Treatment Approaches to the Low-Grade Lymphomas

By Sandra J. Horning

Clinical trials conducted in the 1970s demonstrated that low-grade lymphomas were exquisite sensitive to single alkylating agents, a variety of chemotherapy combinations, and irradiation delivered to lymphoid regions, including total nodal irradiation or total body irradiation.1-3 Despite the high overall and complete response rates, a continuous pattern of relapse was observed with median survival times of 6 to 10 years. In contrast to the experience with aggressive lymphomas, the addition of doxorubicin did not improve overall survival or freedom from recurrent lymphoma.4 Time to failure was prolonged with maintenance chemotherapy in some series, but the pattern of continuous relapse and the duration of median survival were not altered.5,6

Based on these results, together with the fact that many patients are over 60 years of age and asymptomatic at diagnosis, investigators at Stanford University adopted a policy of conservative management in which treatment was deferred until indicated by disease progression. The survival characteristics of a group of 83 patients managed in this way were not different from a group of patients treated immediately after diagnosis.7 Young et al8 directly tested the policy of deferred treatment in a randomized trial involving selected, asymptomatic patients. In the most recent update of this study, there was no survival advantage to immediate ProMACE-MOPP chemotherapy plus total lymphoid irradiation (TLI) over deferred treatment, although the complete response rate was higher among patients treated immediately. These investigators have questioned overall survival as the standard of treatment success, suggesting that disease-free survival may be a more appropriate therapeutic endpoint. This important concept of therapeutic objective in the low-grade lymphomas will be further discussed.

Recently, a number of interferon α trials in low-grade lymphoma have become sufficiently mature for analysis and discussion. As a single agent, interferon α has modest antitumor efficacy with a response rate of 30% to 50% in patients with relatively indolent, low-grade non-Hodgkin's lymphoma.9-11 Synergy between interferon and cytotoxic agents has been demonstrated in vitro.12 These objective data, together with the theoretical attractiveness of the unique mechanism of action of the interferons, provide the rationale for large-scale clinical study of combined therapy. Five major randomized clinical trials have addressed the potential value of chemotherapy plus interferon α in low-grade lymphoma.13-17 These studies differ in design with regard to use of interferon as induction therapy, maintenance therapy, or both; the chemotherapy regimen; and patient selection factors. In each study, patients with low-grade lymphoma were randomized to receive combined chemotherapy plus interferon or chemotherapy alone.

To date, the time to failure results favor the interferon arm in four of the five clinical trials. Overall and complete response rates were increased in the interferon arm only in the French-Belgian study, and this is the first study to report a survival advantage for combined interferon and chemotherapy in low-grade lymphoma.17 However, interferon provides no evidence of a cured population in any study to date, ie, whereas the slope of Kaplan-Meier time to failure curves is favorably altered, the familiar pattern of continuous relapse is observed. These results are reminiscent of some of the previous reports of maintenance chemotherapy in low-grade lymphoma in which the benefit in time to failure was offset by time on treatment.5,6 Similar to low-grade lymphoma, clinical trials with chemotherapy plus interferon in myeloma differ with regard to potentially important treatment and patient variables, and the results have been mixed.18-20

Dose intensified chemotherapy approaches, alone or in combination with irradiation, are also under investigation. As noted above, the National Cancer Institute has tested ProMACE-MOPP and TLI.8 Clinical investigators at the British Cancer Control Agency in Vancouver and the M.D. Anderson Tumor Institute in Houston have presented data on new, multiagent chemotherapy combinations in a more aggressive approach to low-grade lymphoma.21,22 Preliminary results from each of these trials are concordant; despite a suggestion of prolonged time to failure, the familiar pattern of remitting disease without evidence of cure is seen. Myeloablative therapy and stem cell rescue is being used extensively for patients with relapsed low-grade lymphoma. Unfortunately, most of these patients are not being transplanted as part of a carefully designed clinical trial. The largest series of patients has been treated with high-dose radiochemotherapy and autologous purged marrow in a joint study conducted at St. Bartholomew's Hospital in London and the Dana Farber Cancer Institute (DFCI) in Boston, MA. In a recent, preliminary report of this study, the time to treatment failure is longer for study patients compared with historical controls managed with chlorambucil, but there is yet no survival advantage.23 Follicular lymphoma patients in first remission are being treated with high-dose radiochemotherapy and autologous purged marrow in phase II studies in progress at the DFCI in Boston and at Stanford University. It is too early to assess whether early use of this approach will result in a survival benefit or a subset of cured patients.

It is clearly disappointing that the application of modern therapy has failed to eradicate an apparently sensitive disease. It is even more frustrating that new treatments have had essentially no impact on the median survival of low-grade lymphoma patients over the past 30 years. Part of the explanation may reside in the fact that low-grade lymphomas have a low mitotic rate, whereas cytotoxic therapy is relatively specific for rapidly proliferating cells. A number of new treatments that
may complement traditional cytotoxic approaches are attractive because they are less dependent on cycling cells.

Investigations with naked antibodies, generic or idioype-specific, have met with mixed results because of a variety of factors, including antigen-negative tumor escape and production of tumors.\textsuperscript{24,25} However, of note, sustained remissions have been achieved in some individuals after anti-idiotypic therapy. Although immunotoxins have the theoretical advantage of direct cytotoxicity, clinical benefit has been modest.\textsuperscript{26} A recent report of impressive clinical responses to the anti-CD20 pan-B-cell monoclonal antibody conjugated to the radioisotope I\textsuperscript{131} has been received enthusiastically.\textsuperscript{27} The attributes of this antibody appear to result in superior tumor targeting and less myelosuppression than previously studied radioimmunoconjugates.\textsuperscript{28-30} Kwak et al\textsuperscript{31} have pioneered the use of active immunity achieved by vaccinating B-cell lymphoma patients with their own tumor-specific idioype. This approach has the theoretic advantage over passive immunotherapy of inducing a polyclonal humoral response and a cellular immune response, both of which may be relatively long-lived. Logistics have necessitated careful patient selection in these preliminary studies of immunotherapeutics; definitive clinical trials designed to determine efficacy require timely and widely available therapy. The new purine analogues, 2-chlorodeoxyadenosine, fludarabine, and deoxycoformycin, have significant single agent activity in chronic lymphocytic leukemia and low-grade lymphoma, with response rates as high as 40% to 50% in follicular subtypes.\textsuperscript{32-34} Although the mechanism of action is incompletely understood, it appears that these agents have activity in resting cells.

An additional explanation for the failure of current therapies may be provided by recent insights into the biology of \textit{bcl-2}, the proto-oncogene that is deregulated and overexpressed in the majority of follicular lymphomas.\textsuperscript{35,36} The \textit{bcl-2} gene was initially discovered because of its association with the t(14;18) chromosomal translocation, which has been demonstrated in 90% of follicular, low-grade lymphomas.\textsuperscript{37} Transcriptional deregulation results from the juxtaposition of the \textit{bcl-2} gene at 18q21 within enhancer elements of the \textit{Ig} heavy-chain locus at 14q32. This novel oncogene confers a death-sparing effect to certain hematopoietic cells lines after growth factor withdrawal.\textsuperscript{38} Specifically, \textit{bcl-2} blocks the nuclear condensation, plasma membrane blebbing, volume contraction, and endonucleolytic cleavage characteristic of programmed cell death, known as apoptosis. The \textit{bcl-2} protein is a 24-kD integral-membrane protein found in mitochondria, the nuclear envelope, and endoplasmic reticulum.\textsuperscript{39-41} The molecular mechanisms of this protein are still unknown.

Two series of experimental results suggest that \textit{bcl-2} plays an important role in the natural history of low-grade lymphoma. McDonnell et al\textsuperscript{42} demonstrated that the course of transgenic mice bearing the \textit{bcl-2}-Ig minigene resembled human follicular lymphoma. Initially, an expanded population of IgM/IgD B cells, 97% of which were in G0 or G1, accumulated in the mice. However, the follicular lymphoproliferation in the mice was polyclonal rather than monoclonal. The mice were quite well initially, despite the increased cell numbers. Over time, the follicular proliferation progressed to diffuse, large-cell immunoblastic lymphoma, a phenomenon known as histologic transformation in the clinical literature.\textsuperscript{7} It appears that the t(14;18) is not sufficient to produce a clonal malignant phenotype; a stochastic second event or coexpression of a second proto-oncogene is required. In individual patients, comparison of nucleotide sequences of the \textit{Ig} heavy chain variable region genes in follicular lymphoma tissues and the corresponding germline DNA demonstrates that mutations accumulate during clonal expansion.\textsuperscript{43,44} This supports the hypothesis that follicular lymphoma begins with the t(14;18) translocation and this is followed by antigen-driven clonal expansion.

In another series of experiments with clinical implications, Miyashita and Reed\textsuperscript{45} showed that transfection of \textit{bcl-2} into cell lines confers a relative resistance to cell killing by glucocorticoids and several chemotherapeutic agents. In experimental systems, the \textit{bcl-2} protein blocks multiple forms of apoptosis, including that induced by gamma radiation and essentially all chemotherapeutic agents.\textsuperscript{46} Recently, Oltvai et al\textsuperscript{47} have identified a new gene, \textit{Bax}, that heterodimerizes with \textit{bcl-2} and accelerates programmed cell death. These data suggest that the ratio of \textit{bcl-2} to \textit{Bax} may determine survival or death after an apoptotic stimulus. These experimental results must be reconciled with clinical observations of the exquisite sensitivity of follicular lymphomas to initial treatment with alkylating agents and prednisone as well as the lack of prognostic significance of \textit{bcl-2} expression in some immunohistochemistry studies.\textsuperscript{48}

The detection of minimal disease by DNA amplification of translocated \textit{bcl-2} has been proposed as a surrogate marker for residual or recurrent disease in the series of patients treated with high-dose therapy and purged autologous marrow by the Boston group.\textsuperscript{49} A surrogate with high predictive accuracy and significant lead time could circumvent the long follow-up required for clinical trials in low-grade lymphoma, a significant obstacle to therapeutic progress. However, the \textit{t}(14;18)-containing cells have been detected in the peripheral blood of patients who have been in remission for a number of years, indicating that a positive result does not have absolute prognostic significance.\textsuperscript{50} The detection of the \textit{t}(14;18) translocation in normal tonsil tissue by sensitive DNA amplification assays suggests that its presence does not invariably lead to lymphomagenesis. Therefore, a reproducible pattern of increasing quantity of translocated \textit{bcl-2} or conversion from a negative to a repeatedly positive result may yield the greatest information.

Where do these observations from the clinic and the laboratory take us in developing new treatment approaches for the low-grade lymphomas? First, clinical trials in progress must mature and be subjected to critical analysis. The interferon trials require careful interpretation with attention to patient selection factors, dose and schedule of interferon, and combined or sequential use with chemotherapy. Only one of these trials has been formally analyzed and reported in the peer-reviewed literature; we must not prematurely abandon a potentially useful treatment. Myeloablative therapy in first or subsequent remission should be appropriately investigated in controlled clinical trials, with attention to patient selection factors, to determine if phase III investigation is indicated. Second, newly available therapeutic de-
mand further evaluation. It will be important to test the new purine analogues in combination with other chemotherapy drugs in phase II studies. The immunotherapy approaches discussed above should be further explored with attention to feasibility for broad application in phase II studies.

Third, the determination of minimal residual lymphoma cells should be incorporated as a measurement of response for these studies and attempts should be made to make them more quantitative. Serial evaluation of markers of minimal disease may establish patterns that serve as surrogates for early relapse or persistence of disease. Fourth, future strategies could be directed toward overcoming the survival advantage conferred by bcl-2 and other suppressors of apoptosis, which presumably allows lymphoma cells to accumulate and remain vulnerable to additional genetic events. The isolation and characterization of the genes that promote or inhibit cell death within multiple death pathways is an area of active laboratory investigation. Hopefully, this work may ultimately lead to new lymphoma treatments in which the expression or activity of specific proteins can be regulated.

Finally, the relatively long natural history of the low-grade lymphomas and the wide range of patient age at diagnosis requires special consideration. With median survivals of 6 to 10 years, therapeutic index is an important consideration for all patients. Selected, particularly older and asymptomatic patients, may benefit most from watchful waiting. Younger patients face reduced longevity as a consequence of the diagnosis. Although the endpoints of therapy have been debated, patients and physicians alike seek the greatest quantity of high-quality life. The challenge and the opportunity is to translate our understanding of the biology of the low-grade lymphomas and technological advances in therapy to meet this objective.

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