Advances in the Management of Lymphoma

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This special “Annual Highlights” supplement to Oncology News International is a compilation of the major advances in the management of the lymphomas and leukemias during 2002, as reported in ONI. Commentaries by the editors, Drs. Gregory Bociek, James Armitage, and Michael Keating, provide perspective and prediction as to how these developments may affect clinical practice.

The past year has seen a number of exciting advances in the management of patients with hematologic malignancies. The principal developments have been those focused on the concept of targeted therapy. Though this concept is not new, continued evolution in therapeutic strategies and advances in knowledge of the biology of various cellular targets more than ever are bringing about the potential for new therapies with additive or synergistic potential and minimal additional toxicity. In this special supplement to Oncology News International (ONI), we present a compilation of reports on hematologic malignancies published in ONI over the past year. In this commentary we review some of the important data and news regarding the lymphomas. The original reports from ONI follow on the subsequent pages. Dr. Michael Keating presents a commentary on happenings in leukemia on page 17, and again this is followed by highlights from ONI 2002.

CHOP/Rituximab Superior to CHOP Alone

The results of the GELA trial randomizing patients with diffuse large B-cell lymphoma aged 60 years or older to cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) vs CHOP/rituximab (Rituxan) are particularly exciting and encouraging (see page 4 for more on the Groupe d'Etude des Lymphomes de l'Adulte [GELA] trial). The first peer-reviewed manuscript for study was published in the New England Journal of Medicine in January 2002 (346:235-242, 2002). This study provides level I evidence that the addition of rituximab is superior to CHOP alone in this patient group. Whether or not these are the best results that can be achieved with this combination or particular strategy remains to be seen. An Eastern Cooperative Oncology Group (ECOG) study (E4494) with a similar design but a different administration schedule for rituximab contained a second randomization to maintenance rituximab vs no further rituximab. This trial has now completed accrual, and is awaiting preliminary results. The data published by Czuczman et al using the combination of CHOP/rituximab in patients with indolent non-Hodgkin's lymphoma (NHL) also lends some insight into the potential benefit of this combination in the setting of indolent NHL. In this phase II study CHOP was administered at standard doses along with six infusions of rituximab at a dose of 375 mg/m². The high complete response rate (67% in evaluable patients) and duration of progression-free survival (median not reached at 5.4 years follow-up) is superior to that expected with CHOP alone, although the phase II nature of the design makes it difficult to determine whether or not other factors such as inadvertent selection bias might have had any influence on the results. The conversion of many patients to polymerase chain reaction (PCR) negativity for bcl-2 suggests clearance of minimal residual disease with this regimen. Again, a relevant question particularly in this setting would be the issue of maintenance therapy.

Maintenance Therapy Offers Benefit

A study presented by Ghielmini et al at the Eighth International Conference on Malignant Lymphoma (ICML) in Lugano, Switzerland treated newly diagnosed/relapsed or resistant patients with indolent NHL with rituximab 375 mg/m² weekly for 4 weeks. Patients with at least stable disease were randomized to further rituximab every 2 months for 8 months vs observation, and experienced a longer event-free survival. This type of preliminary data should revitalize interest in further trials looking at the concept of maintenance therapy, particularly for indolent lymphomas. Monoclonal antibody therapy appears to be well tolerated and efficacious when used repeatedly, and most physicians would agree in concept that indolent lymphomas are a good model in which to explore the maintenance concept.

New Standards for Aggressive NHL?

Two parallel-randomized trials from Germany for patients with aggressive lymphomas have led to provocative results (see page 5). Each study had an identical 2x2 factorial design (looking at the effect of varying the treatment interval for CHOP between 14 and 21 days and the effect of adding etoposide to CHOP [CHOEP]). The first study treated patients 18 to 60 years of age and concluded that in this patient population complete response rates and time to treatment failure were superior for the CHOEP regimens without added nonhematologic toxicity, while varying treatment intervals had no effect on outcome.
The second study treated patients between 61 and 75 years of age and concluded that in this patient population, CHOP delivered at 14-day intervals was superior to CHOP delivered at 21-day intervals (time to treatment failure and overall survival), whereas the addition of etoposide was of no detectable benefit. With identical designs leading to such disparate results based on age only and the current trend toward the use of rituximab in conjunction with CHOP for aggressive NHL, these studies would probably require replication and/or longer follow-up for most clinicians to consider a change in practice. **NCCN Guidelines for NHL Updated** The most recent version of the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of early Hodgkin's disease have been altered based on recent results from European randomized trials (see page 7). Present recommendations are following the pendulum in its path back toward combined-modality therapy in an attempt to minimize long-term toxicity resulting from more aggressive use of either single modality. Consideration of staging laparotomy has been removed from the guidelines, because combined-modality therapy is recommended as preferred front-line therapy for virtually all patients with early-stage disease. Though certain situations may arise where radiation therapy alone is acceptable, it is unlikely to be the preferred therapy in any setting. The guidelines appropriately continue to stress the importance of participation in clinical trials for patients with advanced disease, such as the ongoing US cooperative group randomized trial of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) vs Stanford V (doxorubicin, vinblastine, mechloretamine, vincristine, bleomycin, etoposide, and prednison) for newly diagnosed patients with bulky or advanced stage disease. **Zevalin Approved in Refractory NHL** The approval of ibritumomab tiuxetan (Zevalin) for patients with relapsed/refractory indolent or transformed indolent NHL marks the first ever radiolabeled antibody approved for use in cancer treatment (see page 10). The antibody is labeled with indium-111 for initial imaging/biodistribution, and is labeled with yttrium-90 for the therapeutic infusion. The addition of yttrium-90 to the anti-CD20 antibody produces significant myelosuppression in approximately half of treated patients. However, life-threatening complications such as bleeding and infection are extremely rare, and can be minimized by careful monitoring (and where appropriate treatment) of cytopenias until clear resolution occurs. When compared with rituximab in a randomized trial, ibritumomab demonstrated a higher response rate but no clear advantage in time to progression was seen. Given this observation, and given that patients even refractory to rituximab can respond to ibritumomab, it seems most likely that ibritumomab will find its way into the clinic as a salvage therapy for patients who have had prior rituximab. It should be remembered that the safety profile for ibritumomab is defined only in patients with < 25% bone marrow involvement by lymphoma and a platelet count of at least 100,000/μL. **Radiotherapy for NHL Defined** Recent data have perhaps helped further define the role of radiotherapy in patients with early-stage NHL (see page 10). A trial by Miller and colleagues first reported in the *New England Journal of Medicine* in 1998 randomized patients with early-stage NHL to three cycles of CHOP/involved-field radiation vs eight cycles of CHOP. This trial was initially reported as showing a small but statistically significant advantage for patients randomized to the combined-modality therapy arm. With a median follow-up of more than 8 years, updated results continue to show an advantage for patients receiving combined-modality therapy through 7 to 9 years post-treatment. However the Kaplan-Meier estimates now overlap at 7 years for failure-free survival, and 9 years for overall survival, suggesting the benefit of combined-modality therapy may not carry over past this point in time. One possible conclusion from this study is that patients with early-stage disease actually require more or different initial systemic therapy than three cycles of CHOP. The randomized ECOG study for patients with untreated bulky or extranodal stage I or stage II aggressive NHL demonstrated a reduction in relapse rates for patients who received involved-field radiotherapy in first complete remission, but intent-to-treat data were unable to demonstrate a survival advantage with this approach. However, of note, involved-field radiotherapy delivered to sites of residual disease for patients in first partial remission after CHOP converted 28% of those patients to complete response. **Autologous/Nonmyeloablative SCT Approach Promising** The notion of using autologous stem cell transplants (ASCT) as initial therapy, followed by consolidative nonmyeloablative stem cell transplantation (NST) is receiving considerable attention, particularly for chemo-sensitive indolent diseases such as follicular lymphoma and multiple myeloma. A pilot study by Maloney et al treated 41 patients with myeloma with melphalan/ASCT followed by NST using total body irradiation/unmodified allogeneic stem cells from HLA-identical siblings (see page 15). The majority of patients did not require hospitalization, and all patients successfully engrafted with a median of 90% donor cells by day 28 post-NST. Treatment-related mortality was 12% at 1 year, and progression-free survival 85% at a median of 328 days post-NST. Though graft-vs-host disease was seen in nearly 50% of patients, this two-phase approach appears to be much less toxic than full
allografting, and is one of the randomized treatment arms in a study being conducted by the Bone Marrow Transplant Clinical Trials Network. **What Can We Expect in 2003?** The year 2003 will see a continuing evolution in our knowledge of the roles of various targeted therapies. Expect to see a continued emphasis on determining the role of monoclonal antibody therapy in a number of settings such as early-stage diffuse large B-cell lymphoma, with other chemotherapy combinations, and in the setting of autologous stem cell transplantation. Also look for studies examining the possible role of multiple antibody combinations with or without cytokines or other cytotoxic therapy. An example of this is the National Cancer Institute trial of apolizumab and rituximab in the setting of relapsed lymphomas and chronic lymphocytic leukemia. The development of agents like rituximab and ibritumomab has led to a sometimes confusing myriad of phase II data over the past few years. We must not forget that the principal role of phase II studies is to identify therapies with acceptable toxicity and reasonable evidence of efficacy, but that the gold standard remains the testing of these new therapies against existing standard therapies in large well-designed randomized phase III trials.

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