The Follicular Lymphoma International Prognostic Index (FLIPI) separates high risk from intermediate or low risk patients with advanced stage follicular lymphoma treated front-line with Rituximab and the combination of Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP) with respect to treatment outcome.

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ABSTRACT

The Follicular Lymphoma International Prognostic Index (FLIPI) was developed to predict prognosis of patients with follicular lymphoma (FL). However, it was based on different protocols, none of which included Rituximab. The current analysis aimed at evaluating the predictive value of the FLIPI for treatment outcome in 362 patients with advanced stage FL treated front-line with Rituximab/CHOP in a prospective trial of the German Low Grade Lymphoma Study Group. According to the FLIPI, 14% of the patients were classified as low risk, 41% as intermediate risk and 45% as high risk patients. With a 2-year time to treatment failure (TTF) of 67%, high risk patients had a significantly shorter TTF as compared to low or intermediate risk patients (2-year TTF of 92% and 90%, respectively; p = 0.0002). Our data demonstrate that the FLIPI is able to identify high risk patients with advanced stage FL after first-line treatment with Rituximab/chemotherapy.
INTRODUCTION

The introduction of the anti-CD20 monoclonal antibody Rituximab into the treatment of advanced stage follicular lymphoma (FL) has markedly changed the approach to patients with this disease\(^1\). Despite the overall improvement in treatment outcome by combining Rituximab with chemotherapy, response to treatment varies substantially between individual patients\(^2\)\(^-\)\(^4\). Thus, treatment recommendations are still difficult and may range from a ‘watch and wait’ strategy to single agent Rituximab or different Rituximab chemotherapy combinations up to intensive multimodal concepts including myeloablative therapy followed by autologous stem cell reinfusion\(^5\)\(^,\)\(^6\). An important tool for the pre-therapeutic assessment of prognosis and the adaptation of treatment strategies in distinct groups of patients has been introduced by the ‘Follicular Lymphoma International Prognostic Index’ (FLIPI). Based on five easily evaluable clinical and laboratory parameters (age, Ann Arbor stage, number of nodal areas, LDH and hemoglobin level) the FLIPI discriminates between three major subgroups of FL patients with regard to overall survival, carrying a low (0-1 risk factors), intermediate (2 risk factors) or high risk (3-5 risk factors)\(^7\). The FLIPI was derived from the analysis of patients with FL who were treated in different, mostly multicenter study group protocols. At the time of its assessment Rituximab was not established in the first line treatment of FL and in fact none of the respective regimens contained this agent. Since Rituximab has recently been shown to improve the efficacy of anti-lymphoma chemotherapy substantially when added to various regimens\(^2\)\(^,\)\(^8\)\(^,\)\(^9\), the combination of Rituximab and chemotherapy (R-chemo) has become a widely accepted approach for the first line therapy of advanced stage FL.

In order to evaluate the predictive value of the FLIPI in terms of treatment outcome under the conditions of a R-chemotherapy combination, we analyzed a patient cohort of the prospective trial by the German Low Grade Lymphoma Study Group (GLSG) comparing front line immunochemotherapy R-CHOP with CHOP\(^8\).
PATIENTS AND METHODS

Data Collection

The GLSG trial included previously untreated patients of ages 18 years and older with advanced stage follicular (FL), mantle cell or lymphoplasmacytic lymphoma as previously reported. Clinical entry criteria were described previously and comprised the need for therapy and Ann Arbor stage III or IV. After the trial had shown the superiority of R-CHOP, recruitment was still continued and all patients were assigned to R-CHOP induction. The current analysis included all the registered FL patients, who had received at least one cycle of therapy and were staged at least once for treatment outcome. The trial was approved by the responsible local ethics committees and all patients gave written informed consent according to the Declaration of Helsinki.

Evaluation of Treatment Outcome

Initial cytoreduction with four to six cycles of CHOP or R–CHOP was performed as previously described. Patients achieving a complete (CR) or partial remission (PR) after induction were offered either consolidating myeloablative therapy followed by autologous stem cell transplantation or long-term Interferon alpha (IFNα) maintenance. Response to therapy was evaluated according to the International Working Group Criteria after every two cycles of induction therapy and 4 weeks after the completion of the last course. Follow-up evaluations were performed every three months except for CT scans of previously involved areas, which were repeated every six months.

Time to treatment failure (TTF), the main trial efficacy endpoint, was defined as the interval between the start of treatment and the documentation of stable disease after completion of initial therapy, progressive disease or death from any cause. Response duration (RD) was calculated from the end of successful (CR or PR) induction therapy to progression or death.
from any cause. Overall survival (OS) was the time between recruitment and death from any cause.

**Statistical Analysis**

The predictive value of the FLIPI was evaluated in terms of the TTF, which was the primary efficacy parameter of the trial. Secondary parameters were the rate of CR or PR (overall response rate), the RD and the OS. TTF, overall response rate, RD and OS were analyzed according to the three FLIPI risk groups. If the three-group comparison showed a significant effect, two-group comparisons were done on the same significance level according to the closed testing procedure\(^2\). An explorative regrouping of patients according to the number of risk factors aimed at achieving a better discrimination between the risk groups. A multivariate analysis was performed to determine the impact of the FLIPI risk factors (excluding stage which was III or IV in all patients). The time-to-event variables were analysed using the Kaplan-Meier method and comparisons of risk groups were done by means of the logrank test. 2-year event free survival probabilities were reported as this value was close to the median follow-up time. Cox Regression was performed to calculate hazard ratios as well as 95% confidence limits (CI), and for the multivariate analysis. Response rates were compared by Fisher’s exact test. The significance level was 5% for all statistical procedures. All statistical analyses were performed with SAS, Version 9.1.3.

**RESULTS AND DISCUSSION**

*Patients*

Between May 4\(^{th}\) 2000 and March 1\(^{st}\) 2005, 780 patients with advanced stage FL were included into the trial. From a total of 415 patients treated with R-CHOP 362 were evaluable for the target parameter TTF, including 75 patients assigned to R-CHOP after the end of randomization in August 2003. Of the 338 patients that were evaluable for the FLIPI, 14%
had a low risk (LR), 41% an intermediate risk (IR) and 45% a high-risk (HR) score (Table 1).

In addition, 268 patients treated with CHOP were evaluable for TTF, 260 patients for the
distribution to FLIPI risk groups, which was similar to the R-CHOP group (12% in LR, 44% in IR, and 45% in HR).

_Treatment outcome according to the FLIPI after R-CHOP_

After a median follow-up of 20 months 63 of 362 patients treated with R-CHOP failed from
therapy with a 2-years TTF of 80% and the median not yet reached. Patients with a high risk
FLIPI had a 2-year TTF of 67%, which was significantly lower as the TTF observed for LR
and IR patients with a 2-year TTF of 92% and 90%, respectively (p = 0.0002 for the three-
group comparison, Fig.1a). In contrast, LR and IR patients showed an almost identical TTF (p
= 0.62). Compared with the combined low and intermediate risk group, patients in the high
risk group had a relative risk for treatment failure of 3.0 (95% CI, 1.7 to 5.1).

In the multivariate analysis including the individual FLIPI risk factors, a serum LDH level
higher than the upper normal limit (relative risk 2.6, 95% CI, 1.5 to 4.5) and a hemoglobin
level below 12 g/dl (relative risk 2.5, 95% CI, 1.4 to 4.3) were independently associated with
a shorter TTF. In contrast, age (≥ 60 years versus < 60 years, relative risk, 1.1; 95% CI, 0.7 to
1.9) and number of nodal areas (> 4 versus ≤ 4, relative risk, 1.6; 95% CI, 0.9 to 2.8) did not
significantly influence the TTF in our cohort.

The FLIPI also separated HR from IR or LR patients with regard to response duration (RD).
The 2-years RD in HR patients was 69% compared to 88% for LR and 89% for IR patients (p
= 0.0002, relative risk of HR to LR or IR, 3.3, 95% CI, 1.8 to 6.0). With regard to post-
induction treatment, the index separated the high risk from the intermediate/low risk group for
the patients treated with consolidating myeloablative therapy and autologous stem cell
transplantation (ASCT) (n= 65; relative risk, 6.0, 95% CI, 1.4 to 25.2) as well as for the
patients treated with IFN maintenance (n= 166) or no further therapy (n=76)(relative risk, 3.2,
95% CI, 1.8 to 5.8). With an overall response rate of 96% in the total cohort, no significant differences between the three FLIPI subgroups could be seen (OR Rate of 100% in LR, 97% in IR and 95% in HR patients, p = 0.31). With regard to overall survival, no event was observed in 54 LR patients, 2 events in 152 IR patients and 10 events in 166 HR patients, resulting in a 2-years OS of 100%, 99% and 92% (p = 0.0121). However, the number of events was still low, given the comparatively short follow-up.

**Treatment outcome according to the FLIPI after CHOP**

The FLIPI also showed a significant impact on the TTF of 260 patients treated in the CHOP arm of the trial (p = 0.0071). The HR group (n = 116, 2-years TTF 48%) was clearly separated from the IR group (n = 114, 2-years TTF 68%), and from the LR group (n = 30, 2-years TTF 70%, Fig.2). The relative risk for treatment failure of high risk FLIPI patients as compared to low or intermediate risk patients was 1.8 (95% CI 1.2 to 2.6). With regard to RD, the FLIPI also separated HR from IR or LR patients (relative risk, 2.0, 95% CI, 1.4 to 3.1). When the postremission therapy was taken into consideration, the index separated high risk patients from the intermediate/low risk patients for the group, which received IFN maintenance (n=133) or no further therapy (n=53) after initial cytoreduction (relative risk, 2.8, 95% CI, 1.4 to 5.4). This separation was not seen in the subgroup of responding patients, which was treated with consolidating ASCT, however, the patient number was limited in this cohort (n=45; relative risk, 2.1, 95% CI, 0.55 to 8.0).

Taken together, the analysis shows that the FLIPI is able to separate high risk patients from patients with an intermediate or low risk profile after initial therapy with the Rituximab/chemotherapy combination R-CHOP. The discriminative power of the FLIPI after immunochemotherapy was also documented when the post-remission therapy was taken into consideration. These observations underline that the FLIPI is a robust tool to identify high risk
patients in the era of rituximab/chemotherapy approaches and divergent post-induction treatments. Of note, there were no significant differences for the TTF between IR and LR patients treated with R-CHOP induction or CHOP. There might be several reasons such as the relatively small number of patients and events in the low risk group due to the inclusion criteria of the trial. Furthermore, this study was based on TTF and not on overall survival and incorporated Rituximab into the front-line treatment strategy in comparison to the original report of the FLIPI. In addition, post-remission therapy as offered to patients in this study might influence the ability of the FLIPI to discriminate between low and intermediate risk groups. However, in an explorative analysis when patients with 1 or 2 risk factors (55% of the patients), patients with 3 risk factors (27%) and patients with 4 or 5 risk factors (18%) were re-grouped, a significant separation of three distinct risk groups could be achieved (2-years TTF 90% vs. 74% vs. 57%, respectively; p < 0.0001, Fig.1b). These results suggest that after Rituximab/chemotherapy with its increased anti-lymphoma activity a modified definition of risk groups may facilitate the discrimination of LR and IR patient groups with regard to TTF.

Our results are in concordance with recent results of a smaller study (n=132). In this trial patients were treated with R-CVP. The assessment of the FLIPI revealed that HR patients had a median TTP of only 26 months as compared to 39 months for IR patients and a median not reached for LR patients. Hence, the FLIPI remains a useful tool for the pre-therapeutic assessment of treatment outcome and for the development of risk adapted treatment strategies in patients with FL. It also provides the basis for interstudy comparisons and for judging the impact of different treatment strategies on the outcome of distinct subgroups of patients. The FLIPI therefore promises to facilitate further improvements in FL therapy and is an important step forward towards individualized treatment concepts.
Legends:

Figure 1:
Time to treatment failure of patients with advanced stage FL treated with R-CHOP front-line: patients were grouped into three different risk groups as previously published (LR = 0,1 risk factors, IR = 2 factors, HR = 3-5 factors) or analyzed separately according to the number of risk factors (RF) as indicated (Fig.1a) or analyzed separately according to the number of risk factors (RF) as indicated (Fig.1b). The statistical significance between the three risk groups is shown.

Figure 2:
Time to treatment failure of patients with advanced stage FL treated with CHOP front-line: patients were grouped into three different risk groups as previously published (LR = 0,1 risk factors, IR = 2 factors, HR = 3-5 factors). The statistical significance between the three risk groups is indicated.
Table 1. Baseline characteristics of patients analyzed for TTF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>R-CHOP (n = 362)**</th>
<th>CHOP (n = 268)</th>
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<tr>
<td></td>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Age</td>
<td>Years*</td>
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<td>57 (21 – 81)</td>
</tr>
<tr>
<td></td>
<td>Age</td>
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<tr>
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<tr>
<td>Stage</td>
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<td>LDH</td>
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<tr>
<td>Hb</td>
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<td>2 – 4</td>
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<td>No. inv. nodal areas</td>
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<tr>
<td>No. inv. extranodal sites</td>
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<tr>
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<tr>
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<td></td>
<td>High Risk</td>
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<td>45</td>
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</table>

* median (range)

**In the R-CHOP cohort randomized patients as well as patients assigned to R-CHOP after stop of randomization were included.
Figure 1

(a) 

(b)
Figure 2
References:


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