Management of Mantle Cell Lymphoma

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Manifestations of mantle cell lymphoma were recognized in the 1970s as distinct from those associated with the more readily classifiable lymphomas. It was not until the 1990s, however, that observation of a combination of immunologic, cytogenetic, and molecular genetic abnormalities characteristic of this new malignancy confirmed its existence. The clinical and pathologic entity was named mantle cell lymphoma and in 1994 was incorporated into the Revised European American Lymphoma Classification. Mantle cell lymphoma is a CD5 positive, B-cell lymphoma that usually displays the t(11;14). The lymphoma has a striking male predominance and is widely disseminated at diagnosis in 80% of patients. Mantle cell lymphoma responds poorly to available therapies, and the median survival is approximately 3 years.[ONCOLOGY 12(Suppl 8):49-55, 1998]

Introduction

Mantle cell lymphoma is a recent addition to the group of malignancies lumped under the term "non-Hodgkin"s lymphomas.[1-2] However, despite being newly recognized, the disease itself is not new. In the 1970s, investigators in both Europe and America recognized that some lymphomas of small cells did not fit well into previously utilized categories. In the United States, Berard et al proposed the term, "lymphocytic lymphoma of intermediate differentiation" to describe a group of lymphomas that were not easily classifiable as diffuse well-differentiated lymphocytic lymphoma or diffuse poorly differentiated lymphocytic lymphoma using the Rappaport Classification.[3-5] At approximately the same time in Europe, Lennert et al proposed an entity they termed "centrocytic lymphoma."[7-9] In both cases, the tumors were B-cell lymphomas that expressed surface immunoglobulin. The nuclei were intermediate in shape between the round cells of small lymphocytic lymphoma and the cleaved cells of follicular lymphoma.

In the 1980s, Weisenburger et al, and Palutke et al, described a type of follicular lymphoma that was atypical in that there were wide mantles of malignant cells around apparently benign general centers.[10,11] Weisenburger et al proposed the term "mantle zone lymphoma" for these tumors, and believed that the malignancy might represent the follicular counterpart of the diffuse intermediate lymphocytic lymphoma described by Berard et al.[10,12]

Immunologic, cytogenetic, and molecular genetic studies all contributed to resolving this dilemma. Immunologic studies showed that the tumors called diffuse intermediate lymphocytic lymphoma, centrocytic lymphoma, and mantle zone lymphoma were usually positive for CD5 (eg, a T-cell antigen) and negative for CD10. However, they were consistently positive for CD20 and expressed surface immunoglobulin confirming their B-cell origin.[14-17]

The cytogenetic abnormality t(11;14)(q13;q32) that was originally described in patients with chronic lymphocytic leukemia is the characteristic cytogenetic abnormality seen in mantle cell lymphoma.[18,19] Studies of the break point in the (11;14) identified the immunoglobulin heavy chain on chromosome 14 as one break point and a new oncogene designated bcl-1 on chromosome 11.[20] The oncogene has also been referred to as PRAD1 and in codes for the protein cyclin, D1, which is overexpressed in almost every case of mantle cell lymphoma, but rarely expressed in other malignancies.[21,22]

The combination of characteristic immunologic, cytogenetic, and molecular genetic abnormalities confirmed the existence of a new clinical/pathologic entity that is now termed "mantle cell lymphoma" and unified the diagnosis of pathologists on both sides of the Atlantic (Table 1).[1,2] Mantle cell lymphoma is one of the entities incorporated into the Revised European American Lymphoma (REAL) Classification.[23] In a clinical evaluation of that new classification involving study sites in North America, Europe, Africa, and Asia, mantle cell lymphoma made up approximately 6%
Clinical Characteristics

The study performed by the non-Hodgkin’s lymphoma classification project investigators found 83 cases of mantle cell lymphoma.[24] The diagnosis of mantle cell lymphoma was able to be made accurately in 70% of cases on stained slides without the need for immunologic studies.[24] The addition of immunologic staining improved the accuracy of diagnosis to 87%.[24] The availability of clinical information did not further improve the accuracy of the diagnosis. Thus, with expert pathologists working with clear definitions, mantle cell lymphoma can be diagnosed quite accurately. However, the availability of immunologic studies makes a significant improvement in the accuracy of the diagnosis. Mantle cell lymphoma is not a rare diagnosis and is the fifth most common B-cell non-Hodgkin’s lymphoma.[24]

Mantle cell lymphoma is largely a tumor of males, with a 74% male predominance in the Non-Hodgkin’s Lymphoma Classification Project study (NLCP).[24] Mantle cell lymphoma is rarely seen in young patients; the median age of patients is 63 years (Table 2).[24] In the non-Hodgkin’s lymphoma classification project, mantle cell lymphoma is one of the lymphomas most likely to have bone marrow involvement, with 63% of the cases studied having positive bone marrow biopsies.[24] There is a high proportion of cases with disseminated disease and only 19% of the cases are clinical Stage I or II using the Ann Arbor staging system.[24]

An improved method of predicting treatment outcome in non-Hodgkin’s lymphoma utilizes the International Prognostic Index.[25] This system, developed after a study of patients with diffuse large-cell lymphoma, predicts the outcome of patients with other subtypes of non-Hodgkin’s lymphoma. The International Prognostic Index simply sums the number of adverse prognostic characteristics. These include an age of 60 years or greater, a depressed performance status, a serum lactic dehydrogenase level higher than normal, more than one extra nodal site of involvement by lymphoma, and disseminated disease as indicated by Ann Arbor Stage III or IV. Only 19% of patients with mantle cell lymphoma had an International Prognostic Index score of 0 or 1, and 19% had an International Prognostic Index score of 4 or 5.[24]

Surprisingly, given the existence of a small-cell, B-cell lymphoma, the clinical course has been unfavorable in patients with mantle cell lymphoma. In the Non-Hodgkin’s Lymphoma Classification Project study, the 5-year overall survival for mantle cell lymphoma was 27%, and the 5-year failure-free survival was 11%.[24] Only peripheral T-cell lymphoma and lymphoblastic lymphoma had a comparably poor 5-year overall survival, and mantle cell lymphoma stood alone with the poorest 5-year failure-free survival. The shape of the failure-free survival curve is not encouraging in suggesting a significant proportion of cured patients.

Most patients with mantle cell lymphoma present with enlarged lymph nodes and a biopsy leads to the diagnosis. However, there are other presentations characteristic of this entity. Mantle cell lymphoma can present as chronic lymphocytic leukemia and should be considered in the differential diagnosis of that disorder. The cytologic characteristics of the tumor, immunologic staining, and cytogenetic and molecular genetic studies should help resolve any confusion. Mantle cell lymphoma is the most common lymphoma to present with multiple polyps in the colon. The entity that sometimes has been called lymphomatous polyposis, usually represents mantle cell lymphoma. Mantle cell lymphoma can present with isolated involvement of essentially any organ.

Histopathologic Subtyping of Mantle Cell Lymphoma

A number of histologic subtypes have been proposed for mantle cell lymphoma. As was noted previously, a subset of these lymphomas has a [follicular] appearance with the tumor cells forming wide mantles around normal germinal centers.[10-12] At least focal appearance of this pattern is seen in approximately one-quarter of the cases of mantle cell lymphoma.

The other major subdivision of patients with mantle cell lymphoma that has been proposed is a distinction between the cases with more mature nuclei with coarse chromatin and inconspicuous
nucleoli, and other cases with larger nucleoli, finer, more dispersed chromatin, and more obvious nucleoli. The latter have been referred to as blastic variants of mantle cell lymphoma, making up approximately 20% of all mantle cell lymphomas. [14,15,26-28]

Some studies have suggested that mantle cell lymphomas retaining a follicular growth pattern have a more indolent natural history, and those tumors with more immature or blastic nuclei pursue a more unfavorable clinical course.[26] It is unclear whether this is simply a reflection of tumor proliferative rate, or other molecular genetic abnormalities in the blastic subtypes.[29,30]

**The Differential Diagnosis of Mantle Cell Lymphoma**

As was noted previously, mantle cell lymphoma is a diagnosis that can be made accurately by experienced hematopathologists. Each case should be reviewed by an expert hematopathologist before therapy is initiated. Even so, the clinician should always consider the possibility in any new patient with non-Hodgkin’s lymphoma that the diagnosis might not be correct. The most serious error would be the diagnosis of mantle cell lymphoma in a patient who has a benign condition. Confusion here would be most likely in cases of Castleman’s disease and benign lymph node hyperplasia.[31] Both of these conditions would be more likely in young patients, which should raise a flag about the possibility of a misdiagnosis of mantle cell lymphoma. Demonstration of monoclonality and a characteristic immunologic staining pattern along with bcl-1 overexpression will usually help resolve any confusion.

In the Working Formulation, mantle cell lymphoma was found most often in the category of diffuse small-cleaved-cell non-Hodgkin’s lymphoma. It was also sometimes diagnosed as small lymphocytic lymphoma, follicular small-cleaved-cell non-Hodgkin’s lymphoma, diffuse large-cell lymphoma, and lymphoblastic lymphoma. The possibility that patients diagnosed with any of these entities might truly have mantle cell lymphoma should always be considered.

**Treatment of Patients with Mantle Cell Lymphoma**

In general, the treatment of mantle cell lymphoma utilizing chemotherapy, radiation therapy, and surgery, has been disappointing. The median survival has varied between 3 and 4 years in most series, and it is unclear that any significant subset of patients is cured. Therapeutic trials of mantle cell lymphoma have focused on identifying those factors that predict treatment outcome and the relative merits of available therapies. These will be dealt with in turn.

**Prognostic Characteristics**

In general, the same prognostic characteristics that predict outcome in other types of non-Hodgkin’s lymphoma also are useful in mantle cell lymphoma. The International Prognostic Index is useful in predicting survival in patients with mantle cell lymphoma.[25] In one large series, the 5-year survival for patients presenting with zero or one adverse risk factor in the International Prognostic Index was 57%, while the 5-year survival for patients presenting with four or five adverse risk factors was 0%.[24]

In a study of 53 patients, Bosch and colleagues found high stage and an elevated LDH as independent predictors of a poor response to therapy.[32] In a multivariate analysis, only poor performance status, splenomegaly, and a high mitotic index predicted survival.[28] In a study of 80 patients, Argotoff found performance status the only independent clinical factor that predicted survival. Also found was that a high mitotic activity, blastic morphology, and leukemic transformation, also predicted a shorter survival. Decaudin et al described 45 cases of mantle cell lymphoma.[33] Overall survival was predicted by liver and bone marrow involvement, leukemic transformation, and achieving a complete remission.

The response to therapy and survival in patients with mantle cell lymphoma worsens with an increased number of adverse risk factors in the International Prognostic Index, a high tumor proliferative rate, and other signs that reflect more extensive disease such as an elevated beta-2 microglobulin and leukemic transformation. The value of these prognostic factors is in predicting the
chances of a patient to achieve a remission—an event that correlates with improved survival. Whatever the patient’s initial prognostic factors, achieving a complete remission is an important initial goal of therapy.

**Traditional Chemotherapy**

Very little data have been published regarding the use of single-agent chemotherapy in patients with mantle cell lymphoma. Decaudin et al reported the use of fludarabine (Fludara) in 15 patients. Patients were treated for 5 days and treatments repeated at four weekly intervals.[34] There were five partial responses and no complete response in this series. The response duration ranged from 4 to 8 months. Although there is little published information, chlorambucil (Leukeran) is an active single agent. Although complete responses are rare, partial response can palliate symptoms. This can be particularly important in elderly patients who cannot tolerate more aggressive therapy. Cladribine (Leustatin) has been utilized, but once again, with low response rate and short response duration.

A number of combination chemotherapy regimens have been utilized to treat patients with mantle cell lymphoma. The most common of these have been either COP (cyclophosphamide [Cytoxan, Neosar], vincristine [Oncovin, Vincasar], prednisone), or a CHOP-like regimen (cyclophosphamide, doxorubicin [Adriamycin], vincristine, prednisone). Overall response rates have usually been between 60% and 80%, and complete response rates from 30% to 60%.[35] Meusers and colleagues have published a randomized trial comparing COP vs CHOP.[36] The overall response rate, complete response rate, and median relapse-free survival for COP (84%, 41%, and 10 months) did not differ from that seen with CHOP (88%, 58%, and 7 months). The median overall survival was 32 months for COP and 37 months for CHOP, with no significant difference between these results.

Romaguera et al have described an intensive combination chemotherapy regimen hyper C-VAD (cyclophosphamide, vincristine, dexamethasone, doxorubicin) for use in mantle cell lymphoma based on the VAD (vincristine, dexamethasone, doxorubicin) regimen frequently used in both myeloma and acute leukemia.[37] This regimen incorporates cyclophosphamide at 300 mg/m² every 12 hours for six doses; vincristine 2 mg on days 4 and 11 of each treatment cycle; Adriamycin 50 mg/m² by continuous infusion over 2 days beginning day 4; and dexamethasone 40 mg daily from days 1 to 4 and days 11 to 14 of each treatment cycle. Patients receive hematopoietic growth factors until recovery. These drugs are alternated with cycles of high dose methotrexate (Folex, Rheumatrex), and high dose cytarabine (Cytosar). This is a very intensive regimen that is difficult to administer and is associated with considerable toxicity. However, the initial results included a complete response rate of 63% in contrast to 21% in the authors’ previous experience utilizing a CHOP-like regimen.

At present, it is unclear that there is a superior combination chemotherapy regimen for all patients with mantle cell lymphoma. Young patients with a good performance status might benefit from use of very intensive approaches such as the hyper C-VAD. Most patients will initially be treated with a combination chemotherapy regimen such as CHOP or COP. Some elderly patients who are asymptomatic at diagnosis might be best observed initially and treated with an oral chemotherapeutic agent when symptoms develop. Unfortunately, it has not been proven that long-term disease-free survival can be achieved, other than in occasional patients utilizing combination chemotherapy regimens alone. The use of traditional chemotherapy to salvage patients who have failed a primary regimen in mantle cell lymphoma has generally been disappointing. Cisplatin-based (Platinol) chemotherapy regimens such as DHAP (cisplatin, cytarabine, dexamethasone) can cause objective responses and might be utilized to prepare a patient for high dose therapy and bone marrow transplantation.

**Cytokines and Antibodies**

The use of alpha interferon to treat patients with mantle cell lymphoma has been reported from the German Low Grade Lymphoma Study Group and from the European Organization for Research on the Treatment of Cancer.[38,39] Initial data suggest that alpha interferon might be useful in prolonging the duration of initial remission. In the study from Germany, 47 patients with mantle cell lymphoma who were included in a low grade lymphoma trial and randomized to receive maintenance interferon or no further therapy have been reported.[39] Twenty-two patients received interferon.
and 25 patients were observed. However, only 13 of the interferon patients and 22 of the observation patients were evaluable at the time of the report. The disease-free survival was 47% for the patients receiving interferon and 27% for the patients being observed without therapy.

It might be expected that patients with mantle cell lymphoma would benefit by therapies directed against the CD20 protein. Initial results using the antibody rituximab (Rituxan) showed a response rate of 33% in relapsed patients.[40] More trials are needed, including incorporating the antibody into the initial treatment of such patients. It will also be important to test the new radiolabeled antibodies also directed against CD20 that will soon be available for study.

**Bone Marrow Transplantation**

Several trials of high dose therapy and autologous bone marrow transplantation in mantle cell lymphoma have been described. Stewart et al first reported the use of high dose therapy and autologous transplantation in nine patients with relapsed mantle cell lymphoma.[41] The patients received high dose therapy utilizing chemotherapy only regimens (N = 7) or cyclophosphamide and total body radiotherapy (N = 2). At the time of the report, three patients remained failure-free at 7, 12, and 25 months post-transplant.

Freedman et al reported 28 patients who underwent autotransplantation using cyclophosphamide and total body radiotherapy.[42] Twenty patients received the transplant after relapse and eight patients were treated in first complete remission. At the time of the report, 19 of the 28 patients had relapsed after 3 to 70 months of follow-up including 5 of the 8 patients transplanted in first complete remission. Nine patients were in continuous remission with a follow-up ranging from 10 to 135 months. The overall disease-free survival was estimated to be 31% at 4 years. The same group has suggested that immunologic purging is generally unsuccessful in patients with mantle cell lymphoma.[43]

Dreger et al reported on nine consecutive patients who underwent autotransplant for mantle cell lymphoma, with six patients treated as part of their primary therapy or in first complete remission, and three patients treated after relapse or progression.[44] With a follow-up of 3 to 33 months, all patients remained in complete remission. Khouri et al described eight patients who underwent autotransplant for mantle cell lymphoma as part of their initial therapy after initial induction with hyper C-VAD.[45] Patients were treated with cyclophosphamide and total body radiotherapy. One patient died of treatment-related toxicity and another relapsed 3 months post-transplant. The remaining six patients are alive in remission with a follow-up period of 2 to 24 months. Similar results have been reported by Haas et al, and Nademanee et al.[46,47]

The use of allogeneic bone marrow transplantation in mantle cell lymphoma has been initially described to give good results as reported by Coriadini et al, and Khouri et al.[45,48] However, the treatment-related mortality rate with allogeneic transplantation is much higher than with autologous transplantation, and most patients with mantle cell lymphoma are too old to undergo allogeneic transplantation.

At the University of Nebraska Medical Center, we have now treated 45 patients for mantle cell lymphoma utilizing either autologous (N = 39) or allogeneic (N = 7) transplantation. Most patients received blood cell transplants. One patient received both an autologous and an allogeneic transplant. Twenty-one patients who received autologous transplants remain in remission for 3 to 61 months with an estimated event-free survival of 41% at 2 years. In contrast, 5 of the 7 patients undergoing allogeneic transplantation are alive in remission for 3 to 45 months with no relapses and two treatment-related deaths.

**Conclusion**

Mantle cell lymphoma represents the most difficult therapeutic problem facing oncologists today when confronted with a patient with non-Hodgkin’s lymphoma. While treatment options are numerous, the results of therapy to date have been disappointing (Table 3, Figure 1). Because of the poor results of aggressive therapy in very elderly patients, observation is appropriate in
asymptomatic patients and initial therapy with chlorambucil or other oral, single agents can be appropriate. Judicious use of radiotherapy to treat symptomatic lesions can be helpful. In younger patients or fit elderly patients, combination chemotherapy utilizing CHOP or COP are most often utilized. However, the results with hyper-C-VAD are sufficiently encouraging that this regimen might be considered in very young patients.

In patients who respond to initial therapy, adjuvant treatment should be considered. If a patient is a candidate for autologous or allogeneic bone marrow transplantation, this treatment should be pursued in initial remission. In young patients with HLA-matched sibling donors, allogeneic transplantation appears to be the regimen that is associated with the highest chance for long-term disease-free survival, although the treatment-related death rate is high. In patients who are not candidates for bone marrow transplantation, there is initial, encouraging data for adjuvant alpha interferon to prolong remission, but more data are needed. Mantle cell lymphoma is an example of an illness where further clinical research testing of innovative treatment approaches is desperately needed. As much as possible, patients should be encouraged to participate in clinical trials.

References:


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