Examination of the follicular lymphoma international prognostic index (FLIPI) in the National LymphoCare study (NLCS): a prospective US patient cohort treated predominantly in community practices


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Background: Because follicular lymphoma (FL) patients have heterogeneous outcomes, the FL international prognostic index (FLIPI) was developed to risk-stratify patients and to predict survival. However, limited data exist...
regarding the role of FLIPI in the era of routine first-line rituximab (R) and R-chemotherapy regimens and in the setting of community oncology practices.

Patients and Methods: We evaluated the outcome data from the National LymphoCare Study (NLCS), a prospective, observational cohort study, which collects data on patients with FL in the United States (US) community practices.

Results: Among 1068 male and 1124 female patients with FLIPI data, most were treated in US community practices (79%); 35% were FLIPI good risk, 30% intermediate risk, and 35% poor risk. FLIPI risk groups were significant predictors of overall survival (OS) and progression-free survival (PFS) for patients who undergo watchful waiting (WW), and those who receive non-R-containing regimens, R-alone, and R-chemotherapy combinations.

Conclusions: In the setting of contemporary practice with routine R use, stratifying patients into good, intermediate, and poor FLIPI risk groups predicts distinct outcomes in terms of OS and PFS. FLIPI remains an important prognostic index in the R era and should be used in clinical practices to support discussions about prognosis.

Key words: community practice, FLIPI, follicular lymphoma, nlCS

Introduction

Follicular lymphoma (FL) is the second most common form of non-Hodgkin's lymphoma (NHL); and the most prevalent indolent lymphoma in United States (US); representing 35% of adult NHL in United States and 22% worldwide [1]. Treatment outcomes have improved substantially with the introduction of rituximab (R), better sequential and combination therapies, and improved supportive measures [2, 3]. A retrospective single-institution analysis reviewing the treatment experience of patients with stage IV FL from 1972 to 2002 showed that over this time period, 5-year overall survival (OS) and failure-free survival improved from 64% to 95% and 29% to 60%, respectively [4]. However, outcomes for FL remain heterogeneous. Risk stratification of FL patients at presentation can support discussions about prognosis and theoretically could improve treatment selection by identifying patients who might require an intensified approach and those who could avoid unnecessary intervention.

Solal-Céligny et al. proposed the follicular lymphoma international prognostic index (FLIPI) as a model to predict FL survival in patients receiving chemotherapy and tested the FLIPI in FL patients diagnosed between 1985 and 1992 [5]. Using five adverse prognostic factors, age (>60 years), stage (III–IV), hemoglobin (<12 g/dl), number of nodal areas (>4), and lactate dehydrogenase (LDH) level (>upper limit of normal (ULN)), FLIPI separates patients into low/ good risk (0–1 adverse factors), intermediate risk (2 factors), and high/poor risk (>3 factors) with statistically different OS. An external validation of this model in another group of 919 patients with FL also showed significant differences in OS [5]. Although widely used in clinical trials, the role of FLIPI in routine clinical care has not been well characterized in large cohort studies with sufficient clinical and laboratory data. Therefore, we examined the FLIPI in the National LymphoCare Study (NLCS) dataset, a large national prospective observational study of newly diagnosed FL patients [6], to determine whether FLIPI maintains its prognostic significance in the modern chemoimmunotherapy era especially, in the setting of US-based clinical practices.

patients and methods

The NLCS is a prospective, observational study of patients with FL in the US sponsored by Genentech, Inc. (South San Francisco, CA) and Biogen Idec (Cambridge, MA). The NLCS has an advisory board composed of academic investigators and a patient advocate, some of whom co-authored this manuscript (TPM, JWF, ADZ, BKL, JRC, HD, and CRF). The advisory board participated in all phases of the study, including initial protocol design, prospective determination of data to be collected, and consideration of participating sites. The advisory board meets quarterly, has full access to data listings, and collaborated with the investigator (AKN) and the sponsor regarding interpretation and publication of the data. The design, analysis, and data interpretation of this study adhered to scientific standards and guidelines for comparative effectiveness analysis that build upon initiatives to improve the quality and transparency of clinical science [7, 8]. This article was written de novo by the investigator and the members of the advisory board following approval of a protocol with pre-specified end-points, hypotheses, and plans for analysis.

A total of 2742 patients were recruited from academic and community oncology practices between March 2004 and March 2007 at 265 sites in the US. 2192 assessable patients with non-missing FLIPI scores were included in the analysis. Fifteen patients were ineligible, primarily due to missing date of diagnosis. Final selection of academic and community sites and the data collection occurred as previously described, was determined by study sponsors based on the responses to a survey assessing capability to participate in an observational study of FL. Questions included number of newly diagnosed FL patients seen annually, logistics and support for clinical research, and previous experience with sponsored clinical research [6]. All patients signed a written informed consent before participation, and the protocol was approved by a designated institutional review board at each institution. At enrollment, all patients were within 6 months from their initial FL diagnosis and had no prior history of lymphoma. Per protocol, to minimize potential patient selection bias, investigators at participating sites were encouraged to invite all eligible patients to participate in the study consecutively. The eligibility criteria included age ≥18 years and did not exclude patients based on the performance status (PS) or comorbidities. There was no central pathology review; the local pathology report defined FL diagnosis after investigator education on World Health Organization classification system definitions of FL [9]. Grade and evidence for concurrent second lymphoma were evaluated when available.

Patients were evaluated and treated according to each physician’s standard practice, without study-specific treatments, visits, or evaluations required either at baseline or during the course of the study. Collected
information included demographics, clinical data (including PS, stage, and number of nodal and extra-nodal sites), routine laboratory studies including LDH, serial management strategies, response to treatment, and outcomes including relapse and death. From the inception of the NLCS study, the treating physicians were requested to obtain LDH at diagnosis with the primary objective of calculating FLIPI. Follow-up data regarding treatment and outcomes (including response, progression, and survival) were actively solicited from providers and collected quarterly. Enrolled patients are to be observed for up to 10 years from enrollment or until death, withdrawal of consent, or loss to follow-up. Enrollment sites were categorized as academic or community practices based on self-report.

FLIPI score and risk groups
For each patient, a FLIPI score was assigned according to the algorithm defined by Solal-Célingy et al. as the sum of each of the five risk factors at diagnosis. The risk groups were classified for 191 patients with some missing FLIPI components where missing data did not impact the risk categorization to a FLIPI group (e.g., a patient with 1 missing FLIPI component and 0 risk factors for the four non-missing FLIPI components would be classified as low/good risk).

outcomes

overall survival
OS was calculated as the number of days from the date of diagnosis up to and including the date of death from any cause. For patients who were not confirmed dead at the time of analysis, OS was censored at the date that the patient was last known to be alive. For patients who discontinued from the study, OS was censored at the date of discontinuation. For patients who had not discontinued enrollment, OS was censored at the last study assessment recorded in the database or last contact.

progression-free survival
PFS was calculated as the number of days from the date of diagnosis up to and including the date of the first event, which was either disease progression as assessed by the treating physician or death from any cause. The receipt of new antilymphoma treatment was not considered an event since treatment in community practice did not require progression. PFS for patients who had not yet experienced an event at the time of analysis was censored at the date of the last recorded response assessment.

time to next treatment
Time to next (subsequent) treatment (TTNT) was defined as the number of days from the date of treatment initiation (for patients receiving

Figure 1. Distribution of FLIPI risk groups in the overall sample and in specific demographic and clinical subgroups.
The FLIPI was examined for all treatments combined and specifically for the effects of treatment setting (academic versus community), gender, and race. The prognostic value of FLIPI was validated by calculating the hazard ratios (HR) from the Cox proportional hazards model with the FLIPI risk group as the single-independent variable. Additional Cox proportional hazards analysis was examined for each outcome to evaluate the predictive function of FLIPI adjusting for the demographic characteristics between FLIPI risk groups. For the outcomes of OS, PFS, and TTNT, the prognostic value of the FLIPI risk groups was validated by estimating survival function using the Kaplan–Meier method and calculating the hazard ratios (HR) from the Cox proportional hazards model with the FLIPI risk group as the single-independent variable. Additional Cox proportional hazards analysis was examined for each outcome to evaluate the predictive function of FLIPI adjusting for the effects of treatment setting (academic versus community), gender, and race. The FLIPI was examined for all treatments combined and specific treatment regimens.

**Results**

A total of 2192 assessable patients with identified FLIPI status were included in the analyses. Among the 1068 male and 1124 female patients, 52% were >60 years, 69% were stage III–IV, 22% had Hb < 12 g/dl, 37% had >4 nodal areas involved, and 22% had elevated LDH levels. Most patients were white (92%), treated in US community practices (79%), and had Eastern Cooperative Oncology Group (ECOG) PS of 0/1 (67%/28%). Approximately one-third of the patients were in each FLIPI risk group (Figure 1). One-third of the patients in the low/good FLIPI had none of the five risk factors. In the high-/poor-risk FLIPI group, 4.8% patients had five risk factors, 25.8% had four risk factors, and 69.4% had three risk factors. A higher percentage in the poor-risk FLIPI group had follicular grade 3, B symptoms, ECOG score of 1 or more, extra-nodal sites, and bone marrow involvement (P < 0.05). The distribution of FLIPI risk groups in the overall sample and in specific demographic and clinical subgroups is summarized in Figure 1. The distribution of patients in the FLIPI risk groups was similar between academic and community practices.

As shown in Table 1, approximately two-thirds of the patients were initially treated with R either as a monotherapy (13.5%) or in combination with chemotherapy (51.6%); while 17.0% underwent a WW strategy; and 15.3% received non-R-containing therapies. Compared with patients in good or intermediate FLIPI risk groups, a higher percentage of patients in the poor-risk FLIPI group were treated with immunochemotherapy, and fewer underwent WW strategy.

Kaplan–Meier survival curves are presented in Figure 2 for the three outcomes (i.e. OS, PFS, and TTNT) for the overall patient population and for patients who received R-containing regimens. With a median follow-up of 57.9 months, OS was significantly different between FLIPI groups. Furthermore, PFS and TTNT were best in good-risk FLIPI patients compared with those in the intermediate- and poor-risk categories.

The unadjusted and adjusted HR with 95% confidence intervals (CI) by the FLIPI group for OS, PFS, and TTNT are shown in Table 2. Compared with the good-risk group, the unadjusted HR for OS was 2.37 for the intermediate-risk group and 6.17 for the poor-risk group. In this cohort, there were significant differences in OS (but not PFS or TTNT) by treatment setting [HR community versus academic (95% CI) = 1.65(1.23, 2.21)] for OS, 1.01 (0.86, 1.19) for PFS, and 1.05 [0.89, 1.25] for TTNT]. There were no differences in any outcome across gender categories. As seen previously by Nabhani et al. [10], PFS was not significantly different between African American and White but was improved in Hispanic patients (HR = 0.53 [0.33, 0.83] vs White). The Cox proportional hazards models adjusted for treatment setting, gender, and race/ethnicity produced similar results to unadjusted models (Table 2).

The prognostic value of FLIPI was further assessed with patients in six treatment subgroups: (R-containing treatment; non-R-containing treatment; single-agent R (R-mono); R, cyclophosphamide (Baxter Healthcare Corporation, IL, USA), doxorubicin (Pfizer Inc, NY, USA) (Adriamycin), vincristine (Hospira Inc, IL, USA) and prednisone (R-CHOP); R, cyclophosphamide, vincristine and prednisone (R-CVP); and WW using a Cox proportional hazards model with adjustment for treatment setting (Table 3). In patients provided with R-containing treatment, there was an incremental increase in the usage of therapy from FL grade 1 to grade 2 to grade 3 (R-CVP–8.7%, 9.7%, and 17.4%; and R-CHOP–21.4%, 27.1%, and 31.4%, respectively). FLIPI appears to be a useful predictor across treatment strategies for events of interest OS, PFS, and TTNT (supplementary Tables S1 and S2 available at Annals of Oncology online, Figure 3 and supplementary Figure S1, available at Annals of Oncology online).

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>FLIPI risk group</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good N (%)</td>
<td>Intermediate N (%)</td>
</tr>
<tr>
<td>Watch and wait</td>
<td>770 (100)</td>
<td>666 (100)</td>
</tr>
<tr>
<td>RR-containing regimen</td>
<td>170 (22.1)</td>
<td>129 (19.4)</td>
</tr>
<tr>
<td>RR-Mono</td>
<td>95 (12.3)</td>
<td>88 (13.2)</td>
</tr>
<tr>
<td>RR-Chemo</td>
<td>304 (39.5)</td>
<td>348 (52.3)</td>
</tr>
<tr>
<td>Combined modality–XRT</td>
<td>42 (5.5)</td>
<td>7 (1.1)</td>
</tr>
<tr>
<td>Combined modality–BMT</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Any of the above</td>
<td>442 (57.4)</td>
<td>443 (66.5)</td>
</tr>
<tr>
<td>Non-RR-containing regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo</td>
<td>18 (2.3)</td>
<td>21 (3.2)</td>
</tr>
<tr>
<td>XRT</td>
<td>99 (12.9)</td>
<td>9 (1.4)</td>
</tr>
<tr>
<td>Combined modality–XRT</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Investigation</td>
<td>31 (4.0)</td>
<td>61 (9.2)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (1.0)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Any of the above</td>
<td>158 (20.5)</td>
<td>94 (14.1)</td>
</tr>
</tbody>
</table>
FLIPI is a reproducible prognostic index based on routinely available clinical data. This index allows for risk stratification, predicting OS outcomes for patients treated with chemotherapy. One potential shortcoming of FLIPI is that the scoring system was developed in the pre-R-era questioning its significance in modern era. Prognostic models for FL: the ILI [11], IPI [12], and FLIPI [3] were compared by Perea et al. [13], demonstrating an overall concordance between the three classification systems of 54% for good-risk groups, 10% for intermediate-risk groups, and 36% for poor-risk groups. FLIPI

Figure 2. Kaplan–Meier (K–M) survival functions for OS, PFS, and time to next treatment (TTNT) by the FLIPI risk group. (A) Overall survival (OS) by the FL international prognostic index (FLIPI) risk groups for all treatments. (B) OS by FLIPI risk groups for R-containing regimens. (C) Progression-free survival by FLIPI risk groups for all treatments. (D) Progression-free survival by FLIPI risk groups for R-containing regimens. (E) Time to next treatment by FLIPI risk groups for all treatments. (F) Time to next treatment by FLIPI risk groups for R-containing regimens.

discussion

FLIPI is a reproducible prognostic index based on routinely available clinical data. This index allows for risk stratification, predicting OS outcomes for patients treated with chemotherapy. One potential shortcoming of FLIPI is that the scoring system was developed in the pre-R-era questioning its significance in modern era. Prognostic models for FL: the ILI [11], IPI [12], and FLIPI [3] were compared by Perea et al. [13], demonstrating an overall concordance between the three classification systems of 54% for good-risk groups, 10% for intermediate-risk groups, and 36% for poor-risk groups. FLIPI
All patients (N = 2190)
Intermediate (N = 666) 2.38 (1.65, 3.43) 1.63 (1.37–1.94) 1.39 (1.17–1.66)
Poor (N = 756) 6.24 (4.51, 8.82) 2.37 (2.01–2.79) 1.72 (1.45–2.03)

Watchful waiting (W&W) (N = 372)
Intermediate (N = 666) 1.63 (1.36, 1.94) 1.82 (1.33–2.49) 1.54 (1.11–2.14)
Poor (N = 756) 2.36 (2.01, 2.78) 1.96 (1.38–2.77) 1.47 (1.00–2.16)

R-Mono (N = 296)
Intermediate (N = 666) 2.73 (2.15–9.26) 1.82 (1.33–2.49) 1.54 (1.11–2.14)
Poor (N = 756) 4.46 (2.15–9.26) 1.96 (1.38–2.77) 1.47 (1.00–2.16)

R-CVP (N = 264)
Intermediate (N = 666) 6.38 (4.66–22.03) 1.61 (1.02–2.55) 0.84 (0.51–1.37)
Poor (N = 756) 14.55 (4.50–47.03) 2.63 (1.74–3.99) 1.87 (1.25–2.80)

R-CHOP (N = 583)
Intermediate (N = 666) 1.35 (0.41–4.44) 1.28 (0.64–2.57) 1.37 (0.69–2.70)
Poor (N = 756) 5.94 (2.36–14.99) 3.69 (2.11–6.45) 2.34 (1.32–4.15)

R/R-containing regimen (N = 1482)
Intermediate (N = 666) 1.75 (0.77–3.96) 1.65 (1.09–2.50) 1.22 (0.83–1.80)
Poor (N = 756) 4.81 (2.37–9.75) 2.48 (1.70–3.63) 1.49 (1.04–2.13)

Non-R-containing regimen (N = 336)
Intermediate (N = 666) 2.31 (1.42–3.76) 1.67 (1.31–2.14) 1.29 (1.01–1.63)
Poor (N = 756) 7.09 (4.63–10.86) 3.01 (2.41–3.76) 1.82 (1.47–2.26)

Reference group—good risk patients (HR 1.00).
*Adjusted for treatment setting (academic or community).
original FLIPI study, the observations made from this registry may be generalized and reflect the 'real world' FL patients in the US. However, this observational study is limited by variations in practice patterns for patients treated in the United States, variations in patient follow-up due to the lack of protocol pre-specified treatment strategies. While data generated from randomized, controlled trials is the most desirable to formulate clinical decisions, completing such trials may not always be possible due to cost considerations and the length of time involved. Data from prospective observational studies and well-defined endpoints, such as the NLCS, can help to corroborate the results of data from trials in which observational studies yield similar findings. FLIPI remains a simple, validated index demonstrating discriminatory power to aid in defining poor-risk patients across treatment strategies and provide estimates of prognosis for patients treated in community practices.

Our prospectively collected data show that FLIPI is a valid and important prognostic tool for patients receiving contemporary immunochemotherapy regimens. It is encouraging to acknowledge that US cooperative groups are using FLIPI to stratify patients and design risk-specific studies in FL. The results from this NLCS study indicate that this approach is reasonable and needed in the current immunochemotherapy era. We propose that FLIPI should be used in community practices to provide prognostic information for patients with FL receiving commonly administered modern therapies and to support discussions regarding expected treatment outcomes. Future studies are needed to determine whether patients in different FLIPI risk categories should be treated differently.

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Adjuvant therapy with cetuximab for locally advanced squamous cell carcinoma of the oropharynx: results from a randomized, phase II prospective trial

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Background: Cetuximab combined with radiotherapy (RT) is a treatment option for head and neck cancer. The objectives of this randomized, phase II trial were to evaluate the efficacy and safety of cetuximab maintenance therapy following definitive RT with concomitant cetuximab in patients with oropharyngeal cancer.

Patients and methods: Ninety-one patients with stage III–IV M0 oropharyngeal tumors were randomly assigned to the treatment with accelerated concomitant boost RT (69.9 Gy) + cetuximab or the same treatment with the addition of 12 consecutive weeks of cetuximab maintenance therapy. The primary end point was locoregional control (LRC) at 1 year.

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