Histological Impact on Follicular Lymphoma Grade 3 Treated With Frontline RCHOP Regimen

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Abstract

Background

Histologically, follicular lymphoma (FL) grade 3 is subdivided into grade 3A and 3B. However, there are limited studies on outcomes of FL grade 3A and 3B treated with frontline of RCHOP treatment.

Methods

We retrospectively analyzed 61 patients of FL grade 3 treated with frontline RCHOP regimen between January 2009 and December 2019. We divided them into FL grade 3A (n = 42) and aggressive FL (n = 19). Aggressive FL included grade 3A with an additional 3B component (n = 2), grade 3B (n = 8), and grade 3 with areas of diffuse large B cell lymphoma (n = 9).

Results

The baseline characteristics were similar between FL grade 3A and aggressive FL. The 3-year overall survival (OS) was 97.1% in FL grade 3A and 81.9% in aggressive FL (P = 0.041). The 3-year progression free survival (PFS) was not significantly different between two groups, with 69.1% and 71.1%, respectively (P = 0.546). However, patients of aggressive FL reached a plateau in the PFS curve after 2 years.

Conclusions

Compared with patients of aggressive FL, FL grade 3A patients presented an uncurable feature but associated with a better OS with frontline RCHOP treatment.

Introduction

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma. In 2001, WHO graded FL by estimating the number of centroblasts per high-power field (HPF). FL grade 3 is diagnosed as more than 15 centroblasts per HPF and further subdivided into 3A with admixed centrocytes and 3B without admixed centrocytes[1].

Rituximab plus CHOP (RCHOP) has greatly improved the outcomes of FL patients and become one of the frontline treatment strategies for these patients [2–7]. FL grade 3 is a rare entity accounting for 10–20% of FL. There is a consensus on FL grade 3B treated as aggressive lymphoma. However, whether FL grade 3A should be treated as aggressive or indolent lymphoma is controversial. Besides, FL grade 3B patients are regularly excluded from FL directed clinical trials. Therefore, there were limited data on comparing the outcomes of FL grade 3A and 3B using uniformed aggressive treatment. Previous studies suggested a similar clinical course between these two groups with initial RCHOP regimen [3, 8, 9]. It is unclear whether

subdivision of FL grade 3A and 3B had clinical significance when aggressive treatment approaches were applied to these patients. In this study, we aimed to evaluate the histological impact on FL grade 3 treated with frontline RCHOP regimen and to provide more data on this area.

Methods

Patients

A total of 61 patients of newly diagnosed FL grade 3, consisting of FL grade 3A (n = 42) and aggressive FL (n = 19) treated with frontline RCHOP regimen were identified from our department (the hematology department of Zhongshan Hospital, Fudan University) between January 2009 and December 2019. Aggressive FL included grade 3A with an additional 3B component (n = 2), grade 3B (n = 8), and grade 3 with areas of DLBCL (n = 9). The slides of all cases were assessed according to the WHO Classification of Tumors of the Haematopoietic and Lymphoid Tissues by two experienced pathologists independently in our pathological center. If there was a divergence in diagnosis, more than two pathologists discussed the findings and made the final decision. The study was approved by the ethics committee of Zhongshan Hospital, Fudan University and performed according to the Declaration of Helsinki. Informed consent was provided by all patients.

Treatment and evaluation

All patients in this study received initial RCHOP induction therapy. Forty-seven patients finished 6 cycles of RCHOP regimen, 10 patients switched to other therapies before 6 cycles of RCHOP because of disease progression or intolerance, 1 patient died after 5 cycles, and 3 patients lost follow-up before interim evaluation. Seventeen patients had rituximab maintenance at the discretion of the treating physician and patient preference. Treatment response was evaluated according to the International Working Group criteria and assessed after 3–4 cycles and 4 weeks at the end of RCHOP regimen. The patients were followed-up every 3 months of first 2 years and then at intervals of 6–12 months later.

Statistical analysis

Differences between categorical variables were compared using Chi-square test. Progression free survival (PFS) was measured from the time of initial diagnosis to the date of disease progression, relapse, death, or last follow-up. Overall survival (OS) was measured from the time of initial diagnosis to the date of death or last follow-up. Kaplan-Meier method was used to estimate all survival endpoints. Log-rank test was used to compare the survival between two groups. Because a small number of patients were dead, Cox proportional hazards models were only performed to analyze the risk factors of PFS. All statistical analyses were performed using R statistical package (Version4.0.2). A two-sided P value less than 0.05 was considered statistically significant.

Results

Patients characteristics

Of the 61 patients, 42 patients were FL grade 3A and 19 patients were aggressive FL. Their baseline characteristics are described in Table 1.There were no significant difference between these two groups. The median age of all patients was 53 (range 28–84) years, with 34 patients (55.7%) of female. Fifty patients (82.0%) were at advance stage, and 22 patients (36.1%) had bone marrow involvement. These two groups of patients were well distributed in FLIPI-1, FLIPI-2, IPI and PRIMA-PI prognostic models. Thirteen patients (31.0%) of FL grade 3A and 4 patients (21.1%) of aggressive FL had rituximab maintenance.

Table 1
Baseline characteristics of patients with FL grade 3

	Total	Grade 3A FL	Aggressive FL	P value
	(n = 61)	(n = 42)	(n = 19)	
Gender				0.544
Female	34 (55.7)	25 (59.5)	9 (47.4)	
Male	27 (44.3)	17 (40.5)	10 (52.6)	
Age				0.577
< 60yr	40 (65.6)	29 (69.0)	11 (57.9)	
≥ 60yr	21 (34.4)	13 (31.0)	8 (42.1)	
β2-MG				1
Normal	24 (39.3)	17 (40.5)	7 (36.8)	
High	37 (60.7)	25 (59.5)	12 (63.2)	
LDH				0.927
Normal	47 (77.0)	33 (78.6)	14 (73.7)	
High	14 (23.0)	9 (21.4)	5 (26.3)	
Hemoglobin				0.268
< 12g/dl	17 (27.9)	14 (33.3)	3 (15.8)	
≥ 12g/dl	44 (72.1)	28 (66.7)	16 (84.2)	
ECOG (score)				0.958
< 2	50 (82.0)	35 (83.3)	15 (78.9)	
≥ 2	11 (18.0)	7 (16.7)	4 (21.1)	
Nodal sites				0.577
≤ 4	21 (34.4)	13 (31.0)	8 (42.1)	
4	40 (65.6)	29 (69.0)	11 (57.9)	
Extranodal sites				0.372
< 2	35 (57.4)	22 (52.4)	13 (68.4)	

β2-MG, β2 microglobulin; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; BM, bone marrow; #Bulky disease, diameter 6cm; FLIPI, follicular lymphoma international prognostic index; IPI, international prognostic index; PRIMA-PI, PRIMA prognostic index; R, rituximab.

	Total	Grade 3A FL	Aggressive FL	P value
≥ 2	26 (42.6)	20 (47.6)	6 (31.6)	
Stage				0.440
□-□	11 (18.0)	6 (14.3)	5 (26.3)	
□-□	50 (82.0)	36 (85.7)	14 (73.7)	
B symptom				0.571
No	47 (77.0)	31 (73.8)	16 (84.2)	
Yes	14 (23.0)	11 (26.2)	3 (15.8)	
BM involvement				0.436
No	39 (63.9)	25 (59.5)	14 (73.7)	
Yes	22 (36.1)	17 (40.5)	5 (26.3)	
Bulky disease[#]				0.310
No	52 (85.2)	34 (81.0)	18 (94.7)	
Yes	9 (14.8)	8 (19.0)	1 (5.3)	
FLIPI-1 (score)				0.872
0–2	36 (59.0)	24 (57.1)	12 (63.2)	
3–5	25 (41.0)	18 (42.9)	7 (36.8)	
FLIPI-2 (score)				0.452
0–2	46 (75.4)	30 (71.4)	16 (84.2)	
3–5	15 (24.6)	12 (28.6)	3 (15.8)	
IPI (score)				1
0–2	42 (68.9)	29 (69.0)	13 (68.4)	
3–5	19 (31.1)	13 (31.0)	6 (31.6)	
PRIMA-PI				0.123
Low	28 (45.9)	16 (38.1)	12 (63.2)	
Intermediate-high	33 (54.1)	26 (61.9)	7 (36.8)	

β2-MG, β2 microglobulin; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; BM, bone marrow; [#]Bulky disease, diameter□6cm; FLIPI, follicular lymphoma international prognostic index; IPI, international prognostic index; PRIMA-PI, PRIMA prognostic index; R, rituximab.

	Total	Grade 3A FL	Aggressive FL	P value
R maintenance				0.624
Yes	47 (77.0)	33 (78.6)	14 (73.7)	
No	44 (72.1)	29 (69.0)	15 (78.9)	

β2-MG, β2 microglobulin; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; BM, bone marrow; #Bulky disease, diameter≥6cm; FLIPI, follicular lymphoma international prognostic index; IPI, international prognostic index; PRIMA-PI, PRIMA prognostic index; R, rituximab.

Survival outcome

After a median follow-up period of 40.2 (range 1.7-142.7) months, fifteen patients with FL grade 3A and 5 patients with aggressive FL had disease progression/relapse, and 1 patient with grade 3A and 3 patients with aggressive FL patients died due to disease progression/relapse. Among seven patients with disease progression who had biopsies, one patient with FL grade 3B transformed more aggressive form of DLBCL (non-GCB type). The 3-year OS was 97.1% (95% CI: 91.5–100%) in FL grade 3A and 81.9% (95% CI:65.3–100%) in aggressive FL (P = 0.041), (Fig. 1). The 3-year PFS was 69.1% (95% CI: 55.9–85.5%) and 71.1% (95%CI: 52.5–96.1%), respectively (P = 0.546). Patients with aggressive FL reached a plateau in the PFS curve after 2 years, (Fig. 2).

Prognostic factors for PFS

In univariate analysis (Table 2), no significant difference of PFS was found between grade 3A and aggressive FL, with hazard ration (HR) of aggressive FL versus 3A of 0.73 (95% CI:0.26–2.02), P = 0.546. Patients with more than 2 extra nodal sites involvement (HR = 2.45; 95% CI: 0.98–6.15; P = 0.057), and those with a higher risk based on PRIMA prognostic index (HR = 2.52; 95% CI: 0.91–6.93; P = 0.074) were associated with a trend of worse PFS. Besides, in our study, rituximab maintenance did not prolong the PFS of FL grade 3 patients (HR = 0.76, 95%CI:0.27–2.08, P = 0.589). When adjusted the variables of number of extra nodal sites and PRIMA prognostic index, there was no significant difference of PFS between patients with FL 3A and aggressive FL (HR = 0.94; 95% CI: 0.32–2.70; P = 0.902).

Table 2
Univariate analysis of risk factors for progression free survival

Variable	HR (95%CI)	P value
FL grade 3 (3A as ref.)	0.73 (0.26–2.02)	0.546
Gender (female as ref.)	0.70 (0.28–1.75)	0.445
Age (< 60 year as ref.)	0.61 (0.23–1.62)	0.324
β2-MG (≤ UNL as ref.)	1.89 (0.69–5.20)	0.219
LDH (≤ UNL as ref.)	1.53 (0.59–3.98)	0.387
Hemoglobin (≥ 12g/dl as ref.)	2.09 (0.86–5.05)	0.102
ECOG (score < 2 as ref.)	1.75 (0.66–4.67)	0.260
Nodal sites (≤ 4 as ref.)	0.85 (0.34–2.13)	0.730
Extranodal sites (< 2 as ref.)	2.45 (0.98–6.15)	0.057
Stage (Ann Arbor Ⅲ-Ⅳ as ref.)	0.97 (0.28–3.33)	0.966
B symptom (no as ref.)	1.53 (0.59–3.98)	0.386
BM involvement (negative as ref.)	1.55 (0.64–3.74)	0.334
Bulky disease (≤ 6cm as ref.)	1.66 (0.55–5.02)	0.369
FLIPI-1 (score 0–2 as ref.)	1.54 (0.63–3.73)	0.343
FLIPI-2 (score 0–2 as ref.)	1.54 (0.63–3.73)	0.343
IPI (score 0–2 as ref.)	1.63 (0.67–3.97)	0.282
PRIMA-PI (low as ref.)	2.52 (0.91–6.93)	0.074
R maintenance (no as ref.)	0.76 (0.27–2.08)	0.589

HR, hazard ratio; CI, confidence interval; ref, reference; β2-MG, β2 microglobulin; UNL, upper normal limit; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; BM, bone marrow; FLIPI, follicular lymphoma international prognostic index; IPI, international prognostic index; PRIMA-PI, PRIMA prognostic index; R, rituximab.

Discussion

In this study, we analyzed a total of 61 patients with newly diagnosed FL grade 3 treated with frontline RCHOP regimen, including 42 patients with FL grade 3A and 19 patients of aggressive FL. The 3-year OS was better in patients with FL grade 3A (97.1%) than aggressive FL (81.9%). The 3-year PFS was not significantly different between two groups, with 69.1% and 71.1%, respectively. Of note, patients of aggressive FL reached a plateau in the PFS curve after 2 years.

FL grade 3 is a rare disease. The outcomes of FL grade 3 patients have not been well evaluated. The linear progression of FL grade 3A to 3B and then to grade 3 with areas of DLBCL represents an evolution of FL from an indolent to more aggressive form. This study included a relatively large number of patients treated uniformly by frontline RCHOP regimen. Our results reflect this feature of FL, with a better OS in FL grade 3A but a plateau of PFS curve in aggressive FL.

Generally, FL grade 3B is considered as aggressive lymphoma, whereas FL grade 3A is controversial. Biologically, FL grade 3B, compared with grade 3A, is often IRF4/MUM1 positive but CD10 negative and less likely to harbor Bcl2 rearrangement[10]. Moreover, patients with FL grade 3B or 3B with DLBCL were associated with a higher level of Ki-67 than those of FL grade 3A[11]. This support the concept the underlying genetic events were different between these two subtypes. FL grade 3A is relatively indolent lymphoma.

Clinically, our study showed that a longer OS in patients with FL grade 3A than those with aggressive FL when treated with frontline RCHOP regimen. In the rituximab era, most investigators found a higher OS rate in FL grade 3A versus aggressive FL. However, no significant difference was observed[8, 12–14]. Consistent with our results, studies from Wahlin et al and Durate et al suggested that, compared with FL grade 3A, grade 3B was related to significantly worse OS[15–17]. The discordant results may be due to a relatively small number of patients were included in these studies. Besides, our results were in line with previous studies that the PFS was similar between FL grade 3A and aggressive FL[3, 8, 14, 18–20]. Of note, three studies analyzed FL grade 3 patients with RCHOP treatment all found that grade 3A and 3B had a similar outcome in term of PFS[3, 8, 9]. Whereas we do observe a plateau in the PFS curve in aggressive FL. This could be explained by the fact that aggressive FL is a curable disease which was confirmed in a recent study showed a better PFS in aggressive FL compared with FL grade 3A[11].

The patients included in our study represent a group of patients between low grade FL and DLBCL. Our results suggested histological subtype is a prognostic factor for OS but not for PFS. FL and DLBCL had different prognostic models. Up to now, it is unclear which prognostic model, such as FLIPI-1, FLIPI-2, IPI, and PRIMA-prognostic index could better differentiate high-risk patients with FL grade 3. Our data indicated PRIMA-prognostic index may be a better PFS prognostic index than others. Besides, we found patients with more than 2 extra nodal sites involvement trend to have inferior PFS. Whereas we did not find rituximab maintenance could prolong PFS, maybe due to small number of patients received rituximab maintenance in this study. Although, some investigators have showed that certain factors, such as older age, MYC breaks, higher ECOG scores, bone marrow involvement, larger nodal dimension, B symptoms, more than 4 lymph node sites involvement, elevated serum β2 microglobulin or LDH levels were related with poor outcome in FL grade 3, these factors were not consistent in different studies [7, 8, 20].

Several limitations of this study should be addressed. Firstly, the sample size is small in this study. On the one hand, it is due to the rarity of FL grade 3 patients which only accounts for less than one fifth of the whole FL entity. One the other hand, various treatment strategies were used in these group of patients and

we only included uniformly RCHOP regimen treated patients. However, compared with previous studies, our study analyzed relatively large number of FL grade 3 patients. Secondly, the median follow-up time was 40.2 months in our study which is not long enough. Further long-term follow up is needed to observe more events.

Conclusion

In summary, our results suggested that FL grade 3A presented an uncurable feature but associated with a better OS versus aggressive FL when treated with frontline RCHOP regimen. Although demonstrated indolent nature, FL grade 3A patients could benefit more from early aggressive treatment strategy. However, our study was hindered by a relatively small number of cases from single center and the retrospective nature. Thus, prospectively designed multicenter studies or meta-analyses are warranted to confirm these findings. Moreover, further research on potential biomarkers and prognostic models are necessary to better characterize and classify patients with FL grade 3.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Zhongshan Hospital, Fudan University and performed according to the Declaration of Helsinki. Informed consent was provided by all patients.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used and /or analyzed during the current study are not publicly available due to restriction by the ethics committee of Zhongshan Hospital to protect patient privacy but are available from the corresponding on reasonable request.

Competing interests

None

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Authors' contributions

F-FC and AM were responsible for data collection and interpretation, statistical analysis, literature research, and manuscript writing. ZW, L-YC, W-GW, J-LZ, LY, Z-XC, Z-MW and L-LJ treated the patients and

provided data. X-WG was responsible for pathological consultation. PL designed the study and approved the final version. All authors reviewed the manuscript.

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None

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Figures

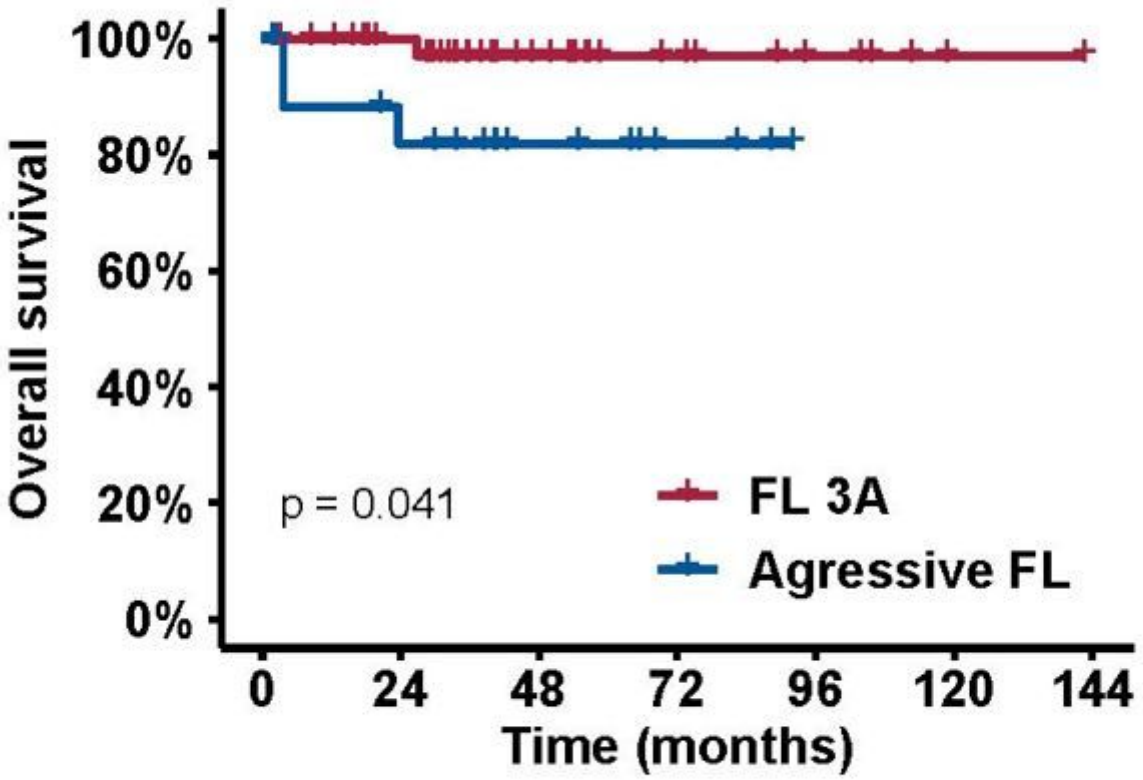

Figure 1

Overall survival of patients with FL grade 3

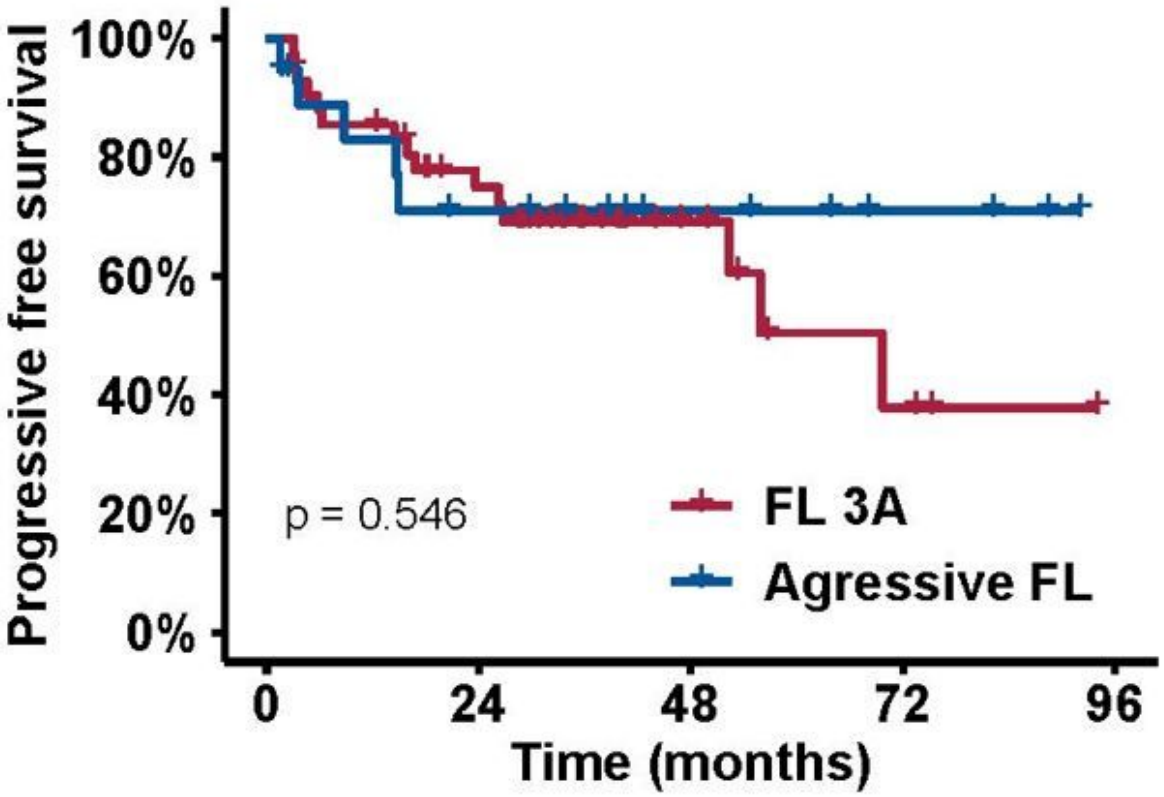

Figure 2

Progressive free survival of patients with FL grade 3