Is Observation Dead in Follicular Lymphoma? No, But the Apoptosis Pathway Has Been Activated

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Abstract

Follicular lymphoma (FL), the most common indolent type of non-Hodgkin's lymphoma, presents with a highly variable clinical course and affects the overall survival (OS) of patients. Although observation has been adopted widely by clinicians in the management of patients with FL, the benefits of early treatment must be reviewed in light of the significant progress made in the treatment of symptomatic or higher-tumor-burden FL. When treatment is indicated, a variety of combination chemotherapeutic regimens have proven efficacy and have shown improvements in both progression-free and event-free survival, and the addition of rituximab to these regimens has shown a statistically significant improvement in OS. Additionally, single-agent rituximab has been added to the possible therapeutic options for patients with low-tumor-burden FL. Although a paucity of clinical data exists on the upfront treatment of the low-tumor-burden population, the question of whether early treatment, especially with the newer rituximab-containing chemotherapy regimens, would improve OS is thought-provoking. Furthermore, novel targeted therapies with tolerable side effect profiles are rapidly advancing in the treatment of non-Hodgkin's lymphoma. The future for patients with low-tumor-burden FL is brighter than ever before. (J Natl Compr Canc Netw 2015;13:363–366)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Review the pros and cons of early treatment versus observation in the management of patients with FL
- Discuss the potential benefits of chemoimmunotherapy as initial treatment for the management of patients with FL
- Identify the indications of therapy in patients requiring treatment for FL

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The concept of observation, or the "watch and wait" approach, was originally proposed in 1979 by Portlock and Rosenberg[1] at Stanford University, when they reported results on 44 patients who, for various reasons, had not received initial therapy after being diagnosed with follicular lymphoma (FL). The reasons for the decision not to treat were complex and not entirely evident on review, but included assessment by the treating oncologists that these patients presented with a benign or indolent disease course, and that it was the patients' personal choice to defer treatment. Portlock and Rosenberg were also impressed with the toxicity associated with the chemotherapy administered to these patients in the absence of clear evidence of long-term benefit, at least from a survival perspective. At that time, and for many years after, the median survival of patients with newly diagnosed, advanced-stage FL ranged from 5 to 7 years, with no evidence of a plateau in the survival curve (ie, no suggestion that any patients were cured). A rarely considered and little known fact is that the original Stanford policy of watch and wait permitted local radiation therapy to be administered in up to 3 different locations.

Over the years, most physicians treating FL adapted the concept of watch and wait, although the criteria for selection of this treatment have varied somewhat. In general, watch and wait was the preferred therapy for newly diagnosed patients who presented with low tumor burden and no symptoms of FL. Instead of defining the criteria for watch and wait, some groups have defined the criteria for treatment, such as the Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria.[2] More recent randomized trials have confirmed that the watch and wait approach has comparable survival to initial treatment with single-agent alkylating agents, such as chlorambucil. A major advantage of this approach was that it afforded the patient a reasonably long period (2.5–3.0 years) of treatment-free survival, based on the results of retrospective studies in the pre-rituximab era.[3]

Fortunately, much has changed since the initial reports of watch and wait in the 1970s. A major advancement in the treatment of FL was the introduction of the monoclonal antibody rituximab. As a single agent, rituximab maintenance produced an 84% overall response rate, and at 3 years, 88% of patients on the maintenance arm still did not require therapy, compared with 46% of those undergoing watchful waiting.[4] Furthermore, it is extremely well tolerated, with very little of the toxicity associated with conventional chemotherapy. It is well-known by lymphoma experts that there is a subset of patients with disease with a median survival of 5 to 7 years for whom the concept of watch and wait is unacceptable and associated with significant psychological stress; the size of this group has never been accurately characterized. Thus, single-agent rituximab now provides practitioners and patients with a well-tolerated and effective initial treatment to consider as an alternative to watch and wait, while prolonging the time to chemotherapy.

However, the combination of rituximab with conventional chemotherapy offers insight into the potential benefits of initial therapy for the low-tumor-burden population. Until the past decade, no evidence showed that different initial therapies for FL could impact overall survival (OS). However, recent studies of rituximab in combination with chemotherapy have clearly shown that this is no longer true. The study by Marcus et al[5] randomized previously untreated patients who required initial therapy to either CVP (cyclophosphamide, vincristine, and prednisone) and R-CVP (cyclophosphamide, vincristine, and prednisone with rituximab). The R-CVP group showed improvement in not only failure-free survival (FFS) but also OS (83% vs 77%; P=.03). Similarly designed studies from the German Low Grade Lymphoma Study Group (GLSG) compared CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab). Again, FFS and OS were improved (median overall response rate, 96% vs 90%; P=.01).[6]

In 2005, a study reported the survival of patients with previously untreated FL treated on a sequential series of treatment approaches by the SWOG Lymphoma Committee spanning 3 decades.[7] The survival of patients treated with R-CHOP was superior to that of those observed on prior treatment regimens. Finally, data derived from the SEER database showed that the survival of patients with FL had improved dramatically on a population basis, from the time period of 1979 to 1999.[8] In the most recent studies reported by Press et al[9] for SWOG, the 5-year PFS rate of patients with FL treated with immunochemotherapy was 60% or higher and the 5-year OS was 86%, but approaches 80% at 10 years for patients treated with R-CHOP.

Clearly, patients with newly diagnosed FL now have a dramatically better prognosis than 20 years ago, when 50% died by 5 to 7 years.[7]

This improvement in the ability to allow patients with FL to enjoy prolonged initial remissions is evident in the PRIMA study.[10] In this study, Salles et al[10] showed that maintenance therapy with rituximab for 2 years after initial rituximab in combination with chemotherapy resulted in prolonged progression-free survival, although OS was not impacted. Notably, centers participating in the PRIMA study had to select one combination rituximab/chemotherapy regimen for use in all patients entering the trial; approximately 75% chose R-CHOP, 20% chose R-CVP, and only 5% chose a fludarabine-based regimen. A retrospective analysis clearly showed that the patients who received R-CHOP had superior survival compared with those receiving R-CVP; too few patients were treated with fludarabine-based regimens to analyze. These data suggested that in the combination rituximab/chemotherapy era, intensity of treatment, which also resulted in higher complete response rates for the R-CHOP group, might matter.

Bendamustine, a bifunctioning alkylating agent, has demonstrated efficacy in the treatment of FL and has emerged as part of frontline therapy in the treatment of patients with FL. The first randomized study to compare R-CHOP versus bendamustine with rituximab (BR) was the StiL study.[11] Patients with advanced-stage FL had similar OS, whether treated with R-CHOP or BR, and, notably, median progression-free survival was superior in the BR arm compared with R-CHOP (70 vs 31 months; $P<.0001$). Subsequently, the BRIGHT study showed that BR is noninferior to R-CHOP in patients with advanced FL.[12] Given the largely acceptable toxicity profile of BR, it has emerged as a preferred therapeutic option for both upfront and relapsed disease, by many clinicians.

Finally, it is important to consider whether the other well-known paradigm describing FL, that "it is an incurable disease," is still valid. How do we define cure? Understanding that no data show that patients with FL have the same survival as a matched population without this lymphoma, several other surrogates can be evaluated to demonstrate curability. If a significant number of patients with a given disease do not experience recurrence after initial therapy and die from other unrelated causes, does that observation suggest some patients are being cured? It is well-known that the uncommon patient with localized FL treated with radiation therapy can have extraordinarily good 5- and 10-year FFS and OS. Patients with newly diagnosed FL present at an average age of 60 years. Median 5-year progression-free survival for patients in this age group who have low Follicular Lymphoma International Prognostic Index-2 scores now approaches 80%. Thus, considering the ability to attain initial remissions exceeding 10 years with therapy, are some patients with FL now considered cured? If one accepts the argument that some patients with FL are now cured with rituximab-containing regimens, does that change the accepted concept of watch and wait? What curable diseases are permitted to go untreated for a prolonged period?

In summary, initial observation, or watch and wait, has been a standard approach to treating asymptomatic patients with FL with a low tumor burden for several decades. It provides patients with an opportunity to avoid treatment for a significant period. However, most patients will require therapy at some point. Recall that watch and wait was never shown to be superior to initial therapy. Single-agent rituximab therapy now provides an alternative for that same population, especially those who are not comfortable with the concept of withholding treatment for a malignant and ultimately fatal disease. If one accepts the potential curability of some patients with FL, does that change one's willingness to delay treatment?

Furthermore, much excitement currently surrounds the new targeted oral agents being developed for the treatment of B-cell lymphomas. Impressive single-agent activity has been seen in relapsed/refractory FL treated with the newer kinase inhibitors. Will these inhibitors replace rituximab-containing chemotherapy or, as an adjunct, will they make rituximab-containing chemotherapy even more active? These studies are ongoing and the positive impact that they will have on treatment strategies for FL are eagerly anticipated. Further future stratification of patients according to molecular and clinical features may allow clinicians to determine which patients with low tumor burden are likely to benefit from an upfront strategy.

Old paradigms die hard in medicine, such as "observation is the only reasonable treatment for asymptomatic patients with low-tumor-burden FL"; "OS is not an end point that can be used in studies of FL"; and "FL is noncurable." In many ways, these paradigms delay the goal of scientific investigation into

the treatment of an ultimately fatal malignancy, and the ultimate goal to cure the disease with reasonable therapy.

Observation may not be dead, but upfront therapy for FL remains an appropriate strategy. Although for now the debate over the best initial treatment approach in FL continues, this will likely not be a debatable subject 10 years from now.

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Posttest Questions

1. True or False: Initial observation, or "watch and wait," is an appropriate strategy for selected patients with FL.
2. In a retrospective analysis of the PRIMA study, which regimen clearly showed superior survival benefit?
   a. Fludarabine-based regimen
   b. R-CVP
   c. R-CHOP
   d. None of the above
3. True or False: Bendamustine and rituximab is noninferior to RCHOP in patients with advanced FL.