



Patterns of relapse after successful completion of initial therapy in primary central nervous system lymphoma: a case series

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Abstract

Purpose Primary central nervous system lymphoma (PCNSL) is a subtype of non-Hodgkin's lymphoma that involves the brain, spinal cord, or leptomeninges, without evidence of systemic disease. This rare disease accounts for ~3% of all primary central nervous system (CNS) tumors. Methotrexate-based regimens are the standard of care for this disease with overall survival rates ranging from 14 to 55 months. Relapse after apparent complete remission can occur. We sought to understand the outcomes of patients who relapsed.

Methods This is an IRB-approved investigation of patients treated at our institution between 12/31/2004 and 10/12/2016. We retrospectively identified all cases of PCNSL as part of a database registry and evaluated these cases for demographic information, absence or presence of relapse, location of relapse, treatment regimens, and median relapse-free survival.

Results This analysis identified 44 patients with a pathologically confirmed diagnosis of PCNSL. Mean age at diagnosis was 63.1 years (range 20–86, SD = 13.2 years). Of the 44 patients, 28 patients successfully completed an initial treatment regimen without recurrence or toxicity that required a change in therapy. Relapse occurred in 11 patients with the location of relapse being in the CNS only (n = 5), vitreous fluid only (n = 1), outside CNS only (n = 3), or a combination of CNS and outside of the CNS (n = 2). Sites of relapse outside of the CNS included testes (n = 1), lung (n = 1), adrenal gland (n = 1), kidney/adrenal gland (n = 1), and retroperitoneum (n = 1). Median relapse-free survival after successful completion of therapy was 6.7 years (95% CI 1.1, 12.6).

Conclusion After successful initial treatment, PCNSL has a propensity to relapse, and this relapse can occur both inside and outside of the CNS. Vigilant monitoring of off-treatment patients with a history of PCNSL is necessary to guide early diagnosis of relapse and to initiate aggressive treatment.

Keywords Central nervous system lymphoma · PCNSL · Relapsed disease · Extranodal sites

Introduction and background

Primary central nervous system lymphoma (PCNSL) is an uncommon parenchymal brain neoplasm confined to the brain, eyes, spinal cord, or leptomeninges without evidence

of systemic disease [1, 2]. The histopathology of this aggressive tumor is typically diffuse large B cell lymphoma (DLBCL) [3]. PCNSL is a subtype of non-Hodgkin's lymphoma (NHL) that accounts for up to 3% of all primary CNS tumors [4]. The incidence of PCNSL is increasing,

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particularly in immunocompetent individuals, with a recent rate reported in the literature of 0.5 per 100,000 [1, 3].

Historically, treatment primarily focused on whole brain radiotherapy (WBRT) alone [3]. WBRT demonstrated favorable responses; however, these responses were not durable, and this treatment modality was associated with significant neurotoxicity [3, 5, 6]. For neuro-oncology providers today, methotrexate (MTX)-based chemotherapy regimens are the standard of care [7]. High-doses of intravenous MTX, typically at least 3 g/m² or higher, have improved tumor responses with sufficient penetration of the blood brain barrier resulting in increased survival [8]. However, its use as a single-agent is not adequate and most consensus guidelines recommend a multimodal treatment approach, though the ideal regimen remains unknown. PCNSL is a markedly chemo-sensitive neoplasm often resulting in a complete response (CR) to initial treatment. Unfortunately, relapse is not uncommon. Rates of recurrence range between 30% up to 90% in the first 2 years after initial treatment [1, 9]. We sought to describe the outcomes of patients treated at our institution who relapsed after apparent complete remission with induction chemotherapy.

Methods

Study design

We conducted this retrospective, Institutional Review Board (IRB)-approved analysis of patients initiating care at Duke University Medical Center between 2004 and 2016. We identified patients using a registry database of rare brain tumors that included PCNSL and queried the following diagnoses: Diffuse Large B-Cell Lymphoma, CNS Lymphoma, and B Cell Lymphoma. Patients with systemic disease were not included in this review.

The primary aim of this analysis was to describe the patterns of relapse among PCNSL patients with a complete response after completion of initial treatment. Complete response (CR) was identified as brain imaging revealing widespread loss of all enhancing lesions as well as patients being off corticosteroid therapy [10]. In addition to demographic information, we collected the following measures: absence or presence of relapse, location(s) of relapse, treatment regimens, date of relapse, and date of death / last follow-up. As part of the staging workup at our institution, patients routinely had the following workup and tests, including: slit lamp exam, testicular ultrasound (if male), bone marrow biopsy, cognitive testing, as well as PET scan. On occasional case-by-case basis, some patients did not have one or more of these tests due to the discretion of the treating physician. After patients completed treatment and achieved a CR, they had surveillance monitoring with

a brain MRI. For the first year MRI frequency was every 2 months, followed by every 3 months for the second year, and then every 4 months for the third year. This eventually transitioned to every 6 months for the fourth year, and then annually thereafter.

Statistical analyses

Descriptive statistics were used to characterize the demographics of the patient cohort. We utilized frequency distributions to summarize categorical variables, and used means with standard deviations and quantiles for interval descriptors. We used the Kaplan–Meier estimator to describe the distribution of survival time, where overall survival (OS) was defined as time from date of diagnosis to date of death or last follow-up. Relapse-free survival (RFS) was defined as time from completion of treatment to date of relapse or death among those that completed treatment respectively. Time-to-event endpoints were censored for patients who had not experienced the event at the time of the analysis.

Ethics approval and informed consent

We performed all study processes involving human subjects in accordance with the ethical standards of the IRB of the Duke University Health System.

Results

Our single institution retrospective analysis identified 44 cases with pathologically confirmed PCNSL. The mean age at diagnosis was 63.1 years (range 20 – 86, SD = 13.2 years). Demographic data are presented in Table 1. Patients were 54.5% female, 86.4% white, and 70.5% had a KPS ≥ 80%. Treatment and response are reported in Fig. 1. Of the 44 patients identified in this review, 43 received treatment with high-dose chemotherapy; the remaining patient pursued hospice care. Of the 43 patients treated with curative intent, all but one patient received a methotrexate-based treatment regimen. This one patient opted to receive care at a facility close to home for ease of care and received a cytarabine-based regimen. A majority of our patients received a regimen which included high-dose methotrexate 3.5 g/m² and rituximab 375 mg/m² therapy (n = 32), with 3 additional patients receiving concurrent intravitreal chemotherapy. A much smaller group received a multidrug regimen with high-dose methotrexate 3.5 g/m², rituximab 375 mg/m² and temozolomide 100 mg/m² (n = 2), with an additional 1 patient receiving concurrent intravitreal chemotherapy. Lastly, 5 patients received other regimens and 1 patient did not receive treatment. Of note, 90.9% of patients (n = 40) in our cohort received rituximab therapy in combination

Table 1 Patient characteristics

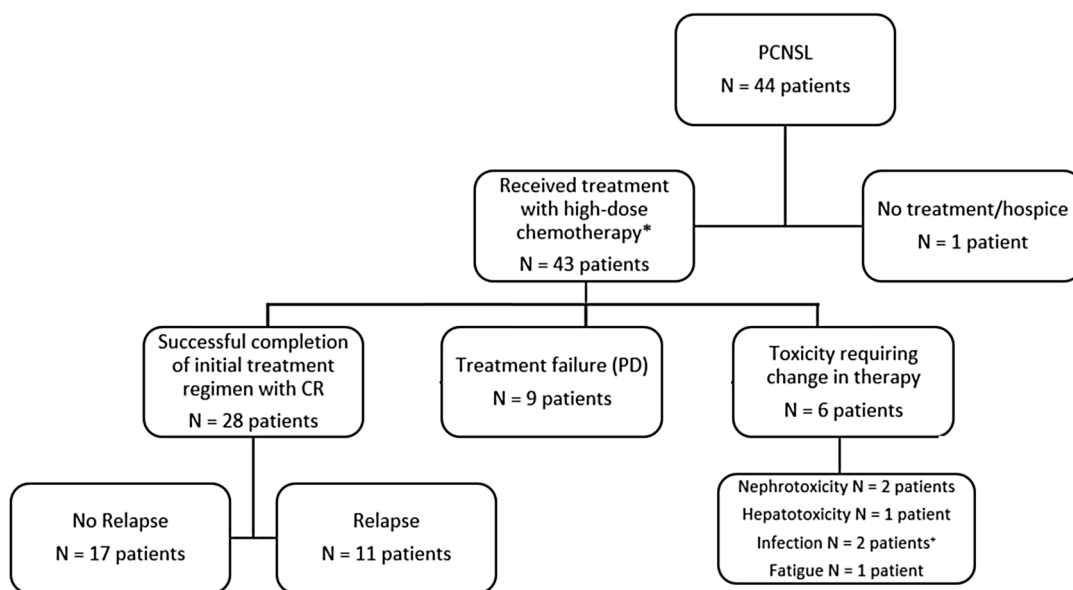
Characteristic	All (n = 44)	
	N	%
Gender		
Female	24	54.5
Male	20	45.5
Race		
White	38	86.4
African American	2	4.5
Asian	2	4.5
Native American	1	2.3
Unknown	1	2.3
KPS		
100	0	0
90	12	27.3
80	19	43.2
70	3	6.8
60 or lower	4	9.1
Unknown	6	13.6

KPS measured prior to treatment initiation at Duke

experiencing a toxicity that necessitated a change in therapy. There were 15 PCNSL patients who did not successfully complete their initial treatment regimen; 9 patients (60%) had progressive disease (PD) prior to completing treatment and the remaining 6 patients (40%) had toxicity that required treatment modification. Toxicity included: nephrotoxicity (n = 2), hepatotoxicity (n = 1), infection (n = 2), and fatigue (n = 1). The median OS among all 44 patients was 5.8 years (95% CI 3.7, 13.6) and 5-year OS was 53.4% (33.6%, 69.7%; Fig. 2).

Of the 28 patients who achieved a CR from initial treatment, 17 (60.7%) remained stable with no relapse. The remaining 11 patients (39.3%) had relapsed disease. The median RFS after successful completion of therapy was 6.7 years (95% CI 1.1, 12.6) and 5-year RFS was 55.4% (95% CI 30.9%, 74.4%; Fig. 2). Sites of relapse include the following: CNS only (n = 5), eyes only (n = 1), outside CNS only (n = 3), or a combination of CNS and outside CNS (n = 2). Sites of relapse outside the CNS include: testes, lung, kidney/adrenal gland, adrenal gland only and retroperitoneum (1 patient each; Table 2). On review of these 11 relapsed patients, the relapse for all patients that occurred in the CNS only was detected on MRI imaging only and not confirmed by pathology. For three of the five patients that experienced relapse outside of the CNS, we examined the available pathology. Specimens for these three samples exhibited monoclonal B-cell population of the same clonal

with aforementioned regimens. Twenty-eight (28) of these 43 curative intent patients (65.1%) successfully completed an initial treatment regimen and achieved a CR without



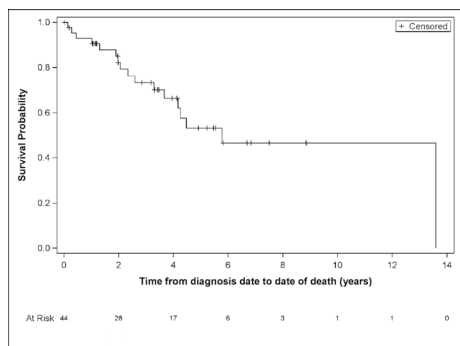
* 42 of 43 patients received treatment with high-dose methotrexate-based regimens
 + Patients with infection, include: Bacteremia and PCP Pneumonia
 CR = Complete Response, PD = Progressive Disease

Fig. 1 Treatment and response for PCNSL patients

PCNSL Retrospective Survival Estimates

Estimate	Total	# failed	Median survival in years (95% CI)	2-year survival (95% CI)	4-year survival (95% CI)	6-year survival (95% CI)	8-year survival (95% CI)	10-year survival (95% CI)
OS	44	17	5.8 (3.7, 13.6)	82.2% (66.1%, 91.1%)	66.5% (48.1%, 79.7%)	46.6% (25.9%, 64.9%)	46.6% (25.9%, 64.9%)	46.6% (25.9%, 64.9%)
RFS	28	11	6.7 (1.1, 12.6)	68% (44.3%, 83.3%)	62.4% (38.3%, 79.3%)	55.4% (30.9%, 74.4%)	36.9% (8.6%, 66.8%)	36.9% (8.6%, 66.8%)

Overall Survival Kaplan-Meier



Relapse-Free Survival Kaplan-Meier

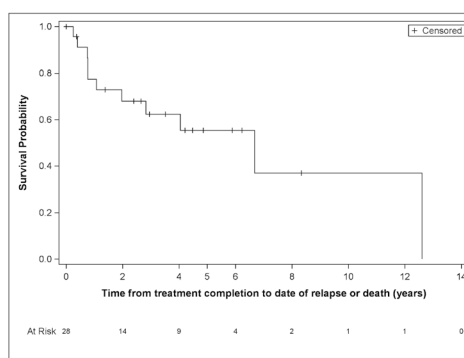


Fig. 2 Kaplan–Meier survival curves

Table 2 Site of relapse of PCNSL after complete response

Site of relapse (n = 11)	
Local	6 (55%)
CNS	5
Eyes	1
Distant	3 (27%)
Testes	1
Lung	1
Adrenal gland	1
Combination	2 (18%)
Kidney/adrenal gland and CNS	1
Retroperitoneum and CNS	1

process as determined by Ig kappa chain polymerase chain reaction (PCR). This retrospective analysis illustrates that PCNSL patients can experience relapse at distant sites after a complete response, including sites outside of the CNS.

Discussion

The definitive treatment regimen for patients with PCNSL is still unknown. While high-dose chemotherapy and radiation therapy both have merits and a role in eradicating this disease, they are not without toxicity. MTX-based polychemical or polypharmacy regimens are currently considered a mainstay in upfront treatment of PCNSL. However, long-term

follow-up is imperative, as some patients progress after an initial CR to induction therapy. As demonstrated by other small case series of PCNSL patients with relapse after initial CR, investigators sought to understand the mechanism through which patients undergo relapse [4, 11, 12]. One consideration is that relapse at distant sites occurs due to seeding from the blood and bone marrow [11]. Provencher and colleagues hypothesize that having a late recurrence introduces the question of whether the relapse is clonally related to the original disease or whether it is a distinct and separate cancer [4]. Others consider the possibility that current screening methods to determine initial staging and extent of disease may not fully elucidate presence of systemic disease [4, 12]. In our cohort, no patient had evidence of systemic disease at initial diagnosis based upon the following routine screening tools: whole body PET scan, brain and spine MRI, lumbar puncture, slit lamp exam, as well as testicular ultrasound in male patients 70 years and older. A small portion also had a bone marrow biopsy and cognitive testing, which was determined on a case-by-case basis. In further review of our cohort of patients who received treatment, 26 patients (60.5%) had a bone marrow biopsy performed as part of their routine screening. However, of those 17 patients (39.5%) who did not have a bone marrow biopsy initially, the decision was based on the discretion of the treating physician or initiation of treatment occurred at an outside facility. We posited whether PET scans need to be ordered annually for follow-up and subsequent staging. However, PET scans are costly monitoring tools and insurance coverage can be

problematic. In a review by Yang et al., the authors tried to understand better the contribution of imaging to cancer care costs [13]. They utilized cost data from the US Centers for Medicare & Medicaid Services, due to challenges obtaining accurate cost information from private insurers across the US health system. They found that while overall imaging costs are increasing relative to the cost of care, PET scans only account for a small percentage (1.5%) of this cost. While NHL is a Medicare approved indication for PET imaging [13], the optimal frequency of monitoring with a PET scan has not been addressed in guidelines [7].

In our study, a majority of our patients had a CR (28/43, 65.1%) to initial treatment. The median survival after successful completion of therapy was 6.7 years. We compared survival in our cohort of patients to those who were treated with high-dose methotrexate based regimens with or without rituximab therapy [14]. In their cohort of patients, both overall CR rate (60%) and median survival in those who achieved a CR (6.7 years), were found to be similar to our cohort of patients. This data is therefore suggestive that our cohort is representative of the typical PCNSL patients. However, of those patients with a CR to initial treatment, eleven patients (39.3%) subsequently relapsed. In our retrospective review, as well as similar case series reported in the literature, there is evidence that relapse after CR can occur at sites outside the CNS [9, 11, 15]. As most PCNSLs express CD20, use of an agent targeted against this receptor seems logical. In our cohort of patients, 90.9% of patients (n=40) received rituximab therapy in conjunction with their high-dose chemotherapy regimen. The addition of rituximab, a large, monoclonal antibody targeted against CD20, to high-dose MTX-based regimens remains controversial. The debate stems not from whether there may be benefit, but from uncertainty that the molecule itself can pass through the blood brain barrier to have activity against this disease. Holdhoff and colleagues describe a study in which 81 patients received either high-dose MTX alone or high-dose MTX in combination with rituximab therapy with each infusion. They showed that the addition of rituximab improved the CR rate, progression-free survival, and survival of newly diagnosed PCNSL patients treated with high-dose MTX [14]. A larger randomized study that sought to explore both the use of rituximab and multi-chemical MTX-based regimens reported improved outcomes with multi-chemical regimens that contained rituximab [16]. In contrast to these studies by Holdhoff and Ferreri, a recently published randomized, open-label, phase 3 study failed to show a distinct benefit from rituximab [17]. In spite of the contradictory evidence, we believe that it might be useful to consider maintenance treatment with an anti-CD20 targeted agent, due to our sizable percentage of patients with relapsed disease. Harjama and colleagues discuss the late relapse pattern of PCNSL patients and suggest that in addition to long-term follow-up, there may be a role

of maintenance rituximab therapy [18]. In a recently published paper, Ambady and colleagues retrospectively evaluated the effect of maintenance rituximab therapy on survival and risk of recurrence in PCNSL [19]. Their cohort included 66 total patients, with 20 receiving maintenance rituximab (dose = 375 mg/m² IV every 1–2 months for 3 months, then every 3 months until progression). They found that in patients who received maintenance rituximab therapy compared to the control group (surveillance only), there was a significant increase in duration of survival (HR 0.27, 95% CI 0.08–0.98, P=0.046). Unfortunately, the risk of recurrence was not found to be statistically significant (HR: 0.61, 95% CI 0.26–1.43, P=0.259) with the addition of maintenance rituximab therapy compared to surveillance alone. Interestingly, the authors did observe a disparity of approximately 20 months in median CR duration between the two groups; there was ~40% reduction in the risk of relapse in the maintenance rituximab group. These observations support further investigation in a larger, prospective study design to determine the potential benefit of maintenance targeted therapy. The role of rituximab in PCNSL continues to be an area of debate, both in the upfront setting and in maintenance therapy. Anti-CD20 targeted agents have been shown to be relatively safe and well-tolerated in this setting [20] and further research in larger sample sizes of patients will need to be evaluated to gain a true understanding of whether maintenance therapy targeted against CD20 may decrease distant relapses in patients with PCNSL after initial CR.

Conclusion

Many investigators have evaluated PCNSL patients at disease relapse; however, only limited case series are available for review due to the rarity of this disease. These patients need long-term follow-up in order to capture relapsed disease and to better understand best monitoring practices as relapses may occur both inside and outside of the CNS. Further investigation into maintenance treatment with anti-CD20 targeted therapy may provide additional guidance in this treatment's effect on RFS, OS, and the mitigation of relapsed disease. Vigilant monitoring of off-treatment patients with a history of PCNSL is necessary to guide early diagnosis of relapse and to initiate aggressive treatment.

Funding There was no funding for this study.

Compliance with ethical standards

Conflict of interest John P. Kirkpatrick reports grants from Varian Medical Systems. He is also an owner in limited partnership for Clear-Sight RT Products, not related to this work. Annick Desjardins owns stock in Istari Oncology. She has a consulting/advisory role for the

following companies: Celgene, Istari Oncology and Orbus Therapeutics. She has received research funding from the following companies: Orbus Therapeutics, Genentech/Roche, Symphogen, and Triphase Accelerator Corp. Dina Randazzo has a consulting/advisory role for the following company: Optune. She has receiving research funding from the following company: Medicenna. Henry S. Friedman owns stock and other ownership interests in 2X Oncology and Istari Oncology. He has received honoraria from and has a consulting/advisory role for Genentech/Roche. He is on the speaker's bureau for Genentech/Roche and has received travel, accommodations and expenses. David M. Ashley owns stock in Diverse Biotechnology. He has a consulting/advisory role for the following companies: Istari Oncology, Inc and The Jackson Laboratory. He has received research funding from the following companies: Midatech Pharma Plc. Katherine B. Peters has a consulting/advisory role for the following companies: Novocure, Agios, Eisai, Abbvie, Boehringer Ingelheim, and Monteris Medical. She has received research funding from the following companies: Agios, Abbvie, Bristol-Myers Squibb, Monteris Medical, and BioMimetix. Mallika P. Patel, Margaret O. Johnson, Patrick Healy, James E. Hurdon II, Eric S. Lipp and Elizabeth S. Miller declared that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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