Clinical Status and Optimal Use of Rituximab for B-Cell Lymphomas

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The standard management of low-grade lymphoma remains controversial. Long-term follow-up studies of patients treated with conventional regimens have shown that currently available treatments are not curative.

New Treatment Approaches for Low-Grade Lymphoma

Nucleoside Analogs—Newer chemotherapeutic agents, such as fludarabine (Fludara) and cladribine (2-chlorodeoxyadenosine [Leustatin]), have significant single-agent antitumor activity in low-grade lymphoma and are currently being tested in combination regimens.[1,2] Because these nucleoside analogs cause significant myelosuppression and immunosuppression and are associated with an increased risk of opportunistic infections, their role in the treatment of low-grade lymphoma remains undefined.

Interferon-Alfa—Recently, a meta-analysis of randomized trials evaluating the role of interferon-alfa (Intron A, Roferon-A) in the treatment of follicular lymphoma concluded that interferon-alfa prolonged overall survival in patients receiving more intensive initial therapy with regimens containing doxorubicin or mitoxantrone (Novantrone), as compared with patients receiving less-intensive therapy with single-agent alkylator therapy or CVP (cyclophosphamide, vincristine, and prednisone).[3] In contrast, the Southwest Oncology Group (SWOG) reported that the use of interferon-alfa after intensive induction chemotherapy with ProMACE-MOPP (prednisone, methotrexate, Adriamycin, cyclophosphamide, etoposide, mechlorethamine, Oncovin, and procarbazine) did not extend relapse-free or overall survival in patients with advanced low-grade lymphoma.[4]

These conflicting results make it difficult to specify recommendations regarding the role of interferon-alfa in the management of low-grade lymphoma.

Stem-Cell Transplantation—Autologous stem-cell transplantation is an effective therapy for relapsed diffuse aggressive lymphoma and histologically transformed lymphoma,[5] but its role in low-grade lymphoma is still under investigation. A number of phase II trials have demonstrated the feasibility of this intensified approach in patients with low-grade lymphoma.[6] In the absence of randomized trials, however, it has been impossible to demonstrate that autologous stem-cell grafting has curative potential or prolongs survival in patients with low-grade lymphoma. Although the acute toxicities of autologous stem-cell transplantation have been significantly reduced during the 1990s, there is still a significant risk of long-term complications, such as treatment-related myelodysplasia and acute leukemia.

Monoclonal Antibody Therapy of Lymphoma

The development of monoclonal antibodies (MoAbs) with defined specificities to lymphoma-associated antigens represents a revolution in the treatment of patients with lymphoma. Phase I/II clinical studies have been conducted using native or modified MoAbs directed against lineage-specific surface markers, such as CD19, CD20, and CD22. To enhance cytotoxicity, modified MoAbs, such as toxin-conjugated or radiolabeled antibodies, have also been designed. Rituximab (Rituxan) is a genetically engineered, chimeric, murine/human MoAb that targets the CD20 antigen found on the surface of most B-cell lymphomas. This product was recently approved by the FDA for use as a single agent in the treatment of relapsed low-grade lymphoma. It also is under investigation for use in combination regimens for follicular, mantle cell, and diffuse aggressive lymphomas.

McLaughlin and colleagues provide an excellent review of the mechanisms of action and
pharmacokinetics of rituximab, as well as clinical experience with its use in the treatment of B-cell lymphoma. Because it is a chimeric molecule, rituximab is less immunogenic and has a longer half-life than murine MoAbs. The authors review preclinical data demonstrating that rituximab mediates human effector functions (eg, complement-mediated cell lysis and antibody-dependent cell-mediated cytotoxicity) in an antigen-specific manner. In addition, induction of apoptosis and sensitization of resistant cells lines by rituximab have been seen in some cell culture models, providing a rationale for combining rituximab with chemotherapy in clinical trials.

Unresolved Questions

Dosing Schedule
The weekly schedule of rituximab administration was based on pharmacokinetic studies. However, it is unclear from these observations what peak serum rituximab levels are required to attain a maximum anti-tumor response. Since the half-life of rituximab is prolonged after each successive dose, would a decreased frequency of administration after the second or third dose lead to prolongation of therapeutic serum rituximab levels? Future studies need to compare the efficacy of four vs eight doses of rituximab. Similarly, the use of rituximab as an adjuvant or maintenance therapy needs to be investigated, particularly in patients with minimal residual disease.

Premedication
The use of cortico-steroid premedications prior to rituximab administration was specifically prohibited in all of the trials reported to date. The primary reason for this exclusion was to avoid the confounding factor of concurrent corticosteroid administration in assessing the efficacy of rituximab therapy.

As the authors point out, adverse events occurring in these trials included hypotension, bronchospasm, chills, and fever, which developed in 8%, 10%, 32%, and 49% of patients, respectively. Similar adverse events are being reported as part of post-marketing surveillance, some of which are considered to be serious and unlabeled (ie, not listed in the Rituxan package insert). These side effects may be clinically significant, especially in elderly patients with compromised cardiopulmonary reserve. In the absence of any specific data suggesting that corticosteroids are contra-indicated, it may be prudent to premedicate patients with a dose of corticosteroid prior to rituximab administration to avoid important side effects and hypersensitivity reactions in this generally older patient population.

Immunosuppression
Treatment with rituximab produces profound B-cell depletion, which persists for at least 6 months and recovers slowly thereafter. The incidence of serious infections does not appear to be increased in patients given rituximab.

Recently, Tetreault et al described a patient who developed Coomb’s positive hemolytic anemia and immunoblastic peripheral T-cell lymphoma 18 months after receiving rituximab for low-grade follicular small cleaved cell lymphoma.[7] This report raises the possibility that the immune defects resulting from depletion of CD20-positive cells may be clinically important.

Other available therapies for low-grade lymphoma also produce altered states of immunity. For example, treatment with nucleoside analogs often results in profound T-cell depletion, which can lead to the development of opportunistic infections and immune-mediated cytopenias. Whether prior, concomitant, or subsequent therapy with nucleoside analogs increases the risk of infections or complications of immunodeficiency in patients receiving rituximab remains to be determined.

Patient Selection
All of the clinical trials of rituximab conducted to date have enrolled only patients with measurable disease. However, rituximab is ideally suited for randomized studies in low-grade lymphoma patients with minimal disease (ie, following conventional chemotherapy or autologous stem-cell transplantation).

Other promising areas for further investigation of rituximab include: (1) in vivo purging prior to autologous stem-cell transplantation, with or without post-transplant rituximab consolidation; (2) treatment of other subtypes of B-cell lymphoma, such as small lymphocytic, mantle cell, lymphoplasmacytic, and marginal zone (eg, mucosa-associated lymphoid tissue [MALT] lymphoma) histologies; (3) incorporation into front-line chemotherapy regimens for low-grade and aggressive lymphomas; (4) identification of patients who are more likely to benefit from an extended course of therapy, such as those with bone marrow or peripheral blood involvement; and (5) treatment of elderly patients with comorbid conditions.

Summary
Rituximab compares quite favorably with other treatment approaches available for low-grade lymphoma and provides an alternative to the use of more toxic interventions, such as nucleoside analogs, interferon-alfa, and autologous stem-cell transplantation. Although the development of rituximab represents a major advance in the treatment of B-cell malignancies, it is not a curative therapy for recurrent low-grade lymphoma. It is conceivable that the use of rituximab as a
consolidation or maintenance therapy may lead to prolongation of survival; however, the majority of patients with recurrent or advanced low-grade lymphoma will die as a consequence of their disease. Alternative treatment strategies are needed, particularly in younger patients whose lifespan is likely to shortened because of their low-grade lymphoma. The ability of radioimmunotherapeutic approaches to selectively target radiation to malignant B-cells may improve the efficacy of MoAb therapy when administered as front-line[8] or autologous stem-cell transplantation-based salvage therapy.[9]

Finally, carefully selected patients with low-grade or follicular lymphoma may be candidates for autologous bone marrow transplantation. This aggressive approach is associated with high early mortality but a very low rate of relapse, presumably because of the graft-vs-lymphoma effect seen in this setting.[10]

References:


