EJMA

DOI: 10.14744/ejma.2022.35220
EJMA 2022;2(1):7–12

Research Article

Detailed Analysis of Follicular Lymphoma over 25 Years: A Single-Center, Retrospective Study

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Abstract

Objectives: Follicular lymphoma is the most common indolent non-Hodgkin lymphoma. The course of the disease varies according to several parameters, so individualized treatments should be pursued. Many studies have shown positive effects of complete response to first-line chemoimmunotherapy on progression free survival (PFS) and overall survival (OS). In our study, we aimed to determine prognostic value of the risk factors that will predict the response to first-line chemoimmunotherapy.

Methods: Demographic data, histopathological characteristics, imaging and laboratory tests of the patients were evaluated retrospectively and recorded with survival data. Patients with and without complete response (CR) were compared.

Results: Ninety-one patients diagnosed and treated over 25 years were included in this study. Seventy-six patients who met GELF criteria received first line chemoimmunotherapy, followed by with or without maintenance rituximab for 2 years. Diagnosis at the age>60, higher FLIPI score, bone marrow involvement and hyperuricemia were associated with lower complete response rates (p=0.045, p=0.001, p=0.048, p=0.004, respectively). There was no significant association between rituximab therapy and PFS-OS rates.

Conclusion: In our study, age over 60 years, high FLIPI score, bone marrow involvement and high uric acid levels were associated with low CR rates to first-line chemoimmunotherapy. The impact of CR and maintenance therapy on PFS and OS was not achieved.

Keywords: Chemoimmunotherapy, follicular lymphoma, predictive factors

Cite This Article: *Yildirim HC, Atilla FD, Sahin F, Saydam G, Vural F, Tombuloglu M. Detailed Analysis of Follicular Lymphoma over 25 Years: A Single-Center, Retrospective Study. EJMA 2022;2(1):7–12.*

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL) in the world and accounts for approximately 35% of all NHLs.[1] Since it is a low grade disease, it is usually diagnosed at advanced ages and stages. Median age at diagnosis is 65.[2] With the discovery of anti CD 20 monoclonal antibodies, the average life expectancy has reached 20 years.[3] The disease has a very heterogeneous clinical course making individualized treatment decisions vital. Prognostic systems have been developed in order to apply individualized treatments. The most commonly used is The Follicular Lymphoma Prognostic Index (FLIPI). It divides patients into 3 different groups as low risk, medium risk and high risk. This system includes age, Ann Arbor stage, number of nodal areas involved, hemoglobin level and lactate dehydrogenase (LDH) value.[4] Although this system was developed in pre-rituximab era, it still retains

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Submitted Date: December 02, 2021 **Accepted Date:** January 13, 2022 **Available Online Date:** January 20, 2022

its importance. In the FLIPI-2 system, developed after the introduction of rituximab, age, hemoglobin value, B2 microglobulin level, bone marrow involvement, largest lymph node diameter are evaluated.[5] There are also other prognostic scoring systems which aim to predict treatment response by b2 microglobulin and LDH. There is a correlation found between this scoring and FLIPI-1 and FLIPI-2.[6]

Apart from the scoring systems, the disease stage and the presence of disease-related symptoms are also important in the treatment decisions. According to Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, asymptomatic patients with stage III and IV disease is followed without systemic treatment.and systemic chemoimmunotherapy should be given to patients who meet the GELF criteria while applying close follow-up or involved area radiotherapy in asymptomatic patients with early-stage disease.[7] If a complete response is obtained with treatment, observation or maintenance immunotherapy can be given. In a phase 3 study in which maintenance immunotherapy was investigated, it had an effect on recurrence, but did not create a survival difference, and an increase in the frequency of grade 3-4 adverse events occurred.[8] Patients with CR can be followed-up without treatment, both to avoid adverse events due to immunotherapy and to avoid the high cost of immunotherapy. So, the factors predicting the CR are valuable. In this study, we aim to determine the predictive factors for achieving CR with first-line chemoimmunotherapy.

Methods

Study Population

This retrospective study included a total of 91 patients diagnosed with FL between 1993-2019 at Ege University Hospital in Izmir/Turkey. All patients were older than 18 years and diagnosed with FL according to the World Health Organization criteria. Patients with concomitant large cell lymphoma (n=2), below 18 years of age and missing data (n=10) were all excluded.

Data Collection

The recorded clinical and demographic features were age, gender, pathological grade, stage (according to Ann Arbor Staging System), laboratory parameters (hemoglobin, lymphocyte, uric acid, LDH, b2 microglobulin), first-line treatment and the best treatment response (according to Lugano's revised response assessment system). PFS was defined as the time from the diagnosis to the recurrence. OS was defined as the time from the diagnosis to the death or last follow-up.

Ethical Consideration

This retrospective study was performed in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University of Ege University School of Medicine (18-10.2T/42).

Statistical Analysis

Descriptive data were presented as mean, standard deviation, minimum & maximum values for parametric variables and as numbers & percentages for categorical variables. Parametric variables were compared by student t-test and non-parametric variables were compared Mann-Whitney U test. The comparison of the nonparametric variables was carried out by chi-square and Fischer's exact tests. Survival analyzes were performed by using Kaplan-Meier analysis and log-rank test. Statistical package for social sciences (SPSS, Version 22.0, IBM Corp. 2013, Armonk, NY) for Windows software was used for statistical analysis. P-value less than 0.05 was accepted as statistically significant.

Results

Ninety-one patients were included in the study. Among the entire cohort, nine patients were followed up with a watch and wait approach and six patients received involved field radiotherapy without chemotherapy. Seventy-six patients who met the GELF criteria were treated with first-line R-CVP or R-bendamustine or R-CHOP therapies (11%, 4%, 85% respectively), followed with or without maintenance rituximab (78% and 22% respectively) for 2 years.

The mean age at diagnosis was 55 +13.38. Females were slightly predominant than males (58.3% vs 41.7%). Of the patients, 29 (31.9%) had B symptoms, 28 (30.7%) had bone marrow involvement, 11 (12%) had extranodal involvement. According to prognostic scores; 27 (29%) had low, 27 (29%) had intermediate and 37 (40%) had high FLIPI scores. Of histopathologic grading 18 (20%), 43 (47.7%), 19 (21.1%) and 10 (11%) of the patients were grade 1, 2, 3A and 3B, respectively. Disease stage, clinical-pathological characteristics and laboratory findings and are shown in Table 1. All detailed laboratory characteristics are shown in Table 2.

Patients with or without complete response were evaluated with imaging performed after sixth cycles of chemoimmunotherapy. Patients with advanced age (>60) had significantly lower CR rates than the younger ones (p=0.045). Patients with higher FLIPI scores had a significantly lower CR rates compared to other patients (p=0.001). Bone marrow involvement was an independent poor prognostic factor and associated with lower CR rates (p=0.048). The presence of hyperuricemia was an important marker in

Table 1. The clinical and pathological characteristics of the patients

	No	%
Gender		
Male	38	41.7
Female	53	58.2
Age		
>60	32	35.2
<60	59	64.8
B symptoms		
Presence	29	31.9
Absence	62	68.1
Bone marrow involvement		
Presence	28	30.7
Absence	63	69.3
FLIPI score		
Low	27	29.7
Intermediate	27	29.7
High	37	40.6
Grade		
1	18	20
2	43	47.7
3A	19	21.1
3B	10	11.1
Stage		
1-2	23	25.3
3-4	68	74.7

FLIPI: Follicular Lymphoma Prognostic Index.

Table 2. Laboratory characteristics of the patients

	No	%
Anemia		
Presence	16	17.5
Absence	75	82.5
Lymphopenia		
Presence	2	2.2
Absence	89	97.8
Uric acid		
>ULN	32	35.1
Normal	59	64.9
LDH		
>ULN	37	40.6
Normal	54	59.4
Beta 2 microglobulin		
High	21	45.7
Normal	25	54.3

ULN: Upper limit of normal; LDH: Lactate dehydrogenase.

predicting response. Patients with high uric acid levels had lower CR rates (p=0.004). No relationship was found between gender and treatment response (p=0.32). In addition there was no relationship between grade and treatment response. While CR rates was higher in early-stage patients compared to advanced-stage, statistical significance was not reached (p=0.069). Although there was a proportionally lower CR in patients with high b2 microglobulin, no statistical significance was reached (p=0.235). No relationship was found between anemia and elevated LDH with teatment responses (p=0.18, p:0.59 respectively). Other parameters evaluated for association with treatment response are shown in Table 3.

The median PFS and OS were not reached in patients with or without CR and no statistically significant difference was found (p=0.213, p:0.497, respectively). The relationship between CR and PFS and OS is shown in Figure 1.

PFS and OS were not reached and no statistical difference was found in patients with and without maintenance rituximab therapy. The relationship between maintenance rituximab treatment and PFS and OS is shown in Figure 2.

Discussion

The slow course of the disease in patients diagnosed with FL and the existence of different approaches at different stages of treatment necessitate individualized treatment. Response rates increased with the introduction of immune-therapeutics in the treatment of FL. In the PRIMA study, in which the effectiveness of maintenance rituximab treatment was evaluated, 10-year PFS rates were determined as 51% and 35%, respectively, in patients who received and did not receive maintenance therapy, while the 10-year overall survival was around 80% in both groups.[9] Grade 3-4 adverse events were seen at the rate of 24.4 and 16.9, respectively. In our study, the effect of maintenance rituximab treatment on PFS and OS was not observed. As shown in Figure 2, the contribution of maintenance therapy with rituximab on PFS in the early period was not seen, but after 10 years, its contribution on PFS may occur. The contribution of maintenance therapy on OS was not achieved. Although it does not provide an overall survival advantage, maintenance rituximab is recommended for high-risk patients, while follow-up without treatment is an option in patients with low risk of recurrence and complete response with first-line chemoimmunotherapy. In a multicenter study conducted in Italy, it showed the effect of obtaining CR with treatment on survival.[10] The 13-year overall survival was 77% and 36.8%, respectively, in patients with CR with first-line therapy and in patients in whom CR could not be obtained. In our study, no difference in PFS and OS was found between patients with and without CR. Whether the racial and genetic differences could be the reason for this different results should be further investigated.

Table 3. The relationship between patients characteristics and laboratory parameters with complete response

	CR+	CR-	p score
Gender			0.32
Male	17	14	
Female	21	24	
Age			0.045
>60	9	17	
<60	29	21	
B symptoms			0.31
Presence	11	14	
Absence	27	24	
Bone marrow involvement			0.048
Presence	10	18	
Absence	28	20	
FLIPI score			0.001
Low-intermediate	29	14	
High	9	24	
Stage			0.069
1-2	10	4	
3-4	28	34	
Anemia			0.18
Absence	5	9	
Presence	33	29	
Uric acid			0.004
>ULN	8	20	
Normal	30	18	
LDH			0.59
>ULN	16	16	
Normal	22	22	
Beta 2 microglobulin			0.235
>ULN	6	11	
Normal	11	10	

CR: Complete response; ULN: Upper limit of normal; FLIPI: Follicular Lymphoma Prognostic Index; LDH: Lactate dehydrogenase.

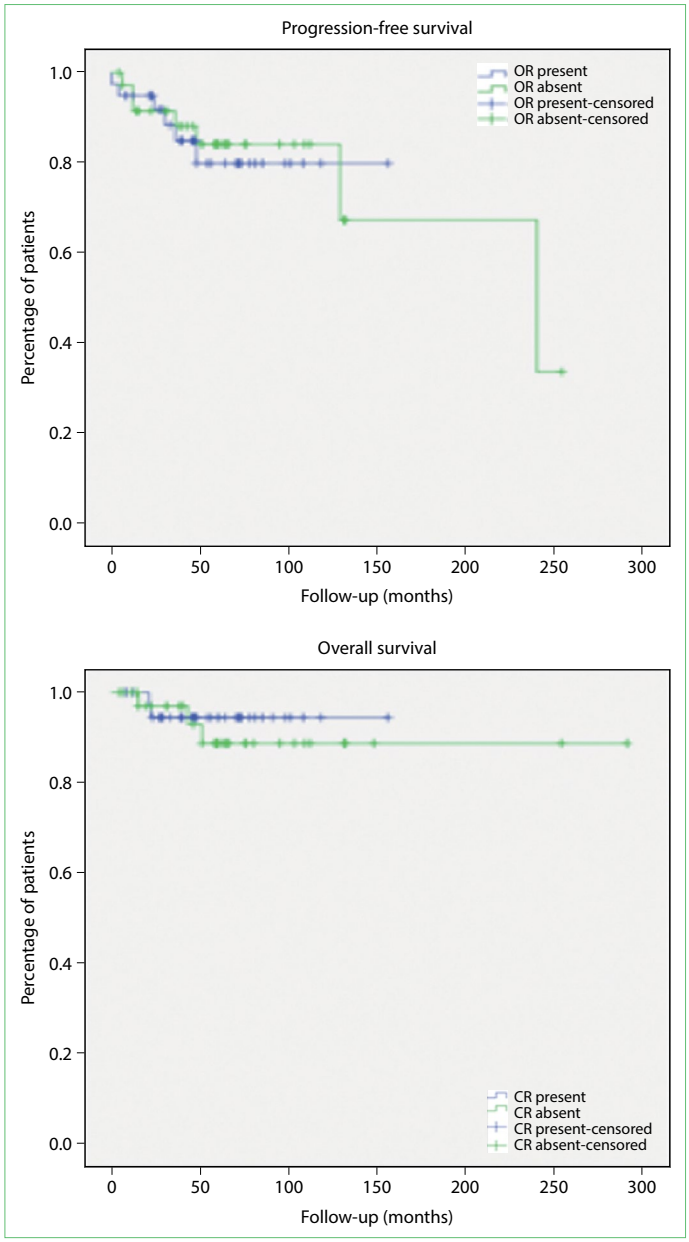

Figure 1. Impact of complete response on progression-free survival and overall survival.

In many different studies, advanced age (>60) is associated with poor response.[4] However, in the study conducted by Magnano et al.,[11] no significant difference was found between age groups in terms of achieving a CR with first-line treatment. In the study conducted by Vitolo et al.,[12] patients with advanced aged, no superiority of short-term maintenance rituximab treatment over the observation arm was found in patients who had CR after chemoimmunotherapy. The effect of long-term maintenance therapy on PFS was shown. However, an increase in the frequency of adverse events may be observed in elderly patients due to multiple comorbidities. Therefore, if there is no high risk of recurrence in patients with CR in elderly patients with first-line chemoimmunotherapy, following-up without treatment should be considered. In our study, unlike the study of Magnano et al. the rate of CR in patients with advanced age was lower than younger ones (p=0.045).

In the study evaluating over 2000 patients with Non-Hodgkin Lymphoma treated with anthracycline-containing chemotherapy in the period before the routine use of rituximab, being over 60 years old, having a high serum LDH level, ECOG score ≥2, stage 3-4 and >1 extranodal involvement was found to be associated with poor prognosis and IPI score system was created.[13] Because the IPI score could not predict overall survival in FL, the FLIPI-1 system was created.[14] In this scoring system, presence of >4 nodal involvement, high LDH, age> 60, stage 3-4, Hb

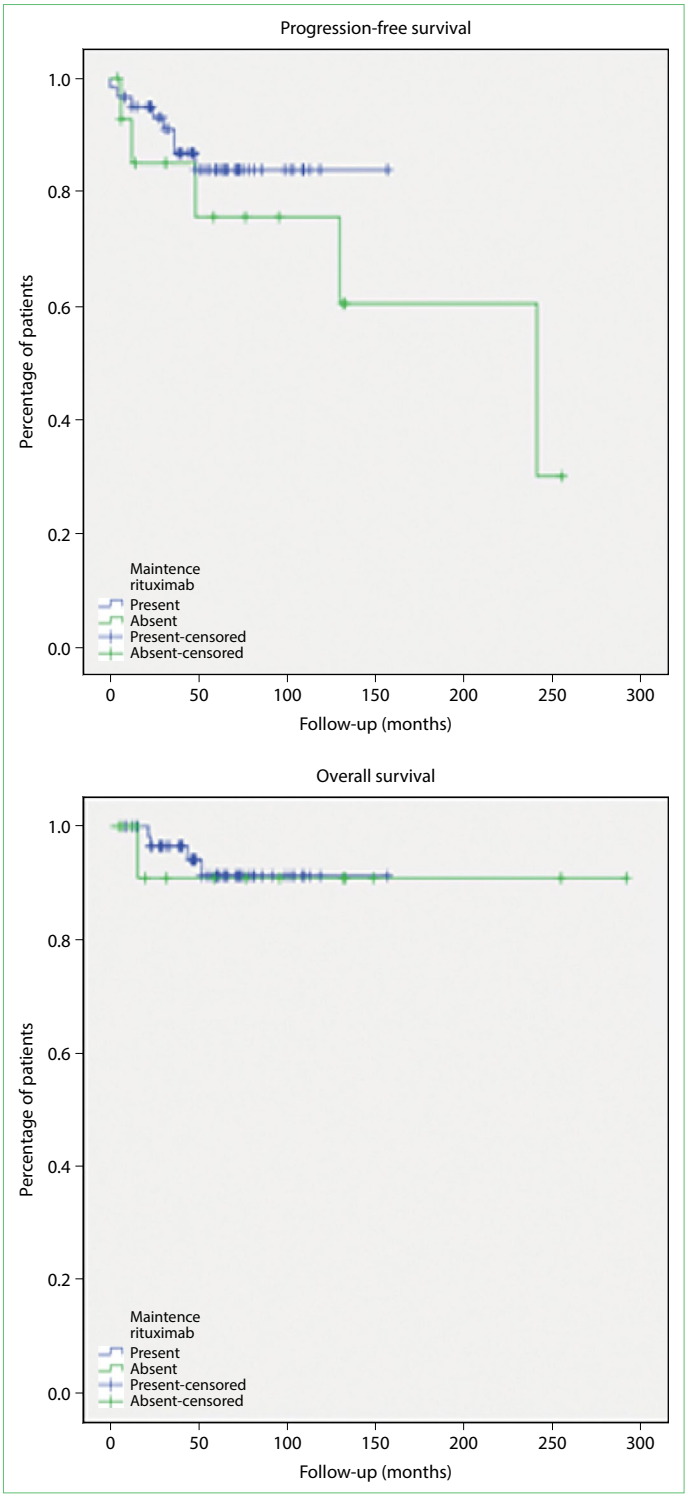

Figure 2. Impact of complete response on progression-free survival and overall survival.

<12 g/dL were used. It was shown that 5-year survival was predicted with this system. In other study which aimed to correlate FLIPI score, 4000 patients were enrolled. CR and PR was achieved in 62% and 28% of the patients respectively. But there was no significant association between scoring system and response rates.[15] In an analysis that included multiple randomized controlled studies in 2017, a strong association was found between the 30-month CR and PFS and high FLIPI score.[16] In our study, the rate of obtaining CR response was significantly lower in the group with high FLIPI-1 score (p=0.001).

Disease stage is a part of the FLIPI scoring system, and there are studies showing the association of advanced stage with poor prognosis. In the study conducted by Batlevi et al.,[17] a prolonged PFS-OS response was observed in stage 1 patients after chemoimmunotherapy compared to other stages. In another study, CR was assessed at 30 months in FL patients in Spanish population screening and found 84% in stage 1-2 and 68% in stage 3-4.[11] In our study, 71% of the patients had a CR to first-line treatment in the early stage and 45% in the advanced stage, and although it was numerically higher, it could not reach statistical significance.

Bone marrow involvement is a risk factor in both FLIPI-1 and FLIPI-2 prognostic scoring system, and it has been shown that it is a poor prognostic factor on CR.[11] A new prognostic system was studied on the patients included in the PRIMA study, and patients were defined as high, intermediate and low risk according to b2 microglobulin and bone marrow involvement. Survival data were obtained in proportion to the risk scores.[18] In our study, bone marrow involvement was associated with poor response to chemoimmunotherapy (p=0.048). High b2 microglobulin level was associated with poor treatment response in lymphoma patients and was subsequently included in the FLIPI-2 scoring system.[6,19] In our study, due to the small number of our patients, no relationship was found between b2 microglobulin and treatment response.

Although there is no study examining the relationship between uric acid level and treatment response in patients with FL, there are studies showing that high uric acid levels are associated with lower survival in lymphoma patients.[20] In our study, the CR rate was significantly higher in patients with normal uric acid compared to patients with high uric acid levels (p=0.004).

Although it is difficult to generalize to all patients with FL due to the insufficient number of patients included in our study, the results obtained in the study are correlated with many other studies. In our study, a strong association was found between uric acid level and treatment response, but it should be supported by randomized multi-centered prospective studies. Although it should be considered that uric acid level can easily be effected by diet and renal function.

Conclusions

In conclusion, in our study, the poor risk factors to treatment response with first line therapy are: Age>60 years, bone marrow involvement, high FLIPI score, and high uric acid level.

Disclosures

Ethics Committee Approval: The Ege University Clinical Research Ethics Committee granted approval for his study (Date: 18.10.2018, number: 18-10.2T/42.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – H.C.Y., M.T., F.D.A., G.S.; Design – H.C.Y., M.T., F.S.; Supervision – H.C.Y., M.T., F.V.; Materials – H.C.Y., M.T., G.S.; Data collection and/or processing – H.C.Y., M.T., G.S.; Analysis and/or interpretation – H.C.Y., M.T.; Literature search – H.C.Y., M.T.; Writing – H.C.Y., M.T., F.D.A.; Critical review – H.C.Y., M.T., F.D.A.

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