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EDITORIAL

Mantle Cell Lymphoma: At Last, Some Hope for Successful Innovative Treatment Strategies

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While it is quite unusual for totally new types of cancer to develop, it is not unusual for new and distinct forms of cancer to be recognized among what were previously thought to be well-defined homogeneous diseases. Such is the case with mantle cell lymphoma (MCL). Originally recognized in Europe and subsequently called many different names, the unifying term MCL was proposed by an international consensus conference in 1992.[1] Morphology alone was not sufficient to accurately separate these cases from other "small round cell" lymphomas. However, morphology plus an immunophenotype consisting of CD20+, CD22+, IgM+, IgD+, and CD5+, as well as either detection of the characteristic chromosomal translocation t(11;14) or overexpression of the resultant gene product cyclin D1, result in an accurate diagnosis.[2] Furthermore, the previously unrecognized entity of MCL was not rare and actually represented 6% of all non-Hodgkin's lymphomas. A retrospective review of 375 patients enrolled on Southwest Oncology Group (SWOG) indolent lymphoma clinical trials demonstrated that these cases did not have an indolent course: the median progression-free survival following initial treatment was only 20 months, the median survival was only 36 months, and no patients were cured of their disease.[3] A subsequent review of 524 patients treated on 12 different clinical trials revealed amazing uniformity in the treatment results.[4] Thus, in comparison with the indolent lymphomas, which were incurable but had a median survival of 7 to 10 years, and the aggressive lymphomas, which could be cured in 40% to 50% of all cases, patients with MCL could be viewed as having the worst prognosis of all forms of lymphoma. That manuscript concluded that patients with MCL "are candidates for innovative (and hopefully more successful) therapy."[3]

Clinical trials conducted in the intervening years have generally yielded disappointing results. Although there is no established standard of care for patients with MCL, combination chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) remained the most commonly used initial treatment, especially in the United States. There still remains some controversy over the value of doxorubicin. Fludarabine-based regimens are also utilized. After rituximab was shown to have an approximately 30% response rate in patients with relapsed MCL,[5] Howard et al[6] conducted a phase II study of CHOP plus rituximab (*R*-CHOP) in untreated patients. Although they did note an increased complete remission rate compared with historical controls, there did not seem to be any difference in progression-free or overall survival. Hiddeman et al[7] recently reported the initial results of a relatively small randomized trial in untreated MCL comparing CHOP and *R*-CHOP. Although there seemed to be some improvement in time to treatment failure from the addition of rituximab, the magnitude of the benefit was not great. The study also had a second randomization to interferon maintenance therapy or autologous stem-cell transplantation; those aspects of the study have not yet been analyzed. The only published trial that reported greatly improved results in MCL was a single-institution study by The M.D. Anderson Cancer Center group, with relatively short follow-up, utilizing HyperCVAD (fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone) with or without stem-cell transplantation.[8] However, allogeneic transplantation is not an option for most patients with MCL because of their median age of 60 years; the vast majority of patients who undergo autologous stem-cell transplantation will relapse. Subsequently, the same group reported that the addition of rituximab to the HyperCVAD regimen eliminated the need for stem-cell transplantation. A national phase II trial of that same regimen is currently being conducted by SWOG.

Thus, it is clear that new therapeutic approaches for the treatment of patients with MCL need to be developed. A series of new agents, including bortezomib, thalidomide, flavopiridol, pixantrone, *m*-TOR inhibitors, and others, has shown some initial activity in pretreated patients. In this issue of the *Journal*, O'Connor et al[9] and Goy et al,[10] report the results of

two separate phase II clinical trials conducted in relapsed or refractory indolent non-Hodgkin's lymphoma with the novel proteasome inhibitor bortezomib. While it is beyond the scope of this Editorial to review in detail the ubiquitin-proteasome pathway, there is ample preclinical evidence to support trials of proteasome inhibition in hematologic malignancies, and particularly in indolent lymphomas. Both studies used a dose of 1.5 mg/m^2, which is higher than the 1.3-mg/m^2 dose currently recommended in multiple myeloma. However, the schedule of administration remains the same in all studies: twice-weekly intravenous injections administered during the first 2 weeks of a 3-week cycle. The median number of prior therapies exceeded three in both studies. Although bortezomib is clearly active in follicular lymphoma, the results in follicular lymphoma differ somewhat between the two studies and will need to be better defined in larger trials. In addition, there are many more active agents for patients with follicular lymphoma. However, the results in MCL patients are remarkably consistent and quite exciting. Five of the 10 assessable MCL patients in the O'Connor study achieved objective responses (50%; one complete response [CR], four partial response [PR]). Response durations were 6, 6+, 7+, 9+, and 19 months. The last patient has been re-treated and achieved a second PR that continues at 4 additional months. Of the 29 assessable MCL patients who were treated on the Goy et al study, there were six CR and six PR, for an objective response rate of 41% (95% CI, 24% to 61%). The median time to progression for MCL has not been reached, and an estimated 80% are still in response at 6 months, with a median follow-up of 9.3 months. In general, both studies report reasonably tolerable toxicity profiles, similar to those seen in patients with multiple myeloma. The National Cancer Institute of Canada is also conducting a phase II study of bortezomib in MCL using the 1.3-mg/m^2 dose.[11] They initially reported an overall response rate of 39%.[11] Thus, three separate phase II studies report an overall response rate of 40% to 50%, with durations of response in the two published studies exceeding 6 months in heavily pretreated patients with MCL. This author is currently leading a large, multicenter, industry-sponsored phase II trial of bortezomib at a dose of 1.3 mg/m^2 to accurately define clinical benefit for patients with relapsed or refractory MCL. In an initial attempt to combine bortezomib with combination chemotherapy, the National Cancer Institute is conducting a phase I/II study of bortezomib combined with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) chemotherapy in relapsed or refractory diffuse large B-cell lymphoma. Preliminary results suggested that gastrointestinal toxicity, but not neurotoxicity, might be increased compared with historical controls; the authors concluded that bortezomib can be given with combination chemotherapy at full dose without significant overlapping toxicity.[12] However, to date, there was only one PR among 13 enrolled patients with diffuse large B-cell lymphoma. Currently, studies of bortezomib in combination with chemoimmunotherapy are being conducted in untreated patients with MCL. Until the value of adding bortezomib to the treatment of patients with MCL is fully evaluated, these patients should continue to be entered on clinical trials, which offer the best hope for changing the prognosis of patients with MCL.

Author's Disclosures of Potential Conflicts of Interest

The following author or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Consultant/Advisory Role: Richard I. Fisher, Genentech, IDEC, Millennium Pharmaceuticals. Honoraria: Richard I. Fisher, Genentech, IDEC, Millennium Pharmaceuticals. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the "Disclosures of Potential Conflicts of Interest" section of Information for Contributors found in the front of every issue.

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