Follicular Lymphoma
International Prognostic Index

Philippe Solal-Celigny, MD, PhD

Introduction

Follicular lymphomas (FLs) account for 25% to 30% of all non-Hodgkin's lymphomas (NHLs). Their estimated incidence in the United States is approximately 3.3 per 100,000 per year, ie, 100,000 new cases per year. Because the median survival of these patients now reaches 10 to 12 years, the prevalence in the United States is approximately 1,000,000 patients [1]. Until 20 years ago, there was no curative treatment for patients with FL. Therapies were proposed to symptomatic patients and were initially active on tumor bulk and symptoms but did not significantly improve survival. Most FL patients died from their disease after a long course of relapses and remissions, the latter being less and less complete and of shorter and shorter duration. In most patients, a histological transformation into a high-grade diffuse large-cell lymphoma occurred and hastened the clinical course. Until 1997, cytotoxic chemotherapy was the most widely used treatment. Several randomized studies did not demonstrate any difference in clinical efficacy, and more specifically in overall survival, between chemotherapy with a single alkylating agent or polychemotherapies, with or without adriamycin. Treatments vary considerably between centers and/or physicians. Interferon-α has demonstrated clinical efficacy in several randomized trials but was not widely used because of its adverse effects on quality of life. Results of high-dose therapy with autologous stem cell transplantation (ASCT) are conflicting.

In 1997, a pivotal trial clearly demonstrated the benefits of rituximab in previously treated patients, most of them with chemoresistant disease [2]. Since this first report, numerous clinical trials have been conducted, and the number of treatment options that can be proposed to patients as initial treatment has considerably increased. They can be summarized as follows:

1. Radiotherapy to involved areas for patients with localized disease
2. No treatment for asymptomatic patients with disseminated but of low tumor burden disease
3. Rituximab as a single course or followed by a maintenance treatment
4. Rituximab combined with CVP (cyclophosphamide, vincristine, prednisone)
5. Rituximab combined with an adriamycin-containing polychemotherapy, ie, CHOP (cyclophosphamide-hydroxydaunomycin-vincristine-prednisone) regimen anti-CD20 monoclonal antibodies
6. Treatment with radioimmuno conjugates ($^{131}$I-tositumomab or $^{90}$Y-tiuxetan-ibritumomab)

Opinion statement

Although numerous treatment approaches are proposed for patients with follicular lymphoma, criteria to help in choosing a treatment for a given patient and for comparing trial results are lacking. Several retrospective studies have analyzed prognostic factors, but their conclusions rely on limited numbers of patients treated during long periods, and their results are discordant. The Follicular Lymphoma International Prognostic Index was designed from the data recorded over 8 years of nearly 5000 patients registered worldwide. Five factors are used (age, Ann Arbor stage, number of nodal sites, serum lactate dehydrogenase level, and hemoglobin level) to build a three-category index. This index, together with new biologic markers such as gene profiling and proteomics, could help provide an optimal treatment option for patients with follicular lymphoma.
patients with a locally established diagnosis of FL was undertaken. Demographic, pathological, clinical, and biological data were collected, and their influence on overall survival was analyzed. After several statistical analyses and discussions between a clinical committee and statisticians, five parameters were selected for building the Follicular Lymphoma International Prognostic Index (FLIPI) [4••]:

1. Age ≤ 60 years versus > 60 years
2. Ann Arbor stage I to II versus III to IV
3. Serum lactate dehydrogenase (LDH) level ≤ normal versus > normal
4. Number of nodal areas involved ≤ 4 versus > 4
5. Hemoglobin level > 120 g/L versus ≤ 120 g/L

Three of these parameters (Ann Arbor stage, serum LDH level, number of nodal areas) are related to tumor bulk, one to the characteristics of the patient (age), and one to the consequence of the lymphoma on the patient (hemoglobin). Because determining the number of nodal areas involved may not be obvious, Figure 1 provides assistance for accurate use of this parameter of the FLIPI.

This index is simple and relies on routinely performed tests, and is discriminant because it separates the patients into three groups with approximately equal size (Table 2 and Fig. 2). The International Prognostic Index, which was originally designed for aggressive lymphomas, also discriminates patients with FL into groups with significantly different survivals, but the percentage of patients with high-risk disease is small. The FLIPI has been validated in other groups of patients, showing distribution of patients and overall survivals of each risk group very similar to that of the group of patients used for designing this index [4••, 5, 6].

In the era of anti-CD20 monoclonal antibodies, overall survival cannot be used as the endpoint for analyzing the prognostic accuracy of the FLIPI because the number of events (ie, deaths) is too small. Thus, initial progression-free survival has been tested as a surrogate for overall survival. In several phase III trials of patients treated with CVP with or without a subsequent maintenance treatment with rituximab [7], with CVP with or without rituximab [8], and with ibritumomab (a radiolabeled murine anti-CD20 monoclonal antibody) [9], the FLIPI discriminated patients with significantly different progression-free survivals.

The FLIPI has been shown to be discriminant in subgroups of patients that are chosen for clinical trials, such as patients with disseminated disease (Ann Arbor stage III–IV) or patients aged 60 years or younger, or elderly patients [4••].

The FLIPI was also discriminant in patients who relapsed or progressed after initial treatment and thus can be used for designing salvage treatment approaches [10].