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Primary Central Nervous System Lymphoma

Mihnea Zdrenghea, Delia Dima, Ciprian Tomuleasa,
Horia Bumbea and Cristina Bagacean

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Abstract

Although non-Hodgkin's lymphoma (NHL) is a frequent cancer worldwide, primary central nervous system (CNS) lymphoma (PCNSL) is a rare presentation, with an incidence of less than 0.5 per 100,000 persons-years in the western world. In the vast majority of cases, it has the histology of a diffuse large B-cell lymphoma (DLBCL) and is a hardly curable disease with high relapse risk. Therapeutic options are limited by blood-brain barrier penetration of drugs and because of its low-incidence high-grade evidence from large studies is lacking, current management being based on reports on rather small cohorts. The current standard first-line treatment for PCNSL consists of high-dose methotrexate (HD-MTX) in combination with a variety of drugs and consolidation whole-brain radiotherapy, the latter being progressively replaced by chemotherapy. For patients relapsing after first-line treatment, intensive chemotherapy with autologous stem cell support is a feasible and relatively safe salvage therapy. In the present chapter, we briefly discuss primary central nervous system lymphoma management and review current therapeutic options and evidence-based recommendations. We discuss the role of whole-brain radiotherapy (WBRT) and new prospects to avoid this side effect-ridden approach. Also, we will look at new therapeutic approaches currently under investigation, including immunotherapy.

Keywords: PCNSL, primary cerebral tumor, aggressive lymphoma, whole-brain radiotherapy, blood-brain barrier

1. Introduction

One of the deadliest hematologic malignancies of our days, primary central nervous system (CNS) lymphoma (PCNSL), is a major unmet in oncology, with an outcome similar to that of acute leukemia, and a commonly used phrase to coin this poor prognosis states that the majority of patients die of their disease.

Of all primary CNS tumors, PCNSL represents a small percentage of around 4% in the United States [1]. With the exception of rare, anecdotal reports of primary CNS Hodgkin's lymphoma, they are extranodal non-Hodgkin's lymphomas (NHLs), the vast majority being of aggressive, diffuse large B-cell type. According to the European Cancer Observatory's (EUCAN) national estimates report on cancer incidence in Europe, the mean EU 27 incidence in 2012 of brain and CNS tumors was of 6.9 per 100,000 persons, ranging from a high of 11.9 in Sweden to a low of 5 in Hungary, allowing for an estimate of around 0.3 new cases of PCNSL per 100,000 persons in 2012 across the EU.

The percentage of PCNSL presentation among all NHL cases is estimated at 2–3% [2]. More than 90% of PCNSL are diffuse large B-cell lymphomas (DLBCLs), other histological forms encountered being Burkitt's and lymphoblastic lymphomas (5%) and marginal zone and T-cell NHL (3%) [3]. These low-incidence figures underscore the difficulty in patient accrual for clinical studies and, implicitly, for the formulation of evidence-based recommendations. Therapeutic advance is thus difficult, in a tumor ranked as one of the deadliest lymphomas, with a present estimated cure rate lower than 50%. The 2016 World Health Organization classification update of lymphoid neoplasms lists primary DLBCL of the central nervous system as a distinct entity among mature lymphoid neoplasms [4].

The etiology of PCNSL is unknown, as with the majority of cancers. However, increased incidence is observed in HIV infection, PCNSL being, with 15–20% of all cases, one of the favorite presentations of AIDS-related lymphomas. The high incidence of PCNSL in AIDS patients declined with the advent of the contemporaneous highly active antiviral therapy, and an improvement in its prognosis was noted, as well [2]. An increased incidence is also observed in other immunosuppressed patients, notably in recipients of allogeneic transplantation on long-term immunosuppressive therapy. Although the spread of HIV infection offered a tempting explanation for the continuous increase in PCNSL (and NHL overall) incidence reported over the last decades of the twentieth century, the trend remains positive even after subtracting AIDS patients. As with many cancers, incidence of PCNSL increases with age, and it is estimated that approximately a half of the patients are over 65 years of age, with limiting implications in intensive management options. The disease favors men, with a 2:1 male to female gender ratio.

In the next sections, we will review the pathogenesis and diagnostic workup, as well as the current treatment paradigm for PCNSL. Novel therapeutic approaches currently under investigation will be also discussed

2. Pathobiology of PCNSL

Primary central nervous system lymphoma (PCNSL) has been historically known by many other names, including reticulum cell sarcoma, diffuse histiocytic lymphoma, and microglioma. The proliferation of names reflects initial uncertainty about the cell of origin. PCNSL is in the overwhelming majority of cases an aggressive extranodal diffuse B-cell lymphoma. The cell of origin of the tumor obviously belongs to the lymphoid lineage, but the lympho-

matous histology of PCNSL was established only during the 1970s. Before that, PCNSL was regarded as a microglioma or reticulum cell sarcoma. The lack of a precise histological definition of the disease did not, however, impact on therapy outcomes in that era, as the sole therapeutic modality employed for brain tumors, besides surgery, was brain radiotherapy [5]. Evolution in the understanding of the pathobiology of PCNSL lagged behind that of nodal lymphomas because of the dame reasons that hampered therapeutic evolution, namely, the rarity of the tumor.

PCNSL is, in an overwhelming majority of approximately (95%) of cases, an aggressive extranodal diffuse large B-cell lymphoma (DLBCL) [6]. Other histologies have been described including lymphoma of T-cell origin, lymphoblastic lymphoma, Burkitt lymphoma, mucosa-associated lymphoid tissue (MALT), and marginal zone lymphoma (MZL) [7, 8]. Studies have generally focused on the features of primary DLBCL arising in the brain. Based on overexpression of B-cell lymphoma 6 (BCL-6) protein and V(H) gene sequence mutational status, PCNSL was thought to be of germinal center (GC) origin [9–11]. More recent immunohistochemical studies have shown that at least 95% of cases stain positive for MUM-1, regardless of their BCL-6 status; therefore, the majority have an activated B-cell (ABC) profile [12].The immunoprofile association with clinical outcome was evaluated, and high BCL-6 expression is usually associated with poor prognosis factors (elderly patients, high ECOG performance status) and correlates with refractory disease and shorter progression-free and overall survival [12, 13].

More recently, important progress has been made on the transcriptional profile of PCNSL. Overexpression of MYC, high expression of miRNA involved in MYC pathway, and MYC translocations have all been identified and seem to have an important role in this disease pathogenesis [13–15]. Other common genomic aberrations include loss of chromosome arm 6q and losses on 6p21 involving tumor suppressor genes, regulators of B-cell differentiation, and NF-κB signaling [16, 17]. In addition, activating mutations of CARD11 and MyD88 are recurrent in PCNSL and support the aberrant activation of NF-κB pathway [18, 19]. Given the distinct genomic features and the necessity of an adapted treatment, different from its systemic counterpart, PCNSL is now recognized as a distinct subtype of large B-cell lymphoma by the WHO [6, 20].

The selective tropism and whether PCNSL arises in the central nervous system (CNS) or outside the brain are still unresolved issues. The initial hypothesis was that B cells transform outside the CNS and due to certain adhesion molecules and chemokines, the modified lymphomatous cells have neurotropism and are preserved in the brain tissue [21]. Moreover, high chemokine CXCL-13 concentration in the cerebrospinal fluid (CSF) of PCNSL patients correlates with adverse prognosis and together with IL-10 are highly specific for the diagnosis of CNS lymphoma [22, 23].

The theory of development of neurotropic lymphomatous cells outside the brain was mainly based on the information that there is a lack of classical lymphatic drainage system in the CNS. A fundamental discovery that could change these assumptions about the pathogenesis of PCNSL was recently published and reports the presence of functional lymphatic vessels lining the dural sinuses, able to carry immune cells from the CSF to the deep

cervical lymph nodes [24]. There is an ongoing controversy on the pathobiology of PCNSL, and new insights, which could change the current understanding of this disease group, are expected.

3. Clinical presentation, diagnosis and workup

The clinical presentation of PCNSL reflects its localization and typically consists of neurologic symptoms, which can be extremely polymorphic, depending on the tumor site. Psychiatric and ocular/visual manifestations are also common. Usually, these symptoms prompt neurologic imaging which points to the tumor. Despite significant progress in imaging techniques and in the interpretation, there is a significant risk in attributing too much diagnostic power to neuroimaging, succumbing to the temptation to formulate a diagnosis based on tumor appearance. Statistically, the most frequent localization of PCNSL is supratentorial and periventricular, accounting for approximately 80% of cases, and 60% of PCNSL are presenting as a single mass at diagnosis, but leptomeningeal, cerebellar, and intraocular presentations are not uncommon. CSF cytology is positive demonstrating meningeal involvement in 16% of cases, but only rarely (<5% of cases) is leptomeningeal disease present without a cerebral lesion. Primary spinal cord presentation is extremely rarely encountered [3]. Eye involvement is seen in up to 20% of patients, either as a primary localization or accompanying other CNS localizations. Also, subsequent development of brain lesions by spread from an initial intraocular localization is not uncommon [25]. Symptoms at presentation vary according to the tumor localization and may include headache, lethargy, visual disturbances, and focal neurological signs, while B symptoms are extremely uncommon [3].

The timely and correct diagnosis of primary CNS lymphoma can be significantly hampered by the administration of corticosteroid therapy, which occurs frequently in the neurological setting, where patients are likely to be referred because of their clinical presentation. Response to corticosteroid therapy has been and still is wrongly regarded as a major argument sustaining a lymphoma diagnosis in patients with brain tumors. Although corticosteroids are extremely active in lymphomas and can lead to a significant response and, sometimes, to the disappearance of the initial tumor, other histological types of primary CNS tumors may respond well to systemic corticosteroids, and thus response to corticosteroids cannot be regarded as an argument for the lymphomatous origin of the tumor. As with the vast majority of solid cancers, the correct positive diagnosis is anatomopathological (with rare exceptions discussed below) and involves the obtention of a bioptic fragment of the tumor. There is no evidence that surgical tumor removal is beneficial in lymphomas, and, thus, current evidence-based guidelines recommend a minimal invasive diagnostic approach for suspected CNS lymphoma, which is usually a stereotactic biopsy.

PCNSL workup consists of positive diagnosis and the evaluation of disease extension, patient status, prognostic markers, as well as treatment tolerance.

Clinical evaluation must include neurological examination, a general clinical exam, and performance status. Both ECOG/WHO score and Karnofsky performance status scale are used to assess status by different guidelines.

Imaging. In practice, it is not infrequent for a cerebral CT scan to be the first brain examination to describe the lymphoma, because of the typical patient presentation with neurological symptoms with a CT scan being employed to rule out ischemic or hemorrhagic stroke (**Figure 1**). Whole-brain MRI is the first step to sustain a suspicion of brain tumor, and it allows for the assessment of local extension of the brain tumor, as well as for the preparation of a minimal invasive bioptic approach for diagnosis. The MRI appearance can strongly suggest a lymphomatous nature of the tumor (**Figures 2–6**). **Figure 7** demonstrates the MRI appearance of a very good partial response after first-line chemoimmunotherapy, and **Figures 8–10** depict MRI appearance of a multifocal, bilateral relapse at 2 years. Complementary chest-abdominal-pelvic CT scan is the standard investigation for the exclusion of systemic disease, but PET-CT can replace it when available. Testicular examination including ultrasound may complete imaging, as testicular involvement is more frequent in cerebral lymphomas.
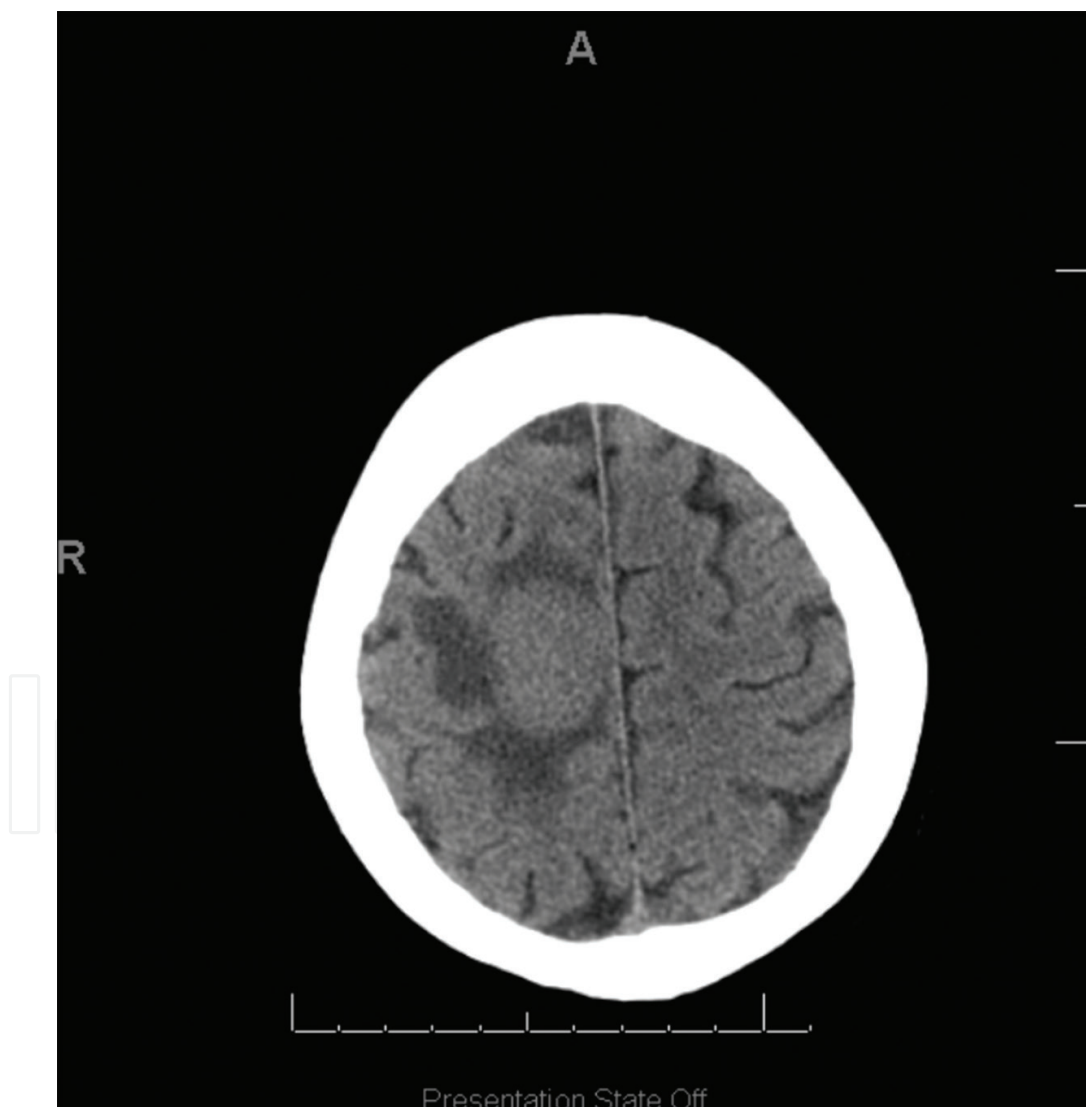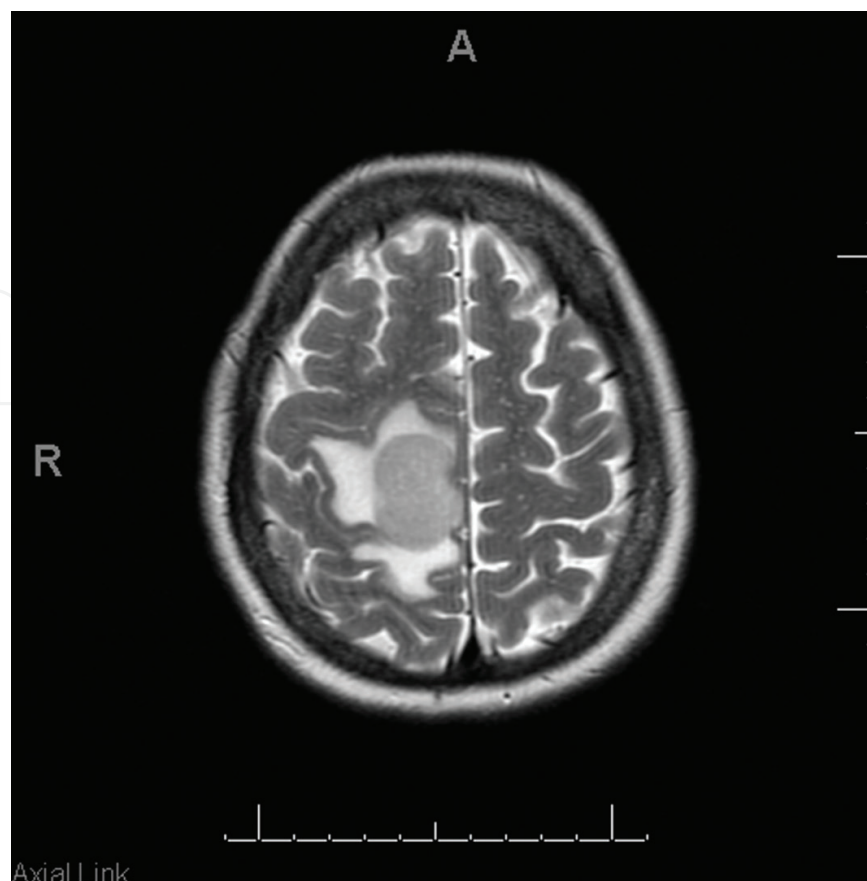

Figure 1. Nonenhanced CT of the head at presentation, axial slice at the level of the convexity, showing a single right subcortical frontoparietal mass. The lesion appears isodense to gray matter (suggestive for CNS lymphoma) surrounded by vasogenic edema. Please note gray matter sparing.

Figures 2–6. MRI of the brain, initial presentation. Axial T2, DWI/ADC, T1, T1 postcontrast, coronal T1 postcontrast. Right centrum semioval focal intra-axial mass is shown. The lesion is hypointense in T2, with vasogenic edema (Figure 2), restricted diffusion (Figure 3), and hypo-T1 (Figure 4) with homogeneous enhancement (Figures 5 and 6). MRI appearance is suggestive of hypercellularity (low T2, low ADC) as seen in CNS lymphoma.
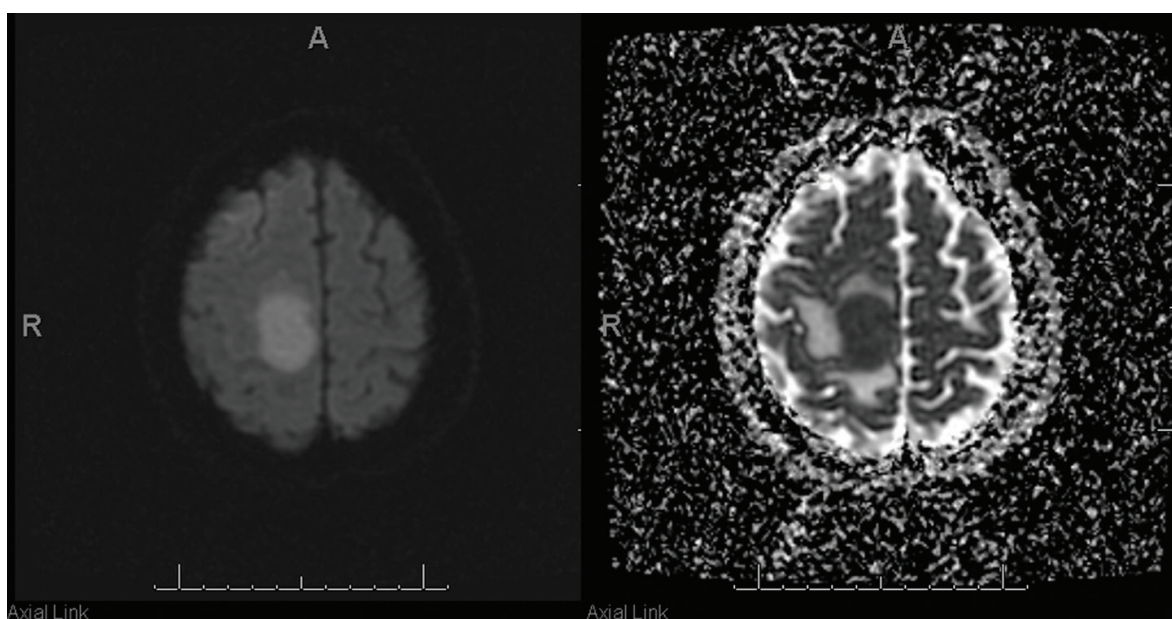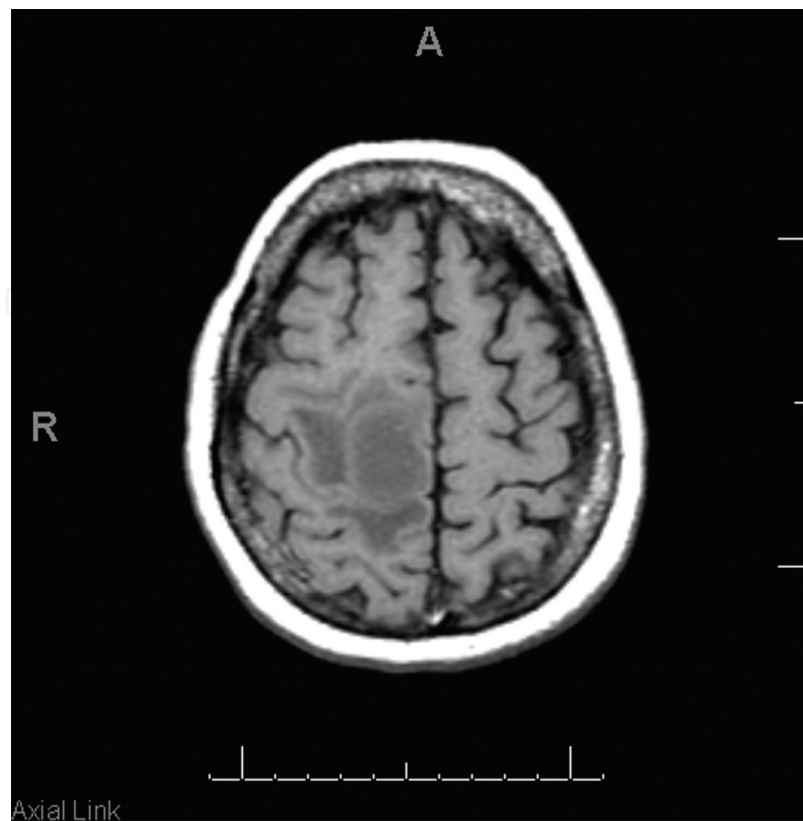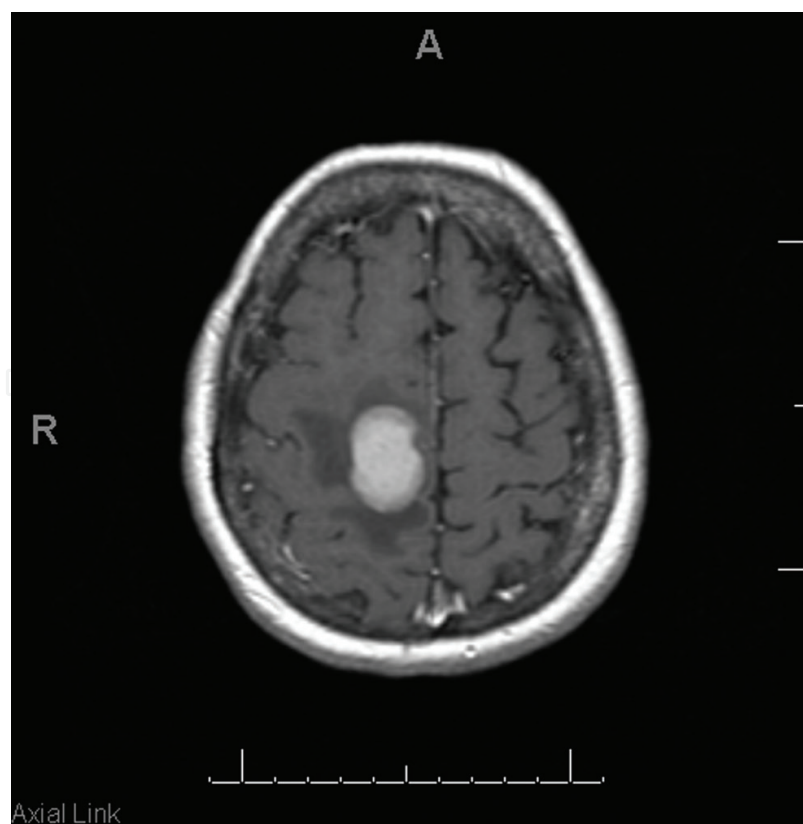

Figure 3.
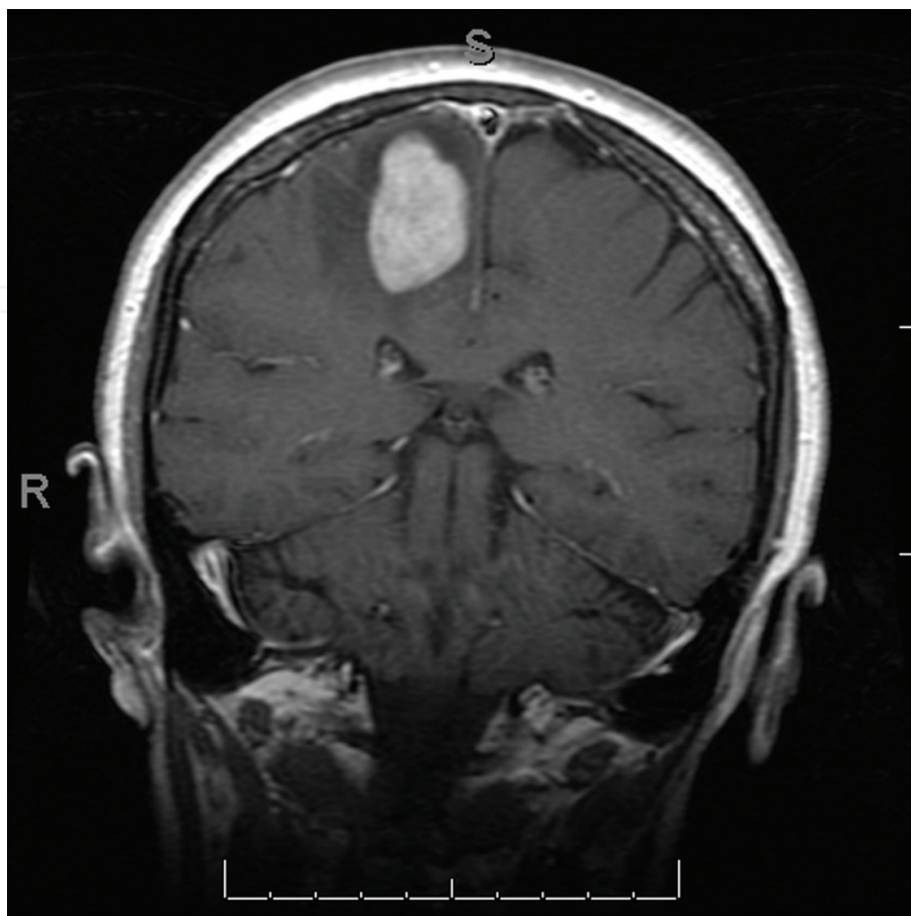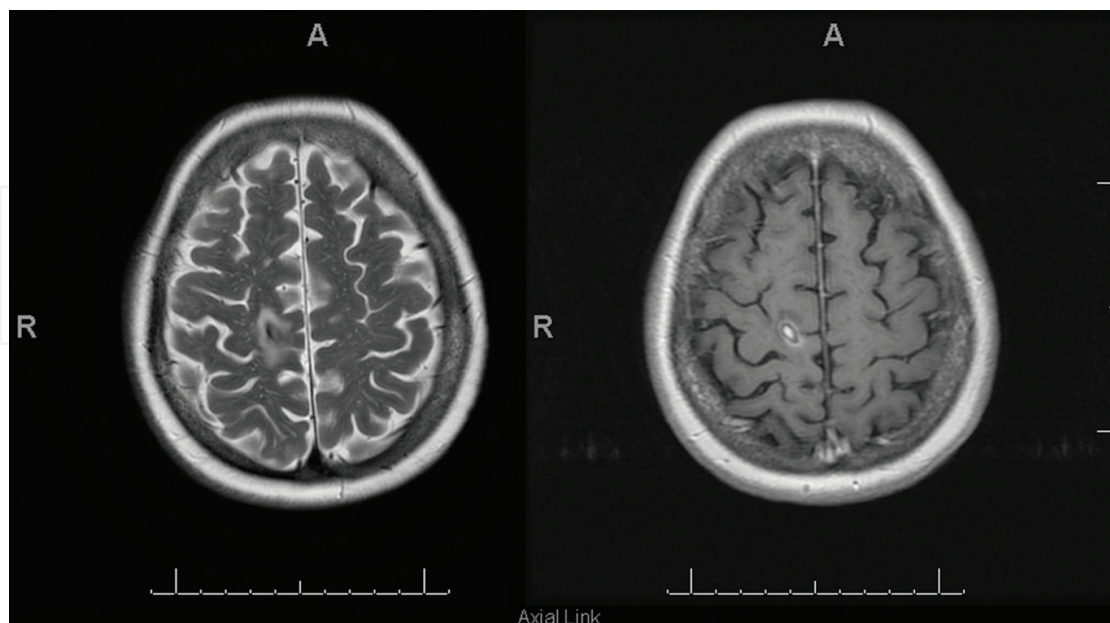
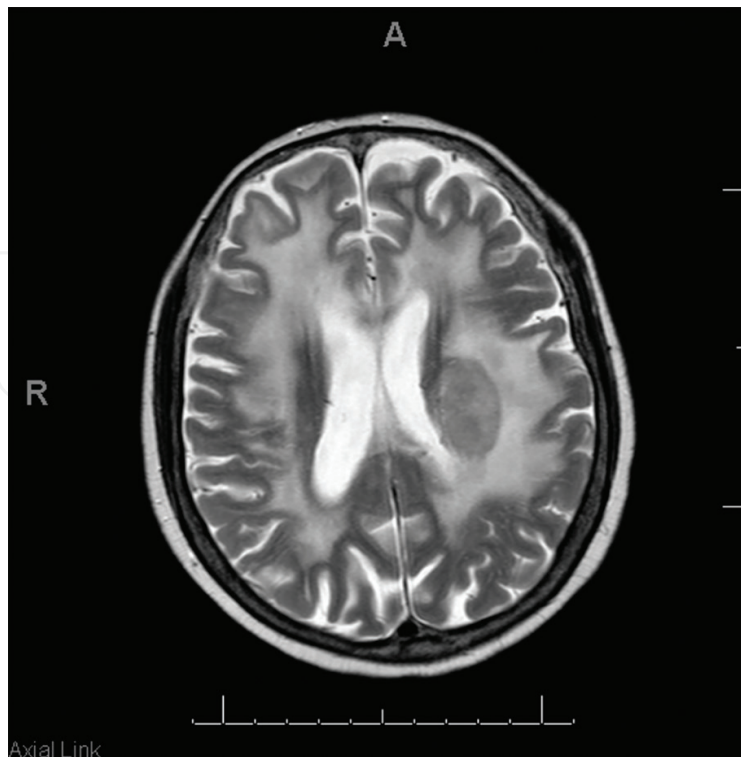**Figure 4.**

Figure 5.

Figure 6.

Figure 7. Follow up MRI of the brain at 3 months (post-HD-MTX and rituximab treatment). Axial T2, T1 postcontrast. Excellent treatment response with nearly complete resolution of the initial lesion. Please note the presence of small amounts of products within the lesion related to the initial stereotactic biopsy.

Figures 8–10. Brain MRI axial T2, T1 with contrast. Recurrence at 18 months, post-HD-MTX/rituximab/temozolomide and whole-brain radiation treatment. Bilateral tumor recurrence, with new lesions, similar in MRI appearance to the initial lesion. Please note the typical distribution in the deep hemispheric white matter and near the corpus callosum. Please note extensive diffuse postradiation white matter changes.
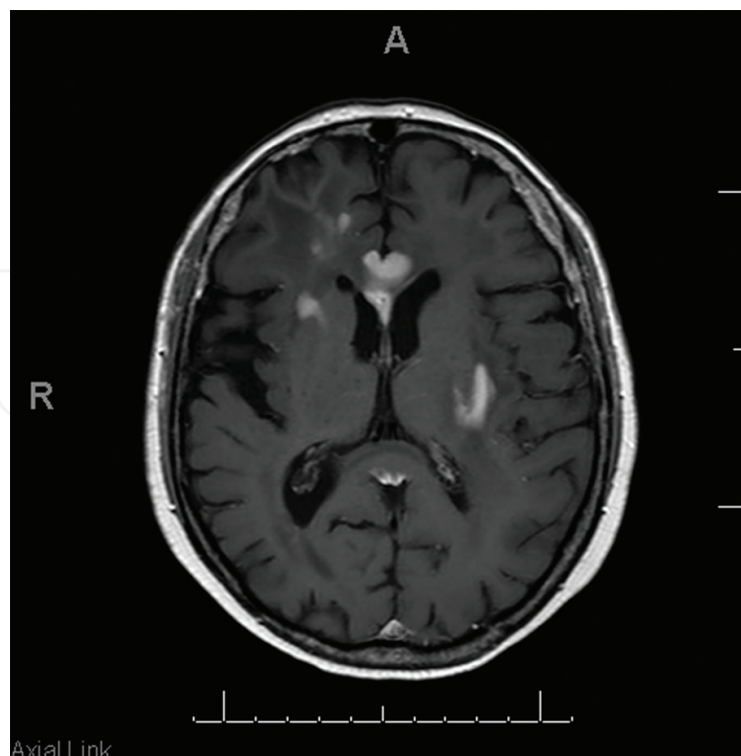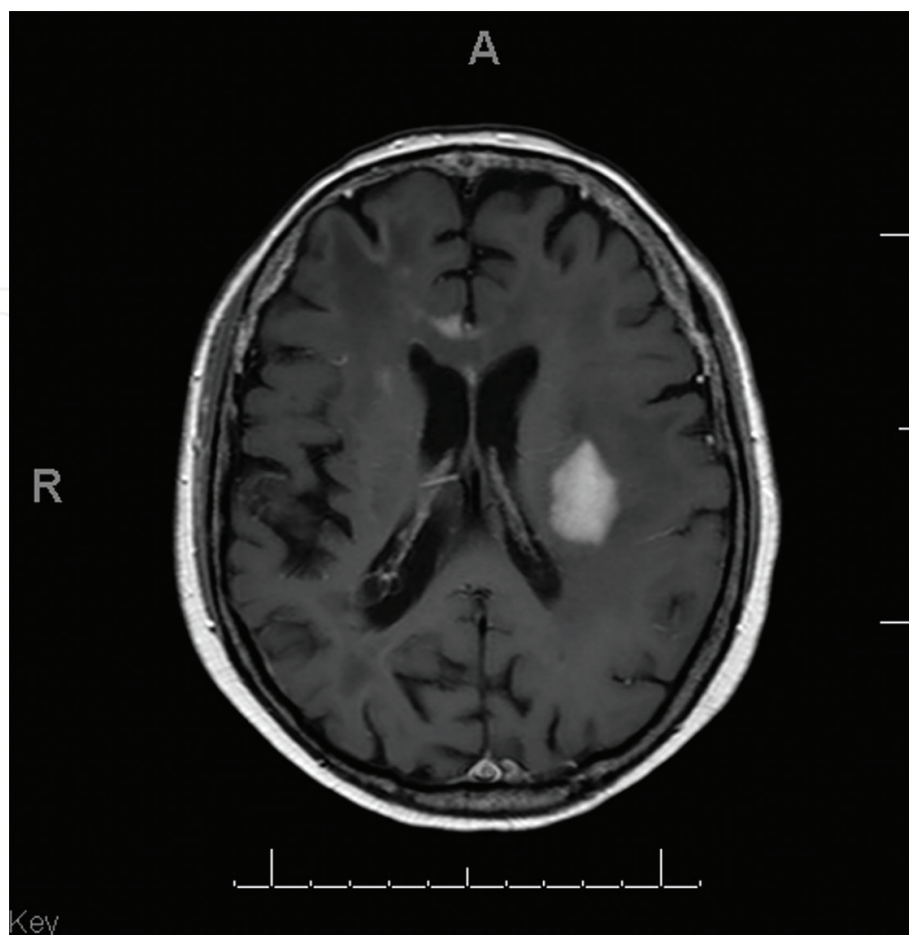

Figure 9.

Figure 10.

Eye slit lamp examination is an integral part of the tumor extension workup, because of the frequent ocular involvement, and can prompt for subsequent imaging approaches like MRI. Also, if eye examination is positive for involvement, a vitreous biopsy can replace the brain biopsy and allow for a positive diagnosis.

Corticospinal fluid (CSF) examination by lumbar puncture should be performed in cases where it can be performed safely, which represents the majority of patients, as judged by the imaging and eye examinations. Cytology of CSF is rarely positive in PCNSL. However, cytologic and flow cytometric examination, as well as clonality assays, is warranted, and if evidence for lymphoma is strong enough by this approach, the brain lesion biopsy may become unnecessary. Also, there are new proposals for diagnostic approaches, which investigate CSF levels of interleukin (IL)-10, CXCL13, or micro RNAs (miRs) to sustain the suspicion of lymphoma, currently under investigation [23].

Histological examination of a tumor biopsy is the standard diagnostic approach. Biopsies should be as noninvasive as possible, and stereotactic biopsy is the best choice. Large tumor excision does not improve disease prognosis, can lead to significant neurologic sequelae, and also can delay the onset of treatment because of the surgical trauma and the risk of complications.

Laboratory tests include:

—Full blood count plus differential.

—Viral testing: HIV (mandatory, because of an increased PCNSL incidence in HIV-infected patients), hepatitis B and hepatitis C (especially if administration of immunotherapy is contemplated which can lead to viral reactivation or flaring).

—Basic pretherapeutic blood biochemistry to evaluate chemotherapy tolerance: liver function tests, kidney function, and electrolytes. Lactate dehydrogenase levels are of prognostic significance.

3.1. Staging and prognostic markers

There currently is no dedicated staging system for PCNSL. Using the Ann Arbor staging, PCNSL is usually a stage IEA lymphoma and as such is of limited clinical relevance. Prognostic indices commonly employed are the International Prognostic Index (IPI) and age-adjusted IPI, both including staging as a criterium. The International Extranodal Lymphoma Study Group has proposed a prognostic score for PCNSL based on five parameters: age>60 years, ECOG performance status>1, increased lactate dehydrogenases, elevated CSF protein levels, and deep brain localization of the tumor and proposed three prognostic groups: good risk (0–1 factors present), intermediate risk (2–3 factors), and high risk (3–4 factors). Although at the time of publication, in 2003, this score could discriminate well the outcomes of the three groups, it is of limited clinical use, because of the scarcity of therapeutic options limiting treatment adaptation according to the calculated score.

Performance status either according to ECOG/WHO or Karnofsky performance status scale is a useful indicator of the patient's tolerance profile for aggressive approaches and may help in the adaptation of dose intensity of therapeutic regimens.

4. Treatment of PCNSL

Prognosis of PCNSL is dismal, and therapeutic results are rather poor, especially when compared to other aggressive lymphomas. The outcome has witnessed a constant improvement over the last decades. As with other malignancies, it is unclear to what extent this improvement can be credited to a progress in anticancer agents, which have not dramatically changed for PCNSL until recently and how much of the progress should rather be attributed to a constant improvement in supportive measures, including the management of treatment-related complications. The development of better antibiotics and antifungals, as well as the advent of hematopoietic stimulating agents, allowed for drug dose and regimen intensity escalations and reduced treatment-related mortality, which could explain the ascending trend of therapeutic results.

As with other hematologic cancers, the treatment paradigm of PCNSL involves the induction of a complete remission (CR), followed by consolidation strategies aimed at preventing disease recurrence. Radiotherapy was, historically, the first nonsurgical therapeutic approach in

lymphoma. Due to the particularities of CNS lymphoma, whole-brain radiotherapy (WBRT) is the standard radiation therapy approach and may include a boost to the involved CNS area. Unfortunately, WBRT is not only highly ineffective in curing lymphoma outside a combination with systemic treatment, but it is also associated with severe immediate and delayed neurotoxicity, including alteration of cognitive functions, sometimes severe and irreversible.

The addition of methotrexate (MTX)-based Systemic therapy has allowed in the 1970s for a significant improvement in cerebral lymphoma outcome, while the classical combination chemotherapy is used for nodal NHL, consisting of CHOP or CHOP-like regimens, demonstrating unsatisfactory results in PCNSL [26]. The standard first-line regimens today are constantly including high-dose MTX (HD-MTX) as the backbone of chemotherapy. MTX, aracytine; alkylating agents like busulfan, carmustine, lomustine, thiotepa, and ifosfamide; and platinum compounds have demonstrated their ability to cross the blood-brain barrier in efficient amounts. Although the CNS/CSF to plasma ratio for systemic MTX is low at around 5%, the CNS penetrance is sufficient for achieving therapeutic results but only at high systemic doses which usually start at 1.5 g/m^2 and go up to above 8g/m^2 [27]. An algorithm of the typical frontline treatment of PCNSL is presented in **Figure 11**.
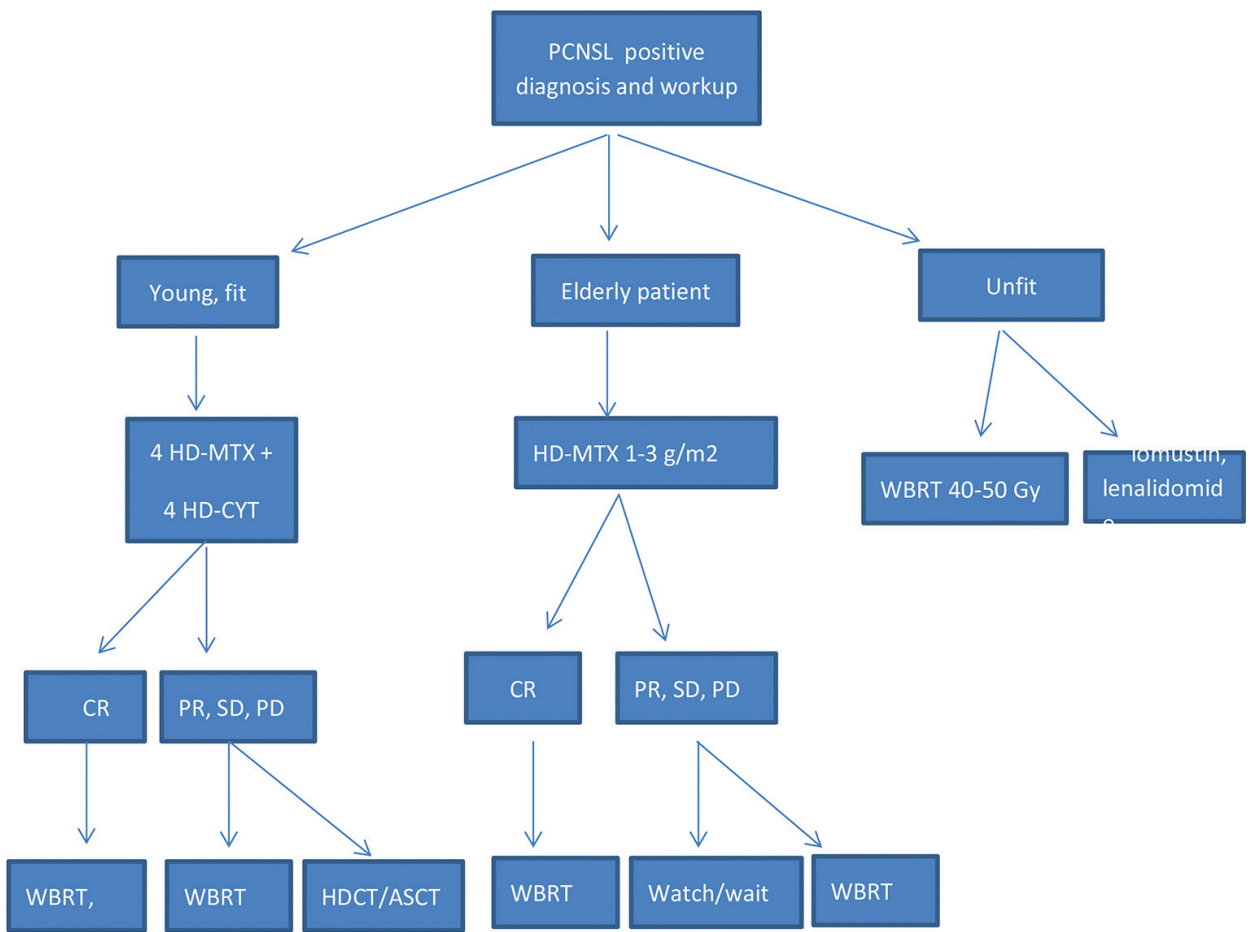

Figure 11. Treatment algorithm for newly diagnosed patients, according to the National Comprehensive Cancer Network [45] and European Society for Medical Oncology [29] evidence-based guidelines.

4.1. First-line induction therapy

The remission induction treatment for PCNSL is chemotherapy based, with anti-CD20 immunotherapy being added in recent years. MTX, which had been previously used in high doses with leucovorin rescue in the management of CNS involvement of acute lymphoblastic leukemia has been reported as efficient in CNS lymphoma, either primary or secondary to systemic disease, in the late 1970s, at doses ranging from 1 to 7.5 g/m^2. Subsequently, HD-MTX became the backbone of PCNSL induction therapy and currently used doses which range from 3 to 8 g/m^2, and it was demonstrated that systemic MTX at doses over 3.5 g/m^2 alleviates the need for concomitant intrathecal administration of the drug [6, 28]. Although a great step forward in PCNSL, single-agent MTX achieved complete remission (CR) rates of only approximately 30% as frontline induction therapy [29]. The addition of cytarabine to MTX allowed for an improvement of CR rates to 46% versus 18% with MTX as single agent with an overall response rate of 69% versus 40% in one of the few randomized prospective studies performed [26]. The addition of alkylating agents or vincristine to MTX and cytarabine did not alter induction treatment efficiency [29, 30]. The optimal number of cycles of induction chemotherapy is not clearly established, but six to eight two-weekly administrations are currently used [6]. For the frail or elderly patients not able to withstand intensive regimens, alkylating agents like temozolomide and lomustine are proposed, with temozolomide achieving CR rates of nearly 50%, comparable to HD-MTX-based regimens [31].

Association of immunotherapy with anti-CD20 antibodies, which greatly improves outcomes in nodal B-cell NHL, was not expected to be efficient in PCNSL, as rituximab is a macromolecule unable to bypass the blood-brain barrier (BBB). CSF concentrations of rituximab are normally less than 1% of systemic concentrations but can reach higher levels when coadministered with chemotherapy possibly due to BBB disruption. Inclusion of rituximab in the induction therapy of PCNSL has yielded controversial results and is not a current evidence-based guideline recommended standard practice, but is routinely used by many hematologists. Another approach currently under investigation is the intrathecal administration of rituximab, either by lumbar puncture or via an Ommaya reservoir. Adjunction of rituximab to chemotherapy was reported to significantly improve PCNSL outcome in a recently published retrospective study [32], and one of the largest prospective randomized studies in PCNSL, including 227 patients of up to 70 years of age, recently reported preliminary results showing that rituximab with or without thiotepa, plus HD-MTX and cytarabine, achieved superior remission rates as compared to HD-MTX and cytarabine alone, and the authors proposed the thiotepa, rituximab, plus HD-MTX and cytarabine (MATRix) regimen as the new standard induction regimen for fit patients [33]. Qian et al. reported interesting results with R-IDARAM in combination with intrathecal chemotherapy for newly diagnosed PCNSL patients. Treatment consisted of six cycles, administered at 3 weeks of interval, of rituximab 375 mg/m^2 (day 1), idarubicin 10 mg/m^2 (day 2 and 3), dexamethasone 100 mg/m^2 (12 h infusion on days 2, 3, and 4), cytarabine 1 g/m^2 (1 h. infusion on days 2 and 3), MTX 2 g/m^2 (6 h infusion on day 4 with folinic acid rescue), intrathecal rituximab 10 mg, MTX 15 mg, dexamethasone 5 mg ,and cytarabine 50 mg once a week. The reported CR rate for the 19 patients treated was an impressive 89% [34].

4.2. Consolidation therapy

Initially used as the single available therapeutic approach besides tumor excision, WBRT in dosed of 40–45 Gy became the standard consolidation regimen after the advent of methotrexate-based therapies. WBRT is a side effect-ridden approach, with high risk of neurotoxicity including cognition and memory impairment, brain atrophy, leukoencephalopathy, dementia, and endocrine abnormalities estimated at 25–35% at 5 years and up to 30% mortality rate [30, 35].

Dahlborg et al. published in 1996 what they called a first example of a durable response in PCNSL patients with chemotherapy alone, reporting, in a 58 PCNSL patient cohort retrospective analysis, similar results in patients treated with chemotherapy alone versus WBRT followed by chemotherapy [36]. Since, there has been a continuous quest for improving systemic therapy to alleviate the need for brain irradiation. Although the advent of combination chemotherapy rendered radiotherapy obsolete in many types of lymphoma, it is still an integral part of some currently employed treatment regimens, especially in Hodgkin's lymphomas and their histologically close relative, primary mediastinal B-cell lymphoma. In PCNSL, WBRT including the eyes is used because the diffuse infiltrative pattern of lymphoma, with focal radiotherapy resulting in a higher recurrence rate. Higher doses of irradiation did not improve the results and was associated with more severe neurotoxicity. A meta-analysis was published in 2001 investigating radiotherapy and optimal induction chemotherapy in PCNSL; radiation doses higher than 40 Gy did not show improved OS, and there was no outcome difference between immediate and delayed consolidation WBRT in patients achieving CR after chemotherapy [37]. As results of trials investigating the omission of radiotherapy as a consolidation therapeutic modality are conflicting, to date there are no definitive answers to this question. The majority of local protocols omit, however, WBRT as part of the first-line treatment of PCNSL, but its importance in relapsed/refractory disease is clearly established [5]. Also, WBRT at doses of 40–50 Gy is an option for patients where chemotherapy is contraindicated. In patients with the usual DLBCL aggressive histology, this strategy has a merely palliative role, with a chance of CR of less than 20% and short overall survival. However, in patients with the rarer, indolent lymphoma histology including marginal zone, lymphoplasmacytic, lymphocytic, plasmocytoma, and Hodgkin's, WBRT can be used with curative intent.

4.3. Bone marrow transplantation

High-dose chemotherapy followed by autologous stem cell transplantation (HDCT/ASCT) is usually reserved for the relapsed/refractory setting. The 2-year overall survival rate is less than 50%. Usually, conditioning regimens are thiotepa based and busulfan based, but the BEAM conditioning regimen typically employed for nodal lymphomas is still used in PCNSL, despite its low BBB penetrance. HDCT/ASCT has been recently investigated as a consolidation therapy after high-dose MTX-based regimens, particularly to avoid the neurological risk of WBRT. There are ongoing trials to establish the role of ASCT as first-line consolidation therapy [38].

4.4. Second-line/salvage therapy

If the long-term disease-free survival in newly diagnosed PCNSL approaches 50%, in relapsed/refractory disease, the CR and overall survival rates are discouraging, and there

currently is no standard of care. Ideally, the second-line therapy should employ agents not used in frontline treatment and be followed by ASCT. If the first remission was longer than 12 months, HD-MTX-based re-induction can be attempted, followed by either autologous transplantation or WBRT, depending on which of those has been used in the frontline approach

Alkylating agents such as temozolomide, thiotepa, or lomustine with or without rituximab are another therapeutic option in this setting. Like with all cancers, patient inclusion on a clinical trial is highly recommended. Novel therapeutic approaches, some of which are discussed below, are either under investigation or in development, in a disease group where therapy represents a major unmet of current hematologic clinical practice.

4.5. Novel approaches in PCNSL treatment

Ibrutinib is a novel agent acting as a covalent Bruton tyrosine kinase inhibitor, belonging to the B-cell receptor signaling inhibitors and showing remarkable activity in B-cell malignancy. It has been approved by the Food and Drug Administration and the European Medicines Agency in chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenstrom's macroglobulinemia, and trials in other B-cell malignancies are ongoing. Ibrutinib was shown to penetrate the blood-brain barrier and to be active in cerebral involvement of mantle cell lymphoma and Waldenstrom's macroglobulinemia [39, 40]. Recently, preliminary results in relapsed/refractory PCNSL and secondary CNS lymphoma were available from a phase I study, where, in a small group of 10 patients, the drug demonstrated a good tolerance profile and an overall response rate of 78% [41].

Lenalidomide and other immunomodulatory drugs. After thalidomide, the infamous sedative drug withdrawn during the 1970s because of its teratogenic effects, was reinvented as an effective and well-tolerated anti-myeloma oral drug two decades ago, spice-up successors like lenalidomide and pomalidomide with better anti-myeloma activity and less side effects were developed. Although their efficacy was initially credited to anti-neoangiogenetic effects, hampering tumor growth, other immune-enhancing pathways of action were subsequently characterized, and the class is currently referred to as immunomodulatory drugs (IMiDs) and was shown to be active not only in B-cell malignancies but also in particular myeloproliferative neoplasms and myelodysplastic syndromes. Lenalidomide has shown efficacy in aggressive B-cell lymphomas like DLBCL or mantle cell lymphoma and also as a graft-versus-disease enhancer in the post-allogeneic transplantation setting. Lenalidomide has the advantage of a good safety profile and tolerance, making it extremely useful in elderly or frail patients, not able to withstand intensive therapeutic approaches [42]. Lenalidomide is being investigated in PCNSL and has been shown to penetrate the BBB, with good intraventricular, intraocular, and brain tissue penetrance. Lenalidomide has been administered either as a single agent or in combination with systemic or intraventricular rituximab. Although efficacy of lenalidomide was only reported in isolated case reports or small case series and phase I trials, it seems to be an interesting agent credited with great expectations especially in the frail PCNSL patients where therapeutic options are extremely limited [43, 44].

5. Conclusions

PCNSL is presently one of the deadliest lymphomas, with a cure rate estimated as being lower than 50%, and therapeutic improvement lags behind that of nodal lymphomas due to the rarity of the disease, making patient accrual for prospective studies difficult. There is ongoing controversy about the pathobiology of PCNSL, and consensus evidence-based guidelines for its management are difficult to formulate. The current treatment for PCNSL consists of combination chemotherapy with a high-dose methotrexate-based backbone. Brain radiotherapy has demonstrated its efficiency as a consolidation regimen, but newer approaches tend to avoid radiotherapy and replace it with chemoimmunotherapy including high-dose therapy with autologous stem cell support, because of the serious side effects of the former. Despite significant progress, PCNSL therapy remains a major unmet for hematologists, and the development of new therapeutic approaches is warranted.

Acknowledgements

Author details

Mihnea Zdrenghea[1, 2*], Delia Dima[2], Ciprian Tomuleasa[1, 2], Horia Bumbea[3] and Cristina Bagacean[1, 4]

*Address all correspondence to: mzdrenghea@umfcluj.ro

1 Department of Hematology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

2 Department of Hematology, Ion Chiricuta Oncology Institute, Cluj-Napoca, Romania

3 Department of Hematology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

4 Laboratory of Immunology and Immunotherapy, Brest University Medical School, CHRU Morvan, Brest, France

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