Nodular Lymphocytic Predominant Hodgkin Lymphoma (NLPHL); Treatment Outcome Study in a Tertiary Care Cancer Hospital in Pakistan

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ABSTRACT

Objective: To determine the demographics, clinical characteristics and treatment outcomes of nodular lymphocytic predominant Hodgkin lymphoma (NLPHL) patients treated at our hospital.

Study Design: Retrospective longitudinal study.

Place and Duration of Study: Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan from 1996 to 2016.

Methodology: We collected clinical data of all the cases of HL diagnosed over twenty years (between 1996 and 2016) from our electronic hospital information system (HIS). A total of 3426 HL patients were identified, out of whom the pathologically confirmed diagnosis of nodular lymphocytic predominant Hodgkin lymphoma (NLPHL) was identified.

Results: In this study, eighty-four patients were studied. The majority of the patients were male (80%). B symptoms were present in 35%. There were 24% patients in stage-I (n=20/84), 33% in stage-II (n=28/84), 12% in stage III (n=10/84) and 31% in stage IV (n=26/84). Hence, early-stage was seen in 57% (n=48/84) and advanced stage was 43% (n=36/84) respectively. The Median follows up time was 30 months (range: 1-60 months). Patients were treated with chemotherapy in most cases (48%), radiotherapy alone in 14% cases, and combined modality (chemotherapy and radiotherapy) was used in 38% patients. The estimated 5–year disease-free survival was 73% and overall survival was 86%. Autologous stem cell transplant was done in only one patient whose disease had transformed from NLPHL to T-rich cell B cell lymphoma.

Conclusion: This study confirmed the divergent features of NLPHL with a comparatively good long-term prognosis. Most patients achieved an excellent response to first-line therapy. There was a tendency towards multiple relapses but improved outcomes.

Keywords: B symptoms, First-line therapy, Hodgkin lymphoma, Nodular lymphocytic predominant hodgkin lymphoma, Shaukat khanum memorial cancer hospital and research centre lahore.

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INTRODUCTION

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) represents a less frequent, distinct histopathologic subtype that accounts for less than 5% of cases of Hodgkin lymphoma (HL).[1] Both NLPHL and classic Hodgkin lymphoma (CHL) are characterized by large neoplastic cells in an inflammatory background arising from the germinal centre. NLPHL has distinctive histologic, immunophenotypic and genetic features that distinguish it from CHL.[2,3] It is characterized by lymphocyte-predominant cells (LP cells), formerly called lymphocytic and histiocytic cells. In contrast to CHL, NLPHL expresses B-cell markers (CD20 and CD79a) and epithelial membrane antigen (EMA) but not CD30 or CD15.[4]

Until 1993, patients with NLPHL were treated in the same clinical trials as patients with classic HL. The European task force reported the largest review on the Lymphoma Project on lymphocyte-predominant HL, which confirmed only 51% of cases on pathology review and immunohistochemistry. NLPHL was classified as a separate entity in 2008 in WHO lymphoma classification.[5] Clinically, NLPHL predo-minantly affects males, is often localized at diagnosis, and has a favourable prognosis despite a tendency for multiple disease recurrences.[6,7] The reported rate of histologic transformation (HT) of NLPHL to high-grade lymphomas ranges from 5-14% and even high on longer follow up.[8] Because of the rarity of NLPHL, its treatment has not been standardized and has not been homogeneous. It consists of surgery, chemotherapy and radiation therapy,[9,10] and more recently, immunotherapy (anti-CD20, Rituximab).

The objective of our study was to determine the disease and patient characteristics, treatment modalities used, and outcomes of NLPHL patients treated at

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METHODOLOGY

This was a retrospective longitudinal study on the all patients with NLPHL enrolled at Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore, Pakistan, over 20 years from 1996 to 2016. The Ethical Committee of the hospital approved this study (EXMPT-03-09-18-01).

Inclusion Criteria: All the nodular lymphocytic predominant Hodgkin lymphoma (NLPHL) patients of either gender and >18 years of age were included in the study.

Exclusion Criteria: Patients of other varieties of Hodgkin lymphoma (Nodular sclerosis HL, Mixed cellularity HL, Lymphocyte-depleted HL) were not included in the study.

Based on morphology and immunohis to chemistry, all the newly diagnosed patients with nodular lymphocytic predominant Hodgkin lymp-homa were studied. All the patients were CD 20 positive. A standard proforma was used for data collection from the computer-based hospital information system (HIS). Parameters like age, gender, clinical characteristics, staging, and treatment were included. All the patients underwent clinical history, physical examination and blood reports such as complete blood count, erythrocyte sedimentation rate and imaging CT scan at baseline. Patients were treated according to the decisions and recommendations by a multi-disciplinary team (MDT). Evaluation of response depends on history, physical examination and imaging. All the patients either received chemo-therapy, radiotherapy or both. Overall survival (OS) was measured from the date of diagnosis to the date of either the last follow-up or death. Disease-free survival (DFS) was measured from the end of treatment to the date of either recurrence/relapse or last follow-up. Patients who died with no evidence of recurrence/relapse were censored at the time of death.

Statistical Package for Social Sciences (SPSS) version 23.0 was utilized for statistical analyses. Meanv ± standard deviation were employed to summarize quantitative data, whereas frequencies and percentages were used to organize qualitative data. Kaplan–Meier survival curves were used to assess the patients overall survival (OS) and disease-free survival (DFS).

RESULTS

Eighty-four patients with NLPHL were treated at our centre during the study period. Mean age at diagnosis was 30 ± 10 years. 67 (80%) patients were males, 20 (24%) patients presented in stage-I, 28 (33%) in stage-II, 10(12%) in stage-III and 26 (31%) in stage IV of the disease. B symptoms were present in 29 (35%) patients. As the first-line therapy, 40(48%) patients received chemotherapy, 12 (14%) patients radiotherapy alone, i.e., five patients each received 30Gy and 36Gy, while two patients each received 46Gy and 50 Gy, respectively. Furthermore, radiotherapy was given in five patients at the axillary region; five patients were given at the neck and cervical region. 32 (38%) patients were given combined treatment (radiotherapy and chemotherapy). Two protocols of chemotherapy ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) and CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone) were administered in 27 (32%) and 13 (16%) patients, respectively (Table-I).

Table-I: Baseline characteristics of the patients with nodular, lymphocyte-predominant hodgkin lymphoma.

Parameters	Categories	n (%)
Age (Year)		30.71 ± 9.83
Gender	Male	67 (79.8%)
	Female	17 (20.2%)
Relapse	No	64 (76.2%)
	Yes	20 (23.8%)
Status	Death	13 (15.5%)
	Alive (on follow up)	55 (65.4%)
	Loss to follow up	16 (19.1%)
Treatment	Chemotherapy	40 (47.6%)
	Radiotherapy	12 (14.3%)
	Chemotherapy ± Radiotherapy	32 (38.1%)
Chemotherapy type	ABVD*	27 (32.1%)
	ABVD* ± radiotherapy	21 (25.0%)
	CHOP**	13 (15.5%)
	CHOP ± radiotherapy	10 (11.9%)
	GDC*** ± radiotherapy	1 (1.2%)
	Radiotherapy	12 (14.3%)
B-symptoms	No	55 (65.5%)
	Yes	29 (34.5%)
Stage	I	20 (23.8%)
	II	28 (33.3%)
	III	10 (11.9%)
	IV	26 (31.0%)

Adriamycin), bleomycin sulfate, vinblastine sulfate, dacarbazine, **Cyclophosphamide, doxorubicin hydrochloride, vincristine (Oncovin), prednisone, * Gemcitabine (G), Carboplatin (C), Dexamethasone (D).*

Disease recurrence occurred in twenty patients. All the relapsed cases were treated with salvage chemotherapy regimens; only four received Rituximab therapy due to financial constraints. The histological transformation occurred in eight patients; three patients' disease transformed into diffuse large B-cell lymphoma and T-cell rich large B-cell lymphoma each, and one case had mixed features of both (TCR BCL and NLPHL). Additionally, 2 (10%) relapse cases occurred in stage-I and II, while 18 (90%) cases occurred with stages-III and IV. The majority of the recurrences were reported in patients who received only chemotherapy (13, 65%) compared to those who received chemotherapy plus radiotherapy 7(35%). Patients who received ABVD had more relapses 9(45%) as compared to patients who received CHOP4 (20%), as shown in Table-II.

Table-II: Management of the patients with nodular, lymphocyte-predominant hodgkin lymphoma.

Parameters	Categories	No-Relapse 64 (7 6.2%)	Relapse 20 (23.8%)
Treatment	Chemotherapy	27 (42.2%)	13 (65.0%)
	Radiotherapy	12 (18.8%)	-
	Both	25 (39.1%)	7 (35.0%)
Chemotherapy type	ABVD*	18 (28.1%)	9 (45.0%)
	ABVD* ± Radiotherapy	18 (28.1%)	3 (15.0%)
	CHOP**	9 (14.1%)	4 (20.0%)
	CHOP** ± Radiotherapy	6 (9.4%)	4 (20.0%)
	GDC*** ± Radiotherapy	1 (1.6%)	-
	Radiotherapy	12 (18.8%)	-
Stage at presentation	I	19 (29.7%)	1 (5.0%)
	II	27 (42.2%)	1 (5.0%)
	III	6 (9.4%)	4 (20.0%)
	IV	12 (18.8%)	14 (70.0%)

(Adriamycin), bleomycin sulfate, vinblastine sulfate, dacarbazine, **Cyclophosphamide, doxorubicin hydrochloride, vincristine (Oncovin), prednisone, * Gemcitabine (G), Carboplatin (C), Dexamethasone (D)*

The mortality rate was 15%. The estimated three and 5-year disease-free survival rates were 75% and 73%, respectively, while 3 and 5 years overall survival rates were 88% and 86% respectively (Figure-1 & 2).

DISCUSSION

This study reviewed the clinical hallmarks and outcomes of NLPHL patients at SKMCH&RC Lahore Pakistan, focusing on management strategies. The literature review suggests that NLPHL is a unique and distinct disease where most of the patients are young, have male predominance, and present at early-stage disease. Our study showed similar characteristics with most young patients and male to female ratio of 4:1.

Since NLPHL is a rare disease, few prospective studies are available to guide therapy decision-making. Preliminary data for prognosis, outcomes and treatment strategies in NLPHL is derived from studies of Hodgkin Lymphoma, as previously NLPHL was not considered a separate entity.[11]A tiny percentage of NLPHL patients comprised the total number of patients in those studies. Outcomes of patients with NLPHL are better in comparison to CHL. The GHSG analysis of >8000 HL patients illustrated a better prognosis for NLPHL compared to CHL patients.[10] Almost two-thirds of patients in our study were treated after 2008, and a large proportion of patients (68%) was maintained in observation after treatment. This analysis provides an excellent chance to reassess the role of radiotherapy, chemotherapy or both and immuno-chemotherapy in the treatment decision-making. Many of the patients who present with early-stage NLPHL have excellent outcomes with radiotherapy alone or radiotherapy combined with a brief course of chemotherapy ABVD/CHOP. This was also demonstrated in the present study.

There have been few prior studies evaluating the outcome of patients with advanced-stage NLPHL.[11,12] The largest study reported by the German Hodgkin lymphoma study group (GHSG) described 82 patients with advanced-stage NLPHL (stage-IIB with risk factors and stage-III to IV) who were evaluated as part of a larger retrospective study comparing patients with all stages of NLPHL or CHL treated on GHSG trials from 1988 to 2002.[10] Different treatment protocols like ABVD, COPP and BEACOP with or without radiation were used in all the trails. However, the comparison of clinical outcomes of protocols was not described.

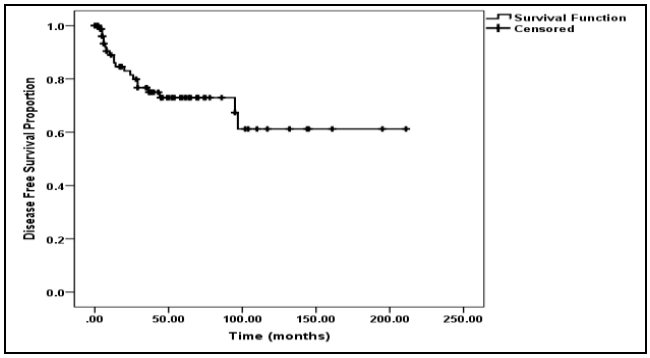

Figure-1: Disease Free Survival of patients with nodular, lymphocyte-predominant Hodgkin lymphoma.

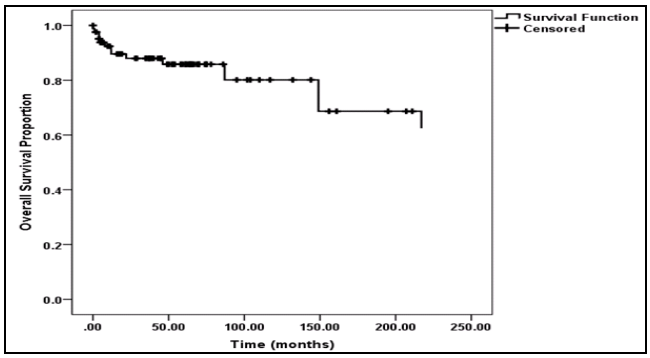

Figure-2: Overall survival of patients with nodular, lymphocytepredominant Hodgkin lymphoma.

In a recent MD Anderson Cancer Center trial,[15] patients were treated with R-CHOP. The Median follow up was 42 months, and there has been no relapse or transformation.[12] Treatment protocol for advanced disease is controversial. A recent review by Fanale *et al*, demonstrated an excellent outcome in patients treated with CHOP based protocol.[13] In the advanced stage, chemo immunotherapy and radiotherapy may be given.[14,15] However, results of our patients with higher stages NLPHL treated with ABVD or CHOP based regimens suggested a greater tendency of relapse in patients treated with ABVD.

The presence of high-risk features such as bulky disease, B symptoms and infra diaphragmatic involvement, especially splenic disease, are indications of more aggressive therapy, and CHOP based regimens are recommended.[13] However, there was a greater tendency of recurrence in advanced NLPHL confirming observations in other series. Therefore, baseline staging is also necessary for treatment and prognosis and is important for survival.[16] In this study, the five-year overall survival was 86% compared to a large retrospective study of 1162 patients of NLPHL with ten years OS was 83%.[17] We observed survival rates close to those reported by international groups.

In relapsed/refractory cases, an excellent response to chemo-immunotherapy with autologous transplant may be achieved.[18] A study was conducted in MACC, in which ASCT ± Beam ± rituximab was given. Five years PFS was 69% and OS was 76%. The study was conducted by GHSG, in which 28 patients underwent ASCT, five years PFS was 90%, and OS was 96%.[15-18] Twenty patients (23%) in our study had a relapse, comparable to a recent study from Farrell et al, with a relapse rate of 10%.[13] In the study with the highest numbers of patients (40%) relapsed within a median follow-up of 9.5 years on the watch-and-wait strategy.[14]

Despite frequent relapses, NLPHL has better survival than classical Hodgkin lymphoma.[19] The significant difference in overall survival in patients with disease progression and relapse depends upon the recurrences occurring before or after 24 months of initial diagnosis. Therefore, the intensity of salvage therapy should be chosen accordingly. Aggressive treatment with high dose therapy and autologous stem-cell transplant in most early relapses and less intensive treatments in late relapses or low disease burden.[20]

This study highlighted different behaviour of NLPHL compared to classical Hodgkin lymphoma. It is mandatory to repeat biopsy at relapse to rule out histologic transformation. There was an excellent response to salvage therapy despite multiple relapses in our study. Prospective studies are needed with current standard management practices to know the real outcome of these patients.

STUDY LIMITATION

This retrospective analysis of all the treated patients at our centre has its inherent limitations. Although Rituximab is a current standard of care for all CD 20 positive lymphomas, it was not used in most patients due to financial constraints.

CONCLUSION

This study confirmed the divergent features of NLPHL with a comparatively good long-term prognosis. Most patients achieved an excellent response to first-line therapy. There was a tendency towards multiple relapses but improved outcomes.

Conflict of Interest: None.

Authors' Contribution

C: Research idea, manuscript writing, MIS: Data cleaning, MAB: Advised on the study design and analysis plan and wrote result section, FS: Manuscript writing, IN: Data collection, UK: Proof reading, NS: Major contributor in writing the manuscript.

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