Evaluation of four prognostic indices in follicular lymphoma treated in first line with immunochemotherapy.

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Abstract

Several clinical risk models have been proposed to predict outcome in follicular lymphoma (FL). The development of Next Generation Sequencing (NGS) technologies has allowed the integration of somatic gene mutations in clinical scores to build genotyped-based risk models, such as m7-FLIPI. We explored four clinical or clinicogenetic risk models in patients with symptomatic FL who received frontline immunochemotherapy. Out of 191 patients with FL grade 1-3a, 109 were successfully genotyped. Treatment consisted on rituximab (R) plus CVP/CHOP (72.5%) or R-bendamustine (R-B) (27.5%). The proportion of cases classified as high-risk in FLIPI, FLIPI-2, PRIMA-PI or m7-FLIPI were 39.3%, 14%, 30.3%, 22%, respectively. No case with low-intermediate FLIPI was upgraded in m7-FLIPI, but 18 out of 42 higher-risk patients in FLIPI were downgraded to low-risk m7-FLIPI. Sensitivity and specificity for the prediction of POD24 was highest for FLIPI. The discrimination for progression free survival (PFS) and overall survival (OS) was best for FLIPI (c-index: 0.644 and 0.727, respectively). When analyzed only R-B patients, m7-FLIPI had higher discrimination for PFS and OS. Thus, FLIPI remains as the clinical risk score with higher discrimination in advanced FL patients treated with immunochemotherapy, but the performance of m7-FLIPI should be further investigated in patients treated with R-B.

Key points:

- FLIPI remains as the prognostic index with higher discrimination for survival in advanced FL patients treated with immunochemotherapy.
- Research efforts in FL should go towards the design of clinical studies incorporating more precise molecular markers for both outcome prediction and optimal selection of treatment.

Introduction

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma (NHL) in western countries. Its clinical behavior is usually indolent with a median survival currently greater than 15 years[1,2]. However, even with modern immunochemotherapy schedules, up to 20% of patients progress or relapse within the first two years (POD24) and these patients have a significantly decreased overall survival (OS)[3–5].

Several clinical risk models have been developed to predict progression free survival (PFS) and OS, such as FLIPI,[6] FLIPI-2[7] and PRIMA-PI[8]. The development of next generation sequencing (NGS) technologies have allowed the integration of somatic gene mutation information in clinical risk models to build clinicogenetic risk models, such as m7-FLIPI and POD24 prognostic index (POD24-PI)[4,9]. These risk models have improved pretreatment risk stratification before initiation of frontline treatment and can also identify a high-risk group of patients who have an increased risk of developing POD24.

These studies included patients with advanced FL who were mainly treated with frontline rituximab (R), cyclophosphamide, vincristine, and prednisone (R-CVP) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Rituximab and bendamustine (R-B) has become the preferred regimen as first-line therapy for a symptomatic patient with FL at many centers[10], but patients treated with R-B were not included in these models. Moreover, these clinicogenetic risk models need to be validated with real-world data.

In the present study, we have evaluated four clinical or clinicogenetic risk models to determine their utility in previously untreated patients with symptomatic FL who were treated with R-CVP, R-CHOP or R-B.

Methods

A cohort of 191 patients with newly diagnosed FL grade 1 to 3a from 3 Spanish tertiary hospitals have been reviewed in this study, with a final number of 109 cases with successful characterization by NGS (Supplementary table 1). The diagnosis of FL was based on World Health Organization (WHO) criteria. FL grade 3b were not included. All patients fulfilled the Groupe d'Etude des Lymphomes Folliculaires (GELF) high tumor burden criteria. Patients with HIV were not included. Treatment consisted of R plus CVP (R-CVP), R plus CHOP (R-CHOP) or R plus bendamustine (R-B), according to standard practice. In responding patients, maintenance with R for 2 years was performed according to physician or patient preference. Lymphoma response was assessed by the Lugano Classification[11,12]. The study was carried out in accordance with the modified Declaration of Helsinki and was approved by the ethics committees of participating centers. All patients provided written informed consent.

Tumoral FL mutational analysis was performed on FFPE tissue by NGS through a DNA targeted custom panel of 64 FL-related genes implicated in epigenetics, BCR signaling, cell survival, immune response, mTORC1 pathway and cell migration, as previously reported (Supplementary Methods and Supplementary table 2)[13]. The FLIPI, FLIPI-2, PRIMA-PI and m7-FLIPI were calculated as previously described [6–9]. The same cut-off as used in the original publication was applied for discrimination between the high- and low-risk groups (m7-FLIPI score ≥0.8 and <0.8, respectively)[9].

Statistical analyses were carried out with the statistical software R (version 4.1.0) (RStudio version 1.4.1106) using the packages survival 3.2-13 and ggplot2_3.3.5. In this study, progression free survival (PFS) was calculated from the date of treatment initiation to the date of death from any cause, disease relapse or progression, or the date of last contact. Overall survival (OS) was calculated from the date of treatment initiation until the date of death from any cause or the date of last contact. Progression of disease within 24 months (POD24) was

defined as progression or relapse of the disease within the first 24 months after first-line treatment initiation (modified definition)[3]. OS for POD24 was calculated considering survival from time of POD for the POD24 cohort, or from 2 years after initial treatment of patients without POD24, according to recently proposed definitions[4]. The Kaplan-Meier method was used to describe time-to-event end points and the differences between two groups were compared by log-rank test. The differences were considered significant at $p < 0.05$. The c-index was calculated with the R package survcomp 1.44.1, the Akaike's information criterion (AIC) with the R package flexsurv 2.1 and the Gönen-Heller's concordance probability estimate (CPE) with the R package CPE1.5.2. Sensitivity, specificity and accuracy of risk scores for time-to-event end points were estimated with R package confusionMatrix 3.45 and circular plots were done using R package circlize 0.4.14.

Results

Clinical characteristics for the 109 patients are shown in Table 1. Median age at diagnosis was 58 years (range 24-90), 56% were males and 93.6% had stage III-IV. Median time from biopsy to initial treatment was 0.91 years (IQR: 0.35-1.7). Immunochemotherapy regimens were as follows: R-CVP in 8 patients (7.3%), R-CHOP in 71 (65.1%) and R-B in 30 (27.5%). Maintenance rituximab was administered in 95 patients (87.2%), 66 (83.5%) with R-CHOP/CVP and 29 (96.7%) with R-B. With a median follow-up of 8 years (IQR: 5.25-11.83), PFS and OS at 8 years were 55% and 80%, respectively (47 progression events and 23 death events (10 were lymphoma-related)).

All patients presented mutations, with a median of 6 mutations (range 2-23) per patient. Mutation frequency distribution is shown in Supplementary Figure 1. Frequency of mutated genes included in m7-FLIPI score was: *EZH2* (23%), *ARID1A* (17%), *MEF2B* (19%), *EP300* (19%), *FOXO1* (10%), *CREBBP* (75%) and *CARD11* (17%).

The proportion of patients according to the four risk scores is shown in Table 1. Risk stratification could not be calculated in 4, 8, 10 and 4 patients for the FLIPI, FLIPI-2, PRIMA-PI and m7-FLIPI scores, respectively. In the distribution of patients among risk categories in the four risk scores, it is noteworthy that the proportion of cases classified as low-risk in FLIPI was only 16.8%, and, conversely, the proportion of cases allocated to the high-risk group in FLIPI-2 was only 14%. No case with low-intermediate FLIPI score was upgraded in m7-FLIPI. However, 18 out of 42 higher-risk patients in FLIPI were downgraded to low-risk m7-FLIPI. Risk categories among FLIPI, FLIPI-2 and PRIMA-PI compared with m7-FLIPI are shown in Figure 1.

Response and early relapse

The rate of complete remission (CR) was 84.3% for the whole series, and 85.9% and 80.0% for patients treated with R-CVP/R-CHOP and R-B, respectively (p=0.556). A 77 years-old patient was not evaluated due to early death by myocardial infarction after 2 cycles of R-CHOP. FLIPI was the

only score that showed statistically significant differences for CR rates between risk categories (Table 2 and Supplementary table 3). Twenty-two patients (20.4%) relapsed early and were considered as POD24. FLIPI showed statistically significant differences, being the patients in the high-risk category those with a higher proportion of POD24 (34.1%) (Supplementary table 3). However, patients within FLIPI low or intermediate risk subsets had a similar proportion of POD24 (11.1 and 13.1%, respectively). The PRIMA-PI was also significant but identified patients in the intermediate category as those at the highest risk of POD24 (34.5%) (Table 2). POD24 in this cohort of patients was predictive of shorter OS ($p<0.0001$) (Supplementary Figure 2).

To evaluate the performance of the four risk scores, given that the m7-FLIPI has 2 risk categories, the other prognostic indices were merged into two categories in such a way that the proportion of high-risk was similar among them (Supplementary Table 4).

Sensitivity for the prediction of POD24 was highest for FLIPI (87%) and lowest for FLIPI-2 (78%), specificity was highest for FLIPI (34%) and lowest for PRIMA-PI (21%), and accuracy was highest for m7-FLIPI (69%) and lowest for FLIPI-2 (56%) (Table 3).

Progression-free and overall survival

Forty-two patients had relapse (38.9%) and twenty-three (21.1%) died during the time of follow-up. Median PFS was 9.1 years and median OS has not been reached.

According to original description, FLIPI, FLIPI-2 and PRIMA-PI scores showed differences for PFS (0.0031, 0.025 and 0.019, respectively), but m7-FLIPI score did not reach statistical significance (0.076; Figure 2). Regarding OS, FLIPI and FLIPI-2 showed statistically significant differences among original described groups (0.0026 and 0.048, respectively), but PRIMA-PI and m7-FLIPI scores did not (0.28 and 0.06, respectively; Figure 3). Cox regressions for PFS and OS according to the mutation status of the 7 genes included in m7-FLIPI are described in Supplementary table 5.

When PFS and OS were compared among the low and high-risk categories of the four risk scores, FLIPI was significantly better in pairwise comparisons (Supplementary Table 6).

To evaluate the performance of the four risk indices, we assessed discrimination for PFS and OS, that is, the ability to anticipate PFS and OS, respectively. Harrell's c-index for PFS and OS was best for the FLIPI (0.644, p=0.001 and 0.727, p=0.001, respectively) and the other three scores reached similar results (Table 3). The AIC for PFS was best for PRIMA-PI (532), being similar the other three risk scores (from 543 to 556). The AIC for OS was best for FLIPI (316), with higher values in the other three scores (from 326 to 329). Therefore, FLIPI had higher level of parsimony (the ability to eliminate unnecessarily complicated models including too many parameters for an accurate estimation). CPE was highest with FLIPI both for PFS and OS, indicating higher concordance than the other three regimens, including m7-FLIPI (Table 3).

Subgroup analyses

Finally, we assessed the impact of the four scores on PFS and OS in the group of patients treated with R-CVP/R-CHOP and R-B (Supplementary tables 7 and 8). Discrimination parameters for PFS and OS were better for the FLIPI score in comparison with the other three scores in patients treated with R-CVP/R-CHOP. In contrast, m7-FLIPI had higher discrimination for PFS and OS in the group of patients treated with R-B when compared with the other 3 scores. However, these results should be taken with caution given the limited number of patients treated with R-B.

Discussion

Our study has assessed the clinical value and statistical performance of the four most broadly applied risk scores in a cohort of FL patients treated in the real-world setting. In our cohort of symptomatic FL patients treated with immunochemotherapy and with a median follow-up of 8 years, we have shown that FLIPI remains as the prognostic index with higher discrimination for survival. Nevertheless, the predictive value of FLIPI is better for R-CVP/R-CHOP than for R-B.

For performance analysis, we applied binary categories to FLIPI (low/intermediate risk vs high risk), FLIPI2 (0-2 vs 3-5 risk factors) and PRIMA-PI (low/intermediate risk vs high risk) because several studies have not observed significant differences for failure-free survival between low-risk and intermediate-risk patients[14–16] and also to allow us a more direct comparison with the m7-FLIPI that only has two categories. In our cohort, 42% of patients with high-risk FLIPI were reclassified into the low-risk m7-FLIPI category. This is similar to the original publication of m7-FLIPI[9], but in contrast to that recently reported in a cohort of advanced FL patients randomized to consolidation with high-dose therapy and autologous stem cell transplantation, where only 9% of patients with high-risk FLIPI were reclassified to low-risk m7-FLIPI[16]. This might be related, at least in part, to the dependence on age of the FLIPI and m7-FLIPI[17]. These well-known clinicogenetic-risk scores are not appropriate to stratify younger patient groups[16]. Moreover, the role of age as a relevant element of prognostic indices for FL has been questioned since decreased survival in older patients is significantly due to an increased rate of non-relapse deaths[14]. Recently, the PRIMA-PI, an age-independent tool, was found to identify a smaller cohort of high-risk FL cases than FLIPI or FLIPI-2, but in this study patients were treated exclusively with R-CHOP[17]. In our series, performance of PRIMA-PI did not improve FLIPI both in R-CVP/R-CHOP or R-B subgroups. However, the limited number of patients treated with R-B in our study preclude us to definitive conclusions.

In our cohort, m7-FLIPI showed prognostic value in FL patients treated with first-line rituximab-based chemotherapy including R-B, although it was not as powerful as FLIPI, similar to the observation in FL patients receiving rituximab without chemotherapy[18]. Interestingly, m7-FLIPI had higher discrimination for PFS and OS in the group of patients treated with R-B compared with the other 3 scores. This is in contrast with a recent analysis of the GALLIUM trial, in which the m7-FLIPI was prognostic in patients treated with R-based regimens but not in obinutuzumab-based regimens[19]. Moreover, when analysed by chemotherapy regimen, the m7-FLIPI was prognostic in patients receiving CHOP/CVP-based treatment but not in the bendamustine-based treatment. These results should be taken with caution given the limited number of patients treated with R-B in both studies.

When evaluating the ability to predict POD24, FLIPI had the highest sensitivity and specificity, however m7-FLIPI showed best accuracy among the four risk scores. Regarding the comparison of performance metrics, all four risk-scores displayed a similar calibration. In addition, our study supports the association between POD24 and OS after first-line immunochemotherapy (R-CVP, R-CHOP and R-B), an assertion widely validated by multiple studies and recently confirmed in a pooled analysis involving 5225 FL patients[20].

Recently, other risk scores have been proposed. We did not evaluate the FLEX score, developed to improve the identification of high-risk patients in the GALLIUM trial and later validated using data from the SABRINA trial, since we did not perform natural killer cell count analysis in peripheral blood in the routine practice[21]. A novel score model called PReDiCt-FL has also been developed considering the mutation status of 11 genes and cases with high-risk according to this novel score have longer failure-free survival when treated with high dose intensification followed by autologous transplant. However, no differences were observed for OS[16].

Beyond mutation-based scores, other genetic-models are being proposed. A gene-expression profiling predictive model using 23 genes reflecting both B-cell biology and tumour

236 microenvironment was built in advanced FL patients treated with R-based chemotherapy. This
237 score identified two groups of FL patients with remarkably different PFS independently of
238 rituximab maintenance and FLIPI score[22]. Recently, a transcriptomic predictor based on machine
239 learning models have been developed and validated for OS in FL[23].

240 To the best of our knowledge, this is the first study to directly compare the FLIPI, FLIPI-2, PRIMA-
241 PI and m7-FLIPI in patients treated with R-B. At many centers the standard treatment of patients
242 with advanced FL has switched to R-B. Our study provides a careful analysis of FL patients treated
243 with R-CVP/R-CHOP and R-B in the real-world setting. However, apart from its retrospective
244 nature, some limitations of this analysis include the relatively small sample size. Moreover, 43%
245 of initially identified cases could not be included for final analysis mainly due to exhausted blocks
246 or sequencing failure. The latter might have some impact on the outcomes of the study since
247 clinical characteristics differed from the final selected cohort. The long median follow-up of our
248 real-world series, essential for an adequate evaluation of survival in FL, caused a considerable
249 number of samples to be unsuitable for performing NGS studies. In addition, we also observed
250 higher number of NGS failures in the older samples. However, this study includes patients with
251 long follow-up after treatment with conventional R-CVP/R-CHOP. Follow-up of R-B patients was
252 shorter due to the later approval of this regimen in our country.

253 In conclusion, our data from a real-world cohort with long follow-up show that current available
254 scores provide information to predict outcome in FL patients, but the FLIPI remains the best in
255 identifying patients at high risk. The observation that m7-FLIPI might have better performance
256 than FLIPI in R-B treated patients remains to be confirmed. Efforts should now be directed
257 towards the development of tools that may help in selecting the optimal treatment in a more
258 precise way.

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Authorship contributions. JJRS performed the research and the statistical analysis, analyzed and interpreted the results and wrote the manuscript. CFR performed the research, collected and analyzed the NGS data and wrote the manuscript. LB, RDF, SP, AF, BS, EG and JS collected and analyzed the clinical data. LFI and ML collected and analyzed the NGS data. JG performed the bioinformatic analysis of NGS data. RR, JFG and LC performed histologic diagnostic. BB and AG designed the research, analyzed and interpreted the results and wrote the manuscript. AS designed the research, performed the research, analyzed and interpreted the results, performed the statistical analysis and wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

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