Mantle-cell lymphoma: Classification and therapeutic implications

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Summary
Mantle-cell lymphomas have been recognized in the new Revised European-American Lymphoma Classification as a peripheral B-cell neoplasm that has a distinct morphologic, immunologic, and genetic phenotype. Mantle-cell lymphomas have been subtyped into four categories, termed 'mantle zone', 'nodular', 'diffuse', or 'blastoid'. The incidence of the 'mantle-zone' pattern remains controversial. The fact that patients with the nodular, diffuse, or blastoid subtypes of mantle-cell lymphoma have a high proliferative rate resulting from overexpression of the cyclin D1 and a very short median survival demonstrates conclusively that these patients should be categorized as having an aggressive lymphoma. Most authorities believe that the 'mantle zone' variant pursues a more benign clinical course than the other subtypes. Trials of the new purine analogs are of great interest in these mantle-zone lymphoma patients.

Key words: B-cell lymphoma, classification systems, MCL, purine analogs, REAL classification, Working Formulation

Introduction
The inclusion of a manuscript on mantle-cell lymphoma (MCL) in this supplement, which explores the role of the purine analogs in the treatment of low-grade lymphomas, is obviously based on the premise that patients with MCL have a malignancy that shares the characteristic presentations and natural history of other patients classified as having low-grade or indolent non-Hodgkin's lymphoma. Although this premise may have been a reasonable assumption several years ago, the data are now quite compelling that the majority of patients with MCL have disease with different clinical presentations, different immunologic and genetic characteristics, and a very different natural history than patients with low-grade lymphoma. However, a subset of patients with MCL actually appear to have a more indolent course. In this paper, data that support the previously described concepts as well as the preliminary data about the use of purine analogs in some patients with MCL will be reviewed.

Mantle-cell lymphomas
Terminology
Mantle-cell lymphomas have previously been given different names in various lymphoma classification systems, and in some other classifications, they have not been recognized at all. The International Working Formulation (WF) [1], which has been used extensively in the United States and serves as a common language to translate between six different classification schemes, fails to recognize MCL as a distinct entity. Thus, in the United States, many hematopathologists adopted the terminology of Berard and Dorfman, who called these tumors 'lymphocytic lymphomas of intermediate differentiation' or 'intermediate cell-lymphomas' [2]. Weisenburger described a nodular subtype produced by expansion of the mantle zone surrounding normal germinal centers, and named this variant 'mantle zone lymphoma' [3]. The Kiel classification system, described by Lennert and widely utilized throughout Europe, recognized the unique features of this lymphoma subtype and coined the term 'centrocytic lymphoma' to distinguish it from lymphomas arising from follicular center cells (centroblastic lymphomas) [4]. Because of the confusion generated by these multiple terms, an international consensus conference led by Banks proposed MCL as a consensus term in 1992 [5], and this terminology appears to have gained widespread acceptance [6] and will be used throughout this review.

Morphology
Lymphomas of mantle-cell type have a characteristic morphologic appearance [3, 5, 7, 8]. Mantle-cell lymphomas are characterized histologically by neoplastic expansion of the mantle zone surrounding lymph-node germinal centers with a homogeneous population of small- to medium-sized lymphoid cells with irregular nuclei, inconspicuous nucleoli, and scant pale cytoplasm [5, 6, 9, 10].

In addition to three well-recognized subtypes of
MCL, termed 'mantle zone', 'diffuse pattern', and 'blastoid', some authorities recognize a separate 'nodular' subtype, intermediate between the mantle-zone and diffuse subtypes [9, 11, 12]. Although the prognostic significance of the various subtypes remains somewhat controversial, as will be discussed later in this manuscript, most authorities believe that the 'mantle-zone' variant pursues a more benign clinical course than the other subtypes, with the blastoid variant demonstrating the most aggressive clinical behavior [9, 12, 13]. If this latter 'mantle-zone' actually behaves as an indolent lymphoma, patients with this histologic subtype may be excellent candidates for therapy with purine analogs.

**Immunophenotype and molecular genetics**

The morphologic diagnosis of MCL remains very difficult except for the most experienced hematopathologist. Immunophenotyping and molecular genetics have proven to be of tremendous value in corroborating the diagnosis. In fact, these techniques really proved beyond a reasonable doubt that MCL was a distinct entity. Flow cytometry and immunocytochemical techniques have demonstrated that the malignant lymphocytes of MCL characteristically express monotypic surface IgM and IgD; pan-B-cell antigens CD19, CD20, CD22; and the pan-T-cell antigen CD5 [6, 10, 14–16]. They rarely express CD10 or CD23.

A characteristic chromosomal translocation t(11;14) is seen in MCL and involves the Ig heavy chain locus and the bcl-1 oncogene that results in the overexpression of a gene known as PRAD-1, which encodes for cyclin D1 [17–21]. Cyclin D1 promotes progression of cells from the G1 to the S phase of the cell cycle and therefore results in excessive B-cell proliferation. The resultant overexpression of cyclin D1 can be detected at the mRNA level and at the protein level [20, 22–24]. There is extensive breakpoint heterogeneity for this translocation, and most studies detect the t(11;14) translocation in only 55% to 60% of MCL cases using the polymerase chain reaction, since the available primers cover only ~80% of the gene locus. For this reason, the detection of cyclin D1 protein overexpression may be a more reliable and sensitive test for MCL than detection of the translocation by using the polymerase chain reaction [17, 21, 22, 24].

**Incidence**

To determine the incidence and biologic behavior of MCL, the Lymphoma Committee of the Southwest Oncology Group (SWOG) reviewed the pathology and clinical course of 376 previously untreated patients with stage III or IV non-Hodgkin’s lymphoma and WF categories A, B, C, D, or E, who had received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy on three sequential randomized clinical trials (SWOG 7204, 7426, and 7713) between 1972 and 1983 [9, 25].

A diagnosis of MCL was made in 36 patients (10%). The majority of these patients (21 patients) had been previously categorized as WF E (diffuse small cleaved cell); the remaining 15 patients were identified in the WF A (small lymphocytic, 6 patients) and WF B (follicular, small cleaved cell, 9 patients) categories. No patients were identified in WF C (follicular, mixed) or D (follicular, large cell). The 36 patients with MCL could be further subclassified into nodular, diffuse, or blastic variants (Table 1). The results of that subdivision are as follows: nodular 14 (39%), diffuse 10 (28%), and blastic 12 (33%). No patients with the more indolent 'mantle-zone' variant were identified in this series [9].

The European Organization for the Research and Treatment of Cancer (EORTC) has recently published a similar retrospective analysis of patients with MCL who were previously entered on two of their non-Hodgkin’s lymphoma clinical trials [26]. They identified 64 patients among the 562 patients (11%) evaluated in those trials. Originally the MCL patients had been categorized as follows: WF A, 1 patient; WF B, 22 patients; WF C, 4 patients; WF E, 31 patients; WF F, 3 patients; and WF G/H, 3 patients. Their attempts at subtyping the MCL resulted in only two cases being called mantle-zone pattern while no blastic cases were identified (Table 1). These results are obviously very similar to those reported in the SWOG studies.

In contrast, the M.D. Anderson Hospital reviewed 46 previously untreated cases of MCL [12]. The distribution of histologic subtypes was as follows: mantle zone, 26%; nodular, 13%; and diffuse, 61%, suggesting that a significant percent of patients actually have the indolent or mantle-zone pattern (Table 1).

Thus, the true percentage of patients with MCL that have the mantle-zone pattern remains unclear. One suspects that the histologic criteria for the subtypes of MCL may not be uniform throughout these studies.

**Clinical characteristics**

The clinical characteristics of the patients in the SWOG study with MCL were as follows: median age 55 (range: 18–76); 81% were male; 97% had performance status of 1 or 2; 53% had bone marrow involvement; and 19% had gastrointestinal involvement. As noted previously,

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<th>Table 1. Incidence of various subtypes of mantle-cell lymphoma.</th>
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Abbreviations: EORTC - European Organization for the Research and Treatment of Cancer; SWOG - the Southwest Oncology Group; NA - not applicable.
the subclassification of the MCL resulted in three groups of between 10 and 14 patients. The blastic subgroup was younger (median age 40 years vs. 61 years for the remaining patients); the diffuse group had fewer males (60% males vs. 89% for the remaining patients); and the nodular group had the highest percent with gastrointestinal involvement (43% vs. 5% for the remaining patients) [9, unpublished data].

In a recently published review by Press et al. [27] of 13 small clinical series containing 575 patients with MCL, a male predominance of greater than 2:1 and a median age of onset of 58 years were noted [3, 9, 13, 26, 28-35]. In these 13 series, authors reported B-symptoms in 35% to 55%, generalized adenopathy in 71% to 90%, bone marrow positivity in 53% to 93%, splenomegaly in 35% to 81%, hepatomegaly in 18% to 35%, and gastrointestinal involvement in 15% to 28%. Extranodal involvement was common, particularly in the gastrointestinal tract (occurring in ~25% of patients). The lactate dehydrogenase (LDH) was elevated in 30% to 50% in SWOG 13 series, and β2 microglobulin was elevated in 54% of cases.

The clinical characteristics of the mantle-zone subtype identified in the M.D. Anderson series were somewhat unique. Bone marrow involvement was reported in only 33% of those patients compared to 50% of the nodular form and 89% of the diffuse form (P < 0.05) [12]. When the International non-Hodgkin's Lymphoma Prognostic Factor Index [36] was applied to these patients, 83% of the mantle-zone lymphoma patients fell in the favorable and favorable/intermediate risk groups compared to only 23% of the diffuse patients. This again supported the concept that the mantle-zone variant had a more favorable prognosis [12].

**Therapy**

**Therapeutic trials**

After a median follow-up of 16.5 years, the median failure-free survival of the 36 patients in the SWOG trials was 20.5 months. The 10-year failure-free survival estimate was only 6%. The median overall survival was only 36 months, and the overall 10-year estimated survival was 8%. In fact, the failure-free survival and overall survival estimates for the patients with MCL were lower than those for WF A, WF B, WF C, WF D, or WF E when examined as separate groups (Figure 1) [9].

The subclassification of the MCL into blastic, diffuse, and nodular did result in statistically different failure-free survival and overall survival curves (P = 0.05 for both), although the biologic significance of these differences is not clear since the 10-year failure-free survival estimates were 0%, 10%, and 7%, respectively, and the 10-year estimated overall survivals were 0%, 10%, and 14%, respectively. Again, no patients with the more indolent ‘mantle-zone’ variant were identified in this series, so patients in the potentially indolent subgroup were not included in these trials (Figure 2).

Press et al. [27] reviewed the overall results of treating 524 patients with MCL treated in 12 trials with conventional chemotherapy (e.g., cyclophosphamide, vincristine, prednisone [CVP], or CHOP). There has been no convincing evidence from any of these studies suggesting that any conventional chemotherapy regimen is curative, including those containing doxorubicin [9, 26, 27, 29]. The median progression-free survival was 20 months in these patients, and the median overall survival was 36 months, which is almost identical to that reported in the SWOG trials.

In the M.D. Anderson series [12], the 3-year survival rates were as follows: for patients with the mantle-zone variant, 100%; for patients with diffuse variant, 55%; and for patients with the nodular variant, 50%. The survival of patients with the mantle-zone variant was significantly better than that of the other two subtypes (P = 0.05).
Purine analogs

There are no completed clinical trials published in the literature analyzing the efficacy of the new purine analogs, fludarabine, cladribine, and pentostatin, for the treatment of MCL. Anecdotal responses have been reported to fludarabine and cladribine by Press and other workers, but these have generally been partial in nature and short in duration [11, 27]. Of interest, the group from M.D. Anderson report that the purine analogs are not capable of inducing complete remissions in the nodular and diffuse subtypes [11]. This is consistent with the hypothesis presented here that these agents will potentially be useful in only the indolent variant of MCL and not the very aggressive subtypes. Future reports are awaited with interest.

Conclusions

Mantle-cell lymphoma is a distinct clinicopathologic entity that will now be diagnosed in approximately 5% to 10% of non-Hodgkin's lymphoma. In the WF, the majority of these cases were classified as WF E or diffuse, small cleaved; they are now recognized as a separate entity in the Revised European–American Lymphoma (REAL) Classification [6]. Previous clinical studies of these patients have demonstrated a heterogeneous natural history in that some patients had very aggressive disease while others behaved similarly to patients with classic indolent histology [37]. It now appears that the typical patients present with a relatively high proliferative rate probably as a result of dysregulation of the cell cycle caused by over-expression of cyclin D1 and pursue an aggressive clinical course like the previously reported behavior of diffuse small cleaved cell lymphomas in the 1970s and 1980s [38].

These clinical characteristics obviously also distinguish patients with MCL from the patients with indolent lymphoma with which they were frequently grouped in the past. The one exception to this may be the 'mantle-zone' variant, which some believe pursues a more benign clinical course than the other subtypes. However, it appears relatively uncommon.

The median survival of patients with MCL is only 36 months, and the available conventional chemotherapy regimens do not appear curative. Therefore, MCL now appears to represent the worst prognosis category of all the common non-Hodgkin's lymphomas: it lacks both the long survival of the indolent lymphomas and the curative potential of the aggressive lymphomas.

Hence, consideration of innovative treatment protocols appears to be the optimal choice for most patients with MCL. Again, CHOP chemotherapy, which is the standard therapy currently available for patients with intermediate- and high-grade non-Hodgkin's lymphoma has proven ineffective in curing these patients. Patients presenting with slowly progressive disease (especially those with the 'mantle-zone' variant) might be managed with any of a number of standard indolent lymphoma treatment programs. In this situation, trials of the new purine analogs remain of great interest.

References


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