Introduction

Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin lymphoma considered incurable using conventional chemotherapeutic approaches. Emerging clinical data suggest considerable clinical heterogeneity, with some patients showing a chronic/indolent course, while others have a more fulminant course and short survival, similar to that of patients with acute leukemias. This review highlights the epidemiology, prognosis, and management of this protean and challenging condition.

Diagnosis

MCL cells are typically described as slightly increased in size with an indented nucleus that lacks nucleoli. The classic immunophenotype includes positivity for CD5,
CD19, CD20, and sIgM (Fig 1A).1,6 Differentiating MCL from marginal zone lymphoma and from chronic lymphocytic leukemia can be challenging; however, MCL is more likely to have a higher expression of CD20 and is typically negative for CD11c. Although CD23 is also typically negative, positive cases have been seen in up to 25% of cases.1,2 MCL is more specifically identified by the presence of the translocation t(11;14)(q13;q32), which juxtaposes the cyclin D1 gene to the immunoglobulin locus. Rare cyclin D1-negative variants do exist, which may be characterized by increased expression of cyclin D2. However, additional confirmatory testing is needed in such situations, as the specificity for cyclin D2 immunostaining in MCL is low. Although methodology continues to be refined, dual-color fluorescence in situ hybridization (FISH) remains the most sensitive method for detection at this time (Fig 1B).1,3

Epidemiology and Etiology

MCL accounts for 2% to 10% of the non-Hodgkin lymphomas, with a recently reported incidence rate of 0.51 to 0.55 per 100,000 persons. In general, patients are typically Caucasian (about 2:1), male (about 2.5:1) and elderly (median age of onset, 68 years), and they usually present with extensive disease, including widespread lymphadenopathy, bone marrow involvement, splenomegaly, circulating tumor cells, and bowel infiltration.7 US cancer registry data suggest an increase in the incidence of MCL between 1992 and 2007.8,9 Interestingly, this is coupled with a decrease in the number of cases of CLL, suggesting that improvements in diagnosis have facilitated an improvement in differentiating between these two entities.10 This may similarly help to explain improvements in survival if patients are diagnosed in earlier, more indolent phases.

While some non-Hodgkin lymphomas have been found to be related to specific inherited, environmental, or infectious exposures, no strong and consistent relationship has been made for MCL. Weaker associations have been noted with exposure to European strains of *Borrelia burgdorferi* (odds ratio [OR] = 3.5, 95% confidence interval [CI], 1.8–7.4),11 a family history of hematologic malignancy (OR = 2.0, 95% CI, 1.2–3.0),12 and genetic polymorphisms in the pro-inflammatory cytokine interleukin 10 (OR = 1.3 per allele, P for trend = .04).13 Nevertheless, observed restrictions in immunoglobulin diversity suggest there may be as yet unidentified exposures that play a critical role in the development and potentially in the maintenance of this malignancy.14,15

Indolent MCL

Retrospective data demonstrate that up to 30% of patients with MCL may have an indolent presentation, with no acute indication for therapy.16,17 Patients with this condition were identified by studying time to treatment, with indolent patients showing a delay of approximately 1 year before initiation of therapy. Notably, once patients require therapy, their outcome does not appear to be appreciably different from those with more classic presentations of disease.16,17 This may suggest a progression from indolent to aggressive disease similar to that seen in multiple myeloma, where patients may progress from an indolent asymptomatic stage (smoldering myeloma) to more fulminant disease.

Distinguishing indolent MCL from in situ MCL is important. Those with in situ MCL show scattered lymphocytes possessing the cyclin D1 translocation in the mantle zone without accompanying expansion of this region.18-20 The natural history of in situ MCL is not clearly delineated. Most series, including our own (T. Kubal, unpublished observations, 2012), have identified cases of in situ MCL retrospectively, only after patients present with more aggressive disease.18-20 This suggests that a cohort of patients with in situ disease may exist but do not ultimately develop disease. Among those who do progress to aggressive disease, latency periods of up to 12 years have been noted, suggesting that these patients may be closely monitored without beginning therapy.21 Attempts to prospectively identify patients with indolent MCL have proven difficult. Clinically, such
patients often present with mild lymphocytosis and splenomegaly, with bone marrow and/or gastrointestinal involvement. However, some patients also present with slowly progressive lymphadenopathy. The use of positron emission tomography and computed tomography (PET-CT) has helped to identify highly proliferative, so-called blastoid variants of MCL, which typically show maximum standard uptake values (maxSUVs) in excess of 14. However, PET-CT has not been shown to reliably facilitate identification of indolent variants. An obligate marker of proliferation, has been shown to correlate with prognosis, but it is limited by significant interobserver variability in measurement. Current research using quantitative image analysis to account for this is ongoing but is not yet routinely available.

Molecular exploration has identified two potential candidates for discrimination of indolent cases: SOX11 and HDAC11. SOX11, a DNA-binding protein important in cell ontogeny, is commonly and aberrantly expressed in MCL. Emerging data suggest that indolent cases may lack expression of this protein. Mechanistically, however, enforced suppression of SOX11 in cell culture increased proliferative rates, suggesting that further confirmation by other groups is needed before any definitive conclusions can be reached in this regard. Finally, our experience suggests that expression of the histone deacetylase HDAC11 may correlate with prognosis. Specifically, blastoid MCL demonstrated very high expression of this enzyme (approximately 15- to 20-fold), while classic MCL had an intermediate level of expression (approximately 10-fold), and indolent MCL had only a minimal elevation (approximately 2- to 3-fold). Further research to better clarify the role and mechanism of HDAC11 on proliferation is ongoing.

Prognosis
The prognosis in MCL appears to be improving. This is likely a reflection of both earlier identification of more indolent cases and the application of modern therapeutic modalities, including rituximab and autologous transplantation. Characterization of prognosis using algorithms tailored to either indolent lymphomas (the Follicular Lymphoma International Prognostic Index) or aggressive lymphomas (the International Prognostic Index) fail to effectively stratify patients into distinct subgroups. This has culminated in the development of an MCL-specific algorithm: the Mantle Cell Lymphoma International Prognostic Index (MIPI). This algorithm relies on measures of chemotherapy tolerance (eg, age, performance status) and indirect measures of disease activity (eg, white blood cell count, lactate dehydrogenase [LDH]) to stratify patients into low-, intermediate-, and high-risk groups. With a median follow-up of 32 months, the estimated 5-year survival rate for those in the low-risk group was 60%, while those in the intermediate- and high-risk groups had a median 5-year survival of 51 and 29 months, respectively.

Importantly, the MIPI is prognostic for overall survival (OS), not chemotherapy response or progression-free survival (PFS). Furthermore, the MIPI has been validated only when calculated prior to first therapy. Ki-67, when ≥ 30%, may be associated with inferior PFS; however, as mentioned above, this is limited by poor interobserver agreement, particularly around this threshold. A study by the French GOELAMS group found that PET-CT might predict for worse event-free survival when using a cut-off of maxSUV values of 6, but the sample size was small, and these data await confirmation. Furthermore, as with Ki-67, PET-CT is also limited by interobserver variability.

First-Line Treatment
Therapeutic strategies in MCL have evolved over the past decade in an effort to improve the depth and duration of remission. These approaches can be thought of in two broad contexts: treatment of the young/fit individual and treatment of the old and/or infirm individual. Among young patients with limited comorbidity, the emphasis has been on increased treatment intensity, coupling targeted agents to aggressive chemotherapeutic regimens to improve the depth of response in anticipation of autologous stem cell transplantation. Alternatively, in older and/or infirm patients, the emphasis has been placed on de-intensification of therapy, using targeted agents to replace high-dose therapy and/or as a form of maintenance to prolong remission duration (Fig 2). These approaches are described below.

![Prognosis Diagram](image-url)
**Treatment of Indolent Disease**

MCL in its indolent phases can be observed with no therapy without apparent detriment to survival. One clinical presentation includes asymptomatic lymphocytosis, splenomegaly without lymphadenopathy. Alternatively, some patients may present with asymptomatic, slowly progressive, nonbulky adenopathy.\(^{56,57}\) Either group of patients can be followed clinically without introduction of therapy until development of symptoms, rapidly growing lymphadenopathy, cytopenias due to splenomegaly, or progression in bone marrow. However, some patients may be uncomfortable with watchful waiting, or they may present with fatigue related to disease. In such cases, rituximab can be administered as a single agent, given once weekly for 4 weeks, and followed with maintenance dosing once every 2 months for 2 years, akin to follicular lymphoma.\(^{58-62}\) While rare infections and infusion reactions have been reported in conjunction with rituximab, overall there appears to be a favorable benefit to toxicity ratio with this approach.\(^{42}\)

Some patients with similar presentation may progress to a leukemic form of disease, with marked elevation in the white blood cell count (> 100 k/µL), high LDH, progressive splenomegaly, and decline in the hemoglobin and/or platelet count. Leukemic MCL is frequently associated with p53 mutation and/or MDM2 overexpression (which binds active p53) and accordingly shows low response to standard chemotherapies. Such patients may benefit from palliative splenectomy, which has been shown to forestall the introduction of chemotherapy for as long as 4 years.\(^{43-45}\)

**Treatment of Limited-Stage Disease**

Up to 6% to 8% of patients with MCL present with stage I or II disease, with limited data on treatment outcome.\(^{9}\) The largest retrospective analysis in this regard included 26 patients with nonbulky stage I and IIA disease treated with chemotherapy with or without involved-field radiotherapy.\(^{46}\) Receipt of radiation was associated with a significant improvement in PFS (5-year PFS 68% vs 11%), with no patients demonstrating progression beyond 6 years. For stage I MCL, our practice at Moffitt Cancer Center and the Weill Cornell Medical College has been to recommend involved field radiation in accordance with NCCN guidelines.\(^{47}\)

**Treatment of Advanced Disease**

Formal randomized comparisons of chemotherapeutic approaches are uncommon, given the infrequency of MCL relative to other non-Hodgkin lymphomas. One of the earliest trials conducted by the European Organization for the Research and Treatment of Cancer (EORTC) retrospectively compared two highly aggressive regimens, CHVmp-VB (cyclophosphamide, doxorubicin, teniposide, prednisone, vincristine, and bleomycin) with ProMACE-MOPP (doxorubicin, cyclophosphamide, etoposide, mechloretamine, vincristine, procarbazine, and prednisone) in intermediate- and high-grade MCL.\(^{48}\) While CHVmp-VB demonstrated a slight improvement in complete response (CR) rate (57%) and PFS (21 months) compared with ProMACE-MOPP, other trials using cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy alone demonstrated lower toxicity and similar time to treatment failure (approximately 2 years) despite lower CR rates (15%).\(^{48-50}\)

The introduction of rituximab to the therapeutic armamentarium was explored in several phase II studies and ultimately in a pivotal randomized comparison of R-CHOP and CHOP.\(^{59-61,51,52}\) This trial demonstrated a significant improvement in response rates (94% vs 75%, \(P = .0054\)) and CR rate (34% vs 7%, \(P = .00024\)) in the R-CHOP arm vs the CHOP arm. Interestingly, median time to treatment failure was also improved in the R-CHOP arm (21 months vs 14 months, \(P = .0131\)), while PFS and OS were not improved. In this respect, it is important to note that time to treatment failure was measured from the time of treatment initiation, while PFS was measured from the time of treatment completion only among responders, ie, those with a CR or partial response (PR). This suggests that the primary benefit for rituximab was in improving chemotherapy response in otherwise refractory patients.

**Evolution of Therapy for Young Patients**

Cytarabine was the next drug to be incorporated into the therapeutic paradigm for MCL. Initial data came from a small French trial in which patients without a CR after 4 cycles of CHOP were subsequently treated with dexamethasone, high-dose cytarabine, and cisplatin (DHAP). Among 25 patients who failed to obtain a CR, DHAP was able to produce a CR in 84% and a median PFS of 51 months.\(^{53}\) This led to the development of regimens alternating cycles of CHOP-like chemotherapy with high-dose cytarabine given together with rituximab. Indeed, a recent comparison of R-CHOP (6 cycles) vs R-CHOP/R-DHAP (given sequentially for 3 cycles each) demonstrated that the cytarabine-containing arm produced a higher rate of complete molecular response.\(^{54}\) Interestingly, while molecular response did not correlate with radiologic response, those with molecular response demonstrated an improved PFS. One regimen in particular, consisting of rituximab in combination with fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine (R-HyperCVAD/MA), has shown significant promise in MCL.\(^{55,56}\) Although this regimen was complicated by significant toxicity, particularly for those over 65 years of age, the CR rate was 87% with an overall response rate of 97%. Unlike early applications of high-dose multiagent chemotherapy, this approach was associated with a prolonged time to treatment failure (median 4.6 years) and OS rate when compared to historical controls.
(64% at 10 years with a median follow-up duration of 8.3 years). Notably, time to treatment failure was far worse among those over age 65 years, with only 16% still in remission and 53% alive at 8 years (vs 46% and 68%, respectively, among those under 65 years, \( P < .05 \)). This may be attributed to decreased compliance with prescribed therapy related to increased toxicity in this subgroup.

Early data with R-CHOP-based inductions suggested that remission data could be prolonged using consolidation with high-dose therapy and autologous stem cell transplantation.\(^{52,57}\) Furthermore, outcomes appeared to be best among those transplanted in first complete remission.\(^{58,59}\) These data prompted further study of regimens containing high-dose cytarabine administered in conjunction with autologous stem cell transplant.\(^{60}\) Pivotal phase II data were reported by the Nordic group in 2008,\(^{61}\) in which patients were treated with alternating cycles of maxi-CHOP (similar to HyperCVAD) and high-dose cytarabine for a total of 6 cycles, followed by high-dose conditioning using either BEAM (carmustine, etoposide, cytarabine, and melphalan) or BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide) and autologous transplant. Rituximab was also administered during cycles 4 to 6 and in the event of molecular relapse posttransplantation. This approach yielded a CR rate of 54% and an overall response rate of 96%. With a median follow-up duration of 3.8 years, the 4-year event-free survival rate was 63%. A similar approach was explored by the Cancer and Leukemia Group B (CALGB 59909), utilizing an induction of R-CHOP and methotrexate for 2 to 3 cycles followed by high-dose cytarabine and etoposide combined with rituximab and filgrastim. Patients then received high-dose carmustine, etoposide, and cyclophosphamide followed by autologous transplant.\(^{62}\) All patients went on to receive an additional 2 doses of rituximab at weeks 6 and 7 after transplantation. With a median follow-up of 4.7 years, this study demonstrated a 5-year PFS rate of 56% (95% CI, 43%–68%), and a 5-year OS rate of 64% (95% CI, 50%–75%). Unlike the Nordic study, which was limited to patients who were 65 years of age and under, this study allowed patients up to age 69 years to be enrolled (median age, 57 years). Although responses were not stratified by age, those with high-risk MIPI had a significantly lower survival than those with low- or intermediate-risk disease (33% vs 75%, \( P < .05 \)). Indeed, significant grade 3/4 toxicity was observed in both trials, largely related to neutropenic fever and infection.\(^{54,62}\)

This has prompted further study of alternative approaches to induction as well as additional retrospective evaluation of high-dose cytarabine-containing regimens. One alternative approach utilized a sequential regimen of R-CHOP for 4 cycles, followed by R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) for 2 to 3 cycles, and autologous transplant with BEAM conditioning.\(^{24}\) With a median follow-up of 4.8 years (1.0–11.5 years), the authors observed a median PFS of 5 years and a 5-year OS rate of 76%. Toxicity data were not presented in detail; however, despite inclusion of patients over the age of 60 years (29% of cohort), this variable did not correlate with survival. Rather, proliferative index, as measured by Ki-67, was the only variable to be associated with this outcome. A more recent retrospective analysis from the Non-Hodgkin Lymphoma Database of the National Comprehensive Cancer Network (NCCN) reviewed outcomes among patients receiving R-CHOP or R-HyperCVAD/MA with or without autologous stem cell transplant.\(^{63}\) With a median follow-up of 33 months, this study demonstrated similar 3-year PFS rates for the R-HyperCVAD/MA arm (58%; 95% CI, 44%–69%), the R-HyperCVAD/MA + transplant arm (55%; 95% CI, 22%–79%), and the R-CHOP + transplant arm (56%; 95% CI, 33%–74%), while the R-CHOP arm was the only to demonstrate an inferior 3-year PFS rate (18%; 95% CI, 6%–36%). A comparison of 3-year OS data showed no significant differences among the R-CHOP arm (69%; 95% CI, 46%–83%), the R-CHOP + transplant arm (87%; 95% CI, 64%–95%), and the R-HyperCVAD/MA arm (85%; 95% CI, 74%–92%). Data were not mature enough to allow comparison with the R-HyperCVAD/MA + transplant arm. Also confirmed was a higher rate of complications and a decreased ability to tolerate all 6 prescribed cycles among those receiving R-HyperCVAD/MA ± transplant. Together, these data suggest that it may be possible to achieve a prolonged remission with less intensive therapy when coupled to autologous transplant.\(^{64}\) This may be related to increasing depth of response, as measured by molecular response, when transplant is coupled to a less intensive induction. Alternatively, it may be premature to withhold autologous transplant even after more intensive therapy, as further differences may emerge with time.\(^{64}\)

**Evolution of Therapy for Elderly Patients**

While intensification of therapy to improve remission depth and duration has been the paradigm for young and fit patients, the approach in elderly patients has instead emphasized the addition, and increasingly the substitution, of novel agents with prolonged maintenance approaches to improve outcomes.

Important in this regard are seminal data presented at the 2009 American Society of Hematology annual meeting comparing R-CHOP with rituximab-bendamustine. Among 93 patients with MCL (with a median age of 70 years), rituximab-bendamustine was shown to improve CR rates (39.6% vs 30%, \( P < .05 \)) and PFS (33 vs 23 months, \( P < .05 \)). Perhaps more relevant to this population, the rituximab-bendamustine regimen was also associated with significantly less toxicity, including hematologic/infectious toxicity, alopecia, stomatitis, and parathesias.\(^{65}\) Although final published data are still pending, the significance of these findings has propelled
the rituximab-bendamustine regimen to the front line in many patients (including younger patients). Ongoing cooperative group trials in older and younger patients are further evaluating the role of this combination.

Another promising approach includes the combination of cladribine and rituximab. This was initially explored by the North Central Cancer Treatment Group in a cohort of 29 elderly patients with untreated MCL (median age, 70 years).66 This regimen was associated with an overall response rate of 66% (CR = 52%). The median PFS for all patients was about 1 year. However, among those who obtained a CR, the duration of response was prolonged, with only 20% relapsing after a median follow-up of 21.5 months. Furthermore, this combination was associated with a 2-year survival rate of 78%, despite a lack of autologous transplant consolidation. Given the strength of these data, a follow-up trial was performed with cladribine and rituximab.67 Importantly, this trial administered rituximab once per week for the first cycle, after which rituximab was given once with each additional cycle. Additionally, rituximab was continued in the majority of responders as a maintenance therapy. In this study of 31 untreated patients, an improved overall response rate (87%) and CR rate (61%) were observed. After a median follow-up of 32.5 months, the median PFS and OS were 37.5 and 85 months, respectively. Among those who obtained a CR, only 1 has relapsed after median follow-up of 23 months.

Given the importance of rituximab in the induction setting, current studies are attempting to address the importance of this agent when administered as maintenance following chemotherapy in lieu of autologous stem cell transplantation. Two trials recently examined this approach. The first trial explored the role of rituximab maintenance administered for 2 years to those with a CR or PR following modified R-HyperCVAD (in which high-dose cytarabine and methotrexate were omitted).68 Among 22 patients with newly diagnosed MCL, the median age was 65 years (range, 40 to 81 years). Despite omission of high-dose cytarabine, the overall response rate after induction was 77% (CR = 64%). With a median follow-up of 62 months, the median PFS in this cohort was 38 months, and the median OS was 70 months. This is surprisingly similar to the aforementioned data using rituximab and cladribine with rituximab maintenance.67 A subsequent trial was recently performed by the European MCL Network and presented at the 2011 annual meeting of the American Society of Hematology.69 This trial recruited only patients over the age of 60 considered ineligible for more intensive approaches. In this trial, rituximab or interferon alpha maintenance was administered until progression in those with either a CR or PR following induction with standard R-CHOP or R-FC (rituximab plus fludarabine/cyclophosphamide). The overall response rate following R-CHOP was 87% (CR = 50%). With a median follow-up of 38 months, the median remission duration in those randomized to rituximab maintenance was 56 months compared to 26 months with interferon (P = .01). In addition, rituximab maintenance resulted in an OS benefit in those patients who were initially treated with R-CHOP (4-year OS rates of 87% vs 57%, P < .01). These outcome data are similar to the more intensive approaches described for younger patients.

**Relapsed Disease**

Despite intensive and/or prolonged chemotherapeutic approaches, MCL remains incurable in the absence of allogeneic transplantation. This approach, however, is encumbered by significant toxicity and is likely best tailored to young, fit patients with chemosensitive disease.70 Although a complete discussion of treatment approaches in this setting is beyond the scope of this review, a few are worthy of mention.

Lenalidomide, a second-generation immunomodulatory agent derived from thalidomide, is showing increasing promise in this malignancy. Lenalidomide as a single agent appears to show response rates as high as 53% with a median PFS of nearly 6 months.71 Perhaps reflective of its immune-potentiating effects, when coupled to rituximab, the median PFS increases to approximately 14 months.72,73 This is a dramatic response in the relapsed and refractory setting and has prompted the development of phase II studies to study the role of this combination as a front-line regimen for patients considered ineligible for more intensive approaches (clinicaltrials.gov identifier NCT01472562).

Bortezomib has similarly shown promise in the relapsed and refractory patients and has been approved by the US Food and Drug Administration for use in this setting. Response rates and median PFS mirror those seen with single-agent lenalidomide, hovering around 50% and 6 months, respectively.74-77 Interestingly, however, among responding patients, the median PFS is prolonged (10 to 24 months). These data have fueled numerous phase I and II studies in which bortezomib has been coupled to cytotoxic backbones, including bendamustine,78 gemcitabine,79 CHOP,80,81 and HyperCVAD.82 Perhaps the most compelling data in this regard comes from a small phase II trial investigating the combination of bortezomib with rituximab and dexamethasone in 16 heavily pretreated patients.83 This combination produced an overall response rate of 81.3% with a CR rate of 43.8%, a median PFS of 12.1 months, and an OS of 38.6 months. Furthermore, of the 7 patients who obtained a CR, 5 sustained this response beyond 48 months in the absence of further therapy.

Several preclinical studies have suggested that aberrant signaling via the AKT-MTOR pathway might play a dominant role in driving proliferation in MCL.84 However, attempts to inhibit this pathway with temsirolimus, an inhibitor of the MTORC1 complex, have proven only...
moderately successful, with response rates of approximately 20% and a corresponding PFS of approximately 5 months.85

Several malignancies have shown significant disruption of gene expression as a consequence of aberrant epigenetic modification. Histone deacetylases, in particular, appear to play an important role in immunological escape, proliferation, and autocrine cytokine signaling, which may be important in maintaining the microenvironmental niche and facilitating drug resistance.86-90

As a single agent, the nonspecific histone deacetylase inhibitor vorinostat failed to show significant response in relapsed/refractory MCL; however, 1 of the 9 treated patients maintained stable disease for over 2 years.91

To build on this approach, an ongoing study is evaluating the efficacy of vorinostat given in conjunction with bortezomib in relapsed/refractory MCL, with early data showing a 47% overall response rate.92 Of particular interest are isotype-specific HDAC inhibitors, including those targeting HDAC6, which may contribute significantly the malignant phenotype of MCL.89

**Emerging Agents**

Several drugs currently being explored in phase I and II studies are showing exquisite promise in MCL. One particularly promising approach has focused on disruption of B-cell receptor downstream signaling. Two agents are notable in this regard: PCI-32765 and CAL-101. Administration of PCI-32765 leads to targeted inhibition of Bruton’s tyrosine kinase and so far is showing an overall response rate of 67%.93 CAL-101 is targeted to the specific isoform of phosphatidylinositol 3-kinase delta and has shown an overall response rate of 62%.94 Interestingly, both agents are associated with lymphocytosis, suggesting that inhibition of this pathway may be associated with disruption of microenvironment, perhaps via secondary influences on CXCR4 signaling.95,96

The failure of temsirolimus to produce dramatic responses has fostered further preclinical study showing that MCL may escape MTORC1 inhibition via increasing signaling through MTORC2 and phosphorylation of AKT, a survival pathway.97 This has led to the development of several dual MTORC inhibitors, including OSI-202 and PP242, both of which are currently in phase I clinical testing.

Given that overexpression cyclin D1 is central to pathogenesis of MCL, current studies are also underway to inhibit this molecule. Interestingly, targeted disruption of cyclin D1 was associated with increased signaling via cyclin D2 and cyclin D3 in preclinical models.98 Therefore, research has been focused on inhibiting downstream targets of cyclin D1. One such novel agent is PD0332991, which targets cyclin-dependent kinases 4 and 6 to effectively inhibit proliferation in MCL. Clinical studies using this as a single agent have shown an overall response rate of 18% in relapsed cases.

Although this response rate was lower than expected, subsequent pharmacodynamic studies demonstrated significant inhibition of cell cycling.99 This has fueled an alternative approach, currently under study, in which PD0332991 is administered to coordinate cell cycling in order to facilitate enhanced sensitivity to the agent bortezomib.100

**Conclusions**

Mantle cell lymphoma is a protean disease with both indolent and highly aggressive presentations that must be reconciled with host factors, including patient age and comorbid conditions, to appropriately tailor therapy. Although increases in treatment intensity and duration have yielded significant benefit for many with this disease, mantle cell lymphoma continues to be characterized by a pattern of continuous relapse. Novel approaches are showing promise in these settings, with many agents currently poised to make significant additional impact.

**References**


42. Nabhan C, Smith SM, Kahl BS. Maintenance rituximab following rituximab given at the standard schedule or as prolonged treatment in patients with relapsing or relapsed aggressive mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). *Leukemia*. 2010;24(4):705-711.


50. Niederer M, Johnson JL, Niedzwiecki D, et al. Immunochemothera-