ARC Journal of Hematology
Volume 2, Issue 1, 2017, PP 1-8
www.arcjournals.org

Follicular Lymphoma

Slavisa Ninkovic[1], Christopher McNamara*[1]

[1]Department of Hematology, University Colle ge London Hospital, London, United Kingdom

***Corresponding Author:** **Christopher McNamara,** Department of Hematology, University College London Hospital, London, United Kingdom E-mail: cmcnamara1@nhs.net*

Abstract: *FL is a highly heterogeneous disease with various outcomes and is characterised by a chronic, relapsing and remitting course. Upfront, patients may be presented with multiple treatment options including observation alone or chemo-immunotherapy.Further refinement in the understanding of the immune microenvironment and the genomic landscape of FL is likely to lead to more accurate prognostic tools that will allow for better stratification of patients and a more individualized and targeted treatment approach*

1. Introduction

Follicular lymphoma (FL) is the commonest indolent Non-Hodgkin's Lymphoma (NHL) in the United Kingdom with an estimated 1890 new cases per year.[1]The incidence increases with age with a median presentation in the 7th decade of life and a slight female: male predominance. It is generally considered an in - curable, though manageable, chronic hemato - logical malignancy characterized by a remitting and relapsing course. The 5-year overall (OS) and relative (RS) survival is estimated at 75.3% and 86.5% respectively, while the OS and RS in patients <65 years is 86.9% and 90% respectively and 49.2% and 70.2% in those ≥ 75 years of age.[1]

Patients frequently present without symptoms. Approximately 85% of patients have advanced stage disease (stage III or IV) at time of diagnosis with bone marrow involvement relatively common. Classical B symptoms of fevers, night sweats and significant weight loss as well as symptoms due to local mass effect from lymph node enlargement and bone marrow failure symptoms can also be observed.

Treatment of FL should be individualized whenever possible, and a therapeutic alliance with the patient from the outset is key as there are many potential treatment options such that a long term strategy and management plan with discussion of relative benefits and objectives of different treatment options is recommended. In addition, consideration must be given to poten - tial long-term complications such as myelodys - plastic syndrome and other secondarymal - ignancies, anthracycline induced cardio toxi - city and the effects on fertility in the younger patient.

2. Pathogenesis

In normal B-cell development, naïve B-cells, under the influence of T-cell dependent antigens, move to the germinal centre of lymphoid follicles becoming proliferating centroblasts. Centroblasts express CD10, BCL6 and low levels of BCL2 protein making their progeny susceptible to cell death through apoptosis. In the germinal centre, centroblasts mature into centrocytes via somatic hypermutation of the immunoglobulin (Ig) heavy and light chain variable regions and Ig class isotype switching.[2] In follicular lymphoma, at the molecular level, a characteristic *t*(14;18) translocation relocates the *BCL2* anti-apoptosis gene adjacent to an Ig promoter leading to the over-expression of BCL2 protein. This alone however is not sufficient for the development of FL and other genetic abnormalities, such as an inactivating mutation in the *MLL2* gene or rearrangement of the *BCL-6* gene are seen commonly.

3. Diagnosis of FL

All cases of FL require a histological diagnosis, ideally obtained by excisional lymph node biopsy or at the least multiple core biopsies providing adequate tissue to facilitate grading of tumor and exclusion of transformation to diffuse large B cell lymphoma (DLBCL), as well as ancillary investigations such as immuno-histochemistry, polymerase chain reaction (PCR) and fluorescent in situ hybridisation (FISH) where required. Fine needle aspiration of a suspicious lymph node is never sufficient and is not a recommended line of investigation.

Histologically, proliferation of neoplastic follicles in general leads to the distortion of normal nodal architecture and loss of normal zonal arrangement of lymphocytes. Grading of FL is based on the proportion of centroblasts in neoplastic follicles with the WHO classification identifying a low grade category of grade 1-2 (<15 centroblasts per high power field (HPF)) and grade 3 (>15 centroblasts per HPF). Grade 3 is further sub-classified according to the presence or absence of centrocytes with grade 3B solely composed of centroblasts. Histologically, grade 3B is indistinguishable from DLBCL and a diagnosis of grade 3B FL is clinically regarded as equivalent to a diagnosis of DLBCL.

Immunophenotypically, FL is characterised by a light chain-restricted population of B-cells expressing CD10, BCL6, BCL2, CD21, although higher grade FL can lose expression of CD10 and occasionally BCL2. Bone marrow involvement is seen in approximately half of all FL cases at presentation, typically consisting of para-trabecular aggregates of lymphoid cells showing follicle centre cell morphology. Cases with atypical clinical and/or pathological features should be confirmed with molecular investigations including PCR and FISH for IGH@/BCL2 translocations.

4. Disease Staging and Assessing Patient Fitness for Therapy

Staging via contrast enhanced computerized tomography (CT) of the neck, chest, abdomen and pelvis enables initial assessment of disease extent, identification of sites of bulky disease and facilitates the assessment of the Follicular Lymphoma International Prognostic Index (FLIPI). In addition, complete staging is essential in guiding initial treatment decisions, allows appropriate on-going disease monitoring and facilitates comparative post-treatment assessment. Magnetic resonance imaging (MRI) of the brain and spine should be performed if there is clinical suspicion of central nervous system (CNS) involvement and this should be complemented by examination of the cerebrospinal fluid. Retrospective studies suggest that 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) with CT increases the accuracy in initial staging with implications for treatment in some patients.[3] PET-CT may also be valuable in the evaluation of cases with suspected disease transformation and in response assessment after first-line therapy. PET-CT however is insensitive for bone marrow involvement and assessment via bone marrow aspirate and biopsy is required if documentation of bone marrow disease is important.

Additional investigations prior to commencement of immuno-chemotherapy focus on assessing the patient's fitness for treatment, both clinically and using relevant investigations like echocardiography. Lymphoma may arise in patients with previously undiagnosed HIV and prompt diagnosis and treatment of both is crucial to achieving optimal outcomes. Reactivation of hepatitis B may occur in chronic carriers and as such screening for these viruses is essential. In addition, fertility preservation should be considered in the relevant patient group prior to treatment commencement.

5. Prognosis

Clinical prognostic scores such as the FLIPI are used to identify patients with aggressive disease and the shortest remission times.[4] The index uses age >60 years, elevated serum LDH, haemoglobin <120 g/L, >4 nodal sites and advanced stage (III or IV) to predict overall survival. It has been validated prospectively in the rituximab (R) era while the FLIPI-2 is a prognostic score developed during the rituximab era and includes additional parameters of β_2-microglobulin, bone marrow involvement and nodal mass >6cm.[5]These indices however cannot be used to guide treatment and do not incorporate any biological data influencing the evolution of follicular lymphoma. An integrated clinico-genetic risk model, the m7-FLIPI, which includes high risk FLIPI score, poor ECOG performance status, and non-silent mutations in 7 genes known to be dysregulated in FL canidentify high- and low-risk groups of patients more robustly than FLIPI alone but is unable to predict early relapse.[6]To date, the strongest prognostic factor is duration of response following first-line immuno-chemotherapy with progression within two years of treatment associated with 50% 5-year OS, compared to 90% in patients who progress later.[7]

6. Management

6.1. Management of Limited Stage Disease

Localised FL (Ann Arbor stage I or contiguous stage II) is uncommon and needs to be confirmed using FDG-PET/CT and bone marrow biopsy. Due to the relative rarity of localised FL, there are no randomised studies to guide management. Options include observation

alone, combined modality chemoradiotherapy or radiotherapy alone. FLis highly radiosensitive and involved field radiotherapy delivering a dose of 24 Gy in 12 fractions usually results in prolonged disease-free progression (≥10 years), and may be curative in some cases. The majority of relapses occur outside the irradiated field. Combined modality therapy (chemoradio ther - apy) results in increased progression free survival (PFS) but no impact on overall survival (OS).[8]Observation alone in this group is associated with a 10-year OS of 86% which is non inferior to patients treated with radiotherapy [9]A retrospective review of the National Lymp - hoCare Study database of 471 stage I FL patients demonstrates no difference in OS between the different approaches in this group and treatment, therefore, should be patient-specific.[10] For example, observation may be appropriate for patients with no residual disease following an excisional biopsy in the frail patient with significant co-morbidities or in those wishing to avoid radiotherapy side effects.

6.2. Management of Advanced Stage Disease

Using the Group d'Etude des Lymphomes Folliculaires (GELF) criteria, patients with advanced stage FL can be divided into two main groups: asymptomatic with low tumour burden, and symptomatic with high tumour burden. GELF criteria for high tumour burden are met if at least one of the following is present: any nodal or extra-nodal tumour mass >7cm in diameter, involvement of at least >2 nodes in 3 nodal sites with each >3cm in size, presence of any systemic or B symptoms including ECOG performance status >1,symptomatic splenome - galy, organ compression, pleural or peritoneal serous effusion (irrespective of cell co ntent) or serum LDH or β_2-microglobulin level above normal. Other factors that must be considered include patient preference, age, co-morbidities and ultimate goals of therapy.

6.2.1. Asymptomatic/Low Tumour Burden

Randomised studies have shown there is no difference in OS in patients with asymptomatic advanced stage disease assigned to a 'watch and wait' approach when compared to cytotoxic chemotherapy including ProMACE-MOPP chemotherapy and total nodal irradiation, predmustine/interferon or chlorambucil monotherapy. [11-13] These studies were however performed in the pre-rituximab era and Ardeshna *et al.* Demonstrated that compared to 'watch and wait', single agent rituximab for 4 weekly doses or 4 weekly doses with two monthly maintenance for a period of 2 years leads to a significant prolongation in PFS and time to first chemotherapy but doesn't provide any survival benefit with OS of 95% in all three arms of the study.[14]Initial rituximabmono - therapy may also improve quality of life in patients finding it psychologically distressing to carry a diagnosis of a malignant condition and having observation as the main mode of treatment and as such this option should be discussed with all patients at diagnosis. When counseling patients, it is important to note that the median interval between diagnosis and needing chemotherapy is 31 months and nearly 20% of patients will not need chemotherapy for a decade following a diagnosis of FL.

6.2.2. Symptomatic/High Tumour Burden

Multiple studies have demonstrated the PFS and OS benefits of rituximab in front line therapy in this group of patients[15-20] but the optimal chemotherapy backbone is yet to be determined. The most common regimens include -CHOP (cyclophosphamide, doxorubicin, vincristine prednisolone), or -CVP (cyclophosphamide, vincristine, prednisolone). Bendamustine, an alkylating agent, has entered widespread clinical practice with a phase III study demonstrating that bendamustine- rituximab (BR) therapy results in longer median PFS (not reached vs. 40.9 months) with less serious toxicity compared to R-CHOP.[22] No difference in OS was shown in this study and others have shown BR to be non-inferior to R-CHOP/R-CVP with higher rates of gastrointestinal toxicity and drug hypersensitivity though less peripheral neuropathy and alopecia.[23]

Thus, the current standard of care for induction treatment is rituximab-based immuno-chemotherapy. Subsequently, the PRIMA study highlighted that FL patients achieving at least a partial response to R-chemotherapy benefit from R maintenance administered at at a dose of 375mg/m^2 every 2 months for a period of 2 years.[24] The benefits of maintenance include prolonged 2-year PFS (75% in the maintenance arm vs. 58% in the observation arm) and prolonged time to initiation of next anti-lymphoma therapy at the expense of an increased risk of grade 2-4 infections (39% vs. 24%; predominantly bronchitis, upper respiratory infections, sinusitis and urinary tract infections). The study did not demonstrate any survival benefit or difference in quality of life

and as such, the role of maintenance should be discussed and individualized for each patient.

Lenalidomide, an immune modulatory agent, exhibits direct anti neoplastic activity and modulates the tumour microenvironment. Twelve-month treatment with lenalidomide and rituximab in patients with newly diagnosed FL results in an ORR of 98% with a CR rate of 87% and a 3-year PFS of 79%.[25] The treatment was well tolerated with grade 1 or 2 fatigue common but not dose limiting, grade >3 neutropenia observed in 35% patients with rash in >40% patients during the first two cycles of treatment. Currently, an international phase III study (RELEVANCE) comparing lenalidomide and rituximab to R-chemotherapy (-Bendamustine, -CHOP or –CVP) is closed to recruitment and results are awaited.

Latterly, obinutuzumab (GA101:G), a humanised, glyco-engineered type II anti-CD20 monoclonal antibody with enhanced direct cell killing and antibody-dependent cellular cytotoxicity has been shown to have promising activity when combined with bendamustine in rituximab-refractory indolent NHL.[26]Results from an interim efficacy analysis of the GALLIUM study assessing G-chemotherapy followed by G maintenance compared to R-chemotherapy followed by R maintenance in untreated advanced stage FL were reported recently.[27] After a median follow-up of 34.5 months, there was a 34% reduction in risk of disease progression or death in the obinutuzumab treated group (Hazard ratio (HR) = 0.66; 95% CI 0.51, 0.85; p=0.001). The investigator-assessed estimated 3-year PFS was reported as 80% in the G-chemotherapy and 73.3% in the R-chemotherapy groups (p=0.001) with no difference in OS; 94% and 92.1% respectively. Frequency of grade 3-4 adverse events including infusion-related reactions, cytopenias and infections were higher in the G-chemotherapy group. The final results of the GALLIUM study, when reported, may lead to G-chemotherapy becoming the new standard of care over R-chemotherapy in this group of patients.

6.3. Relapsed and Refractory Disease

Despite high rates of initial response, most FL patients relapse and in general, the goals of re-treatment are similar to that at diagnosis which are to optimise OS while preserving quality of life. Of importance to the general discussion with patients is that the likelihood of response and duration of response generally decreases with each subsequent line of treatment.

The type of re-treatment utilised depends on the type and duration of response following initial treatment. Bendamustine monotherapy in rituximab-refractory NHL results in an overall response rate (ORR) of 75% with a median PFS of 9.3 months.[28] Rituximab should be added to patients who are rituximab naïve and in those who had initial rituximab based therapy if duration of response was >6 months. Rituximab monotherapy results in an ORR of 69% (95% CI 53%-82%) with a 15.6 month median PFS in patients with relapsed or refractory NHL, 89% of which had FL.[29]Maintenance rituximab in patients previously exposed to maintenance following upfront therapy has not been investigated in a phase III trial.

Patients who respond inadequately to conventional regimens should be considered for treatment with new, targeted agents, preferably within the setting of a clinical trial. These include novel anti-CD20 monoclonal antibodies (e.g. obinutuzumab), immunomodulatory agents (e.g. lenalidomide) and small molecule inhibitors (e.g. ibrutinib, a BTK inhibitor; venetoclax, a BCL-2 inhibitor; and idelalisib, a PI3-kinase inhibitor). Combination obinutuzumab and bendamustine in rituximab-refractory NHL cases results in significant prolongation of PFS (not reached vs. 14.9 months, HR 0.55; p=0.0001). [26]Similarly, patients refractory to both rituximab and alkylating agents achieved a 57% response rate following idelalisib therapy, with a median response duration of 12.5 months.[30] Idelalisib therapy however was associated with grade 3 or greater diarrhoea and/or colitis in 16% of patients, occurring at a median of 6 months. Furthermore, combination idelalisib and lenalidomide therapy was associated with severe, and in some cases fatal hepatotoxicity and immune dysregulation.[31] Patients with localised, symptomatic disease may also be considered for palliative radiotherapy, delivering doses of 4Gy to 24Gy.

6.4. Stem Cell Transplantation in FL

High dose chemotherapy with autologous stem cell rescue (autoSCT) as first line therapy for FL patients in first remission has in some studies been shown to prolong PFS but leads to no OS

benefit and is associated with higher rates of long-term toxicity including a considerable increased risk of secondary malignancy, such that outside of a clinical trial setting, upfront autoSCT is not recommended.[32-35]Patients achieving remission following second-line or, less preferably, subsequent therapy, if fit enough, should be considered for autoSCT.[35]AutoSCT is an appropriate option especially in those with short responses after immuno-chemotherapy or with high risk FLIPI and is associated with improved 3-year overall survival, 92% (95% CI 78%-97%) compared to 63%(95% CI 51-72%) in those treated without autoSCT.[36] Other studies have demonstrated a plateau in the PFS curve, with around one third of patients being alive without disease at 10 years.[37] While autoSCT may prolong PFS it is not considered curative in nature. Myeloablative allogeneic stem cell transplantation (alloSCT) may offer longer term disease control but has a higher treatment associated mortality. Reduced-intensity conditioning (RIC) and T-cell depletion with alemtuzumab was associated with a 15% non-relapse mortality, a 76% 4-year PFS (90% for those with sibling donors), and low rates of graft-versus-host disease.[38] At this stage, a RIC alloSCT should be considered in suitable patients with relapse post autoSCT but there is no consensus as to when a RIC alloSCT should be preferred over autoSCT in patients with poor prognosis FL.

6.5. Transformed Disease

Transformation to aggressive large cell lymphoma is seen in approximately 2-3% of FL patients per year and histological assessment may be necessary in patients at time of a presumed relapsed FL depending on patient presentation with rapidly enlarging lymphadenopathy, high serum LDH or extra-nodal disease increasing the suspicion for transformation.[39]PET-CT imaging may also suggest transformation and may help identify target lesions for biopsy. Based on a retrospective review of 2652 FL patients, the risk of transformation is similar in patients treated upfront with either R-CHOP or R-CVP and reduced in patients having rituximab maintenance.[39] Treatment in these cases is individualised as there are no randomised studies to guide management. The young, fit patient who is anthracycline naïve should have R-CHOP based induction therapy followed by consolidation autoSCT or platinum-based salvage chemotherapy in patients previously exposed to anthracyclines. Older patients can be considered for modified mini-CHOP or alternative regimens like R-CEOP or R-CVGP. Recent reports on outcomes in patients with high grade transformation in the era of immuno-chemotherapy are better than previously thought with a median OS of 50 months and 5-year OS of 73%.[40,41]

7. Conclusions and Future Direction

FL is a highly heterogeneous disease with various outcomes and is characterised by a chronic, relapsing and remitting course. Upfront, patients may be presented with multiple treatment options including observation, single-agent rituximab, radiotherapy or various combinations of immuno-chemotherapy. With increased understanding of the immune microenvironment and the genomic landscape contributing to aberrant signaling via the B-cell receptor, more accurate clinico-pathologic prognostic tools will allow better stratification of patients and a more individualised, targeted treatment approach.

References

[1] Patmore R, Roman E, Smith A, Appleton S, Bagguley T, Blase J. Patient's age and treatment for haematological malignancy: a report from the Haematological Malignancy Research Network. 2014.

[2] Basso K, Dalla-Favera R. Germinal centres and B cell lymphomagenesis. Nat Rev Immunol 2015; 15(3): 172-84.

[3] Smith SD, Redman M, Dunleavy K. FDG PET-CT in follicular lymphoma: a case-based evidence review. Blood 2015; 125(7): 1078-82.

[4] Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004; 104(5): 1258-65.

[5] Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009; 27(27): 4555-62.

[6] Pastore A, Jurinovic V, Kridel R, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. Lancet Oncol 2015; 16(9): 1111-22.

[7] Casulo C, Byrtek M, Dawson KL, et al. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015; 33(23): 2516-22.

[8] Seymour JF, Pro B, Fuller LM, et al. Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2003; 21(11): 2115-22.

[9] Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2004; 22(8): 1454-9.

[10] Friedberg JW, Byrtek M, Link BK, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012; 30(27): 3368-75.

[11] Young RC, Longo DL, Glatstein E, Ihde DC, Jaffe ES, DeVita VT, Jr. The treatment of indolent lymphomas: watchful waiting v aggressive combined modality treatment. Semin Hematol 1988; 25(2 Suppl 2): 11-6.

[12] Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1997; 15(3): 1110-7.

[13] Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet 2003; 362(9383): 516-22.

[14] Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncol 2014; 15(4): 424-35.

[15] Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005; 106(12): 3725-32.

[16] Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008; 26(28): 4579-86.

[17] Herold M, Dolken G, Fiedler F, et al. Randomized phase III study for the treatment of advanced indolent non-Hodgkin's lymphomas (NHL) and mantle cell lymphoma: chemotherapy versus chemotherapy plus rituximab. Ann Hematol 2003; 82(2): 77-9.

[18] Bachy E, Houot R, Morschhauser F, et al. Long-term follow up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. Haematologica 2013; 98(7): 1107-14.

[19] Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. Blood 2008; 112(13): 4824-31.

[20] Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst 2007; 99(9): 706-14.

[21] Federico M, Luminari S, Dondi A, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013; 31(12): 1506-13.

[22] Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013; 381(9873): 1203-10.

[23] Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of

indolent NHL or MCL: the BRIGHT study. Blood 2014; 123(19): 2944-52.

[24] Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011; 377(9759): 42-51.

[25] Fowler NH, Davis RE, Rawal S, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. Lancet Oncol 2014; 15(12): 1311-8.

[26] Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol 2016; 17(8): 1081-93.

[27] Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: Primary results of the randomized phase 3 GALLIUM study. American Society of Haematology San Diego, CA.; 2016

[28] Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a Multicenter Study. Cancer 2010; 116(1): 106-14.

[29] Tobinai K, Igarashi T, Itoh K, et al. Rituximab monotherapy with eight weekly infusions for relapsed or refractory patients with indolent B cell non-Hodgkin lymphoma mostly pretreated with rituximab: a multicenter phase II study. Cancer Sci 2011; 102(9): 1698-705.

[30] Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. The New England journal of medicine 2014; 370(11): 1008-18.

[31] Cheah CY, Nastoupil LJ, Neelapu SS, Forbes SG, Oki Y, Fowler NH. Lenalidomide, idelalisib, and rituximab are unacceptably toxic in patients with relapsed/refractory indolent lymphoma. Blood 2015; 125(21): 3357-9.

[32] Lenz G, Dreyling M, Schiegnitz E, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. Blood 2004; 104(9): 2667-74.

[33] Deconinck E, Foussard C, Milpied N, et al. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. Blood 2005; 105(10): 3817-23.

[34] Sebban C, Mounier N, Brousse N, et al. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). Blood 2006; 108(8): 2540-4.

[35] Montoto S, Corradini P, Dreyling M, et al. Indications for hematopoietic stem cell transplantation in patients with follicular lymphoma: a consensus project of the EBMT-Lymphoma Working Party. Haematologica 2013; 98(7): 1014-21.

[36] Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2003; 21(21): 3918-27.

[37] Rohatiner AZ, Nadler L, Davies AJ, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow-up. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2007; 25(18): 2554-9.

[38] Thomson KJ, Morris EC, Milligan D, et al. T-cell-depleted reduced-intensity transplantation followed by donor leukocyte infusions to promote graft-versus-lymphoma activity results in excellent long-term survival in patients with multiply relapsed follicular lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010; 28(23): 3695-700.

[39] Wagner-Johnston ND, Link BK, Byrtek M, et al. Outcomes of transformed follicular lymphoma in the modern era: a report from the National LymphoCare Study (NLCS). Blood 2015; 126(7): 851-7.

[40] Montoto S, Davies AJ, Matthews J, et al. Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2007; 25(17): 2426-33.

[41] Link BK, Maurer MJ, Nowakowski GS, et al. Rates and outcomes of follicular lymphoma transformation in the immunochemotherapy era: a report from the University of Iowa/MayoClinic Specialized Program of Research Excellence Molecular Epidemiology Resource. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013; 31(26): 3272-8

Citation: *Slavisa Ninkovic, Christopher McNamara. Follicular Lymphoma. ARC Journal of Hematology. 2017; 2(1):1–8.*