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Review

Diagnostic advances and new trends for the treatment of primary central nervous system lymphoma

U. Basso, A.A. Brandes*

Department of Medical Oncology, Azienda Ospedale-Università, Via Giustiniani 2, 35100 Padova, Italy

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Abstract

Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin's lymphoma arising in the brain. Recent increase in its incidence has been noted both in immunocompetent individuals and patients with immunodeficiency. This review will focus on the epidemiology, pathogenesis, diagnosis and treatment of this aggressive extranodal lymphoma in immunocompetent patients. Stereotactic biopsy is usually required for diagnosis, while molecular biology and/or cytofluorimetric analysis may confirm the presence of clonal proliferation in the cerebrospinal fluid (CSF). Methotrexate-based chemotherapy plus whole-brain radiotherapy are the standard treatment for PCNSL and achieve a high rate of complete remissions (CR), but long-term neurotoxicity may heavily compromise the patient's quality of life. The metabolic rate of controversial gadolinium-enhancing lesions on magnetic resonance (MR) scans may be assessed with positron emission tomography (PET), which discriminates radiation necrosis from true recurrence. Withholding radiotherapy in patients achieving CR after first-line chemotherapy is a new and interesting treatment option, while the role of high-dose chemotherapy with stem cell rescue is still uncertain.

Keywords: Primary central nervous system lymphoma; Non-Hodgkin's lymphoma; Chemotherapy; Radiotherapy; Review

1. Introduction

Primary central nervous system lymphoma (PCNSL), known as a distinctive nosological entity since 1974 [1], is a rare form of extranodal lymphoma confined to the brain. In the last three decades, PCNSL has undergone a dramatic increase in incidence and is presently the subject of numerous epidemiological, biological and clinical studies [2–4].

PCNSLs arising in patients with congenital or acquired immunodeficiencies (especially HIV infection) must be differentiated from those affecting immunocompetent individuals because the two forms display different pathogenetic and clinical aspects with a clear-cut difference in prognosis, and thus require different therapeutic approaches. Most immunocompetent patients receive intensive chemotherapy plus radiotherapy because prolonged survival is obtained, albeit at the price of substantial cognitive deterioration. 5-year overall survival (OS) is lower than that of other high grade extranodal lymphomas, and ranges from 25 to 42% according to published data [5,6], the prognosis of PCNSL is therefore still considered poor.

2. Epidemiology

PCNSLs account for 1–6% of all intracranial tumours, and 1–2% of all extranodal lymphomas [2,7]. Some authors report that its increase in incidence in the last three decades exceeds that of gliomas, and the entire group of non-Hodgkin's lymphomas (NHLs) [8,9]; the PCNSL/glioblastoma rate was 1/250 in 1974 and rose to 1/36 in 1980, reaching 1/6 in 1991 [10]. According to the Surveillance, Epidemiology, End Results (SEER) database of the National Cancer Institute [11], PCNSL incidence increased more than 10-fold from 0.025/100 000 in 1973 to 0.3/100 000 in 1991, and the forecast for the year 2000 was 0.5/100 000.

The reasons for this increase are still unknown; environmental or behavioural risk factors have not been

* Corresponding author. Tel.: +39-049-821-5931; fax: +39-049-821-5932.

E-mail address: aabrandes@unipd.it (A.A. Brandes).

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proposed, and the wide availability of computed tomography (CT) and magnetic resonance (MR) neuro-imaging appears to play a minor role. These findings, however, were not confirmed in other areas of the USA [12], Denmark [13], Scotland [14] and Canada [15].

3. Pathogenesis

The Central Nervous System (CNS) is usually considered an 'immunological sanctuary' because it lacks lymphoid tissue, and is virtually inaccessible to circulating lymphocytes. It is believed that trauma or infectious processes may attract peripheral blood lymphoid cells that are stimulated to proliferate locally, and may undergo clonal selection. The rarity of extracranial spread of neoplastic lymphocytes even in the advanced phase of disease, a specific feature of PCNSL, is consistent with the hypothesis that the brain lacks some regulatory mechanisms of lymphoid proliferation that are normally present in peripheral tissues. Indeed, PCNSLs arising in patients with a previous histological documentation of polyclonal inflammatory lesions of the brain have been described [16].

It was proposed that occasional lymphomatous cells generated in other tissues might acquire a preferential 'homing' for brain endothelium, extravasate and proliferate only inside the CNS. However, a comparison of adhesion molecules and other surface antigens expressed by PCNSL and systemic NHLs did not show any significant difference [17,18].

Unlike HIV-related lymphomas, PCNSL of immunocompetent individuals only rarely correlate with Epstein–Barr virus infection [19], and HHV-8 does not seem to have any pathogenetic role [20]. It was recently found that the BCL-6 protein is highly expressed by PCNSL and frequently mutated in its 5′-extremity, while BCL-2 and/or p53 are rarely expressed [21,22]; in addition, the immunoglobulin heavy chain gene of the neoplastic clone undergoes frequent events of somatic mutation. Hence, it has been speculated that PCNSL originates from the subgroup of mature B-lymphocytes that, after an encounter with the antigen, normally reside and proliferate within the germinal centre of secondary lymphoid organs. At present, we do not know which antigenic stimulus (exogenous or endogenous) might trigger what appears to be, at least in its early phase, an antigen-dependent clonal proliferation.

PCNSLs usually exhibit high levels of telomerase, a ribonucleoprotein that prevents the shortening of chromosomal extremities (telomeres), prolonging cell survival. Harada and colleagues [23] have reported a negative correlation between telomerase hyperexpression and both the time to progression (TTP) and OS in 12 patients treated with chemo- and radiotherapy.

In 8–13% of cases, PCNSL affects individuals with a previous or concomitant solid tumour; in these patients, a tumour-dependent immunosuppressive action has been speculated, along with the contribution of the chemo- and radiotherapic treatments [24].

4. Clinical aspects

PCNSL has been described at all ages, but most cases arise in the sixth decade, with a male to female ratio of 1.5 [2]. Because of the high replicative index, the interval between the onset of symptoms and diagnosis is usually short (1–3 months); focal neurological deficits are frequent (motor and/or sensitive) with personality disturbances and behavioural changes (when the frontal lobe is affected), as well as manifestations of intracranial hypertension. Systemic B symptoms are very rare, and epileptic seizures are less frequent than in glial tumours due to the preferential involvement of the white matter and deep structures rather than the cortex [2,25].

The lymphomatous lesion is usually single at diagnosis (up to 70% of cases) and supratentorial, but frequently becomes multifocal in the late phase of disease. In most cases, the site of origin lies in the basal ganglia, the corpus callosus and/or the periventricular subependymal regions. This peculiarity accounts for the frequent liquoral spread of neoplastic lymphocytes, even though cytological examination of the cerebrospinal fluid (CSF) is positive in no more than 40% of patients. Ocular involvement may be found in 15–20% of cases, and causes visual field defects and focal amaurosis, while diplopia is infrequent [26]. Only 7% of PCNSL have an exclusively leptomeningeal localisation [27], while a single and circumscribed involvement of the spine is a very sporadic finding [28].

5. Pathology

Most PCNSLs are histologically high grade and show a B phenotype. In a series of 226 patients Blay and colleagues [29] found that more than 90% fell within groups G (diffuse with large cells) and H (immunoblastic) of the Working Formulation, only 5% were group J (Burkitt), while the remaining were low-grade (small lymphocytic). According to the Revised European–American Classification of Lymphoid Neoplasm (REAL) classification [30], PCNSLs belong to two main categories, diffuse large cells, and high grade Burkitt-like [31]. Large cell CD30/Ki-1$^+$ anaplastic lymphomas, T cell-rich B-lymphomas, true T-phenotype lymphomas [32], and primary Hodgkin's disease of the brain [33] are very rare.

Angiotropism and infiltrating growth are characteristic of PCNSL and have clinical and therapeutic

relevance: the formation of perivascular cuffings of neoplastic cells with subendothelial tear and infiltration [1] seems to confer a predisposition for vascular damage induced by radiotherapy, while the neoplastic lymphocytes invading normal brain parenchyma (protected by an intact blood–brain barrier) are exposed to lower doses of chemotherapeutic drugs and will contribute to local disease recurrence [34].

6. Neuro-imaging

MR scanning is the standard imaging technique for all brain tumours. Most lymphomas appear as nodules with indistinct borders (because of infiltrative growth and vasogenic oedema) with an isointense signal in T1-weighted, pregadolinium images, and a hyperintense signal on T2 scans; they show a characteristic dense and homogeneous incorporation of gadolinium, as a consequence of the local breaking down of the blood–brain barrier [35]. A routine MR of the spine is not unanimously recommended in all patients. Contrast enhancement may be completely lacking in some cases (approximatively 10%), and appears to be an unfavourable prognostic factor because it predicts lower delivery of chemotherapeutic drugs [2,36].

Thallium^{201}-based single photon emission CT (Ta^{201}-SPECT) may be useful to discriminate PCNSL from gadolinium-enhancing infectious lesions because the lymphomatous nodules incorporate the radioactive tracer more intensely, and retain it for a longer time compared with inflammatory tissues; the determination of delayed retention index increases the specificity of Ta^{201}-SPECT up to 100% [37]. Given the high expression of somatostatin receptors shown by lymphomatous cells, indium^{111}-pentetreotide scintigraphy has been very recently proposed as a highly sensitive tool to recognise false complete remissions (CR) after first-line treatments, and for the early detection of systemic spreading of disease [38]. F^{15}-deoxyglucose positron emission tomography (FDG-PET) is a most promising diagnostic technique because PCNSL has a very high cellular density, with an accelerated glycolytic metabolism, and therefore displays a huge concentration of the metabolic tracer, superior not only to normal brain tissue, but also high-grade gliomas [39]. Total body PET has an elevated sensitivity ($>85\%$) in finding asymptomatic localisations of disease in all patients with lymphoma [40]. The appearance of enhancing areas on MR in patients achieving CR with first-line treatments should not be conclusively interpreted as recurrence, as radio-necrotic tissues may also become permeable to gadolinium. In this setting, FDG-PET is considered highly specific ($>90\%$) for differentiating metabolically active neoplastic tissue from 'cold' scar tissue [39,41].

7. Diagnosis and staging

Whenever possible, PCNSL should be diagnosed on stereotactic biopsies, and common causes of immunodeficiency must be promptly investigated. For patients who cannot undergo surgery due to the involvement of deep vital structures, or have an inconclusive biopsy or CSF cytology, a 'radiological diagnosis' may be acceptable for ordinary clinical practice if MR scans are highly suggestive for PCNSL (homogeneous enhancement and periventricular localisation); a confirmatory Ta^{201}-SPECT or FDG-PET is recommended, but not indispensable. These patients, however, should not be enrolled in clinical trials, in order to avoid a possible bias of glial tumours or inflammatory and/or infectious lesions.

The definition of PCNSL implies the absence of systemic lymphadenopathies and other extracranial localisations of disease. Therefore, all PCNSLs are stage I_E according to the Ann Arbor staging system, but large or multifocal masses should be classified as stage IV due to extensive involvement of an extranodal organ.

CSF analysis usually reveals an increase of proteins, and immuno-electrophoresis may show a monoclonal immunoglobulin. Lactate dehydrogenase (LDH) or β2-microglobulin may be elevated while glucose is often normal, except in the presence of diffuse lymphomatous meningitis. While lymphocytic pleocytosis may be frequent, immunohistochemistry usually demonstrates the prevalence of reactive, T-phenotype elements. To discern the presence of rare neoplastic cells in the CSF, molecular analysis of the rearrangement of immunoglobulin heavy chain genes by means of the polymerase chain reaction (PCR) and Southern blotting, or cytofluorimetric analysis of surface immunoglobulin light chains (kappa or lambda restriction) may often be helpful.

Ocular disease must always be accurately assessed by ophthalmological ultrasonography and slit-lamp examination: the lymphomatous cells may infiltrate the retina, the vitreum and/or the anterior chamber bilaterally, while extension to orbit tissues is rare [26]. Some authors [2,42] have questioned the necessity for intensive staging with total-body CT and bone marrow biopsy (plus testicular echography in some centres), given the extreme rarity of systemic NHLs presenting with exclusively neurologic symptoms; moreover, extracranial spread, even in advanced phases of disease, is rare (occurring in less than 7% of cases), and is never the cause of death [2,29].

8. Prognosis

Age $\leqslant 60$ years and good Performance Status are the most important favourable prognostic factors in multivariate analysis, while involvement of the brain stem or

spine, multiple lesions, and increase in CSF protein levels are predictive for a worse outcome [2,5,29,31,43,44]. Ocular extension and high levels of LDH and β2-microglobulin in the CSF do not appear to be significant.

Contrary to other extranodal NHLs, different histological subtypes do not correlate with differences in clinical course and response to therapy, therefore no treatment modification is required [18]. According to Blay and colleagues [29], achievement of a CR after first-line treatment is not a determinant of long-term outcome, while Corn and colleagues [45] reported that patients with CR had a better survival (24 and 11% 4-year OS, respectively).

9. Treatment

PCNSL was treated in the past with radiotherapy alone with the support of steroids, while, at present, most patients receive more or less intensive chemotherapy regimens in association with radiotherapy. These integrated treatment modalities improve survival but, at the same time, a high incidence of severe disability due to neurotoxicity has been reported. To preserve adequate cognitive functions and improve the quality of life, since the early 1990s some centres have proposed chemotherapy alone as first-line treatment and, in patients achieving complete remission, radiotherapy is deferred to the time of relapse.

9.1. Steroid therapy

Patients suspected as having intracranial lymphomatous localisation should not be given steroids before a histological diagnosis is obtained, because the shrinkage of tumour nodules may compromise the execution of the biopsy ('ghost tumour'), and obviously also induce a falsely negative CSF cytology. The anti-oedematous and blood–brain barrier stabilising effects of dexamethasone account for the rapid improvement in neurological symptoms seen after its administration.

Indeed, CRs have been described in patients with PCNSL receiving only steroids [46]; however, disease invariably recurs within few months, and becomes poorly responsive to a second treatment with steroids. The reasons for this resistance to steroid-induced apoptosis are not clear. Mutations of steroid nuclear receptors and/or hyperexpression of the anti-apoptotic protein bcl-2 have been proposed as being responsible, but do not appear to be the main mechanisms [18].

For patients that refuse or cannot be treated with radio-chemotherapy, chronic administration of steroids represents the best option to control the symptoms of disease, but requires strict monitoring of the side-effects [47]. A study evaluating radiotherapy in elderly patients with PCNSL followed by a maintenance therapy with methylprednisolone is ongoing [48].

9.2. Surgery

The infiltrating growth pattern and the frequently multifocal presentation of PCNSL are the main reasons for the disappointing control of disease obtained with surgery alone, with OS never exceeding 3–5 months [49]. As the extension of resection does not improve the prognosis [3,29,43], the neurosurgeon should perform the less invasive stereotactic biopsy that provides adequate material for the pathologist.

9.3. Radiotherapy

Notoriously, PCNSL is remarkably sensitive to irradiation (response rate $>90\%$), but historical trials of patients treated with radiotherapy alone reported that more than 80% relapsed within 10–14 months, with a rapid fatal outcome (OS of 13–16 months, 5-year OS of 3–4%) [4,50].

Due to its frequently multifocal presentation, whole-brain irradiation is mandatory. Standard treatment for newly diagnosed patients at present consists of 40 Gy to the brain with or without an additional boost of 10 Gy on the tumour bed [51]. In patients achieving CR after first-line chemotherapy, irradiation may be delivered at a lower dose ($30+10$ Gy-boost) or, according to modern trends [50], even withheld until the appearance of relapse. Prophylactic irradiation of the spine should be avoided [43,44], unless CSF cytology is positive and high doses of methotrexate (MTX >3 g/m^2) cannot be tolerated [50]. Dose escalation above 50 Gy does not increase the response rate nor prolong the TTP, but worsens neurotoxicity [43,51]. If MR detects one or more disease localisations in the spine, the entire spine must be irradiated.

Memory loss or disabling cognitive impairment may be seen after 1 or 2 years; advanced age and concomitant association with chemotherapy increase the risk [52].

Eye involvement requires irradiation with 35–45 Gy to both ocular compartments; however, the optimal dose is still debated due to the limited experiences reported in the literature; local relapse is not unusual [26].

9.4. Combined radio- and chemotherapy

It is now generally agreed that all patients with PCNSL must receive chemotherapy, and that it should be administered before radiotherapy [4,31,53]; in some centres, however, it has been used to consolidate the remission obtained with radiotherapy [54,55]. Various phase II studies have demonstrated that high-dose

MTX, with or without other drugs, is able to yield high response rates (60–90%) with an OS of 33–45 months (Table 1 and 2), and these results are clearly better than historical reports on radiotherapy alone [56].

It is not known whether PCNSLs have a different intrinsic chemosensitivity compared with systemic NHLs. Were it not to decline rapidly after the first cycles of chemotherapy, the rupture of the blood–brain barrier seen in contrast-enhancing nodules theoretically would also allow a good penetration of the water-soluble drugs [57]. This implies that the hydrophilic drugs, even if active in the first weeks, do not suffice to eradicate the disease, and that chemotherapeutic drugs able to cross an intact blood–brain barrier are indispensable.

9.4.1. MTX-based regimens

Due to its good lymphocytolytic action and high penetration into the CNS if administered at doses >1 g/m^2 [58], MTX is the drug most extensively used in patients with PCNSL [3,4,29] and the results of major clinical trials are summarised in Tables 1 and 2. When injected directly into the subarachnoidal space, it diffuses to the leptomeningeal surface, but very little reaches the deep brain tissue [59]. MTX is usually administered at high dosage (3–8 g/m^2 infused over 4, 6 or 24 h) with various schedules (every 7, 14 or 21 days), with acceptable, but not negligible toxicity. According to Glass and colleagues [60], there are no substantial differences in terms of response rate to MTX if recycling takes place on the 10th or 21st day. It was recently reported that an initial bolus followed by a short 3-h infusion of MTX could determine higher peak plasma levels, and higher concentrations within the CNS compared with a 6-h infusion of an equal dose, with an improvement in the response rate (93.8% versus 58.3%, respectively) [61]. The height of the peak plasma concentration is probably more influential than the total time of exposure in regulating the penetration rate of MTX through the blood–brain barrier.

Intrathecal injection is seldomly used today due to the high risk of local toxicity (chemical meningitis), and is justified only following the demonstration of CSF involvement, or in the presence of contra-indications to the use of intravenous MTX at doses >3 g/m^2. In fact, at these doses MTX reaches CSF concentrations that are superior to the threshold level for therapeutic activity (10 μM) [62].

Glass and colleagues reported an 88% response rate in 25 patients that received 1–6 cycles of 3.5 g/m^2 MTX followed by whole brain radiotherapy, with an OS of 33 months [60]. DeAngelis and colleagues [44] treated 31 patients with 1 g/m^2 MTX plus intrathecal MTX followed by 3 g/m^2 Ara-C and radiotherapy (40 Gy$\pm$14 Gy boost). A median OS of 42 months was obtained and later confirmed [5], and 7 patients were still disease-free after 5 years of follow-up. DFS was 40.3 months, 4-fold that previously obtained in another series of patients treated with radiotherapy alone at the same centre (10 months).

These same authors [63] recently proposed a more intensified scheme consisting of five doses of 3.5 mg/m^2 MTX plus intrathecal MTX, in association with vincristine and procarbazine. 52 patients were enrolled in this study, but only 30 received RT (45 Gy, with no boost), while 35 were consolidated with two cycles of high dose Ara-C. OS reached 60 months, and though a comparison with the former study [44] is limited by the shorter follow-up, 2-year OS is better (83% versus 53%). Haematological toxicity was important (Grade 3–4 in 59% of patients). Performance status and age were strongly prognostic; patients $\leqslant 60$ years fared extremely well, and at the time of publication had not yet reached the median DFS and OS, while patients >60 years lived on average 32 and 33 months with and without radiotherapy, respectively. The authors question the role of radiotherapy in this older cohort is questioned because most irradiated patients died of leucoencephalopathy without histological evidence of relapsed disease.

Herrlinger and colleagues [64] treated 21 patients with a similar protocol (without intrathecal MTX) and obtained a 67% CR with an OS of 23 months; severely symptomatic white matter changes developed in 66% of the 15 examinable patients.

In a retrospective analysis of the outcome of 226 PCNSLs treated with various chemotherapy protocols followed by radiotherapy, Blay and colleagues [29] confirmed the superiority of the regimens containing high dose MTX and/or Ara-C, both in terms of response rate and survival; multivariate analysis showed that high dose MTX was a positive and independent prognostic factor for survival.

When MTX is given at high doses, the risk of acute and late neurotoxicity is considerable and potentiated by radiotherapy. After a period of 8–14 months, some patients develop a progressive dementia, with ataxia and urinary incontinence; MR shows cortical atrophy, white matter density abnormalities, and *ex-vacuo* dilatation of ventricules [65]. Blay and colleagues estimated that the risk of delayed neurotoxicity induced by radio- and chemotherapy was 26% at 6-year follow-up [29]. In 46 patients treated with MTX (1 g/m^2 on days 1 and 8) and radiotherapy, O'Brien and colleagues reported serious cognitive dysfunctions in 13% (50% fatal) [66]; in this study OS reached 33 months.

Intrathecal drug delivery, age >60 years and previous radiotherapy are the major risk factors of late neurotoxicity [56]. Radiotherapy damages the endothelium and the walls of cerebral vessels, thus augmenting the permeability of MTX and other drugs, and probably also reducing the oxygen supply to the highly aerobic nervous tissue [67]. It has been reported that patients showing a radiological CR may manifest focal symptoms

Table 1
Combined treatments for PCNSL

Authors	Pts (age)	Protocols	CR + PR (%)	PFS	OS% (at 5 yr)	OS (months)	Toxicity (% of pts)
Nelson [51]	41 (27 ⩾ 60 yr)	Rt (40 Gy + 20 Gy boost) 9 pts Rt + Ct (various schemes)	81 (62 CR, 19 PR)	NR	28 (at 2 yr)	12.2	1 (2.4) fatal leucoencephalopathy, 1 (2.4) skin toxicity G4, 4 (9.8) sepsis in pts non-receiving Ct.
Glass [60]	25 (m 61 yr, r 27–80 yr)	3.5 g/m^2 MTX for 1–6 cycles + Rt	88	NR	20	33 (42.5 in R pts)	2 (8) pts with serious cognitive impairment.
DeAngelis [44] Abrey [5]	31 (m 59 yr)	1g/m^2 MTX for 2 cycles + 12 mg IT-MTX (intra-Ommaya) for 6 doses + 3 g/m^2 Ara-C for 2 cycles + Rt	87 (all CR)	40.3 months	22.3	42	10 (32.2) pts with serious neurotoxicity, fatal in one third of cases.
Abrey [63]	52 (m 65 yr, r 27–89 yr)	Vincristine and 3.5 g/m^2 MTX every other week for 5 cycles + 12 mg IT-MTX (intra-Ommaya) on alternate weeks, procarbazine 100 mg/m^2/daily during first, third and fifth week of MTX + (only 30 pts) Rt + (only 35 pts) 3 g/m^2 Ara-C for 2 days×2 cycles	94 (87 CR)	Not reached at the time of publication	83 (at 2 yr)	60 (all pts) 32 (pts > 60 yr receiving Rt) 33 (pts > 60 yr not receiving Rt)	31 (59.6) pts with G3-4 haematological toxicity, 5 (9.6) deep venous thrombosis, 3 (5.7) G2 mucositis, 2 (3.8) G3 nephrotoxicity, 2 (3.8) sepsis, 2 (4) procarbazine-related rush. 13 (25) delayed neurotoxicities.
O'Brien [66]	46 (m 58 yr, r 25–76 yr)	1g/m^2 MTX for 2 cycles + Rt	95 (82 CR, 13 PR)	NR	62 (at 2 yr) (95% CI: 47–77)	33	Neurotoxicity in 6 (13) pts in CR, 1 (2) fatal sepsis.
Lachance [34]	6 (5 ⩾ 60 yr, r 49–65 yr)	CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for 2–4 cycles + Rt	66 (all CR)	NR	NR	8.5	NR
O'Neill [68]	46 (m 63.5 yr, r 24–75 yr)	CHOP for 2 cycles + Rt + 2 cycles of high-dose Ara-C	63 (33 CR, 30 PR)	11% at 36 months	14 (at 3 yr)	10.3	2 (4.3) fatal pulmonary haemorrhages and 2 (4.3) fatal sepsis.
Schultz [70]	52 (34 ⩾ 60 yr)	CHOD (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 on day 1, dexamethasone 6 mg/m^2 for 5 days) for 2–3 cycles ±12 mg IT-MTX twice a week + Rt	59 (38 CR, 21 PR)	34% at 24 months	42 (at 2 yr)	16.1	30 (57) pts with G3-4 haematological toxicity, 1 (1.9) fatal sepsis, 1 (1.9) fatal pulmonary embolism.
Glass [71]	18 (m 57 yr, 27–74 yr)	M-CHOD (CHOD + 3.5 g/m^2 MTX) for 1–7 cycles + Rt	83 (72 CR, 11 PR)	19.5 months (all pts) 37.5 months (in R pts)	NR	25.5 (m) (42,5 in R pts)	2 (11) delayed neurotoxicities, 1 (5.5) brain haemorrhage, 2 (11) deep vein thrombosis, 1 (5.5) hepatotoxicity, G3-4 haematological toxicity in 19 out of 50 cycles, 3 (16) pts with neutropenic fever.
Bessel [72]	34 (m 59.5 yr, r 32–72 yr)	BVAM (BCNU, vincristine, MTX and Ara-C) or CHOD/BVAM + Rt	NR	NR	33 95% CI: 14–52)	NR	3 (8.8) treatment-related deaths, 16 (47) pts with G4 neuropathy.
Dent [73]	7 (m 47 yr, r 25–78 yr) (2 systemic NHLs)	ProMACE/MOPP (procarbazine, MTX, doxorubicin, cyclophosphamide, VP-16, mechlorethamine, vincristine and prednisone) for 3–4 cycles + Ara-C and IT-MTX + Rt	86 (all CR)	NR	23.3	23,3	1 (14.3) pt with fatal pneumonia, 2 (28.5) pts with G3-4 thrombocytopenia.
Mead [69]	53 (m 57 yr, r 22–70 yr)	Rt + CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for 1–6 cycles (38 pts) versus Rt alone (5 pts)	NR	12 months versus 12 months	28 (at 3 yr) versus 29 (at 3 yr)	14 versus 26	No G3-4 haematological toxicity, frequent neurotoxicity.

(continued)

Table 1 (*continued*)

Authors	Pts (age)	Protocols	CR + PR (%)	PFS	OS% (at 5 yr)	OS (months)	Toxicity (% of pts)
Brada [74]	31 (m 51 yr, r 18–72 yr)	MACOP-B or MACOP modified (MTX, doxorubicin, cyclophosphamide, vincristine, prednisolone) for 1–12 weekly cycles + Rt	89 (67 CR, 22 PR)	32 months	34	23	3 (9.6) pts with severe neurotoxicity, 2 of whom were relapsing, 21 (67.7) with G3-4 haematological toxicity, 15 (48.3) with septic fever.
Shibamoto [55]	23 (m 57 yr, r 24–77 yr)	Rt + VEPA (vincristine, cyclophosphamide, prednisolone and doxorubicin) every month for a maximum of 6 cycles	96 (all CR)	NR	23 (32 if >4 cycles)	25 (34 if >4 cycles)	9 (39) pts with neurotoxicity, 7 of whom in CR.
Chamberlain [54]	16 (m 52 yr, r 11–65 yr)	oral hydroxyurea concomitant with Rt + adjuvant PCV (procarbazine, cyclophosphamide and vincristine) for 1–6 cycles	100	NR	NR	41	No late neurotoxicity in CR pts.

MTX, methotrexate; PCNSL, primary central nervous system lymphoma; NHL, non-Hodgkin's lymphomas; G, grade; m, median; yr, years; r, range; i.a., intra-arterial infusion; i.v., intravenous infusion; IT, intrathecal infusion; pts, patients; CR, complete remission; PR, partial remission; DFS, disease-free survival; PFS, progression-free survival; OS, median overall survival; R, responsive patients (CR + PR); NR, not reported; Rt, radiotherapy; Ct, chemotherapy.

Table 2
First-line chemotherapy in PCNSL

Authors [Ref.]	Pts (Age)	Protocols	CR + PR (%)	PFS	OS% (at 5 yr)	OS (months)	Toxicity (% of pts)
Cher [81]	11 (m 65 yr, r 46–84 yr)	8 g/m^2 MTX every 10 days for 3 cycles, 3.5 g/m^2 every 4 weeks for 3 cycles, then 3.5 g/m^2 every 3 months until PD	90 (81 CR, 9 PR)	NR	NR	NR	No late neurological toxicity.
Guha-Thakurta [82]	31 (m 63 yr, r 35–87 yr)	8 g/m^2 MTX every 15 days until CR, then every 3 months until PD	100 (65 CR, 35 PR)	17 months (26 months in CR pts)	63 (at 2 yr)	30	No late neurological toxicity.
Siobhan [83]	10 (all >60 yr, m 72.5 yr)	8 g/m^2 MTX every 2 weeks for 3 cycles, then 3.5 g/m^2 every 4 weeks for 3 cycles, then 3.5 g/m^2 every 3 months for 2 cycles	90 (60 CR, 30 PR)	18 months (18.5 in CR pts)	NR	36 (43 in CR pts)	No sepsis, 2 (20) G2 mucositis, 2 (20) urinary tract infection, 2 (20) mild elevation of liver transaminases.
Freilich [76]	13 (mean 74 yr, r 54–89 yr)	High-dose MTX alone (4 pts) + thiotepa (5 pts) or + Ara-C (4 pts)	92 (77 CR, 15 PR)	60% at 20 months	NR	30	1 (7.7) pt with delayed neurotoxicity.
Sandor [77]	14 (m 57 yr, r 34–69 yr)	8.4 g/m^2 MTX + 35 mg/m^2 thiotepa and vincristine i.v. + IT-Ara-C and IT-MTX	100 (79 CR, 21 CR)	69% at 54 months	68.8 (at 4.5 yr)	Not reached at the time of publication	3 (21.4) neurotoxicities, G 3-4 haematological toxicity in 50% of cycles.
Neuwelt [78]	16 (average 53.7 yr) + 11 treated after Rt	15 mg/kg i.v. cyclophosphamide, i.a. 25% mannitol immediately before 2.5 g MTX, on days 1 and 2 + oral procarbazine (100 mg/daily) and dexamethasone (24 mg/daily) for the following 14 days for 3 or more cycles	100 (81 CR, 19 PR) 100 (54 CR, 46 PR)	NR NR	NR NR	44 17.8	5 (16.6) sepsis, 2 of which (6.6) fatal, 2 (6.6) ischaemic strokes, 6 (20) deep vein thrombosis.
McAllister [6]	74 (38 ⩾ 60 yr)	High-dose MTX i.a. + VP-16 i.v/i.a. and cyclophosphamide i.v for 2 days + procarbazine and dexamethasone for 14 days ± G-CSF every 28 days for a maximum of 12 cycles	80 (65 CR, 15 PR)	48% at 24 months	42	41	No late cognitive impairment in the pts achieving CR, 4 (5.4) deaths due to sepsis, transitory neurological deficits in 8 (10.8) pts, ictus in 5 (6.8) pts.

G-CSF, granulocyte-colony stimulating factor; G, grade; PCNSL, primary central nervous system lymphoma; m, median; yr, years; r, range; i.a., intra-arterial infusion; i.v., intravenous infusion; IT, intrathecal infusion; pts, patients; CR, complete remission; PR, partial remission; DFS, disease-free survival; PFS, progression-free survival; OS, median overall survival; R, responsive patients (CR + PR); NR, not reported; Rt, radiotherapy; Ct, chemotherapy.

that are often correlated with the primary site of disease, probably because of a primary vascular damage induced by the locally invasive lymphomatous cells.

9.4.2. Other chemotherapy regimens

Cyclophosphamide and anthracyclines are poorly efficacious in PCNSL, mainly because they do not efficiently cross the blood–brain barrier. In fact, CHOP and CHOP-like schemes did not show improved survival compared with radiotherapy alone, and seem to be associated with an increased risk of meningeal recurrence [34,68,69].

In the Radiation Therapy Oncology Group (RTOG) protocol 88-06 [70], two or three cycles of cyclophosphamide, doxorubicin, vincristine and dexamethasone (CHOD) followed by radiotherapy (41.4 Gy + 18 Gy boost) obtained 59% of responses (38% CR); OS reached 16.1 months and was not statistically different from that observed in a preceding series of patients treated with radiotherapy alone (RTOG protocol 83-15) [45].

Other authors administered CHOD with high-dose MTX (M-CHOD) [71], or other schemes such as BCNU, vincristine, MTX and Ara-C (BVAM) or the hybrid CHOD/BVAM [72], or procarbazine, MTX, doxorubicin, cyclophosphamide, VP-16, mechlorethamine, vincristine and prednisone (ProMACE/MOPP) [73], followed by radiotherapy, but none obtained better results compared with high-dose MTX alone.

Using third generation schemes (such as MTX, doxorubicin, cyclophosphamide, vincristine and prednisolone with or without bleomycin (MACOP or MACOP-B)) followed by standard radiotherapy, Brada and colleagues [74] reported slightly better results, with an OS of 23 months. Shibamoto and colleagues [55] administered vincristine, cyclophosphamide, prednisolone and doxorubicin (VEPA) after radiotherapy (50–60 Gy), for a maximum of six cycles; the overall CR rate was 95%, and OS reached 25.5 months. 30% of patients unfortunately experienced treatment-related neuropsychological dysfunctions in the absence of relapse.

Ara-C is active against PCNSL, but high doses (>3 g/m^2) are needed to reach active concentrations within the CNS [75], where cytosine deaminase is less expressed than in peripheral tissues and thus the permanence of the active phosphorylated metabolites is prolonged [58]. Ara-C has frequently been used in patients with PCNSL [44,63,64], and the benefit of adding it to multi-drug combinations was confirmed by Blay and colleagues [29].

Thiotepa is an alkylating agent usually injected intrathecally to treat lymphomatous or carcinomatous meningitis after failure of MTX and Ara-C. When administered intravenously, it rapidly diffuses to the brain (plasma/CSF ratio = 1), and appears to be effective in PCNSL [76,77].

Nitrosoureas and procarbazine have also been administered in patients with PCNSL with favourable results [72,78–80]. Adjuvant PCV (CCNU, procarbazine, and vincristine) has been used after radiotherapy concomitant with hydroxyurea as radiosensitiser, with an OS of 41 months, and no severe toxicity [54].

9.5. New therapeutic approaches: chemotherapy alone

The favourable results obtained with the addition of chemotherapy to radiotherapy, and the concern for late neurotoxicity have induced some authors to propose deferring radiotherapy in patients achieving CR after first-line chemotherapy with high-dose MTX. Although only applied to date in small, single-centre series, this innovative approach seems promising (Table 2). Withholding radiotherapy might be particularly useful in both young patients considering their chances of longer survival, and in older ones, because of their higher risk of cognitive impairment [52].

Still to be addressed is the role of a maintenance chemotherapy with low MTX doses or prolongation of the glucocorticoid uptake. Cher and colleagues [81] treated 11 patients (median age 60.5 years) with high-dose MTX (8 g/m^2 every 10 days for three cycles, 3.5 g/m^2 every 4 weeks for three cycles, and then 3.5 g/m^2 every 3 months until recurrence) and obtained nine CR (82%) with modest nephrotoxicity, negligible haematological toxicity, and no neurological complications; furthermore, 1 relapsed patient achieved a second CR with high-dose MTX alone. In a more recent study [82] of 31 patients treated with high-dose MTX (8 g/m^2), the CR rate was 65% (plus 35% partial remissions (PR)) but follow-up was short and only 2-year OS was reported (63%). Follow-up MR scans of patients in CR were negative for MTX-related neurotoxicity, and all tests for cognitive functions, quality of life and social integration showed no important impairment.

A retrospective review of 10 elderly patients (80% >70 years) treated with this intensive MTX-based protocol [83] found no Grade 4 toxicities and, most importantly, no chemotherapy-related neurological deterioration. Although 3 patients (30%) required a dose reduction or delay due to a decline in the glomerular filtration rate, CR was documented in 6 patients (60%) who reached an OS of 43 months; 2 of them achieved a second CR with high-dose MTX.

Freilich and colleagues [76] treated 13 patients, all >50 years, with high-dose MTX alone (4 patients) or followed by thiotepa (5 patients) or Ara-C (4 patients), and observed a response rate $>90\%$, with an OS approaching 31 months; there was only 1 case of severe neurotoxicity. Sandor and colleagues [77], instead, administered high-dose MTX (8.4 g/m^2) together with thiotepa and vincristine (plus intrathecal MTX and Ara-C) to 14 patients, and obtained 79% CR and a

4.5-year OS of 34.3%, with 3 cases of permanent neurological impairment.

Cheng and colleagues [79] and Korfel and colleagues [80] proposed the association of high-dose MTX with nitrosoureas; however, the results of their studies are not clearly evaluable because patients with intracranial localisations of systemic NHL were included.

At the time of writing this paper, less than 190 patients have been treated with chemotherapy-only regimens (Table 2). The findings of multicentre randomised trials are awaited to clarify whether deferring radiotherapy in patients responsive to first-line chemotherapy allows them to maintain a better quality of life without reducing the possibility of local control of disease. According to Abrey and colleagues [63] and Siobhan and colleagues [83], deferring radiotherapy indefinitely did not impact the survival of patients aged >60 years, because the high incidence of severe neurological deterioration provoked by radiotherapy is balanced by the uncertain survival advantage. Indeed, the elderly are much more sensitive to cranial irradiation than young patients [52] for whom radiotherapy remains a valid therapy option, even when employed as a salvage therapy after one or more chemotherapy regimens.

9.6. Blood–brain barrier disruption and intra-arterial chemotherapy

An intra-arterial infusion of 25% mannitol solution exerts a potent osmotic action on the brain microcirculation, probably consisting in a shrinkage of the endothelial cells with a loosening of their tight junctions, the so-called phenomenon of 'disruption' of the blood–brain barrier. In patients receiving MTX after blood–brain barrier disruption with intra-arterial mannitol, the serum/ventricular CSF ratio is 3- to 4-fold greater than that in patients administered MTX alone [84].

In a pilot study conducted on 30 patients with PCNSL [78], 2.5 g MTX was given concomitantly with intra-arterial mannitol, followed by intravenous cyclophosphamide and oral procarbazine, for three or more cycles. 13 patients had previously been treated with radiotherapy before chemotherapy; in the other 17 patients, irradiation was deferred until the appearance of relapse. In this latter group, there were 13 CR and three PR, with a remarkable OS of 44.5 months, clearly superior to the 17.8 months observed in the former group. This same centre very recently [6] treated 74 new patients with a similar protocol containing also intravenous or intra-arterial etoposide, and both the high response rate (80%) and the appreciable OS (40.7 months) were confirmed. There were three premature deaths due to sepsis, but no cognitive worsening was recorded in the follow-up of the patients who remained disease-free.

Hence, treatments with osmotic blood-barrier disruption seem promising both for their efficacy and safety, but are available only in a very few centres. Further studies, however, are needed to improve some technical aspects before recommending their administration on a large scale.

9.7. Second-line chemotherapy

Approximately 50% of the patients who achieve CR after chemo- and radiotherapy experience disease relapse within 1–2 years. Recurrence may be limited to the initial site of disease (65%); less frequently, it is multifocal, while concomitant extracranial localisations are quite sporadic ($<7\%$) [2,29]. Approximately half of the patients who are disease-free at 5 years are expected to relapse within 13 years of the initial diagnosis [49].

Treatment of relapses is problematic, but it has been demonstrated that second-line chemotherapy may obtain important response rates with a prolongation of survival [60,63,78,81]. In a retrospective analysis of 173 patients who were enrolled in various clinical trials and progressed or relapsed after different radio- and chemotherapy regimens, Reni and colleagues [85] found that survival was clearly superior when a second-line chemotherapy was applied (14 to 2 months, respectively); response rates ranged from 45 to 85% in the single series, with a remarkable 20–30% of second CR being observed. The most important prognostic factors for survival were second-line chemotherapy, long interval before relapse and addition of further radiotherapy, with age being less important. Unfortunately, due to the wide range of chemotherapeutic schemes employed, the most active one could not be identified. Systemic localisations are usually treated with standard systemic lymphoma regimens, but patients usually die of refractory intracranial disease. Herrlinger and colleagues [86] administered PCV to 7 patients who recurred after high-dose MTX $\pm$ radiotherapy; four CR and two PR were achieved, with a 1-year DFS of 57% and no important haematological toxicity. Recently, a few patients with recurrent PCNSL were treated with new drugs such as temozolomide [87], topotecan [88], and anti-CD20 antibodies (rituximab) [89]; the preliminary results are promising, and further investigation is warranted.

10. High-dose chemotherapy with stem cell rescue

Only anecdotal reports of high-dose chemotherapy with peripheral stem cell transplantation [90] were available before Sussain and colleagues [91] reported the results of their experience on 22 patients with refractory or recurrent disease after high-dose MTX or multiagent chemotherapy $\pm$ radiotherapy (Table 3). 3-year DFS and OS were 53 and 63.7%, respectively; at a

Table 3
High-dose chemotherapy with autologous stem cell rescue for PCNSL

Authors [Ref.]	Pts (Age)	Protocols	CR + PR (%)	EFS (% at 3 yr)	OS% (at 3 yr)	Long-term CR (% of pts)	Toxicity (% of pts)
Sussain [91]	22 (m 53 yr, r 27–64 yr) (10 relapsed and 12 refractory to high-dose MTX-based treatments)	2 cycles of high dose Ara-C + VP-16 (CyVE) + G-CSF + 250 mg/m^2 thiotepa on days −9 through to −7, 10 mg/kg (total dose) busulfan on days −6 through to −4, 60 mg/kg cyclophosphamide on days −3 and −2) autologous stem cell transplantation	81 (72 CR, 9 PR)	53	64	12 pts (54) at a median follow-up of 41.7 months	All pts experienced G4 hsematological toxicity, 2 (9) deaths during CyVE, 1 (4.5) death for haemorrhage, 19 infectious complications (86), 7 (31) severe neurotoxicities, with 2 (9) deaths.
Marks [92]	6 (all <65 yr) (newly diagnosed)	High-dose MTX + Ara-C + thiotepa + high-dose BCNU and thiotepa + autologous stem cell transplantation + hyperfractionated Rt (45 Gy)	66 (all CR)	NR	NR	NR	No extra-haematological G3–4 toxicities.

G, grade; MTX, methotrexate; PCNSL, primary central nervous system lymphoma; G-CSF, granulocyte-colony stimulating factor; m, median; yr, years; r, range; pts, patients; CR, complete remission; PR, partial remission; EFS, event-free survival; OS, median overall survival; NR, not reported; Rt, radiotherapy; Ct, chemotherapy.

median follow-up of 41.5 months, 12 of 16 CR patients were still disease-free. Toxicity was high: 7 patients experienced severe neurological dysfunction (fatal in 2 cases) and, comprehensively, 5 of 7 patients aged >60 years died because of the treatment. High-dose chemotherapy was also applied by Marks and colleagues [92] to consolidate the CR achieved with high-dose MTX plus high dose Ara-C and thiotepa, but the paucity of the sample and the brief follow-up preclude a reliable evaluation of this approach. Further studies are needed to verify whether these extremely intense regimens are able to impact upon the survival of patients with PCNSL.

11. Conclusions

PCNSL is best treated at centres with recognised experience in the management of brain tumours. The main innovations in their diagnosis, prognosis and therapy that emerge from recently published clinical studies [4,6,31,50,53,63,82,85,91] may be summarised as follows:

a. Never administer steroids to patients suspected to have cerebral lymphoma (primary or secondary) before performing a diagnostic biopsy and lumbar puncture, unless symptoms and/or radiological signs of intracranial hypertension are present. After diagnosis, steroids are an indispensable component of chemo- and radiotherapic treatments.
b. PCNSL is diagnosed histologically. Cytological examination of CSF may substitute for the biopsy if it is contraindicated; in this case, cytofluorimetric analysis of surface immunoglobulin light chains, or immunohistochemical/molecular analysis of immunoglobulin heavy chain genes should be carried out to demonstrate the presence of clonal populations.
c. Staging must always include ophthalmological evaluation (with slit-lamp examination), and exclude HIV infection and other primary or secondary causes of immunodeficiency. Total-body CT may be waived if symptoms or signs suggestive of systemic localisation of disease are absent, or perhaps substituted by total body PET.
d. Surgery is performed only for diagnosis; extensive resection does not improve survival.
e. Chemotherapy is the best initial treatment for all patients and must contain MTX, preferably at doses >3 g/m^2, and possibly, but not necessarily, high-dose Ara-C. The optimal number of cycles, and the possible role of a maintenance chemotherapy have not yet been elucidated. In the absence of a documentated meningeal and/or CSF diffusion of neoplastic cells, intrathecal infusion of MTX should be avoided, and is considered superfluous when the intravenous doses of MTX are >3 g/m^2. MTX should never be administered after the radiotherapy.
f. Radiotherapy to the whole brain must not exceed 40–45 Gy (50 Gy to the tumour bed) and must be performed after chemotherapy. According to some authors, patients achieving CR after intensive chemotherapy protocols may be spared radiotherapy unless they recur; this currently favoured approach still needs to be validated in phase III trials. Radiotherapy to the spine is justified only to treat spinal localisations of disease, or when the CSF is positive and the patient cannot receive high-dose MTX.
g. No agreement exists regarding the best second-line treatment, but it was shown that various combinations of chemotherapeutic drugs can induce a second CR, with significant improvement not only in the quality of life, but also the survival of relapsing patients. The role of high dose chemotherapy with stem cell rescue still awaits definition.
h. Withholding radiotherapy at first diagnosis and even at the time of relapse appears be a valid option for elderly patients, in whom the inevitable neurotoxicity is balanced by a controversial gain in survival.
i. Any well-conducted clinical trial must comprehend a long-term assessment of the quality of life, and the neuropsychological functions of the patients.

The successful elucidation of the currently most debated issues (best chemotherapy regimen, no brain irradiation in complete responder patients, and second-line treatment) depends on well-designed, multicentre and possibly randomized trials. In this setting, the rigorous application of inclusion criteria (histological diagnosis, no other concomitant tumours, complete staging work-up), and appropriate follow-up duration [93] undeniably constitute the premises for reliable estimations of survival parameters.

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