNS-DLBCL) has been classified as a specific lymphoma subtype in the World Health Organization lymphoma classification system since 2008 (6). Since the majority of PCNSL cases are DLBCL and other pathological types are very rare, PCNS-DLBCL and PCNSL are almost the same concept. The median age at diagnosis of PCNSL is 65 years and the incidence is rising rapidly in the elderly population (7,8). Patients >60 years old account for $>50\%$ of all PCNSL cases and up to 20% of all patients with PCNSL are aged ≥ 80 years (2). Notably, age has been identified as an independent poor prognostic factor for PCNSL (9). For PCNSL, two major scoring systems have been established and are widely used. Elderly patients have an inferior prognosis compared with that of younger patients and are more severely affected by iatrogenic toxicity; therefore, they represent a unique and vulnerable treatment subgroup (10,11). There is an unmet clinical need to define optimal treatment for this population. In the present review, the available literature has been reviewed to provide an improved understanding of the epidemiology, clinical characteristics, diagnosis, prognosis and management of PCNSL in the elderly; the present review focused on the recent advances in prognosis and treatment.

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1. Epidemiology

PCNSL accounts for ~4% of all intracranial malignancies, 5% of all extranodal lymphomas and <1% of all non-Hodgkin lymphomas (12). The incidence rate for PCNSL worldwide is 0.47 per 100,000 people per year, occurring mostly in the 6th decade of life, with a male:female ratio of 1.2:1.7 (7,13,14). Moreover, a rising incidence has been observed in patients aged >60 years in the last 10 years, with patients aged 70-79 years old having the highest incidence (15). Notably, African-American individuals tend to present with PCNSL at a younger age (<50 years), whereas Caucasian individuals usually present with the disease when >50 years old (7).

PCNSL can affect immunocompetent and immunocompromised patients. Most cases occur sporadically; however, a compromised immune system, both primary and acquired, has been reported to be a predisposing factor for PCNSL (16). The risk of PCNSL has also been reported to be 2-6% in patients with AIDS and 1-5% in those that have received organ transplants (13). Primary immunodeficiency has been reported to confer a 4% risk of developing PCNSL. In addition, the incidence of PCNSL has been shown to be inversely correlated with CD4 cell counts (17) and has declined in HIV-infected individuals since the widespread use of highly active antiretroviral therapy (7,18). Currently, immunocompetent patients represent the vast majority of patients with PCNSL (19); in addition, these patients are often diagnosed between the ages of 50 and 70 years, whereas immunocompromised patients often present with the disease earlier in life, in their 30s and 40s (20).

2. Clinical manifestation

The clinical manifestation of PCNSL varies depending mainly on the primary location of the lesions. The symptoms often progress rapidly and are non-specific. The most common presentation is focal neurological symptoms, which have been observed in 70% of patients (21). In addition, a total of 43% of patients presented with neuropsychiatric symptoms, followed by signs of increased intracranial pressure, such as headache and vomiting in 33%, seizures in 14% and ocular symptoms in 4% of cases (21). In addition, 'B symptoms', such as weight loss, fever and night sweats have been reported to be rare in PCNSL (21) (Fig. 1).

3. Brain imaging

PCNSL nearly always exhibits significant contrast uniform enhancement, with or without necrosis, on computed tomography (CT) and magnetic resonance imaging (MRI) scans (21). Furthermore, linear enhancement along perivascular spaces is highly characteristic of PCNSL (22). On a CT scan, PCNSL in immunocompetent individuals

often presents as a single hyper- or iso-attenuated lesion. On an MRI scan, PCNSL is typically iso-hypointense on T1-weighted imaging and iso-hypointense to gray matter on T2-weighted imaging; in a previous study, in 85% of patients, a strong homogeneous pattern of enhancement was detected, due to its hypercellularity (21). However, PCNSL lesions may be non-contrast-enhancing, and can contain atypical features of hemorrhage, calcification, cysts and necrosis (23).

Lesions are often centrally located within cerebral white matter, and are often found in the periventricular region. A total of 87% of PCNSL lesions were previously reported to be supratentorial, with 39% of them having frontoparietal involvement in a retrospective analysis from French and Belgian medical centers (12). A total of 9-25% of newly diagnosed PCNSL were also demonstrated to have cerebellar involvement (24,25). Malikova *et al* (26) demonstrated that parenchymal involvement was much more common than previously hypothesized. Leptomeningeal lesions of CNSL often involve the cranial nerves, subependymal regions spinal cord or spinal nerve roots, whereas dural involvement is rare in PCNSL or secondary CNSL (22).

While immunocompetent patients usually have solitary lesions with homogenous enhancement, 20-40% of cases have been reported to present with multiple lesions, and up to 13% with ring-like enhancement (27). The typical appearance of PCNSL in patients with immunodeficiency is different from that in immunocompetent patients. A total of 30-80% of immunodeficient patients have been shown to present with multiple lesions that usually have necrosis, resulting in an irregular ring-enhancing pattern and a higher propensity for spontaneous hemorrhage (27).

4. Pathology

Notably, ~95% of PCNSL cases are classified histologically as DLBCL, and 5% as other histologies, including T-cell, Burkitt, lymphoblastic and marginal zone lymphomas (28). Gene expression profiling has been used to establish three major DLBCL subtypes: Germinal center B-cell-like (GCB), activated B-cell-like (ABC) and type 3. The type 3 subgroup is not well defined, but the type 3 and ABC subtypes appear to have a poor outcome and are often grouped together as non-germinal center (non-GC) subtype (29). Further genomic sequencing revealed that the pattern of somatic mutations in DLBCL was classified as GCB tumors and non-GC tumors depending on the cell of origin. GCB tumors were revealed to more likely have mutations in EZH2 and GNA13, and translocations in bcl-2. Non-GC tumors were associated with mutations in MyD88, CD79B, CARD11 and TNFAIP3, all of which are involved in B-cell receptor (BCR) signaling activating NF- κ B (30). Tumors can be subdivided into GCB and non-GC types based on the expression pattern of CD10, bcl-6 and MUM-1/IRF4. Staining of PCNSL biopsies to distinguish these DLBCL subgroups (CD10⁻, bcl-6⁺, MUM-1/IRF4⁺) showed that the vast majority (>80%) of PCNSL-DLBCLs were the non-GC immunophenotype (31). To the best of our knowledge, age-related pathological characteristics in PCNSL tumor tissue have not been identified.

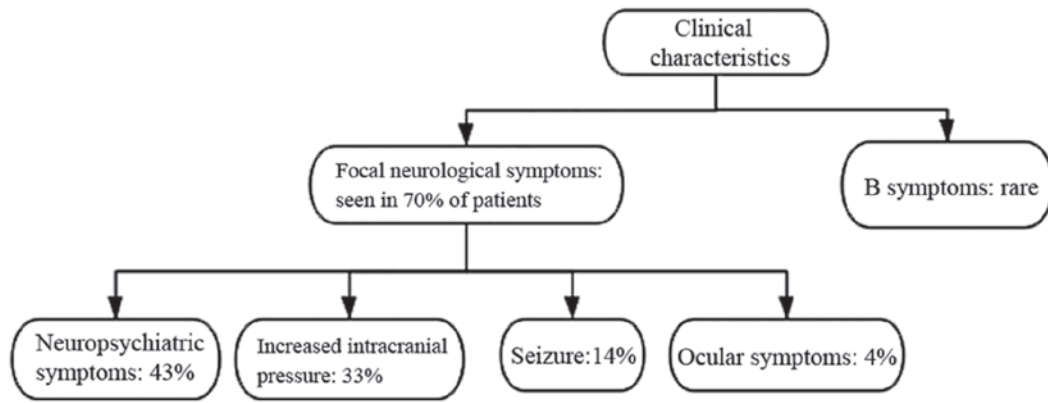


Figure 1. Clinical characteristics of PCNSL. PCNSL, primary central nervous system lymphoma.

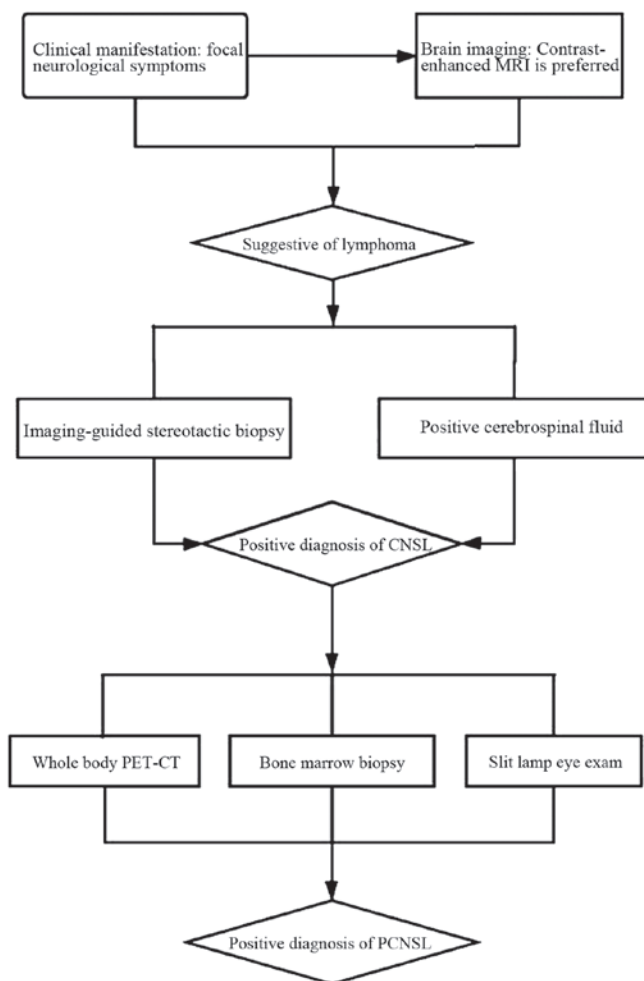


Figure 2. Diagnosis of PCNSL. MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; PCNSL, primary central nervous system lymphoma.

5. Diagnosis

PCNSL typically presents as an intracranial mass lesion, alongside a combination of generalized symptoms, including headaches, confusion and lethargy, and lateralizing symptoms, such as hemiparesis. Focal neurological deficits have been reported to affect 50% of patients, and PCNSL is usually

misdiagnosed early on as a cerebrovascular disorder (2). Contrast-enhanced brain MRI scan is the preferred method of diagnosis (2). Definitive diagnosis requires pathological confirmation. For the diagnosis of CNSL, histological analysis of biopsy material, usually obtained by imaging-guided stereotactic biopsy, is regarded as the gold standard (3). An early brain biopsy when CNSL is suspected is considered a valid option to reduce diagnostic delay, with a high rate of definitive diagnosis and a low complication rate (24). A positive cerebrospinal fluid (CSF) test for lymphoma, referring to the presence of lymphoma cells in CSF by flow cytometry and cytology, can obviate the need for a surgical procedure (32). For the diagnosis of PCNSL, a body positron emission tomography-computed tomography scan, bone marrow biopsy and slit lamp eye exam should be performed to exclude extraneural disease (Fig. 2).

Notably, PCNSL is sensitive to corticosteroids, and pathological evaluation of corticosteroid-pretreated PCNSL has been shown to lead to a final diagnosis in only 50-85% of cases (33). Sensitivity may also be significantly reduced when tissue is obtained through a stereotactic biopsy after the patients were treated with corticosteroids (24). Therefore, corticosteroids should be avoided prior to biopsy as much as possible, in order to decrease their impact on diagnosis.

When stereotactic biopsy is not possible or conclusive, certain biomarkers have been shown to help establish the diagnosis of CNSL (Table I). In HIV-positive patients with CNSL, Epstein-Barr virus (EBV) DNA in the CSF may be used as a diagnostic biomarker (34). In HIV-negative patients, several diagnostic biomarkers, including interleukin (IL)-10, IL-6, CXC chemokine ligand-13 (CXCL13), neopterin, β 2-microglobulin (β 2-MG), osteopontin, soluble CD27, specific microRNAs and cell-free DNA, have been described (35-45). Soluble transmembrane activator and CAML interactor, and soluble B-cell maturation antigen in the CSF have also been identified as promising novel biomarkers for the diagnosis and treatment monitoring of PCNSL (46). In addition, a proliferation-inducing ligand, alone or in combination with B-cell activating factor, in the CSF may serve as a diagnostic biomarker for patients with CNSL (3). Furthermore, next-generation sequencing of circulating tumor DNA isolated from CSF samples may provide a promising diagnostic biomarker (47). Moreover, in recent years the

Table I. Diagnostic biomarkers associated with primary central nervous system lymphoma.

A, In HIV-positive patients		
First author, year	Biomarkers	(Refs.)
Antinori, 1999	EBV DNA in the CSF	(34)
B, In HIV-negative patients		
First author, year	Biomarkers	(Refs.)
Sasagawa, 2015	IL-10	(35)
Song, 2016	IL-6	(36)
Rubenstein, 2013	CXCL13	(37)
Viaccoz, 2015	Neopterin	(38)
Caudie, 2005	β 2-MG	(39)
Strehlow, 2016	Osteopontin	(40)
Kersten, 1996	sCD27	(41)
Baraniskin, 2011	Specific microRNAs	(42)
Rimelen, 2019	Cell-free DNA	(45)
Thaler, 2017	sTACI and sBCMA in the CSF	(46)
Mulazzani, 2019	APRIL alone or in combination with BAFF in the CSF	(3)
Ho, 2019	Next-generation sequencing of ctDNA from CSF	(47)
Deguchi, 2019	SWI	(48)

EBV, Epstein-Barr virus; CSF, cerebrospinal fluid; IL, interleukin; CXCL, CXC chemokine Ligand; β 2-MG, β 2-microglobulin; sTACI, soluble transmembrane activator and CAML interactor; sBCMA, soluble B-cell maturation antigen; APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; ctDNA, circulating tumor DNA; SWI, susceptibility-weighted imaging.

clinical significance of susceptibility-weighted imaging has been established in the differential diagnosis of PCNSL (48).

6. Prognosis

PCNS-DLBCL is an aggressive malignancy that has been reported to be associated with an overall survival (OS) of 12-18 months (28,49,50). Without treatment, OS has been shown to decrease to 1.5-3.3 months (51). Since the introduction of high-dose (HD)-methotrexate (MTX)-based chemotherapy regimens, OS has increased substantially; it has been reported to be 16.3-66 months with a 2-year OS rate of 42-80.8% (52-56).

Outcomes for patients aged >60 years remain poor, with 1-year progression-free survival (PFS) rates being reported at ~40% and a median OS in the range of 8-43 months in elderly patients receiving multi-drug regimens, including HD-MTX (57-63). Until now, only a few randomized controlled trials (10,59-65) dedicated to treating PCNSL in the elderly

population have been performed (Table II). An epidemiological analysis demonstrated that, while the median OS of all patients with PCNSL doubled, from 12.5 months in the 1970s to 26 months in the 2010s, this progress was restricted to young patients. Conversely, the median OS of patients with PCNSL aged ≥ 70 years has not improved in >40 years (6 months in the 1970s vs. 7 months in the 2010s) (66). Furthermore, patients aged >70 years have been excluded from several clinical trials; it has been reported that ~1/4 of patients aged >70 years with PCNSL who survive for >3 months from diagnosis do not receive chemotherapy at all in the US (53). Notably, in a previous study, the fraction of patients who were not treated with chemotherapy increased from 14 to 23, and to 44% in the of 61-70, 71-80 and >80 years age groups, respectively (2). Therefore, the treatment of PCNSL, particularly in elderly patients, remains challenging.

Although PCNSL is a significantly chemosensitive neoplasm, often achieving complete response (CR) after initial treatment, 30-50% of patients may not benefit from this intensive treatment due to old age, delayed neurotoxicity, drug resistance or relapse (67,68). Despite advances in induction and consolidation regimens, relapse has been observed in 35-60% of patients 2 years after the initial diagnosis, and in 4% of patients 5 years after the initial diagnosis (69). In a large population-based study, overall prognosis was found to be poor following salvage therapy, with the median PFS and OS following recurrence at 2.2 and 3.5 months, respectively, with elderly patients having the worse outcome (67). In addition, ~1/3 of the patients with PCNSL had primary refractory disease, that is, they failed to respond to the first-line treatment (32). In a French prospective cohort, refractory patients were found to have a poor prognosis (median OS, 2.1 months) (68). Despite the development of novel and intensified therapeutic regimens, PCNSL has a very poor prognosis and its incidence in people aged ≥ 65 years is increasing in the US (8).

For PCNSL, two major scoring systems have been established and are widely used. The Memorial Sloan-Kettering Cancer Center prognostic model describes three groups, based on age and Karnofsky performance score (KPS; Table III). The most relevant are poor performance status and advanced age. Patients aged >50 years with a KPS of <70 have been reported to have the worst prognosis, with a median survival of 1.1 years (70). The International Extranodal Lymphoma Study Group (IELSG) described five prognostic factors as independent predictors of poor prognosis with a low OS (Table IV). Each factor was set at 1 point. According to the degree of integration, they were divided into three groups, 0-1, 2-3 and 4-5. The 2-year survival of patients with 0-1, 2-3 or 4-5 of these unfavorable factors was 80, 48 and 15%, respectively (71).

Although the aforementioned two prognostic scoring systems already exist, risk assessment at the time of diagnosis remains unsatisfactory. Several prognostic markers have been reported in patients with PCNSL (Table V).

Gross total resection following surgery is a significant independent favorable prognostic marker for OS (72). The completion of three cycles of HD-MTX chemotherapy was also found to be a significant independent prognostic factor for patient survival (73). In a previous study, patients with CR following initial HD-MTX had a longer survival time (74). CR status following HD chemotherapy with autologous stem cell

Table II. Summary of randomized controlled trial research to treat primary central nervous system lymphoma in the elderly.

First author, year	Treatment protocol	Phase	Patients, n	Median age, years	Median OS, months or %	Median PFS, months or %	(Refs.)
Omuro, 2007	HD-MTX + TMZ	II	23	68	35	8	(10)
Fritsch, 2017	R + HD-MTX + procarbazine + lomustine (R-MPL)/RMP → procarbazine maintenance	II	107	73	2-year OS 47%	2-year PFS 37.3%	(59)
Hoang-Xuan, 2003	HD-MTX + lomustine + procarbazine + methylprednisolone + IT MTX and cytarabine	II	50	72	14.3	1-year PFS 40%	(60)
Illerhaus, 2009	HD-MTX + procarbazine + CCNU	II	29	70	15.4	5.9	(61)
Roth, 2012	HD-MTX-based chemotherapy	III	126	≥70	12.5	4	(62)
Olivier, 2014	HD-MTX + VDS + PRED + idarubicin	I	35	65	19	13	(63)
Omuro, 2015	HD-MTX + TMZ vs. HD-MTX + PCZ + VCR → cytarabine (MPV-A)	II	48 47	73 72	14 31	6.1 9.5	(64)
Pulczynski, 2015	HD-MTX + IT liposomal cytarabine → TMZ maintenance	II	27	70	2-year OS 55.6%	2-year PFS 44.4%	(65)

OS, overall survival; PFS, progression-free survival; HD-MTX, high-dose methotrexate; TMZ, temozolomide; R, rituximab; IT, intrathecal injection therapy; VDS, vindesine; PRED, prednisone; PCZ, procarbazine; VCR, vincristine.

Table III. Memorial Sloan-Kettering Cancer Center prognostic model.

Parameters (Age, KPS)	Prognostic groups	Median OS, years
Age ≤50 years	Age ≤50 years	8.5
or >50 years;	Age >50 years	3.2
KPS <70	and KPS ≥70	
or ≥70	Age >50 years and KPS <70	1.1

KPS, Karnofsky performance status; OS, overall survival. Data taken from study by Abrey *et al* (70).

Table IV. International extranodal lymphoma study group score.

Parameters (each factor, 1 point)	Prognostic groups (according to the score)	2-Year OS, %
Age >60 years; ECOG	0-1	80
PS >1; LDH >normal	2-3	48
level; high CSF protein; deep brain lesions	4-5	15

CSF, cerebrospinal fluid; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; OS, overall survival. Data taken from study by Ferreri *et al* (71).

transplantation (HDT/ASCT) and the use of thiotepa in a HDT regimen have also been identified as independent prognostic predictors for OS and PFS, respectively. Multivariate analysis identified non-CR at HDT/ASCT as an independent prognostic factor for poor OS (75). Notably, patients treated with thiotepa-containing HDT had a significantly superior 5-year PFS and OS compared with those receiving HDT without thiotepa (75). Bcl-6 expression has also been determined to be a favorable prognostic marker (76). Bcl-6 expression and high KPS, as independent prognostic parameters, have been associated with a favorable outcome (77). In addition, an Eastern Cooperative Oncology Group (ECOG) score of ≤2, multiple brain lesions, a maximum tumor diameter of <5 cm and

CD10⁺ expression were found to be significantly associated with a prolonged OS (78). Furthermore, the texture analysis of contrast-enhanced MRI may have the potential to predict PCNSL prognosis. In a previous study, grey-level co-occurrence matrix-homogeneity (<0.2864) was associated with a favorable survival and could be considered an independent predictor (79). Alame *et al* (80) reported that the expression of programmed death-1 protein (PD-1) on tumor-infiltrating lymphocytes (TILs) and programmed death-1 ligand (PD-L1) on tumor-associated macrophages was correlated with favorable survival. The serum level of soluble PD-L1 (sPD-L1) has also been reported to act as a reliable biomarker to predict the probability of relapse and survival outcome in patients with PCNSL; sPD-L1 (<0.432 ng/ml) has been associated with

Table V. Prognostic markers associated with PCNSL.

A, Favorable prognostic markers in HIV-associated PCNSL		
First author, year	Prognostic markers	(Refs.)
Gopal, 2012	CD4 count >200 cells/ μ l HIV RNA viral load <400 copies/ml	(98)
B, Favorable prognostic markers		
First author, year	Prognostic markers	(Refs.)
Weller, 2012	Gross total resection after operation	(72)
Makino, 2015	Completion of three cycles of HD-MTX chemotherapy	(73)
Nakasu, 2016	CR status after completion of initial HD-MTX	(74)
Kondo, 2019	CR status at HDT/ASCT, thiotepa use in HDT regimen	(75)
Levy, 2008	Bcl-6	(76)
Preusser, 2010	Bcl-6 expression and high KPS	(77)
Niparuck, 2019	ECOG score \leq 2, multiple brain lesions, MTD <5 cm, CD10 ⁺	(78)
Chen, 2019	GLCM-homogeneity (<0.2864)	(79)
Alame, 2020	PD-1 on TILs and PD-L1 on TAMs	(80)
Cho, 2020	Serum level of soluble PD-L1 (<0.432 ng/ml)	(81)
Cambruzzi, 2020	Expression of MHC II genes, expression of bcl-6, IMO2 and CD10	(82)
Nayyar, 2019	CD79b mutations	(94)
Kim, 2019	tPD-L1 ⁺ patients with a large number of CD8 ⁺ or PD-1 ⁺ TILs	(97)
C, Poor prognostic markers		
First author, year	Prognostic markers	(Refs.)
Villano, 2011	Patients aged 0-49 years: Male sex, HIV infection and African-American descent; patient aged >50 years: Increasing age	(7)
Yuan, 2020	ECOG >3 and multifocal lesions	(83)
Tabouret, 2017	Infratentorial location and large tumor volume (>11.4 cm ³)	(84)
Chunsong, 2006	CXCL13	(85)
Le, 2019	Anemia	(86)
Oyama, 2007	EBV-positive	(87)
Wu, 2019	ABCB1 rs1045642 CC genotype, PS >2 and older age	(88)
Yang, 2020	Elevated CSF IL-10 and STAT3 phosphorylation	(89)
Hatzl, 2020	DEL	(90)
Yin, 2019	Bcl-2 gene aberrations and DH	(91)
Villa, 2019	Bcl-6 rearrangements	(92)
Cambruzzi, 2020	Expression of MUM1, cyclin D2, p53, CD5, FOXP1, ICAM1, HLA-DR and bcl-2; and strong FOXP1 positivity, myc and bcl-2 overexpression, bcl-6 translocations, and high Ki-67 index	(82)
Takano, 2018	MyD88 mutations	(93)
Mondello, 2020	Tumor expression of activated STAT6, and elevated levels of IL-4 and IL-10	(95)
Hyung, 2019	Serum β 2-MG (\geq 1.8 g/ml)	(96)
Kim, 2019	tPD-L1 ⁺ patients with a small number of CD8 ⁺ or PD-1 ⁺ TILs	(97)

PCNSL, primary central nervous system lymphoma; HD-MTX, high-dose methotrexate; CR, complete remission; HDT/ASCT, high-dose chemotherapy with autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; CXCL, CXC chemokine ligand; EBV, Epstein-Barr virus; MTD, maximum tumor diameter; GLCM, grey-level co-occurrence matrix; PD-1, programmed death-1; TILs, tumor-infiltrating lymphocytes; PD-L1, programmed death-1 ligand; TAMs, tumor-associated macrophages; tPD-L1, tumoral PD-L1; STAT, signal transducer and activator of transcription; PS, performance status; DEL, double-expression lymphoma; DH, bcl-2/c-myc gene double-hit; β 2-MG, β 2-microglobulin.

a longer OS and PFS (81). The expression of MHC II genes was also found to predict a favorable outcome following chemotherapy (82). The expression of bcl-6, IMO2 and CD10 has also been associated with a favorable prognosis (82).

Male sex, HIV infection and being of African-American descent have been reported as independent predictors of mortality in patients aged 0-49 years. In patients aged >50 years, only advanced age was associated with decreased survival (7). Furthermore, ECOG >3 and multifocal lesions have been found to be significant independent unfavorable prognostic markers for PFS (83). Infratentorial location and large tumor volume (>11.4 cm³) were also revealed to be associated with poor OS and PFS, respectively (84). CXCL13 and the presence of anemia have also been found to be poor prognostic markers in PCNSL (85,86). In addition, patients with EBV-positive PCNSL had a shorter OS than those with EBV-negative PCNSL (87). In a previous study, the most important prognostic factors associated with a higher risk of progression were ABCB1 rs1045642 CC genotype, ECOG performance status >2 and older age (88). Elevated CSF IL-10 and STAT3 phosphorylation have also been shown to be associated with a worse prognosis (89). Furthermore, as demonstrated by immunohistochemistry, concurrent expression of myc and bcl-2, also known as double-expression lymphoma, was associated with inferior OS and PFS (90). Bcl-2 gene aberrations, bcl-2/c-myc gene double-hit and bcl-6 rearrangements have also been associated with adverse outcomes (91,92). In addition, the expression levels of MUM1, cyclin D2, p53, CD5, FOXP1, ICAM1, HLA-DR and bcl-2 have been related to poor prognosis. A strong FOXP1 positivity, myc and bcl-2 overexpression, bcl-6 translocations, and a high Ki-67 index have been associated with unfavorable prognosis in a previous study (82). Takano *et al* (93) reported that MyD88 mutations occurred more frequently in elderly patients and were associated with poor prognosis. However, another previous study demonstrated that MyD88 mutations were not associated with a change in PFS or OS, whereas CD79b mutations were associated with improved PFS and OS (94). The tumor expression levels of activated STAT6, and elevated levels of CSF IL-4 and IL-10 have been suggested as potential adverse prognostic biomarkers for PCNSL (95). Serum β 2-MG (≥ 1.8 g/ml) may be associated with a shorter OS in PCNSL (96). It has also been reported that tumoral PD-L1 (tPD-L1) expression and the number of PD-1⁺ TILs were independent prognostic factors for PCNS-DLBCL. tPD-L1⁺ patients with a small number of CD8⁺ or PD-1⁺ TILs exhibited the worst prognosis, whereas tPD-L1⁻ patients with a large number of CD8⁺ or PD-1⁺ TILs exhibited the best prognosis (97). Notably, in HIV-related PCNSL, the CD4 count and HIV RNA viral load have been found to be correlated with survival (98).

7. Treatment

PCNSL often has a favorable response to chemotherapy and radiotherapy (RT). Currently, the mainstay of treatment for patients with PCNSL is induction chemotherapy, which aims for CR, followed by consolidation therapy that aims to eradicate residual disease and improve OS (99). The treatment of PCNSL is based on age and performance status (100).

Older age is associated with an accumulation of physiological deficits that alter the pharmacokinetics and pharmacodynamics of therapies, and may increase the risk of toxicity. Performance status should be considered an important predictor of OS and drug toxicity. When selecting a treatment for elderly patients, multiple parameters should be considered. The American Society of Clinical Oncology Guidelines advocates for the use of geriatric assessment tools in patients ≥ 65 years who have received chemotherapy to identify vulnerabilities not routinely captured in oncology assessments (101). These tools are useful in predicting chemotherapeutic toxicity and mortality. The chemotherapy risk assessment scale for high-age patients (CRASH) score developed by Extermann *et al* (102) considers the specific chemotherapy regimen to be used, laboratory values, and functional, mental and nutritional status assessments. The CRASH score then stratifies patients into four risk categories: Low, medium-low, medium-high and high. The routine use of such a score may increase the proportion of elderly patients that receive optimal treatment. For example, a 'fit elderly' individual may tolerate standard doses and schedules of chemotherapeutic drugs, and may thus reap the same benefits as younger patients.

In the elderly population, an individualized treatment that aims at prolonging survival while minimizing toxicity is required (Fig. 3). Despite the fact that the median OS of all patients has doubled over the last 40 years, this survival benefit is restricted to patients aged <70 years (66). Therefore, identifying effective and tolerable treatment strategies for elderly patients is one of the key future challenges.

Steroid treatment. PCNSL is sensitive to corticosteroids, with reported response rates between 20 and 40% (103,104). Corticosteroids have been shown to decrease tumor-associated edema and may result in a partial radiographic regression of tumors. However, certain studies have reported that the preoperative use of steroids can compromise the efficacy of brain biopsy in patients with PCNSL (105,106). As such, the classic rationale recommends withholding steroid treatment for ≥ 14 days prior to a brain biopsy (24). An initial response to corticosteroids has been reported to be associated with a favorable outcome in PCNSL (107). As such, corticosteroids should be avoided prior to biopsy as much as possible, in order to decrease their impact on diagnosis. However, when the symptoms are serious and life-threatening, corticosteroids should be used to relieve the symptoms and prevent cerebral herniation. Treatment should be given in the smallest possible dose and for the shortest possible time to avoid long-term adverse reactions. In addition, almost all patients relapse quickly after an initial response to corticosteroids (108).

Induction therapy

HD-MTX. In newly diagnosed patients with PCNSL, the standard management approach, according to the 2018 NCCN guidelines (109), is HD-MTX-based chemotherapy, followed by consolidation therapy with whole brain RT (WBRT). MTX is an antifolate that suppresses DNA synthesis by inhibiting dihydrofolate reductase activity in purine and thymidine synthesis, which controls the expression of glucocorticoid receptors in blood cells (110,111). HD-MTX, one of the few drugs able to penetrate the blood-brain barrier (BBB), is

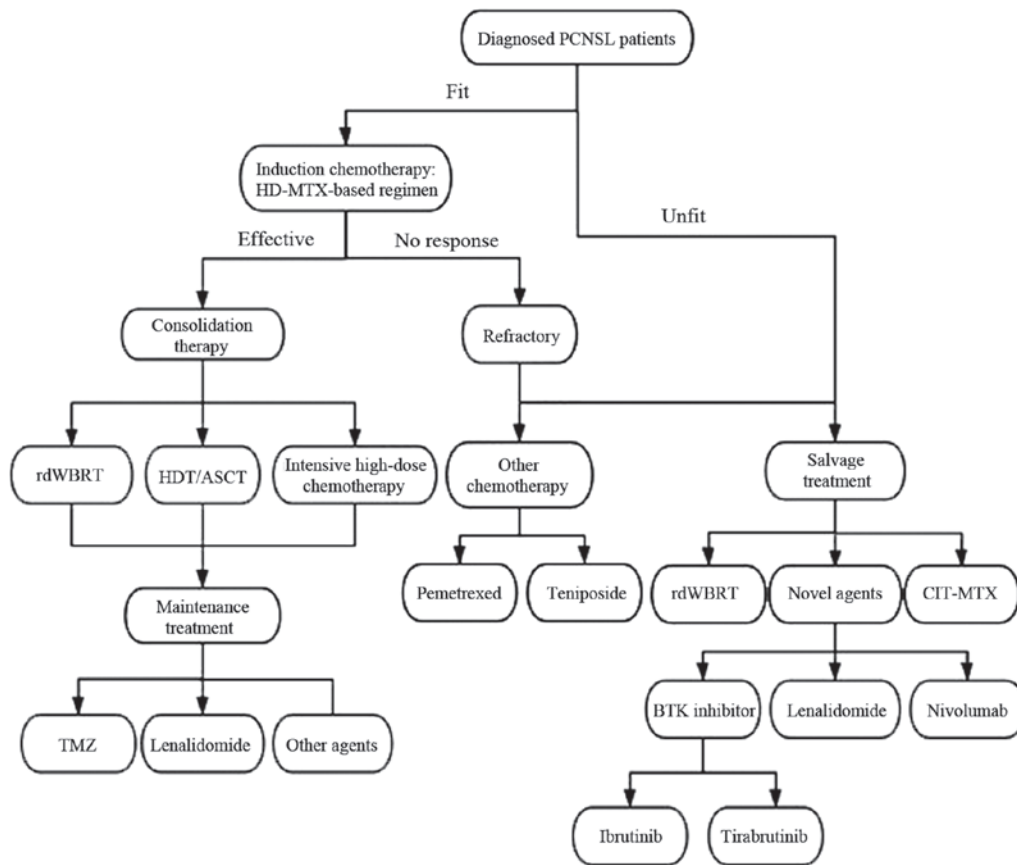


Figure 3. Key points in the treatment of PCNSL in elderly patients. PCNSL, primary central nervous system lymphoma; HD-MTX, high-dose methotrexate; rdWBRT, reduced-dose whole brain radiotherapy; HDT/ASCT, high-dose chemotherapy with autologous stem cell transplantation; TMZ, temozolomide; CIT, continuous intrathecal injection therapy; BTK, Bruton's tyrosine kinase.

commonly used as a first-line treatment for PCNSL. When combined with other agents, such as HD-cytarabine, temozolomide (TMZ) and rituximab, HD-MTX combination therapy has been revealed to offer a better prognosis compared with that of single therapeutics alone (55,112,113). Moreover, HD-MTX is considered a relatively safe treatment for patients with PCNSL regardless of age (114), and is even tolerable to patients aged ≥ 80 years (115). While HD-MTX-based treatment is widely accepted in clinical settings, 50% of patients may have a risk of progression or recurrence, and HD-MTX can cause renal dysfunction (116,117).

Pemetrexed. Pemetrexed is also an antifolate and is similar to MTX in its ability to penetrate the CNS; however, it has an advantage of targeting more than one site in folate metabolism. Pemetrexed interrupts purine synthesis by inhibiting thymidylate synthase and dihydrofolate reductase, and interrupts pyrimidine synthesis via inhibition of glycinamide ribonucleotide formyltransferase and aminoimidazole carboxamide for methyltransferase (118). Raizer *et al* (119) investigated the antitumor activity and safety of pemetrexed in recurrent PCNSL, and found that pemetrexed had single-agent activity in R/R PCNSL and possible toxicities were due to the use of higher than standard doses. Han *et al* (120) studied 12 patients with newly diagnosed PCNSL that were >65 years old; four patients presented CR and six patients had partial response (PR), with a median PFS of 9.0 months and a median OS of

19.5 months. This previous study demonstrated that the single agent pemetrexed may be feasible, active and well tolerated in elderly patients with PCNSL.

Rituximab. Rituximab is a large, monoclonal antibody against CD20. Since $\sim 98\%$ of small molecule drugs and most macromolecular drugs are unable to pass through the BBB (121), the addition of rituximab to HDMTX-based regimens remains controversial.

Several clinical studies have demonstrated that rituximab can promote CR and prolong survival (113,122-125), an effect that occurs regardless of age (126). Houillier *et al* (58) reached the same conclusion, and revealed that the addition of rituximab improved the response rate of an MTX-based regimen (77 vs. 53% without rituximab) with a good tolerance profile, except for an increased rate of leucopenia. In addition, there is evidence that disruption of the BBB by the presence of CNS lymphoma permits an enhanced penetration of rituximab into the CNS compartment to reach therapeutic concentrations (127). The international randomized trial IELSG32 suggested that the addition of rituximab to HD-MTX and HD-cytarabine improved response, PFS and OS (128). A meta-analysis suggested a possible beneficial effect of rituximab on PFS and supported the addition of rituximab when MTX-based chemotherapy was planned (129).

Conversely, in the recently published HOVON trial, rituximab was not found to have an effect on response or survival in

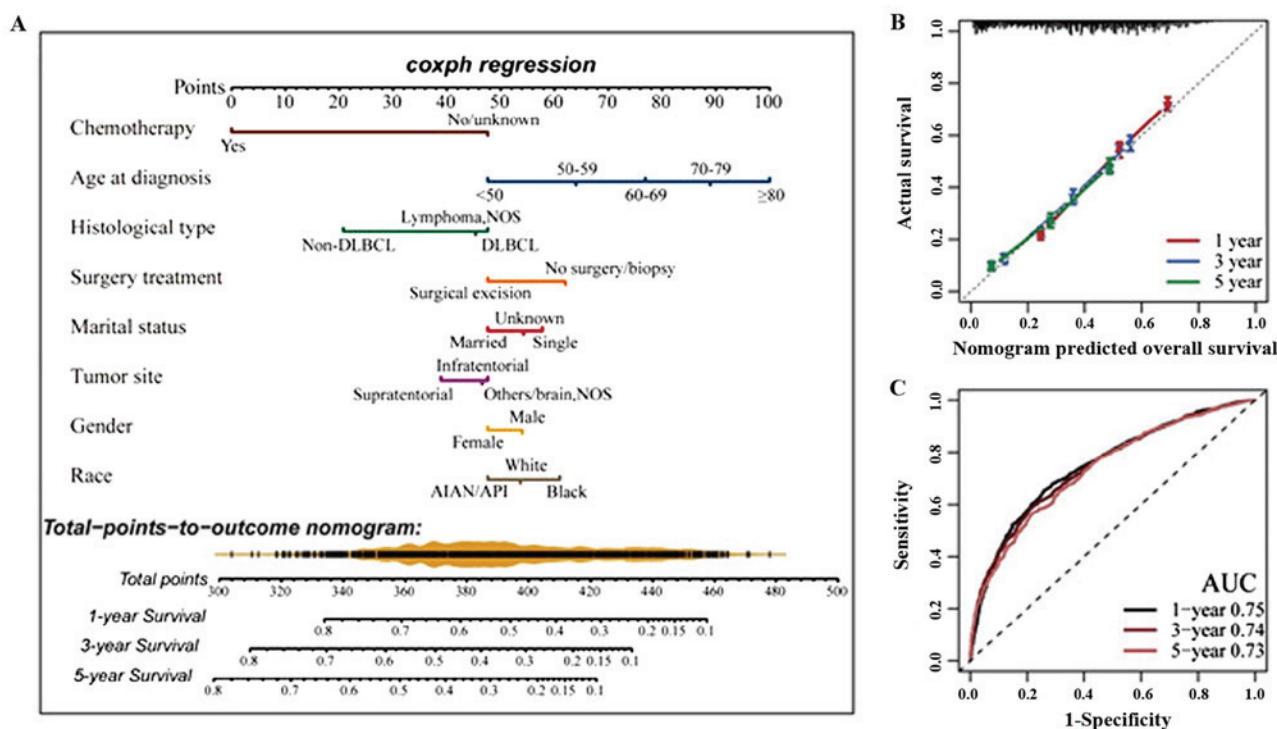


Figure 4. Nomogram development and internal validation. (A) Nomogram construction to estimate the probability of 1-, 3- and 5-years OS for PCNSL. (B) Calibration plot of the nomogram for predicting the probability of OS at 1, 3 and 5 years. (C) Time-dependent ROC curve analysis confirmed that the nomogram had the best performance. Images taken from the study by Deng *et al* (136). AUC, area under the curve; OS, overall survival; PCNSL, primary central nervous system lymphoma; ROC, receiver operating characteristic.

the treatment of PCNSL. There was no difference in survival or response for patients treated with or without rituximab, after a median follow up of 32.9 months (130).

Teniposide. Teniposide is a topoisomerase inhibitor, highly lipopolysaccharide, which can cross the BBB and has been used in the treatment of PCNSL (131,132). The penetration of teniposide has been widely examined in normal brain tissue and in brain tumor tissue (133). The phase II trial by the European Organization for Research and Treatment of Cancer Lymphoma Group indicated that the use of MTX, teniposide, carmustine and methylprednisolone resulted in improved outcomes, with a 3-year OS rate of 58% (132). A randomized phase II trial also identified that a chemotherapy regimen, which included fotemustine, teniposide and dexamethasone, was an effective and safe protocol for treating patients with newly diagnosed PCNSL (134). In a previous retrospective study, 56 patients were admitted, with a median age of 54.5 years. The results indicated that the HD-MTX + teniposide regimen, compared with HD-MTX alone, not only improved the CR rate in the short-term, but also improved long-term efficacy in the treatment of PCNSL (135).

Combined surgery, and chemotherapy or RT. A previous study demonstrated that the combination of surgical excision and chemotherapy conferred a more favorable outcome than chemotherapy alone, suggesting that multimodal treatment might be more beneficial. With regard to the specific extent of excision, a more extensive resection was revealed to be associated with a more favorable survival (136). Kinslow *et al* (137)

identified a significant survival advantage for patients with PCNSL treated with adjuvant RT following surgery.

A new nomogram model (Fig. 4) was established, which may offer an individualized quantitative potential benefit from surgical excision to patients with PCNSL (136). The nomogram model was internally validated using the bootstrap validation method. The nomogram predicted 1-, 3- and 5-year OS rate for patients with PCNSL based on the results of a multivariate Cox analysis (Fig. 4A). Calibration curves showed the consistency between the nomogram-predicted survival and the actual results (Fig. 4B). In addition, the nomogram model had favorable prognostic accuracy for OS through the analysis of the receiver operating characteristic (Fig. 4C). This practical clinical tool may provide more distinct and direct data to assist clinical decision-making and optimization of therapeutic approaches in clinical care (136).

Consolidation therapy. It has been reported that a total of 20-30% of patients with PCNSL relapse within 6 months, even after intensive MTX treatment (113), indicating consolidation therapy is necessary to eliminate minimal residual disease in PCNSL. Until the beginning of this century, WBRT was the only consolidation therapy available for PCNSL. Thereafter, clinical trials investigating various types of consolidation have fit into an emerging concept, which suggests that the treatment of PCNSL is most efficient if HD-MTX-based treatment is followed by a type of consolidation treatment (138).

WBRT. WBRT is an important means of treating PCNSL with a total response rate of 90%; however, the OS has been reported to be only 12-16 months and it can be accompanied

by marked neurotoxicity (139). Radiation-induced neurotoxicity includes progressive severe cognitive dysfunction, ataxia and urinary incontinence. The elderly are also susceptible to the detrimental cognitive side effects of WBRT. In a previous study, neurotoxicity occurred in 19-83% of patients aged >60 years who received WBRT following MTX-based chemotherapy (2). Furthermore, neurotoxicity tends to occur more severely and rapidly in patients with advanced age at the time of treatment (2).

As WBRT is associated with a substantial risk for cognitive impairment, alternative consolidation methods have been used, including reduced-dose WBRT (rdWBRT). A study that used rdWBRT as consolidation therapy reported good PFS and OS rates following treatment (140). Furthermore, a recent study demonstrated that rdWBRT (≤ 23.4 Gy) combined with HD-MTX exhibited no statistical difference in terms of OS and PFS, as compared with higher-dose WBRT, and suggested that patients aged <60 years might benefit from rdWBRT (141). The value of consolidation WBRT and the optimal dose of RT remain controversial, particularly in older patients.

HDT/ASCT. Based on the available data, HDT/ASCT as consolidation therapy for patients with PCNSL is considered an effective and feasible strategy, with less overall neurotoxicity compared with WBRT; however a higher risk of treatment-related mortality has been reported with HDT/ASCT compared with WBRT (142). Conditioning regimens that contain CNS-penetrant agents, including carmustine, thiotepa and busulfan, have exhibited the most encouraging results. In a retrospective study, patients treated with thiotepa-containing HDT/ASCT were found to have a significantly better 2-year PFS (62%) and OS (70.8%); however, the associated toxicity limited their use in elderly patients. Therefore, for selected 'biologically young' patients, MTX-based chemotherapy with HDT/ASCT as consolidation therapy is a viable option (143).

Intensive HD chemotherapy. Intensive HD chemotherapy as consolidation therapy may also be a reasonable option for those patients who respond to first-line chemotherapy, but the advanced age and poor general condition of most patients are major obstacles to this approach. While intensive consolidation may improve outcomes in patients aged <70 years, HD chemotherapy is not an option for the majority of elderly patients with PCNSL (144). A previous study showed no additional benefit of a prolonged consolidation treatment with cytarabine following HD-MTX-based chemotherapy in the elderly (58).

Maintenance treatment. In elderly patients who cannot tolerate consolidation therapy, maintenance treatment may serve as a feasible alternative approach to prolonging remission, delaying relapses and maintaining tumor dormancy. Several available and promising chemotherapy and targeted agents, such as TMZ, procarbazine, lenalidomide and ibrutinib may serve a role in maintenance therapy for PCNSL (145). To the best of our knowledge, there has been no randomized clinical trial conducted proving that maintenance treatment is beneficial in PCNSL.

TMZ, an oral alkylating agent, is known to effectively penetrate the BBB and have a tolerable toxicity profile. It is generally an easily administered drug, given orally for 5 days

for a 4-week cycle. TMZ has been incorporated into induction treatment for elderly patients with PCNSL (10,64). It has been reported that TMZ may be effective as single-agent maintenance therapy against PCNSL in elderly patients to maintain quality of life and functional independence with the best neurocognitive preservation results (65). Notably, a previous study introduced TMZ as a maintenance treatment in elderly patients with promising results (65). It is a potential option for elderly patients with PCNSL, who have achieved CR or PR and wish to avoid WBRT neurotoxicity, particularly those considered unsuitable for ASCT (117).

Salvage treatment of relapsed/refractory (R/R) PCNSL. Despite advances in induction and consolidation regimens, 10-15% of patients with PCNSL have been reported to become refractory to initial treatment and 35-60% relapse within 1-2 years (9,146). The ideal approach to treat patients with R/R PCNSL is unclear.

Continuous intrathecal injection therapy of MTX (CIT-MTX). CIT-MTX has been reported to be a promising therapy not only for patients treated with conventional common therapy, but also those at high risk from HD-MTX. A better prognosis in patients treated with CIT-MTX may be derived from the stable concentration of MTX in the CSF (147).

rdWBRT and HDT/ASCT. HDT/ASCT has been used to treat patients with R/R PCNSL with a 3-year event-free survival of 53% and an OS of 64% (148). In relapsed patients, HDT/ASCT appears to have an equivalent or improved efficacy compared with other salvage therapies; however, the risk of treatment-related mortality is a consideration (85). A previous study suggested that HDT/ASCT and rdWBRT may be associated with white matter abnormalities in patients with PCNSL who have achieved long-term remission, and that patients treated with rdWBRT may be at greater risk (149). Moreover, HDT/ASCT cannot be used to treat frail elderly patients.

Allogeneic hematopoietic cell transplantation (Allo-HCT). Allo-HCT has been studied in R/R PCNSL; however, to the best of our knowledge, the only available data is from two case reports by Atilla *et al* (150) and Varadi *et al* (151). The results of these studies were encouraging, suggesting Allo-HCT might be an alternative option for R/R PCNSL. Evaluating the safety and efficacy of allo-HCT in PCNSL requires further clinical trials, particularly phase III randomized trials.

Chimeric antigen receptor T-cell (CART-cell) therapy. Cumulative data have revealed that immunotherapy with CART-cells provides hope for a high response rate in patients with R/R DLBCL (152). However, clinical trials on CART-cell therapy usually rule out PCNSL because of the occurrence of lethal cerebral edema after CART-cell therapy. A case report from Tu *et al* (152) reported that combination treatment with CD19- and CD70-specific CART-cells may effectively target PCNSL and maintain disease-free survival without inducing cytokine release syndrome or CART-related encephalopathy syndrome, thus indicating that CART-cell therapy may be a potentially promising treatment for patients with R/R PCNS-DLBCL.

Novel agents. Based on new insights into the pathogenesis of PCNSL, novel agents have been introduced to treat PCNSL. These agents, such as ibrutinib (153), tirabrutinib (154), lenalidomide (137), pomalidomide (155) and nivolumab (156), are currently being evaluated both as single agents and in combination with other agents in clinical trials. The incorporation of novel agents into the treatment of PCNSL may enable the application of precision medicine in the treatment of patients with R/R PCNSL.

Bruton's tyrosine kinase (BTK) inhibitor. BTK, a nonreceptor protein kinase, is important for the amplification of B-cell signaling. BTK integrates BCR and Toll-like receptor signaling, linking them to downstream NF- κ B signaling; therefore, it may be considered an attractive candidate for targeted inhibition (4,157). Mutations leading to activation of the NF- κ B signaling pathway, such as mutations in MyD88, CARD11 and CD79, and TNFAIP3 and TBL1XR1 deletions, have been observed in almost all PCNSL cases, thus indicating that NF- κ B activation may serve a role in the pathogenesis of PCNS-DLBCL and could represent a potential therapeutic target (4,157).

Ibrutinib, a small molecule BTK inhibitor, has been identified as a potential novel therapeutic agent for the treatment of PCNSL. A small retrospective study in R/R PCNSL demonstrated the feasibility of ibrutinib treatment, with promising responses reported in several patients (158). Even patients without genomic alterations in the BCR pathway have been shown to respond to ibrutinib (159); however, as a single drug, ibrutinib is prone to drug resistance, limiting PFS. A phase II study on ibrutinib revealed treatment resistance in the absence of a CARD11 mutation and presence of a mutation in the BCR pathway (160). A phase Ib trial investigating ibrutinib monotherapy for 2 weeks, followed by its combination with conventional chemotherapies, including adjusted TMZ, etoposide, doxorubicin, dexamethasone, cytarabine and rituximab, demonstrated a PR rate of 83% prior to the initiation of the combination regimen, with a subsequent CR rate of 86% following combination chemotherapy in the patients with R/R PCNSL (153). Resistance to ibrutinib monotherapy could be overcome through combination regimens with chemotherapy and/or targeted biological agents.

Tirabrutinib is a second-generation, potent, highly selective, irreversible oral BTK inhibitor. A phase I/II study evaluated the safety, tolerability, efficacy and pharmacokinetics of tirabrutinib in Japanese patients with R/R PCNSL, and displayed an objective response rate (ORR) of 64% and PFS of 2.9 months. Furthermore, median OS was not reached, indicating a favorable efficacy of tirabrutinib in patients with R/R PCNSL (154).

Immunomodulatory drugs (IMiDs). IMiDs, such as lenalidomide and pomalidomide, are thalidomide-derived agents with antiproliferative and immunomodulatory properties. These drugs have been tested in recurrent PCNSL. A previous study indicated that lenalidomide may exert cytotoxic effects relevant to PCNSL, including the inhibition of IRF4 and myc pro-survival signals (161). Lenalidomide has been used as a single agent in the treatment of patients with relapsing PCNSL, with two patients achieving CR in a small

retrospective cohort (162). The activity was confirmed in a phase I trial, with 9/14 patients with R/R PCNSL treated with lenalidomide monotherapy exhibiting objective response (163). A phase II study evaluated lenalidomide in combination with rituximab in 50 patients with R/R PCNSL or primary vitreoretinal lymphoma, and found an ORR of 35% (164). Maintenance therapy with lenalidomide alone was recommended to responding patients, and the median PFS and OS were 7.8 and 17.7 months, respectively (164). In addition, a previous study revealed that reduced-dose MTX-based treatment followed by low-dose lenalidomide maintenance was well-tolerated in patients aged ≥ 70 years, and associated with excellent PFS and OS (136). Pomalidomide is a novel immunomodulatory drug with anti-lymphoma activity. The combination of pomalidomide with dexamethasone resulted in an ORR of 48% and a median PFS of 5.3 months (155).

PI3K/AKT/mTOR signaling inhibitors. Mutations and copy number variations of PIK3CA and PTEN have been detected in next-generation sequencing analyses of PCNSL (165,166). These genes are associated with the PI3K/AKT/mTOR signaling pathway, indicating the potential role of this pathway in the pathogenesis of PCNSL (167). PI3K/AKT/mTOR inhibitors have also been used to treat R/R PCNSL. In a formal phase II trial, the first targeted agent investigated, the mTOR inhibitor temsirolimus, was used to treat 37 patients with R/R PCNSL, with an acceptable ORR of 54%, a median OS of 3.7 months, and a poor median PFS of 2.1 months (168). Moreover, in a small retrospective series, the response rate to the PI3K inhibitor buparlisib was even lower (1/4 of patients responded) (169). These findings indicate that PI3K/AKT/mTOR inhibitors may not be appropriate as a single agent for R/R PCNSL treatment.

Notably, it is common for the active PI3K/AKT/mTOR pathway in PCNSL to carry a CD79B mutation (159). In addition, in an ABC-DLBCL model, ibrutinib was reported to achieve a synergistic effect when combined with PI3K/AKT/mTOR inhibitors through concerted inhibition of multiple pathways (170,171).

Immune checkpoint inhibitors. PD-1 is an inhibitory receptor expressed on activated T cells, and its interaction with PD-L1 produces an immunosuppressive activity, protecting tumor cells from antitumor immunity and possibly releasing sPD-L1 from PD-L1-expressing tumor cells. Since immune checkpoint inhibitors that block PD-1 have been reported to be effective in patients with R/R lymphoma, the role of PD-1 inhibitors as a salvage treatment has been emerging in patients with R/R PCNSL. sPD-L1 in the serum may serve as a feasible biomarker for determining a risk-adapted treatment strategy for patients with PCNSL (91).

Nivolumab, an antibody targeting PD-1, and dendritic cell vaccinations have been reported to lead to CR in one case (172). In addition, in a small case series, a response was recorded in four patients with PCNSL treated with nivolumab (156). Low-dose nivolumab has been reported to induce durable CR in relapsed PCNS-DLBCL (173). In summary, PD-1 blockade with nivolumab could be considered an option in the treatment of R/R PCNSL.

Cyclin-dependent kinase (CDK)4/6 inhibitors. The biallelic deletion of CDKN2A has been observed in 44% of PCNSL cases, suggesting that CDKN2A loss may be an early clonal event in PCNSL evolution, raising the possibility of investigating the efficacy of CDK4/6 inhibitors in patients with PCNSL (94).

8. Conclusion

The incidence of PCNSL in immunocompetent elderly patients, particularly men, is increasing. Notably, the symptoms of PCNSL and brain imaging are often non-specific. For the diagnosis of CNSL, imaging-guided stereotactic biopsy is regarded as the gold standard; if stereotactic biopsy is not possible or conclusive, certain biomarkers can help establish a diagnosis. PCNSL has a very poor prognosis in the elderly, even though several prognostic scoring systems have been generated and numerous prognostic markers for PCNSL have been reported. Therefore, the treatment of elderly patients with PCNSL remains challenging. An individualized treatment that aims at prolonging survival while minimizing toxicity is required. It is unlikely that a novel agent could have curative effects as a monotherapy; however, its rational combination with chemotherapeutic agents or its combination with other new drugs may have therapeutic potential. Consequently, patients should be urged to enter clinical trials, whenever possible. Further clinical studies should offer more evidence of optimal doses or combinations of polychemotherapeutic regimens and new drugs in the elderly.

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Authors' contributions

YL is responsible for writing the review. QY revised the review. FZ contributed to finalize the draft. QY and FZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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