RESEARCH ARTICLE

Follicular lymphoma: an Institutional Analysis

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Abstract

Background: Follicular lymphoma (FL) is second most common lymphoma in adult, constituted 20% of all lymphoma cases in the west. There is limited information is available on FL from India. **Methods:** The clinico-pathological profile, treatment outcome and prognostic factors for survival were assessed retrospectively in 181 patients of FL seen at our center over a period of 17 years (1996-2012). **Results:** There were 120 males and 61 females. The median age was 51 years (24-80 years). The common presenting features were lymphadenopathy 71%, fatigue 23% and fever 20%. Ann Arbor stage distribution was: stage I - 9%, stage II - 11%, stage III -22 % and stage IV - 58%. Extra nodal involvement and bulky disease were present in 22% and 19% patients respectively. Follicular Lymphoma International Prognostic Index (FLIPI) 1 score : Low -25%, Intermediate-45% and high risk in 30% of cases. One forty five patients (80%) received treatment at presentation or during follow-up. Chemotherapeutic regimen used were: CHOP-45 , CVP-51, chlorambucil and prednisolone -7 , BR (bendamustine and rituximab)-12, RCHOP- 14 RCVP – 7 and other regimen were used in 5 cases. The overall response (ORR) and complete remission (CR) rates were 70% and 35% respectively. Median overall survival (OS) and event free survival (EFS) was 5.5 years and 2.5 years respectively, with median follow up period of 3.0 years. Grade 3 histology, failure to attain CR, low serum albumin, and high risk FLIPI were significantly associated with lower event free survival. High risk FLIPI (HR 1.46, 95% CI 1.03-2.10, p=0.003) and failure to attain CR (HR 2.64, CI 1.10-4.30, p=0.001) were predictors of poor OS. **Conclusions:** FL represents 9 % of all lymphoma in adult. This is the largest data from single institute from India. Eighty percentage of patients presented in stage III/IV disease. High risk FLIPI and failure to attain CR were important prognostic variables for OS.

Keywords: Follicular lymphoma- outcome- India

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Introduction

Follicular lymphoma (FL) is the second most common subtype of non Hodgkin lymphoma (NHL), accounting 20-30% of all lymphoma in the west, however, precise data from India are not available. In the Indian National Cancer Registry (INCR), FL is coded in " NHL " (International Classification of Diseases [ICD] code 10- C82- 85) with age-adjusted rates of 2.9 and 1.2 per 100 000 population for males and females, respectively (Manoharan et al., 2010). FL is characterized by an indolent course , widespread disease at diagnosis, predominately involving lymph nodes , bone marrow and less commonly extra nodal sites. The highly variable clinical course leads to difficulties in evaluating the prognosis and efficacy of therapy in individual patients. Unlike diffuse large B cell lymphoma, a diagnosis FL does not necessitate treatment , even with low burden advanced disease (Horning et al., 1984). The outcome of patients with follicular lymphoma substantially improved in recent years due to use of rituximab (anti-CD20 monoclonal antibody) (Salles et al ., 2008; Hochster et al., 2009; Salles et al ., 2011)

The objective of this study was to characterize the clinico-pathological features and assess outcomes of FL cases among our population.

Material and Methods

This retrospective analysis were carried out at the Medical Oncology Department of All India Institute of Medical Sciences (AIIMS), New Delhi between period of January 1996 to December 2012. During the study period from 231 patients of follicular lymphoma were registered in our clinic. Nineteen patients did not take treatment at our centre, have been excluded. Eleven patients had received treatment prior to coming to our center and were also excluded. Twenty another patients also excluded because of missing major valuable data from case records. Hence 181 treatment naive patients of follicular lymphoma were included in the study for analysis. Cases were selected from central computer database, Leukemia and Lymphoma Register and all files were retrieved from medical record section. Clinical, demographic, treatment and outcome related information were collected from the

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case record files .The initial work-up included detailed clinical evaluation (history and physical examination), complete blood counts, renal and liver function tests, serum LDH and CECT scan of neck, chest abdomen and pelvis, lymph node (LN) and bone marrow biopsy. Disease was staged according to Ann Arbor staging with Cotswold's modification. Any LN mass more than 10 cm in longest diameter was taken as bulky disease. Patients with early stage (Stage I and II) follicular lymphoma were planned for observation or involved field radiotherapy (IFRT). While patients with symptomatic (according to Groupe d'Etude des Lymphomes Folliculaires [GELF] criteria) in advanced stages (Stage III and IV) were planned for 6-8 cycles of chemotherapy with or without rituximab and radiotherapy was used only at the site of bulky disease or residual disease. Treatment response was assessed by detailed clinical examination and contrast enhanced CT-scan of neck, chest, abdomen and pelvis after 3-4 cycles of chemotherapy cycles and at the end of treatment. Responses were labeled according to International response criteria (Cheson et al., 2007) and defined as complete response (CR) when there was no clinical or radiological evidence of disease lasting for at least 1 month duration. Partial response (PR) was defined as >50% reduction in the size of baseline measurable disease. Progressive disease (PD) was defined by appearance of any new lesions and/or >25% increase in any lesion's size. Stable disease (SD) was labeled when the response was in between PR and progressive disease. Patients in complete remission were followed every 3 months for the first 2 years, and 6 months thereafter till 5 years and then annually. Detailed physical examination, blood counts were done on each visit. Imaging was used as per clinical assessment. Study end points were overall survival (OS) , defined as the time from the date of diagnosis to death from any cause or being lost to follow up, and event free survival (EFS) was defined as the time from the date of diagnosis to occurrence of any one of the following event: relapse, progression or death from any cause. Data of those patients who lost to follow up before any event were censored at the date of last contact. Most of the patients (75%) recruited in last 7 years (2006-2012) Entire data was censored on 30th April 2013 for survival analysis. Descriptive statistics was used for describing demographic and clinical characteristics. Survival was estimated by the Kaplan-Meier method and the Log-rank test was used to identify significant prognostic factors. Uni-variate Cox proportional hazard model followed by Step wise Multivariate Cox-regression analysis was done to identify independent predictors of the outcome. Analysis was done using the STATA(version 11.1).

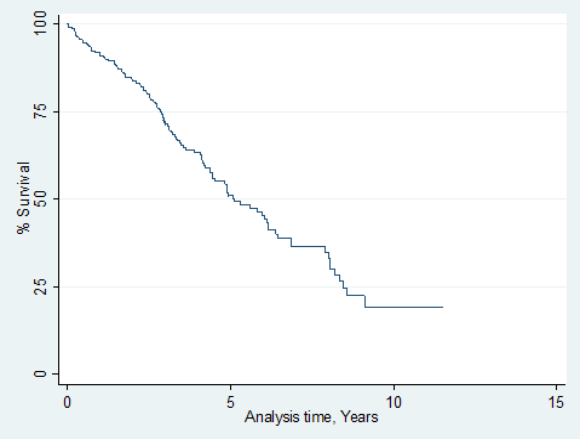
Results

Median age of study population was 51 years (range 24-80 years). The common presenting features were lymphadenopathy 71%, fatigue 23% and fever 20%. Hepatomegaly and splenomegaly were seen in 30% and 40% of cases respectively. Ann Arbor Rai stage distribution was: stage I -16(9%), stage II – 20 (11%), stage III -40(22 %) and stage IV – 105 (58%). Twenty six patients had ECOG performance status III/IV. Extra nodal involvement and bulky disease were present in 22% and 19% of cases, respectively. Follicular Lymphoma International Prognostic Index (FLIPI) 1 score : Low -25%, Intermediate-45% and high risk in 30% of cases. Table 1 shows the base line characteristics of patients with FL. Histopathology slides and blocks of available cases were reviewed and attempt was made to classify them according to WHO classification for lymphoid malignancies. FL grade 1, 2 and 3 were seen in 47, 47 and 40 patients respectively. Among 40 patients of grade 3, 6 patients have found to be 3b histology and did not included in survival outcome because of different biology. Patients

Table 1. Patients Characteristics at Base Line

Characteristics	Frequency
Age , median , years(range)	51 (24-80)
Sex (male/female ratio)	2:1
Ann Arbor Stage, n (%)	
Stage I	16(9%)
Stage II	20(11%)
Stage III	40(22%)
Stage IV	105 (58%)
Grade (n= 134), n (%)	
Grade 1	47 (35%)
Grade 2	47 (35%)
Grade (3a and 3b)	40(30%)
FLIPI 1 Score (n=120), n (%)	
low	30 (25%)
Intermediate	54 (45%)
High	36 (30%)
B-symptoms present , n=151 n (%)	30(20%)
Extra nodal Involvement n (%)	40(22%)
ECOG- performance status (3&4) (n= 131) , n (%)	26 (20%)
Bulky disease, n (%)	35(19%)
Hemoglobin (<8 g/dL), %	15%
Albumin (< 3.5 g/dL), %	20%
High LDH (n=120)	24(20%)

Follicular Lymphoma International Prognostic Index (FLIPI) Lactate dehydrogenase (LDH)



Figue 1. Overall Survival in Follicular Lymphoma

Table 2. Treatment Characteristics (First Line)

Chemotherapy - Regimen	n=141
CVP	51
CHOP	45
CP+ others	(7+5)
RCHOP	14
RCVP	7
BR	12

CHOP, (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone); CVP, (Cyclophosphamide, Vincristine and Prednisolone); BR, (Bendamustine Rituximab); CP, (Chlorambucil +Prednisolone)

Table 3. Effect of Rituximab on Treatment

Regimen	Rituximab based regimen n=33	Other regimen (without rituximab) N=108	P value
Complete response	43%	24%	0.003
Overall response rate	84%	65%	0.001

Table 4. Multivariate Cox Regression Analysis for EFS, Follicular Lymphoma

Variables	Hazard Ratio (95% CI)	p-value
Extra Nodal Disease	1. 11(0.73-1.71)	ns
B Symptoms	1.82(0.71-3.2)	ns
Bulky Disease	1.36(0.73-3.82)	ns
High LDH	1.52(0.51-3.72)	ns
Stage 1 and 2	1	
Stage 3	1.22 (0.58- 2.65)	
Stage 4	1.16 (0.44 -1.51)	ns
ECOG (3,4)	2.01 (0.76 - 5.23)	ns
Albumin <3.5g/dl	2.46 (1.19 -5.16)	0.001
Response<CR	2.11(1.52-4.8)	0.01
FLIPI -low	1	
FLlPI2 -intermediate	0.76 (0.19 - 2.98)	
FLIPI -high	1.29 (0.30 -5.49)	<0.001
Grade 1 and 2	1	
Grade 3	1.71(0.87-2.77)	0.01

ns, not significant; FLIPI, Follicular Lymphoma International Prognostic Index; CR, complete response

Table 5. Multivariate Cox Regression Analysis for OS, Follicular Lymphoma

Variables	Hazard Ratio (95% CI)	p-value
Extra Nodal Disease	1. 67(0.88-2.71)	ns
B Symptoms	1.02(0.79-2.2)	ns
Bulky Disease	1.42(0.73-3.99)	ns
High LDH	1.12(0.88-2.72)	ns
Stage 1 and 2	1	
Stage 3	1.36 (0.94- 1.97)	ns
Stage 4	1.66 (1.44 -2.51)	ns
ECOG (3,4)	1.01 (0.76 - 2.23)	ns
Albumin <3.5g/dl	1.46 (1.1 -3.16)	ns
Response<CR	2.64(1.10-4.3)	0.001
FLIPI -low	1	
FLlPI -intermediate	0.86 (0.42 – 1.98)	
FLIPI -high	0.77 (0.72-0.83)	<0.001
Grade 1and 2	1	
Grade 3	1.71(0.87-2.77)	ns

ns, not significant; FLIPI, Follicular Lymphoma International Prognostic Index; CR, complete response

with follicular lymphomas (FL) were first assessed for indication of treatment. Asymptomatic patients were kept on close observation alone. Majority of the treated patients were given either CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone) or CVP (Cyclophosphamide, Vincristine and Prednisolone) regimen with or without rituximab . One forty five patients (80%) received treatment at presentation or during followup. Chemotherapeutic regimen used were: CHOP-45 , CVP-51, chlorambucil and prednisolone -7, BR (bendamustine and rituximab)-12, RCHOP- 14 and RCVP in 7 cases, others regimen including fludarabine , in 5 cases (Table 2). The overall response (ORR) and complete remission (CR) rates were 70% and 35% respectively. Only 33 patients received rituximab based treatment, which have shown better complete response and overall response rate (Table 3). Only 12 patients received rituximab maintance. Relapse occurred in 40 patients, 50 patients died and progression was observed in 63 patients. Median overall survival (OS) and event free survival (EFS) was 5.5 years and 2.5 years respectively, with median follow up period of 3 years (Figure 1). Grade 3 histology, failure to attain CR, low serum albumin, PS III/IV, bulky disease and high risk FLIPI were significantly associated with lower event free survival and OS on univariate analysis. On multivariate analysis grade 3 tumor

Table 6. Randomized Trial of Chemo-Immunotherapy

Study		n	ORR,%	CR,%	OS,%
Marcus et al.	CVP	159	57%	10%	77%
	RCVP	162	81%	41%	83%
Hiddemann et al.	CHOP	205	90%	17%	90%
	RCHOP	223	96%	20%	95%
Rummel et al.	RCHOP	274	93%	-	31.2 months PFS
	BR	275	91%	-	69.5 months PFS

, failure to attain CR and low albumin were associated with poor EFS. When similar analysis was done for overall survival high risk FLIPI (HR 1.46, 95% CI 1.03-2.10, p=0.003) and failure to attain CR (HR 2.64, CI 1.10-4.30, p=0.001) were found to be an independent predictor of outcome (Table 4,5). Eleven patients had transformed to high grade lymphoma (Richter's transformation) . Grade 3b patients were treated as Diffuse large B-cell lymphoma with CHOP chemotherapy. Out of 6, 4 patients died of progressive disease, one patient died of disseminated tuberculosis and one patient was alive at the time of analysis

Discussion

Follicular Lymphoma is the second most common type of NHL and most common of the indolent lymphoma. It accounts 20-30% of all NHLs in the west. Precise data from India is sparse. The median age of current study is 51 years which is a decade earlier then reported literature. Similar observations has been made for other hematological malignancies also (Gogia et al., 2012) This might be due to lower life expectancy in Indian population as compared to the west or influenced by a referral bias in developing nations, where older patients are less likely to be referred to a tertiary care center. The most common presenting symptoms was lymphadenopathy in studies from the west and a similar finding was observed by us, while fatigue and B symptoms were predominant in our study. Stage IV was the most common stage at presentation due to bone marrow infiltration, which is similar to the reported literature At baseline 20% patients presented with poor performance status (PS III-IV) and 19% cases had bulky disease. These parameters were higher than published reports, are largely due to delayed diagnosis or delayed contact with health care by the patients for their symptoms. The distribution of FLIPI groups was similar to that described in other studies. FL in advanced stage is still considered an incurable disease , and patients tends to recur after a long period of time. Median time to relapse is 18-36 months, in our study it was found to have 30 months. The median follow up of this study was period was 36 months, it appears short in this analysis because most of patients have recruited in later part of study and 35 patients were lost to follow-up. The treatment of symptomatic FL have been evolved in last 3 decades. The alkylating agents chlorambucil and cyclophosphamide in combination with prednisone or vinca alkaloids with (CHOP) or without anthracycline (CVP) have been the standard therapy for decades in FL (Steffanoni S., et al) Different doses and schedules of alkylating agents as single agent were proposed, but none of them appeared to be superior in terms of efficacy or toxicity. The CVP combination showed higher CR rates and a longer PFS in comparison to chlorambucil alone but no survival benefit has ever been demonstrated. In this study 96 patients received CHOP and CVP regimen, with similar response rate and toxicity profile reported in literature (Jones SE et al .,1972). In our study 7 patients received chlorambucil and prednisolone with ORR of 60%. Chlorambucil with prednisone and mitoxantrone (MCP regimen) was frequently used in first-line in earlier published literature of FL, with overall response of 70-75%, complete response of 15- 20%, median event free survival 20- 24 months but associated with high incidence of leucopenia and infection (Herold M et al., 2007).

The prognosis of FL has been changed over last 2 decades with the introduction of anti – CD20 antibody rituximab (Vidal et al., 2011; Overman et al., 2008) Rituximab based chemo immunotherapy is the standard of care of FL and has been proved in multiple randomized trials (Table 6). The best choice of chemotherapy to combine with rituximab has changed in recent years. Bendamustine plus rituximab (BR) has been compared to R-CHOP in a randomized phase III trial demonstrate superior median PFS and less toxicity with same response rate (Rumell et al., 2013)The overall response rate was 70% and CR rate was 30 % was seen in current study . These results are consistent with other reports of treatment response (Marcus et al., 2008; Hiddeman et al., 2005). In our study only 33 patients have received rituximab based regimen. Median EFS was 30 months and at 3 years EFS was 40 % while OS was 80%. We found that failure to attain CR was significantly associated with poor EFS and OS. Historically it is reported that achievement higher CR rates by aggressive regimen does not translate into survival benefit in FL. However in our study attainment of CR was significantly associated with both EFS and OS. We also found that rituximab based regimen showed better overall response rate and complete remission rate but does not correlate with EFS and OS. Most likely reason is that a small number of patients received rituximab based regimen and median follow up period is too short to comment on the same. OS and EFS were higher in western studies than the present studies, whether this is because of late presentation, different biology or infrequent use of rituximab, are not clear. The short comings of retrospective analysis are obvious. Changes in pattern of referral and in therapeutic strategies may also affect the natural course of the disease.

Clinical Practice Points

Follicular Lymphoma is the most common indolent lymphoma and constitute 9 % of all lymphoma at our centre. Combination chemo immunotherapy is the standard of treatment . The overall response to rituximab-based therapy was encouraging, in our study. CR rate is important surrogate for long term outcome along with conventional FLIPI prognostic score.

References

Cheson BD, Pfistner B, Juweid ME, et al (2007). Revised response criteria for malignant lymphoma. *J Clin Oncol*, **25**, 579-86.

Gogia A, Sharma A, Raina V, et al (2012). Assessment of 285 cases of chronic lymphocytic leukemia seen at single large tertiary center in Northern India. *Leuk Lymphoma*, **10**, 1961-5.

Jones SE, Rosenberg SA, Kaplan HS, et al (1972). Non-Hodgkin's lymphomas. *Cancer*, **30**, 31-8

Herold M, Haas A, Srock S, et al (2007).Rituximab added to first-line mitoxantrone,chlorambucil, and

prednisolonechemotherapy followed by interferon maintenance prolongs survival in patientswith advanced follicular lymphoma: an Eastgerman study group hematology andoncology study east german study group hematology and oncology study. *J ClinOncol*, **25**, 1986-92.

Hiddemann W, Kneba M, Dreyling M, et al (2005). Frontline therapy with rituximabadded to the combination of cyclophosphamide, doxorubicin, vincristine, andprednisone (CHOP) significantly improves the outcome for patients withadvanced-stage follicular lymphoma compared with therapy with CHOP aloneresults of a prospective randomized study of the German Low-Grade LymphomaStudy Group. *Blood*, **106**, 3725-32.

Hochster H, Weller E, Gascoyne RD, et al (2009) Maintenance rituximab after cyclophosphamide,vincristine, and prednisone prolongs progression-free survival inadvanced indolent lymphoma: results of the randomized phase III ECOG1496study. *J Clin Oncol*, **27**, 1607-14.

Horning SJ, Rosenberg SA (1984). The natural history of initially untreated low-gradenon-Hodgkin's lymphomas. *N Engl J Med*, **311**, 1471-5.

Manoharan N, Tyagi BB, Raina V (2010). Cancer incidences in rural Delhi-2004-05. *Asian PacJ Cancer Prev*, **11**, 73-77

Marcus R, Imrie K, Solal-Celigny P, Catalano, et al (2008). Phase III study of R-CVP comparedwith cyclophosphamide, vincristine, and prednisone alone in patients with previouslyuntreated advanced follicular lymphoma. *J Clin Oncol*, **26**, 4579-86.

Overman MJ, Feng L, Pro B, et al (2008). The addition of rituximab to CHOPchemotherapy improves overall and failure-free survival for follicular grade 3lymphoma. *Ann Oncol*, **19**, 553-9.

Rummel MJ, Niederle N, Maschmeyer G, et al (2013) Bendamustine plus rituximabversus CHOP plus rituximab as first-line treatment for patients with indolent andmantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 noninferioritytrial. *Lancet*, **381**, 1203-10.

Salles G, Mounier N, de Guibert S, et al (2008) Rituximab combined with chemotherapyand interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. *Blood*, **112**, 4824-31.

Salles G, Seymour JF, Offner F, et al (2011) Rituximab maintenance for 2 years inpatients with high tumour burden follicular lymphoma responding to rituximabplus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet*, **377**, 42-51.

Steffanoni S, Ghielmini M, Moccia A (2015). Chemotherapy and treatment algorithms for follicular lymphoma: a look at all options. *Expert Rev Anticancer Ther*, **15**, 1337-49.

Vidal L, Gafter-Gvili A, Salles G, et al (2011). Rituximab maintenance for the treatment of patients with follicular lymphoma: an updated systematic review and meta analysis of randomized trials. *J Natl Cancer Inst*, **103**, 1799-806.