ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Current Treatment Approaches in Follicular Lymphoma

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H&O What are the notable disease characteristics of follicular lymphoma?

BK Follicular lymphoma tends to be a fairly slow-growing malignancy that typically does not cause symptoms until late in the disease course. As a result, by the time most patients come to medical attention, the disease is at an advanced stage. However, disease stage in follicular lymphoma is not highly prognostic. Patients with a diagnosis of stage 3 or 4 follicular lymphoma can still have an excellent prognosis.

The staging is typically determined through physical examination, blood work, and imaging. The imaging can be performed with computed tomography (CT) or positron emission tomography (PET). The use of PET scans to stage follicular lymphoma is becoming more common. PET scans tend to be somewhat more sensitive and accurate than CT scans. A bone marrow evaluation can be performed but is not always essential.

H&O What is the prognosis?

BK Currently, the average life expectancy after the diagnosis is probably more than 15 years. The precise number of years is unknown because it takes a long time to determine that number. Treatment options are increasing, and outcomes are improving. An estimation of the prognosis given in 2015 is based on the available treatments. Future therapies could impact the prognosis for an individual patient.

H&O What is the frontline treatment approach?

BK Many newly diagnosed patients do not require immediate therapy. Asymptomatic patients with a low tumor burden can often be considered for the so-called watch-and-wait strategy. Patients who present with a high tumor burden or symptoms should be started on treatment. In 2015, the most common approach for these patients is chemotherapy, such as bendamustine (Treanda, Teva), combined with the monoclonal antibody rituximab (Rituxan, Biogen Idec/Genentech). Another common first-line strategy is rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Rituximab alone, without chemotherapy, may be appropriate for some patients. Selection of the treatment approach requires integration of all baseline information, including the patient's age, his or her underlying health, the stage of the disease, the tumor burden, the presence or absence of symptoms, and the goals of therapy.

More aggressive treatment approaches tend to produce more durable remissions. However, these more aggressive treatments also tend to produce more adverse events and quality-of-life detriments, at least in the short-term. Therefore, there is a trade-off between the more aggressive and less aggressive approaches to treatment. Selecting the best treatment for a particular case requires thoughtful discussion between the patient and the treating physician.

H&O How often will patients require additional treatment?

BK Follicular lymphoma is not typically considered a curable cancer. In a minority of patients, a single course of treatment can lead to a first remission lasting longer than 10 years. Whether such patients are cured is unclear. More typically, the disease will recur between 3 and 6 years after the initial treatment. Most follicular lymphoma patients will therefore require several lines of treatment throughout the course of their disease.

H&O What are some of the newer agents in follicular lymphoma?

BK In 2014, idelalisib (Zydelig, Gilead) was approved for relapsed follicular lymphoma. Idelalisib is an oral, small-molecule inhibitor of the phosphoinositide 3-kinase δ. In a large study, idelalisib was very effective in patients with follicular lymphoma whose disease was no longer responding well to traditional treatments. The overall response rate was 54% (95% CI, 0.42-0.66; see the figure). As a result, there is considerable interest in studying idelalisib earlier in the disease course of follicular lymphoma.

Idelalisib is generally well-tolerated. It does not substantially affect the patient's blood counts. There are some risks of diarrhea and injury to the liver and lungs. Fortunately, these adverse events are fairly uncommon, and the treating physician can monitor for them. When these toxicities do occur, prompt cessation of idelalisib will usually result in complete resolution.

Several therapies are currently under investigation in follicular lymphoma. The oral agent ibrutinib (Imbruvica, Pharmacyclics/Janssen) is a kinase inhibitor that targets the enzyme Bruton's tyrosine kinase. Ibrutinib has shown remarkable activity in chronic lymphocytic leukemia and small lymphocytic lymphoma. It also has very good activity in mantle cell lymphoma. It is well tolerated. Ibrutinib is currently being investigated in follicular lymphoma.

Another exciting oral agent is ABT-199, which was recently given the name *venetoclax*. It acts by inhibiting the protein BCL-2. Follicular lymphoma cells typically have high levels of the BCL-2 protein, which sends a strong survival signal to the cells. With inhibition of the BCL-2 protein, the cells lose this survival signal and are much more susceptible to eradication by other therapies. Venetoclax appears to have reasonably good single-agent activity in follicular lymphoma, and it may prove to be an important component of combination therapy. It has a favorable side effect profile.

Lenalidomide (Revlimid, Celgene) is an oral immunomodulatory agent that has impressive activity in follicular lymphoma, particularly when combined with the monoclonal antibody rituximab. In fact, the activity of this combination is so promising that it is being compared head-to-head with rituximab chemotherapy combinations in ongoing clinical trials.

H&O Is there any information on the best sequencing of therapies?

BK How to best sequence therapy in follicular lymphoma is an area of ongoing controversy. There are a variety of different sequences that can produce equivalent overall outcomes. Much of the sequencing of therapy reflects the preferences of the physician and patient, which are perfectly reasonable criteria.

H&O When is combination therapy an option?

BK There are several instances in which combination approaches are more desirable than single-agent therapies. Typically, for frontline treatment, most patients will receive combination therapy. Combination therapy is less likely to be used with some of the newer oral targeted agents, but these drugs are under intensive study to determine the best combination partners and strategies.

H&O What is the role of maintenance therapy?

BK Maintenance therapy is fairly common in follicular lymphoma. The most frequent strategy is to administer single-agent rituximab for 2 years after the induction course of therapy is completed. Studies have shown that the application of this type of maintenance strategy will generally extend remission beyond that seen without maintenance. To date, maintenance strategies have not been shown to prolong overall survival. Most investigators therefore believe that maintenance therapy is optional and will typically discuss the pros and cons with patients when deciding whether to use it.

H&O Are there any recent insights into the biology of follicular lymphoma that might impact treatment?

BK There is considerable research aimed at trying to better understand the underlying biology of follicular lymphoma. A goal is to prospectively distinguish patients likely to have a more favorable course, who can receive less aggressive treatment, from patients likely to have a less favorable course, who might benefit from a more aggressive approach. Unfortunately, at this time, we lack the ability to precisely identify these different groups of patients.

There are no reliable biomarkers in follicular lymphoma that allow us to tailor therapy to an individual patient. It is a high-priority goal of lymphoma investi-

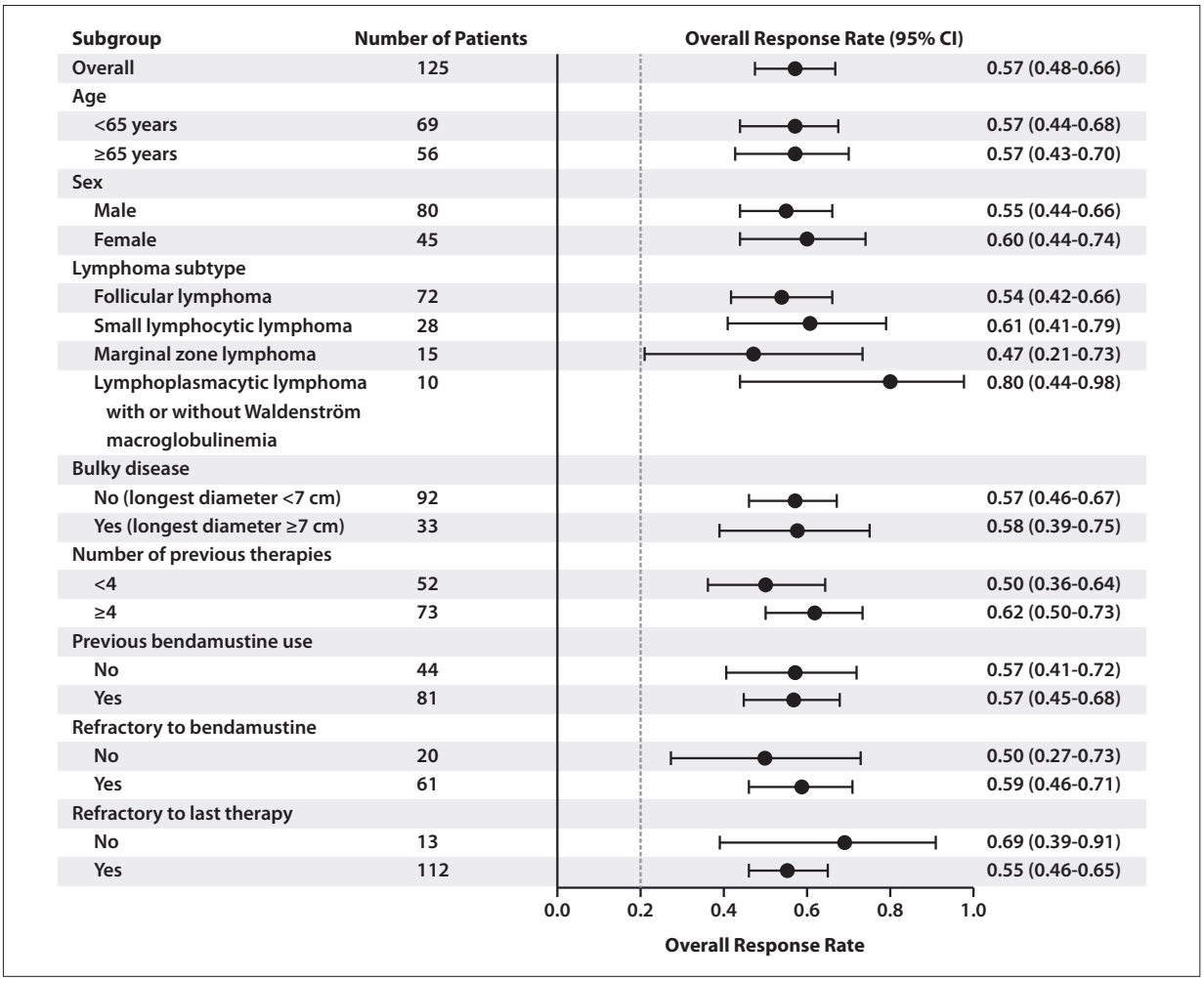

Figure. In a phase 2 trial of idelalisib in indolent non-Hodgkin lymphomas, the overall response rate among patients with follicular lymphoma was 54%. Adapted with permission from the *New England Journal of Medicine*. Gopal AK et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. Volume 370, Pages 1008-1018. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

gators to identify biomarkers that will allow for rational selection of targeted agents for individual patients.

H&O You are the chair of the ECOG's lymphoma committee. Are there any current studies in follicular lymphoma?

BK Our group recently completed a 2-part study that utilized the rituximab/bendamustine chemotherapy backbone. In the first part, patients were randomly assigned to receive that regimen with or without the proteasome inhibitor bortezomib (Velcade, Takeda/Millennium). When our study is mature, we should be able to determine whether the addition of bortezomib to the rituximab/bendamustine chemotherapy backbone improves overall response and complete response. The second part of this study is evaluating whether lenalidomide improves outcome when added to rituximab maintenance therapy. That cohort recently completed accrual, and we will report those data as soon as they mature.

In a recent study of follicular lymphoma patients who received frontline treatment with rituximab and chemotherapy, those who experienced a progression event within 2 years had a substantially worse prognosis compared with those who achieved more durable responses. These patients represent a true unmet need in follicular lymphoma, and novel strategies are required. Therefore, we are currently designing an intergroup trial with our colleagues in the Alliance for Clinical Trials in Oncology cooperative group and the SWOG cooperative group to develop a strategy specifically aimed at improving outcomes for this high-risk group of follicular lymphoma patients.

Disclosure

Dr Kahl has performed consulting for Roche, Seattle Genetics, Takeda, Cell Therapeutics, Celgene, Juno, Pharmacyclics, and Infinity.

Suggested Readings

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