Mantle Cell Lymphoma: Clinicopathologic Features and Treatments

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Drs. Baidas, Cheson, Kauh, and Ozdemirli present a thorough and balanced review of mantle cell lymphoma (MCL) and the various current treatment options. MCL has been recognized as a distinct pathologic entity for over a decade. It represents 6% to 9% of all non-Hodgkin’s lymphoma cases, and the diagnosis is based on a combination of morphologic, immunophenotypic, and cytogenetic criteria as discussed in the article. The hallmark of MCL is t(11;14)(q13;q32), a translocation that juxtaposes the Bcl-1 gene on chromosome 11 and immunoglobulin (Ig)H promoter on chromosome 14, leading to overexpression of cyclin D1. Although it had been considered an indolent lymphoma for many years, MCL has a poor prognosis with short remissions and a median survival of 3 to 4 years.[1,2]

Conventional Chemotherapy

As discussed in the article, numerous chemotherapy regimens have been reported in the treatment of MCL, and optimal therapy is yet to be established. The role of anthracyclines in the treatment of this disease is still unclear, as some studies[3-6] have demonstrated improved overall survival and others[7-11] have failed to demonstrate such benefit. In a retrospective study in 68 MCL patients treated at the University of Nebraska Medical Center, 79% received an anthracycline-based regimen and 21% received a non-anthracycline-based regimen. Survival among patients treated with anthracycline-based regimens was no better than that in the other group.[12] More recently, more intensive regimens have been evaluated for the treatment of MCL, such as the hyper-CVAD regimen (hyperfractionated cyclophosphamide [Cytoxan, Neosar], vincristine, doxorubicin [Adriamycin], dexamethasone).[13] As pointed out in the review, when combined with rituximab (Rituxan), this regimen produces promising results; further study of the combination in a cooperative group setting is planned. The need for the addition of high-dose chemotherapy and stem cell transplantation in patients in first complete response who are receiving hyper-CVAD is still unknown and also needs further evaluation.

High-Dose Chemotherapy Followed by Stem Cell Transplant

Because conventional chemotherapy is not thought to be curative in most patients with MCL, high-dose chemotherapy followed by stem cell transplant has been evaluated in an effort to improve survival rates. No prospective randomized study comparing conventional therapy with high-dose chemotherapy followed by stem cell transplant has yet been published. However, several phase II trials of stem cell transplant in MCL patients have been published. Most of these studies demonstrated that patients are more likely to benefit from this approach if the transplant is performed earlier in the course of the disease (ie, first complete response).[14] Improvements in this approach include better induction chemotherapy, such as rituximab/hyper-CVAD, and the addition of other agents to modify the transplant regimen, such as rituximab for in vivo purging[15] or radioimmunotherapy with tositumomab/iodine-131 tositumomab (Bexxar) or ibritumomab tiuxetan (Zevalin).[16-18] However, as the authors point out, autologous stem cell transplant may only improve the response rate and time to treatment failure without achieving cure. An alternative to this approach, which was not discussed extensively in the article, is the use of high-dose chemoradiotherapy and an allogeneic stem cell transplant. Such a protocol was evaluated in a selected population of young MCL patients.[19,20] At the University of Nebraska Medical Center, we performed transplants in 20 MCL patients using a fully myeloablative regimen with a related...
allogeneic donor; 45% of patients are alive and disease-free between 1 and 9 years posttransplant (Figure 1). However, allogeneic stem cell transplant has a limited role in MCL, as most patients with this disease are over 60 years old. The toxicity of allogeneic transplant could be reduced by using nonmyeloablative regimens.

**Immunotherapy**

When used as a single agent in clinical trials, rituximab has produced response rates of 20% to 40% in MCL patients. Phase II trials of rituximab plus combination chemotherapy have achieved promising results in MCL patients, with overall response rates ranging from 92% to 100% and complete response rates, from 48% to 98%. The German Low-Grade Lymphoma Study Group (GLSG) has conducted two randomized trials comparing standard chemotherapy with chemotherapy plus rituximab in patients with MCL and follicular lymphoma. In the first study, patients were randomized to FCM alone (fludarabine [Fludara],

cyclophosphamide, mitoxantrone [Novantrone]) or FCM with rituximab (R+FCM). Patients who achieved a complete or partial response underwent a second randomization to either maintenance therapy with rituximab or observation alone. The overall response rate to R+FCM was 65% (35% complete response) compared with a 33% overall response rate (0% complete response) to FCM alone.[21] In the second phase III randomized study of R-CHOP (rituximab plus cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone) vs CHOP, the subset of evaluable MCL patients who received R-CHOP achieved higher overall response rates than did those treated with CHOP alone (95% vs 76%).[21] An additional therapy for MCL currently being evaluated is the idiotype vaccine as an adjuvant to immunotherapy. In these studies, the patient's lymphoma is biopsied and a patient-specific vaccine is manufactured. The EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) plus idiotype vaccine and the CHOP plus idiotype vaccine are examples of two such regimens being tested in clinical trials.[22,23]

**Novel Agents**

Because standard therapies are not curative in MCL and many patients are not candidates for transplant, novel agents are being evaluated to enhance the efficacy of MCL treatment. Examples of ongoing trials not discussed in the article include studies of novel agents such as bortezomib (PS-341, Velcade) and Bcl-2 antisense (Genasense) for the treatment of both newly diagnosed and refractory MCL patients. Bortezomib is a reversible proteasome inhibitor. Proteasome inhibition can lead to cell-cycle dysregulation, resulting in apoptosis. Initial results from a small pilot trial demonstrated that multiply treated MCL patients showed evidence of some clinical response.[24] Bcl-2 antisense inhibits Bcl-2 gene expression by hybridization arrest, followed by cleavage of the m-RNA by RNAase-H. In vitro studies have demonstrated synergistic antitumor activity when Bcl-2 antisense is used in combination with standard chemotherapy. The agent is currently being
evaluated in a phase II trial, alone or in combination with R-CHOP in patients with newly diagnosed, refractory, or relapsed MCL. Additional novel agents with activity in MCL are needed. **Conclusions**

This article presents a balanced review of the literature on MCL. Because standard therapies for MCL are not curative, clinical trials of novel therapies, immunotherapies used in combinations, and high-dose chemotherapy with autologous or allogeneic stem cell transplant should be considered for all patients with newly diagnosed or recurrent MCL.

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**References:**


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