



Editorial

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Management of Follicular Lymphoma and the Role of Novel Agents Need to be Defined

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Submission: October 02, 2017; **Published:** October 05, 2017***Correspondence Address:** Nahla AM Hamed, Professor of Clinical Hematology, Faculty of Medicine, Alexandria University, Egypt, Email: drhamedn@hotmail.com**Abstract**

FL is a very heterogenous disease as would be expected by the diversity of mutation seen at genomic level and in the microenvironment from patient to patient. With the exception of limited-stage disease, FL is generally considered an incurable malignancy with a median life expectancy of approximately ten years. In patients for whom standard therapies fail, several novel agents are promising.

Abbreviations: FL: Follicular lymphoma; FLIPI: The Follicular Lymphoma International Prognostic Index; GELF: The Groupe d' Etude des Lymphomes Folliculaires; DLBCL: Diffuse Large B-cell lymphoma; DC-SIGN: Dendritic Cell-Specific Intercellular Adhesion Molecule-3-Grabbing Non-Integrin; CT: Computed Tomography, PET: Positron Emission Tomography; HBsAg: Hepatitis B Surface Antigen; HBcAb: Hepatitis B Core Antibody; LDH: Lactate Dehydrogenase; OS: Overall Survival; PFS: Progression-Free Survival; BR: Bendamustine-Rituximab; BCR: B-cell Antigen Receptor; GC: Germinal Center; AH SCT: Autologous Hematopoietic Stem Cell Transplantation.

Introduction

FL is the second most common NHL in the western world and is the most common indolent lymphoma [1]. It has an estimated incidence of 6 new cases per 100000 persons per year [2]. It typically occurs in mature and older adults [3]. FL arises in germinal centers and maintains [4] a resemblance to primary lymphoid follicles. The close association and interaction of the infiltrating immune cells, especially T cells, with the tumor B cells play an important part in determining the disease biology [5]. Despite advances in the treatment of FL, 15% to 28% of cases in 10 years will transform typically to DLBCL [3].

Pathobiology of FL

The pathobiology of FL is complex and involves cell-intrinsic genetic changes as well as alterations within the FL microenvironment [6]. The mutational landscape of FL is dominated by 2 recurrent alterations:

- i. The t(14;18) translocation and
- ii. Inactivating mutations of the MLL2 gene.

The t(14;18) translocation is present in 85-90% of FL patients. It results from repair failure during V(D)J recombination in bone marrow pre-B cells [1]. It places the BCL2 gene under the IGH regulatory elements. Dysregulation of BCL2 expression activates the antiapoptotic programs that are repressed by BCL6

in GC B cells. Inactivating mutations of MLL2 are found in >80% of FL and interfere with the ability of MLL2 to activate gene transcription [7]. t(14;18) and MLL2 inactivation appears to be an early event in FL, suggesting that epigenetic dysregulation combined with dysregulated BCL2 may drive the malignant transformation of GC B cells.

Mutations of the histone modifiers (CREBBP, EZH2, MEF2B, and EP300) are found in ~33%, 27%, 15%, and 9% of FL, respectively. Inactivating mutations of TNFRSF14 and loss of tumor suppressors TNFAIP3/A20 and EPHA7 contribute to the pathogenesis of FL [7]. Histone H1 genes, B-cell receptor signaling genes, STAT6, POU2F2, and others have also been identified [6]. Lectins within the microenvironment promote tumor survival at least in some FL subsets. The high-mannose glycans present in surface Ig (Mannosylated Igs) of FL interact with C-type lectins, including DC-SIGN expressed by dendritic cells and macrophages.

DC-SIGN binding to FL cells triggers BCR aggregation, intracellular Ca²⁺ increase, sustained phosphorylation of the kinases SYK, AKT, PLCγ2, and ERK1/2, and increased expression of cMYC. There is a dispute regarding the Ig isotype that can bind lectin and trigger activation of FL. BCRs of IgG+ FLs are more commonly self-reactive compared to those derived from IgM+ FLs. Treatment with anti-mannose antibodies or with glycomimetics

may disrupt tumor interaction with environmental lectins at least in some FL subsets [4].

Transformation occurs via the activation of known or putative oncogenes (MYC, CCND3) and inactivation of known or putative tumor suppressor genes (TP53, CDKN2A/B, B2 microglobulin). On the molecular level, higher numbers of single-nucleotide mutations, small insertions and deletions, copy-number changes, and structural rearrangements are found [2]. Clinically, FL is characterized by widespread disease at diagnosis, predominately involving lymph nodes, bone marrow and less commonly extranodal sites. Stage IV was the most common stage at presentation due to bone marrow infiltration [8]. The staging is performed according to the Ann Arbor classification system [3]. Transformation is characterized clinically by enlarging disproportionate masses, presence of B symptoms [2].

Investigation

Complete blood test, including chemistry and screening for HIV, HCV, and HBV must be done at baseline [3]. CT scan, PET-CT and a bone marrow aspirate and biopsy should be included for staging [7]. Grading of lymph node biopsies is performed according to a number of blasts/high power fields. Grade 1-2 FL is defined as <15 centroblasts per high-powered field, whereas grade 3 FL has >15 centroblasts per high-powered field. Grade 3 FL is further classified as 3A or 3B. FL3B is characterized by absence of centrocytes with frequent absence of t(14;18) and CD10 expression and increased p53 and MUM1/IRF4 expression [7]. Relatively rapidly (i.e., over the course of days to weeks) elevated serum LDH or calcium and acceleration of proliferation kinetics, for example, increased expression of Ki67 within the tumor or high levels of maximum standardized uptake value on PET scanning denote transformation [2].

Prognosis

With the exception of limited-stage disease, FL is generally considered an incurable malignancy [2] with a median life expectancy of approximately ten years [3]. Transformation of FL to DLBCL [3] is associated with poor prognosis [6]. The highly variable clinical course leads to difficulties in evaluating the prognosis and efficacy of therapy in individual patients [8].

Clinical Prognostic Tools

Ageing may be a possible reason for poorer outcome due to changes in drug pharmacokinetics and pharmacodynamics, deterioration of DNA-damage repair mechanisms and a decrease of both cellular mediated and humoral immune response. Moreover, older patients are more likely to develop cardiotoxicity, neurotoxicity, kidney injury, and mucositis [3].

FLIPI, FLIPI-2 and M7- FLIPI

The FLIPI developed in the prerituximab Era. It divided FL patients into three different classes of risk according to five parameters:

- i. Number of nodal sites of disease (>4);
- ii. Elevated LDH;
- iii. Age >60 years;
- iv. Stage III or IV disease; and
- v. Hemoglobin <12 g/dL.

The 10-year OS rates were 71% for low risk (0-1 factor), 51% for intermediate risk (2 factors), and 36% for high risk (>3 factors). FLIPI-2 index developed in the rituximab-chemotherapy era, identified age >60 years, elevated B2-microglobulin, hemoglobin <12 g/dL, bone marrow involvement, and lymph node diameter >6 cm as independent risk factors for PFS [7]. The M7- FLIPI which integrates seven gene mutations (EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, CARD11) with performance status and the FLIPI is prognostic in patients receiving chemo immunotherapy [9]. The FLIPI and FLIPI-2 are difficult to apply at an individual level [9] while M7- FLIPI merits further study [9].

Histological Grading

Grade I/II FL is considered as indolent lymphoma [10]. The clinical course of FL3A is similar to FL1-2 [7], while grade 3B FL is regarded as an aggressive NHL [10] with a clinical course more similar to DLBCL and no relapses beyond 5 years [7].

MRD

Patients achieving MRD negativity showed a significantly longer event-free survival. In the transplanted patients, higher percentage of MRD-negative cases after autologous transplantation remained relapse-free and alive than those persistently MRD-positive [11]. Gene expression signatures of the nonmalignant stromal cells were prognostically more important than that of the neoplastic B cells. The gene expressed by T cells was associated with favorable outcomes whereas the genes expressed by macrophages and follicular dendritic cells were associated with less favorable outcomes suggesting a role in dictating the disease course [7] and increasingly chemo-resistant relapses [1]. There are no prospectively validated biologic tools capable of identifying the highest risk groups or pathobiologic predictors of outcome in patients treated with monoclonal antibodies or non-cytotoxic therapies [9].

Predicting transformation remains a challenge, with no robust biomarker currently available in routine clinical practice [2]. Indeed, several genetic alterations, gene signatures, or immunohistochemical markers have been reported in the literature to be associated with transformation, but have not been sufficiently validated to warrant their assessment outside the research setting [2]. No treatment strategy appears to mitigate the risk of transformation [2]. A deeper understanding of tumor biology and evolution will open new avenues for the investigation of strategies aiming at circumventing it [2].

Treatment

The management of FL is mainly determined by histologic grading, clinical stage, and tumor burden [10]. The GELF criteria are commonly used to assess tumor burden. High-tumor-burden FL, include at least 1 of the following: 3 distinct nodal sites, each ≥ 3 cm; single nodal site ≥ 7 cm; symptomatic splenomegaly; organ compression or compromise; pleural effusions, ascites [12]. Asymptomatic or/and low-tumor-burden patients may be candidates for a strategy of watchful waiting [12]. There are no benefits on OS if starting immediately specific treatment in the absence of high-tumor-burden criteria [12]. For patients with stage I and II disease, an involved-site radiation therapy is recommended and may be potentially curative approach with 60% to 80% of 10-year OS rates. Patients with stage III and IV should be treated with systemic therapy [10].

The major indication for systemic therapy is symptomatic disease, threatened end organ function, cytopenia secondary to lymphoma bulky disease and steady progress etc [10]. Therapy is also indicated in the presence of 1 criteria of high-tumor-burden; B symptoms or any systemic symptoms; LDH or B2 microglobulin above the upper limit of normal [12]. Rituximab based chemoimmunotherapy is the standard of care of FL [8]. R-CVP, R-CHOP, and BR are recommended as initial regimen [10]. Rituximab significantly reduced the molecular tumor burden when administered after the CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) regimen [11]. It seems that R-CHOP may be preferred over R-CVP in patients with adverse prognostic features, and BR may be preferred to R-CHOP [10]. Individualized chemotherapy dose adjustment is essential for older patients [10].

Routine baseline and regular HBsAg and HBcAb testing is strongly recommended before the initiation of immuno-chemotherapy to minimize HBV reactivation which has been observed in approximately 20% to 50% of positive HBsAg patients and 3% to 45% of positive HBcAb patients. Prophylactic antiviral treatment in HBsAg-positive or HBcAb-positive patients is indicated before immuno-chemotherapy [10].

Since relapse is a common event, even in FL patients achieved complete remission after first-line therapy, maintenance or consolidation therapy is needed [12]. Rituximab maintenance for 2 years seems to be an effective strategy and should also be administered in elderly patients. However, the efficacy of rituximab maintenance depends on the clinical contexts and induction therapy used [12].

Relapsed FL

It is strongly recommended to obtain a new biopsy to exclude any transformation into an aggressive lymphoma [3]. Selection of salvage treatment depends on the efficacy of prior regimens. In early relapse (<12-24 months), a non-cross-resistant scheme should be preferred (e.g. bendamustine after CHOP or vice versa).

Other options, including fludarabine-based, platinum salts-based or alkylating agents-based regimens, could also be useful, but not applicable in older or unfit patients. Rituximab should be added if the previous anti-CD20 antibody-containing scheme achieved > 6-12-month duration of remission. In rituximab-refractory cases, second generation anti-CD20 antibodies such as obinutuzumab, improve PFS in comparison to chemotherapy alone [12].

The most appropriate time to perform AHSCT is subsequent to the second-line cytotoxic treatment, to obtain best survival benefit. The second-line chemotherapy in combination with rituximab followed by AHSCT produced a favorable 5-year survival rate of 90% [10]. Novel agents (such as new monoclonal antibodies, idelalisib, lenalidomide, and antiPD1 nivolumab), with a good safety profile, should be considered in early relapsed FL in elderly and frail patients [3].

Novel Agents

Disease factors such as duration of remission and patient factors such as age, comorbidities, and treatment preferences have to be taken into account. In patients for whom standard therapies fail, [13] novel agent such as ibrutinib is promising [10]. The US FDA has approved the novel PI3K copanlisib for the treatment of relapsed FL who had received at least two prior systemic therapies. The most common AEs (>20%) associated with copanlisib were decreased strength and energy (36%), diarrhea (36%), hyperglycemia (54%), hypertension (35%), leucopenia (36%), lower respiratory infections (21%), nausea (26%), neutropenia (32%) and thrombocytopenia (22%).

Serious AEs were reported in 26%. The most frequent serious AEs were hypoglycemia (5%), pneumonia (8%), and pneumonitis (5%). In 21% of patients, AEs resulted in dose reductions; in 16%, AEs resulted in treatment discontinuation [14]. The combination of a third PD-1-blocking antibody, pidilizumab and rituximab, in relapsed follicular lymphoma was well tolerated in a phase II study and induced an ORR and CR rate of 66 and 52 %, respectively. The ORR to the combination appeared promising compared to historical controls treated with rituximab alone [15].

Conclusion

Individualized management of FL remains challenging and the role of novel agents needs to be defined. Wide based studies are needed to expand our knowledge on molecular alterations associated with transformation.

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