Commentary: Let the Tail Wag the Dog: The Case for Radioimmunotherapy of Low-Grade Follicular Lymphoma

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There are numerous therapeutic approaches to the management of low-grade follicular lymphoma (grades 1 and 2), ranging in intensity. For asymptomatic patients with advanced-stage disease, observation is an option, given the usually indolent nature of low-grade lymphomas. When disease is limited in stage, local radiation therapy can potentially cure patients [1]. For advanced-stage patients who need treatment, there is a variety of single-agent or multiagent chemotherapy options with high response rates. However, even very intensive regimens, such as high-dose chemotherapy with autologous stem cell transplant (ASCT), do not lead to longer overall survival times compared with less intensive regimens despite some improvement in progression-free survival (PFS) times. Relapse following therapies using conventional chemotherapy agents is common, and serial treatment is usually hampered by decreased response rates and ever shortening durations of remission with each successive treatment [2, 3]. When evaluating these various treatment options, median survival times or hazard functions are often compared; however, there is more to the story, namely, the tale that is told by the tail of the curves. The median survival time is a standard measurement for clinical trials that facilitates comparisons by taking all the data from a survival curve and compacting them into a single number that can be used for statistical evaluations. In this process, the tail of the curve (if there is a tail) can be overlooked. The presence of a tail or plateau on a PFS curve connotes that long-term continuous remission is possible for some patients.

The review by Buchegger et al. [4] in this issue describes the exciting addition of antibody-based therapies to the therapeutic armamentarium for follicular lymphoma by including radioimmunotherapy (RIT), in which radioactive isotopes are targeted to lymphoma cells by highly specific monoclonal antibodies. The authors hypothesize that combinations of optimized biological treatments together with radiolabeled antibodies and chemotherapy early in the disease course of advanced-stage follicular lymphoma may be an ideal strategy for prolonging disease-free survival. Rituximab, a nonradiolabeled anti-CD20 antibody, has enjoyed success as a single agent and as an adjunct to traditional chemotherapy regimens, and, used together with combination chemotherapy, can result in longer survival times than with chemotherapy alone when used as a first therapy [5–7]. Radiolabeled anti-CD20 antibodies (131I-tositumomab, Bexxar®; GlaxoSmithKline, Philadelphia...

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and 90Y-ibritumomab, Cell Therapeutics, Inc., Seattle, WA) have shown very impressive response rates and the potential for a long PFS duration for some patients. In heavily pretreated patients, 131I-tositumomab achieved a 5-year PFS rate of 17%, and for patients with "durable responses" (>1 year), 44% continued to have long-term remissions [8]. In patients who were treated up front with 131I-tositumomab, the tail on the PFS curve is >40% [9], rivaling the event-free survival time of ASCT with a much simpler and less toxic treatment [10, 11]. 90Y-ibritumomab has been reported to improve the PFS time (13.5 months versus 37 months; \( p < .0001 \)) when used as consolidation therapy after first-line induction treatment [12]. Based on this phase III trial, the European Commission has approved extended marketing of 90Y-ibritumomab for first-line therapy after remission induction in previously untreated patients with follicular lymphoma. The Southwest Oncology Group has piloted cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy followed by 131I-tositumomab in patients with untreated, advanced-stage follicular lymphoma with an excellent 5-year PFS rate of 67% [13]. This has led to an ongoing phase III Intergroup study comparing this regimen with CHOP plus rituximab.

Despite these apparent advantages, RIT has been underused, with very slow sales of both 90Y-ibritumomab and 131I-tositumomab [14]. This underuse has been attributed to the lack of a proven overall survival difference, fears of toxicity, unfamiliarity and inconvenience to treating physicians, reimbursement issues, and the requirement in some settings for referral to nuclear medicine or radiation oncology [15]. Nevertheless, the available information suggests that it is about time to let the tail wag the dog.\(^\text{1}\)

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**REFERENCES**