Original Research Paper

Volume-9 | Issue-9 | September - 2019 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Oncology

NEUTROPHIL TO LYMPHOCYTE RATIO PREDICTS SURVIVAL IN PRIMARY CNS LYMPHOMA : CASE SERIES FROM A TERTIARY CARE CENTRE

Arun Philip — Assistant Professor, Department of Medical Oncology, Amrita Institute of Medical Sciences, Ponekkara, Kochi, India.

Wesley Jose

Beena K — Professor Department of Radiation Oncology, Amrita Institute of Medical Sciences, Ponekkara, Kochi, India.

Pavithran K* — Professor, Department of Medical Oncology, Amrita Institute of Medical Sciences, Ponekkara, Kochi, India. *Corresponding Author

KEYWORDS :

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 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 … 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 Mann- Whitney 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 19.0. A p value <0.05 was considered statistically significant.

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. 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	Males Females	16 16
ECOG Performance status 1 & 2 3		21 9
Histology n (%) DLBCL T cell Low grade B cell		 27 (84%) 2 (6%) 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 Radiation alone Chemotherapy + Radiation		 3 (10%) 17 (53%) 12 (37%)
Median NLR (29 patients)		3.6 (0.3-20.5)

ECOG : Eastern cooperative oncology group

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 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, 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.
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 and subject to a univariate analysis, as expected, it was seen that patients above 65 survived longer than their younger counterparts. 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.

The median NLR of the study population was 3.6. The cutoff for NLR to define High vs Low values was 1.85 (As inferred from the Receiver Operator Curve [ROC] plotted for the dataset). Patients with a low NLR (NLR<4.0) had a better median disease free survival [33 months vs 2.5 months; p=0.015] compared to the high NLR group (NLR>4.0).

Figure 1
NLR vs Nodal status

Figure 2
OS vs Nodal status

Figure 3
NLR vs Overall survival

Figure 4

DISCUSSION

The early treatment protocols in the 1980s revolved around radiation therapy (RT) which induced reasonable responses, but the median overall survival (OS) ranged from 12-18 months.[5,6] With the introduction of High dose Methotrexate (HDMTX) into the treatment protocols, the results markedly improved and HDMTX became standard of care along with RT.[7,8]

NLR is one such marker which is being explored in relation to many malignancies

NLR and malignancy

In solid tumors, baseline neutrophil count, as a surrogate marker of inflammation, has been associated with survival. Furthermore, the neutrophil/lymphocyte (N/L) ratio at diagnosis in solid tumors has been reported to be a prognostic factor for clinical outcome[6]. The rationale behind NLR is to compare the inflammatory response (i.e., neutrophils) produced by the tumour on one side to the host immunity (i.e., 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[1]. Neutrophils suppress the cytolytic activity of lymphocytes, natural killer cells, and activated T-cells in invitro cultures of neutrophils and lymphocytes from normal healthy donors[7]. The tumor-associated neutrophils, probably promote remodeling of the extracellular matrix, releasing basic fibroblast growth factor, migration of endothelial cells, and may help in dissemination of tumor cells[8]. Also, a low lymphocyte count has also been shown to be associated with poor outcome in advanced malignancy[9]. Many authorities believe that the cell mediated immunity protects against resurgence of residual disease after cancer therapy and keeps micrometastasis under check[10]. Based on these findings it seemed possible that a high NLR correlated to poor prognosis and further investigation in this regard were undertaken.

, the results indicated that a high NLR can influence the lymph node metastasis in breast cancer. This was very much in concordance with our study where we found a significant correlation between pre treatment NLR and nodal stage

CONCLUSION

The NLR is a unique and simple prognostic factor that predicts survival in PCNSL. Our data also shows that the treatment outcome for PCNSL is less than satisfactory. Although the median age of our patient population was 55, a decade younger than their western counterparts, majority of our patients were not considered candidates for any form of intensive therapy.

REFERENCES

1. Christian Grommes, Lisa M. DeAngelis: Primary CNS Lymphoma. J Clin Oncol 35:2410-2418.
2. Villano JL, Koshy M, Shaikh H, et al: Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer 105: 1414-1418, 2011
3. Ferreri AJ, Blay JY, Reni M, et al: Prognostic scoring system for primary CNS lymphomas: The International Extranodal Lymphoma Study Group experience. J Clin Oncol 21:266-272, 2003
4. Abrey LE, Ben-Porat L, Panageas KS, et al: Primary central nervous system lymphoma: The Memorial Sloan-Kettering Cancer Center prognostic model. J Clin Oncol 24:5711-5715, 2006
5. Hany Noh, Minseob Eomm, and Airi Han. Usefulness of Pretreatment Neutrophil to Lymphocyte Ratio in Predicting Disease-Specific Survival in Breast Cancer. J Breast cancer 2013 March, 16.1: 55-59
6. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. Oncology 2007;73:215–220.
7. Sarraf KM, Belcher E, Raevsky E, Nicholson AG, Goldstraw P, Lim E. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. J Thorac Cardiovasc Surg 2009;137:425–428
8. Nelson DF, Martz KL, Bonner H, et al: Non-Hodgkin's lymphoma of the brain: Can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys 23:9-17, 1992
9. Shibamoto Y, Ogino H, Hasegawa M, et al: Results of radiation monotherapy for primary central nervous system lymphoma in the 1990s. Int J Radiat Oncol Biol Phys 62:809-813, 2005
10. DeAngelis LM, Yahalom J, Thaler HT, et al: Combined modality therapy for primary CNS lymphoma. J Clin Oncol 10:635-643, 1992
11. Glass J, Gruber ML, Cher L, et al: Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: Long-term outcome. J Neurosurg 81:188-195, 1994