Treatment Strategies in the Follicular Lymphomas

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Once a simple choice between single alkylator therapy and combinations such as CVP or CHOP, treatment-planning for patients with follicular lymphomas (FL) and their physicians has become a complicated process in which the relative advantages and disadvantages of many new effective approaches must be weighed. Within a relatively short period of time, an unprecedented number of novel potent agents have become available. The challenge is to devise appropriate treatment strategies for individual patients – optimizing quality of life as well as disease-free and overall survival.

In this issue, Wöhrer and colleagues report favorable outcomes in a small number of patients with advanced-stage indolent non-Hodgkin’s lymphoma (NHL) treated with the combination of mitoxantrone, chlorambucil and prednisone (MCP) [1]. Toxicity was limited to myelosuppression. This regimen has now been the subject of a large randomized trial comparing MCP alone to MCP plus rituximab [2]. For patients with FL, both the overall response rate and 2 year event-free survival were significantly better with chemoimmunotherapy than with chemotherapy alone (92 vs. 75%, p < 0.0001; 83 vs. 43%, p < 0.0001, respectively). These results are consistent with those of three other phase III trials investigating the addition of rituximab to combination chemotherapy [3–5]. In all four trials, rituximab plus chemotherapy was superior to chemotherapy alone with regard to overall response rates and either median time to treatment failure or event-free survival. Rituximab as a single agent has been studied in previously untreated FL patients with excellent results [6, 7]. Despite the fact that eligibility was restricted to asymptomatic patients with ‘low tumor burden’ according to the GELF criteria, less than half of all cases enrolled on this trial proved to be low-risk when the Follicular Lymphoma International Prognostic Index (FLIPI) was applied retrospectively [8]. The overall response rate to rituximab was 80%, with 49% of cases achieving CR (complete remission) or CRu (unconfirmed CR). A median progression-free survival (PFS) of 18 months has been reported. Of particular interest is the fact that 28% of all patients and 34% of responders maintained their responses for 5 or more years. Hence, rituximab alone may be an effective and appropriate therapy for selected patients.

With the goal of increasing complete response rates, the Swiss Group for Clinical Cancer Research randomized patients who did not progress during 4 weekly doses of rituximab to receive either no further therapy or an additional dose of rituximab every 2 months for a total of 4 additional doses (maintenance). Event-free survival was significantly improved for chemotherapy-naïve patients and responders who received maintenance therapy [9]. In patients treated with CVP by members of the Eastern Cooperative Oncology Group, maintenance rituximab substantially improved PFS (2-year PFS: 74 vs. 42%) [10]. Outcome was superior in patients with follicular histology, high tumor burden at enrollment, and minimal residual disease at the time of randomization, who received maintenance rituximab. Whether or not maintenance rituximab will benefit patients with FL receiving chemoimmunotherapy as induction treatment is not yet known. In the diffuse, aggressive NHLs, there was no advantage to rituximab maintenance in patients who received rituximab as part of induction therapy (R-CHOP) [11].

Radioimmunotherapy has the capacity to deliver high doses of irradiation to disseminated tumor cells while having only limited effects on normal tissues. The radiolabeled anti-CD20 antibodies, Y-90-ibritumomab tiuxetan (Zevalin; Biogen Idec, Inc., Cambridge, MA, USA) and I-131-tositumomab (Bexxar; Corixa, Seattle, WA, and GlaxoSmith Kline, Philadelphia, PA, USA), both target ionizing irradiation to antigen-positive cells and their neighbors, retaining the capacity for mediating complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity and apoptosis. Both radioimmunoconjugates are relatively easy to administer, safe and effective and provide an alternative treatment modality to rituximab or rituximab plus chemotherapy. CHOP followed by tositumomab/I-131-tositumomab has been shown to be a highly effective initial therapy for FL, and is currently being compared to CHOP-R.
in a phase III trial for previously untreated patients [12, 13]. Radioimmunotherapy may prove to have its greatest impact when used as part of the initial treatment program. Studies in the upfront setting are in progress.

The morphologic and clinical heterogeneity of the FL reflects the underlying biologic heterogeneity of the disease, and treatment results are likely to be related to the characteristics of the patients enrolled. Dave and colleagues have recently reported that gene expression signatures representing the nonmalignant cell populations associated with immune regulation within FL biopsy specimens are strong predictors of outcome [14]. Others – notably Glas and colleagues – have also used gene expression profiling to distinguish between FL cases with indolent and aggressive clinical behaviors [15]. In the near future, biologic characteristics will be used to distinguish subgroups most likely to benefit from specific therapies. Established clinical or biologic prognostic markers may lose their predictive power in the face of new therapies. Hence, prognostic markers must be reevaluated with each new treatment approach.

There are many unanswered questions. Is follicular lymphoma curable with current therapies? How can we maximize survival? And quality of life? When should treatment be initiated? Does the sequence of therapies make a difference? Do we combine strategies or is it best to use therapies in sequence? Do we transplant early, late, or not at all? How can we use our evolving understanding of biology to develop new strategies? What is the role of targeted therapy – bortezomib, the many new small molecules, new antibodies, anti-idiotype vaccines? Can gene expression patterns or biomarkers help identify the patients most likely to benefit from a specific therapy?

Only well designed clinical trials can answer these questions. Every patient should be treated on a carefully crafted study, and whenever feasible the biologic character of the tumor should be evaluated. All patients must be followed until death to assess the effect of initial therapy on subsequent responses. We must also track long-term complications. Quality of life must be studied along with clinical response. It will take the combined efforts of the bioinformatic community to address the many pressing questions posed by the follicular lymphomas.

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References


