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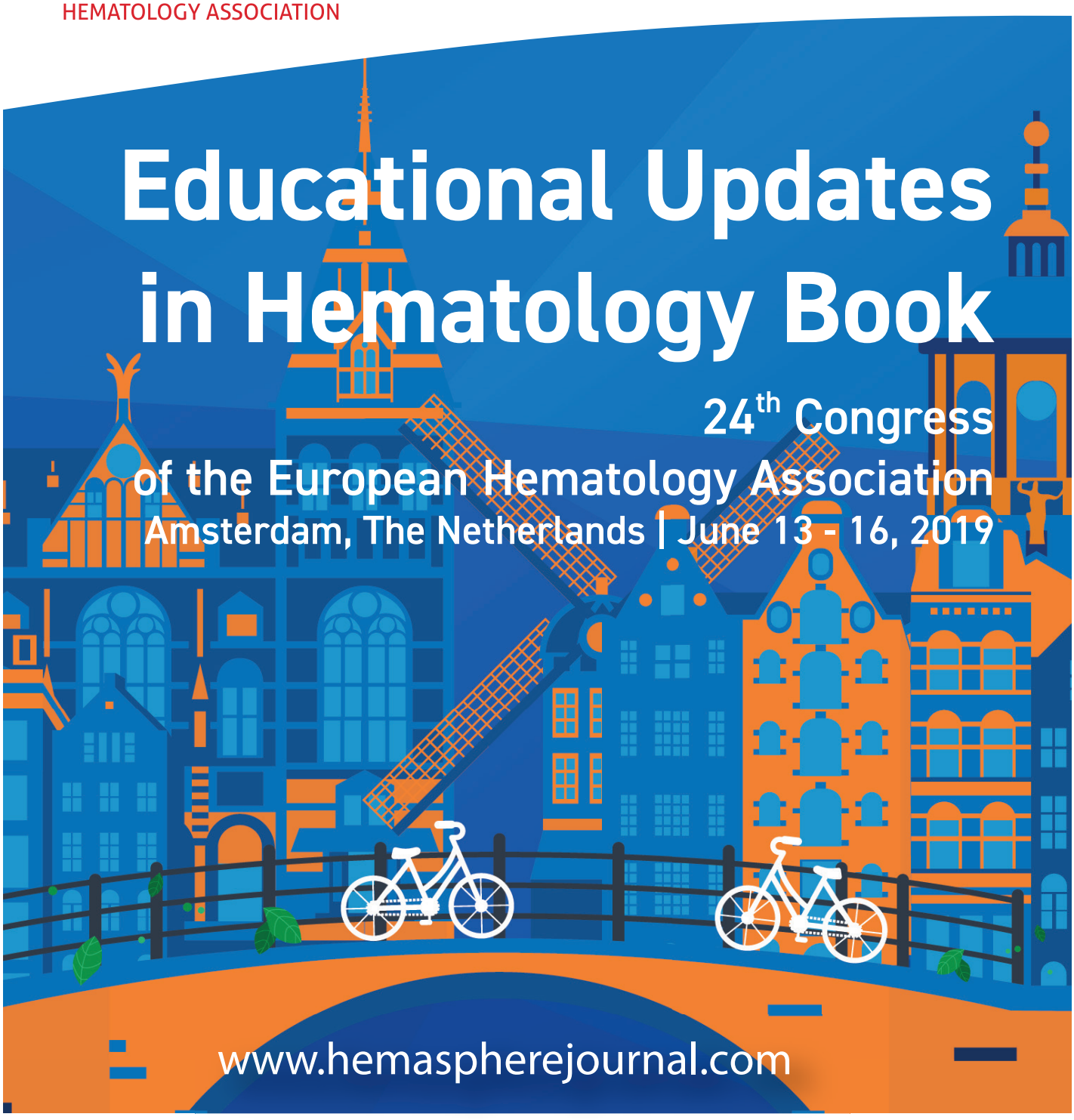

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Follicular lymphoma

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Introduction

Follicular lymphoma (FL) is the most frequent indolent non-Hodgkin lymphoma. The risk of tumor-related death and FL-transformation has been significantly reduced thanks to currently available therapies, including first- and second-generation anti-CD20 antibodies, which might be complemented using Pi3K-inhibitors or immunomodulating agents in relapsed-refractory FL patients. Nevertheless, advanced FL remains an incurable disease, which is particularly difficult to treat in 20% to 30% of high-risk FL patients, having a specifically bad outcome. Accurate risk-stratification is thus a medical need. However, none of the prognostic factors identified so far (eg, follicular lymphoma international prognostic index (FLIPI/FLIPI2), total metabolic tumor volume, minimal residual disease), is able to accurately risk-stratify FL patients, alone. Most FL harbor the translocation t(14;18)(q32;q21) and alterations in genes involved in epigenetic regulation. A core set of alterations including the t(14;18) and mutations in epigenetic regulators (eg, *MLL2*, *CREBBP*, *EZH2*) were shared among sequential biopsies and found to be clonal events, suggestive of early driver events. Instead, FL transformation is rather driven by genetic alterations affecting cell cycle regulation, DNA damage response, immune surveillance and NF-κB signaling. Interestingly, the M7-FLIPI, which is based on the FLIPI and the mutation status of 7 genes (incl. 5 epigenetic regulators), allowed to predict the risk of progression to disease within 24 months in ~80% of high risk FL patients after first-line immunochemotherapy. Moreover, clinical trials with the *EZH2*-inhibitor Tazemetostat in relapsed/refractory FL showed an overall better response in *EZH2*-mutant cases. One strategy to improve prognosis and to guide more personalized therapeutic approaches might thus be to combine currently available prognostic factors and to initiate further clinical trials with molecular inhibitors.

Learning goals

- Understand how the genetic landscape, heterogeneity and clonal evolution shapes the pathogenesis of FL.
- Understand the need for a better risk stratification in FL using novel prognostic factors to identify patients with high-risk FL, in order to guide better risk-adapted therapeutic strategies.
- Understand that the majority of FL patients diagnosed in 2018 will probably die with the disease and not of the disease and that the increased clinical efficacy of new regimens has thus to be balanced against their adverse effects and quality of life.

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Follicular lymphoma - Section 9

Follicular lymphoma genomics

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Take home messages

- The genetic landscape of follicular lymphoma (FL) is skewed toward frequent mutations in epigenetic regulators.
- Divergent clonal evolution from a therapy-evading common progenitor cell is proposed as the predominant mechanism underpinning relapse and transformation.
- Genomic studies are revealing new disease biomarkers and therapeutic targets, with the promise of achieving a precision medicine approach for subsets of FL patients.

Introduction

Next-generation sequencing has improved our understanding of the genomic events that underpin follicular lymphoma (FL). In most FL tumors, the hallmark chromosomal translocation, t (14;18), co-occurs with additional genetic alterations affecting numerous biological pathways, particularly genes involved in epigenetic regulation.[*1,2,*3–*6,7] We appreciate the levels of molecular heterogeneity between tumors from different patients, but also the heterogeneity that exists within an individual as their disease evolves and progresses in space and time.[*3–*6,7] This is paralleled by our recognition of the variation in clinical phenotypes between patient populations, for example, those with localized disease versus high-risk systemic disease (such as early progressors and those who experience transformation to a high-grade lymphoma); although we have yet to fully define the molecular drivers behind such clinical behaviors. Better delineation of these, together with the molecular determinants of response and resistance to existing and emergent therapies will empower the next tranche of potential precision strategies in FL.

Current state of the art

Genome-wide analyses now provide a comprehensive catalog of the somatic changes in FL tumors including chromosomal alterations, copy number variation, and gene mutations, the latter being the focus of this update. Recurrent gene mutations target specific biological processes, including epigenetic regulation, immune surveillance, and signaling pathways.

An unexpected revelation has been the high prevalence of alterations in epigenetic regulators involved in histone post-translational modifications. Mutations in histone methyltransferases (*KMT2D*, *EZH2*) and acetyltransferases (*CREBBP*, *EP300*) are a defining feature of FL (Fig. 1).[*1,2,*3–*6,7] Almost all patients have at least one such "epimutation,"[*5] with most carrying multiple insults.

KMT2D, *CREBBP*, and *EP300* mutations are commonly inactivating, leading to loss of transcriptionally activatory marks (mono-, di-methylation of H3K4 for *KMT2D* and acetylation of H3K27 for *CREBBP* and *EP300*); whereas gain-of-function mutations in *EZH2* increase the repressive mark, H3K27 trimethylation. Functionally, these aberrations seem to exert transcriptional changes that lock cells in a germinal center (GC) stage of differentiation, while on one hand, promoting survival signaling pathways through CD40, JAK-STAT, and BCR (*KMT2D*),[*8] and on the other hand, perturbing immune recognition by downregulating MHC Class II expression (*CREBBP*).[*5,*9]

Frequent mutations affect genes involved in immune recognition (*TNFRSF14*), BCR-NFκB (*CARD11*, *TNFAIP3*), JAK-STAT (*STAT6*), and mTOR signaling (*RRAGC*, *ATP6V1B2*, *ATP6AP1*). Loss-of-function *TNFRSF14* aberrations trigger aberrant stromal activation and T follicular helper cell expansion, overall promoting a tumor-favorable microenvironment.[10] Meanwhile, activating *RRAGC* mutations render the nutrient-sensing arm of mTORC1 signaling resistant to amino acid deprivation.[11]

Longitudinal studies have crucially delineated the clonal dynamics of progression by providing multiple snapshots of the evolving genetic repertoire during a patient's disease course. These demonstrate that relapse and transformation predominantly occur via a divergent pattern of clonal evolution: whereby all sequential tumors in a patient share a core set of mutations (Fig. 1).[*3–*6] This shared "trunk" of aberrations is postulated to

Funding/support: None.
Disclosure: The authors have indicated they have no potential conflicts of interest to disclose.

HemaSphere (2019) 3:S2
Received: 28 January 2019 / Received in final form: 13 March 2019 / Accepted: 14 March 2019
Citation: Kumar E, Okosun J. Follicular Lymphoma Genomics. *HemaSphere*, 2019;3:S2. http://dx.doi.org/10.1097/HS9.0000000000000213.

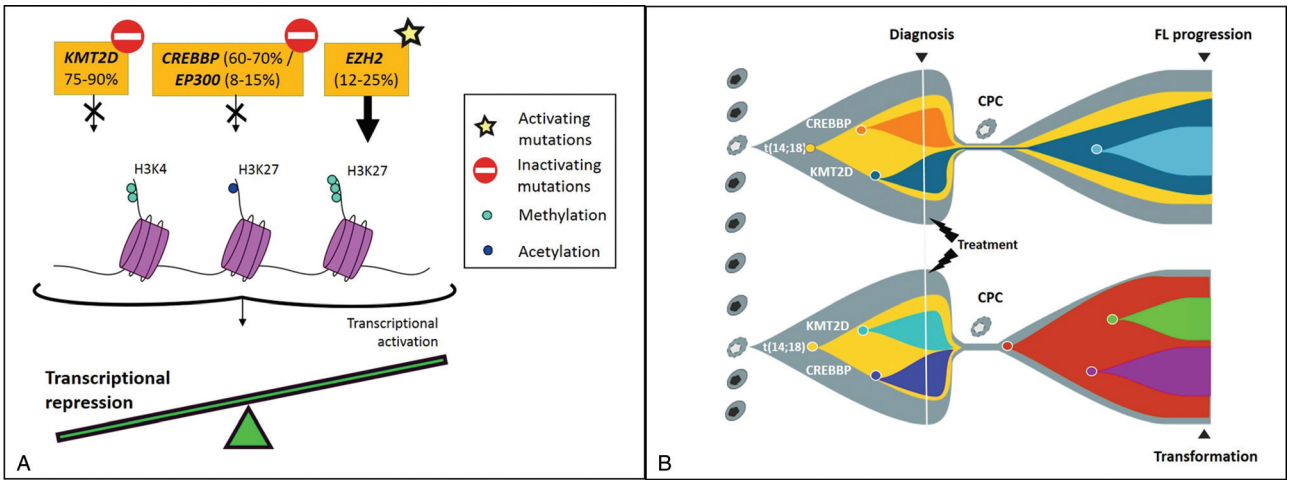

Figure 1. (A) Frequently altered epigenetic modifiers in follicular lymphoma (FL) and their downstream transcriptional effects. (B) Visualization of the clonal structure of progressed and transformed FL inferred from sequencing studies. Shown is the expansion of preexisting, therapy-resistant clones between diagnostic and progression, contrasting with dramatic clonal expansion of undetectable clones in transformed FL. All incidences arise from the common progenitor cell (CPC) harboring key genetic events.

be harbored within a putative population labeled the common progenitor cell (CPC), that can evade therapy, lay clinically quiescent over time, and act as the tumor-propagating reservoir. Importantly, these shared aberrations predominantly encompass t(14;18) together with the epigenetic mutations, affirming them as early driver events. Recently, Kridel and colleagues utilized ultra-sensitive mutation detection to describe contrasting clonal dynamics between early-relapsed FL tumors; characterized by expansion of clones already pre-existing at diagnosis, implying an inherent treatment resistance; compared with transformed FL tumors that arise from the dramatic expansion of a clone undetectable or present at extremely low levels at diagnosis.[*6] Unsurprisingly, the genetic drivers of transformation are heterogeneous and include alterations affecting cell cycle regulation and DNA damage response (*CDKN2A/B*, *MYC*, *TP53*), immune surveillance (*B2M*, *TNFRSF14*), and NF-κB signaling (*MYD88*, *TNFAIP3*).[*3,*4,*6] However, they are imperfect predictors for FL transformation, as many of these events also occur in untransformed FL, albeit at lower frequencies. The mutational profiles of transformed FL broadly overlap with the GC B-cell subtype of DLBCL,[*4] although, a minority of FL, that are predominantly t(14;18)-negative, transform to the activated B-cell (ABC) DLBCL subtype.[12] Notably, a higher incidence of localized FL tumors lack the t(14;18) compared with advanced FL (50% cf 15%)[13] and while t(14;18)-negative tumors share a number of typical FL-associated mutations, they also show some molecular features typical of ABC-DLBCL.[14]

The 2016 WHO revision of lymphoid neoplasm classification reflects an appreciation of the diversity of FL-related conditions,[15] emphasized by recent genomic insights into these entities. In situ follicular neoplasia, a premalignant BCL2+ entity with low rate of progression to overt FL, has much lower genomic complexity than classical FL but already has a number of epigenetic mutations,[16] reiterating epimutations as early events. The highly curable pediatric-type follicular lymphoma is typically t(14;18)-negative with prominent mutations affecting MAPK signaling, and a conspicuous absence of epimutations.[17] Duodenal-type FL also follows a benign clinical course, yet bears a similar mutational profile to classical FL, although differs in its immune microenvironment gene expression signature,[18] highlighting the significance the microenvironment niche may have in driving clinical phenotypes.

Future perspectives

The next priorities focus on translating our increased genomic knowledge into refined diagnostic, prognostic, and therapeutic capabilities, which ultimately improve patients' outcomes. Genomic information is beginning to be integrated into molecular-based prognostic tools that allow patients to be risk stratified at diagnosis. Molecular determinants of treatment response and resistance can serve as predictive biomarkers and are appealing as they may provide the best strategy in rationalizing how we adopt an ever-increasing armamentarium of novel therapies. This is exemplified by clinical trials examining the EZH2-inhibitor, Tazemetostat, in relapsed/refractory FL patients, with *EZH2*-mutant cases showing a superior overall response over wild-type cases.[19] We evidently cannot rely on single-site biopsies due to the longitudinal[*3–*6] and spatial[7] genetic heterogeneity in FL, and dynamic disease monitoring will be needed to overcome this hurdle. Tracking genetic signatures in circulating tumor DNA (ctDNA) could function as a multipurpose surveillance tool for monitoring tumor responses, forecasting treatment failures, and detecting disease progression.[*20] Application of this promising approach requires prospective validation and correlation with imaging and other biomarker strategies.

Finally, we must remember that tumor genomics represents one piece of a complex puzzle, and understanding its reciprocal interplay with aberrant epigenetic mechanisms and the tumor microenvironment will yield deeper insights into the biology.

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Follicular lymphoma - Section 9

Novel prognostic tools that identify high-risk follicular lymphoma

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Take home messages

- In 20% to 30% of patients with follicular lymphoma (FL), the disease shows an aggressive behavior.
- Novel biomarkers are available in FL each with a different ability to identify high-risk patients.
- Further improvement in the management of FL will likely be achieved by means of risk adapted therapies.

Introduction

For many years, risk in follicular lymphoma (FL) has been defined with conventional clinical prognostic factors and indexes with the follicular lymphoma international prognostic indexes (FLIPI and FLIPI2) being the most frequently used scores.[1,2] None of these indexes, however, has ever been able to unequivocally identify high-risk patients.

Current state of the art

Recently, Casulo et al[*3] correlated the concept of high-risk FL with time to progression. The authors showed that patients with high tumor burden FL who progress or relapse within 24 months (POD24) after immunochemotherapy (here: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone [CHOP] with the anti-CD20 antibody Rituximab [R]) had a significantly shorter overall survival (OS) compared with patients without POD24. These findings were recently validated in independent FL patient cohorts and with immunochemotherapy regimens different from R-CHOP.[4,5]

POD24 is an important step toward a better understanding of FL; however, patients would rather benefit from a better risk stratification closer to FL diagnosis, thereby allowing the development of risk-modifying approaches. In that respect, the heterogeneity of high-risk FL which is so far defined by refractoriness and transformation needs to be better understood. These patients' higher risk of dying is mainly caused by lymphoma[6] and might be driven not only by a more aggressive biology of FL but also by refractoriness to immunochemotherapy and by a higher risk of transformation. Indeed, the combination of different dimensions contributes to increasing the risk in FL. In this context, novel tools have recently been studied to identify high-risk FL, with most of the available data coming from the analysis of molecular, pathologic, and metabolic features of the disease.

Baseline biomarkers

A number of studies have found associations between several pathologic features such as histologic grading, proliferation index, and microenvironment in diagnostic FL biopsies and varying degrees of disease aggressiveness, but have not confirmed these features as reliable prognosticators in the era of immunochemotherapy.[7] Advanced noninvasive methods for the detection of cell-free DNA in general and more specifically of circulating tumor DNA are underway, to determine the tumor load which could be used for pretherapeutic risk assessment.[8]

Two attempts have been made to integrate clinical prognostic factors with molecular biomarkers: Pastore et al[*9] integrated the mutational status of 7 genes recurrently mutated in FL in the context of the FLIPI backbone and Huet et al[10] used gene expression analysis to identify a 23-gene predictor model. Both the m7-FLIPI and the 23-gene model identified a high-risk group of 28% and of 21% to 35% of patients, respectively, who had a shorter PFS. A simplified version of m7-FLIPI was also validated allowing to predict the risk of POD24 in up to 80% of high-risk patients.[11]

Finally, since ^{18}F-fluordesoxyglucose (FDG) avidity was confirmed in the majority of FL, the prognostic value of quantitative parameters obtained from baseline FDG-PET/computed tomography has been analyzed. Of these parameters, standardized uptake value (SUV) has been shown to be a good

Funding/support: None.
Disclosure: The authors have indicated they have no potential conflicts of interest to disclose.

HemaSphere (2019) 3:S2
Received: 25 January 2019 / Received in final form: 15 March 2019 / Accepted: 15 March 2019
Citation: Luminari S. Novel Prognostic Tools That Identify High-risk Follicular Lymphoma. *HemaSphere*, 2019;3:S2. http://dx.doi.org/10.1097/HS9.0000000000000214.

Table 1

Summary of Prognostic Factors Used to Identify HRFL Patients and Correlation With POD24

Score/Factor	HRFL Def.	HRFL%	Time, y	PFS, %	OS, %	POD24% in HRFL	Ref.
Baseline							
FLIPI	3–5 RF	28	5	—	53	55	1,*3
FLIPI2	3–5 RF	27	5	19	77	—	2
TMTV	>510 cm^3	29	5	33	85	41	12
m7-FLIPI	Calculated	22–28	5	38 (FFS)	42–65	43–61	*9
POD24-PI	Calculated	36–42	5	36–50 (FFS)	48–71	61–78	11
23-Gene model	Calculated	35	5	26	—	38	10
Postinduction							
EOI PET	DS 4–5	17	4	23	87	—	*14
EOI PET	DS 4–5	12	2.5	54	84	—	16
MR t (14;18)	>10 e^{-4} DNA copies @12 mo	20–50	3	41	—	—	13
Combined models							
TMTV + FLIPI2	>510 cm^3 and 3–5 RF	14	5	20	87	—	12
EOI PET + EOI-MR	DS 4–5 or > 10 e^{-4} DNA Copies @EOI	16	2.5	69	—	—	19
TMTV + EOI PET	>510 cm^3 and DS 4–5	8	5	23	83	—	17

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

tool to identify areas at higher risk of histologic transformation and could thus be used to guide diagnostic biopsies. More importantly, in a recent study by Meignan et al,[12] baseline total metabolic tumor volume (TMTV), defined as the sum of the volumes of sites with an SUV value above a significant threshold, has been confirmed as the strongest pretreatment prognostic factor, able to identify a third of patients at higher risk of progression and of dying from FL, independently of FLIPI and FLIPI2 (Table 1).

The above-mentioned molecular and metabolic biomarkers represent new tools to identify high-risk patients at diagnosis and might be used to support biology guided therapies (ie, EZH2 inhibitors). However, they both show limitations in their reproducibility and require further investigations in the context of prospective studies and in different subgroups of FL patients (ie, low tumor burden cases and patients treated with new drugs).

Postinduction prognostic tools

Response to therapy assessed either with FDG-PET or with highly sensitive molecular techniques that are able to measure cell-free DNA or to determine low levels of the t(14;18) chromosomal translocation (minimal residual disease [MRD]) have recently been suggested as useful prognostic tools.[13–15] Trotman et al recently reported the results of the largest study ever conducted, to investigate the prognostic role of metabolic response in more than 500 patients with treatment-naïve advanced-stage FL enrolled in the GALLIUM trial. The authors were able to confirm that metabolic response to induction immunochemotherapy is prognostic both for PFS and OS, and that Lugano response criteria are accurate and reproducible in FL. More importantly, this study showed that metabolic response is associated with prognosis in nearly all advanced-stage FL patients, including those who receiving maintenance therapy and those who treated with the new generation anti-CD20 monoclonal antibody (ie, obinutuzumab) and different chemotherapy backbones.[16]

Future perspective

In summary, several biomarkers and prognostic factors are currently available to identify a subgroup of approximately 20% to 30% of patients with FL whose lymphoma show an aggressive clinical behavior. The use of novel techniques to measure cell-free or tumor-free DNA holds promises to a deeper understanding of FL heterogeneity, and for a better monitoring of response to treatment, hopefully leading to the identification of novel biomarkers.[8] Each available biomarker has a different ability to predict outcome and likely describes different features of the higher individual risk. Since none of the prognostic factors identified so far is currently available to accurately identify high-risk FL and applies to the clinical and biological heterogeneity of FL, a reasonable strategy might be to combine available factors. Indeed, recent results showed that baseline and postinduction factors can be successfully combined (ie, TMTV + FLIPI2, TMTV + metabolic response, metabolic response + molecular response).[12,17,*18,19,20] Clinical trials are underway that investigate the efficacy of a response-adapted approach, based on the use of novel prognostic biomarkers including FDG-PET and/or MRD, aiming to tailor the postinduction maintenance phase of therapy to the quality of response (NCT02063685 and EudraCT 2016-004010-10).

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Follicular lymphoma - Section 9

Treatment of high-risk follicular lymphoma

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Take home messages

- The majority of follicular lymphoma (FL) patients diagnosed in 2018 will probably die with the disease and not of the disease—in assessing new regimens, their increased clinical efficacy has thus to be balanced against their adverse effects and quality of life.
- The choice of the right first-line therapy in high-risk FL patients remains an unmet medical need, which has to be addressed in randomized clinical studies. The introduction of new anti-CD20 antibodies and "small molecules" inhibitors targeting intracellular pathways, such as PI3K inhibitors, can be regarded as milestones in FL therapy, prolonging overall survival.

Introduction

A quarter of follicular lymphoma (FL) patients are refractory to first-line immunochemotherapy and/or progress within the first 24 months (POD24), having a 5-year survival rate of <50%.[1] Identification of high-risk patients before first-line therapy is thus an unmet medical need.

Median overall survival (OS) of FL patients exceeds 10 years. Therefore, it is no longer feasible as the primary endpoint of clinical trials. Instead, median progression-free survival (PFS) is an adequate primary efficacy endpoint, especially if supported by objectively assessed improvement of life quality. It varies from 4 to 10 years after first, <2 years after the second and about 1 year after the third and subsequent therapy lines.[2]

Current state of the art

First-line therapy

Immunochemotherapy (chemotherapy in combination with an anti-CD20 antibody; eg, Rituximab [R]) is the standard of care in high-risk FL patients. In an update of FOLL05 trial, 504 advanced FL patients were randomized to R-CVP (Cyclophosphamide, Vincristine, and Prednisone), R-CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) or R-FM (Fludarabine and Mitoxantrone) regimens, all without R-maintenance. None of the regimens was superior with regard to the overall response rate (ORR) or 8-year OS.[3] The 8-year PFS was inferior in R-CVP ($P=0.009$), while nonlymphoma-related mortality was higher in R-FM ($P=0.005$).

R-maintenance after initial immunochemotherapy significantly prolonged median PFS in FL patients as shown. In a long-term follow-up of the PRIMA study (N=1018) where median PFS was 10.49 in patients treated with R-maintenance versus only 4.06 years in patients treated without R-maintenance ($P=0.0001$).[*4] There were, however, no differences in projected median OS. (The 10-year OS was 80%.) Additionally, in low tumor burden FL, similar results to R-maintenance may be obtained by R re-treatment at the time of relapse (RESORT study).[5]

In the GALLIUM study, 1202 previously untreated, advanced FL patients were randomized to R or Obinutuzumab (a second-generation CD20 antibody) immunochemotherapy with subsequent maintenance.[*6] The first evaluation after 41 months revealed that PFS was significantly longer in the Obinutuzumab plus chemotherapy (here: CVP, CHOP, or Bendamustine) arm (hazard ratio 0.68; $P=0.0016$). The POD24 events were reduced from 16.7% to 9.7%. Again, neither median OS nor quality of life was improved. A 3-year PFS was higher in the Bendamustine group, but so was the frequency of adverse events (AE) such as grade 3 to 5 infections, particularly during maintenance. Thus, Bendamustine-based regimens should be used with caution in patients older than 70 years.[*6] Although Obinutuzumab compared with R increased the number of grade 3 to 5 AEs from 69% to 75%, therapy-related deaths were less frequent.

Another alternative in advanced FL is an immunomodulatory regimen R2 (R plus Lenalidomide). In the RELEVANCE study (N=1030), the ORR to R plus Lenalidomide 120 weeks after therapy was fully comparable with R plus chemotherapy.[*7] A 3-year PFS was 77% and 78% for the R2 plus Lenalidomide and immunochemotherapy arms, respectively, with more grade 3 and 4 neutropenia (32% vs. 50%) and febrile neutropenia (2% vs. 7%) in the latter.[*7]

Funding/support: None.

Disclosure: The authors have indicated they have no potential conflicts of interest to disclose.

HemaSphere (2019) 3:S2

Received: 31 January 2019 / Received in final form: 20 March 2019 / Accepted: 22 March 2019

Citation: Jurczak W. Treatment of High-risk Follicular Lymphoma. *HemaSphere*, 2019;3:S2. http://dx.doi.org/10.1097/HS9.0000000000000230.

Table 1

Comparison of Obinutuzumab + Bendamustine and Idelalisib Registration Trials

Characteristics	Obinutuzumab + Bendamustine[10]	Idelalisib[11]
Study group description		
Number of participating patients (all patients/FL)	204/164	125/125
Patients failing 4 or more regimens, %	4	58
Number of prior regimens chemotherapy lines, median [range]	3 [1–8]	4 [2–12]
Median time since completion the previous regimen, mo	3.9	3.9
"Double refractory" to rituximab and alkylating agents, %	77	100
Resistant to Bendamustine, %	0	75
Resistant to the last regimen, %	92	90
After failing ASCT, %		11
Efficacy assessment		
RR, %	65.3	57
Median PFS, mo	33.6	11
Adverse effects		
AE (G3–5), %	65.5	54
Neutropenia, %	34.8	27
Thrombocytopenia, %	10.8	6
Anemia, %	7.4	2
Transaminase elevations, %		13
Diarrhea, %		13
Skin rash, %		2
Infections, %	10.1	9
Thromboses, %		
AE which led to treatment discontinuation, %	20.1	20
SAE, %	43.5	26
Fatal AE, %	7.8	3.2

AE = adverse events, ASCT = allogenic stem cell transplantation, FL = follicular lymphoma, PFS = progression-free survival, RR = relapsed refractory, SAE = serious adverse events.

The risk of FL transformation before introduction of immunochemotherapy regimens was relatively high (28% at 10 years).[8] In a recent, retrospective analysis of 8116 European patients, the 10-year cumulative hazard of transformation was significantly lower (7.7%). The inclusion of R in first-line therapy reduced the risk of transformation significantly ($P=0.003$).[9]

None of the protocols is clearly superior with respect to OS; therefore, the choice of the regimen should be discussed with the patients on individual basis, considering their preferences and possible adverse reactions (infection rate, cytopenias, alopecia, and cardiotoxicity). If there is an evidence of a more aggressive lymphoma, based on histology (Grade 3B), clinical picture (dynamic or asynchronic progression) or PET-CT results R-CHOP should be considered.

Relapsing refractory (R/R) disease

Patients with a late relapse may be re-treated. Those R/R FL patients with POD24, as well as "double refractory patients" (to both alkylator agents and R), should be subjected to an alternative regimen.

Bendamustine with Obinutuzumab (BO) is an effective regimen, best for those who were not treated first-line with Bendamustine. In the GADOLIN study, where 77% of patients were "double refractory," <20% received 3 or more previous regimens, BO allowed to achieve a median PFS of 25.3 months.*[10] In the Idelalisib registration study, median PFS was 11 months, but 100% of patients were "double refractory," 70% resistant to Bendamustine and nearly 60% resistant to at least 3 previous regimens*[11] (Table 1). With a recent approval of the PI3K inhibitors Copanlisib and Duvelisib, followed by a better understanding of pneumonitis and viral infection prophylaxis, PI3K inhibitors became the backbone of R/R FL therapy in third and further therapy lines. Radioimmunotherapy results are still impressive (ORR 57%, median PFS—11 months), although it remains a niche therapy available for specialized centers.[12] Betalutin, a first-in-class antibody radionuclide conjugate which targets CD37 and has an improved efficacy and safety profile is being developed, but is not yet approved. The R2-regimen in R/R FL was explored predominantly in first or second relapse (ORR—76%, median PFS—24 months).[13] Moreover, administering Obinutuzumab with CC-122 (ceroblon inhibitor), a new immunomodulatory agent, revealed comparable response rate and a similar median PFS.[14]

The autologous or reduced-intensity conditioning allogenic stem cell transplants (ASCT, RIC allo SCT) may be considered in R/R cases. An analysis of 197 Grade 3 FL patients revealed that in the first 24 months post-transplant, ASCT was associated with improved OS ($P=0.005$), but in long-time survivors (beyond 24 months) it was associated with inferior OS ($P=0.04$). The increased nonrelapsed mortality of RIC allo SCT (4% vs. 27%, $P=0.001$) was compensated by a lower relapse/progression rate (61% vs. 20%, $P=0.0001$).[15]

Future perspectives

Introducing even better anti-CD20 antibodies and PI3K inhibitors were milestones in FL therapy. Moreover, other novel agents targeting cell surface molecules, intracellular pathways or the microenvironment have been developed and are currently under investigation in clinical trials. For instance, preliminary results, assessed 28 months after a CAR-T cell therapy, are very encouraging with 70% PFS and 93% OS in R/R FL patients who were failing 2 to 10 previous therapy lines.[16]

Overall, treating high-risk FL patients remains a great challenge and enrolling them to clinical studies might be the best way to improve the treatment regimens for these patients.

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