How I Treat . . .

How I Treat Mantle Cell Lymphoma

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Mantle-cell lymphoma (MCL) is a rare subtype of non-Hodgkin's lymphoma with a poor prognosis, which comprises approximately 6% of non-Hodgkin's lymphoma cases in the United States.[1] Because consensus on the appropriate treatment is currently lacking, I will suggest some treatment approaches, which although based on the limited available data, I have found useful.

Pathology and Cytology

The malignant cells in MCL resemble lymphocytes in the mantle zone adjacent to the lymphoid follicles. The tumor cells have monoclonal surface immunoglobulin (Ig) M and often surface IgD, express B-cell antigens and CD5, but unlike small cell lymphoma, chronic lymphocytic leukemia type, they do not express CD23. When subjected to cytogenetic analysis, they have a characteristic reciprocal translocation, t(11; 14), in which the bcl-1 locus containing the PRAD-1 or cyclin D1 gene on chromosome 11 is placed in proximity to the Ig heavy chain gene on chromosome 14, resulting in deregulation and overproduction of cyclin D1 protein, a cell cycle protein not usually expressed in lymphoid cells.

Clinical Presentations

This disease is usually stage IV at diagnosis, and bone marrow involvement as well as a leukemic presentation—where circulating mantle cells are found in the peripheral blood—are common. A variant of MCL can present as multiple polyps throughout the gastrointestinal tract (lymphomatous polyposis). MCL has an indolent course in a small subset of patients.[2] It has been difficult to identify these patients, but they are often elderly and asymptomatic at presentation. Approximately 5% to 15% of patients will present with limited stage I and II disease.[3,4]

My Approach to Therapy

The prognosis of advanced stage MCL is poor with conventional chemotherapy. Perhaps the best characterized experience is that reported by the Southwest Oncology Group, in which the median failure-free survival (FFS) was 20.5 months and overall survival (OS) was 36 months. FFS at 10 years was 6% and OS was 8%.[5] The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) improves the response rate but not the progression-free survival (PFS) rate or the OS rate.[6] This observation has lead to development of more intensive treatment approaches for patients with good performance status or those who are otherwise able to tolerate rigorous chemotherapy. Because MCL is usually a systemic disease, the role of radiation therapy is limited to local control of disease if this is of paramount clinical concern.

Autologous stem-cell transplantation (ASCT) has not been successful in achieving durable remissions in relapsed/refractory MCL.[7,8] However, promising results have been reported with the inclusion of ASCT as part of the initial treatment of MCL, particularly with the addition of rituximab as part of the regimen. A combination of chemotherapy including rituximab followed by ASCT in untreated MCL was recently reported from Cancer and Leukemia Group B (CALGB trial 59909). At a median follow-up time of 27.5 months, PFS was 75% at 2 years and 56% at 3 years. The OS was 82% at 3 years.[9]

For a relatively young patient who is a potential candidate for ASCT, I usually recommend treatment based on our experience at the Memorial Sloan-Kettering Cancer Center, New York, New York. We have employed four to six cycles of CHOP every 2 weeks (CHOP-14) with or without rituximab followed by two to three cycles of ifosfamide, carboplatin, and etoposide (ICE) with or without rituximab followed by ASCT. At a median follow-up time of 2.5 years, the reported the 5-year PFS and OS rates were 58% and 83%, respectively. Only one of 26 patients who received rituximab as part of the treatment relapsed, in contrast with 10 of 20 patients who did not receive rituximab.[10] These data are promising although inconclusive because these results are not derived from randomized prospective data and the follow-up was longer for patients who did not receive rituximab. As a result of this experience, I usually plan four cycles of rituximab plus CHOP-14, three cycles of rituximab plus ICE, and proceed to ASCT if a good response is obtained with the first two regimens.

For younger patients who can tolerate intensive chemotherapy, the intensive rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimen is another approach. A high complete response (CR) rate of 87% has been reported with hyper-CVAD alternating every 21 days with rituximab plus high-dose methotrexate and cytarabine for three or four cycles of both regimens. The FFS and OS at 3 years were 64% and 82%, respectively, but there does not seem to be a plateau in either actuarial curve. Although the CR rate was lower for the blastoid variant of MCL, unlike the other variants of MCL, there appears to be a FFS plateau of approximately 50%.[11,12]

In an elderly asymptomatic patient with limited disease, a period of careful observation without immediate initiation of treatment

may be warranted. If the patient develops symptoms, rituximab and fludarabine alone or in combination with cyclophosphamide with or without mitoxantrone are effective palliative regimens.[13]

In a small number of patients (approximately 15%) who present with limited stage I and II disease radiation therapy may have a role —after careful staging including bilateral bone marrow biopsies, upper and lower gastrointestinal endoscopy, and [^{18}F]fluorodeoxyglucose positron emission tomography scanning.[3,4] Radiation therapy, with or without chemotherapy, has been reported to be associated with 5-year OS and PFS rates of 70% and 46%, respectively.[14] It is unclear whether or not radiation therapy is necessary for this small group of patients with a relatively favorable prognosis if intensive chemotherapy with the addition of rituximab, as mentioned earlier, is used. Circumstances where I would definitely add radiation therapy are those in which local control of disease is of major clinical concern and has not been achieved with systemic treatment. MCL is exquisitely sensitive to radiation therapy, and excellent local palliation has been reported with involved-field radiation therapy.[15]

Relapsed or Refractory Mantle Cell Lymphoma

There are a number of choices for palliation of relapsed/refractory MCL including the fludarabine-based regimens,[13] radioimmunotherapy[16,17] bortizomib,[18] thalidomide and rituximab,[19] and temsirolimus.[20] Nonmyeloablative allogeneic stem cell transplantation resulted in a 65% OS rate and a 60% disease-free survival rate at 2 years, although the treatment-related mortality was 24%.[21] Among 154 patients with relapsed or refractory MCL treated with bortezomib, the overall response rate was 31% (CR + CR/unconfirmed [CRu] = 7%) and duration of response 4.6 months by central radiology review.[18] Based on these data, bortizomib has been approved for this indication. Among 15 patients with relapsed or refractory MCL, five achieved CR (n = 3) or CRu (n = 2) after treatment with Yttrium 90 ibritumomab tiuxitan.[17] High CR rates have also been reported with chemotherapy followed by iodine-131 tositumomab[16] and with high-dose iodine-131 tositumomab with ASCT.[22]

MCL is a therapeutic challenge, and, hopefully, well-designed randomized controlled trials incorporating present and new therapeutic tools will result in an improved outcome in the future.

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