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Original Research

Outcome of Primary CNS Lymphoma; A Retrospective Analysis

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Background: Rituximab along with high dose Methotrexate is nowadays the standard of care in treatment of PCNSL. We report the retrospective analysis of PCNSL patients who were treated with and without Rituximab at Aga Khan University Hospital, Karachi.
Patients and Methods: While analyzing seven years' data of PCNSL patients at Aga Khan University hospital, 52 patients encounter this rare disease. Patients diagnosed were around 54 years of age and with male predominance. HIV status though checked in 50% of patient was found to be negative in all. 36 patients completed treatment and among them 60% patients could not receive Rituximab during the course of treatment with high cost being the only reason of not receiving anti-CD 20 monoclonal antibody. Radiation as a part of consolidation therapy was received by 20 patients who achieved CR followed by two cycles of Cytarabine.
Results: Out of 36 treated patients, 17% patients (6 out of 36) had disease progression. The median progression free survival was 51 months (Hazard Ratio of 0.594, 95% Confidence Interval CI, 0.182, 1.934; $p < 0.388$). The addition of Rituximab monoclonal antibody to the chemotherapy regimen improved the PFS. However, 41% patients (9 out of 22) who did not receive Rituximab had no response after induction as compared to 29% patients (4 out of 14) who received Rituximab. The mean overall survival of treated PCNSL patients was 67 months (Hazard Ratio of 8.52, 95% CI 0.974, 74.51, $p< 0.053$). Within the cohort of 36 patients, 61% patients (22 out of 36) were still alive at the time of analysis. Among 39% who were dead, the most common causes were sepsis and progression of disease.
Conclusion: Primary CNS lymphoma though an aggressive entity can be cured with the combination of chemo-immunotherapy with a progression free survival and overall survival of about four to five years.

Introduction

Primary CNS Lymphoma (PCNSL) is a rare form of extra-nodal Non-Hodgkin's Lymphoma (NHL), which accounts for approximately 2% of all CNS tumors [1].It commonly exhibits a Diffuse large B cell lymphoma (DLBCL) histology and [2] it's survival is inferior to DLBCL of any other site [3]. It affects both the immunocompromised as well as the immunocompetent population, though it is markedly more aggressive in the former and especially when the CD4 count is less than 50 cells/mm3 [4]. Though it is aggressive in nature, it usually remains localized within the central nervous system and involves the eyes and meninges in 42% and 35% of cases [5].

Patients with PCNSL usually present with neurological symptoms such as altered mental status, seizures, focal neurological deficits and symptoms of raised intracranial pressure (e.g. headache, vomiting, blurring of vision) [6]. Older age at diagnosis, co-morbidities and poor performance status poses a great challenge in the treatment of PCNSL patients [7].

Prognosis of PCNSL has improved since last decade because of effective combination therapies, which has resulted in improvement in progression free survival as well as overall survival [8]. High dose Methotrexate is the backbone in the treatment of PCNSL and has shown to be highly effective

even as a single agent [9, 10]. Over the years, with the addition of multiagent chemotherapy, radiation and rituximab has led to an improvement of overall response and progression free survival to approximately 80% and 60% respectively [11].

At our center we predominantly use the modified DeAngelis Protocol which consists of five to seven cycles of MVP (Methotrexate, Vincristine and Procarbazine) followed by radiation and consolidation with two cycles of high dose Cytarabine [12]. This decision is based on the results of a phase II study, which reports a median PFS and OS of 3.3 years and 6.6 years respectively. In addition, there were acceptable rates of long-term neurotoxicity, which was desirable [13].

Treatment of PCNSL in a resource-constrained country is fraught with challenges. Cost of drugs especially rituximab, repeated inpatient hospital stays for chemotherapy infusions and management of toxicities results in modifications in the treatment protocol with impact to survival. Here, we report the patterns of treatment and outcomes of patients with PCNSL treated at Aga Khan University Hospital (AKUH) over a 7-year period.

Materials and Methods

The Ethical Review Committee (ERC) at AKUH approved this retrospective study. The recruited patients included all PCNSL patients treated at AKUH from February 2012 up until February 2018. Data was extracted from the Cancer Registry and Health Information and Management System (HIMS) at AKUH. Review of the patient's files provided data regarding disease diagnosis, treatment, complications, survival and cause of death, if any. Biopsy date was considered as the date of diagnosis. Patients who were lost to follow up were contacted through telephone calls and data regarding their health was recorded telephonically. The confidentiality of the patients was respected throughout the entire process and only the research team had access to the patient data.

Progression free survival and Overall survival were the two main outcome parameters assessed in this study. Progression free survival is defined as the time from diagnosis until radiological progression of disease [14]. Overall survival may be defined as the length of time for which the patient remained alive after the diagnosis of the disease [15]. Last hospital visit date provided information for the above two parameters.

Results

This study included fifty-two patients with PCNSL. They were recruited from February 2012 until February 2018. Out of these fifty-two patients, only thirty-six patients completed treatment (Table 1).

Characteristics	N = 36	(%)
Age in years		
Median (minimum, maximum)	54 (24 – 72)	11.5
Gender		
Male	21	58.33
Female	15	41.67
ECOG Performance status		
I and II	9	25
III and IV	7	19.44
Not known	20	55.56
HIV Status		
Negative	18	50
Not known	18	50
Treatment		

HDMTX + IT	3	8.33
MTX	1	2.78
MVP	24	66.67
MVP+IT	6	16.67
Not known	2	5.56
Response after Induction		
Complete Remission	18	50
Partial Remission	5	13.89
Not known	13	36.11
Second Line Chemotherapy		
Yes	1	2.78
No	35	97.22
WBRT		
Yes	20	55.56
No	16	44.44

Table 1. Patient Characteristics.

Patient Characteristics

The median age of included patients was 54 years (Range = 24 – 72 years). There was slight male pre-dominance. Twenty-four patients had an Eastern Cooperative Oncology group performance status of less than two [16]. HIV status was un-known in half of the patients. Out of 50% patients in which HIV status was checked, none was found to be HIV positive.

Treatment

The treatment of PCNSL evolved from single agent high dose methotrexate in 2009 to combination of high dose methotrexate with vincristine and procarbazine (MVP) in the subsequent years. Administration of combination chemotherapy is followed by brain irradiation and high dose cytarabine. 80% of the study population received combination chemotherapy. Sixty percent patients could not receive rituximab during treatment with high cost being the only reason of not receiving anti-CD20 monoclonal antibody.

Fifty percent patients (N=18) achieved complete remission (CR) after receiving methotrexate based induction regimen. Out of these 18 patients, 11 acquired CR without addition of rituximab in the induction regimen (p value = 0.006). Three patients had to receive two more cycles of the combination chemotherapy to obtain complete remission. One patient had disease progression while on induction chemotherapy. Since it was chemo-refractory, he received cranio-spinal radiation followed by monthly Temozolamide.

Twenty patients who achieved CR received radiation as a part of consolidation therapy. The dose of radiation was 45 Gray (Gy) which was given in an average of 20 to 25 fractions. As a final step in the treatment, the patients received two cycles of high dose cytarabine. Eighty-eight percent of the study population tolerated it easily with manageable toxicities.

Efficacy

Out of 36 treated patients, 17% patients (6 out of 36) had disease progression. Among these, three patients progressed while on first line therapy. In patients who had received Rituximab, 50% patients achieved complete remission (N=7 out of 14). This is equivalent to the number of patients who did not receive the targeted therapy (N=11 out of 22). Partial response was seen more frequently in the Rituximab group (21% vs 9%). Refractory disease was more likely in patients who

did not receive Rituximab (41% vs 9%). This illustrates that the addition of Rituximab improved the overall response rate (p value = 0.006).

In our PCNSL patients study, the mean Progression free survival (PFS) was about 51 months (Table 2).

Disease Progression		
Yes	6	16.67
No	30	83.33
Died		
Yes	14	38.89
No	22	61.11
Progression free survival (in months)	Mean	Std.Err
	51.1	8.03
Overall survival (in months)	Mean	Std.Err
	66.79	8.71

Table 2. Outcome.

Addition of rituximab to the chemotherapy regimen improved progression free survival with a hazard ratio for progression free survival in the rituximab arm as 8.52 (95% Confidence Interval CI, 0.974, 74.51, p-value 0.053) (Table 3).

Variable	Crude Hazard Ratio	95% CI	P-value
Targeted therapy received	8.52	0.974, 74.51	0.053

Table 3. Factors Affecting Progression Free Survival.

Mean overall survival (OS) of PCNSL patients treated at AKUH was 67 months (Table 2). There was no difference in overall survival amongst patient who did or did not receive rituximab, with the crude hazard ratio for overall survival in the rituximab arm of 0.594 (95% Confidence Interval CI, 0.182, 1.934; p value = 0.388) (Table 4).

Variable	Crude Hazard Ratio	95% CI	P-value
Immunotherapy received (Drug)	0.594	0 .182, 1.934	0.388
Response after Induction			
Complete Remission	0.064	0.015, 0.272	< 0.001
Partial Remission	0.286	0.068, 1.193	0.086

Table 4. Factors Affecting Overall Survival.

Within the cohort of 36 patients followed for median four years, 61% patients (22 out of 36) were still alive at the time of analysis. Among 39% patients (14 out of 36) who died, the most common cause of death was sepsis while on treatment (9 out of 14) followed by disease progression (5 out of 14).

Discussion

High dose MTX is the cornerstone in the treatment for PCNSL and is given in all patients without contraindications [17]. Because of the rigid monitoring required of electrolytes and urine output for clearance and prevention of complications, only tertiary care centers in Pakistan have the ability to treat this aggressive lymphoma [18]. This retrospective study conducted at one of the largest tertiary care center represents a snapshot of the behavior and outcome of the disease in Pakistan.

To the best of our knowledge, this is the first reported series of PCNSL patients from Pakistan.

Patient characteristics in our study is similar to the data reported from other institutions worldwide. HIV positivity is well described risk factor for PCNSL and is seen in 2-6% of the patients. In our study, none of the patients were HIV positive. A confounding factor is that only about half of the patients were not tested. Additionally, the prevalence of HIV/AIDS is low in Pakistan, which can contribute to the negative results [19].

In this study, the median age of the patients was 54 years (Range 24 – 72 years) which is consistent with the data from west and middle East [20]. Sixteen patients (31%) could not receive treatment. The reasons were mostly poor performance status and cost of treatment. Outcome data on ten of these patients is not available as they did not return for a follow-up visit. This is a recurring issue in LMIC countries as cost of medical care, lack of awareness or education and distance to the cancer center results in a significant proportion of patients opting for palliative care.

In our center, 84% patients received the modified DeAngelis protocol which consists of MVP alternating with MV as an induction regimen. Patients in complete remission (CR) after five cycles of induction therapy went on to receive the radiation therapy followed by two more cycles of high dose cytarabine. All patients were universally admitted to the hospital for HD-MTX in order to maintain adequate hydration and urine alkalization to ensure timely methotrexate clearance. In general, the induction treatment was well tolerated and all the patients were able to complete it without significant delays and toxicities. This illustrates that with the close monitoring and timely intervention, HD-MTX can be delivered in any age group.

Rituximab, anti-CD20 monoclonal antibody, is also an important component in the management of PCNSL patients. However, its role in the management is still controversial. In the HOVON 105/ALLG NHL 24 study, Jacoline et al found no role of rituximab in the treatment of PCNSL. Jacoline reports the event free survival rate of 49% (95% CI, 39 – 58) without rituximab vs 52% (Hazard ratio 1.0, 95% CI 0·70–1·43) with rituximab [21]. Caroline Houiller also found no impact of addition of rituximab to chemotherapy in terms of PFS and OS [22]. A retrospective analysis of the Czech Lymphoma study group registry concluded that Rituximab results in no significant improvement in OS in PCNSL patients, but was found to improve the PFS [23].

Owing to the high cost of Rituximab, it is not financially possible for all patients to afford adding this to their regimen. Therefore, only 39% patients (n=14) received Rituximab. Mirroring the data reported previously, Rituximab did not result in a significant CR benefit in induction therapy [18]. In terms of overall survival, we too report that there was no difference between the two groups. However, we did find improved partial response resulting in improvement of the overall response rate with the addition of rituximab to the treatment protocol.

There are studies who have found an increased response rate with addition of Rituximab, although one of these studies administered both Rituximab and Thiotepa concurrently and so the increased response rate cannot be solely attributed to addition of Rituximab as Thiotepa is known to be a highly active drug in PCNSL [24, 25]. Given these results, the true benefit gained by addition of Rituximab needs to be evaluated prospectively. This is of paramount importance in resource constrained countries where mitigation of cost will likely result in more patients being able to afford therapy.

The PFS and OS varies remarkably in the literature, owing mainly to variation in treatment modalities and patient demographics and the evolution of the treatment over the time. Mean PFS and OS reported in our study are 51 months and 67 months respectively. This is in sharp contrast to other recent studies where the median PFS and OS were significantly less, at about 9.9 and 29.8 months, respectively. Another large study conducted by xx et reports a similar median PFS and OS of 10.5 and 25.3 months respectively were achieved in a large study conducted [22, 24, 26]. Our outcomes are markedly higher than what is reported in the literature. One of the plausible

explanation is that our patient population is somewhat younger than the west. Also, there is likely a selection bias for offering treatments to those patients who are more likely to tolerate the intensity if the regimen. In addition, financial constraints of the family play a huge role in the decision making. This is evident as about 30 % of the patients either did not start or did not complete the treatment. All these factors, in turn, selects out a population who is most likely to benefit and have a superior outcome which has been highlighted in our analysis.

Over the last few years, management of PCNSL has evolved. Short course of high intensity regimen followed by upfront autologous stem cell transplant is currently considered the standard of care of patients with PCNSL. This protocol negates any benefit provided by whole brain radiation. Omitting radiation is an attractive strategy as it ameliorates the long term cognitive decline that is a known side effect of radiation. With regards to survival, autologous stem cell transplant has also been shown to improve Disease free survival (DFS) and Overall survival (OS) [27].

Unfortunately, we have not yet been successful in incorporating stem cell transplant in our treatment plan. The reasons are multifold, but the two most prominent ones are unavailability of Thiotepa and the significant financial cost of the transplant. Despite this shortcoming, we are still able to achieve excellent outcomes for our patients. We are currently in the process of analyzing the cognitive parameters of our survivors.

In conclusion, PCNSL is a rare disease with a variable outcome. Despite issues with drug availability, financial toxicity and lack of appropriate follow-up in a significant proportion of the patients, we are still able to demonstrate a favorable survival is patients who are able to adhere to the protocol. Rituximab is commonly used in the management of PCNSL, however, the exact benefit of rituximab is controversial and should be revisited.

Declarations

The authors have no conflicts of interest to declare.

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