

Evaluation of Haematological Parameters and Lymphocyte Monocyte Ratio as a Prognostic Marker in Diffuse Large B-cell Lymphoma and T Cell Lymphoma Patients- An Observational Study

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Background: The present study is a retrospective observational analysis of patients diagnosed with DLBCL and T cell lymphoma during the period of January 2011 to December 2015 at Malabar Cancer Centre, Thalassery. Several studies have shown that ALC and LMR can be used as prognostic indicators for diagnosis, treatment and survival in DLBCL. But there were very few studies done on the correlation of these parameters with T cell lymphoma. So we analysed the influence of haematological parameters in both DLBCL and T cell lymphomas. The primary objective of the present study was to correlate haematological parameters and LMR as predictors of DLBCL and T cell lymphomas.

Methods: We analysed total cases of 108 with DLBCL and 25 with T cell lymphomas. The study was done to determine the changes in haematological parameters including WBC count, Platelet count, Hb, HCT, lymphocyte count, monocyte count, ALC, AMC and lymphocyte monocyte ratio in diffuse large B cell lymphoma and T cell lymphomas before and after chemotherapy.

Results: The results showed a significant decrease ($p < 0.05$) in the blood platelet counts after chemotherapy in DLBCL. AMC in female patients with DLBCL were decreased (0.69 ± 0.36 to 0.53 ± 0.31 ; p -value = 0.023) and this was highly significant. LMR was also increased (3.47 ± 3.05 to 5.22 ± 4.34 ; p -value = 0.048) in female patients with DLBCL.

Conclusion: Haematological parameters can be used as a prognostic marker in predicting the extent of disease progression and the effectiveness of the treatment adopted.

Introduction

Lymphoma is the general term for cancers that develop in the lymphatic system. The Non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) are the most commonly occurring hematologic malignancies [1]. NHL represents a heterogeneous group of malignancies that arise from the lymphoid system. NHL can start almost anywhere in the body either in a single lymph node, a group of lymph nodes, or in another organ and can spread to other parts of the body, including the liver, bone marrow and Spleen (non-contiguous spread). Sub-types of NHLs are broadly divided into two main groups: B-cell lymphomas - those that arises from developing B-cells, called Diffuse large B-cell lymphoma (DLBCL) and T cell lymphomas - those that arises from developing T cells [2]. DLBCL was the most common type of lymphoma and constitutes about 30% of all the cases. Peripheral T-cell lymphomas accounted for only 6% of lymphomas, reflecting their

rarity [3]. DLBCL is the most common lymphoid malignancy in adults accounting for approximately 30% to 40% of all cases. It is one of the most frequent subtypes of NHL, accounting for 25% of all newly diagnosed cases worldwide [4]. It is a large B lymphoid cell neoplasm with a diffuse growth pattern composed of large B-lymphocytes with nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of normal lymphocytes. Patients typically present with a rapidly enlarging symptomatic mass, with B cell symptoms in one third of the cases [5]. Localized (stage I or II) extra nodal disease occurs in up to 30%; bone marrow involvement was seen in 16%. Common extra nodal sites include the gastrointestinal tract, bone, and CNS. The prognosis was highly associated with the international prognostic index (IPI) score. DLBCL of certain extra nodal sites, such as the CNS, may be clinically distinctive and may have specific treatment protocols [6]. Peripheral T-cell lymphomas are a heterogeneous group of neoplasms presenting as advanced disease and are characterized by widespread dissemination, aggressive behaviour, and a very poor outcome despite aggressive therapy. The prognosis is dismal, with more than half the patients dying of their disease [7].

Patients with DLBCL should be staged according to both the Ann Arbor and IPI staging systems. The Ann Arbor staging system continues to be in use in DLBCL, provides limited prognostic information, but is of use in determining therapeutic management. The IPI provides more precise and reproducible prognostic information than the Ann Arbor stage, but does not distinguish patients eligible for combined modality therapy for localized disease [8, 9]. Treatment regimens rely up on the size and location of the tumor. It also depends on the purpose of the treatment, that is, whether it is intended to cure, to shrink the tumor prior to surgery or chemotherapy or to palliate an incurable tumor. Treatment for lymphoma may involve the use of chemotherapy, corticosteroid therapy, immunotherapy, radiotherapy, Stem cell transplant etc. [10, 11]. The US Food and Drug Administration (FDA) granted approval to rituximab and hyaluronidase as a subcutaneous injection for the treatment of diffuse large B cell lymphoma (DLBCL) in adult patients. Since 2002, the treatment has changed after addition of rituximab to CHOP chemotherapy (R-CHOP) which has led to advanced improvement in overall survival (OS) [12]. As a result, the IPI needed to be re described as to whether it still maintained its predictive value. Treatment regimens for peripheral T-cell lymphoma are the same as those used for DLBCL, but with the exclusion of rituximab [13, 14]. Overall survival in PTCL was very low when compared with DLBCL and so bone marrow transplantation was more frequently carried out. Bone marrow transplantation may be as effective in PTCL as in DLBCL [15, 16].

Prognostic factors in cancer patients provide information about possible clinical outcomes and help classify patients into different risk groups [17]. It is evident that components of the Complete Blood Cell (CBC) count can provide valuable prognostic information in solid tumours and hematologic malignancies and are important tools when evaluating response to treatment [18]. Anaemia is a common morbidity encountered in cancer patients and can be due to the malignancy itself or be a direct consequence of treatment. Therefore level of Hb and RBCs can provide relevant prognostic information in case of NHL and has also been studied as a prognostic factor in malignant disorders [19]. Chemotherapy drugs and radiation therapy can affect the bone marrow and lead to a low platelet count. Due to side effect there may be the destruction of some healthy cells and results in thrombocytopenia [20, 21]. The role of the WBC count has gone beyond the assessment of infectious processes and it has become an important prognostic measurement of outcomes in cancer treatment. The absolute WBC count has been historically used as a marker of infection and inflammation. It is a widely available tool for clinicians to identify the presence of infection and monitor the patient's response to treatment, such as antibiotics. An absolute lymphocyte count (ALC) is known to be a strong prognostic factor in DLBCL and is proven to be an independent prognostic factor for survival, independent of cancer type. Lymphopenia is an adverse prognostic factor in NHL of various subtypes, including DLBCL [22, 23]. Monocytes, which are considered immunologically relevant, are regarded as a surrogate marker of the tumor microenvironment, were also recently reported to be a prognostic factor in DLBCL. It has been postulated that monocytes promote tumor progression and support host antitumor immunity [24].

The lymphocyte-to-monocyte ratio (LMR) is the ratio calculated by dividing the absolute lymphocyte counts by the absolute monocyte counts from the blood test. Studies have indicated that the LMR at diagnosis can predict long-term outcome in patients with DLBCL [25]. LMR at diagnosis, as a simple biomarker combining an estimate of host immune homeostasis and tumor microenvironment, was recently shown to be an independent prognostic indicator in DLBCL. LMR can present the status of pro-tumour and antitumor ability in response to inflammation, and its value combining with lymphocyte and monocyte counts index may reflect the pro tumour ability and antitumor capacity of the host more concisely [26]. In addition, it is convenient and inexpensive to measure the parameter of LMR in clinical application, which makes it a fascinating marker for the prediction of DLBCL. LMR at diagnosis showed promise as a prognostic factor of survival outcomes in DLBCL patients receiving R-CHOP therapy [27, 28]. However, the present study checked the level of blood parameters like WBC, platelet count, Hb and HCT, ALC and LMR in patients with DLBCL and T cell lymphoma in pre chemotherapy and post chemotherapy period. It also assessed the effectiveness of ALC and LMR in predicting extend of disease progression and the effectiveness of the treatment adopted.

Materials and Methods

The present study is a retrospective observational analysis of patients diagnosed with B cell and T cell lymphomas during the period of January 2011 to December 2015 at Malabar Cancer Centre, Kerala, India. Since there were no ethical issues in this study we could easily cope up with the further formalities. This study was approved by the Institutional Review Board of Malabar Cancer Centre and data was abstracted from those that were maintained by the Cancer registry and Medical records division. We consecutively analysed case reports of 201 patients who were diagnosed with and treated for DLBCL and T cell lymphomas during the period of 2011 - 2015. All patients underwent a physical examination, lymph node biopsy and bone marrow aspiration and biopsy. The disease stage was assessed using enhanced computerized tomography scans from the neck to the pelvis and whole-body positron emission tomography scans. We restricted the analysis to those patients with complete laboratory data in the medical records. Among the 201 case reports, we analysed the medical records of those patients who underwent chemotherapy as a part of their treatment. Those case reports with laboratory test results of the patients prior to chemotherapy and after chemotherapy were abstracted and thus we had to exclude 68 of them. It was found that 108 and 25 records maintained complete treatment data of the patients with DLBCL and T cell lymphomas respectively. The following clinical and laboratory parameters were available at the time of diagnosis: MRD No., age, gender, WBC count, platelet count, Hb and HCT, lymphocyte count and monocyte count. The Absolute Lymphocyte count (ALC) and Absolute monocyte Count (AMC) were derived. The Lymphocyte Monocyte ratio (LMR) was calculated using the equation

$$\text{LMR} = \text{ALC} / \text{AMC}$$

Recorded the haematological parameters prior to the initiation of chemotherapy and after chemotherapy and entered in a computerized database. Patient files with missing data on monocyte or lymphocyte counts or one of the above CBC parameters before treatment were excluded.

Criteria For Analysis

Inclusion Criteria - Subjects with B cell and T cell lymphoma with complete treatment records were included in the study. Patients with incomplete medical records were excluded from the study.

Statistical Analysis

Statistical analysis was done by IBM SPSS version 23.0. Paired t test was done to assess the

changes in the B cell and T cell lymphoma before and after chemotherapy. P value <0.05 should be considered as statistically significant. Data was expressed n (%), Mean± SD, 95% CI etc.

Results

A total of 201 patients were diagnosed with DLBCL and T cell NHL during the period of January 2011 to December 2015. Among them 68 were excluded based on exclusion criteria. 36 of them dropped out treatment; 22 did not have complete treatment records; 2 died due to disease progression during treatment and 8 of them were sent to palliative centres. 108 cases with DLBCL and 25 with T cell lymphoma were enrolled. The changes of ALC, AMC and LMR and other haematological parameters before and after treatment were analysed in particular for DLBCL and T cell NHL. Then a comparison of all those parameters was made between the two NHLs to find out for significant changes.

Gender distribution of DLBCL and T cell lymphoma

The DLBCL patient's ages ranged from 10 to 77 years; the mean age was 55.12 years. Of these 68.51% were males and 31.48% were females and 5 patients were aged less than 30 years. The age of patients with T cell lymphoma ranged from 14 to 79 years and the mean age was 50.52 years. Of these 60% were males and 40% were females. 3 patients were aged less than 30 years (Figure 1).

Figure 1. Gender Distribution of DLBCL and T Cell NHL in Percentage.

Occurrence of stages and Percentage of incidence of stage subtypes in DLBCL

In DLBCL cases, 50.5% were diagnosed in the early stages and 49.5% in the advanced stages of lymphoma (Figure 2).

Figure 2. Percentage Incidence of Stage in DLBCL and T Cell Lymphoma.

Out of the early diagnosed cases, 64.2% of them come under sub-type A and 31.5% under sub-type B. In the advanced stages, it was found that 35.8% was A and 68.5% was B sub-types (Table 1).

		DLBCL			T Cell Lymphoma	
Stage	I/II		III/IV	I/II		III/IV
A	64.2		35.8	25		20
B	31.5		68.5	75		80

Table 1. Percentage of Incidences of Stage Subtypes in Lymphoma.

Occurrence of stages and Percentage of incidence of stage subtypes in T cell lymphoma

In case of T cell lymphoma, 34.8% NHL were diagnosed in the early stages and 65.2% in the advanced stages. Out of the early diagnosed cases, 25% of them come under sub-type A and 75% under sub-type B. In advanced stages, 20% are of A and 80% of B sub-types were observed. It is notable that large number of cases of T cell NHL is diagnosed only in the later stages (Table 1).

Effect of chemotherapy in haematological parameters in patients with DLBCL

In DLBCL, there were variations of haematological parameters before and after chemotherapy treatment. The WBC count before treatment was 8.75 ± 3.90 and after was 8.87 ± 8.52 . The level of Hb before treatment was 12.03 ± 2.04 and after was 12.23 ± 2.15 . The haematocrit value increased from 35.98 ± 6.19 to 37 ± 8.48 . Since their p values were not < 0.05 , the result was not statistically significant. The platelet count decreased from 304.37 ± 111.21 to 263.56 ± 105.68 and this was a remarkable variation. This result was highly significant as the p values were < 0.05 . The values of lymphocyte count and ALC increased from 25.25 ± 13.21 and 2.21 ± 2.59 to 27.51 ± 14.91 and 2.64 ± 4.02 respectively. Monocyte count and AMC decreased from 8.61 ± 3.99 and 0.72 ± 0.37 to 7.79 ± 3.88 and 0.66 ± 0.65 respectively. There was an increase of lymphocyte monocyte ratio from 3.66 ± 3.70 to 4.23 ± 3.73 after treatment. These variations were insignificant ($P > 0.05$) (Table 2).

Parameters	Chemotherapy		95% CI	P value
	Before	After		
WBC count (cmm)	8.75 ± 3.90	8.87 ± 8.52	(-1.88, 1.64)	0.893
Platelet Count (cmm)	304.37 ± 111.21	263.56 ± 105.68	(18.59, 63.03)	0*
Haemoglobin (g/dl)	12.03 ± 2.04	12.23 ± 2.15	(-0.59, 0.19)	0.315
Haemetocrit value	35.98 ± 6.19	37.00 ± 8.48	(-2.80, 0.75)	0.256
Lymphocyte (%)	25.25 ± 13.21	27.51 ± 14.91	(-5.43, 0.92)	0.162
Monocyte (%)	8.61 ± 3.99	7.79 ± 3.88	(-0.19, 1.82)	0.113
ALC	2.21 ± 2.59	2.64 ± 4.02	(-1.17, 0.31)	0.258
AMC	0.72 ± 0.37	0.66 ± 0.65	(-0.08, 0.18)	0.437
LMR	3.66 ± 3.70	4.23 ± 3.73	(-1.28, 0.14)	0.117

Table 2. Effect of Chemotherapy in Haematological Parameters in Patients with DLBCL.

Values are mean \pm SD. Significance was calculated by paired t test. * $P < 0.05$ considered as significant

Statistical analysis of patients with DLBCL based on gender perspective also showed variations of parameters before and after treatment. A significant variation was observed in the platelet count of male and female patients, with P value of 0.005 and 0.039 respectively. A decrease in AMC from 0.69 ± 0.36 to 0.53 ± 0.31 was observed in female patients. Since the P value was 0.023, this was highly significant. LMR in female patients increased from 3.47 ± 3.05 to 5.22 ± 4.34 with a P value of 0.048, which is statistically significant.

Effect of chemotherapy in haematological parameters in patients with T cell lymphoma

In T cell NHL, there were variations of haematological parameters before and after chemotherapy treatment. The WBC count before treatment was 7.39 ± 4.32 and after was 7.75 ± 3.62 . Level of Hb before treatment was 11.19 ± 2.11 and after was 11.27 ± 1.87 . The haematocrit value increased from 33.44 ± 6.23 to 33.69 ± 6.02 . The result was not statistically significant as their p values were not < 0.05 . The platelet count decreased from 274.08 ± 129.04 to 249.6 ± 182.29 . The values of lymphocyte count and ALC decreased from 21.4 ± 10.99 and 1.43 ± 0.84 to 19.45 ± 9.80 and 1.37 ± 0.78 respectively. Monocyte count and absolute monocyte count decreased from 9.2 ± 5.88 and 0.67 ± 0.61 to 7.62 ± 4.54 and 0.59 ± 0.44 respectively. There was a decrease of lymphocyte monocyte ratio from 3.51 ± 3.45 to 3.05 ± 1.50 after treatment. Since their p values were not

ˆ0.05, variations were statistically in significant (Table 3).

Parameters	Chemotherapy		95% CI	P value
	Before	After		
WBC count (cmm)	7.39±4.32	7.75±3.62	(-1.57, 0.85)	0.549
Platelet Count (cmm)	274.08 ± 129.04	249.6 ± 182.29	(-62.34, 111.30)	0.566
Haemoglobin (g/dl)	11.19±2.11	11.27±1.87	(-0.74, 0.58)	0.805
Haemetocrit value	33.44±6.23	33.69±6.02	(-2.28, 1.77)	0.797
Lymphocyte (%)	21.40±10.99	19.45±9.80	(-3.75, 7.65)	0.488
Monocyte (%)	9.20±5.88	7.62±4.54	(-0.76, 3.92)	0.177
ALC	1.43±0.84	1.37±0.78	(-0.32, 0.45)	0.743
AMC	0.67±0.61	0.59±0.44	(-0.14, 0.31)	0.448
LMR	3.51±3.45	3.05±1.50	(-0.82, 1.74)	0.467

Table 3. Effect of Chemotherapy in Haematological Parameters in Patients with T Cell Lymphoma.

Values are mean ± SD. Significance was calculated by paired t test. * P < 0.05 considered as significant

Discussion

DLBCL, one of the most frequent subtypes of NHL, is an aggressive lymphoma, with a median survival of less than one year if left untreated, but is potentially curable. T-cell lymphomas are a heterogeneous group of neoplasms, accounting about 7-10% of NHL and presenting as an advanced disease with widespread dissemination, aggressive behaviour, and a very poor prognosis and outcome, with more than half the patients dying of their disease [29,16]. Haematologists along with the clinicians can provide an insight in the prompt and accurate diagnosis in NHL patients and proper treatment can be provided immediately. Numerous prognostic markers have been proposed for patients with DLBCL and T cell lymphoma. However, these can be expensive to test and are not always applicable in daily practice. Therefore, inexpensive and readily available parameters are more practical in a clinical context.

Several studies have explored the prognostic significance of LMR in a variety of solid cancers including DLBCL [30,31, 32]. But studies regarding the role of LMR and other haematological parameters as an integrated biomarker in the prognosis of T cell NHL are limited. Many of them had correlated the role of LMR as a prognostic indicator of DLBCL [33, 34]. But certain others did not reveal any remarkable variations in haematological parameters and LMR in both the lymphomas and those results were controversial. So we checked for the importance of variations in parameters and its role as prognostic markers in both lymphomas. We analysed various haematological parameters and determined ALC, AMC and LMR of the patients diagnosed with DLBCL and T cell lymphomas before and after chemotherapy.

In the present study, it was found that there was a variation in haematological parameters and LMR before and after chemotherapy in both the lymphomas. The frequency of anaemia in the patients was 60%. The criterion for anaemia in Bloomfield’s study was haemoglobin level below 12 g/dl for females and below 14 g/dl for males. Rosenberg et al. & Stein et al. have reported that results of hematologic studies are infrequently abnormal in patients with NHL at presentation [35, 36]. However, Bloomfield et al. reported that 57% of patients with NHL have some abnormality in haemoglobin level, leukocyte count, or platelet count at the time of diagnosis [37, 38]. Chen et al evaluated the correlation of the peripheral platelet count at disease onset with the therapeutic outcomes of patients with DLBCL treated with the R CHOP like regimen [20]. In our study we observed a significant decrease (P < 0.05) of platelet count after chemotherapy in male and female patients with DLBCL. We also determined a significant decrease in AMC in female patients with DLBCL with a p value = 0.023. There was a marked increase in LMR after chemotherapy in female

patients with DLBCL and this was highly significant (P value=0.048). Studies have indicated that LMR was an effective prognostic factor in patients with DLBCL treated with R-CHOP. Tadmor et al. assessed the prognostic significance of AMC in patients with DLBCL [39].

We also observed variations in haematological parameters and LMR before and after chemotherapy in patients with T cell lymphoma. Since their p values were not less than 0.05, those results were statistically insignificant.

The present retrospective study that was conducted had influence from various aspects. It depended upon the diversity and nature of patient populations and the factors such as their age group, varying lifestyles, and the unequal percentage of patient population that was considered in both the lymphomas and the various treatment regimens that were adopted during each period. Factors like whether they had undergone previous treatment for the same or for some other diseases might also hold some idiopathic role in the variations of their blood CBC parameters.

Our study had some limitations in finding a statistically significant result in the case of T cell lymphoma. It might be due to the scarcity in the number of patients who were treated during the period of 2011-2015 with T cell NHL and the unavailability of their overall treatment data during the entire period and their increased mortality rate. This may be one of the reasons why T cell NHL still remains as a less explored area of research. In this context, we realized the necessity and importance of further detailed prospective studies in future to explore the correlation of various haematological parameters as a prognostic factor in T cell lymphomas and its comparison with DLBCL.

The present study concludes in the requirement of further observational findings on a substantial number of people to reveal the importance of variations in LMR and haematological parameters as a useful prognostic biomarker in the early diagnosis and treatment in the upcoming era.

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