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Review Article

Prognosis of follicular lymphomas

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Abstract

Follicular lymphoma (FL) is as an indolent neoplasia with median survival measured in decades. Nevertheless, some patients have poor progression-free survival and overall survival. Several treatment approaches are proposed for patients with FL, however criteria to rationalize treatment decisions are lacking. Studies have been performed to build up prognostic indices that are useful for defining risk-adapted treatment recommendations. Available indices are based on parameters that have an independent role in predicting patient survival and that are variably correlated with the features of the disease, with the characteristics of the patient and with the effects of treatment. Two new prognostic indices have recently been proposed for FL: the Italian Lymphoma Intergroup (ILI) index and the Follicular Lymphoma International prognostic Index (FLIPI). Both indices are based on large series of patients and exhibit differences in their ability to discriminate between patients with different probabilities of survival. In recent years, with the advent of gene expression profile studies, our knowledge of the biology of FL is changing as novel data become available about the lymphoma cell and about the role of the microenvironment; these studies have already provided novel prognostic tools for identifying patients with more aggressive disease. Further data and large international cooperative studies are needed to translate into clinical practice the novel acquisitions of biology and therapeutics. Copyright © 2006 John Wiley & Sons, Ltd.

Keywords: **follicular lymphoma; prognostic factors; prognostic index**

Introduction

Follicular lymphoma (FL) is the second most common type of non-Hodgkin's lymphoma, accounting for 15–20% of all cases [1]. The clinical course of FL is variable: in some patients the disease is indolent and slowly progressive over a period of many years, with waxing and waning lymphoadenopathy; in others, disease progresses rapidly, often with transformation to aggressive lymphoma, with survival of less than 1 year. Although patients with FL have relatively long median survival time and exhibit dramatic responses to initial therapy, they should be considered as being affected by a fatal malignancy. Patients tend to relapse over time, their response to salvage treatments is of shorter duration after every relapse, and they eventually die of disease-related causes [2].

Management of FL is one of the most controversial issues in oncology. Over the last 25 years there has been a proliferation of options in the treatment of FL ranging from observation to alkylating agents, anthracyclines, purine nucleoside analogues, combination chemotherapy, radiation therapy, interferon, radiolabelled and unlabelled monoclonal antibodies, antisense oligonucleotides, anti-idiotypic vaccines and autologous or allogenic bone marrow or peripheral stem cell transplantation [3]. Although several of these treatment regimens induce significant tumour response, there is little evidence from controlled clinical trials that these therapies improve overall survival as demonstrated by several studies [2,4–7]. More recently an improvement in the survival of patients with FL was demonstrated in population-based studies; these data can probably be interpreted not only as a consequence of new and more effective drugs, but also as a result of the effective sequential application of therapies during the course of the disease, coupled with improvements in supportive care [8].

Over time several studies on prognostic factors have been developed with the purpose of supporting and rationalizing clinical decisions. The main aim of prognostic studies is to develop predictive models that should be easily reproducible in daily clinical practice, and that allow the stratification of patients into different risk groups. Patients who are known to have a poor prognosis should be suitable for aggressive and experimental procedures whilst on the contrary, those with the best prognosis, may benefit from less toxic regimens.

The study of prognosis is based on the identification of prognostic factors that are able to predict a patient's survival independently from others. Prognostic factors can be grouped into two main categories; those associated with the disease itself and its unique biology and those correlated with the patient, his co-morbidities and ability to undergo effective therapies (Table I). A third group of prognostic factors might include those related to treatment; however, as, so far, no single treatment modality has been shown to improve the outcome of patients with FL, this aspect cannot still be considered of prognostic relevance.

This review will provide an overview of the currently available data on the prognosis of FL starting from clinical studies to the most recent biological findings.

Prior to describing the results of prognostic studies on FL some peculiar aspect of the disease that may be

Table I. Prognostic factors in FL

Disease related factors
Tumour biology
Histological features
Cytological grade
Diffuse areas
Genetic features
Oncogenes or tumor suppressor genes
Chromosomal gains or losses
Gene expression profiles
Tumour microenvironment
Immune signature
Number of infiltrating macrophages
Tumour extent
Ann Arbor Stage
Tumour burden
BM involvement
Systemic symptoms
Laboratory parameters
Lymphocytosis
Hb level
ESR, B2M, LDH
Patients related factors
Age
Performance Status
Gender

Note: FL, Follicular Lymphoma; BM, Bone Marrow; Hb, Hemoglobin; ESR, Erythrocyte Sedimentation Rate; B2M, Beta2 Microglobulin; LDH, Lactic Dehydrogenase, LDH.

relevant for understanding prognostic data should be acknowledged. First, due to the long natural history of FL, which can be measured in decades, follow-up studies should be very long to clearly assess the impact of a factor on survival. As a consequence most studies investigating the prognosis of FL are based on earlier surrogates of Overall Survival (OS), such as Failure Free Survival (FFS), or Duration of Response. Second, as mature follow-up is necessary to verify the prognostic effect of selected parameters for FL, prognostic data usually come from retrospective studies based on old series; currently available models are then the result of a trade-off between the 'modernity' of the prognostic models (ie the inclusion of promising and recently identified biological parameters), and the real representativeness of investigated series.

Lymphoma-related factors

Lymphoma-related factors may reflect the biology of the tumour and the extent of disease (Table I).

Histological features

The prognostic role of histological grading in FL has long been debated and has led to controversial conclusions, which are mainly due to concerns about the subjective nature and poor reproducibility of most used systems. In the recent WHO classification FLs are sub-classified according to the Berard cell-counting method into three main groups [9]. Grades are defined by the absolute number of centroblasts in ten representative neoplastic follicles, expressed per 40× high power microscopic field (hpf); grade 1 cases have 0–5 centroblasts/hps; grade 2 cases have 6–15 centroblasts/hpf; grade 3 have >15 centroblasts/hpf. Several authors suggest that grade 3 cases should be further sub-classified into two groups based on the relative amount of centroblasts (3a if >15 centroblasts/hpf but centrocytes are still present; 3b if only solid sheets of centroblasts are present), and on the percentage of diffuse areas (FLC). Whether or not this distinction has clinical significance is unclear. Grade 1, 2 and 3a seem to be more closely related to each other as indolent entities than grade 3b patients who tend to behave more similarly to de novo Diffuse Large B Cell Lymphoma (DLBCL) with earlier relapses and shorter survival [10]. In a recently published report, Hans *et al.* couldn't find significant differences in the clinical characteristics, overall survival or event-free survival between patients with grades FL-3a, FL-3b, or FLC. However, those cases with a predominant diffuse component (>50% diffuse), had a significantly worse overall survival ($P = 0.0037$), and event-free survival ($P = 0.012$). The authors then concluded that the presence of diffuse areas within grade 3 FLs rather than cytological sub-classification appears to confer more aggressive clinical behaviour to the disease [11].

Proliferation index (PI), and its correlation with outcome have also been evaluated. One series showed a mitotic index greater than 2 to be associated with poor survival, but two other studies have not confirmed this finding [12–14]. In a study performed by Martin *et al.* PI was studied by means of Ki67 staining and was shown to be well correlated with cytological grading in a series of 106 patients [15]. Patients with high PI (> 40%) had a shorter overall survival compared with those with low PI (< 40%) but similar Failure Free Survival. However, in multivariate analysis, the only independent predictor of Overall Survival was histological classification suggesting that the measurement of cellular proliferation does not appear to add additional useful information on the prognosis of the disease.

Other histopathological features have also been confirmed to have prognostic significance such as the degree of follicularity [16–19], absence of fibrosis between the follicles [16], and the degree of T-helper cell infiltration in the lymph node [20]. Recently Farinha *et al.* have shown that FL patients with a high content of macrophages in their biopsy samples show aggressive clinical behaviour [21].

BCL2 rearrangement

The t(14;18)(q32;q21) is the cytogenetic hallmark of FL being present in approximately 80–90% of cases [22]. The translocation results in the juxtaposition of the *BCL2* oncogene into the IGH heavy chain locus on chromosome 14, leading to its constitutive expression. Chromosomal breakpoints mainly occur at two different sites on chromosome 18; Major Breakpoint Region (MBR) and minor cluster region (mcr), which account for 80 and 10% of translocations, respectively [23]. Ten per cent of cases lack t(14;18) and reveal distinct patterns of chromosomal alterations [24].

Although t(14;18) status was correlated with clinical characteristics and survival in one study [25] these data

have not been confirmed by others [26] and there is general consensus that the t(14;18) chromosomal translocation status does not bear any prognostic significance. Recently the number BCL2/IgH + cells in the bone marrow of FL patients, as assessed by real-time quantitative PCR, was demonstrated to have an independent prognostic role in predicting response and event free survival [27].

The unique association between FL and the t(14;18) chromosomal translocation, together with the availability of very sensitive and specific techniques such as Polymerase Chain Reaction (PCR), has generated interest in 'molecular remission' wherein eradication of detectable cells bearing the *BCL-2* gene rearrangement is achieved. Patients achieving molecular remission have been demonstrated to have prolonged survival compared with that of non-molecular responders [28,29], but data are still limited to FFS and as the same authors observed, in spite of strikingly higher FFS favouring molecular responders, no clear-cut plateau was evident in this group [28].

Additional genetic changes

t(14;18) chromosomal translation is necessary, but not sufficient for transformation to the malignant state [22].

A marked heterogeneity of clonal evolution events characterizes FL at diagnosis and these alterations likely underlie the variable clinical behaviour of the disease. A number of genomic alterations have been described in FL including *p53* mutations, loss of *p16*, upregulated MYC expression resulting from translocation or other mechanisms, gains of chromosome arms 7p or 7q, Xp, 12q and 18q, as well as losses on 6q and possibly mutations of *BCL2* and/or *BCL6* genes. The presence of additional genomic aberrations and in particular 17p and 6q deletions are more frequent in grade 2 and 3 FL patients and have been correlated with shorter survival and higher probability of transformation into Diffuse Large B-cell Lymphoma [15,30,31] (Table II).

Gene expression profiling studies

The recently developed microarray technology allows large-scale parallel analysis of gene expression and permits simultaneous comparison of the relative gene-expression level of several thousand genes in different cell types. Several large scale studies involving microarray-based gene expression profiling have already identified novel lymphoma subtypes and improved the accuracy of prediction of outcome [32,33]. Based on microarray studies FL is characterized by a typical genetic signature. Included among the genes that are up-regulated in FLs are cell-cycle regulator proteins CDK10, p120, p21CIP1 and p16INK4A; transcription factors/regulators Pax-5 and Id-2, which are involved in normal B-cell development; and genes involved in cell–cell interactions, tumour necrosis factor, interleukin-2R (IL-2R), and IL-4R. Among the genes that are down-regulated in FLs are *MRP8* and *MRP14*, which are involved in cell adhesion. Interestingly, several of these genes are localized within chromosomal regions already described to be altered in FL [34].

Using supervised classification analyses on a series of patients with FL who experienced either an indolent or aggressive clinical course, Glas *et al* could define a gene expression profile of 81 genes that could predict immediate post-biopsy clinical behaviour. Patients included in the aggressive group were characterized by up-regulation of genes that are involved in cell cycle control, DNA synthesis and metabolism control; differential expression between the two groups also involved signal transduction genes. Indolent cases were typically characterized by the up-regulation of genes derived from the reactive infiltrate of T cells and macrophages. The profile resulting from microarray study accurately classified 93% of the FL samples in an independent validation set. Interestingly the 81 gene profiles couldn't predict long-term survival or the risk of subsequent transformation and this finding led the authors to conclude that additional stochastic genetic alterations that may contribute to transformation were not yet present in the neoplastic cells and thus could not be detected [35].

In another study by the Lymphoma/Leukemia Molecular Profiling Project (LMPP), Dave and colleagues demonstrated a correlation between FL patients' survival and the molecular features of non-malignant immune cells present in the tumour at diagnosis. In particular two signatures of coordinately regulated genes were identified; immune-response1 and immune-response 2 which were mainly expressed by non-malignant cells. The immune-response 1 signature was associated with favourable survival and included genes encoding for

Table II. Single gene aberrations associated with shorter survival and transformation to DLBCL (modified from Sigal *et al.* [62])

Chromosome	Gene	Abnormality	Function	Expression	Reference
17p13.1	P53	Mutations Deletions	cell cycle and apoptosis	Elevated	[63–65]
9p21	CDKN2A (p16) CDKN2B (p15)	Deletions Mutations	CDK inhibitors, cell cycle progression	Decreased p16	[66–68]
3q27	BCL6	Mutations	transcriptional Repressor/GC formation, inflammatory response	No change Increase	[63,69]
18q21	BCL2	Rearrangement Mutations	antiapoptotic	Elevated	[70–72]
8q24	c-MYC	Rearrangement Mutations Amplifications	cell cycle and apoptosis regulation	Decrease No change Increase	[73]

Note: DLBCL, Diffuse Large B-cell Lymphoma.

T-cell markers (eg CD7, CD8B1, ITK, LEF1 and STAT4) and genes that are highly expressed in macrophages (eg ACTN1 and TNFSF13B). The immune-response 2 signature, associated with unfavourable survival, included genes known to be preferentially expressed in macrophages, dendritic cells or both (eg TLR5, FCGR1A, SEPT10, LGMN and C3AR1). Immune-response 1 and 2 were used to sub-classify patients into 4 quartiles; those in the top quartile had a median survival of 13.6 years, whereas those in the bottom quartile had a median survival of only 3.9 years [36]. Various clinical variables were significantly associated with the probability of survival, including the International Prognostic Index (IPI), and some of its components and the presence of systemic symptoms. Taken together, these results represent an important advance for risk stratification in FL as they indicate that the prognosis of the disease is determined not only by the gene expression profile of the malignant cell, but also by a more complex interacting network of genomic and immunologic factors. These results represent an important advance for risk stratification in FL as they indicate that the prognosis of the disease is mainly determined by the cellular microenvironment, and not only by differences in the gene-expression profiles of the malignant cells themselves [22].

Parameters associated with disease extent

A large tumour mass has long been recognized as an important adverse prognostic factor for almost all types of lymphomas including FL; it can be estimated either directly considering stage or tumour burden or indirectly by means of surrogate laboratory markers.

Although most of the patients with FL present with advanced stage disease, the prognostic role of Ann Arbor disease stage was evaluated by several studies and those 10–20% of patients with limited stage disease are likely to have prolonged survival. More interesting [37] single clinical parameters contributing to the quality of advanced stage have been correlated with prognosis; they include number of nodal or extranodal sites, the presence and the extent of bone marrow involvement, the involvement of certain specific locations, or a large tumour diameter [38–40]. Tumour burden, a relatively more complex measure of tumour extent, has been put forward as a very important prognostic factor [38]; however the concept of high tumour burden has been variously defined in terms of the size of lymph node masses, the number of extranodal sites involved, the degree of splenomegaly or hepatomegaly, and the presence of circulating lymphoma cells [37,41,42].

Clinical or Laboratory parameters have been studied as indirect or surrogate measures of lymphoma extent and considered as independent prognostic variables in different prognostic models. These include the presence of B-symptoms that were correlated with shorter survival in several studies [42–44] and laboratory tests; among laboratory tests patients with low hemoglobin levels or elevated Erthrocyte Sedimentation Rate (ESR), have been found to have a poor prognosis in some series [37,43–46]. Elevated lactic dehydrogenase (LDH), levels correlate very well with both a lower response rate and shorter survival [37–39,41,43, 46–48] as do high levels of B2M [25,49].

Also, as well as surrogate measures of tumour extent clinico-biological markers may have a role as indicators of other aspects of cell biology. LDH is an intracellular protein which may be altered in cases of cell damage or increased cell turnover and thus may correlate with tumour proliferation rate. Both ESR or B2M are representative of inflammatory processes thus it may be speculated that the documented prognostic role of these parameters may be surrogate measures of an immune response status.

Patient related factor

The most important patient-related prognostic factors in FL are age and performance status. In general these factors have an important role as independent predictors of survival but in many situations it is advisable to keep them separate from other factors, in particular if they are to form the basis for treatment selection.

Age has been widely reported as an independent prognostic factor for survival in FL [38,43,44,46]. This may be interpreted mainly as a consequence of the elevated median age of patients with FL and of the prolonged natural history of the disease. Age *per se* however doesn't make FL more aggressive; the main determinants of the bad prognostic role of age are known or unknown co-morbid or paraphysiological conditions which are more frequent in elderly patients. Several age limits have been used to identify elderly patients with FL. Differently from aggressive lymphoma, an higher age limit of 70 years seems to better discriminate young versus elderly patients with FL [50].

Performance status also has a relevant influence as an independent factor for patient survival; however only 10–15% of patients with FL however have a poor PS at the time of diagnosis. As in elderly patients poor performance status may be determined by co-morbid conditions or by the presence of lymphoma [41].

Finally an independent correlation with survival was demonstrated for gender but the reason why women seem to have a better prognosis has never been explained [38,41,43,44].

Prognostic scores

Several studies have been performed to design predictive models for patients with FL based on clinical and laboratory parameters, the aim being to identify patients in whom aggressive experimental therapies are warranted. Attempts to define prognosis scores in FL begun in the late '70s (Table III) [18,38,41–44,46,51–55]. Leonard *et al.* [44] have described an index based on age, sex, stage, hemoglobin level and performance status, which separates patients into groups at high, intermediate and low risk. Romaguera *et al.* [38] have in turn, developed an index based on sex and tumour burden defined by using the number of extranodal sites and the size of involved lymph nodes and degree of bone marrow infiltrate.

Other studies aimed at applying to FL patients indices originally developed for patients with intermediate- and high grade lymphoma. This is the case of the LNH 84 index

Table III. Studies focused on the prognosis of patients with FL

Author, year	No.	Disease	Period of study	Endpoint	Factors
Gospodarowicz, 1984 [42]	525	Nodular NHL	1967–78	OS, RFS	age (70 yrs), PS, B symptoms, Bulk, cell type
Leonard, 1991 [44]	236	All stage FL	1979–87	OS	age, PS, stage, gender, anemia
Romaguera, 1991 [38]	96	Stage IV FL	1979–82	CSS, FFS	tumour burden, gender
Cameron, 1993 [53]	514	All stage FL	—	OS	age, PS, B, symptoms, stage, gut involvement
Denham, 1996 [54]	398	All stage FL	1974–80	OS	age, cell type, gender, symptoms, spleen, no. of LN
Soubeyran, 1991 [52]	281	All stage FL	1963–88	OS	age (60 yrs), stage
Lopez Guillermo, 1998 [51]	194	All stage FL	—	FFS	molecular response, Beta2 microglobulin
Decaudin, 1999 [55]	484	Stage III-IV FL	1986–95	OS	age (60 yrs), B symptoms, at least 3 LN >3 cm
Federico, 2000 [43]	987	All stage FL	1986–96	OS	age (60 yrs), gender, stage, ESR, LDH
Solal-celigny, 2004 [46]	4167	All stage FL	1985–92	OS	age (60 yrs), stage, >4 LN, anemia, LDH

Note: FL, Follicular Lymphoma; NHL, non-Hodgkin Lymphoma; OS, Overall Survival; RFS, Relapse Free Survival; PS, Performance Status; CSS, Cause Specific Survival; FFS, Failure Free Survival; LN, lymph node; ESR, Erythrocyte Sedimentation Rate, LDH, Lactic Dehydrogenase.

[56]; patients with localized disease, less than two extranodal sites, a normal LDH level and no Bulky lymph nodes (less than 10 cm in diameter) have the best survival. In contrast those with disseminated disease, bulky lymph nodes, more than one extranodal site or any of these parameters, together with a high LDH level have the worst survival, with a third intermediate group falling between these two extremities.

More important, data are available on the use of IPI for patients with FL; IPI was first developed for aggressive lymphomas in 1993 and several studies demonstrated that it could be successfully applied to patients with FL; although IPI showed a predictive prognostic role also for patients with FL, its discriminating power and clinical efficacy may be limited as most patients are allocated to the favourable or the intermediate risk groups (Table IV) [1,15, 43,46,48,55,57–60]. As FL presents unique features that may not be so relevant for predicting prognosis in other lymphoma subtypes these data demonstrate the need for prognostic models specifically devised for FL.

In the last few years two specific clinical prognostic scores have been proposed by the Italian Lymphoma Intergroup (ILI) [43] and the Follicular Lymphoma International Prognostic Project (FLIPI) [46] (Table V).

The ILI model was developed on a training series of 429 patients and validated on a sample of an additional 475 cases; the score is based on the independent prognostic role of age, gender, B symptoms, number of extranodal sites, ESR and LDH (Table V). These six variables defined a prognostic model with three risk groups associated with different 5- and 10-year survival rates (Table V); patients with 0 or 1 risk factors were considered to be at low risk, those with two unfavourable variables were at intermediate risk, those with three or more unfavourable variables were

Table IV. Initial characteristics of patients with FL reported in the literature with an IPI evaluation

	Decaudin [55]	Bastion [57]	Martin [15]	Hermans [59]	Lopez Guillermo [58]	NHL project [1]	Aviles [60]	Foussard [48]	Federico [43]	Solal Celigny [46]
No. of pts	457	148	106	229	125	304	238	182	427	1647
Age >60 yrs	24	—	52	57	37	<50	—	74	39	37
PS >1	2	—	24	18	20	—	—	34	9	12
Stage III-IV	100	—	62	80	81	67	—	100	75	78
ENS >1	19	—	—	20	32	—	—	39	5	38
Elevated LDH	22	—	25	26	21	—	—	34	17	21
IPI score										
0–1	49	24		32	36	39	22	43	61	49
2	39	50	86	37	32	—	29	24	28	31
3	11	20	14	23	21	—	15	25	11	15
4–5	2	6		8	11	6	31	8	–(*)	5
5 yrs OS										
0–1	79	80	—	78	80	84	20(+)	84	89	88
2	65	70	—	63	75	76	23	60	71	71
3	45	52	—	42	60	44	25	24	47	57
4–5	61	40	—	43	30	17	21	0	–(*)	44
P value	0.001	0.001	<0.05	<0.05	0.001	0.01	NS	<0.0001	<0.01	<0.01

Number are for per cent of studied patients.
(*) patients with 3 or more risk factors were merged together in the high risk group.
(+) values for Aviles are at 7 years.
Note: FL, Follicular Lymphoma; PS, Performance Status; ENS, Extra Nodal Sites; LDH, Lactic Dehydrogenase; IPI, International Prognostic Index; OS, Overall Survival.

Table V. Comparison between ILI and FLIPI and distribution of patients according to risk, based on originally published data

ILI [43]			FLIPI [46]	
		Model definition		
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	
B symptoms			—	
ESR > 30 mm/h			—	
		Period of enrolement		
1985–1996			1985–1992	
		Initial study population		
987 pts			5120 pts	
		Model population		
429 pts			1795 pts	
		Median Follow-up		
54 mos			90 mos	
		Patients' distribution		
Low risk (0–1)	64%		Low risk (0–1)	36%
Intermediate risk (2)	23%		Intermediate risk (2)	37%
High risk (3–5)	13%		High risk (3–5)	27%
		5 and 10 yrs OS according to risk		
Low risk (0–1)	90–65%		Low risk (0–1)	91–71%
Intermediate risk (2)	75–54%		Intermediate risk (2)	78–51%
High risk (3–5)	38–11%		High risk (3–5)	53–36%

Note: ENS, Extra Nodal Sites, LDH, Lactic Dehydrogenase; Hb, Hemoglobin; ESR, Erythrocyte Sedimentation Rate; OS, Overall Survival.

at high risk. Compared to IPI the ILI score confirmed the prognostic role of age, number of extranodal sites and LDH but found that the prognosis of disease depends also on the presence of B-symptoms and elevated ESR. In patients with FL, these latter two parameters probably assume more important prognostic value than the poor performance status itself in accordance with the unique biology and natural history of the disease. Additional advantages of ILI over the IPI model are the remarkably higher discriminating power among groups and the ability to identify a higher number of patients younger than 60 years with a poor outcome. Moreover, also if only 13% of patients are classified in the high risk group, their 10 year survival of only 11% makes these very high risk patients for whom aggressive or innovative approaches are warranted [43].

The FLIPI score was developed more recently and is the result of a large international cooperative effort. The score was defined on a training series of 1795 patients and was based on five variables: age, Ann Arbor stage, hemoglobin level, number of nodal site areas and serum LDH (Table V). As the same author stated in the paper parameters potentially predictive of survival were not included in the final model for different reasons: ESR because it is only measured in European patients and not in US ones; Performance status because of a low prevalence of patients with poor values and of an unexplained difference in the percentage of patients with a poor PS between European and US centres; finally, serum beta2 microglobulin and serum albumin due to the high proportion of patients with missing data. Based on the final model patients with 0 or 1 risk factors were characterized by a 5- and 10-year OS of 91 and 71%, respectively; patients with two risk factors had an intermediate 5- and 10-year OS of 78 and 51%, respectively; those with three or more risk factors, which represented 27% of all cases had the worst 5- and 10-year OS of 53 and 36%, respectively [46]. The FLIPI was also tested in patients younger than 60 years and in patients 60 years or more; the four identified risk factors other than age remained independent prognostic factors.

IPI, ILI and FLIPI have been recently compared in a large group of patients to try to ascertain the relative merits of each of them [61]. The overall concordance of the three systems was 54% and was 37% for low-risk groups, 10% for intermediate groups and 36% for high-risk groups. All three prognostic scores are easily applicable in clinical practice as they include variables that are easy to calculate.

In the comparison study the FLIPI score was able to classify more patients in the high-risk group than IPI and ILI, even when only younger patients were considered. However, the high-risk group identified by the ILI system, although numerically less consistent, was characterized by a worse prognosis than the corresponding IPI and FLIPI group. This confirms that ILI may have a more relevant role than other prognostic models in selecting patients with poor prognosis.

Overall, currently available prognostic indices for FL, even if based on large series of patients, suffer from their retrospective nature. Patients have been recruited over a long time span and this may result in important biases that should be considered; patients treated over a long time span may in fact be difficult to compare as therapeutic approach is continuously evolving as new treatment modalities or diagnos-

tic tools are made available. In addition, due to the retrospective collection of data, several clinical parameters which may show promising prognostic value may have been excluded from the final model only because they were present in a minority of cases. This is particularly true for beta-2 microglobulin and *BCL-2* status or for laboratory tests in general, that have less commonly been included in the initial assessment of a patient with lymphoma.

To overcome the limitation of retrospective studies, a large international project coordinated by the same group that defined the FLIPI, is now running. This study, namely the F2 study, has been defined as an international prospective collection of data for patients with FL diagnosed over a time span of only 2 years. To be included in the study patients should have most important clinical and laboratory parameters available and their data should be collected prospectively. The accrual phase of the F2 study has recently been completed with the enrolment of 1000 patients. Based on first interim analysis the level of completeness of registered cases is very high and clinical and laboratory features that have been excluded from the FLIPI and other models in the past have been collected in almost all of cases.

Conclusion

In conclusion, although FL is generally defined as an indolent lymphoma, patients' outcome may vary and can be correctly predicted by several prognostic factors and by specific available prognostic models. However, studies are needed in which treatment options are defined according to risk group but mature follow-up data are required to verify the clinical usefulness of these prognostic scores. Data from molecular biology and gene expression profile studies are changing our knowledge of the biology of FL and are identifying novel biological prognostic factors which will represent the basis for future development of more effective therapies and of novel prognostic scores.

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