PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS

Adriana Octaviana Dulamea

Department of Neurology, Fundeni Clinical Institute,
„Carol Davila" University of Medicine and Pharmacy, Bucharest

ABSTRACT

Primary central nervous system lymphoma (PCNSL) is an aggressive non-Hodgkin B-cell lymphoma with characteristic clinical behavior, biological features and poor prognosis despite complex treatment. PCNSL has a median survival of 17 to 45 months in immunocompetent patients, and only 20-30% of cases can be cured successfully. Clinical outcome has improved since the advances in combination chemotherapy protocols, addition of whole brain radiation therapy, encouraging responses of rituximab adminsitration in refractory PCNSL and autologous hematopoietic stem-cell transplantation as consolidative therapy. The author review the recent data on pathogenesis, diagnostic methods and treatment strategies of PCNSL in immunocompetent patients.

Keywords: primary central nervous system lymphoma, pathogenesis, magnetic resonance imaging, 18-fluorodeoxyglucose positron emission tomography

INTRODUCTION

Primary central nervous system lymphomas (PCNSL) are rare tumors of the central nervous system (CNS), representing approximately 2% of all primary CNS tumors and less than 1% of non-Hodgkin lymphomas. (1) The concept and understanding of central nervous system (CNS) lymphoma have greatly evolved in the past few years and it is reflected in the complex WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue. Primary central nervous system lymphoma is now restricted to primary diffuse large B-cell lymphoma confined to the CNS (brain, spinal cord, eyes, meninges, and cranial nerves) (2-4). Many other lymphoma subtypes, some of which are primary or exclusive to the CNS, such as lymphomas of the dura and immunodeficiency-associated lymphomas, are excluded from this definition. Intravascular large B-cell lymphoma (IVLBCL), also a rare form of disseminated B-cell lymphoma characterized by selective growth of lymphoma cells within small vessels/capillary lumina, can also present clinically with a predominant neurologic variant secondary to

CNS involvement (4) The majority of PCNSL are sporadic and the incidence increases with age. A minority are attributable to immunosuppressed states, including HIV infection or iatrogenic immunosuppression following organ transplantation. (5) PCNSL in immunocompetent patients are not associated with Epstein-Barr virus and affect older populations, with a median age of 55 years, and with a slight male predominance (male-to-female ratio 3:2). Higher age has consistently been identified as a negative prognostic factor in patients with PCNSL, the poor outcome being attributed to less intensive treatment administered and also to a fundamental difference in the response to treatment.

PATHOGENESIS

The pathogenesis of PCNSL remains largely unclear, which is partly due to the rarity of the tumor tissue available for research studies. Transcriptomic studies have identified deregulated genes involved in the IL4/JAK/STAT6, cell adhesion-related, unfolded protein response (UPR) and apoptosis signaling pathways (6-9). Copy number variation

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Author for correspondence:
Adriana Octaviana Dulamea, Department of Neurology, Fundeni Clinical Institute, 258 Fundeni Str, sector 2, Bucharest
E-mail: adrianadulamea@gmail.com

studies (8, 10-12) have revealed frequent chromosome losses affecting the 6q, 6p21.32 and 9p21 regions. However, the mutational landscape of PCNSL is still poorly known. A whole exome sequencing strategy has successfully identified pivotal gene mutations in several hematologic and brain malignancies (13,14) Eight genes of interest have been further investigated by focused resequencing in a large cohort. The study revealed high mutation rates for genes already described as mutated in PCNSL such as MYD88 (38%), CD79B (30%), PIM1 (22%) and TBL1XR1 (19%) and for genes not previously reported to be involved in PCNSL tumorigenesis such as ETV6 (16%), IRF4 (14%), IRF2BP2 (11%) and EBF1 (11%). PCNSL demonstrates genetic heterogeneity and mutational pattern similarities with extracerebral diffuse large B cell lymphomas, particularly of activated B-cell (ABC) type, suggesting shared underlying biological mechanism. (15) There are several hypotheses which aim to explain the pathogenesis of PCNSL. Since the central nervous system lacks lymphoid tissue or lymphatic vessels, PCNSL may be caused by the monoclonal proliferation of continuously trafficking T-cells or B-cells in CNS, or the specific tropism of neoplastic T or B lymphocytes for CNS where they escape from the attack of the intact peripheral immune system (16). Malignant transformation of T or B cells after a benign inflammatory process within the CNS may also be the origin of PCNSL (17). Additionally, neoplastic lymphocytes that are normally eradicated by the peripheral immune system may escape to the CNS. The special environment, so-called "sanctuary site", where is free from attack of the immune system and penetration of chemotherapeutic agents by blood-brain barrier is deeply related to malignant transformation. (18) This has important therapeutic implications. At presentation and especially at recurrence, there is a heavy disease burden that exists behind an relatively intact blood–brain barrier. These individual tumor cells invade brain and receive their nutrition from normal cerebral blood vessels. They are not supported by the permeable tumor neovessels that sustain bulky tumor. Therefore, effective treatment of PCNSL requires agents that penetrate the blood-brain barrier to reach these individual cells. These data also suggest that antiangiogenic agents are unlikely to be effective against this microscopic disease.

CLINICAL FEATURES

Clinical presentation of PCNSL is frequently characterized by focal mass lesions signs in more than 50% of cases. In 248 immunocompetent patients, 43% had neuropsychiatric signs, 33% had increased intracranial pressure, 14% had seizures, and 4% had ocular symptoms at the time of presentation. (19) Seizures are less common than with other types of brain tumors, probably because PCNSL involves predominantly subcortical white matter rather than epileptogenic gray matter. Patients rarely present with B symptoms such as fever, weight loss, or night sweats that are commonly associated with other forms of NHL (20).

DIAGNOSTIC EVALUATION

The International PCNSL Collaborative Group has established guidelines for the diagnostic evaluation of a patient with suspected PCNSL (Table 1). (21) The guidelines express the goal to evaluate the baseline extent of disease in order to confirm that the disease is restricted to CNS. Physical examination should include palpation for enlarged lymph nodes as well as testicular examination in males be-

TABLE 1. *International PCNSL Collaborative Group Guidelines for Baseline Evaluation for Clinical Trials[a]*

Pathology	Clinical	Laboratory	Imaging
Centralized review of pathological findings	Complete medical and neurological examination	HIV serology	Contrased enhanced cranial MRI[b]
Immunophenotyping	Dilated eye examination, including slitlamp evaluation	Serum LDH level	CT of chest, abdomen and pelvis
	Recording of prognostic factors (age, performance status)	CSF cytology, flow cytometry, immunoglobulin heavu-chain PCR24 h urine collection for creatinine clearence[d]	Bone marrow biopsy with aspirate
	Serial evaluation of cognitive function[c]		Testicular ultrasonography in elderly men

Abbreviations: CSF, cerebrospinal fluid; **CT,** computed tomography; **HIV,** human immunodeficiency virus; **LDH,** lactate dehydrogenase; **MRI,** magnetic resonance imaging; **PCNSL,** primary central nervous system lymphoma; **PCR,** polymerase chain reaction.
[a]Adapted form article by Abrey et al.(21)
[b]Contrast enhanced cranial CT should be obtained in patients who have a contraindication for MRI or who cannot tolerate MRI
[c]Mini-Mental State Examination is used commonly, although improvement instruments are developed.
[d]For patients who will receive high-dose methotrexate.

cause testicular lymphoma has a predilection to disseminate to the brain parenchyma. Contrast enhanced cranial magnetic resonance imaging (MRI), postcontrast cranial computed tomography if MRI is contraindicated, lumbar puncture if not contraindicated (for cell count, protein and glucose measurement, cytology, immunoglobulin heavy-chain gene rearrangement studies, and flow cytometry studies), ophthalmologic examination including slitlamp evaluation, computed tomography of the chest, abdomen, and pelvis, and bone marrow biopsy should be performed. Blood tests for HIV, complete blood cell count, basic metabolic profile, and lactate dehydrogenase level are also recommended. Testicular ultrasonography should be considered in men.

Neuroimaging

Magnetic resonance imaging

On MRI, PCNSL should be differentiate from CNS involvement of a systemic nonHodgkin lymphoma, from glioma and metastases. Although primary CNS presentation of systemic NHL is very rare, staging of all patients first diagnosed as having lymphoma in the CNS is mandatory to exclude this possibility. Neuroimaging findings differ in immunocompetent from immunodeficient patients. Although some imaging findings are characteristic of PCNSL, the frequency of atypical findings on conventional neuroimaging is increasing. Atypical neuroimaging findings do not rule out PCNSL, even in immunocompetent patients (22).

The typical magnetic resonance imaging (MRI) lesions of PCNSL (23-25) include single or multiple intra-axial, homogenous, contrast enhancing lesions with marked perilesional edema and restricted diffusion, usually contacting the cerebrospinal fluid surface. Lesions not in contact with the subarachnoid space are low-grade PCNSL (26). On precontrast T1 weighted images lesions are usually isointense or hypointense (27-29). Strong homogenous enhancement is often present in PCNSL. Some cases (0% to 13%) show ring enhancement, and a few cases show open-ring enhancement and a "notch sign", which is a deep, abnormal depression at the tumor margin (30). Rare cases (0% to 1%) without enhancement have been described (31,32) usually in the setting of low-grade disease (33) or intravascular lymphomatosis (34) in immunocompetent patients. Infiltration of the corpus callosum is commonly regarded as the most characteristic sign of PCNSL. Symmetrical lesions involving the genu or splenium of the corpus callosum are referred to as a "mirror pattern" or "butterfly pattern".

PCNSLs tend to show subependymal and leptomeningeal spread (97% of cases) (35,36). Linear enhancement along perivascular spaces is highly suggestive of PCNSL (37-39) because PCNSL has an affinity for perivascular extension. After steroids are administered, lesions visualized with MRI can disappear in as little as several hours. Some lesions, called vanishing tumors, can disappear spontaneously. About half of vanishing tumors are PCNSLs (40). The eye is involved in 20% to 25% of patients with PCNSL (41). Ocular lymphoma can be diagnosed with cytologic examination of vitreal aspirate or slit-lamp examination. On MRI, ocular lymphoma can manifest as nodular enhancing lesions in the macula or thickening of the uvea (42). On T2-weighted images lesions are usually isointense or hyperintense, but 40% of lesions on T2-weighted images show hypointensity, which is attributed to high cellular density of the tumor. On fluid-attenuated inversion recovery (FLAIR) imaging, both tumors and areas of edema appear hyperintense (43). A characteristic finding is bilateral symmetrical hyperintensity with subependymal extension. Because diffusion is usually restricted within lymphomas owing to high cellular density, hyperintensity on diffusion-weighted images (DWIs) and hypointensity on apparent diffusion coefficient (ADC) maps are usually seen. On perfusion-weighted images PCNSL shows low cerebral blood volume (CBV) (44). On susceptibility-weighted images, there are no particular or specific characteristics and no microhemorrhages or calcifications, which are frequently seen in high-grade glioma. Proton magnetic resonance spectroscopy (1H-MRS) in PCNSL shows an almost complete loss of n-acetyl aspartate, a decrease in creatine, a great increase in choline and an increase in lactate (90%). A reported hallmark of PCNSL on MRS is lipid peaks (90%) much higher than those in glioblastoma (14%) (45,46) and high choline_creatine ratios (>3). In immunocompetent patients lesions of PCNSL are usually solitary, located in a cerebral hemisphere, thalamus/basal ganglia, corpus callosum, periventricular region and cerebellum. Necrosis, peripheral enhancement, hemorrhages and calcifications are unusual, and other diagnoses should be considered if any of these features are present. Neuroimaging findings can be atypical in patients who are immunodeficient or who have been treated with radiation, antineoplastic agents, or steroids. Moreover, in recent years, atypical neuroimaging features have sometimes been obtained in immunocompetent patients, even before treatment. Furthermore,

in 5% of patients with PCNSL, neuroimaging findings are completely normal (47).

Computed tomography

On computed tomography (CT) lesions of PCNSL are typically (86% to 92% of cases) isodense to hyperdense (48) with typically homogenous contrast enhancement.

Nuclear imaging

Whole-body 18-fluorodeoxyglucose positron emission tomography (18FDG-PET) has an increased sensitivity for the detection of systemic DLBCL over conventional CT staging (49), and has an important role in the exclusion of systemic lymphoma at presentation. 18FDG-PET may assist in differentiating PCNSL from other intracranial malignancies where MRI findings are equivocal (50) 18FDG PET-CT in cases of PCNSL reveals hypermetabolic lesions with increased uptake of FDG (86%) as is seen in malignant gliomas. After effective chemotherapy, FDG uptake disappears, and thus, FDG-PET can be used to evaluate the early therapeutic response. After steroid treatment, the degree of hypermetabolic activity in PCNSL may decrease. Nuclear imaging findings facilitate differential diagnosis from other brain tumors and infectious diseases (51). N-isopropyl (123I)-p-iodoamphetamine (IMP) single photon emission CT (SPECT) shows retention in delayed images. (52) On delayed SPECT images the IMP index is 7 in cases of PCNSL but is less than 1 in cases of malignant glioma. High IMP index of PCNSL is similar to that of malignant melanoma. (53) With 201TlCl-SPECT, homogenously enhancing abnormalities are usually observed. (54) With 67Ga scintigraphy, accumulation is observed 72 hours after injection. The sensitivity of 67 Ga scintigraphy is reported to be 83.1%. (55) On 11C-methionine-PET, uptake is extremely high. The area of increased uptake is often larger than the enhancing lesion on MRI. The area and degree of methionine accumulation in the tumor tissue decrease after radiation therapy. In these nuclear images, immunodeficient patients with PCNSL show characteristics similar to those of immunocompetent patients. (56)

Histology

Histological confirmation, despite small tissue stereotactic biopsies, establish the diagnosis because, as autopsy studies reveal, most primary CNS lymphomas (PCNSL) extensively infiltrate the brain (32). The majority of PCNSL are diagnosed via stereotactic biopsy or, less commonly, by flow cytometric analysis of cerebrospinal fluid (CSF) lymphocytes. The conventional approach has been to avoid surgical resection given the risk of neurological sequelae and lack of therapeutic benefit (57). However, a recent unplanned secondary analysis of the G-PCNSL-SG-1 trial has challenged this view, describing an apparently superiorprogression-free survival (PFS) for those undergoing complete or subtotal resection (58). However, this study had a number of limitations, and independent verification in a well-designed and controlled study would be required to change practice (59) Rubenstein et al. recently evaluated the utility of CXCL13 (a mediator of B-cell migration) and IL-10 as potential CSF diagnostic biomarkers with the ability to discriminate CNS lymphoma from other CNS. The positive predictive value of CXCL13 and IL-10 elevation in CSF was 95% in the identification of newly-diagnosed HIV-negative PCNSL, with an 88% negative predictive value. (60)

Primary CNS lymphoma and secondary CNS involvement by systemic DLBCL cannot be distinguished simply on the basis of their morphology and immunophenotype, although CD10 expression, particularly in association with a relatively low Ki67 labeling index (<50%), should prompt an intense search of primary extracerebral DLBCL or follicular lymphoma (22). Neuropathological studies (32,61) revealed no correlation of autopsy findings with neuroimaging assessment of tumor burden. MRI underestimates the tumor burden of PCNSL. Bulky disease is seen as a contrast-enhancing lesion because of disruption of the blood–brain barrier, but microscopic tumor infiltration may lead to T2 hyperintensity or be completely normal, so the disease may infiltrate the entire brain without a corresponding imaging on MRI.

Recently, an algorithm based on a panel of immunohistochemical (IHC) markers (CD10, BCL-6 and MUM-1) was developed to classify DLBCL into two major subtypes: germinal center B-cell-like (GCB) (positive for either CD10 or BCL-6 while negative for MUM-1) and activated B-cell-like (ABC) (positive for MUM-1 and negative for CD10) (7-10). Three studies have shown that in the CNS, GCB DLBCL might have a better prognosis than ABC DLBCL (62-64).

In contrast to systemic DLBCL, high expression of BCL-2, BCL-6, and MYC by immunohistochemistry is frequent in PCNSL (70% of cases studied) (65) and it has been speculated that this may contribute to the adverse prognosis of PCNSL. Recently, the only multi-centre trial to prospectively evaluate PCNSL biomarkers demonstrated that

BCL-6 expression, but not MYC, correlated with inferior survival (66). Whilst some studies support this finding (67,68), other retrospective analyses found that BCL-6 overexpression correlated with superior outcomes.(69,70)

TREATMENT

Chemotherapy

High-dose methotrexate (MTX) combined with high-dose cytarabine (AraC) is currently regarded standard treatment (71). There is general consensus that MTX should be administered as a rapid infusion (2-4 hours) at a dose of at least 3 mg/m^2 to maximise therapeutic CSF concentrations, at an interval of 14-21 days (72). Modern protocols typically employ between four and eight cycles of HD-MTX-based therapy but comparative data on treatment duration is lacking. In the randomised, phase II, multicentre IELSG-20 trial, 75% of maximum responses were achieved following the first two cycles of treatment. However, for patients achieving a partial response, further tumor response was observed in patients receiving combination chemotherapy (HD-MTX/Ara-C, 10/18 patients) but not HD-MTX monotherapy (71). In a recent trial of rituximab, HD-MTX, procarbazine and vincristine (R-MPV), complete response rates improved from 47% after five cycles of chemotherapy to 79% after seven (73) The addition of thiotepa to HD-MTX and cytarabine was piloted in a small multicentre study (n=20), with inferior results compared to the IELSG20 trial, attributed to a 50% protocol reduction in cytarabine dose (1 g/m^2 for four doses) (74), although the optimal thiotepa dose in this setting has not been ascertained. The role of thiotepa is currently being evaluated in the ongoing, randomized IELSG32 study (EudraCT number 2009-012432-32).

OSHO-phase II study evaluated patients with newly diagnosed primary central nervous system lymphoma treated with autologous peripheral blood stem-cell transplantation (aPBSCT) and response-adapted whole-brain radiotherapy (WBRT). 23 patients received high-dose methotrexate. In case of at least partial remission, high-dose busulfan/thiotepa (HD-BuTT) followed by aPBSCT was carried out. Patients refractory to induction or without complete remission after HD-BuTT received WBRT. Follow-up shows an overall survival of 35%. In six of seven patients where WBRT could be avoided, no long-term neurotoxicity has been observed and all patients have an excellent quality of life. (75)

Rubenstein et al. used methotrexate, temozolomide, and rituximab (MT-R) induction followed by etoposide and cytarabine (EA) consolidation in a prospective multi-centre trial of 44 patients, achieving a two-year PFS of 57% and four-year OS of 65% (76)

Ferreri et al, in a phase II trial assessed first-line MATILDE chemotherapy and response-tailored radiotherapy in 41 HIV negative patients with PCNSL. Overall response rate was 76% after chemotherapy and 83% after chemotherapy ± radiotherapy, with a 5-year overall survival of 30% ± 7%. At 10 years from diagnosis, no patient showed chronic hematologic and nonhematologic toxicities, with a Mini-Mental State Examination score of ≥29 in all cases but one. (77)

Rituximab

In contrast to the survival advantage witnessed in systemic DLBCL, the benefit of combining rituximab with chemotherapy for PCNSL remains unclear. Rituximab has limited CNS penetration with intravenous administration. Single-agent efficacy was demonstrated in 12 patients with refractory/relapsed PCNSL with radiographic response to intravenous rituximab

monotherapy in 36% (78) and encouraging response rates have been achieved with rituximab 375-500 mg/m^2 in conjunction with combination chemotherapy in single-arm trials (77,79) Although the quality of responses appears to be improved with the addition of rituximab, no survival advantage has yet been demonstrated on multivariate analysis (80,81). Results from ongoing randomised studies (IELSG32: NCT01011920, and HOVON 105 PCNSL/ALLG NHL24 trial: EudraCT 2009-014722-42) are essential to define the role of rituximab in induction therapy for PCNSL.

Whole brain radiation therapy (WBRT)

It has been suggested that whole brain consolidation radiotherapy has no additional benefit regarding overall survival (OS) after high-dose MTX alone or in combination with ifosfamide (82). Nevertheless, ongoing trials compare whole brain radiotherapy with high-dose chemotherapy followed by autologous stem cell transplantation (auto-SCT) as consolidation (NCT01011920, NCT00863460). Beside whole brain radiotherapy, the application of high-dose chemotherapy with carmustine (BCNU) and thiotepa followed by auto-SCT has been shown to be feasible and highly effective in newly diagnosed eligible patients, but also in the salvage situ-

ation (83-85). In an attempt to ameliorate the long-term neurocognitive sequelae of WBRT at standard doses, investigators have assessed the value of reduced dose WBRT (rdWBRT). Inferior outcomes have been described with a reduced consolidation WBRT dose (30.6Gy) following CHOD/BVAM induction therapy in a non-randomised comparison (86). Morris et al. recently reported encouraging rates of disease control using 23.4Gy radiotherapy as consolidation therapy following the R-MPV protocol, with a PFS of 7.7 years for the selected subgroup (n=31) achieving CR with immunochemotherapy. Prospective neuropsychological evaluation demonstrated no overall cognitive decline, in 12 patients assessed 48 months after rdWBRT. (73)

PROGNOSIS

Prognosis is poor with a median survival of 17 to 45 months in immunocompetent patients, and only 20-30% of cases can be cured successfully (17). Two international prognostic scores have been developed to predict outcome in PCNSL: (1) the International Extranodal Lymphoma Study Group (IELSG) score, which distinguishes three prognostic groups based on serum lactate dehydrogenase (LDH), age, Eastern Cooperative Oncology Group (ECOG) performance status, involvement of Deep Brain Structures (periventricular regions, basal ganglia, brainstem, and/or cerebellum), and cerebrospinal fluid (CSF) protein concentration (87) and (2) the Memorial Sloan Kettering Cancer Center (MSKCC) score, which also distinguishes three groups but only according to age and Karnofsky Performance Status (KPS). (88)

Acknowledgements

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