ORIGINAL ARTICLE

Impact of the Follicular Lymphoma International Prognostic Index risk categorization on survival of patients with follicular lymphoma in Pakistani population: A single centre experience

Sohail Athar,[1] Neelam Siddiqui,[2] Abdul Hameed,[3] Mohammad Tariq Mahmood,[4] Muhammad Zubair Khan[5]

Abstract

Objective: To determine the impact of Follicular Lymphoma International Prognostic Index risk categorisation on the survival of patients with follicular lymphoma treated in one centre.

Method: The retrospective study comprised follicular lymphoma patients treated from 1997 to 2010 at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore. Their baseline prognostic index score, stage, bone marrow involvement and high-grade transformation were recorded. Risk categorisation was done according to the index score. SPSS 19 was used for statistical analysis.

Results: Median age of the 70 patients studied was 54 years (range: 23-98). There were 42 (60%) males. Overall, 58 (83%) patients presented with stage III/IV disease. Bone marrow was involved in 42 (60%) cases. High-grade transformation was reported in 12 (17.1%). According to risk categorisation, 21 (30%) were low risk, 21 (30%) intermediate and 28 (40%) were in high-risk category. Patients were treated with standard chemotherapy. Median follow-up was 3 years (range: 1-9). Median overall survival was 4.1 years (95% CI: 4.7-6.4). The Kaplan Meier estimated overall survival at 5 years was 26 (43%). Five-year overall survival in the low, intermediate and high risk groups was 14 (66%), 10 (47%) and 7 (25%), respectively ($p<0.02$).

Conclusion: The Follicular Lymphoma International Prognostic Index showed significant prognostic value with high scores having poor overall survival compared to patients with low and intermediate scores.

Keywords: Follicular lymphoma, Outcome, Survival, Chemotherapy, Lymph node. (JPMA 64: 563; 2014)

Introduction

Follicular lymphoma (FL) is the most common indolent lymphoma and second most common among non-hodgkin lymphoma (NHL) after diffuse large B-cell lymphoma (DLBCL).[1] FL consists of centrocytes and centroblasts which originate from germinal centre B cell which usually have a partially follicular pattern.[2] It occurs in all races, equally among both genders. This lymphoma commonly occurs in middle aged and elderly patients with median age at presentation being 50 years.[3] Its pathogenesis is not clearly understood but 85% of patients over-express B cell leukaemia antigen known as BCL-2 which is present on chromosome 18. In FL, there is translocation of BCL-2 from chromosome 18 to immunoglobulin genes located on chromosome 14, resulting in translocation t (14:18), which results in blockage of programmed cell death called apoptosis.[4] Patients usually present with nodal enlargement with frequent involvement of spleen, liver and bone marrow.[5] Most of these patients present with advanced stage disease. Despite widespread disease, only 20% patients present with B symptoms and 25% have raised serum lactate dehydrogenase (LDH) levels.[2,6]

Aggressiveness of FL depends on the histological grades from I-III depending upon the number of centroblasts/transformed large cells. Grade I has 0-5 centroblasts cells/high-power field (hpf), grade II contains 6-15 cells/hpf and grade III has >15 cell/hpf.[2,7] Grade III lymphomas are further subdivided into IIIA (centrocytes present) and IIIB (solid sheets of centroblasts). Solal et al proposed the prognostic index known as Follicular Lymphoma International Prognostic Index (FLIPI), which includes five prognostic factors i.e. age >60 years, serum LDH level above normal, Ann Arbour stage III/IV, number of nodal area >4 and haemoglobin <12g/dl (Table-1). Using these factors three groups are defined: low-risk; 0-1 factors; intermediate risk; 2 factors; and poor risk; >3 factors, with 5-year overall survival (OS) rate from 52-91% and 10-year OS rate 36-73%.[6] FLIPI risk categorisation is considered one of the best measures of outcome for FL along with tumour grade.[8]

The treatment of FL depends upon a number of factors e.g. bulky disease, B symptoms, extra-nodal disease, cytopenias etc. The most common system used to decide

[1-3,5]Department of Medical Oncology, [4]Department of Pathology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore.

Correspondence: Sohail Athar. Email: drsohail_71@hotmail.com

treatments are Groupe d-Etude des Lymphomes Folliculaires (GELF) and the British National Lymphoma Investigation (BNLI).[9,10] Treatment ranges from observation, radiation and chemoimmunotherapy followed by maintainance therapy with rituximab.[11]

This study was undertaken to determine the impact of FLIPI risk categorization on the survival of FL patients treated at our centre.

Patients and Methods

The retrospective study comprised data of patients treated for follicular lymphoma at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, from 1997 to 2010. Data collection was done through the computerised database system. Patients' medical record number, age and gender were recorded. Baseline pathology reports were evaluated for nodular growth pattern and tumour grade as per the WHO classification of tumours of Haematopoietic and lymphoid tissue 2008.[2] Emphasis was given to the immunostaining for BCL-2, CD10 (expressed on the surface of germinal center B- cells) and CD20 (B-lymphocyte antigen) positivity. Base line workup, including computed tomography (CT) scans, Ann Arbour staging for nodal and extra-nodal involvement, haemoglobin, LDH and bone marrow involvement were recorded. Since FL can transform to high-grade lymphoma, therefore patients with lymph node biopsy proven transformation were taken into account. After collecting the data, FLIPI score and FLIPI risk categorisation was done i.e. low risk 0-1, intermediate risk 2, and high risk 3 or more factors. The study was approved by the institutional ethics review board.

Statistical analysis was done using SPSS 19.0. Primary end-point of the study was overall survival (OS), which was calculated from the date of registration to the last date of follow-up or death from any cause. Kaplan-Meier survival curves were compared using the log-rank test.[12,13]

Results

The median age of the 70 patients at presentation was 54 years (range: 23-98), and there were 42 (60%) males. Stage at presentation from I-IV was, 5 (7.1%), 7 (10%), 16 (22.9%) and 42 (60%) respectively. At the time of diagnosis 42 (60%) patients had bone marrow involvement (Table-2). FL histological grades from I-III were 32 (46%), 19 (27%) and 19 (27 %) respectively. In 12 (17.1%) patients, disease transformed from FL to large B cell lymphoma. FLIPI risk categorisations according to FLIPI score from low to high risk were: low 21 (30%), intermediate 21 (30%) and high 28 (40%) respectively.

Table-1: The Clinicopathological features of the patients.

Characteristic's	Total number of patients (n= 70)	Percentage
Median Age	54 years (range 23-98)	
Gender		
M	42	60
F	28	40
Current status		
Alive	30	42.9
Dead	19	27.1
Lost to follow up	21	30
Stage at presentation		
I	5	7.1
II	7	10
III	16	22.9
IV	42	60
Histology grades		
Grade 1	32	45.7
Grade 2	19	27.17
Grade 3	19	27.17
Bone marrow involvement		
Yes	42	60
No	28	40
Transformation		
Yes	12	17.1
No	58	82.9
FLIPI Risk Group		
Low risk (0-1)	21	30
Intermediate risk (2)	21	30
High risk > 3	28	40

FLIPI: Follicular lymphoma international prognostic index.

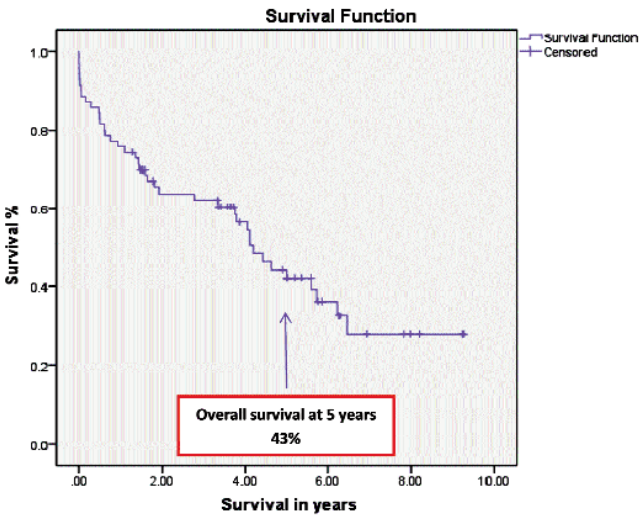

Figure-1: Overall survival at 5 years.

Median follow-up was 3 years (range: 1-9). At the time of analysis, 30 (43%) patients were alive, 19 (27%) were dead, and 21 (30%) had been lost to follow-up. The OS at 5 years

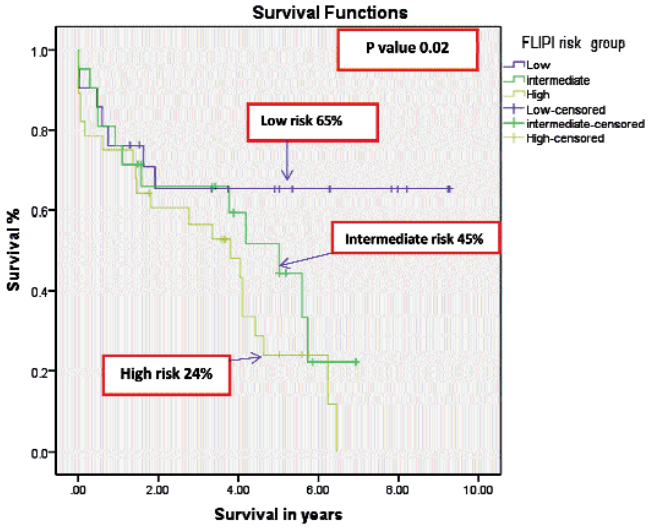

Figure-2: Overall survival at 5 years according to Follicular lymphoma international prognostic index.

was 30 (43%) (Figure-1). OS at 5 years, according to FLIPI low risk, intermediate and high risk groups were 14 (66%), 10 (47%) and 7 (25%) respectively and the difference was statistically significant (p<0.02) (Figure-2).

Discussion

The epidemiology of NHL is considerably variable in different geographical areas of the world. In Western countries low-grade indolent lymphomas are much more common than in the Asian countries where aggressive lymphomas are more predominant. In the USA, FL accounts for 35% of NHLs with an incidence of 3.1/100,000 people compared to Asian population including Pakistan, in whom the lowest rates of FL have been reported.[14-17] This difference could be due to genetic susceptibility, environmental factors or various infective agents.

The median age at presentation of FL patients is reported to be 55-60 years which is similar to our patients, but gender-wise, we saw a slight male preponderance.[3,14] Since FL has an indolent clinical course, it usually presents with advanced stage disease, stage III/IV with great variation in bone marrow involvement (50-80%).[5,16] In our study, 60% patients had bone marrow involvement at the time of diagnosis. FL is known to carry a slow indolent course with 2-3% per year incidence of transformation to aggressive lymphoma. Despite variable options of treatment modalities, including chemotherapy, immune therapy and radiotherapy, in most patients the disease is not curable with frequent relapses.

FLIPI is a prognostic tool based on simple clinical parametres which are easy to use in clinical setting. It takes into account age of the patient, stage of disease at presentation, serum LDH level, number of lymph node sites, and haemoglobin. FLIPI score is considered helpful in selecting treatment in individual patients. In order to avoid toxicity of chemotherapy and to maintain good quality of life, patients, who, according to FLIPI, have an early-stage low-risk disease, may be offered wait-and-watch strategy, involving field radiotherapy or immunotherapy such as anti-CD 20 antibody.

According to FLIPI risk categorisation, a study reported 5-year OS from 52-91 % for high-risk to low-risk groups.[6] In our study, the 5-year OS for low, intermediate and high-risk groups according to FLIPI, were well predicted with statistical significance. The OS of our patients (24-65%) was lower than those reported in literature, probably due to small sample size and because 21 (30%) patients were lost to follow-up. Nineteen patients had died during follow-up due to unrelated non-malignant causes. Life expectancy in the developing world, especially in Pakistan, is considerably low compared to Western population. Many of our patients had come from rural areas and travelled long distances for treatment. Along with financial constraints they generally have poor nutritional status and improper transport facilities. They are, therefore, unable to continue prolonged follow-up for this indolent disease, which is a prerequisite for effective treatment and efficient surveillance.

Limitation of our study is that it is of a retrospective nature, number of patients in this study is small and considerable number of patients were lost to follow up. These factors could be the reason of inferior survival in our cohort as compared to Western population.

Conclusion

FLIPI is a very useful prognostic tool to determine expected survival of patients with follicular lymphoma and may be used to plan the most effective therapy. However this study is a single institution experience so a prospective study is required for validation.

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