

Original Research Article

Clinical profile, prognostication and treatment outcomes in non Hodgkins lymphoma

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ABSTRACT

Background: Non Hodgkins lymphoma is the most prevalent hematopoietic neoplasm, representing approximately 4% of all cancer diagnoses and ranking seventh in frequency among all cancers. Most of the data that we have is of west and data pertaining to Indian subcontinent is lacking. The aim of this study was to study clinical profile, prognostication, and assess treatment outcome in DLBCL patients in a tertiary care hospital.

Methods: 100 patients of DLBCL reporting to a tertiary care hospital between 2013 to 2016 were chosen for the study. All patients were subjected to routine investigation and specialized investigation including bone marrow examination and Positron emission tomography. Patients were treated with standard treatment protocol and their response to treatment were assessed.

Results: Study revealed male predominance with median age of onset was 45.6. Anorexia was the most common symptom. Lymphadenopathy was the most common sign. Bone marrow involvement and anemia commensurate each other. Only 16% cases presented in IPI score 4 and 5. Complete remission achieved with treatment in stage I and II disease were beyond 90% and steep decline in complete remission with treatment was noted in stage III and IV (~70%). 76% patients with DLBCL showed CR, 12.5% showed PR.

Conclusions: The present study revealed male preponderance with relatively early age of onset compared to western population. B- cell lymphoma (DLBCL) constituted maximum number of NHL cases (89%). We have found a higher proportion of B cell subtype as compared to other Indian studies, at the same time it corroborated with the findings of western studies. Complete remission achieved with treatment in stage I and II disease were beyond 90% and steep decline in complete remission with treatment was noted in stage III and IV (~70%).

Keywords: DLBCL, FL, NHL

INTRODUCTION

The Non Hodgkins Lymphoma (NHL) are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment.¹ Since the early 1970s, the incidence rates of NHL have risen dramatically, with incidence rates becoming almost double.² Although some of this increase can be due to earlier detection (resulting from improved diagnostic techniques and access to medical care), rest

can be due to HIV-associated lymphomas or changing classification systems but the most part of this rise is unexplained.³ It is the most prevalent hematopoietic neoplasm, representing approximately 4% of all cancer diagnoses and ranking seventh in frequency among all cancers. NHL is more than 5 times as common as Hodgkin disease.⁴

Incidence varies with race and geographical region. Nearly 12.7 million new cancer cases and 7.6 million

cancer deaths occurred in 2008 worldwide.⁵ The number of new cancer cases ranges from 3.7 million in eastern Asia to about 1800 in Micronesia/Polynesia. In men, the incidence of cancer is high in northern America (ASR 334 per 100,000), Australia/New Zealand (ASR 356.8) and in northern and western Europe (ASRs 288.9 and 335.3 respectively) as a consequence of the high rates of prostate cancer in these regions (ASRs greater than 80 per 100,000 in all).⁶

However most of the data that we have is of studies conducted in west and Indian data with respect to this major disease is lacking. Hence this study was undertaken to have some data in Indian setting.

METHODS

The primary aim of this study was to study clinical profile, prognostication, and assess treatment outcome in non Hodgkins lymphoma patients in a tertiary care hospital, Army Hospital (Research and Referral), Delhi Cantonment. A total of 100 patients of NHL or with clinical suspicion of NHL who reported to this hospital between 2014 to 2016 (2 years) were included in this study.

Cases included both the admitted and OPD patients. Detailed clinical history and thorough clinical examination was done in all cases. All patients were subjected to routine hematological (estimation of hemoglobin, total and differential leukocyte count, platelet count, peripheral smear study for abnormal cells etc.), biochemical (liver function tests, LDH, urea, creatinine, uric acid) and viral markers (HBsAg, Anti HCV and HIV) investigations.

The diagnosis of Non-Hodgkin's lymphoma was established by biopsy from lymph nodes or involved tissues and subjecting them to immunohistochemistry. Bone marrow aspiration smears were stained by leishman's stain. Cell blocks were prepared from the remaining marrow particles, and histological sections were stained by Hematoxylin and Eosin (H and E). Trephine biopsy was also done, stained by H and E and reticulin stain to assess the marrow involvement by the neoplastic cells and reactive fibrosis. These were subjected to immunohistochemistry. The radiological studies included chest radiograph (CXR), ultrasonography (USG) of abdomen, computer axial tomography (CT) of chest and abdomen and whole-body PET scan. Patients were classified according to WHO/REAL classification and staging was done by Ann Arbor staging system.

Statistical analysis

Data was reported as a number (percentages) of patients for categorical variables and mean (SD) for normally-distributed continuous variables and median (IQR) for skewed distributions. It was a prospective study and

obtained data was analyzed using appropriate statistical method.

RESULTS

A total of one hundred (100) patients who were admitted or attended the outpatient department of medical oncology at Army Hospital Research and Referral, New Delhi were included in the study.

A total of one hundred (100) patients were diagnosed as non-Hodgkin's lymphoma during the study period, of them 62 (62%) were male and 38 (38%) were female and male female ratio was 1.63:1. The mean and median age of presentation was 45.36 years and 44 years respectively. The disease shows a bimodal onset with 24 (24%) cases occurring in the age group of 31-40 years and 25 (25%) cases occurring in the age group of >60 years. Most of the patients i.e. 43 (43%) patients have presented beyond 5th decade. 4 (4%) patients gave family history of non-Hodgkin's lymphoma in first degree relatives. Whereas 4 (8%) gave family history of any other malignancy in first degree relatives. However, in 92 (92%) there was no contributory family history.

A total of 100 patients were interviewed for the various symptoms. 34 (34%) patients gave history of fever, 59 (59%) patients gave history of anorexia whereas 58 (58%) of patients complained of fatigue at the time of presentation to the hospital.

35 (35%) patients had complained of neck swelling at the onset whereas 13 (13%) patients also had complains of dyspnea on presentation.

6 (6%) patients had compressive symptoms due to enlarged nodes causing hoarseness of voice and muscle weakness. 6 (6%) patients gave history of bleeding manifestations in form of bleeding from gums, increased flow during menses and petechiae. 30 (30%) patients had significant weight loss of >10% of body weight. B Symptoms (type B symptoms: fever, and/or night sweats, and/or weight loss of more than 10% of body weight) were seen in 45 (45%) of patients. Among signs pallor was present in 25 (25%) patients, Icterus was seen in 7 (7%) patients. Hepatomegaly was found in 17 (17%) of cases and splenomegaly was detected in 9 (9%) patients. 44 (44%) of patients were found to have peripheral lymphadenopathy. Ascites was detected in 8 (8%) patients.

Anemia (Hb of < 10 gm/dl for females and <12 gm/dl in males) was found in a total of 18 (18%) patients. Out of these 18 patients, 11 were males and 7 were females. Mean hemoglobin in the study group was 10.56 gm/dl.

Deranged liver function tests were found in 17 (17%) patients, most of these comprised of raised Bilirubin and AST levels (Serum Bilirubin >1.2 mg/dl; AST>30 IU/L).

Deranged renal parameters were seen in 8 (8%) of cases. (Creatinine > 1.2 mg/dl and BUN > 20 mg/dl). Elevated levels of Serum Lactic dehydrogenase levels were found above the normal laboratory value (>500IU/L) in 57 (57%) patients. Bone marrow involvement by the neoplastic process was detected in 25 (25%) of patients. Most common site involved was GIT, seen in 20 (20%) patients followed by CNS involvement which was observed in 5 (5%) patients. 7 patients (7%) tested positive for HBsAg, whereas 4 (4%) patients tested positive for anti HCV. 3 (3%) patients were detected HIV positive by rapid ELISA method.

Distribution of histological subtypes of NHL

A total of 100 patients in whom the diagnosis was established by meticulous examination of slides and immunohistochemistry which included a) monoclonal antibodies to CD 5, CD 15, CD 20, CD 21, CD 30, CD 43, CD 45, CD 45RO, NK-1, CD 68, CD 74, CD w75, CD 79a. Epithelial membrane antigen (EMA), cytokeratin, BCL-2 protein, cyclin D1, kappa light chain, lambda light chain, Ki-B3, Ki-My2P, and proliferating cell nuclear antigen (PCNA); and b) polyclonal antibodies to CD3, Tdt, kappa light chain, lambda light chain, and S-100 protein, following results were obtained:

B-cell lymphomas formed 89% of the NHLs, whereas T-cell lymphomas formed 11% of all Non-Hodgkin's lymphomas (Table1). Diffuse large B-cell lymphoma (DLBL) was the most common subtype, forming 56% of all NHLs. It was followed by follicular lymphoma which was seen in 17% of all patients. Third commonest was marginal zone B- Cell lymphoma seen in 8% of cases. Among T-Cell lymphoma anaplastic large cell lymphoma (6%) was the commonest.

Table 1: Histological.

Histological subtype	Cases	%
Diffuse large B-cell lymphoma	56	56
Follicular lymphoma	17	17
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma	1	1
Mantle cell lymphoma.	4	4
Marginal zone B cell lymphoma	8	8
Burkitt lymphoma	2	2
Precursor T-acute lymphoblastic lymphoma/LBL	5	5
Anaplastic large cell lymphoma T cell type	6	6

Prognostic factors

25 (25%) patients were aged more than 60 years. 57 (57%) patients had Serum lactic dehydrogenase (LDH) above the normal laboratory value (>500IU/L).

82 (82%) patients presented with performance score of 0-2, whereas 18 (18%) patients presented with a poor Performance Score of 3-4.

32 (32%) patients presented with an Ann Arbor stage 1 or 2 disease whereas 68 (68%) patients were with stage 3 or 4 disease.

Stage wise complete response rates assessment

Stage I patients showed 92% complete response rates, while stage II patients showed 90% complete response rates. However, the complete response rates declined to 77% and 66% with stage III and stage IV respectively. During therapy 46% patients developed febrile neutropenia, out of which 20% had profound neutropenia. Mucositis or diarrhea was present in 38% of patients. 6% patients suffered tumor lysis syndrome. 3% patients developed acute kidney injury, of which one received hemodialysis.

Subset-response analysis

In our study, 76% (43) patients with DLBCL showed CR, 12.5% (7) showed PR. Among Follicular lymphoma patients, 82.3% (14) had a CR, 11.7% (2) had a PR. Other B cell lymphomas, 81.2% (13) had a CR, 12.5% had a PR 36.3% of all other T cell lymphomas had a CR, while PR was seen in 18% (2) of cases.

DISCUSSION

The study has signified male preponderance in all types of NHL. Overall ratio was 1.63:1. Our findings suggested a higher male to female ratio as compared to western literature (UK it was 1.2:1), but it commensurate with the results obtained in Indian studies which showed a ratio of 1.6:1 to 3:1.^{7,8} On the other hand, in north India the ratio was found to be 4.5:1.⁹ In Bangladesh it was 1.8:1 and in Pakistan it was observed to be 1.03:1.¹⁰ Though the general trend of male preponderance has been clearly found in the study. Male predominance was observed in all histological subtypes in the study which was similar to that of Elias (1979).

Average age of onset around 45.36 years with median of 44 years in the present study as compared to 55 years in Western countries.¹¹

Bimodal mode of onset was also observed with maximum incidence occurring in the age group of 31-40 years (entailing 24% cases) and >60 years age group (entailing 25% cases). Though maximum incidence was seen around 5th decade of life. Studies have also showed that, of all B-cell lymphoma highest number of patients are in the 5th and 6th decade and of T-cell lymphoma in the 3rd decade.¹²

With an observation period of 1985 to 2004 reported highest incidence in the 7th decade, which was higher as

compared to age of onset our study. A similar study was done with an observation period of 1991 to 2000 in Austria by Mitterlechner, Fiegl and Muhlbock and concluded for both male and female, age of onset to be around 7th decade. Similar findings were reported from the UK based studies also.¹²

The Indian population has a life expectancy much lower than the age of highest incidence observed by the various investigators i.e. around 7th decade and this has reflected as fewer number of patient in 7th and 8th decade in our study, that too supplemented by possibility of partial discordance attributable to the small number of patients enrolled in the limited institutional study.

In the study, patients with family history or risk factors like exposure to smoking, farming chemicals/pesticides etc. were 8%. A study of 622 white men with newly diagnosed non-Hodgkin's lymphoma and 1245 population-based controls in Iowa and Minnesota found men who ever farmed were at slightly elevated risk of non-Hodgkin's lymphoma (odds ratio=1.2) that was not linked to specific crops or particular animals.¹³ Increased risk amongst family members is thought to possibly be due to shared environmental risk factors between family members.

In the present study, we found that anorexia was the most common symptom reported by 59% of patients, followed by fatigue (58%), neck swelling (35%) and weight loss (30%). Dyspnea was reported by 13% of patient mainly due to compression by enlarged hilar and tracheal nodes. Bleeding manifestations were seen in 6% of cases primarily due to thrombocytopenia due to bone marrow involvement.

A small study by Sudipta et al on Hodgkin's and non-Hodgkin's lymphomas in rural India suggested neck swelling as the predominant symptom followed by weight loss, anorexia and fatigue.¹⁴ We found B Symptoms were present in 45% cases. Weight loss of more than 10% of body weight were seen in 30% of patients. Ours incidence of B symptoms was less as compared to that of Garg et al (1985) and Ramani et al who reported frequency of B symptoms at 49.6% and 65.2% respectively, which could be attributable to the limited size single institutional study.

Lymphadenopathy was the most common sign present in 44% patients followed by pallor (25%), hepatomegaly (17%), splenomegaly (9%), ascites (8%) and icterus (7%). A similar study by Sudipta et al on Hodgkin's and non-Hodgkin's Lymphomas in rural India also suggested corroborating findings.¹⁴ In this study also peripheral lymphadenopathy was the commonest sign followed by pallor, splenomegaly and hepatomegaly.

Raised LDH was most common laboratory finding detected in our study, detected in 57% cases followed by marrow involvement seen in 25% cases and anemia seen

in 18% cases. Our findings were in coherence with findings of Indian study done by Sudipta et al. Similarly, serum LDH was significantly raised in non-Hodgkin's lymphoma cases in a study done in west.¹⁵ Though bone marrow involvement was higher as compared to the study done by Sudipta et al but comparable to the study by Moormeier et al, who concluded that bone marrow examination could detect disease in 20 to 40% of all NHL cases.

68% patients were in advanced stage (Ann Arbor stage III/IV), whereas 32% patients were in limited stage disease (Ann Arbor I/II). Other studies also showed similar results where the patients presented with advanced disease were about 71%.¹⁶

Among the viral markers 03 patients tested positive for HIV, 07 for HBV whereas 04 patients tested positive for HCV. Suggesting a significant correlation between the viral infection and risk of developing NHL. Similar findings were reported by Dalmazo L et al.¹⁷

B-cell lymphoma constituted 89% of total NHL cases whereas T-cell lymphoma contributed to 11% of total cases. We have found a higher proportion of B cell subtype as compared to study done by Naresh et al and Skarin, Dorfman which revealed B cell lymphoma in 80% of the presenting cases.¹¹ Though our findings are corroborating with the studies done in UK and USA.¹⁸ Study also found that diffuse large B-cell lymphoma (DLBL) was the most common subtype, forming 56% of all NHLs which is well in proportion as compared with other Indian studies where it's prevalence at presentation was noted to be 54.66%.¹⁹ It was followed by follicular lymphoma which was seen in 17% of all patients (17.66% as per Indian studies). Broadly the findings were similar to that of a study done by Naresh et al, 2000, hence elucidating DLBCL to be the largest subset of NHL.

Among T-Cell Lymphoma Anaplastic large cell lymphoma (6%) was the commonest which was significantly lower compared to that of Naresh et al where it was reported to be 12%. We found that T- cell acute lymphoblastic lymphoma formed 5% of total lymphoma cases which was similar to that of Naresh et al where they reported T-cell lymphoblastic lymphoma in 6% cases. Though our findings were higher in figures as compared to western studies, in which the incidence has been reported less than 3%.²⁰ We didn't find any case of peripheral T cell lymphoma in our study. Disparity in the presentation may be attributed to the small number of patients in our study.

We also calculated IPI Score for all the patients, which suggested maximum number of patients with IPI Score 3 (27% patients), followed by patients with IPI Score of 2 (23%). Only 15% patients were with IPI Score 4 and 01% in IPI Score 5. This suggests that a significant number of patients present with good prognostic scores, thus they

have favourable treatment outcome and survivability with institution of timely treatment. Complete remission rates with the treatment were 92% for stage I and 90% for stage II. Remission rates showed a steep decline with augmentation of stage with 77% complete remission in stage III and 66% in stage IV. These findings were corroborating with IPI wise complete remission rates of 82%, 38%, and 13% for low, intermediate and high IPI scores respectively. Limitations of the study were that it included small sample size, it is a hospital based study and absence of control group.

CONCLUSION

The present study revealed male preponderance with relatively early age of onset compared to western population. B-cell lymphoma (DLBCL) constituted maximum number of NHL cases (89%). We have found a higher proportion of B cell subtype as compared to other Indian studies, at the same time it corroborated with the findings of western studies. Complete remission achieved with treatment in stage I and II disease were beyond 90% and steep decline in complete remission with treatment was noted in stage III and IV (~70%).

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