Is watch and wait still acceptable for patients with low-grade follicular lymphoma?

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Follicular lymphoma (FL) represents more than 20% of all non-Hodgkin lymphomas worldwide and approximately 30% of the non-Hodgkin lymphomas diagnosed in the United States. Although occasionally localized at the time of diagnosis, most patients have disseminated disease. However, patients are frequently asymptomatic, and this, in combination with a long median survival, led to the initial studies of observing asymptomatic patients without initial therapy, ie, “watch and wait.” Since the initial report of watch and wait as a treatment strategy for patients with low-grade FL, our understanding of the biology of the disease has advanced; multiple active new agents have been introduced into practice, and the survival of patients with low-grade FL has improved. Given these changes, is watch and wait still an acceptable treatment recommendation for a newly diagnosed patient with low-grade FL? (Blood. 2016;127(23):2804-2808)

Follicular lymphoma is a more complex illness than previously thought

In their original description of follicular lymphoma (FL), or nodular lymphoma, in the 1950s, Rappaport recognized that patients with these illnesses could be subdivided based on the proportion of large cells in the tumor.1 Although the names have changed over time, the World Health Organization (WHO) classification continues this distinction by dividing FL into grade 1, grade 2, and grade 3.2 It has been recognized for some time that a subset of patients with what is today called grade 3 FL has a more aggressive illness and one that might have durable responses to therapy used for diffuse large B-cell lymphoma. For example, in the Working Formulation, follicular large cell was included in the intermediate-grade lymphomas, not low-grade lymphomas.3 Grade 3 FL seems to be biologically different based on a higher proliferative rate,4 a higher median standardized uptake value on positron emission tomography scans (Andrew Zelenetz, Memorial Sloan Kettering Cancer Center, oral communication, March 30, 2016), and different immunological characteristics.5,6 Some reports,7-10 but not all,11 have found that a subset of these patients has a plateau on their survival curve when treated with anthracycline containing combination chemotherapy regimens.

The WHO has tried to recognize the fact that some patients with grade 3 FL have an illness that behaves more like diffuse large B-cell lymphoma by subdividing grade 3 into grade 3A and 3B (ie, sheets of centroblasts), with 3B representing those patients who should receive aggressive therapy.2 The difficulty here is that it is not clear that pathologists can make this distinction consistently. For example, a study measuring pathologists’ ability to consistently divide patients into grade 1, grade 2, and grade 3 showed a success rate of only 60% to 70%.12 This does not yield much confidence that they will be able to subdivide grade 3 consistently. For this reason, some have elected to treat patients with grade 3 FL in a manner similar to patients with diffuse large B-cell lymphoma. Certainly, this will mean some patients are overtreated, but it will not lead to withholding aggressive therapy from a patient who might have the possibility of being cured. In the remainder of this paper, low-grade FL will represent patients with grade 1, grade 2, and, if it is reported, grade 3A FL.

It has also become apparent that FL cells have a complex interrelationship with infiltrating immune cells. Initial reports showed that tumors with a high proportion of infiltrating T cells had a superior survival to those with higher proportion of monocyte/macrophages in the tumor.13,14 Initial reports of gene profiling in FL confirmed this finding and found a strikingly better survival in patients whose lymphomas had a profile suggesting a higher proportion of infiltrating T cells.15 More recently, it has been shown that immune checkpoint inhibitors cause responses in a proportion of patients with advanced/refractory FL.16

The survival of patients with low-grade follicular lymphoma is improving

For many years, it appeared that the median survival of patients with low-grade FL was approximately 10 years and that it might not be greatly impacted by therapy.17-20 However, more recently, numerous reports have suggested a significant improvement in the survival of patients with low-grade FL.21-23 The survival of patients with low-grade FL treated by physicians in the Nebraska Lymphoma Study Group diagnosed before or after the year 2000, and those who never received rituximab and those who did, suggests that survival is significantly changing and that the availability of rituximab might be an important component in this improvement (Figure 1).

The increasing evidence that survival is improving for patients with low-grade FL, and that new therapies, particularly monoclonal antibodies, might be responsible for this improvement has led to suggestions that it is no longer appropriate to observe these patients without therapy.
Incidence of transformation to diffuse large B-cell lymphoma

In the 1970s, it was first noted that some patients who underwent biopsies of distinct sites of disease at diagnosis often had different histologic features in different sites: follicular growth pattern in one and diffuse large B-cell lymphoma in another. It was also noted that patients with FL could undergo histologic transformation to diffuse large B-cell lymphoma through the course of their disease. This histologic transformation was heralded by rapid change in the size of one or more lymph nodes and accompanied by a dramatic acceleration in the rate of disease progression. The progression occurred independently of how the patient was treated even being noted in patients who had received no initial therapy. Indeed, an autopsy study of patients with FL who died with lymphoma showed that 90% of the patients had transformed to diffuse lymphoma. A number of groups have more recently reported on the rate of histologic transformation, and a consensus emerged that the rate was not clearly affected by type of treatment. Recent estimates suggest that the rate of histologic transformation may be 2% to 3% per year. However, the explanation for the lower incidence remains unclear.

The clinical acceleration of the disease course after transformation was a universal finding, but results of treatment after transformation were not uniform in different research groups. At the National Cancer Institute, complete response rates were comparable to de novo diffuse large B-cell lymphoma, and some patients were long-term disease-free survivors. By contrast, none of the patients reported from the University of Iowa obtained a complete response, and survival was only a few months. More recent reports of outcome after transformation suggest that both the response rate and survival have improved considerably.

Figure 1. Overall survival of patients with grade 1 or 2 FL treated by physicians in the Nebraska Lymphoma Study Group between 1982 and 2014. (A) Patients treated before or after 2000. (B) Patients who did, or did not, ever receive rituximab.
Despite the considerable efforts to define transformation in molecular terms, no unified picture has yet emerged. The treating physician has no readily available information to predict transformation or prevent it.

What are the data supporting watch and wait?

In his 1984 Kamofsky Memorial Lecture, Saul Rosenberg reviewed the results of patients with low-grade non-Hodgkin lymphoma treated at Stanford University between 1961 and 1982. One important observation was the occurrence of spontaneous regression in some patients who were followed without therapy. This occurred in 30% of patients with follicular small cleaved cell (ie, analogous to grade 1 FL) non-Hodgkin lymphoma. Eighty-three patients with low-grade lymphoma were managed without therapy until symptomatic progression of disease. The median survival of these patients was 11 years (ie, better for follicular small cleaved lymphoma with 80% surviving to 17 years). The median time to requiring therapy was 16.5 months for follicular mixed (ie, presumably grade 2 FL) and 48 months for follicular small cleaved. This same group subsequently reported the outcome of no initial therapy in patients with stage I and II low-grade FL. They described 43 patients of whom 63% still had not been treated at a median follow-up of 86 months. The estimated survival at 10 years was 85%, not different from patients who received immediate treatment.

One of the authors of this paper was involved in a randomized trial of patients with low-grade non-Hodgkin lymphoma (ie, predominantly patients with low-grade FL) where patients were randomly assigned to watch and wait or to a very aggressive combination chemotherapy regimen (ie, ProMACE-MOPP [methotrexate, doxorubicin, cyclophosphamide, etoposide, prednisone, mechlorethamine, vincristine, procarbazine]) followed by total nodal radiotherapy. Patients in the watch-and-wait group could receive involved field radiotherapy for local symptoms. The updated results of this study with a median follow-up of nearly 20 years show that there is no significant difference in overall survival between those randomly assigned to watch and wait vs those receiving aggressive combined modality at diagnosis (D.L.L., unpublished data). Overall survival in both arms is 25 years is about 28%. Three patients assigned to watch and wait have never been treated, whereas the others received ProMACE-MOPP at progression. Some differences in the 2 groups have emerged. For example, the rate of undergoing histologic progression is slightly higher (26% vs 12%, 

In 2015, investigators from Denmark described 286 patients with advanced-stage FL initially seen between 2000 and 2011 who were managed with watch and wait. The 5-year progression-free survival was 35% and the 10-year overall survival was 65%. The cumulative risk of dying from lymphoma within 10 years was 13%. The 10-year risk of histologic transformation was 22%. The authors felt that abandoning watch and wait as a management strategy would lead to overtreatment of selected patients.

Recommendations from treatment guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for the therapy of patients with FL with extensive stage II and stage III/IV include watch and wait as an acceptable initial management approach for patients with low-grade FL who are asymptomatic, have no threatened end-organ function, do not have cytopenias secondary to the lymphoma, or lack bulky disease, and in whom the disease is not steadily progressing. For patients with localized low-grade FL, the NCCN guidelines also include watch and wait as being acceptable management in selected cases in whom the potential toxicity of involved field radiotherapy outweighs the hoped-for clinical benefit. The British Society of Hematology has approved management guidelines for patients with FL. The recommendations include watch and wait as an appropriate approach for patients with asymptomatic, advanced-stage FL, particularly for patients over 70 years of age. The authors also included observation as a possible option for selected patients with localized FL in whom total excision of all macroscopic disease had been done. The Lymphoma Canadian Scientific Advisory Committee issued consensus findings on the management of patients with FL. The authors felt that watch and wait was appropriate for patients with asymptomatic, advanced-stage FL who did not have large masses, bulky disease, symptomatic splenomegaly, impeding organ compromise, cytopenias secondary to bone marrow infiltration, or anxiety without treatment. The authors felt that watch and wait in patients with
believe that a reasonable physician can make the recommendation for watch and wait—and we sometimes do. However, there are caveats in making this recommendation (Table 1). A physician’s enthusiasm for watch and wait in this setting should not override the patient’s preference for therapy based on anxiety about not treating a known cancer. The fact that there is no proof that delaying therapy does not decrease survival does not make it impossible that it is still true. Studies in FL take extended periods of time, and most of the studies suggesting no impact on survival in delaying therapy were done in the time before the availability of monoclonal antibodies.

It would be better if an objective method using a biomarker could be used to choose patients for the watch-and-wait approach. It is possible that identification of patients most likely to benefit, and least likely to be harmed, by observation without therapy for newly diagnosed FL will be able to be identified more definitively in the future. In a recent report in Lancet Oncology, the authors tried to improve on the FL international prognostic index by incorporating gene mutations into the prognostic model. They examined patients who received first-line chemotherapy rather than all patients. The use of biological markers improved the ability to predict treatment outcome. It was particularly good at identifying those patients with a bad outlook. It is reasonable to hope that utilizing similar approaches from all patients at the time of diagnosis might be able to identify those unlikely to progress rapidly and for whom watch and wait might be a favored initial approach. However, until that time, the lack of symptoms, the absence of disease involvement in sites that might be imminently dangerous, and a patient’s desire to avoid therapy as long as possible represent the most practical way to identify those patients for whom watch and wait is a reasonable treatment option.

### Authorship

Contribution: J.O.A. and D.L.L. wrote the paper.

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