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## Mantle Cell Lymphoma: Current Concepts

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### Abstract

Mantle Cell Lymphoma is a rare B-cell malignancy that can invade almost any structure in the body and recur after short-lived clinical responses. The pathogenesis and clinical features are well defined, but management has not yet been optimized. Induction with traditional immune-chemotherapy regimens that are used in other non-Hodgkin lymphomas rarely generate durable remissions. Therefore, clinical research is needed to improve treatment of *de novo* disease and to establish safe and effective regimens for maintenance and salvage options for relapsed or refractory disease. This comprehensive review discusses disease pathogenesis and focuses on emerging treatment paradigms using novel targeted therapies.

**Keywords:** Mantle cell lymphoma; Cyclin D1; MIPI score; Rituximab; Bortezomib; Ibrutinib; Idelalisib

### Introduction

Mantle cell lymphoma (MCL) is an uncommon but aggressive lymphoma, comprising about 6% of all non-Hodgkin lymphomas [1] with a typical median survival of 5-7 years [2]. Patients are much more commonly male and elderly [3] with a median age of onset of 68 years [4]. The disease is less frequent in Asian countries [4]. Most cases are advanced at presentation and often exhibit complete responses to initial treatment followed by frequent relapses [3].

This neoplasm is characterized by mature B-lymphocytes that infiltrate the lymph nodes, bone marrow, peripheral blood, and extranodal sites [3]. Histologic appearance is homogenous with a background of pink histiocytes that stain positively for cyclin D1, surface immunoglobulin B-cell markers, and CD5 [3]. While the t (11;14) (q13;q32) translocation is present in over 90% of MCL, other translocations have been reported. Disease heterogeneity features both a blastoid variant with a high Kiel 67 (Ki67) proliferation index, as well as a more indolent variant that can be appropriately managed with a watch and wait approach until symptomatic [3].

Younger, fit patients can be managed with intensive cytarabine-containing chemotherapy alternating with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone combined with rituximab (R-HyperCVAD) with or without autologous stem cell transplantation for consolidation. Other patients receive CHOP-like (cyclophosphamide, doxorubicin, vincristine, prednisone) therapy plus rituximab. Substitution of vincristine with the proteasome inhibitor bortezomib has emerged as a validated treatment for both relapsed and untreated disease.

Awareness of prognostic factors through the validated MIPI score [5], identification of potential transplant candidates, and careful assessment of response to and tolerance of immunochemotherapies, are all crucial determinants of both survival and quality of life.

### Diagnosis

MCL can be distinguished by immunohistochemistry (IHC) with a profile usually showing positivity for B-cell markers as well as CD5, FMC7, CD43, and cyclin D1. Most cases are negative for CD10 and CD23. The reciprocal translocation t (11;14) results in the overexpression of cyclin D1 [6]. In less than 5% of cases, cyclin D1 and t (11;14) may be negative in MCL if there is an otherwise typical IHC profile, with over half of these cases revealing rearranged CCND2 and consequent overexpression of cyclin D2 mRNA [7]. Most pathologic findings and clinical features of cyclin D1-negative MCL appear similar to those of cyclin D1-positive cases [8], and should be managed the same.

### Pathogenesis

The pathogenesis of mantle cell lymphoma (MCL) occurs through two major events that cause a gain of function and loss of function. Chromosome 11q13 holds the proto-oncogene CCND1, which encodes cyclin D1, and its translocation to chromosome 14q32, the locus of the immunoglobulin heavy chain complex (IGH), deregulates the cell cycle at the G1/S phase transition and makes cyclin D1 constitutively overexpressed in otherwise normal B lymphocytes. Gain of function occurs via t (11;14) translocation, causing BCL-1 over-transcription. Loss of function occurs via 11q22-23 deletion, altering the DNA damage pathway response. Thus, the cyclin D1 protein has a major oncogenic effect through two different mechanisms [9].

MCL carries a high degree of genomic instability, with multiple secondary chromosomal alterations. Its pathogenesis was traditionally thought to derive from naïve B-cells in the pre-germinal center (e.g. mantle zone) since the initial translocation event t (11;14) (q13;q32) occurs during recombination of the V(D)J segments of the IGH variable region (IGHV) in the bone marrow. However, the tumor is composed of mature B lymphocytes. Antigen selection is now thought to play an important role in pathogenesis for the 15-40% of MCLs that carry IGHV hypermutations similar to those in chronic lymphocytic leukemia [10].

Cyclin D1 binds to CDK4 and CDK6, which phosphorylates retinoblastoma 1 (RB1), thereby activating the transcription factor E2F while promoting cyclin E/CDK2 activation to trigger entry into the S phase of the cell cycle [11]. Additional oncogenic interactions by cyclin D1 include chromatin remodeling and histone-modifying enzymes. Secondary chromosome alterations that also affect DNA damage response and cell survival pathways are now thought to facilitate aggressive MCL because the CDKN2A locus (9p21), which encodes for both the CDK inhibitor INK4a and the positive p53 regulator ARF, is frequently deleted in these cases [11].

## Classification

The round cell variant has a CLL-like clinical presentation that tends to behave more like an indolent lymphoma. These cases usually show a rather low cell proliferation (Ki-67 roughly 10%). On the other hand, a blastoid variant occurring 5% of the time shows a much more aggressive clinical course. Biological factors like high cell proliferation (determined by Ki-67 staining) or p53 mutations and p16 deletions are closely related to this MCL subtype. However, more than 80% of MCL still presents with somewhat intermediate characteristics. Whereas immediate initiation of treatment is indicated for the majority of patients, select cases may be closely observed to more reliably estimate the aggressiveness of the disease [12].

## Prognostic markers

In 2008, Hoster et al. [5] devised a system to categorize MCL patients' relative survival probability by grading the following risk factors: age, performance status, lactate dehydrogenase (LDH) level, and white blood cell (WBC) count. This system is outlined in Table 1. A MIPI combined biologic index (MIPIb) score of less than 5.7 classifies patients into a low-risk group comprising 44% of patients with a median overall survival (OS) not reached; a score of 5.7 to less than 6.2 yields an intermediate-risk group comprising 35% of patients with median OS of 51 months; and a score of 6.2 or greater falls into the high-risk group with 21% of the patients and median OS of 29 months. It is notable that the number of extranodal sites is not an independent prognostic factor in the MIPI score. Tumor cell proliferation, assessed on paraffin-embedded tissue by Ki-67, showed a median value of 14.5% (range 1.2–91%). This value was also prognostically significant using a cutoff point of 10%, and was independent of the MIPI. Ki-67 of 30% has been proposed by the NCCN as a cutoff for determining the aggressiveness of the disease, but should not constitute an indication to begin treatment [13].

MIPIb Index Score*	Risk	Patient percentage	Overall survival
<5.7	Low risk	44%	Not reached
5.7 to £ 6.2	Intermediate risk	35%	51 months
≥ 6.2	High risk	21%	29 months

**Table 1:** MIPI Score. \*Survival probability by grading the following risk factors: age, performance status, lactate dehydrogenase (LDH) level, white blood cell (WBC) count, and Ki-67.

## Induction Therapy

### Stage I and non-bulky Stage II

Localized presentation, which is extremely rare, can be managed with observation, radiation therapy, or a combination of radiation and chemotherapy. Retrospective data suggests that use of radiotherapy with or without chemotherapy engendered significantly better progression-free survival (PFS) at 5 years (73% vs. 13%;  $p=0.001$ ) with a trend towards overall survival benefit, when compared to patients who did not receive radiation [14]. Radiotherapy as a primary treatment for stage 1-2 MCL patients analyzed retrospectively showed curative results for 3.6% of patients, with 3-year OS of 93% [15].

### Bulky Stage II, Stage III, and Stage IV

Enrollment in clinical trials is recommended for eligible patients with systemic disease, in whom no cure is currently available. In highly select cases in which the patient is asymptomatic, advanced disease can also be managed with a watch and wait approach.

R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) is considered a preferred aggressive regimen in patients who can tolerate considerable toxicity. A phase II study of 97 treatment-naïve patients with advanced MCL showed failure-free survival of 64% and overall survival of 82% at 3 years, and median overall survival not yet reached at 10 years follow-up [16]. The SWOG 0213 phase II multicenter trial of newly diagnosed patients under the age of 70 who received R-HyperCVAD yielded PFS of 4.8 years and OS of 6.8 years, with 2-year PFS of 63% and OS of 76% [17].

The Nordic regimen includes induction immunochemotherapy with rituximab plus maxi-CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone) alternating with rituximab and high-dose cytarabine. The Cancer and Leukemia Group B (CALGB) regimen features induction with rituximab-methotrexate with augmented CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for at least 2 cycles, with an additional cycle if the bone marrow contains greater than 15% involvement by MCL.

A phase III randomized trial of the German Low Grade Lymphoma study group [18] evaluated the addition of rituximab to CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) in treatment-naïve patients with advanced MCL aged 65 and younger. R-CHOP showed significantly better overall response rate (94% vs. 75%), complete remission rate (34% vs. 7%) and median time to treatment failure (21 months vs. 14 months) than CHOP. However, PFS and OS outcomes were not superior. R-CHOP can also be alternated with R-DHAP (rituximab, dexamethasone, cisplatin, cytarabine) or R-ICE (rituximab, ifosfamide, carboplatin, etoposide) in sequence.

For elderly patients or those with poor performance status, bendamustine plus rituximab (BR) has shown superior PFS than R-CHOP (35 months vs. 22 months; HR=0.49, 95% CI 0.28-0.79;  $p=0.0044$ ) in primary MCL according to subgroup analysis of the phase III STiL study [19]. Of note, adverse events and grade 3 and 4 toxicities were significantly less in the BR treatment arm.

Another less aggressive induction regimen to gain FDA approval is VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone). When compared to R-CHOP in patients who were not transplant-eligible, front-line VR-CAP showed superior PFS (24.7 vs.

14.4 months,  $p < 0.001$ ) and CR rate (48% vs. 41%) with a trend towards OS benefit (64% vs. 54%) in a phase III randomized study [20].

Treatment	Study	Overall response rate (ORR)	Overall survival rate (OS)	Progression Free Survival (PFS)	Failure Free Survival	Complete remission rate (CR)	Median time to treatment failure (TTTF)
R-HyperCVAD	Phase II study of 97 de novo advanced MCL (15)	-	82% at 3 years	-	64%	-	-
R-HyperCVAD	SWOG 0213 phase II study of de novo pts <70 yo (16)	-	76%	4.8 years 2-year PFS of 63%	-	-	-
R-CHOP	Phase III study of advanced MCL pts 65 yo (17)	95%	Not superior	Not superior	-	34%	21 months
Bendamustine + Rituximab	Subgroup analysis of Phase III study (18)	-	-	35 months	-	-	-
VR-CAP	Phase III study (20)	-	64%	24.7 vs. 14.4 months	-	48%	-

**Table 2:** Induction therapy.

Of note, VR-CAP incurred slightly more high-grade adverse events (93% vs. 84%), but most were considered manageable. VR-CAP was again compared to R-CHOP in a recently published study of 487 patients with at least stage II disease [21]. The median PFS was 14.4 months in the R-CHOP group and 24.7 months in the VR-CAP group

(hazard ratio favoring the VR-CAP group, 0.63;  $p < 0.001$ ), and there was consistent progression-free survival benefit across all prespecified subgroups and irrespective of MIPIb and Ki-67 score [21]. VR-CAP is currently the only first-line regimen approved by the FDA.

A Summary of the treatment regimens is presented in Table 2.

### Consolidation therapy

Following successful induction with R-HyperCVAD or CHOP-like immunochemotherapy, high-dose therapy (HDT) with one cycle of etoposide, cytarabine, and rituximab and one cycle of carmustine, etoposide, and cyclophosphamide has been effectively followed by autologous stem cell rescue (ASCR). Thirty-three patients treated at MD Anderson after achieving first remission with HyperCVAD with or without rituximab achieved 5-year disease-free survival of 42% and OS of 77% [22], with 100% OS rate in those patients with a low serum beta-2 microglobulin level. Long-term follow-up showed a median PFS of 42 months and OS of 93 months [23]. Non-randomized analysis suggests an improved PFS in transplanted patients who were induced with HyperCVAD (with or without rituximab) rather than CHOP (with or without rituximab) [24].

Post-induction maintenance therapy with rituximab has been shown to provide extended disease control for patients who cannot undergo high-dose therapy and stem cell transplantation. In one pilot phase II study of 22 patients with newly diagnosed MCL, a dose-reduced R-HyperCVAD (omitting methotrexate and cytarabine) followed by maintenance therapy with rituximab for 5 years yielded a PFS of 37 months and median OS not reached, with acceptable toxicity [25]. Additional studies have also shown promising data for rituximab maintenance after R-CHOP induction [26,27], and it remains unclear whether first-line consolidation with high-dose chemotherapy with autologous stem cell rescue (HDT/ASCR) provides an advantage over rituximab maintenance in patients of any age. No randomized trial data are currently available to compare intensive consolidation regimens against maintenance therapy.

Table 3 provides a summary of the current consolidation/maintenance regimens.

Treatment	Study	Overall survival rate (OS)	Progression Free Survival (PFS)
HyperCVAD +/- Rituximab	Long-term follow-up of auto-SCT in pts with diffuse MCL in first CR (21)	77%-100% (patients with low serum B2 Microglobulin)	42 months
Long-term follow-up HyperCVAD +/- Rituximab followed by MD Anderson after achieving first remission	Mature results of the M.D. Anderson Cancer Center risk-adapted transplantation strategy in MCL (22)	93 months	42 months

**Table 3:** First-line consolidation.

### Second-line therapy

Second-line consolidation therapy can be pursued with autologous or allogeneic stem cell transplantation (SCT) following non-myeloablative or myeloablative conditioning regimens. A study of 112 patients who had previously failed conventional chemotherapy underwent a preparative conditioning regimen that consisted of etoposide, cyclophosphamide, mesna, and fractionated total-body irradiation (TBI). Patients who were not eligible for TBI because of prior exposure to radiation received BEAM (carmustine-etoposide-cytarabine-melphalan) for conditioning instead. Graft-versus-host disease (GVHD) prophylaxis consisted of a combination of

cyclosporin or tacrolimus with mini-dose methotrexate and/or methylprednisolone. Nine patients received interferon- $\alpha$  maintenance after autologous SCT. Allo-SCT in 44 patients resulted in lower recurrence rates but higher treatment-related mortality rates than the 68 patients who underwent high-dose therapy with autologous stem cell transplantation [28]. Outcomes were initially more favorable for the autologous SCT group (significant only for day 100 mortality); however, this pattern changed over time. A plateau was seen amongst the allogeneic SCT group at 44 months after transplantation for OS and at 24 months for DFS, whereas there was a continuous pattern of treatment failure in the autologous SCT group. The improved OS



among the allogeneic SCT group was not statistically significant ( $p>0.05$ ) but the improved DFS was significant ( $p=0.01$ ). A similar pattern of DFS was observed when 19 patients with chemoresistant disease who underwent allogeneic SCT were compared with 26 patients with chemosensitive disease who underwent autologous SCT ( $p=0.04$ ). The rate of disease progression was significantly higher in the autologous SCT group (74%; 95% CI 59% to 88%) than in the allogeneic SCT group (19%; 95% CI 9% to 38%) with  $p=0.003$  [28].

Additional regimens suitable for use in first relapse include: bendamustine with or without rituximab [29]; cladribine [30]; FC (fludarabine plus cyclophosphamide) with or without rituximab; FCMR (fludarabine, cyclophosphamide, mitoxantrone, and rituximab); FMR (fludarabine, mitoxantrone, and rituximab); PCR (pentostatin, cyclophosphamide, and rituximab); and PEPC (prednisone, etoposide, procarbazine, cyclophosphamide with or without rituximab).

### Novel Agents

Bortezomib is approved by the U.S. Food and Drug Administration (FDA) for relapsed or refractory MCL based on the phase II PINNACLE trial, in which bortezomib induced an overall response rate of 33% (CR in 8%), with a median duration of response of 9 months and median time to progression of 6 months [31]. Long-term follow-up confirmed these effects [32]. Bortezomib combined with rituximab has shown activity in heavily pre-treated patients with relapsed/refractory disease.

The immunomodulating agent, lenalidomide, has shown efficacy in relapsed or refractory aggressive non-Hodgkin lymphoma, with subset analysis of MCL patients showing an ORR of 35% and CR rate of 12% at a median follow-up of 12 months in a phase II trial [33]. In this study the duration of response was 16 months, and the median PFS was approximately 9 months.

Another recent phase II study of patients with rituximab-resistant B-cell lymphomas [34] treated 43 patients with lenalidomide 10 mg by mouth daily for 8 weeks followed by 4 weekly doses of rituximab 375 mg/m<sup>2</sup> intravenously. Six out of the eleven patients with MCL showed a clinical response (3 CR, 1 Cru, 2 PR); the addition of rituximab did not change the ORR, although two PR improved to CR [4].

The small-molecule Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, has shown promising activity in several B-cell malignancies. Subgroup analysis of phase I data in 9 patients with relapsed and/or refractory MCL showed response in 7 patients, including a CR in 3 patients, with no dose-limiting toxicities and no significant myelosuppression even with the full dose of 560 mg daily [35]. A multicenter phase II trial of 111 patients who had been previously treated with bortezomib and/or rituximab-containing regimens, 72% of whom had advanced disease and 42% of whom had high-risk MIPI scores, showed an ORR of 68% with CR rate of 21% after 15 months of ibrutinib [36]. The median duration of response was 17.5 months, median PFS was 14 months, and estimated OS rate at 18 months was 58%. The response rates appeared to increase with longer duration of therapy. In November 2013, the FDA approved ibrutinib to treat MCL on the basis of an "unprecedented" response. The most common adverse event rated grade  $\geq 3$  were neutropenia (16%), thrombocytopenia (11%), anemia (10%), pneumonia (6%), diarrhea (6%), fatigue (5%) and dyspnea (5%). The use of ibrutinib causes a transient lymphocytosis that resolves after an average of 8 weeks, and caused grade  $\geq 3$  bleeding events in 5% of patients [37]. Thus, ibrutinib

is emerging as a potential preferred salvage option due to ease of daily oral dosing and favorable side effect profile.

Although ibrutinib can extend the lives of heavily treated, relapsed, or refractory patients with mantle cell lymphoma (MCL), many become resistant to the drug. Analysis of longitudinal functional genomics in MCL [38] showed that 30% of the patients who developed resistance to ibrutinib expressed high levels of activated phosphatidylinositol-3 kinase (PI3K-AKT) and cyclin-dependent kinase 4 (CDK4). (PI3K-AKT proteins promote survival; CDK4 drives MCL cells through the cell cycle.) These two mechanisms appeared to override ibrutinib's inhibitory action in resistant cells. An experimental selective CDK4/CDK6 inhibitor, palbociclib, has demonstrated cytotoxicity against the mutated BTKC481S protein.

Stepwise treatment with palbociclib followed by ibrutinib, or palbociclib followed by the PI3K pathway inhibitor, idelalisib, which is FDA-approved to treat CLL, might treat MCL patients who initially do not respond to ibrutinib. Or, the drugs given together might prevent resistance.

A 48-week study using idelalisib [39] evaluated 39 patients with relapsed or refractory mantle cell lymphoma patients who had received a median of four prior therapies. Overall, nine (18%) patients discontinued therapy due to adverse effects including diarrhea, transaminase elevations, pneumonia, and acute renal failure. Thirty-three (84.6%) patients had some reduction in lymph node size, with CR in two (5%) patients, PR in 14 (35%) patients, and stable disease in nineteen (47.5%) patients.

Table 4 provides a summary of the novel agents used in MCL.

Treatment	Study	Overall response rate (ORR)	Overall survival rate (OS)	Progression Free Survival (PFS)	Failure Free Survival	Complete remission rate (CR)
Bortezomib	Phase II PINNACLE trial [31]	33%	-	Median duration of response of 9 months	Median time to progression of 6 months	
Lenalidomide	Phase II Multicenter Study [32]	35%	-	9 months	Duration of response was 16 months	12% median follow-up of 12 months
Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib	Phase II multicenter data of 111 previously treated pts [34]	68%	58% at 18 months	17.5 months	14 months	21% after 15 months

Table 4: Novel agents.

### Conclusion

Mantle cell lymphoma is an incurable but increasingly well characterized clinicopathologic entity that unfortunately poses persistent obstacles in achieving durable responses with available treatment regimens. Early stage disease is rare, but limited available data suggests that radiation with or without chemotherapy can

effectively manage limited, non-bulky distribution. For advanced disease, referral for enrollment in prospective clinical trials should be pursued. Based on individual patients' performance features, they can be managed up-front with either observation, R-HyperCVAD, CHOP-like chemotherapy, or less aggressive induction regimens including bendamustine and rituximab. Relapsed and refractory disease carries a poorer prognosis, but novel agents including bortezomib, lenalidomide, and ibrutinib have shown promising efficacy and tolerability. Further randomized data are needed to establish clear standards of care and improve rates of survival and quality of life.

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