Follicular lymphomas

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During the last ten years, follicular lymphoma (FL) has evolved from a disease almost constantly fatal to a chronic disorder with very long periods of disease-free survival and hopes of cure. This progress has come (i) from a better understanding of the mechanisms of development and progression of the disease; (ii) from improvement in treatment arms allowing combined approaches which are more and more active.

Pathological aspects

Although the WHO classification separates 4 categories of FLs (grade 1, 2, 3 A and 3 B), there is no consensus on the reproducibility and clinical usefulness of this grading. However, grade 3 B FLs have to be distinguished form other categories by their main characteristics: presence of solid sheets of centroblasts without centrocytes within neoplastic follicles, uncommon presence of the t(14;18) translocation, presence of 3q27 abnormalities, and worse prognosis. This subtype has to be considered as and treated like a diffuse large B cell lymphoma.[1]

Cytogenetics

The t(14;18) translocation is the hallmark of FLs. Aside from this translocation, other recurrent chromosomal abnormalities have been described. The presence of additional abnormalities has per se an adverse influence on prognosis.[2] Some of these abnormalities have a specific influence. Among them those involving the 17p region where the p53 gene is located,[2] the 6q region where several tumor suppressor genes are located2 and the 3q27 region disrupting the BCL-6 gene[1] are associated with a higher risk of histological transformation and/or a poorer survival.

Gene profile

Dave *et al.*,[3] have recently reported the gene profile of 191 patients treated for a FL from 1974 to 2001. Two profiles have been identified: one is characterized by the overexpression of genes associated with T lymphocytes, the other one by the overexpression of genes of macrophages, dendritic cells or both. Patients with the T lymphocyte gene profile have a very significantly better prognosis than those with the *macrophage* gene profile. The methodology used for this study has been debated and confirmation is required.

Clinical course

An understanding of prognostic factors is most helpful in guiding treatment choice. Several retrospective analyses of prognostic factors have been conducted in patients with FL (most often, combined with other types of *indolent* lymphomas). However, the use of the results of these analyses has been hampered by their heterogeneity and their complexity.

The *Follicular Lymphoma International Prognostic Index (FLIPI)* has been designed in order to propose an accurate, simple and validated prognostic index on the basis of routinely performed tests for all patients with FL.[4] From a database of 5,000 patients mostly from Europe and the United States, univariate and multivariate analyses have shown that eight factors have a significant influence on survival. To simplify the prognostic index, the five more discriminant factors were selected: age over 60 years, Ann Arbor stage III-IV, serum lactate dehydrogenase (LDH) level increased, hemoglobin level less than 12 g/dL, and more thant four nodal areas involved. From these five parameters, three risk groups have been created, as summarized in Table 1. The corresponding survival curves are shown in Figure 1. Table 1 and Figure 1 show that the FLIPI places patients in three risk groups with an approximately even distribution and significantly different overall survivals. The FLIPI has then been tested in another group of 912 patients and results in terms of distribution and hazard-ratios for death among the three risk groups were similar to those of the training group.[3] The FLIPI has also been shown to be discrimant for

Table 1. Outcome and relative risk of death according to risk group defined by the Follicular Lymphoma International Prognostic Index.

Group	No. of factors	Distribution (%)	Survival at 5 yrs. (%)	Survival at 10 yrs. (%)	Relative risk
Low	0–1	36	90.6	70.7	1
Medium	2	37	77.6	50.9	2-3
High	≥3	27	52.5	35.5	4-3

progression-free survival in patients treated with CVP followed by rituximab,[5] by radioimmunotherapy.[6]

Treatment modalities

What should be in 2005 the optimal initial treatment of follicular lymphomas? Clearly, the FLIPI demonstrates that not all patients with FL need the same treatment.

In patients with disseminated low-or intermediate-risk FL, the main choice is between watchful waiting and rituximab treatment, either as a single course or followed by a maintenance treatment. Different maintenance schedules have been proposed: four weekly cycles every six months, one cycle every two months usually until progression or for a maximum of two years. From the data reported by Hainsworth *et al.*[7] and the SAKK group[8] several conclusions can be drawn:
- maintenance treatment increases the median progression-free survival and response duration after initial treatment;[7,8]
- however, there is no clear demonstration that a maintenance treatment increases the time to rituximab resistance and/or the time to initiation of conventional chemotherapy when compared with retreatment at relapse;[9]

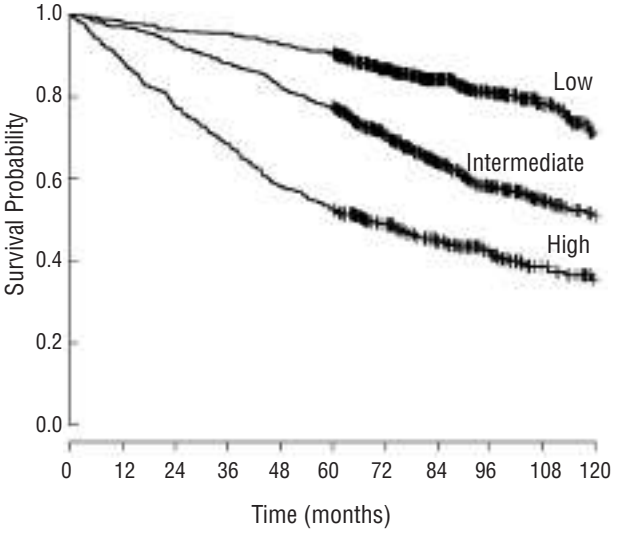

Figure 1. Overall survival according to FLIPI.

- although the follow-up of these studies is short, maintenance treatment does not improve overall survival in any of these trials.[6,9]

Recently, radioimmunotherapy (RIT) with ibritumomab yielded excellent results in previously untreated patients with FL (and for most of them a low or intermediate risk).[10] Because of the lack of data on long-term effects of this treatment, the results must be confirmed before considering RIT for initial treatment of FL patients outside of a clinical trial.

A large phase III trial – denominated RWW – is ongoing and compares watchful waiting, a single course of rituximab and rituximab followed by maintenance in FL patients with a good prognosis. Several years will be required to have the results of this trial.

In patients with poor risk follicular lymphomas, the median survival of patients treated with conventional chemotherapy is around five years.[4] The results of several trials clearly demonstrate that the combination of chemotherapy, whatever the regimen (CVP, CHOP, FCM) and rituximab, significantly increases progression-free survival when compared to the same chemotherapy alone. However, there is no consensus on the optimal chemotherapy regimen to be combined with rituximab.

Schematically, the choice relies between 3 types of chemotherapy :
- a regimen that does not contain any anthracycline, as the CVP regimen;[11]
- an adriamycin-containing regimen like CHOP;[12]
- a fludarabine-based regime like the fludarabine-cyclophosphamide combination;[13]

There is no randomized trial stratified on prognostic factors that demonstrates the superiority of any of these approaches. The pros and cons of each of them will be discussed.

Before the era of anti CD20 monoclonal antibodies, results of randomized trials comparing a conventional chemotherapy with high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) have shown conflicting results with the latter yielding improved event-free survival (EFS) and overall survival (OS)[14] improved EFS but not OS,[15] improved OS but not EFS.[16] Out of a clinical trial, there is presently no role

for HDT. However, the contribution of HDT after a rituximab-containing immunochemotherapy has to be tested. A trial will be soon initiated.

The prognosis of follicular lymphomas has deeply changed during the last ten years. A significant improvement in progression-free survival will most probably translate in an improvement in overall survival. However, there is no standard treatment for most patients and many questions remain unanswered. Inclusion of patients in the several ongoing trials in follicular lymphomas will speed up the answers.

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