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High-risk follicular lymphoma patients: identification and treatment

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Summary. Over the last 15 years, the outcome of patients with follicular lymphoma (FL) has dramatically improved mainly as a result of effective therapies and of a better understanding of lymphoma biology. Although progression-free survival is approximately 10 years with standard treatment and overall survival upwards of 20 years, the clinical behavior among individual patients is highly heterogenous, and a significant number of subjects have a higher and earlier risk of dying from FL within a few years from diagnosis. In this article, we provide an overview of available prognostic tools that can be used to identify high-risk patients with FL and describe which therapies are available and can be recommended for this group of hard-to-treat FL patients.

Key words: follicular lymphoma, prognosis, prognostic factors, high risk, early progression

Introduction

Follicular Lymphoma (FL) is the most frequent subtype among indolent B-cell Non Hodgkin Lymphomas (NHL), typically diagnosed during the 5th to 6th decades (1). Over the last 15 years, the outcome of FL patients has dramatically improved mainly as a result of effective therapies and of a better understanding of lymphoma biology. Standard treatment for patients with advanced stage disease requires the combination of chemotherapy with anti CD20 immunotherapy. R-CHOP or R-bendamustine regimens are alternative options, with similar anti-lymphoma activity and with a different toxicity profile; they can be followed by rituximab maintenance, which allows excellent disease control that translates into a median progression-free survival (PFS) of approximately 10 years and overall survival (OS) upwards of 20 years (2-5). With the use of the novel antiCD20 monoclonal antibody obinutuzumab instead of rituximab, further improvement in patient survival is foreseen (6). Although most patients with follicular lymphoma follow an indolent course, the clinical behavior among individual patients is highly heterogenous, and a significant number of subjects are diagnosed with a hard-to-treat disease, with high risk of dying from FL within a few years from diagnosis.

Among known prognostic factors, duration of response has been recognized as a relevant driver of patient outcome in most lymphoma subtypes for many years now , but the impact of early progression has been well characterized in FL patients treated with standard immunochemotherapy only recently (7). Casulo et al. analyzed 588 FL patients from the National LymphoCare Study who received first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). They identified 19% of cases with early progression of disease within 24 months after diagnosis (POD24), who had a five-year OS of 50%; this was significantly lower compared to the 90% observed for patients without POD24. This trend was maintained after adjustment for FL International Prognostic Index, and the results were validated in an independent set of 147 patients with FL who received first-line R-

CHOP. POD24 results were received with great interest by the lymphoma community as, for the first time in many years, one prognostic parameter was identified in a significant proportion of cases and with a clinically relevant effect on OS. Of note, POD24 was recently validated as a robust indicator of poor FL survival in a pooled analysis of >5.000 patients with FL included in 13 prospective clinical trials (8). Finally, in a subanalysis of the Gallium trial, the risk of POD24 was reduced by 34% in the obinutuzumab arm but its role as a bad prognostic factor for OS was confirmed (9).

POD24 is an important step towards the goal of personalized care for patients with FL but it also defines new, important questions that should be addressed. The two main questions concern the earlier identification of high-risk patients and which treatment should be offered to these patients in an attempt to overcome the bad outcome associated with early progression. Answering these two questions is a high priority. In this review article, we provide an overview of available prognostic tools that can be used to identify high-risk patients with FL and describe which therapies are available and can be recommended for this group of hard-to-treat FL patients. For the purposes of this article, the discussion will be limited to the risk of progression or of death and will thus not consider the risk of transformation of FL into an aggressive lymphoma. Transformation, however, should always be suspected at each relapse and, if possible, ruled out by confirming FL histology with a new biopsy.

Prognostic factors and prognostic scores in FL

Prognostic studies in FL can be classified into two main groups: those based on baseline features and those based on post-treatment assessment. A third group of studies then combines baseline and post-induction prognostics.

Baseline prognostic studies

Different approaches have been identified that use baseline clinical, biologic, or metabolic features to improve our ability to predict the natural history of FL in the individual subject. These include Follicular Lymphoma International Prognostic Index (FLIPI),

Table 1. Summary of prognostic factors used to identify high-risk patients and correlation with POD24

Score/factor	HR def.	HR%	Time	PFS (%)	OS (%)	POD24% in HR	Ref.
Baseline							
FLIPI	3-5 RF	28	5yrs	-	53	55	(10)
FLIPI2	3-5 RF	27	5yrs	29	59	-	(12)
TMTV	>510 cm^3	29	5yrs	33	85	56	(13)
m7FLIPI	calculated	28	5yrs	38 (FFS)	42-65	76	(14, 15)
23 gene model	calculated	21-35	5yrs	26	-	38	(16)
Post-induction							
EOI PET	DS 4-5	17	4yrs	23	-	87	(19)
MR t(14;18)	> 0e-4 DNA copies @12months	20-50	3yrs	41	-	-	(25)
Combined models							
TMTV + FLIPI2	>510 cm^3 and 3-5 RF	14	5yrs	46	87		(13)
FDG-PET + MR	DS 4-5 or > 10e-4 DNA Copies @12months	32	5yrs	35	-	-	(28)
TMTV + EOI PET	>510 cm^3 and DS4-5	8	5yrs	23	-	39	(29)

Table legend: HR: high risk; RF: risk factors; PFS: progression-free survival; FFS: failure-free survival; OS: overall survival; POD24: progression of disease within 24 months from treatment start; FLIPI: follicular lymphoma international prognostic index; TMTV: total metabolic tumor volume; EOI PET: end of induction PET; MR: molecular response, DS: Deauville score

FLIPI-2, baseline study of the Total Metabolic Tumor Volume (TMTV) with FDG-PET, and the definition of biological indexes, namely m7FLIPI and the 23-gene predictor score.

FLIPI and FLIPI2

The FLIPI and FLIPI2 scores are widely used risk models to predict the risk of death and of disease progression; they are both easy to calculate as they are designed to use simple clinical and laboratory features. FLIPI was developed thanks to extensive international cooperation in retrospectively collecting data of patients with FL diagnosed between 1985 and 1992 (10). The score is based on five prognostic factors (age, stage, LDH, number of nodal areas, and hemoglobin level) and was originally developed to predict OS, though none of the evaluated patients was treated with immunochemotherapy. High-risk patients were originally identified by FLIPI as those with 3 to 5 risk factors, accounting for 27% of cases, with these patients showing a 5-year OS rate of 52.5%. The index was subsequently validated for patients treated with standard R-CHOP and for PFS instead of OS (11). Of note, in the first description of POD24, FLIPI was also included in the multivariate analysis of overall survival, but only 55% of early progression was classified in the high-risk group (7).

FLIPI2 was developed by the same international consortium but was the result of prospectively collecting data of FL patients consecutively diagnosed, half of whom were also treated with conventional immunochemotherapy. FLIPI2 was based on the combination of 5 risk factors (age, bone marrow infiltration, hemoglobin level, beta2-microglobulin, longest diameter of largest lymph node), with high-risk patients having 3 to 5 risk factors. Similar to FLIPI, FLIPI2 identified 27% of patients as being at high risk; their 5-year PFS rate was 18.8% (12). Of note, no data are available to correlate FLIPI2 with the risk of early progression or POD24.

TMTV

The prognostic value of quantitative parameters obtained from baseline PET/CT has been recently reported in patients with various subtypes of lymphoma Among them, standardized measurement of the TMTV has shown particular usefulness. In a recent study by Meignan et al., baseline TMTV as a dichotomized variable was the strongest pre-treatment predictor of outcome in high tumor burden follicular lymphoma. The 29% of patients who had a high TMTV>510 cm3 had a markedly inferior 5-year PFS, with a median PFS of less than 3 years and an increased risk of death. Conversely, a metabolic volume below this cutoff in the remaining 71% of patients predicted a median PFS beyond 6 years. Importantly, TMTV was a strong predictor of early progression within the first 1-2 years after commencing therapy. Unlike the original FLIPI, FLIPI2 was also an independent predictor of PFS in this study and the combination of TMTV> 510 cm3 with intermediate-high risk FLIPI2 stratified the population into three risk categories based on the presence or absence of any of these two adverse factors. Of the 14% of patients with both a high TMTV and intermediate-high risk FLIPI2, 46% had a very poor 2-year PFS and 86% a 2-year OS. With a median progression-free survival of only 19 months, this population can no longer be characterized as having an indolent course (13).

A measure of the total burden of viable tumor and environmental cells offers a promising improvement on existing surrogates for tumor burden integrated into the current five-factor prognostic indices, FLIPI and FLIPI2. While the decision to treat follicular lymphoma is highly influenced by tumor burden, no specific study has ever addressed the prognostic role of the TMTV in FL and its added value to these clinical prognostic indices, which fail to adequately identify patients at particularly high risk of progression and early death after modern immunochemotherapy approaches.

m7-FLIPI

A first attempt to integrate clinical prognostic factors with biomarker analysis in the era of immunochemotherapy was made by Pastore et al., who integrated the mutational status of seven genes in the context of the FLIPI clinical backbone in a population of 151 high tumor burden FL patients who were treated

with standard R-CHOP. They used DNA deep sequencing to retrospectively analyze the mutation status of 74 genes and identified mutations associated with shorter failure-free survival in EP300, FOXO1 CARD11, and CREBBP genes, and mutations in EZH2, MEF2B, and ARID1A that were associated with longer failure-free survival. The model, called m7-FLIPI, was then calculated as the weighted sum of predictor values and included high risk FLIPI, poor ECOG performance status, and non-silent mutations in the above-mentioned genes. The m7-FLIPI identified a high-risk group of 28% of cases with a 5-year failure-free survival of 38% and a low-risk group with a 5-year failure-free survival of 77% (p<0.0001). The score outperformed FLIPI alone and FLIPI combined with ECOG performance status, and results were confirmed on an independent validation series (14). M7-FLIPI was also tested with POD24 in a different study, which used two independent series of patients with FL (GLSG 151 pts; BCCA 71 pts) and which showed that m7-FLIPI had the highest accuracy to predict POD24 (76% and 77%, respectively, in the two series). High-risk m7-FLIPI patients were significantly more likely to develop POD24, with an odds ratio (OR) of 5.82 (P=.00031) and 4.76 (P=.0052) in GLSG and BCCA patients, respectively. Compared with the FLIPI, the specificity of the m7-FLIPI in identifying POD24 (i.e., the true negative rate) in the two studies increased from 56% to 79% and from 58% to 86%, respectively (15).

23-gene predictor

An effort similar to m7-FLIPI to improve prognostication of FL patients using biomarker analysis was recently published by the LYSA group, which used a gene-expression profiling approach. The study was based on the gene expression analysis of 160 untreated high tumor burden FL patients enrolled in the phase III randomized PRIMA trial, with results validated using three independent international patient cohorts from LYSA, University of Iowa/Mayo Clinic Lymphoma SPORE, and the Barcelona Hospital Clinic. The study selected the expression levels of 23 out of 395 genes that were associated with a risk of progression to build a predictive model that identified a population at an increased risk of progression. This panel included genes previously described to be involved in B-cell development (VPREB1, FOXO1, FCRL2, AFF3, TCF4), apoptosis, DNA damage response (RASSF6, GADD45A), (E2F5, USP44), cell migration (CXCR4, SEMA4B, EML6, DCAF12, VCL, RGS10), immune regulation (CXCR4, KIAA0040, TAGAP, ORAI2, KIAA0040, METRNL), and other processes (PRDM15, ABCB1, ALDH2, SHISA8). In a multivariate Cox model for progression-free survival adjusted on rituximab maintenance treatment and FLIPI, this score independently predicted progression with an HR of the high-risk group compared with the low-risk group of 3.68 (P=<0.001). The high-risk group accounted for 21% to 35% of patients in the different series, and the 5-year PFS for the training set was 26% (95% CI 16-43) in the high-risk group and 73% (64-83) in the low-risk group. These results were confirmed in each validation group and in a combined validation cohort. In a multivariate analysis, the score predicted progression-free survival independently of anti-CD20 maintenance treatment and of the FLIPI score. In the combined validation cohort, the proportion of patients with POD24 was 19% (95% CI 15-24%) in patients with a low predictor score (low-risk group) but 38% (29-46%) in patients with a high predictor score (high-risk group), showing the model's ability to identify early relapse. Finally, the score was not prognostic for OS (16).

Both m7-FLIPI and the 23-gene model represent an important methodological step forward in the prognostic assessment of patients with FL and in the definition of high-risk patients. However, they both show important limitations mainly due to the difficulty in reproducing results and they both still lack clinical validation in the context of prospective studies and in different subgroups of FL patients (i.e., low tumor burden cases and patients treated with novel drugs).

Post-induction prognostic factors

Since radiology assessment was first used to define response to therapy in FL, the quality of response has rarely been identified as prognostic for PFS or OS (17).

Recently, response to therapy assessed either with FDG PET or with highly sensitive molecular techniques targeting the t(14;18) chromosomal translocation (minimal residual disease – MRD) have been suggested as important prognostic tools and have both been identified as pivotal factors in achieving the goal of personalized treatment.

Metabolic response

18-F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been identified as a strong diagnostic and prognostic tool in patients with Hodgkin lymphoma, diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and peripheral T-cell lymphoma. The prognostic role of metabolic response in FL patient was demonstrated in two large retrospective analyses of data from the PRIMA and from the FOLL05 trials and from one prospective trial by the LYSA group (18–20). In a pooled analysis of 246 patients from these three studies, Trotman et al. analyzed the application of centrally reviewed five-point Deauville scale (5PS) to assess the correlation between post-induction PET status and survival. Overall, 17% of patients were classified as non-responder using the Deauville score 4 (DS4) as cutoff to define PET positivity based on a higher concordance rate among independent reviewers (vs DS3). Interestingly, no significant correlation between most baseline characteristics and post-induction PET status was noted, apart from the grouped Ann Arbor stage, FLIPI score, grouped FLIPI score, and hemoglobin levels. The HR was 3.9 ($p<0.0001$) for PFS for patients with a positive PET scan versus those with a negative PET scan and was 6.7 ($p=0.0002$) for overall survival. Four-year PFS was 23% and 63% for patients with a positive or negative PET scan, respectively; four-year OS was 87% versus 97%, respectively ($p<0.0001$)(21). These data were robust enough to recommend the routine use of FDG-PET in FL patients as stated in the recently updated criteria for staging and response assessment in lymphomas (22, 23).

Actually, the prognostic strength of metabolic response in FL is supported by its stronger predictive role compared to FLIPI and FLIPI2 scores and by its ability to predict not only PFS but also OS. Available data provide a strong rationale to test the efficacy of response-adapted therapy in FL patients as well. Among possible limitations of the use of FDG-PET in lymphoma, we should acknowledge the low rate of high-risk patients, which is about 15% after R-CHOP immunochemotherapy, and the lack of full validation of the prognostic role of metabolic response with the use of bendamustine, of lenalidomide, and in the context of post-induction maintenance therapy with rituximab. New data on the prognostic role of metabolic response will be available with the final results of the randomized Gallium (R-chemio vs Obinutuzumab NCT01332968) and Relevance (R-Chemio vs. R-Lenalidomide NCT01476787) trials.

Molecular response

Most patients with FL achieve a complete response (CR) after treatment, but most of them will eventually relapse due to minimal residual disease (MRD).

The presence of t(14;18) chromosomal translocation and of clonal rearrangement of immunoglobulin genes in FL cells makes it feasible to use high-sensitivity techniques to detect the disease in peripheral blood and bone marrow sample and to work on the concept of molecular tumor burden and molecular response. Rambaldi et al. (24) assessed FL PCR through quantitative polymerase chain reaction (PCR) analysis for t(14;18) and IG gene rearrangement in a prospective study of 128 patients with FL treated with sequential CHOP and rituximab therapy. Molecular response (PCR negativity) was achieved in 32% of cases after CHOP and rose to 57% and 75% after rituximab and during follow up, respectively. For patients with a durable PCR-negative status, a better clinical outcome was also observed since freedom from recurrence was 57% (95% CI, 23-81) compared with 20% (95% CI, 4-46) in patients who never achieved or lost the molecular negativity ($P<.001$). In a second paper, Ladetto et al. studied the concept of molecular response in a randomized trial for untreated high-risk FL patients that compared standard CHOP-R with high dose therapy combined with rituximab (R-HDS). Molecu-

lar remission (MR) was achieved in 44% of CHOP-R and 80% of R-HDS patients (P<.001), and was the strongest independent outcome predictor, suggesting that achieving MR is critical to effective disease control, regardless of which treatment is used (25). More recently, Galimberti et al. analyzed the role of molecular tumor burden and response in patients enrolled in the randomized FOLL05 trial of immunochemotherapy for untreated patients with advanced stage FL.

At diagnosis, the molecular marker t(14;18) was detected in the bone marrow sample of 53% of cases. Patients without molecular marker or with a low molecular tumor burden (<1 × 10–4 copies) showed higher complete remission rate and longer PFS. Moreover, PFS was significantly conditioned by the PCR status at 12 and 24 months, with 3-year PFS of 66% for MRD– cases versus 41% for those MRD+ at 12 months (P=0.015), and 84% versus 50%, respectively, at 24 months (P=0.014) (26).

Based on these data, MR is confirmed as a promising prognostic factor in the post-induction assessment of response, as it is in other lymphomas or hematologic malignancies. The use of MRD in clinical practice, however, is limited due to the lack of consensus and standardization on MRD techniques and timing and to the lack of a molecular marker in all patients with FL; the rate of patients without a measurable marker is around 30%, which can only partially be improved with better methods and technologies (VDJ region analysis or rarer breakpoint regions of BCL2/IGH chromosomal translocation). Over the last few years, the concept that tumor cells undergoing apoptosis or necrosis release cell-free circulating DNA (cfDNA) into the blood has enabled the use of whole exome sequencing ("next-generation sequencing technologies" – NGS) to detect tumor presence from blood samples. Recently, Roschewski et al. used this technology to monitor response in 126 patients with diffuse large B-cell lymphoma; they showed that the presence of detectable cfDNA during surveillance was associated with a higher risk of lymphoma progression compared with that of patients with undetectable circulating tumor DNA (27). This new tool, called liquid biopsy, and the use of peripheral blood might further improve MRD studies in FL.

Combined models

All previously discussed prognostic factors were defined using multivariable models that also included commonly used clinical prognostic indexes of individual factors (13, 14). This suggests that prognostication of FL patients could be improved by combining different parameters as well as by integrating baseline and post-induction factors.

PET response and MRD

Luminari et al. combined metabolic and molecular response in a small group of 41 patients with FL for whom both MRD analysis and central review of post-induction PET were available. PET/MRD concordance was 76%, with Kappa=0.249, suggesting that PET and MRD when done at the end of induction therapy are not strongly correlated. Taken separately, the positivity rates were 27% and 11% for MRD and PET, respectively. In a stratified analysis combining the information on PET and MRD into 2 groups (PET–/MRD– vs. PET+ or MRD+), the achievement of both PET and MRD negativity (32% of cases) was associated to a better outcome, with a 5-yr PFS of 75% and 35% for PET/MRD –/– and PET+ or MRD+, respectively. Although conducted on a small series of patients, this study shows that combining EOT PET and MRD in patients with FL may improve our ability to predict the risk of progression (28). Based on these preliminary results, the Fondazione Italiana Linfomi designed the FOLL12 trial to investigate the efficacy of a response-adapted strategy in patients with FL (ClinicalTrials.gov Identifier: NCT02063685). This multicenter phase III randomized study has recently completed the enrollment of the planned 800 cases with newly diagnosed FLIPI2 intermediate-high risk stage II-IV FL requiring therapeutic intervention; subjects have been randomly assigned to either standard or experimental response-driven treatment (Figure 1). After a common induction treatment consisting of 6 cycles of R-CHOP or R-bendamustine, followed by 2 additional doses of rituximab, responding patients in the standard arm receive rituximab maintenance therapy (every 2 months for 2 years), while responding patients in the experimental arm are

assigned to different post-induction treatments based on PET and MRD results. PET- and MRD-negative patients undergo observation, PET-negative but MRD-positive patients receive pre-emptive rituximab therapy (4 weekly doses for a maximum of 3 courses until negativization of MRD), and PET-positive patients receive a consolidation (90)Y ibritumomab tiuxetan (0.4 mCi/kg) dose prior to starting conventional rituximab maintenance. This study aims to evaluate whether a PET and MRD response-based maintenance therapy is non inferior when compared to standard rituximab maintenance therapy in terms of PFS.

PET response and TMTV

Cottereau et al. combined metabolic response and TMTV in 159 patients with advanced stage FL from three prospective trials. In the univariate analysis, both high TMTV (>510 cm3) and positive EOI PET were independent, significant risk factors for PFS. Their combination stratified the population into three risk groups: 5-year PFS was 67%, 33%, and 23%, respectively, for patients without risk factors (64%), for those with one of the two adverse features (27%), and for patients with both adverse factors (8%); 10%, 39%, and 54%, respectively, were POD24. This model enhanced the prognostic value of PET staging and response assessment and allowed the identification of a small subset of patients with a very high risk of progression and POD24. (29)

Treatment of high-risk patients

Available guidelines for the treatment of FL patients do not recommend the use of prognostic factors

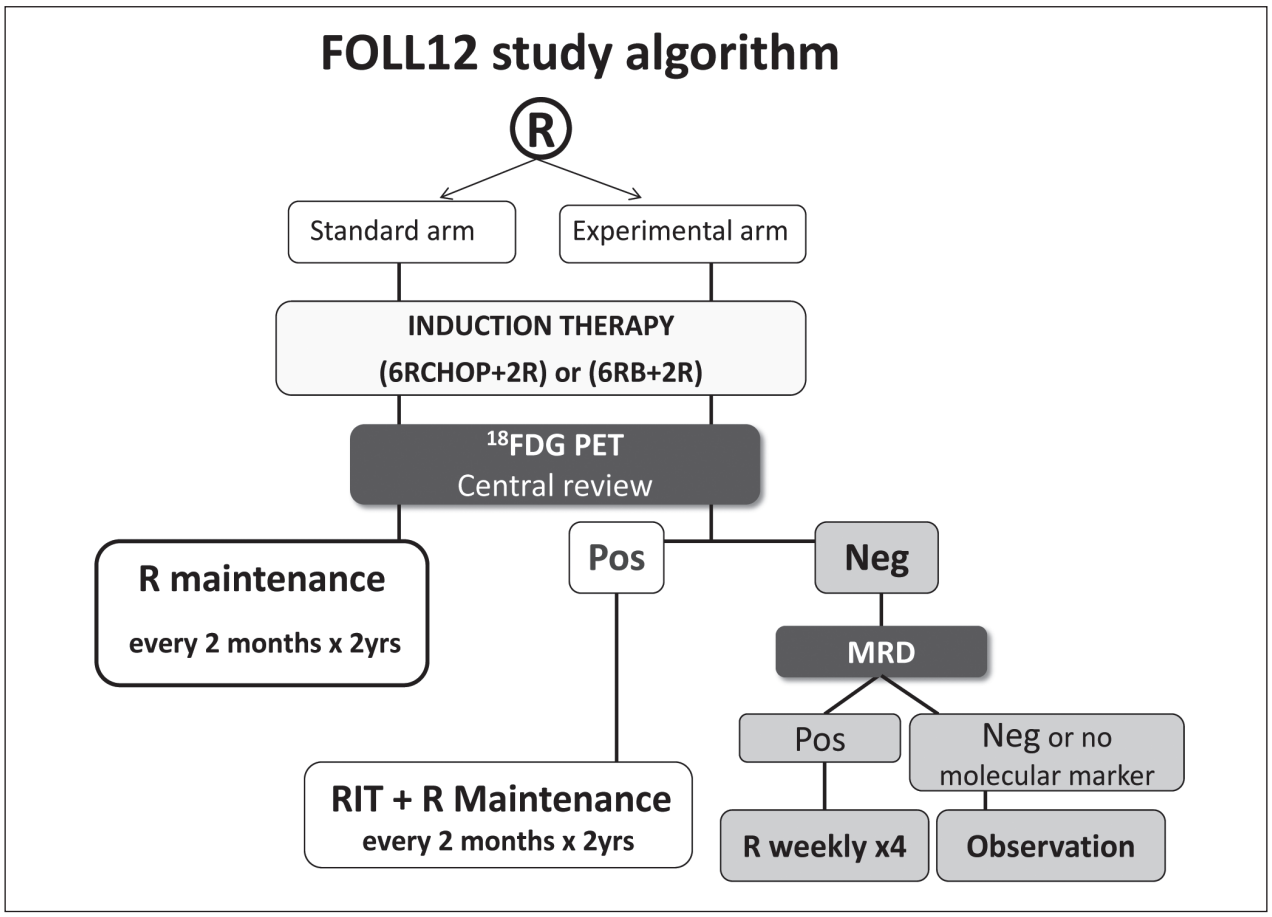

Figure 1. Design of the FOLL12 response-adapted trial for patients with stage II-IV high tumor burden follicular lymphoma.

to decide which treatment should be discussed with the patient. Clinical prognostic indexes are not considered decisional factors, and only stage, symptoms, and tumor burden (TB) are used to identify patients eligible for radiation treatment (stage I-II), immunotherapy or observation (stage II-IV with low TB), and immunochemotherapy (high TB). The same guidelines are extremely vague in defining recommendations for patients with relapsed refractory FL. In this setting, available options range from observation to the use of immunochemotherapy, the use of autologous stem cell transplant (ASCT), or one of the several new available drugs (30).

At first sight, then, no evidence is available to support any suggestions on how to treat high-risk patients with FL. There are, however, some data that can be used to recommend different therapies using validated definitions of high-risk patients. Moreover, clinical trials are starting to explore the concept of risk-adapted therapy in FL patients, as discussed above.

Among available options for relapsed refractory FL, there is a general consensus that ASCT should be used in FL patients who experience a relapse within 3 years from their first line of therapy and who are eligible for intensified treatment. The use of ASCT in relapsed refractory patients is supported by one positive but incomplete randomized trial and by a considerable number of retrospective studies, despite discordant results (31, 32).

The concept that ASCT could be effective in early relapsed patients suggests it is a good option for patients with POD24; unfortunately, in the original POD24 paper, it was not possible to assess the role of ASCT for patients with early relapse as only 8% of them actually followed the guidelines and were treated with ASCT as salvage therapy. Data to support the use of ASCT in early relapses can be found in two recent studies.

In the first, Casulo et al. analyzed data on 348 patients from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the National LymphoCare Study (NLCS) to determine whether ASCT can improve outcomes in this high-risk FL subgroup. A first group of 174 patients with early failure who did not receive ASCT from NLCS was compared with a matched group of 175 patients who received ASCT obtained from CIBMTR. The planned subgroup analysis showed that patients receiving ASCT soon after treatment failure (≤1 year) had higher 5-year OS than those without ASCT (73% vs. 60%, P=.05). On multivariate analysis, early use of ASCT was associated with significantly reduced mortality (33). In the second study, Jurinovich et al. evaluated 113 patients with FL who were enrolled in 2 consecutive randomized trials of the German Low Grade Lymphoma Study Group who had POD24 and had not received prior ASCT. POD24 patients were more likely to receive ASCT as second-line treatment (46% vs 22%; p=0.008) compared to patients without POD24. In univariate and multivariate analyses, ASCT for POD24 patients was associated with significantly better 5-year second-line PFS and OS rates of 51% vs 19% and 77% vs 46%, respectively (34). In two additional retrospective studies, it was suggested that an allogeneic transplant in patients with POD24 could be more effective than ASCT (35, 36), but this option can only be offered to a small number of patients.

In summary, although based on retrospective studies, available data strongly support the hypothesis that standard conventional therapy for patients who are at high risk of POD24 is largely unsatisfactory and that if the patient is fit enough, the ASCT option should always be considered. Randomized trials comparing ASCT vs conventional immunochemotherapy for POD24 patients are strongly warranted.

Although several conventional therapies are available for patients who are not eligible for ASCT, few recommendations can be made, suggesting therefore the enrollment into a clinical trial as first option, if available, and using the most intensive treatment that can be tolerated by the patient as an alternative option. Some interesting data can be found on new drugs that have recently been approved by national health authorities for the treatment of relapsed refractory FL based on the drugs' activity as documented by phase II or phase III data. These include the pI3K inhibitor idelalisib, the immunomodulator lenalidomide, and the new anti CD20 monoclonal antibody obinutuzumab (37-39). Unfortunately, analysis for the subgroup of patients with early relapse are not available for either lenalidomide or obinutuzumab.

Idelalisib is an orally selective active phosphatidylinositol-3-kinase delta (PI3Kδ) inhibitor whose

activity was shown in a phase II study of 125 FL patients who had not had a response to rituximab and an alkylating agent or had had a relapse within 6 months (40). A retrospective post hoc analysis of the main study was conducted to examine whether idelalisib improved clinical outcomes in FL patients experiencing early progressive disease (PD) after initial chemoimmunotherapy. Of the 72 FL patients, 46 received first-line chemoimmunotherapy and 37 had early PD within ≤24 months from the start of treatment. The ORR was 21 out of 37 (57%), with 5 complete responses (14%) and 16 partial responses (43%). The median duration of response for all 37 patients with POD24 was 11.8 months (41). Interestingly, the efficacy and the safety results were not different between this subset analysis and the main study, suggesting that idelalisib can be considered a good option for the treatment of early relapsed patients who are not eligible for ASCT, or in some cases, as a bridge to ASCT.

Promising new drugs have recently started their clinical development, among them the EZH2 inhibitor tazemetostat (42), and checkpoint inhibitors have the best chance of moving ahead in their development(43).

Conclusions

In summary, several prognostic factors are currently available to identify a subgroup of approximately 30% of patients with FL whose lymphoma shows an aggressive clinical behavior and whose life expectancy is significantly reduced. Among available factors, POD24 has the strongest effect on outcome, but there is an urgent need to identify baseline features that can be used to define the prognostic profile earlier in the course of the disease. With highly active available immunochemotherapy regimens, a plateau in the curability of FL has probably been achieved, and a new generation of clinical trials should be started to test the efficacy of tailored treatment intensity to the individual risk of the patient. For the time being, treatment of high-risk FL should be based on available recommended options, including the use of ASCT and of new drugs when properly indicated.

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