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PRIMARY CNS LYMPHOMA : NEUTROPHIL TO LYMPHOCYTE RATIO PREDICTIVE OF SURVIVAL

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ABSTRACT The aim of this study was to analyze the prognostic factors in cases of primary CNS lymphoma (PCNSL) treated at our centre. A retrospective review of case records of PCNSL cases treated at our institute between 2005 and 2016 was performed. The prognostic value of age, sex, Serum Albumin, Neutrophil Lymphocyte Ratio (NLR), were assessed with respect to overall survival. A total of 32 patients were included in the study. The median NLR of the study population was 3.6. It was observed that patients with a low NLR (NLR≤3.9) had a significantly better median overall survival compared to the high NLR group (NLR>3.9) [58 months vs 15 months; p=0.011]. We found that the NLR is a unique prognostic tool that predicts survival in PCNSL.

KEYWORDS : Neutrophil to Lymphocyte ratio, primary CNS Lymphoma

INTRODUCTION

Primary Central nervous system Lymphoma (PCNSL) is a form of extra nodal Non Hodgkin lymphoma (NHL) which is restricted to the brain, spine, eyes and cerebrospinal fluid (CSF). Compared to NHL outside the CNS, the prognosis of PCNSL is poor.[1] It is a very rare tumor, accounting for less than 4% of all intracranial tumors and about 5% of all extranodal NHL.[2] Published data from the Indian population is limited. Prognosis of untreated patients is extremely poor. We wanted to analyze the prognostic factors associated with PCNSL in our patients. A handful of prognostic scores have been validated in PCNSL; age and performance status being the two consistent parameters in this regard.[3,4] The value of other prognostic markers have been inconsistent across studies. Hence, a special focus of the study was on the value of Neutrophil Lymphocyte ratio (NLR) as a prognostic marker in our PCNSL patients. The NLR is a simple tool which is being explored in relation to many malignancies as a prognostic marker and have been proven to be useful in many malignancies including breast, gastric and lung cancers.[5-7]

METHODS

A retrospective review of medical case records of cases of PCNSL treated at Amrita Institute of medical sciences between 2005 and 2016 was performed. Data relating to the clinical presentation, laboratory parameters, treatment modality and outcome were captured. The pre treatment complete blood count was recorded from which the NLR was calculated as the percentage of neutrophils / the percentage of lymphocytes. Cases of PCNSL with associated hematological disorders, Liver and renal dysfunction and documented active infections were excluded from the analysis, as these would affect the NLR independently. Patients who were seropositive for Human immunodeficiency virus (HIV), which is peculiarly common in PCNSL were also excluded. The prognostic value of age, sex, Serum Albumin, NLR (Neutrophil Lymphocyte Ratio) and the type of treatment, were assessed with respect to the survival. A cutoff of 3.9 was used for the NLR group stratification (that is to divide the group into Low and high NLR). This was derived from the receiver operating curve (ROC) plotted for our dataset. Date of progression of disease and dates of death were recorded and used in assessing survival outcomes.

The prognostic significance of each of the variable with respect to survival was assessed by univariate analysis using the cox regression test. The survival curves were derived using the Kaplan-Meier method with the log-rank test. Statistical analysis was performed by the SPSS software version 20. A p value <0.05 was considered statistically significant. Since the dates of progression could not be traced in a significant number of patients, the progression free survival (PFS) estimates are not being reported. The survival outcome used for analysis was overall survival (OS). Details pertaining to the mode of treatment, toxicities and treatment specific outcome are not being reported here

RESULTS

The total of 56 case records of PCNSL were retrieved. Out of these, 24 patients were excluded for lack of the required clinic-laboratory data, leaving 32 for the final analysis. Only two of the 56 patients were HIV positive. Patients who were in poor general condition to receive any therapy and who took treatment elsewhere were excluded from the analysis. Three patients who presented with febrile illness were excluded from the NLR analysis. The baseline characteristics of the study population is summarized in table 1.

Table 1 : Baseline characteristics

Study population (N)	32
Median Age (years)	61 (35-78)
Median follow up (months)	18 (2-155)
Sex distribution	16
Males	16
Females	
ECOG Performance status (n=28)	
1 & 2	19
3 & 4	9
Histology n (%)	
DLBCL	27 (85%)
T cell	2 (6%)
Low grade B cell	3 (9%)
Mean Albumin levels(gm/dl)	3.8 (2.9-4.8)
Mean LDH (units/L) [11 pts]	260 (110—554)
Treatment Received n (%)	
Chemotherapy alone	3 (10%)
Radiation alone	17 (53%)
Chemotherapy + Radiation	12 (37%)
Median NLR (29 patients)	3.6 (0.3-20.5)

[ECOG : Eastern cooperative oncology group , DLBCL: Diffuse large B cell lymphoma]

The median age of the study population was 61 years (35-78). The sex distribution in our patients was identical, showing no predilection for either sex. The most common histopathologic variant was diffuse large B cell lymphoma (DLBCL), which constituted close to 85% of the study group. There were 2 cases of T cell lymphoma and 3 low grade B cell variants of which one was marginal zone lymphoma (MZL). The

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treatment protocols instituted were either radiation (RT) alone (especially towards the earlier part of the study period, when chemotherapy in PCNSL was still evolving and later in patients who were considered unfit for chemotherapy), chemotherapy alone and a combination of chemotherapy and RT . The chemotherapy used was either high dose methotrexate (HDMTX) with Dexamethasone or HDMTX, dexamethasone, Cytosine arabinoside, vincristine and procarbazine (Deangelis protocol). It was interesting to note that more than half of our patients received RT alone as their therapy. Most of these patients were elderly or in poor performance status. Chemotherapy followed by radiation was instituted in 12 (37%) of the patients. Chemotherapy alone was the regime in 3 patients.

Prognostic information

Parameters like Age, sex, performance status (PS), LDH, Serum Albumin levels and NLR were assessed for impact on the survival outcome. The information of CSF cytology were not available in a majority of patients, hence not analyzed. The serum LDH were also available in only 11 patients, hence could not be analyzed as a prognostic marker.

Age & sex: The age of the study group was stratified as above and below 65 years for the purpose of analysis. There were 18 patients who were above 65 years of age. When the age was plotted against survival, it was seen that there was no statistically significant difference in the survival among the two groups. Only 4 among the 18 patients above 65(22%) were fit enough to receive multimodality treatment including chemotherapy and RT whereas in the group below 65, 8 out of the 14 patients (57%) were given multimodality treatment. Inspite of this, there was no significant difference in survival among the two groups. There were 16 males and a similar number of females in the study population. There was no difference in survival between the two groups

Albumin:

The mean albumin of the study group was 3.8 gm/dl, which was better than expected. The median survival in the low albumin group (≤3.5gm/dl) was 27 months compared to 43 months in the normal albumin group [Fig 1]. Although the survival was better in the latter, it did not reach statistical significance (*p*-0.42).

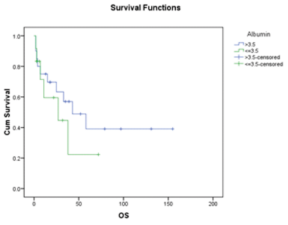

Figure 1 Kaplan Meier curve for Albumin vs OS

PS: The data on PS was available in 28 patients in whom 19 were PS ≤ 2 at presentation and the remaining 9 were PS 3. The survival was better among the better PS group (1&2) compared to the PS 3&4 group, but again did not reach statistical significance. (43 months vs 18 months *p* =0.23) [Fig 2]

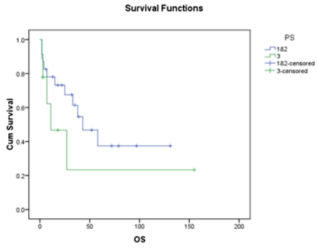

Figure 2 Kaplan Meier curve for Performance status vs OS

NLR: The median NLR of the study population was 3.6. The cutoff for NLR to define High vs Low values was 3.9 (As inferred from the Receiver Operator Curve [ROC] plotted for the dataset). There were 16 patients in the low NLR group (≤3.9) and 13 in the high NLR group (>3.9). The median overall survival in the whole cohort was 38 months. Patients with a low NLR had a significantly better median disease free survival [58 months vs 15 months; p=0.011] compared to the high NLR group [Fig 3]. The univariate analysis performed by the cox regression method revealed a significant association between NLR and survival. The Hazard ratio (95% Confidence Interval) for the high vs low NLR group was 3.8(1.3-11.2) and a *p=0.018*

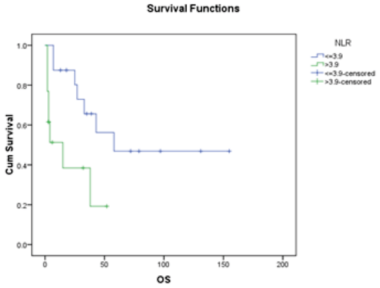

Figure 3 Kaplan Meier curve for NLR vs OS

DISCUSSION

The current study was primarily aimed at studying the various prognostic factors in PCNSL in our population and to get an insight into their clinic-pathological characteristics. The median age of the study population was 61 years, which is at par with the western data. The existing Indian data shows that the median age is between 44-50 years[8,9], which is a decade younger than the west[10]. The sex distribution was identical in our study, as reported by Pasricha S et al from western India[9]. Other Indian and western studies have reported a slight male preponderance. With regards to the histology, 85 % of our cases were DLBCL, with 2 cases of T NHL and 3 cases of low grade B cell neoplasm. This was fairly consistent with the existing literature.

As far as the prognostic markers are concerned, the special focus of our study was on the the value of NLR as a prognostic marker in PCNSL. The most widely used clinical prognostic score is the International extranodal lymphoma study group (IELSG) system, where risk factors such as age (>60 years), ECOG performance status (>1), elevated LDH levels, elevated cerebrospinal fluid (CSF) protein concentration and involvement of deep brain regions are used to derive a combined score between 0-5. The survival is poorer as the score generated is higher. The NLR, in comparison is a simple prognostic tool which is validated in many cancers. It has been explored in PCNSL in a recently published study in the South Asian population[11]. It has so far not been reported in the Indian population of PCNSL patients.

The neutrophil to lymphocyte ratio at diagnosis has been shown to be prognostic with respect to clinical outcome in solid tumours[6]. The rationale behind NLR is to compare the inflammatory response to the tumour on one side (represented by the neutrophils) and the immune status of the host (represented by the lymphocytes) on the other. High neutrophil count has been associated with poor survival in malignancy. Although the cause is not completely understood, a multifactorial process has been hypothesized[5]. Multiple hypothesis exist as to the mechanism to explain the prognostic significance of NLR. Also, a low lymphocyte count has been shown to be associated with poor outcome in advanced malignancy[12]. Many authorities believe that the cell mediated immunity protects against resurgence of residual disease after cancer therapy and keeps micrometastasis under check[13]. Based on these findings it seemed possible that a high NLR correlated to poor prognosis and further investigation in this regard were undertaken.

NLR also has been explored in lymphomas by a number of researchers. It has been shown that NLR is an independent prognostic factor in DLBCL[14]. A similar study by Keam et al also indicated that a high pretreatment NLR was significantly associated with poor PFS and OS in DLBCL patients treated with R-CHOP chemotherapy[15]. The study by Jung et al which explored the role of NLR as a prognostic marker in PCNSL demonstrated that the low NLR group had significantly greater OS and PFS compared with the high NLR group. The 3-year OS was 71.2% in the low NLR group compared to 42.5% in the high NLR group (p=0.031)[11]. The low NLR group in their study was defined as < 2, which was the cutoff derived from their dataset. In our study too we found that the low NLR group had a significantly better overall survival compared to the high NLR group.

In conclusion, the NLR is a unique and simple prognostic factor, easily derived in the labs, that predicts survival in PCNSL. Our study has some limitations. It's a retrospective study with a small study population, because of the rarity of the tumour and the good number of patients excluded due to the study requirements. Parameters to document the IELSG risk scoring in all patients was lacking from the database. Larger prospective studies may be done to validate this simple but promising prognostic tool.

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