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Epidemiology and Outcome of Primary Cerebral Lymphoma in Immunocompetent Patients: A Monocentric Study

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Abstract

Primary cerebral lymphoma (PCL) is a form of extranodal non-Hodgkin's lymphoma with a poor prognosis. Very few cohorts have been reported in the literature. It is a rare form in 1% of extranodal lymphomas, and 3% to 4% of brain tumors. The most common histological type is diffuse large B-cell lymphoma. Survival is improved by combining immunotherapy with chemotherapy. This is a descriptive retrospective study conducted at the Casablanca hematology center over a period of 9 years. The aim of this study was to report our experience by studying the clinical, paraclinical, therapeutic and evolutionary profile of patients with primary cerebral lymphoma. We present a study of 22 patients with PCL. The clinical, radiological and histological findings are shown along with the results of treatment. Patients were aged 25 - 75 years (mean 47 years) with a male predominance (77%). Computed tomography (CT) scans were performed on 16 patients (73%) and Brain magnetic resonance imaging for 16 patients (73%). Typically, lesions were multiple, isodense, and showed uniform enhancement with contrast medium. Immunocytochemical studies demonstrated 21 B-cell and 1 mantle-cell lymphomas. All patients received chemotherapy through high-dose MTX with whole brain radiotherapy (WBRT). After a median follow-up of 19 months, 54% are in complete remission, 32% have died, and 14% are lost to follow-up. Overall survival at 24 months and 36 months were 72% and 52%. The event-free survival at 24 months and 36 months were 60% and 48%. This study was to investigate the clinical features of PCNSL, and evaluate the efficacy of high-dose methotrexate (MTX)-based chemotherapy for immunocompetent Moroccan patients with PCNSL.

Keywords

Primary Cerebral Lymphoma (PCL), Retrospective Study, Management

1. Introduction

Primary cerebral non-Hodgkin's malignant lymphomas correspond to brain intraparenchymal lymphomatous tumors occurring in patients without a history of NHLM and not presenting lymphomatous locations outside the central nervous system (CNS), spinal cord, cerebral spinal fluid (CSF), brain parenchyma or eyes, it represents 4% of intracranial neoplasms and 4% - 6% of extranodal lymphomas [1] [2]. The incidence rate is about 0.47 per 100,000 person/year, and it mainly affects elderly male individuals [3]. PCNSL incidence rates steadily increased from 1960 to 1995. After the late 1990s, it remained stable in those younger than 65 years, likely due to reduction in the incidence of acquired immune deficiency syndrome (AIDS) and improved retroviral treatment. However, for patients aged > 65 years, the incidence continues to increase [4]. The diagnosis is based on the anatomopathological examination of the tumor; in more than 98% we find a diffuse large cell lymphoma B, more rarely a small cell lymphoma [5]

It is considered a curable disease, with a good response to high-dose chemotherapy, Antimetabolites, including methotrexate and cytarabine, are the mainstay of treatment for primary cerebral lymphoma and may be followed by consolidation radiation therapy or high-dose chemotherapy and autologous stem cell transplantation [6]. The prognosis has improved in recent years thanks to new treatment systems; however refractory and relapsed CNSLs have a poorer prognosis and may be resistant to the traditional agents used to treat this disease [7]. Our department recruits 300 new cases of non-Hodgkin lymphoma each year. The aim of our work is to report our experience via a descriptive study of the epidemiological, clinical, therapeutic and evolutionary profile of these lymphomas.

2. Patients and Methods

We conducted a descriptive retrospective study at the clinical hematology and pediatric oncology department of the IBN ROCHD university hospital in Casablanca, over a period of 9 years from January 2012 to December 2020, including adult patients over 18 years old with primary cerebral lymphoma whose diagnosis was based on histological study. The data were collected from patient files using an operating sheet and made it possible to bring epidemiological [age, sex, annual recruitment in the service clinical], biological [anatomopathological study, brain imaging, extension assessment, LDH level] the therapies administered, the response to the treatment, the date of relapse as well as the date of death or last news. All patients received first-line therapy according to the LCP

protocol containing 5 cycles of high-dose methotrexate 3.5 g/m^2 with 4 intrathecal chemotherapy injections followed by total encephalic irradiation at a dose of 40 Gy in 20 fractions then 2 cures of high-dose cytarabine 3 g/m^2. An MRI or CT scan was performed after 5 cycles to assess the therapeutic response. Data collection and statistical analysis are done using Microsoft Excel software. Overall Survival (OS), progression-free survival (PFS), and disease-free survival (DFS) were determined using the Kaplan-Meier method. The log-rank test was used to compare survival curves and to verify the association between categorical variables and survival curves. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 11.0.

3. Results

3.1. Epidemiology

22 patients with PCL were diagnosed during the period of the study. The median age at diagnosis was 47 years old [25 - 75]; 86% (n = 19) of patients were younger than 60 years old, and 4 among them had less than 50 years old. The male/female sex ratio was 3.4 with a male predominance: 17 men (77%) and 5 women (23%) (**Table 1**). The annual distribution was variable. The number of cases per year ranged from 2 cases (9%) in 2012 to 5 cases (23%) in 2020. The median annual incidence was 2 cases per year (**Figure 1**).

3.2. Clinical Data

The median time to consultation was 3 months with extremes ranging from 15 days to 24 months. At diagnosis, headaches were found in all patients (100%), 19 patients had a motor deficit (86%): hemiparesis, paraparesis, hemiplegia and walking disturbance, 4 had diplopia (18%), 3 patients had an aphasia-type language disorder (13%) A generalized seizure was revealed in 7 patients (32%).

1) Paraclinical data:

Radiology: 16 patients (73%) underwent a cerebral computed tomography examination, and 10 (45%) had in addition magnetic resonance imaging (**Figure 2**).

The most frequent localization was supra tentorial, the lesions were mainly iso- to slightly hyperdense on CT without injection. They are strongly enhanced after i.v. injection of iodinated contrast (**Figure 2**).

Histology: The diagnosis was made by stereotactic biopsy in 20 patients (91%) and by surgical excision in 2 (9%). The pathology study with immunohistochemistry diagnosed diffuse large B-cell lymphoma in 21 patients (96%) and mantle cell lymphoma in one patient.

Extension assessment: The lumbar puncture was performed in all patients; 8 at diagnosis and 14 during the first cycle of chemotherapy, it returned positive in 2 (9%). no bone marrow infiltration was noted on bone marrow biopsy performed in 91% of patients. Thoraco-abdominopelvic CT was performed for 99% of patients, without evidence of lymphomatous localization.

Table 1. Epidemiological characteristics of patients.

	N	%
AGE (Y)		
>60	3	14
<60	19	86
Sexe		
F	5	23
M	17	77

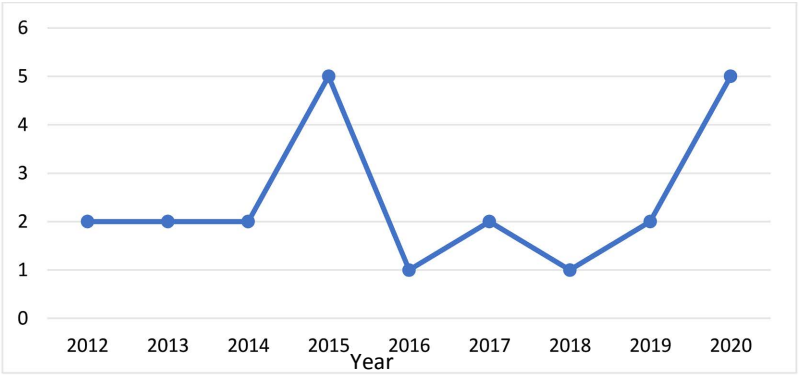


Figure 1. The annual distribution of patients.

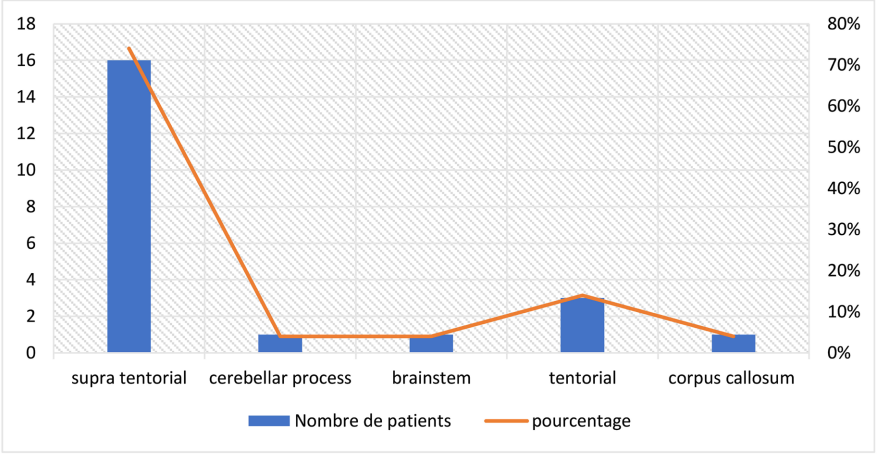


Figure 2. Distribution of patients according to the location of the brain lesion.

3.3. Treatment and Evolution

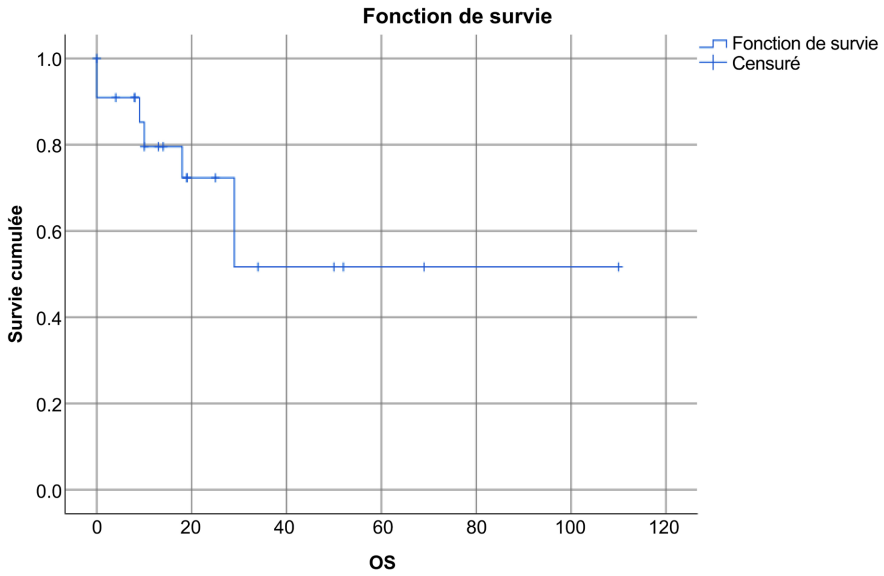
All patients were treated according to the LCP protocol on the first line; 3 patients couldn't be evaluated, and 2 died after the 1st cycle and 1 after the 2nd cycle due to the progression of the disease. The median duration of treatment with 5 cycles of chemotherapy was 3 months. Only 8 patients received procarbazine during all cycles of treatment. Procarbazine was started in the third and fourth cycle in 2 and 4 patients respectively, and 5 patients received treatment without procarbazine. 18 patients had received radiotherapy.

Radiological assessment after induction showed that 15 patients were in complete remission (79%) and 4 patients were in partial remission (21%). At the end

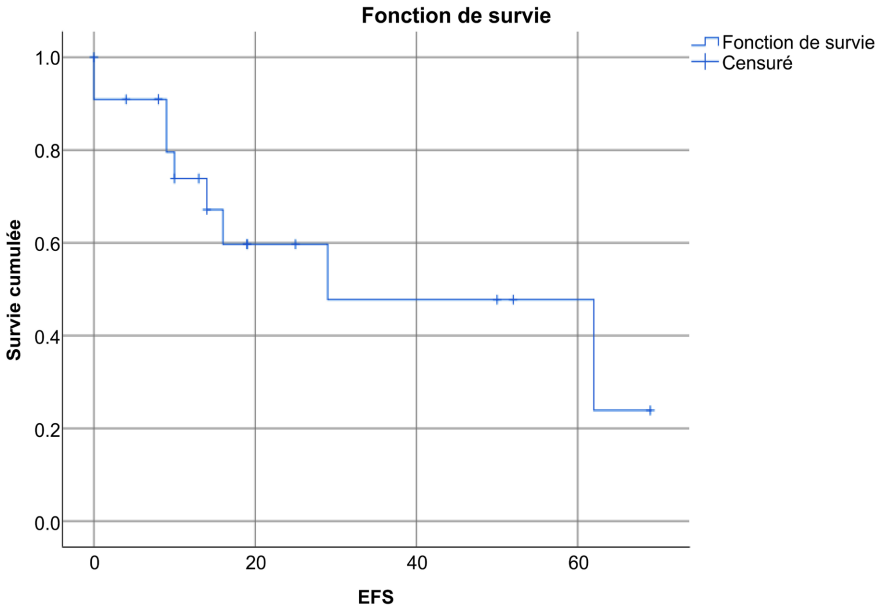
of treatment, 15 patients were in complete remission (79%), 1 died and 3 were lost to follow-up. The relapse was observed in 6 patients (31%): 4 of whom presented an early relapse. The median time for relapse was 1 year [9 months - 18 months] and the site of relapse was testicular in 2 patients and cerebral in 4 patients.

After a median follow-up of 20 months, 58% are in complete remission, 27% have died, and 15% are lost to follow-up. Overall survive at 24 months and 36 months: 72%, 52%. The event-free survive at 24 months and 36 months: 60%, 48%.

Clinical, paraclinical and evolutionary characteristics are summarized in Table 2.



Kaplan-Meier survival curve for 5-year overall.



Kaplan-Meier survival curve for 5-year progression-free survival.

Table 2. Summary of clinical, biological and evolutionary characteristics of patients.

	Nombre	Pourcentage
Clinical		
HTIC syndrome	6	27
Headache	22	100
Motor disorders	19	86
Paresthesias	3	13
Speech disorder	3	13
Seizure	7	32
ECOG PS		
<2	9	41
≥2	13	59
Histology		
Diffuse large B-cell lymphoma	21	96
Mantle cell lymphoma	1	4
LDH level		
Normal	16	73
High	6	27
Lumbar puncture	Total = 8	
Normal	6	75
Infiltrated	2	25
Osteomedullary biopsy		
Normal	21	96
Infiltrated	0	0
Not done	1	4
Median of follow up of 20 months		
Complete remission	11	58
Death	5	27
Lost to follow up	3	15

4. Discussion

Primary CNS lymphoma is a rare tumor with poor prognosis, it has become the second most common malignant brain tumor in the US behind gliomas [8], and the incidence rate is about 0.47 per 100,000 person/year, more frequently affecting elderly and male individuals, with a median age of 60 years at diagnosis [9]. in a study carried out at a reference center for cancer in Brazil (University of São Paulo) between 1995-2016 including 35 patients, the mean age was 62 years, with a sex ratio of 1.3 [10], in another Chinese series about 32 patients the mean age was 50 years [11], in a British study carried out on a cohort of 122 patients the median age was 66 years [12], in our series the population was younger with a median age of 47 years. Primary CNS lymphoma presents clinically with neu-

rological signs: mental status and behavioral changes (32% to 43%), symptoms of increased intracranial pressure (headaches, nausea, vomiting, papilledema, 32% to 33%), and seizures (11% to 14%), focal neurologic deficits represented the most frequent clinical sign in our series 87% VS (56% to 70%) in the literature [13]. Brain Magnetic resonance imaging (MRI) is the imaging modality of choice and PCNSLs appear as a single lesion (60% - 70%) or multiple lesions (30% - 40%) taking contrast intensely and homogeneously and without necrosis, which makes it possible to distinguish them glioblastomas [14]. Usually, it is a single, supratentorial lesion (87%) which agrees with our results (75%) and involvement of the fronto-parietal lobes (39%). Less frequently, eyes (15% to 25%), CSF (7% to 42%), and only in rare cases, the spinal cord are involved [15]. The demonstration of the radiological lesion is then followed by a biopsy for histological confirmation. The morphological pathological examination shows immunoblasts or more often centroblasts around cerebral vessels of small or medium caliber. This angiotropism is an important feature of LCPs and contributes to the breakdown of the blood-brain barrier [5] the immunohistochemical study of which shows almost for all the PCNSL an expression of CD 20, CD 22 or CD 79. Strong expression of IRF4/MUM1 is present in about 90% of cases, expression of BCL6 is observed in 30% - 60%, and expression of BCL2, unrelated to t (14; 18) (q32; q21), is present in 56% to 93% of cases [16] [17]. CD10 + is present in 10% to 20% of cases. Other rarer histologies include T-cell PCNSL (2%) [18], marginal zone intraparenchymal lymphoma, and lymphoblastic and Burkitt's lymphoma. In our series only one mantle cell lymphoma was found, 96% of which was diffuse large B-cell lymphoma.

Currently, several genetic and molecular aberrations have been demonstrated in LCPs; The most frequently identified chromosomal abnormality in PCL is a deletion at 6q21-25, including the HLA locus. Homozygous deletions as well as methylations of the CDKN2A gene (cell cycle regulator) have been found in approximately 45% of cases and are linked to a poor prognosis [19]. Dysregulation of the NFκB pathway, in particular mutations of CARD11 [20], MALT1 [21], and MyD88 have been described in the literature, with a rate that reached 76% in a series of 71 LCPs published in 2015; without significant prognostic value [22] [23]. Some studies showed a relative over-expression of the MYC oncogene in LCPs when compared to systemic DlBCL [24]. In our practice, the genetic and molecular assessment is not a routine examination in our laboratories; its research remains difficult and expensive. As a result, this assessment has not been carried out in any of our patients.

The prognostic factors of CNS lymphoma were established according to the International Extranodal Lymphoma Study Group uses age, the performance score of the Eastern Cooperative Oncology Group, the level of lactate dehydrogenase, CSF protein concentration and profound brain damage the presence of 0 to 1, 2 to 3 or 4 to 5 adverse risk factors correlates with 2-year survival rates of 80%, 48% or 15%, respectively [25].

The therapeutic management of CNS lymphoma combines chemotherapy

with high dose methotrexate and total encephalic irradiation which improved median OS to 30 to 60 months and had 5-year survival rates of 30% to 0%. in our series, radiotherapy was started systematically for all patients, a phase III randomized study conducted in PCNSL examined whether omission of WBRT affected survival and concluded that patients who received radiotherapy had a longer progression-free survival of 18 months compared to 12 months in patients who received chemotherapy alone, but no difference in OS was appreciated. Based on this data and the high risk of neurotoxicity, most clinicians rule out WBRT as part of the routine care of patients with PCNS [25] [26].

For treatment regimens, currently high dose methotrexate and RITUXIMAB should be part of the first-line induction therapy with radiotherapy and high-dose cytarabine or etoposide for consolidation, a comparison between high dose methotrexate with TEMOZOLOMIDE and high dose methotrexate + vincristine + procarbazine in a population > 60 years old concluded that the overall response was 82% in the HD-MTH, vincristine, procarbazine group and was 71% in in the HD-MTX group with TEMOZOLOMIDE, the median OS durations were 31 and 14 months, respectively. Although these trends are not statistically significant, the results favored HD-MTX, vincristine and procarbazine treatment [27]. In our study, Rituximab was not offered with high-dose methotrexate + vincristine + procarbazine in the 1st line, but used as salvage therapy. Concerning intrathecal chemotherapy although it is still used in our department for a total of 4 injections of MTX, two large retrospective studies have shown no additional benefit in combination with high dose methotrexate [28] [29]. Rituximab was also used as monotherapy and in combination with intrathecal MTX in two phase I trials, the results showed its efficacy in meningeal and intraocular localizations and parenchymal lesions < 2 cm [30] [31].

Autologous hematopoietic stem cell transplantation (ASCT) has taken an important place in the consolidation treatment of PCL, whether in the first line or for refractory or relapsed patients. It is currently offered as an alternative to whole brain radiation therapy. A radomised clinical trial compared consolidation by ASCT and by WBRT in 140 patients with PCL in terms of efficacy and toxicity. 2-year progression-free survival was achieved in 63% of patients in the WBRT arm and 87% in the HD-ASCT arm. While toxicity was more marked with worsening of cognitive disorders in patients treated with WBRT [32].

For the 2nd line treatment, the re-introduction of high dose of methotrexate can be proposed in patients who have had a late relapse with an overall survival of 41 to 62 months; radiotherapy is proposed for patients who have not received it as part of the initial treatment. Prospective trials using single agents, such as Trexed, topotecan, temozolomide or rituximab, demonstrated modest ORRs of 31% to 55% and limited median PFS durations of 1.6 to 5.7 months [33] [34] [35] [36] [37], however, to date no randomized trials have been conducted for patients with recurrent or refractory PCNSL to be able to determine an optimal rescue regimen. Results of treatment by different regimen reported in literature are reported in **Table 3**.

Table 3. Therapeutic results according to different regimens.

Study	N	Chemotherapy	intrathecal	radiotherapy	CR (%)	PFS median mos	OS median mos
Pels *et al.* [38]	65	Methotrexate prednisone Ifosfamide vincristine cytarabine	Methotrexate	None	61	21	50
DeAngelis *et al.* [39]	110 102	MPV/cytarabine	Methotrexate	36 - 45 Gy	58	24	36,9
Thiel *et al.* [26]	551	**Arm 1**: Methotrexate	-	45 Gy	35	18	32
		Arm 2: MTX + ifosfamide	-	None	12		37
Hoang xuan *et al.* [40]	50	HD MTH, lomustine procarbazine	Methotrexate cytarabine	None	42	12	14,3
Gavrilovic *et al.* [41]	57	MPV	Methotrexate	45 Gy in those aged < 60 year	56	129	51
Our series	22	HDMTX, VCR, procarbazine	Methotrexate cytarabine	20 - 40 Gy	58	25	29

MPV: Methotrexate, procarbazine, vincristine; HD: high dose; CR: complete response; PFS: progression free survival; OS: overall survival; Mos: months, HD-MTX: high dose methotrexate, VCR: vincristine.

5. Conclusion

Primary cerebral lymphoma remains a rare pathology; our cohort was small 22 cases in 9 years characterized by young age. The problem of chemotherapy in brain tumors is particular since it is necessary to use molecules crossing the blood-brain barrier despite that the therapeutic management has improved with the combination of immunotherapy and chemotherapy; in our experience we was unable to use Rituximab in 1st line and intensification by autologous hematopoietic stem cell transplantation was not performed in any patient. The overall prognosis for PCL remains pejorative, with a median follow-up of approximately 30 to 60 months, which is consistent with our series, noting a median overall survival of 29 months. However, efforts still need to be made to improve the management of primary cerebral lymphomas in Morocco.

Authors' Contributions

Authors' contribution provides literature review, manuscript preparation and editing.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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