

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA: ABOUT 3 CASES AND LITERATURE REVIEW

N'chiepo Kouadio Davy*¹, Seka Evrad Narcisse¹, Tbouada Mohammed², Agbanglanon Douhou Patricia¹, Kietga Gael¹, Houessou Oswald¹, Elkacemi Hanane¹, Elmajjaoui Saana¹, Kebdani Tayeb¹ and Benjaafar Nouredine¹

¹Department of Radiotherapy, National Institute of Oncology, Mohammed V University of Rabat, Rabat, Morocco.

²Departement of Anatomopathology, National Institute of oncology, Mohammed V University of Rabat, Rabat, Morocco.

*Corresponding Author: N'chiepo Kouadio Davy

Department of Radiotherapy, National Institute of Oncology, Mohammed V University of Rabat, Rabat, Morocco.

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) is a very uncommon cancer and rare subtype of extranodal, non-Hodgkin's lymphoma invading structures of the central nervous system (CNS). We report three cases of PCNSL, treated at the radiotherapy department of the National Oncology's Institute of Rabat (INO). All our patients are immunocompetent, and the average age is 33 years (range 25 - 42 years). The main reasons that our patients come to clinical attention were hemiparesis, elevated intracranial pressure, seizures, and dizziness. MRI at the diagnosis revealed unique lesion localized to the cerebral hemispheres, in particular to the parietal (2 cases) and fronto-parietal (1 case) with contrast enhancement founded and perifocal edema and mass effect on the ventricular structures. After stereotaxic biopsy, immunochemistry analysis confirmed diffuse large B-cell NHL (figures 2 and 3), with positivity of CD20 (figure 4), BCL2 (2 cases) and with very high proliferative activity index Ki67 of 40-70% (figure 5) and CD10 (1 case) was positive (figure 6). The extension workup showed that the lymphoma was strictly cerebral in all patients. Patients were RPA class I (MSKCC score) or group I (IELSG score). The treatment consisted of combination of chemotherapy and radiotherapy. All patients received 5 courses of HD-MTX. Two patients which achieved complete remission received WBRT of 40 Gy and 45 Gy. One patient had a partial response and underwent 60 Gy in total dose (WBRT of 40 Gy with a boost of 20 Gy on the residual tumor). After a median follow-up of 65 months (range 38 to 95months), the 3 patients remained in complete remission without signs of relapse and without side effects.

KEYWORDS: Primary central nervous system lymphoma, chemotherapy, radiation therapy.

INTRODUCTION

The entity was first described by Bailey in 1929,^[1] and, from 1974 onward, has been recognized as a distinct nosological entity.^[2] While lymphoma is a common tumor, Primary central nervous system lymphoma (PCNSL) is a very uncommon cancer. PCNSL is a rare subtype of extranodal, non-Hodgkin's lymphoma invading structures of the central nervous system (CNS), with absence of systemic involvement at the time of diagnosis. PCNSL arises from the brain, spinal cord, meninges, including the eyes. This disease jeopardizes for almost 2.2% of primary tumors of the CNS.^[3] It is mostly of diffuse large B-cell lymphoma (DLBCL) histology.^[4] They are rapidly growing tumors that are usually present in a periventricular location. PCNSLs in the immunocompromised have become increasingly rare with the improvement in antiretroviral therapy, but in immunocompetent population, its incidence continues to increase in men over 65 and in women.^[5] The clinical signs are nonspecific and often related to the frequent

frontal localization. High dose methotrexate (HD MTX) chemotherapy followed by radiation therapy significantly improved survival (ranging from 12 months for radiation therapy alone to 35-45 months for combination therapy). This at the cost of sometimes significant cognitive toxicity in the population aged over 60 years. Thus, treatment is the subject of numerous studies, with the common objective of improving disease control while reducing the risk of neurological toxicity. PCNSL is associated with a relatively poor prognosis compared to other extranodal diffuse large B-cell lymphomas.

We report three cases of PCNSL, treated at the radiotherapy department of the National Oncology's Institute of Rabat (INO). Many variables such as Clinical, demographics, treatment details, and outcome data were obtained for each patient through medical chart review.

OBSERVATIONS

Case 1

A 42-year-old woman, consulted in February 2012 for elevated intracranial pressure symptoms and left hemiparesis. The brain MRI revealed a right posterior parietal mass of 71 x 37mm extended by 45mm in height, intensely enhanced after injection of gadolinium; with surrounding edema and a slight mass effect on the ventricular system with no sign of engagement. In diffusion, there is a lowered ADC. The stereotaxic biopsy was performed with histologic and immunochemistry analysis demonstrated diffuse large B-cell non-Hodgkin lymphoma (NHL) with positivity for CD20 biomarker. CD10 and BCL2 were negative. The standard laboratory workup (with a normal blood count, C reactive protein, liver function, and blood ionogram) was without notable abnormalities. Lactate dehydrogenases (LDH) were within normal limits: 235 IU/L. The HIV serology was negative. The bone marrow showed no evidence of lymphomatous involvement. The eye examination performed by an ophthalmologist and lumbar puncture showed no evidence of either ocular or leptomeningeal involvement. The chest, abdominal and pelvic CT scan was normal. The patient underwent five cycles of first-line intravenous HD-MTX chemotherapy. Post-chemotherapy MRI was not performed. Clinical examination found a patient with a WHO score of 0, no functional signs and her neurological examination was normal. The simulation CT scan did not note any residual tumor. Radiotherapy on the whole brain was carried out at a total dose of 40 Gy with 20 sessions of 2 Gy by fraction from 12/05/2012 to 01/02/13. She followed regular clinical, biological and MRI monitoring. After 95 months of follow-up, she remained in complete remission.

Case 2

A 25-year-old patient, with no known pathological history, consulted in October 2014 for left hemiparesis in context of asthenia associated with dizziness and seizures. The Karnofsky index was at 80%. Brain MRI revealed a 40 mm right parietal intracranial expansion process with significant perifocal edema and a limited mass effect. This tumor is enhanced very intensely with gadolinium. The biopsy performed under stereotaxic conditions demonstrated large diffuse B-cell NHL histology with on immunochemistry a positivity for the biomarker CD20 and anti-Bcl2 antibody. The Ki67 was at 70%. CD3, CD5, CD10, CD68 biomarkers were negative. The bone marrow biopsy noted an absence of lymphomatous infiltration or myelofibrosis. The ophthalmologic examination was unremarkable. The blood count, the rate of sedimentation and the hepatic and renal tests were normal. The LDH level was 189 IU/L. The HIV test was negative. The chest, abdominal and pelvic CT scan was normal. The patient received 5 courses of HD-MTX. The post-chemotherapy evaluation noted a patient with a WHO score 1, and the neurological examination was normal with disappearance of

hemiparesis and seizures. The brain MRI noted complete response by a right parietal sequelar lesion not enhanced. The patient received additional radiotherapy from 08/31/2015 to 10/13/15 at a total dose of 45 Gy in 25 sessions of 1.8Gy by fraction on the brain whole. The follow-up assessment at 1 year did not note any cognitive neurological disorders or deficits. The brain MRI of 09/29/16 revealed sequelae on the right parietal area. After 62 months of follow-up, the patient is still in remission with good clinical control; no abnormality on the cerebral MRI carried out on 02/13/20. The standard biological monitoring assessment is normal.

Case 3

A 32-year-old patient with no known pathological history, began to experience in November 2012 high intracranial pressure syndrome. The clinical examination objected to a patient with a 90% Karnofsky index and left hemiparesis. A Brain magnetic resonance imaging (MRI) revealed the presence of a process occupying the right hemispherical intra-axial space, deep fronto-parietal site, presenting a T2 hypersignal, hypersignal in diffusion sequences with low ADC and a T1 hyposignal, intensely enhanced after injection of the product of contrast. The lesion has irregular contours with blurred boundaries. It measured 34.6 x 33 mm in transverse diameters, extending over a height of 34 mm with a range of surrounding edema, infiltrating the white matter (figure 1). This lesion is responsible for a mass effect on the encephalic parenchyma opposite, with erasure of the subarachnoid spaces. It causes a mass effect on the midline and on the body of the right lateral ventricle and a start of falcorial engagement. The spectroscopy sequences objectified a decrease in N-Acetyl Aspartate (NAA), an increase in Choline and a double peak in lipids. Absence of ocular abnormality. Stereotaxic biopsy was taken and revealed large diffuse B-cell NHL histology with on immunochemistry with positivity of biomarkers CD20 and CD10, 40% Ki67 and cyclin D1 was expressed on 30% of cells. Chest, abdominal and pelvic computed tomography was normal. The bone marrow biopsy did not show any medullary infiltration. The LDH level was 230 IU/L. The lumbar puncture came back negative. The patient received 05 high dose methotrexate chemotherapy courses. Brain MRI after chemotherapy (08/18/2013) noted a persistence of the right parietal lesion process of 12 x 18 x 17 mm. The clinical examination noted a good evolution with a considerable regression of the neurological signs. Then the patient received radiotherapy at a total dose of 60 Gy in 2 series from 09/20/12 to 10/30/2013: a phase on the entire brain at a dose of 40 Gy in 20 sessions of 2Gy/session; then a boost on the residual tumor at a dose of 20 Gy in 10 sessions of 2 Gy by session. The MRI at 6 months after completion radiation therapy noted a complete remission. She followed regular clinical and biological monitoring. After a 38-months follow-up in our institute, the patient remained in complete remission.

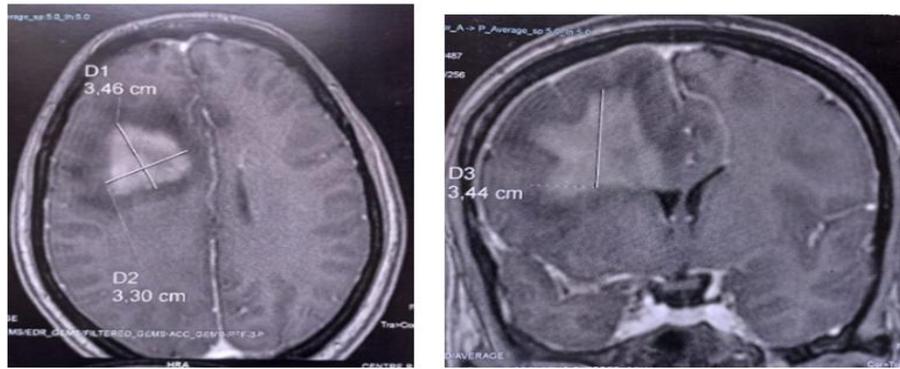


Figure 1 A and B: case 3: Primary central nervous system lymphoma located in the fronto-parietal area measuring 3.46 x 3.3 x 3.44 cm with surrounding edema

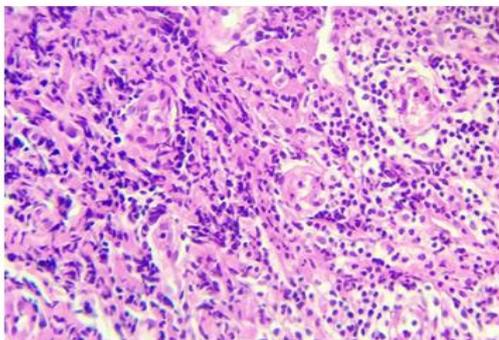


Figure 2: Brain parenchyma site of round cell tumor proliferation (HE x 200)

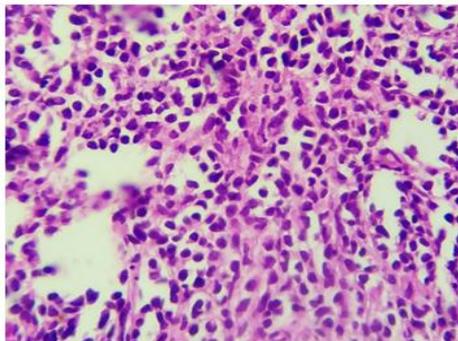


Figure 3: Lymphomatous tumor cells showing atypia

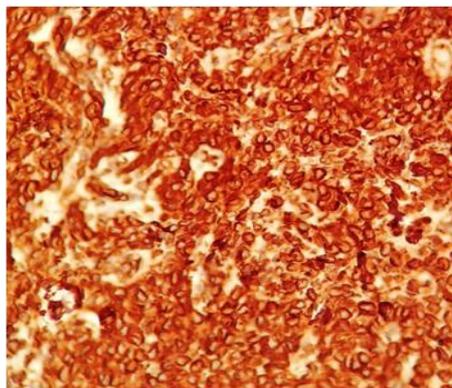


Figure 4: Diffuse positive staining of tumor cells by anti-CD 20 antibody (IHC x 200)

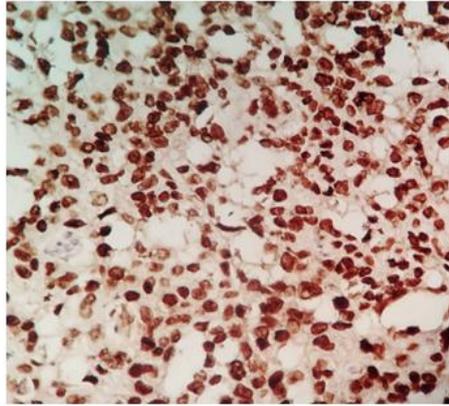


Figure 5: Proliferative Index Ki67 evaluated at 70% (IHC x 200)

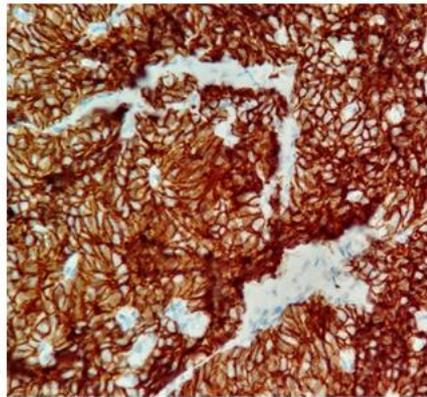


Figure 6: Diffuse positive staining of tumor cells by anti-CD 10 antibody (IHC x 200)

DISCUSSION

PCNSL is a rare subtype of extranodal, non-Hodgkin's lymphoma invading structures of the CNS, with absence of systemic involvement at the time of diagnosis. It represents barely 2.2% of primary tumors of the CNS,^[3] and only 4% to 6% of all extranodal lymphomas.^[6] There is a strong association between immunodeficiency and PCNSL. Immunodeficiency is the only known risk factor, including patients with human immunodeficiency virus (HIV) / acquired immune deficiency syndrome (AIDS), iatrogenic immunosuppression in the setting of solid organ transplant.^[7] However, it also occurs in the immunocompetent population typically in the sixth and seventh decades of life, while immunocompromised individuals are more frequently present in the third and fourth decades. In recent years, there has been an increase in its incidence, particularly in patients over 60 years of age, with an incidence rate of 0.5 per 100,000 per year.^[5] The median age at diagnosis is 65 years.^[8] In our case, the average age is 33 years (range 25 - 42 years). All of our patients were immunocompetent, with HIV negative and no other immunosuppressive factor was found in their clinical history.

The clinical presentations of PCNSL vary depending on the structure of the CNS involved. The clinical symptoms of PCNSL that lead to consultation are nonspecific. It is similar to that of other CNS neoplasms, and usually progress within a few weeks due to rapid

tumor growth. Focal neurological deficits, linked to parenchymal or leptomeningeal involvement, are only observed in 56 to 70% of patients.^[9] Nonspecific neuropsychiatric and behavioral changes can exist in approximately 32 to 43% of cases. High intracranial pressure syndrome consisting of headache, nausea and vomiting is also common (33%). Seizures are less frequent (10 - 14%). Despite that the frequency of ocular involvement is around 20-25%,^[10] it is subtle and rarely symptomatic.^[11] Involvement of the optic nerve, retina, or vitreous humor should be excluded with a comprehensive eye evaluation by an ophthalmologist. In a retrospective review of 248 immunocompetent patients, 4% suffered visual symptoms at diagnosis (4%).^[9] The classic B symptoms such as weight loss, fevers, and night sweats seen in patients with non-CNS lymphoma are infrequent in PCNSL. Leptomeningeal involvement may occur, either localized to adjacent parenchymal sites or in diffuse form (that is, positive cytology) in up to 30% of patients. The main reasons that our patients come to clinical attention were hemiparesis (3 cases), elevated intracranial pressure (2 cases), seizures (1 case), and dizziness (1 case).

Diagnosis always needs to be confirmed pathologically, according to the WHO classification,^[12] in most cases by stereotactic needle biopsy. Histologically, almost all of PCNSLs cases are classified as high grade B-cell lymphomas and are usually indistinguishable from

diffuse large B-cell lymphoma (DLBCL) in more than 9 out of 10 cases; although, in only extremely rare cases (in less than 10%), there are other morphologies including Burkitt, low-grade, or T-cell lymphoma.^[4,13,14] They express Pan-B-cell-markers, as CD20 and CD79a.^[15] Other markers frequently expressed in DLBCL are BCL6 (60–80%), MUM1/IRF4 (90%), CD10 (10–20%) and BCL2.^[15,16] The proliferation index Ki67 frequently is between 70 and 90% of all tumour cells.^[15] Our three patients underwent the stereotaxic biopsy and the histological and immunochemistry analysis confirmed diffuse large B-cell NHL (figures 2 and 3), with positivity of CD20 (figure 4). In two cases, BCL2 was positive and with very high proliferative activity index Ki67 of 40 to 70% (figure 5). In one case CD10 was positive (figure 6). In a study reported by Bataille, all tumors (248 patients) available for review were classic diffuse non-Hodgkin's lymphoma, for which the phenotype was determined in 220 patients: 212 (96.4%) were B-cell and eight (3.6%) were T-cell type tumors.^[9]

The imaging modalities employed for the diagnostic work-up of PCNSL include contrast-enhanced computed tomography (CT) and Magnetic resonance imaging (MRI). MRI is the gold standard for showing the site and assessing tumor extension. In immunocompetent patients, cranial MRI with contrast enhancement typically shows intense and homogeneously enhancing single lesions (70%) or multiple lesions (30%) with modest perifocal edema, usually primarily located in the frontal lobes, corpus callosum, and deep periventricular brain structures.^[17,18] In immunocompromised patients, a multifocal pattern is more common, often with a peripheral ring enhancement and central necrotic area. PCNSL is most frequently located within the cerebral hemispheres. Our patients underwent MRI at the diagnosis, that revealed unique lesion localized to the cerebral hemispheres, in particular to the parietal (2 cases) and fronto-parietal (1 case) with contrast enhancement founded in all cases and perifocal edema and mass effect on the ventricular structures in the majority. The lesion size was between 34 and 71 mm and the mean size was 35 mm. Bataille and colleagues founded in their study that patients with primary cerebral malignant lymphoma usually presented with a single lesion (66%) with a supratentorial (87%) and frontoparietal (39%) location and a size greater than 1 cm. Moderate perifocal edema was present in 85% of cases.^[9] In another study, 65 out of 100 patients had a single lesion and in the 65 patients with a solitary lesion, hemispheric lesions were most frequent ($n=23$) followed by corpus callosum ($n=18$). On the total of lesions, 65 of 170 (38.2%) lesions were located in the cerebral hemispheres, with considerable size (mean diameter 21.3 mm) and showed perifocal edema with one exception.^[18]

The International PCNSL Collaborative Group (IPCG) has developed guidelines to determine extent of disease.^[19] An extra-neural disease must be excluded to

establish a diagnosis of PCNSL. Although involvement outside of the CNS is uncommon, complete systemic staging with either a contrast-enhanced CT scan of the chest, abdomen, and pelvis or and possibly a PET-scan as well as a bone marrow biopsy are important and should be performed to exclude occult systemic disease. A testicular ultrasound must be performed in men. Blood tests should include serum lactate dehydrogenase and human immunodeficiency virus (HIV) serology.^[19]

Many prognostic scoring systems have been developed specifically for PCNSL such as the Recursive Partitioning Analysis (RPA) analysis, the Nottingham-Barcelona score and International Extranodal Lymphoma Study Group (IELSG). Age and performance status are the two variables that have been consistently identified as independent prognostic factors in a wide variety of studies.^[20,21] At Memorial Sloan-Kettering Cancer Center (MSKCC), RPA analysis of 338 patients led to the identification of three RPA classes: class I (age < 50) was associated with median survival of 8.5 years; class II (age > 50 and KPS \geq 70) 3.2 years; and, class III (age > 50 and KPS < 70) 1.1 years.^[20] The IELSG evaluated 378 patients and observed age > 60 years, ECOG > 1, elevated LDH, high CSF protein and deep regions of the brain as prognostic. In patients with 0 and 1 factors, 2 and 3 factors, and 4 and 5 factors, the 2-year survival proportions were 80%, 48%, and 15%, respectively.^[21] All of our patients were RPA class I according the MSKCC prognostic score or in group I according the IELSG score.

Surgical resection is not part of the standard treatment approach for PCNSL given the multifocal nature of this tumor and potential long-term morbidities.^[22] His role is limited to establishing the tissue diagnosis via stereotactic biopsy, considering that PCNSL is a "whole brain disease"^[23] and that surgical resection could be harmful. Several retrospective studies have not shown the benefit of subtotal or total resection.^[9,22,24] In recent years, the treatment of PCNSL has evolved significantly. Owing to its rarity, treatment of PCNSL has not been completely standardized, and many of the available treatment options have not undergone prospective comparison against each other. Historically, WBRT had been applied as the sole treatment modality of PCNSL, to cover the multifocal nature of the disease. Focal radiation resulted in increased relapses in regions excluded from the radiation port, confirming the need for WBRT in PCNSL.^[25] WBRT had induced high proportion of radiographic responses in up to 60% of patients but the duration of remission is usually short and median survival of no more than 1 to 1.5 years. In a multicenter phase 2 trial, 41 patients were treated with WBRT to 40 Gy plus a 20 Gy tumor boost and achieved a median overall survival (OS) of only 12 months.^[26]

The problem of chemotherapy is particular in brain tumors since it is necessary to use molecules that cross the blood-brain barrier well. Thus, the chemotherapies

conventionally used in systemic lymphomas are not effective. Methotrexate, an antimetabolite and antifolate, is considered the most important and beneficial single drug for PCNSL. It is given with intravenous high-dose (HD- MTX), at doses above 3.5 g/m² in intervals of 2–3 weeks. Combination of HD- MTX and WBRT improved outcomes, with a median overall survival of 30 to 60 months and 5-year survival rates of 30% to 50%. (27-33) Our patients underwent 5 cycles of HD MTX, then they received consolidative radiation therapy. Two patients which achieved complete remission with complete resolution of the enhancing lesion after HD MTX, received a WBRT of 40 Gy and 45 Gy. One patient had a partial response and then after radiotherapy of 60 Gy in total dose (WBRT of 40 Gy with a boost of 20 Gy on the residual tumor), the follow-up MRI at 6 months noted a complete response. After a median follow-up of 65 months (range 38 to 95months), the 3 patients remained in complete remission without signs of relapse and without side effects.

HD-MTX-chemotherapy with or without subsequent WBRT is the most commonly used first-line treatment for immunocompetent patients with PCNSL.^[34] However, Radiation therapy and its dose were controversial. The optimal dose of post-chemotherapy irradiation has never been prospectively investigated in PCNSL. Doses of 23–50 Gy to the whole brain, with or without a tumour bed boost, are nowadays used, with most of the protocols delivering a total dose of 40–45 Gy without boost, and standard fractionation (1.8–2.0 Gy/fraction). Consolidation radiotherapy after complete response following HD-MTX-based chemotherapy is currently being debated in the PCNSL Bataille and colleagues, in their study in contrast to other series, evocated that the dose-response relationship could not demonstrate that doses greater than 50 Gy improved survival time for patients.^[9] Ferrari and colleagues, in one study published in 2011, suggested that in patients with residual disease after chemotherapy, complementary WBRT is unavoidable in routine practice because of the lack of valid alternatives and strongly recommended WBRT dose at 40-45 Gy.^[34] Recommendations on consolidation WBRT in patients in complete remission after chemotherapy are less clear. In a retrospective study, a dose reduction from 45 Gy to 30 Gy in young patients with complete response after high-dose MTX-based chemotherapy was accompanied by a significant reduction in progression-free survival and overall survival.^[35] The MSKCC reported their experience with a protocol combining rituximab and HD MTX-based chemotherapy followed by reduced-dose radiotherapy to 23 Gy in patients with complete response and no adverse impact on the prognosis was observed.^[36] Eckhard Thiel and colleagues, in a phase III randomized trial in German (G-PCNSL-SG-1), had shown that the addition of upfront WBRT (at 45 Gy in 1.5 Gy by fractions) to high-dose methotrexate-based chemotherapy significantly prolonged progression free survival (PFS), most prominently in patients who did not

achieve a complete response following chemotherapy. In patients with disease less sensitive or insensitive to high-dose methotrexate, WBRT was observed to be more effective than high-dose Cytarabine. But the benefit on PFS did not translate into an overall survival difference.^[37]

Ferreri and colleagues, updated the results of a phase II trial at a median follow-up of 12 years assessing first-line chemotherapy followed by WBRT. Patients received 3 courses of MATILDE chemotherapy (MTX 3.5 g/m² day 1; cytarabine 1.7 g/m² x 2/d day 2; idarubicin 13 mg/m² day 2; thiotepea 20 mg/m² day 3) followed by WBRT. WBRT dose was 30 Gy in patients with complete remission after MATILDE, 36 Gy in patients with partial response, and 45 Gy in patients with stable or progressive disease, followed by a 9-Gy tumor-bed boost. The follow-up at 12 years showed that 9/41 patients are alive and disease-free, 8 of whom are alive at 10 years. At 10 years from diagnosis, no patient showed chronic hematologic and non-hematologic toxicities, with a good Mini-Mental State Examination score (>29) in all cases but one.^[38]

Although our patients have not observed toxicity linked to radiotherapy, in the literature, this strategy was associated with disabling neurotoxicity, with a cumulative 25%-35% incidence at 5 years and related 30% mortality,^[39] especially in elderly people \geq 60 years. Some experiences suggested alternatives to consolidation radiotherapy with similar results to those obtained with chemoradiation are proposed in order to avoid or delay consolidation WBRT and reduce neurotoxicity.^[30] These alternatives are using consolidation with non-myeloablative chemotherapy (CALGB 50202)^[40] or regimens with high-dose, myeloablative conditioning, and autologous stem cell transplantation (HDC/ASCT) in first-line treatment. The phase 2 trial CALGB (Cancer and Leukemia Group B) proposed combination of HD-MTX, temozolomide, and rituximab followed by consolidation with HD-araC and HD-VP16 without WBRT in 46 patients, with a 3-year PFS and OS of 50% and 67%, respectively, a single toxic death and no evidence for significant iatrogenic neurotoxicity.^[40] The IELSG-32 compared HDC/ASCT versus WBRT as consolidation therapy after front-line HD-MTX based CT and the authors concluded that WBRT and ASCT are both feasible and effective as consolidation therapies after high-dose methotrexate-based chemo-immunotherapy in patients aged 70 years or younger with primary CNS lymphoma. But the risks and implications of cognitive impairment after WBRT should be considered at the time of therapeutic decision.^[41]

CONCLUSION

PCNSL is a “whole brain disease and rare subtype of extranodal, non-Hodgkin’s lymphoma. HD-MTX-chemotherapy with or without subsequent WBRT is the most commonly used first-line treatment. PCNSL shows a fair response to chemotherapy or radiation therapy, but

the survival outcome is inferior compared to lymphomas located outside of the CNS. The neurotoxicity of radiotherapy has triggered the development of novel approaches, including dose reduction of radiotherapy, consolidation with non-myeloablative chemotherapy or regimens with high-dose, myeloablative conditioning, and autologous stem cell transplantation.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest in relation with this article.

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