Special Article

Follicular lymphoma – treatment and prognostic factors

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Follicular lymphoma is the second most frequent non-Hodgkin lymphoma accounting for about 10-20% of all lymphomas in western countries. The median age at diagnosis is 60 years old. The clinical presentation is usually characterized by asymptomatic peripheral adenopathy in cervical, axillary, inguinal and femoral regions. Treatment options for patients with naïve or recurrent follicular lymphoma are still controversial, ranging from a "watch and wait" policy to hematopoietic stem cell transplantation. More recently, the availability of rituximab has substantially changed follicular lymphoma therapeutic approaches to such an extent that R-Chemo is now the standard induction first-line treatment. This review provides a general overview of the state of the art in the management of follicular lymphoma and also, a brief description regarding the current prognostic tools available for treatment decisions.

Keywords: *Lymphoma, follicular/drug therapy; Antineoplastic combined chemotherapy protocols/ therapeutic use; Doxorubicin/therapeutic use; Lymphoma, non-Hodgkin; Antibodies, monoclonal; Prognosis*

Introduction

Follicular lymphoma (FL) is the second most frequent non-Hodgkin lymphoma accounting for about 10-20% of all lymphomas in western countries. The median age at diagnosis is 60 years old and there is a slight predominance in women.(1)

Clinical presentation is characterized by asymptomatic peripheral adenopathy in cervical, axillary, inguinal and femoral regions. Also, waxing and waning lymph node enlargement for years is common. Bone marrow involvement is present in more than 50% of patients. The disease is usually characterized by an indolent clinical course response to initial therapy with frequent relapses and shorter duration responses to salvage therapy.(2)

Treatment options for patients with naïve or recurrent FL are still controversial, ranging from a "watch and wait" policy to hematopoietic stem cell transplantation. More recently, the availability of rituximab has substantially changed FL therapeutic approaches, to such an extent that R-chemo is now the standard induction first-line treatment. The introduction of rituximab is considered to be at least partly responsible for the improved median overall survival (OS).(3-5)

This review will provide a brief description regarding the current prognostic tools available for treatment decisions and a general overview of the state of the art in the management of limited and advanced FL.

Prognostic factors

So far, only a few biological parameters have been validated for defining prognosis in patients with FL that are currently managed according to their clinical and laboratory features. The most important parameters for defining treatment when a new FL is diagnosed are the patient's conditions and the extent of disease.

A patient's status is usually established by assessment of age and performance status, which have been widely confirmed as independent prognostic factors.(6,7) Disease extension is usually acknowledged as one the most important prognostic factors for patients with FL. It can be assessed either directly by means of the Ann Arbor staging system or indirectly by means of surrogates such as tumor burden, bulky disease and bone marrow involvement. In addition to Ann Arbor Staging, and mainly for patients with advanced disease, single clinical parameters contributing to the quality of advanced stage have been correlated with prognosis; these include the number of nodal or extranodal sites of disease, the presence and the extent of bone marrow involvement,

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the involvement of certain specific locations, or the presence of a large tumor diameter. Clinical and laboratory parameters have also been investigated as indirect or surrogate measures of lymphoma extent and are considered to be independent prognostic variables in different prognostic models. These parameters include the presence of B-symptoms, low hemoglobin level (< 10 g/dL), elevated erythrocyte sedimentation rate (ESR), lactic dehydrogenase (LDH) and β2-microglobulin (B2M) values (above normal).[8]

Prognostic scores

There are currently several prognostic indexes that have been developed to predict survival of FL patients. The most relevant among these were developed by the Italian Lymphoma Intergroup (ILI)[6] and the International Follicular Lymphoma Prognostic Factor Project (IFLPFP).[7] The ILI score is based on the independent prognostic roles of age, gender, B symptoms, number of extranodal sites, ESR and LDH. These 6 variables defined a prognostic model with 3 risk groups associated with different 5- and 10-year survival rates. The advantages of the ILI model over the International Prognostic Index (IPI) model are the remarkably higher discriminating power between groups and the ability to identify a higher number of under 60-year-old patients with a poor prognosis. The IFLPFP score was developed more recently as the result of a large international cooperative effort. The score was defined on a training series of 1795 patients and was based on five risk factors: age, Ann Arbor stage, hemoglobin level, number of nodal site areas and serum LDH level. Based on the final model, patients with 0 or 1 vs. 2 risk factors were characterized by 5-year OS of 91% and 78%, respectively; while those with 3 or more risk factors, who represented 27% of all cases, had 5- and 10-year OS rates of 53% and 36%, respectively.[7] When IFLPFP scores were also tested between under and over 60-year-old patients, with the exception of age, the previously identified risk factors remained independent prognostic factors.

In 2003 the IFLPFP started a study which was aimed at verifying whether a prospective collection of data would succeed in developing a more accurate prognostic index. The final results of the study, which accrued 1093 new FL cases between 2003 and 2005 registered at 69 European and American Institutions, have been recently disclosed. Progression free survival (PFS) was chosen as the main efficacy endpoint in order to provide a clinically useful index and to allow for an acceptable factor/event ratio necessary to perform a reliable multivariate analysis. Of note, rituximab was used in 60% of patients, either as a single agent or in combination chemotherapy.[9] This new scoring system is based on the identification of 5 parameters, including age, bone marrow involvement, hemoglobin level, B2M value and longest diameter of largest lymph node (Table 1). Based on the number of risk factors, patients were stratified into 3 risk groups: score 0 (20%): low risk; score 1-2 (53%): intermediate risk; and score 3-5 (27%): high risk. The 5-year PFS rates were 79%, 51%, and 20%, respectively for each risk category (p-value < 0.00001) The model was also predictive of PFS in patients treated either with or without rituximab (p-value < 0.0001). The 3-year survival rates were 99%, 96%, and 84%, respectively, for each risk category.

Table 1 - Comparison between ILI, IFLPFP and IFLPFP2: distribution of patients according to risk, based on the original published data

	ILI[6]	IFLPFP[7]	IFLPFP2[9]
Model definition			
	Age > 60 yrs	Age > 60 yrs	Age > 60 yrs
	ENS > 2	-	-
	Elevated LDH	Elevated LDH	-
	-	Stage III-IV	-
	-	Nodal sites > 4	-
	Male gender	-	-
	-	Hb level < 12 g/dL	Hb level < 12 g/dL
	B symptoms	-	-
	ESR > 30 mm/h	-	-
	-	-	Elevated B2M
	-	-	LoDLIN > 6 cm
	-	-	BMI
Period of enrolment			
	1985-1996	1985-1992	2003-2005
Initial study population (patients)			
	987	5120	1093
Model population (patients)			
	429	1795	832
Median follow-up (months)			
	54	90	38
5-year overall survival (%)			
	77	71	88
Endpoint			
	OS	OS	PFS
Patient distribution (%)§			
Low risk	64	36	20
Intermediate risk	23	37	53
High risk	13	27	27
5-year survival* according to risk (%)§			
Low risk	90	91	79
Intermediate risk	75	78	51
High risk	38	53	20

ILI - Italian Lymphoma Intergroup
IFLPFP - International Follicular Lymphoma Prognostic Factor Project
IFLPFP2 - International Follicular Lymphoma Prognostic Factor Project (phase-2 study)
ENS: Extra Nodal Sites; LDH: Lactic Dehydrogenase; Hb: Hemoglobin; B2M: β2-Microglobulin; LoDLIN: Longest diameter of the largest involved node; BMI: Bone Marrow Involvement; ESR: Erythrocyte Sedimentation Rate; OS: Overall Survival; PFS: Progression Free Survival
§ = Low risk = 0-1 for ILI and IFLPFP and 0 for IFLPFP2; Intermediate risk = 2 for ILI and IFLPFP and 1-2 for IFLPFP2; High risk = 3-5 for all indexes. * OS for ILI and IFLPFP, PFS for IFLPFP2

Treatment strategies in limited stage follicular lymphoma

Approximately 10-20% of FL patients present in limited stages (I-II) and half of them could enjoy durable remission after treatment with involved field radiation therapy (RT). In a population large study of the Surveillance, Epidemiology and End Results (SEER database) of 6568 patients with stage I and II diagnosed from 1973-2004, patients who received RT enjoyed higher 5- (90% versus 81%), 10- (79% versus 66%) and 20-year (63% versus 51%) disease-specific survival rates

and also of 5- (81% versus 71%), 10- (61% versus 48%) and 20-year (35% versus 23%) overall survival rates, when compared with other therapeutic approaches.[10]

Moreover, in selected stage I and II patients, deferred therapy is an acceptable approach. In a retrospective analysis from Stanford University, more than half of patients remained untreated at a median of 6 or more years, and survival was comparable to that observed in patients undergoing immediate treatment.[11]

Treatment strategies in advanced follicular lymphoma

The vast majority of patients have advanced disease at diagnosis and the current approach is to offer immediate treatment only for patients presenting with active or symptomatic disease (Table 2). This approach is supported by randomized clinical trials that compared observation (watch and wait) versus immediate treatment which show that immediate treatment does not yield longer survival.[12-14] At present, the open question is whether these conclusions are still valid in the era of rituximab and only randomized clinical trials will be able to answer this.

Monotherapy with rituximab

The availability of a single agent, rituximab, represents a tempting choice for patients especially for those who have been selected for treatment deferral. The use of rituximab as a monotherapy in low tumor burden FL patients has recently been addressed in a randomized clinical trial conducted by Ardeshna et al.[15] The preliminary results of the study showed that immediate use of rituximab significantly prolonged time to initiation of new therapy compared to watchful waiting. The investigators reported that rituximab was well tolerated and had no impact on quality of life; however no differences in terms of OS has been described as yet thus it still remains to be proven if immediate treatment with rituximab in patients with low tumor burden FL will really be beneficial.

Front-line immunochemotherapy

The benefit of adding rituximab to combination chemotherapy has been established in some randomized trials. All of them have shown improvements in response rates, time to progression or overall survival (Table 3).[16-19]

Table 2 - A comparison between *Groupe d'Etude des Lymphomes Folliculaires* (GELF) criteria, British National Lymphoma Society (BNLI) criteria and criteria of the *Società Italiana di Ematologia* (SIE) and affiliated societies *Società Italiana di Ematologia Sperimentale* (SIES) Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

GELF criteria	BNLI criteria	SIE/SIES/GITMO criteria
High tumor bulk defined by either: a tumor > 7 cm > 2 nodes in 3 distinct areas each > 3 cm Symptomatic splenic enlargement Organ compression Ascites or pleural effusion	Rapid generalized disease progression in the last 3 months Life threatening organ involvement Renal or macroscopic liver infiltration Bone lesions	Extranodal disease Spleen enlargement Leukemic phase Serous effusions Nodal or extranodal mass > 7 cm > 2 nodal masses, each > 3 cm
Presence of systemic symptoms (ECOG performance status > 1)	Presence of systemic symptoms or pruritus	B Symptoms Presence of systemic symptoms (ECOG performance status >1) Discomfort due to tumor masses
Serum lactate dehydrogenase or β2-microglobulin above normal values	Hemoglobin < 10 g/dL or white blood cell count < 3.0 x 10^9 related to bone marrow involvement	Serum lactate dehydrogenase or β2-microglobulin above normal values Erythrocyte sedimentation rate above normal value Cytopenia due to bone marrow infiltration

ECOG: Eastern Cooperative Oncology Group

Table 3 - Randomized clinical trials comparing chemotherapy versus chemotherapy plus rituximab in front-line therapy for follicular lymphoma patients

	Regimens	OS control	OS R-Chemo
Hiddeman et al.[16]	CHOP versus R-CHOP	90% in 2 years	95% in 2 years*
Herold et al.[17]	MCP versus R-MCP	74% in 4 years	87% in 4 years*
Marcus et al.[18]	CVP versus R-CVP	77% in 4 years	83% in 4 years*
Salles et al.[19]	CHVP-I versus R-CHVP-I	79% in 5 years	84% in 5 years **

OS: Overall survival; CVP: Cyclophosphamide, vincristine and prednisone; CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisone; MCP: Mitoxantrone, chlorambucil and prednisone; CHVP-I: Cyclophosphamide, adriamycin, etoposide, and prednisolone plus interferon-α2a ; R: Rituximab

*Statistically significant. ** Not statistically significant for all patients, only high risk patients

Currently, the open question is what is the best chemotherapy regimen to add to rituximab? The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) is by far the most used.[20] However CVP (cyclophosphamide, vincristine, prednisone) and fludarabine-containing regimens are also adopted. The FOLL05 trial by the *Fondazione Italiana Linfomi* (FIL) was recently concluded with the enrollment of 534 patients. This study compared R-CVP, R-CHOP and R-FM in stage II-/IV FL patients. In the preliminary analysis presented at the XI International Conference on Malignant Lymphoma, Lugano in 2011, it was shown that R-CVP was associated to an inferior 3-year time to treatment failure (TTF) (47%) compared to R-FM (60%) and R-CHOP (57%). In addition, R-CHOP had an anti-lymphoma activity similar to R-FM but a better toxicity profile and may now be considered the standard regimen in the treatment of patients with advanced FL.[21]

Other combinations of chemotherapeutic agents with rituximab have been reported. Bendamustine plus rituximab (B+R) was compared to R-CHOP in patients with advanced FL, mantle cell, and other indolent lymphoma subtypes. B+R yielded a higher complete remission rate (40% versus 30%, p-value = 0.03) and also a longer PFS (55 months versus 35 months, p-value < 0.01) compared with R-CHOP. In addition to the improved outcome, patients treated with B+R had significantly lower toxicity both in terms of hematological and extra-hematological events.[22] If these results are confirmed it is likely that R+B will become, in the near future, an important treatment option for patients with newly diagnosed FL, in particularly for the elderly.

Maintenance

The use of maintenance strategies after initial treatment in FL has been considered over a long time. The use of interferon was evaluated and showed benefits in terms of duration of remission and survival; however the safety profile of the drug and the low manageability of treatment has led most physicians to abandon this treatment option.[23] The availability of rituximab as a single effective and low-toxicity agent has suggested the possibility of using it not only to improve efficacy of chemotherapy but also to delay progression after initial treatment.

So far, maintenance with rituximab has been mostly considered in relapsed and refractory FL patients. Recently the results of the PRIMA trial were published providing data on the use of maintenance also after first line therapy.[20] The study included 1217 patients with previously untreated FL needing systemic therapy. Patients received one of three non-randomized immunochemotherapy induction regimens used in routine practice. After induction therapy, 1019 patients achieving a complete or partial response were randomly assigned to receive 2 years of rituximab maintenance therapy (375 mg/m^2) every 8 weeks or observation. The primary endpoint was PFS. With a median follow-up of 36 months, PFS was 74.9% in the rituximab maintenance group and 57.6% in the observation group. Overall survival did not differ significantly between groups (Hazard ratio - HR: 0·87; 95% confidence interval - 95% CI: 0·51-1·47).[20]

In a recent meta-analysis, a search of the electronic databases up to December 31 2010 was performed and nine trials and 2586 FL patients were included. Refractory or relapsed FL patients (i.e. previously treated) treated with rituximab maintenance had improved OS and PFS compared with those without maintenance (pooled HR of death = 0.72; 95% CI = 0.57 - 0.91), whereas previously untreated patients had no overall survival benefit (pooled HR of death = 0.86; 95% CI = 0.60 to 1.25).[24]

Another new post-induction alternative is the use of radioimmunotherapy (RIT) with the anti-CD20 monoclonal antibodies tositumomab, which is conjugated to 131-iodine, or ibritumomab tiuxetan, which is linked to 90-yttrium.[25] One large randomized trial evaluated the efficacy and safety of consolidation with 90-yttrium (Zevalin) in patients with advanced-stage FL in first remission. Patients who achieved a complete response, unconfirmed complete response or partial response after first-line induction treatment, were randomly assigned to receive 90Y-ibritumomab tiuxetan or observation. Consolidation with 90 Y-ibritumomab tiuxetan significantly prolonged median PFS in all patients (36.5 versus 13.3 months in control arm).[26]

Salvage therapy

A number of salvage treatments are currently available and may still have a chance to control relapsed, recurrent, or resistant FL including chemoimmunotherapy regimens not used in first-line, rituximab alone, single-agent alkylators or a variety of nonstandard options; these are to be considered on a patient-by-patient basis. In any case, based on the results of randomized trials and of a recently published meta-analysis, patients with relapsed/progressive FL who respond to salvage immuno-chemotherapy should receive maintenance treatment with rituximab to reduce the risk of progression and of death.[24,27]

The role of stem cell transplantation (SCT) remains an important option in relapsed/progressed patients. Since allogeneic SCT is not available for most patients and does not guarantee better results overall,[28] autologous SCT is most frequently used following high-dose chemotherapy conditioning. Autologous SCT achieves long lasting remission showing a plateau in long-term FL survival curves.[29,30] Moreover autologous SCT seems to succeed independent of the tumor grade[31] and is not adversely affected by the introduction of rituximab in chemo-immunotherapy regimens used before transplantation (PFS at 5 years: 65% versus 33%; p-value < 0.0001).[31-33]

Novel agents and ongoing clinical trials

One novel and yet well-established therapeutic option for relapsed/refractory FL patients is RIT. Literature concerning RIT has convincingly shown that single-agent, radioconjugated monoclonal antibodies are more effective than single-agent rituximab in terms of complete response (30% versus 16%; p-value < 0.04) and overall response rates (80% versus 56%; p-value < 0.002)[34] but are also more myelosuppressive.[35]

Several new agents with different mechanisms of action are currently being studied. Some of them are already in advanced stage of clinical development and will soon be made available to clinical practice. Among them the most interesting results have been obtained with a new generation of humanized anti CD20 monoclonal antibodies that will hopefully have higher anti-lymphoma activity with unchanged safe toxicity profile compared with rituximab (Table 4).

Table 4 - New agents that are currently investigated in follicular lymphoma

Target	Type	Agents
Proteasome	Proteasome inhibitor	Bortezomib, carfilzomib, NPI 00-52
CD 19	MoAb	Blinatumomab
CD20	MoAb	Ofatumumab, IMMU-06, ocrelizumab, GA101
CD22	MoAb	Epratuzumab, inotuzumab, ozogamicin
CD40	MoAb	SGN-40 (dacetuzumab)
CD80	MoAb	Galiximab
DNA	Cytotoxic	Bendamustine
Unknown	IMiD	Lenalidomide
HDAC	HDAC inhibitor	MGCD0103, vorinostat, panobinostat, belinostat, romidepsin
Syk	Syk inhibitor	Fostamatinib
m-TOR	m-TOR inhibitor	Temsirolimus, everolimus
Bcl-2 family	Anti-apoptosis	Oblimersen sodium, obatoclax mesylate, ABT-263

MoAb: Monoclonal antibody; HDAC: Hystone deacetylase; IMiD: Immunomodulatory derivatives

Conclusions

The recent history of FL has shown that the outcome of patients has dramatically changed in recent years, mainly due to the use of very effective immunochemotherapy regimens. Further improvements are likely to affect patients with FL. These will probably come from the identification of new and more effective monoclonal antibodies, by the identification of safer chemotherapy regimens and by the adoption of maintenance therapies. Moreover a better definition of the patient's individual status and prognosis, will come from the study of tumor biology and from the use of highly sensitive techniques such as minimal residual disease analysis and PET and will contribute to improve the outcomes of future patients.

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