Abstract: Mantle cell lymphoma is one of the most challenging hematologic malignancies, owing to an aggressive disease course, a high rate of relapse, and lack of standard of care. In the United States, mantle cell lymphoma accounts for approximately 6% of all newly diagnosed cases of non-Hodgkin lymphoma. Because most patients are initially diagnosed with advanced-stage disease, they are often symptomatic at presentation. Common features include widespread lymphadenopathy and splenomegaly, as well as bone marrow infiltration. Leukemic involvement is found in 20% to 30% of patients. The disease course can be highly variable. Some patients may have very aggressive disease, whereas others may have a much more indolent course. The optimal frontline therapy remains undefined. Strategies include chemotherapy, immunotherapy, radioimmunotherapy, stem cell transplantation, and novel biologic agents. Although mantle cell lymphoma often responds well to frontline chemotherapy, the responses are not durable and often of relatively short duration. Effective treatment options in the frontline setting have included the addition of rituximab to bendamustine. Once mantle cell lymphoma has entered the relapsed/refractory stage, it becomes more difficult to treat. Bortezomib and lenalidomide are approved for treatment of relapsed/refractory mantle cell lymphoma. The novel Bruton’s tyrosine kinase inhibitor ibrutinib appears to be highly active in relapsed/refractory mantle cell lymphoma. Other agents in clinical trials include cladribine, idelalisib, and IPI-145.
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Mantle cell lymphoma (MCL) is an aggressive B-cell subtype of non-Hodgkin lymphoma (NHL) that typically affects adults who are middle-aged or older. Generally, MCL arises from naive, pre–germinal center lymphocytes. MCL characteristically exhibits small-to-medium–sized tumor cells that can infiltrate the lymph nodes, spleen, bone marrow, blood, and gastrointestinal system (Figure 1). Although new treatment strategies are on the horizon, MCL remains one of the most challenging hematologic malignancies, owing to an aggressive disease course, a high rate of relapse, and lack of standard of care.

**Epidemiology**

In the United States, MCL accounts for approximately 6% of all newly diagnosed cases of NHL.1 Worldwide, between 3% and 10% of NHL cases are MCL.2 The average overall incidence of MCL is 0.5 cases per 100,000 person-years.3 In an analysis of data from 1992 through 2004 by the Surveillance, Epidemiology, and End Results (SEER) registry, the overall incidence was 0.55 cases per 100,000 person-years.4 The incidence varied greatly according to age; it was as low as 0.07 cases per 100,000 person-years in patients younger than 50 years, and increased to 0.83, 1.96, 2.97, and 2.78 cases per 100,000 person-years in patients aged 50 to 59 years, 60 to 69 years, 70 to 79 years, and 80 years or older, respectively. The incidence of MCL may be rising, with a significant 5.87% (P<.05) increase in the annual percent change; the age-adjusted incidence rate rose from 0.27 cases per 100,000 person-years in 1992 to 0.69 cases per 100,000 person-years in 2004.4 Interestingly, this increase was much greater than that calculated for other malignancies, including NHL overall (0.2%), diffuse large B-cell lymphoma (0.17%), and follicular lymphoma (1.23%). It may, however, be a reflection of improved disease definition and diagnosis.

The SEER registry analysis identified other demographic characteristics of MCL.4 Men are disproportionately affected, with an incidence rate that was more than doubled compared with women (0.84 cases per 100,000 vs 0.34 cases per 100,000, respectively); the relative risk of MCL in men vs women was 2.48 (95% CI, 1.89-2.71) in whites vs 1.17 in other ethnicities (95% CI, 0.90-1.52). Approximately three-quarters of patients were diagnosed with later stage disease (Ann Arbor stage III or IV [Table 1]).

**Histologic, Immunologic, and Molecular Characteristics**

Three patterns of tumor infiltration are characteristic of MCL: diffuse replacement of the entire lymph node, infiltration into the expanded mantle zone, and vague nodular patterns. The MCL tumor cells typically appear as a monomorphic population of small-to-medium–sized lymphoma cells and the presence of a pink histiocyte. Image from Gabriel Caponetti, MD.

Unmet Needs in Mantle Cell Lymphoma: Introduction

Steven T. Rosen, MD
been reported; these cases were confirmed to be negative for cyclin D1, the feature in MCL. Recently, cyclin D1-negative MCL has been described. For example, CD5-negativity may be present in 5% to 10% of MCL cases.10-13 CD23 may be positive or negative. However, this profile is not necessary for a diagnosis of MCL. Indeed, MCL is readily identifiable, owing to characteristic histologic, immunologic, and molecular phenotypes (Table 2). The immunohistochemistry profile of MCL typically consists of CD5-positive, CD20-positive, CD43-positive, and cyclin D1-positive cells. CD10 and CD23 may be positive or negative. However, this profile is not necessary for a diagnosis of MCL. Indeed, MCL cases with aberrant immunophenotype profiles have been described. For example, CD5-negativity may be present in 5% to 10% of MCL cases.10-13

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As stated in guidelines from the National Comprehensive Cancer Network (NCCN), cyclin D1–positivity is required for a diagnosis of MCL.14 cyclin D1 overexpression is a useful tool to distinguish between MCL and chronic lymphocytic leukemia. Most commonly, cyclin D1 overexpression arises from the translocation t(11;14)(q13;q32) between the cyclin D1 gene (CCND1) and the immunoglobulin heavy chain locus. This translocation is the primary molecular pathogenic feature in MCL. Recently, cyclin D1–negative MCL has been reported; these cases were confirmed to be negative through both immunophenotypic means as well as fluorescence in situ hybridization (FISH) analysis, which showed a lack of the t(11;14) translocation.15-17 Clinically, these cases appear to be similar to those that are cyclin D1–positive. Thus, the hematopathologist should be aware of this possibility when assessing a sample that is CD5-positive and cyclin D1–negative but has morphologic attributes characteristic of MCL.

Recently, much interest has focused on the use of SOX11 transcription factor as a diagnostic tool, based on its high level of expression in classical MCL subtypes. In one study, SOX11 expression was found to be specific for the nucleus of MCL cells compared with other lymphoma cells and noncancerous tissue.18 A follow-up study confirmed strong SOX11 expression in MCL cells, and also found that the protein was strongly expressed in some childhood Burkitt lymphomas as well as B-lymphoblastic and T-lymphoblastic leukemias and lymphomas.19 High levels of SOX11 expression appear to occur independently of cyclin D1 overexpression, and thus may be a useful indicator in patients with cyclin D1–negative MCL.20 SOX11 may have usefulness as a diagnostic marker, and, importantly, it may also prove informative as a prognostic marker, suggesting shorter overall survival.21-23

Interestingly, MCL has one of the highest degrees of genomic instability among the B-cell malignancies, with numerous chromosomal aberrations, including losses, gains, and amplifications.24 Many of these chromosomal alterations occur in genes involved in cell cycle regulation, DNA damage response pathways, and apoptosis.

### Clinical Presentation and Disease Course

Because most patients are initially diagnosed with advanced stage (III or IV) disease, MCL patients are often symptomatic at presentation. Common features include widespread lymphadenopathy and splenomegaly, and bone marrow infiltration.6 Leukemic involvement is found in 20% to 30% of patients.24 B symptoms and bulky disease may occur, but usually not at diagnosis. Extranodal involvement is often observed, most frequently involving the gastrointestinal tract and liver. Gastrointestinal tract involvement is most often manifested as multiple lymphomatous polyposis of the intestine.25 More than 90% of patients have extranodal involvement at diagnosis, and between 30% and 50% of patients show infiltration in more than 2 extranodal areas.26,27 Other areas of infiltration may include the breast, lungs, skin, soft tissue, Waldeyer ring, salivary gland, and orbit.6,25 Although infiltration into the central nervous system may be present, it is rarely observed at the time of diagnosis and instead is more likely to occur as a very late event in the disease. In one study, the actuarial 5-year risk of
central nervous system involvement was 26% (95% CI, 10%-42%), and the median time from diagnosis to the development of neurologic symptoms was 25 months.28

The clinical course of MCL is not uniform, and it correlates with the particular pathologic subtype of the disease. Overall, the median progression-free survival for MCL patients is 20 months, and the median overall survival is between 5 and 7 years.24,29 This survival represents an increase from a previous range of 2 to 3 years, an improvement that is primarily attributed to advances in combination chemotherapy regimens as well as supportive care strategies.6

The blastic variant of MCL is associated with a worse prognosis and decreased survival as compared with the classical variant (survival is 14.5 months vs 53 months, respectively [P<.0001]).30 This subtype has a high mitotic count, a high proportion of Ki67-positive cells, and genetic abnormalities that can include trisomy 12, 3q+, 9q-, or changes in the p53 gene (mutations or abnormalities that result in overexpression of the mutant protein).

A separate subset of patients, representing between 15% and 30% of MCL cases, has a more indolent course and even longer median survival.31,32 These patients typically have an indolent presentation and no acute symptoms. Because they have no immediate need for therapy, treatment can be delayed without markedly affecting overall outcome. It has therefore become increasingly important to be able to identify those MCL patients who have a more indolent disease course. Their presentation may be reminiscent of chronic lymphocytic leukemia, with only mild lymphocytosis and splenomegaly. One potential biomarker for distinguishing indolent MCL patients may be SOX11 expression, which is absent in this patient subset.33

Several tumor-specific and patient-specific factors are known to have a significant effect on prognosis in MCL. Proliferative activity, as assessed by the Ki67 proliferation index, is the most important of these factors in routine clinical practice. A high proliferation rate is associated with a shorter overall survival, as was observed in a study of 304 MCL patients.3 Median overall survival steadily decreased from 42 months in patients with a Ki67 proliferation index of less than 10%, to 30 months in patients with an index of 11% to 40%, to as low as 15 months in patients with an index of more than 40% (P<.0001). However, the Ki67 proliferation index is subject to interobserver variability, and according to the NCCN guidelines, it should not be used to guide treatment decisions.14

Clinical risk factors include age, Eastern Cooperative Oncology Group (ECOG) performance status, presence of B symptoms, spleen involvement, tumor size, leukocyte count and levels of lactose dehydrogenase (LDH), hemoglobin, serum albumin, and β-2-microglobulin (b2M). Advanced disease stage, high tumor burden, occurrence of B symptoms, and poor ECOG performance status are all associated with a worse outcome, whereas younger age (<65 years), normal LDH levels, and normal b2M levels are all associated with a better outcome.26

The immunoglobulin heavy chain (IgHV) gene can be mutated or unmutated in MCL. In contrast to CLL, the prognostic role of this phenotype remains undefined in MCL. Prognostic algorithms and international prognostic indices (IPI) that were developed for assessment of either exclusively indolent lymphomas (such as the Follicular Lymphoma IPI) or aggressive lymphomas (such as the traditional IPI) often fail to effectively classify MCL patients into distinct prognostic subgroups. Therefore, the MCL IPI was developed, based on data from more than 400 MCL patients, to be tailored specifically to this disease.34,35 The MCL IPI incorporates patient age and ECOG performance status (both used to assess chemotherapy tolerance), as well as white blood cell (WBC) count and LDH levels (both indirect measures of disease activity). Using these factors, patients are stratified into 3 groups: low, intermediate, and high-risk, which are associated with approximate median overall survival times of 6 years, 4 years, and 2 years, respectively.25 Studies have validated the MCL IPI and shown that these risk groups correlate well with MCL patient prognosis. When this scoring system was applied to 158 patients from the Nordic MCL2 trial, the MCL IPI was found to predict survival following first-line treatment significantly better than the traditional IPI (Figure 2).36 Notably, the MCL IPI is prognostic for overall survival, but not progression-free survival.

### Table 2. The Immunophenotype of Mantle Cell Lymphoma

<table>
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<tr>
<th>By Immunohistochemistry</th>
<th>CD20</th>
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Ig, immunoglobulin.
Figure 2. Among patients from the Nordic MCL2 trial, the MIPI was found to predict survival following first-line treatment (A) significantly better than the traditional IPI (B). IPI, International Prognostic Index; MCL, Mantle Cell Lymphoma International Prognostic Index. Adapted from Geisler CH et al. Blood. 2010;115(8):1530-1533.

Acknowledgment
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References
Currently, there is no standard treatment approach for the treatment of patients with MCL. Potential strategies include chemotherapy, immunotherapy, radioimmunotherapy, stem cell transplantation, and novel biologic agents. There are 3 major factors to consider when formulating a treatment plan: the course of the disease, treatment goals, and patient characteristics.

The disease course can be highly variable. Some patients may have very aggressive disease, whereas others may have a much more indolent course. As previously described, the Ki67 proliferation index and the MCL IPI can be useful tools when ascertaining the aggressiveness of the disease, as can knowledge regarding the subtype (classical vs blastic).

The second major factor to consider when deciding on a course of therapy is the goals of treatment. A cure is typically thought to be elusive in MCL. Thus, reasonable goals of treatment for MCL patients may include long-term survival, symptom control (if needed), or durable event-free survival. For younger, fitter patients who are potential candidates to proceed to autologous stem cell transplantation (ASCT), the goal of chemotherapy induction should be to obtain as deep a remission as possible.

Patient characteristics are the third essential component when developing the treatment plan. Patients are typically characterized based on their age, which can often be used as a surrogate indicator of how well they will tolerate therapy. Patient comorbidities that require particular attention include renal function, bone marrow function (if the patient has previously been treated), cardiac function, and other conditions that may decrease response to therapy.

Once these factors have been considered, the next step in the decision plan is to ascertain which therapeutic options are realistically available and appropriate for the individual patient. For initial treatment, the 2 primary areas of focus when determining the suitability of a particular regimen are the intensity of the induction therapy and the choice of postinduction management. Initially, the knowledge that informs these choices was limited because it was based primarily on data from retrospective series. However, more recent data from prospective and/or randomized phase 2 or 3 clinical trials has allowed greater confidence in the choice of therapy.

Frontline Therapy

NCCN guidelines group induction treatment regimens into aggressive vs less aggressive options, recommending that the choice be made based on the patient’s age, comorbidities, and disease characteristics. Frontline therapy regimens have historically consisted of a combination of chemotherapeutic agents (Table 3). There is also a universal appreciation for the role of anti-CD20 antibodies, such as rituximab, in the treatment of MCL.

Few patients present with localized stage I or II MCL, and data regarding treatment of these patients are limited. In one retrospective study, progression-free survival was increased in patients who received radiotherapy (with or without chemotherapy) as part of their frontline treatment regimen.

In certain patients, it may be appropriate to defer therapy and instead rely on an initial observational approach, as discussed in the previous article. In a small retrospective study that evaluated the outcomes of MCL patients who deferred initial therapy, patients who underwent observation exhibited a statistically superior median survival compared with patients who underwent immediate treatment (not reached vs 64 months; *P*=.004). However, some patients may be hesitant to postpone therapy. For these patients, single-agent rituximab may be a good treatment choice, as suggested by 2 studies in which it had moderate activity. A study from the Swiss Group for Clinical Cancer Research found that single-agent rituximab was associated with a clinical response rate of 27%...
in newly diagnosed MCL patients. A European phase 2 trial demonstrated a 38% response rate with single-agent rituximab in newly diagnosed MCL.

Overall, rituximab seems to have less robust activity as a single agent in MCL as compared with other B-cell lymphomas such as follicular lymphoma and diffuse large B-cell lymphoma. However, it has a significant role when added to other chemotherapy drugs. A systematic review and meta-analysis of chemotherapy alone vs rituximab plus chemotherapy in MCL concluded that the latter may result in a superior overall survival (hazard ratio, 0.60; 95% CI, 0.37-0.98). However, this conclusion was limited by the availability of only a small number of randomized clinical trials for the analysis.

By itself, the combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is associated with only minimal activity in MCL patients. The addition of rituximab greatly improves response. In a phase 2 study of 40 patients, the combination of rituximab plus CHOP (R-CHOP) was associated with high response rates: 48% of patients achieved a complete response, and 48% achieved a partial response. However, owing to a high rate of relapse, this response rate was not predictive of progression-free survival, despite a lack of PCR-detectable disease in a number of patients.

Similarly, in a prospective, randomized phase 3 trial from the German Low Grade Lymphoma Study Group (GLSG), the addition of rituximab to CHOP significantly improved rates of overall response (75% vs 94%; \( P = .0054 \)), complete response (7% vs 34%; \( P = .00024 \)), and median time to treatment failure (14 vs 21 months; \( P = .0131 \)) compared with CHOP alone. However, these benefits did not translate into an improvement in either progression-free survival or overall survival.

Another effective treatment option in the frontline setting is the addition of rituximab to bendamustine. In a recently updated, prospective, randomized, multicenter, open-label, noninferiority trial from the German Study Group of Indolent Lymphomas (StiL), the combination of rituximab plus bendamustine was compared with R-CHOP as frontline therapy in patients with indolent lymphomas or MCL (comprising approximately 18% of patients). After a median follow-up of 45 months, the median progression-free survival was significantly increased among all patients treated with rituximab plus bendamustine compared with R-CHOP (69.5 vs 31.2 months; hazard ratio, 0.58; 95% CI, 0.44-0.74; \( P < .0001 \)). This benefit in progression-free survival was also evident among MCL patients alone (35.4 vs 22.1 months; hazard ratio, 0.49; 95% CI, 0.28-0.79; \( P = .0044 \); Figure 4). The overall response rate was similar between the treatment groups, but the rates of complete response were higher with rituximab plus bendamustine (40%) compared with R-CHOP (31%). Interestingly, rituximab plus bendamustine seemed to be associated with superior progression-free survival independent of the quality of response. The median progression-free survival for patients who achieved a complete response was not reached for those treated with rituximab plus bendamustine and 54 months for those treated with R-CHOP (\( P = .02 \)). Similarly, for patients who achieved a partial response, the median progression-free survival was 57 months for patients treated with rituximab plus bendamustine and 31 months for patients treated with R-CHOP (\( P = .0002 \)). Importantly, patients were better able to tolerate the rituximab plus bendamustine

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ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; CVP, cyclophosphamide, vincristine, and prednisone; IFN, interferon; PFS, progression-free survival; R-B, rituximab, bendamustine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin.
combination, with lower frequencies of alopecia, hematologic toxicities, infections, peripheral neuropathy, and stomatitis. The addition of cytarabine to bendamustine and rituximab resulted in very high response rates in a recent phase 2 Italian study of 40 elderly patients, and this regimen deserves further study. \cite{15} Cladribine has been evaluated both as a single agent and in combination with rituximab in the frontline setting. \cite{16} In 26 previously untreated MCL patients, the overall response rate to single-agent cladribine was 81\%, with 42\% of patients achieving a complete response. The median progression-free survival was 13.6 months, and the 2-year overall survival rate was 81\%. Among 29 previously untreated MCL patients who received a combination of cladribine and rituximab, the overall response rate was 66\%, and the complete response rate was 52\%. More recently, a retrospective chart review was published that attributed an overall response rate of 87\% and a complete response rate of 61\% to the combination of cladribine plus rituximab. \cite{17} Notably, the majority of responding patients had also received rituximab as maintenance therapy.

In randomized trials, fludarabine inductions perform less well, and there may be a role for cytarabine. Some of the alternatives to anthracycline-based immunochemotherapy regimens in elderly patients should be considered with caution, as a recent study demonstrated that rituximab plus fludarabine and cyclophosphamide (R-FC) was associated with worse outcomes compared with R-CHOP in elderly MCL patients. \cite{18, 19} In this double-randomized, open-label, multicenter trial, R-FC induction had a complete response rate that was comparable to that of R-CHOP (40\% vs 34\%; \(P=.10\)). However, disease progression occurred more frequently in patients randomized to R-FC compared with R-CHOP (14\% vs 5\%), and the 4-year overall survival rate was significantly lower with R-FC compared with R-CHOP (47\% vs 62\%; \(P=.005\)).

Because of the relatively poor prognosis and low survival rates associated with MCL, many physicians and patients have opted for more aggressive frontline treatment strategies. For example, 3-year overall survival rates exceeding 80\% have been reported in small studies evaluating rituximab plus a regimen of cyclophosphamide, vincristine, doxorubicin, and dexamethasone, with alternating high-dose methotrexate and cytarabine (hyper-CVAD), or with ASCT. \cite{20} Long-term (10-year) follow-up of patients treated with this dose-intensive R-hyper-CVAD regimen showed that the median overall survival had not been reached, and the median time-to-treatment failure was 4.6 years. \cite{21} However, a retrospective analysis of 181 MCL patients found that more intensive regimens did not significantly improve overall survival as compared with R-CHOP or rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP). \cite{22} It should be noted that both the 3-year overall survival rate (86\%) and median overall survival (7.1 years) both exceeded what is typically reported following frontline treatment of MCL patients.

There are additional data suggesting that dose-intensive regimens may not have a significant benefit in MCL. The recent phase 2 multicenter Southwest Oncology Group (SWOG) 0213 study demonstrated that the combination of rituximab plus hyper-CVAD was associated with a median progression-free survival of 4.8 years and a median overall survival of 6.8 years. Although the response rates associated with this treatment were high, they proved not to be durable. \cite{23, 24} This regimen was associated with a continuous rate of relapse over time, coupled with marked hematologic toxicity. \cite{25}

More recently, an analysis from the NCCN NHL database was performed to ascertain the benefit of more aggressive frontline regimens in younger (<65 years) MCL patients. \cite{26} Data were evaluated from patients treated with a number of regimens, including rituximab fractionated CVAD (RHCVD), R-CHOP plus high-dose therapy with autologous stem cell rescue, RHCVAD plus high-dose therapy with autologous stem cell rescue, and R-CHOP. There was no significant difference in progression-free survival among the aggressive regimens (\(P>.57\)). Importantly, however, progression-free survival was significantly increased with any one of the aggressive regimens compared with treatment with R-CHOP (\(P<.004\); Figure 5). Cytarabine has again attracted interest as a treatment for younger MCL patients based on a phase 2 study of R-CHOP followed by rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) and consolidation with ASCT, in which R-DHAP led to a complete response rate of 57\% and a median event-free survival of 83 months. \cite{27}

Thus, taken together, these data suggest that dose-intensive frontline therapy may be an appropriate choice...
in certain MCL patients. In cases where the MCL patient is younger and presents with intermediate- or high-risk MCL, aggressive therapy may be considered. For older MCL patients with intermediate- or high-risk disease, a regimen consisting of rituximab added to combination chemotherapy (such as R-CHOP; R-CVP; or rituximab plus bendamustine) may be more appropriate. Cytarabine is currently a drug of active study in both scenarios.

**Postremission Therapy**

Although MCL often responds well to frontline chemotherapy, the responses are not durable and are often relatively short. For MCL patients achieving a response to initial therapy, postremission management options include observation, high-dose chemotherapy with autologous stem cell rescue (HDT/ASCR), or maintenance therapy. The latter 2 options have each shown significant impact on event-free survival and some suggestion of impact on overall survival.

**Role of Stem Cell Transplant**

Patients who are fit and achieve a very good remission in response to initial therapy should be considered for consolidation with high-dose chemotherapy and ASCT. In prospective studies, this approach improved rates of event-free survival and, in some cases, overall survival as compared with historical controls. Disease status at the time of transplantation appears to be the most significant factor affecting survival following HDT/ASCR. Patients who remain in their first remission (either a complete response or a partial response) at the time of transplant achieve the best survival outcomes as compared with patients who have relapsed or refractory disease at the time of transplant.

The only randomized study in this setting compared consolidation with myeloablative radiochemotherapy followed by ASCT vs maintenance therapy with interferon-α (both after achieving a complete or partial response with a CHOP-like induction therapy). There was a significantly prolonged median progression-free survival in the ASCT arm (39 vs 17 months; P=0.0108). Although there was a trend toward an improved 3-year overall survival rate with ASCT (83% vs 77%), this difference did not achieve statistical significance (P=0.18), and longer follow-up is needed.

In the nonrandomized phase 2 multicenter Nordic Lymphoma Group MCL2 trial, 160 previously untreated MCL patients (<66 years) underwent dose-intensified induction therapy, alternating between R-maxi-CHOP and rituximab plus high-dose cytarabine. Responding patients subsequently received high-dose chemotherapy with either carmustine, etoposide, cytarabine, melphalan (BEAM) or high-dose carmustine, etoposide, Ara-C and cyclophosphamide (BEAC), supported by in vivo rituximab-purged autologous stem cells. The 6-year overall and event-free survival rates following treatment were 70% and 56%, respectively, with no patient showing evidence of a relapse throughout 5 years of follow-up. However, in longer follow-up (median 6.5 years), 6 patients experienced a late relapse. The overall results remain encouraging, with a median overall survival exceeding 10 years and a median event-free survival of 7.4 years.

**Role of Maintenance Therapy**

For the majority of MCL patients who are not candidates for an aggressive consolidation strategy, postinduction maintenance treatment with rituximab may be an effective alternative. When older (≥60 years of age) MCL patients who had responded to initial induction therapy with either R-CHOP or R-FC were rerandomized to maintenance therapy with either single-agent rituximab or interferon-α (each administered until disease progression), rituximab was associated with a 45% decrease in the risk of progression or death (hazard ratio, 0.55; 95% CI, 0.35-0.86; P=0.01). For patients who had responded to R-CHOP induction therapy, maintenance rituximab significantly improved the 4-year overall survival rate vs maintenance with interferon-α (87% vs 63%; P=0.005). Maintenance therapy with newer agents demonstrating activity in MCL, such as lenalidomide or ibrutinib, is currently under investigation.

**Management of Relapsed/Refractory Disease**

Once MCL has entered the relapsed/refractory stage, it becomes even more difficult to treat and exhibits even
less sensitivity to treatment, with response rates to single agents generally less than 50% (Table 4). Even with combination therapy, complete response rates seldom exceed 30%. The NCCN guidelines recommend various treatment options for relapsed/refractory patients, and 2 agents have gained approval from the US Food and Drug Administration (FDA) in this setting.

The reversible proteasome inhibitor bortezomib received FDA approval in December 2006 for treatment of MCL patients who have relapsed after at least 1 prior therapy. This approval was based primarily on the pivotal phase 2 PINNACLE (Multicenter Phase II Study of Bortezomib in Patients With Relapsed or Refractory Mantle Cell Lymphoma) trial, in which single-agent bortezomib was administered to 155 relapsed or refractory MCL patients who had received a median of 1 prior therapy (range, 1-3). The response rate was 33%, with 8% of patients achieving a complete response or unconfirmed complete response. Responses were relatively durable, with a median duration of response of 9.2 months and a median time to progression of 6.2 months. At the initial median follow-up of 13.4 months, a median overall survival had not been reached. In an updated analysis with a longer follow-up (median, 26.4 months), the median overall survival was 23.5 months. Among patients who had initially responded to single-agent bortezomib, the median time-to-progression was 12.4 months, and the median overall survival was 35.4 months. The 1-year overall survival rate was also improved among responding patients (91%) as compared with the overall treated population (69%). Notably, bortezomib appeared to be active even in patients who had relapsed following high-intensity treatment. A separately reported phase 2 trial provided further evidence of bortezomib’s activity in this setting, with even heavily pretreated MCL patients exhibiting a 47% overall response rate.

Subsequent studies have evaluated bortezomib in combination with rituximab for the treatment of relapsed/refractory MCL, with promising results. In one such phase 2 trial, the overall response rate among 14 MCL patients was 29%. In a second study, when bortezomib was combined with rituximab and dexamethasone, the overall response rate among 16 heavily pretreated MCL patients was 81.3%, including a 43.8% rate of complete response. The median progression-free survival was 12.1 months, and the median overall survival was 38.6 months, although neither survival endpoint had been reached in patients who had achieved a complete response with this combination.

The class of drugs known to inhibit the mammalian target of rapamycin (mTOR) is also active in relapsed MCL. Temsirolimus is approved for relapsed and/or refractory MCL in the European Union and several other countries outside of the United States on the basis of a randomized phase 3 trial demonstrating a benefit in progression-free survival (4.8 months) compared with investigator choice (1.9 months). The orally available mTOR inhibitor everolimus demonstrated similar activity in a phase 2 trial, with an overall response rate of 20% and a median progression-free survival of 5.5 months.

In June 2013, the immunomodulatory drug lenalidomide gained FDA approval for the treatment of MCL patients whose disease has relapsed or progressed after prior treatment with bortezomib and 1 other therapy. This approval was based on the results of the single-arm, multicenter, phase 2

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Table 4. Select Single-Agent Phase 2 Trials in Salvage Treatment of Mantle Cell Lymphoma

<table>
<thead>
<tr>
<th>Therapy</th>
<th>N</th>
<th>Primary Endpoint</th>
<th>Result</th>
<th>Secondary Endpoint</th>
<th>Result</th>
<th>Reference</th>
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<tr>
<td>Fludarabine</td>
<td>6</td>
<td>OR</td>
<td>16%</td>
<td>Treatment failure</td>
<td>6 months</td>
<td>Tobinai 200647</td>
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<tr>
<td></td>
<td>15</td>
<td>OR</td>
<td>33%</td>
<td>CR</td>
<td>0%</td>
<td>Decaudin 199848</td>
</tr>
<tr>
<td>Cladribine</td>
<td>24</td>
<td>OR</td>
<td>46%</td>
<td>PFS</td>
<td>5 months</td>
<td>Inwards 200849</td>
</tr>
<tr>
<td>Rituximab</td>
<td>40</td>
<td>OR</td>
<td>37%</td>
<td>Response duration</td>
<td>1.2 years</td>
<td>Foran 200010</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>OR</td>
<td>28%</td>
<td>CR</td>
<td>2%</td>
<td>Ghelmini 200551</td>
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<td>Bortezomib</td>
<td>155</td>
<td>OR</td>
<td>33%</td>
<td>CR/CRu</td>
<td>8%</td>
<td>Fisher 200634</td>
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<tr>
<td></td>
<td>24</td>
<td>OR</td>
<td>29%</td>
<td>CR</td>
<td>4%</td>
<td>Strauss 200649</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>OR</td>
<td>43%</td>
<td>CR</td>
<td>12%</td>
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<td>Lenalidomide</td>
<td>134</td>
<td>OR</td>
<td>28%</td>
<td>CR</td>
<td>7%</td>
<td>Goy 201398</td>
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<tr>
<td></td>
<td>15</td>
<td>OR</td>
<td>53%</td>
<td>CR</td>
<td>20%</td>
<td>Habermann 200950</td>
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<tr>
<td></td>
<td>57</td>
<td>OR</td>
<td>42%</td>
<td>CR</td>
<td>21%</td>
<td>Witzig 201151</td>
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<tr>
<td></td>
<td>26</td>
<td>OR</td>
<td>31%</td>
<td>PFS</td>
<td>3.9 months</td>
<td>Eve 201252</td>
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<tr>
<td>Temsirolimus</td>
<td>34</td>
<td>OR</td>
<td>38%</td>
<td>CR</td>
<td>3%</td>
<td>Witzig 200553</td>
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<tr>
<td></td>
<td>28</td>
<td>OR</td>
<td>41%</td>
<td>CR</td>
<td>1%</td>
<td>Ansell 200854</td>
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<td></td>
<td>108</td>
<td>PFS</td>
<td>4+ months</td>
<td>OR</td>
<td>22%</td>
<td>Hess 2009 (phase 3)50</td>
</tr>
</tbody>
</table>

CR, complete response; CRu, complete response, unconfirmed; OR, overall response; PFS, progression-free survival.
MCL-001 EMERGE (Study to Determine the Efficacy and Safety of Lenalidomide in Patients With Mantle Cell NHL Who Have Relapsed or Progressed After Treatment With Bortezomib or Are Refractory to Bortezomib) trial, which included 134 MCL patients who had either relapsed after therapy with bortezomib or were refractory to bortezomib (or a bortezomib-based regimen). These patients were heavily pretreated, with 60% having bortezomib-refractory disease. Patients had received a median of 4 prior therapies. An overall response rate of 28% was reported, with a 7.5% rate of complete response or unconfirmed complete response. Responses were rapid (median time to response, 2.2 months) and durable (median duration of response, 16.6 months; Figure 5). The median progression-free survival was 4.0 months, and the median overall survival was 19.0 months.

Fludarabine-based regimens, either with or without rituximab, show promising activity in relapsed/refractory MCL patients. Among 66 MCL patients enrolled in a randomized, prospective phase 3 study, improved outcomes were observed when rituximab was combined with fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) compared with fludarabine, cyclophosphamide, and mitoxantrone alone. These outcomes included higher overall response rates (58% vs 46%) and complete response rates (29% vs 0%). Additionally, among those patients who had responded to R-FCM induction therapy, rituximab maintenance therapy led to a higher rate of 2-year remission compared with observation alone (45% vs 9%; P=.049). The combination of fludarabine plus rituximab was compared against bendamustine plus rituximab in a phase 3 randomized trial from the StiL group. The study included 208 patients with relapsed/refractory follicular or indolent lymphoma or MCL (approximately 20% of patients had MCL histology). The overall response rate to fludarabine plus rituximab was 52.5%, and the complete response rate was 16%, both of which were significantly inferior to the rates achieved with bendamustine plus rituximab (83.5% and 38.5%, respectively). Although there was no apparent difference in overall survival between the 2 treatment arms, fludarabine plus rituximab was associated with a significantly shorter median progression-free survival compared with bendamustine plus rituximab (11 vs 30 months; P<.0001).

Single-agent cladribine has also been investigated in the relapsed/refractory MCL patient setting. Among 25 patients with recurrent MCL, the overall response rate was 46%, the complete response rate was 21%, and the median progression-free survival was 5 months. Future studies will likely evaluate cladribine combined with rituximab for relapsed/refractory MCL patients.

Acknowledgment
Dr Link is a consultant for Genentech/Roche, Celgene, and Pharmacycics.

References


Novel Treatment Approaches to Mantle Cell Lymphoma

Nathan H. Fowler, MD

Despite several effective options, there is no currently accepted standard of care for the frontline treatment of MCL. Although a number of treatment regimens have been evaluated for frontline therapy, in general, they have not demonstrated a significant and prolonged increase in survival. Intensive therapeutic approaches, often including high-dose chemotherapy with or without stem cell rescue, result in objective responses in the majority of patients, but progression still occurs within 5 years in most patients. Typical chemoimmunotherapy combinations are also associated with significant and often profound morbidity. Furthermore, in these patients, a high—nearly inescapable—risk of relapse is often associated with chemoresistance, creating a large unmet need.

Combining novel and targeted agents with more effective chemotherapeutic backbones, or exploring alternative dosing/maintenance schedules, may provide one means by which long-term patient outcomes can be significantly improved (Figure 6). Bendamustine, a recently rediscovered bifunctional alkylator, has significant activity in MCL. In a recently published phase 3 study, the combination of bendamustine and rituximab was associated with a significant improvement in progression-free survival compared with R-CHOP among a subset of patients with previously untreated MCL.1,2 Toxicity profiles of the combinations did not suggest inferior tolerability of bendamustine compared with R-CHOP.1,2

Although there are a number of effective novel agents in clinical development, the potential benefits of maximizing existing targeted therapeutics are substantial, and were demonstrated in a recent trial that compared R-FC with R-CHOP as induction therapy in 560 older (≥60 years) MCL patients.3 Following induction, responding patients underwent a secondary randomization to maintenance therapy with either single-agent rituximab or interferon-α, each administered until disease progression. This study demonstrated the significant impact that maintenance therapy with single-agent rituximab could have on this difficult-to-treat patient group, with a clear benefit in both duration of remission and overall survival.

Improving Existing Regimens

One strategy for improving patient outcomes is to enhance existing regimens. Although bendamustine belongs to a traditional class of chemotherapeutics, its activity in MCL has resulted in its integration into developing treatment approaches and ongoing clinical trials. Several studies have evaluated bendamustine in both the frontline and relapsed/refractory MCL settings, and the recent frontline StiL study has already been described.

Bendamustine was evaluated in several relapsed MCL studies as well. One of these trials tested the combination of bendamustine with rituximab in a phase 2 multicenter study in patients with relapsed/refractory indolent lymphomas and MCL.5 High rates of overall response (92%) and complete response (42%) were reported among patients with MCL, and the median duration of response was 19 months. A second study found that the combination of fludarabine plus rituximab was associated with inferior response and progression-free survival compared with bendamustine plus rituximab in patients with relapsed/refractory MCL.4

In a small multicenter phase 2 trial, bendamustine and rituximab were combined with bortezomib for the treatment of 29 relapsed/refractory patients with indolent lymphoma or MCL (7 patients had MCL histology).6 In the overall population, the overall response rate was 83%, with a 52% rate of complete response. The 2-year progression-free survival rate was 47%. In the small population of MCL patients, the overall response rate was 71%. Based on these promising results, randomized trials to further evaluate this combination in MCL (and follicular lymphoma) have been initiated by the US Cooperative Groups.

A phase 2 trial evaluated the combination of bendamustine and rituximab with cytarabine for the treatment...
of older MCL patients (≥65 years) who were ineligible for intensive chemotherapy regimens or ASCT. Both previously untreated and relapsed/refractory patients were included. The overall response rate was 100%; the complete response rates were 95% for previously untreated patients and 70% for relapsed/refractory patients. The 2-year progression-free survival rate was 95% for previously untreated patients and 70% for relapsed/refractory patients.

**Agents Targeting the Microenvironment**

A potential strategy for improving MCL patient outcomes is the incorporation of agents targeting and modulating critical components of the immune microenvironment. It is increasingly understood that the immune microenvironment plays a key role in the progression, survival, and chemoresistance of multiple subtypes of lymphoma, including MCL. This understanding, coupled with the development of novel agents with the potential to modulate the activity of nonmalignant immune cell subsets within the lymph node, has led to the exploration of immune modulating agents in MCL studies. One of these agents, lenalidomide, is now approved for the treatment of relapsed MCL. Recently, a combined analysis of 3 lenalidomide studies (NHL-002, NHL-003, and MCL-001) in relapsed/refractory MCL demonstrated an overall response rate of 32% (complete response rate of 10%) among all patients. The overall response rate was 29% (complete response rate of 8%) among patients previously treated with bortezomib. The median duration of response among all patients was 16.6 months, and the median duration of response among bortezomib-exposed patients was 14.8 months.

Another recent report regarding the efficacy of lenalidomide in this setting was a subgroup analysis of the MCL-001 study. MCL-001 found an overall response rate of 28% with lenalidomide in heavily pretreated MCL patients. The subgroup analysis analyzed the efficacy of lenalidomide specifically among those patients who had previously received bortezomib. In these patients, the overall response rate was 28% by central review (32% by investigator review). The median duration of response was 16.6 months by central review and 18.5 months by investigator review.

Combining lenalidomide with CD20-targeted therapies is an intriguing possibility to achieve greater efficacy in MCL patients. This combination was recently tested in a single-arm, open-label, phase 1/2 trial, with promising results. Relapsed/refractory MCL patients who had received between 1 and 4 prior therapies were included; 14 patients were enrolled in the phase 1 dose-finding portion, and 44 patients (including 6 who had received the maximal tolerated dose in the phase 1 portion) were enrolled in the phase 2 study. An overall response was achieved in 57% of patients, of whom 36% achieved a complete response. Importantly, 5 of the patients who achieved an overall response had previously been treated with bortezomib. The median duration of response was 18.9 months, the median progression-free survival was 11.1 months, and the median overall survival was 24.3 months. This combination appeared to be well-tolerated; grade 3/4 adverse events included neutropenia, lymphopenia, leukopenia, and thrombocytopenia.

**Novel Antibody Therapies**

Building on the importance of rituximab in the treatment of MCL, current studies are integrating novel antibody therapies into treatment regimens for MCL. 9Y-ibritumomab-tiuxetan is a novel radioimmunotherapy agent that was evaluated in the phase 2 multicenter GELTAMO (Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea) trial. In this study, previously untreated MCL patients underwent frontline induction therapy with R-hyper-CVAD alternating with rituximab, methotrexate, and cytarabine, followed by consolidation with 9Y-ibritumomab-tiuxetan. Among patients who had responded to induction therapy and underwent consolidation therapy, the failure-free survival rate was 55%, and the overall survival rate was 87%. However, this regimen was associated with significant toxicities.

Obinutuzumab (GA-101) is a glycoengineered, humanized anti-CD20 antibody that was evaluated in a phase 1 trial that included patients with a number of different B-cell lymphomas, including 4 patients with MCL. Of these 4 patients, 1 experienced a short-lived improvement in tumor load that progressed immediately after ending treatment, and 1 had a durable stable disease lasting up to 1 year after study entry.

**Agents Targeting Specific Cellular Pathways in MCL**

Novel agents targeting specific pathways within MCL represent one of the most promising avenues for improving patient survival. Proximal inhibitors of the B-cell receptor (BCR) pathway have recently been explored in MCL with exciting results. The BCR pathway is essential for the development of normal B cells, and it is maintained in most B-cell malignancies. During lymphomagenesis, the malignant phenotype becomes dependent, or “addicted,” to tonic or chronic signaling through the BCR pathway, and hence, key kinases in the pathway represent an attractive target for lymphoma therapy. Several strategies to inhibit the BCR pathway have been tested in MCL.
Ibrutinib was one of the first BCR pathway inhibitors to enter clinical development. Ibrutinib targets Bruton’s tyrosine kinase (BTK) for inhibition. In a recently reported phase 2 trial, ibrutinib was administered as a single agent to 111 patients with relapsed/refractory MCL; patients had received a median of 3 prior therapies. Prior to treatment, patients were divided into 2 groups: those who had previously received at least 2 complete cycles of bortezomib therapy and those who had received 1 or no cycles of bortezomib. Ibrutinib appeared to be highly active in all of these patients, with an overall response rate of 68% and a complete response rate of 22%. Importantly, the degree of prior bortezomib exposure did not affect the response rate. After a median follow-up of 15.3 months, the estimated median duration of response was 17.5 months, the estimated median progression-free survival was 13.9 months (Figure 7), and the median overall survival was not reached (Figure 8). The estimated 18-month overall survival rate was 58%. Interestingly, the response rate improved with longer drug exposure. An initial presentation of this study reported a complete response rate of 16%, whereas longer follow-up (and longer ibrutinib exposure) was associated with a rate of 39%. After treatment was initiated, there was a significant incidence of lymphocytosis, which was associated with a dramatic reduction in tumor volume.

Idelalisib is a selective inhibitor of phosphoinositide-3 kinase (PI3Kδ) (PI3Kδ), a protein known to be critical in the proliferation and survival of B cells and that may also be important in the pathogenesis of some B-cell malignancies. Idelalisib was recently investigated in a phase 1 trial of 40 patients with relapsed/refractory MCL. Patients were heavily pretreated, with a median range of 4 prior therapies. The overall response rate to idelalisib was 40%, including a 7.5% complete response rate. Importantly, among patients who were treated with a dose of 150 mg or higher, the overall response rate was increased to 67%, compared with 29% in patients treated with less than 150 mg. The median duration of response was 2.7 months. The 1-year progression-free survival rate was 22%, which is inferior to that of ibrutinib.

Idelalisib is also being studied in a phase 1 study in which it is combined with everolimus, bortezomib, or bendamustine plus rituximab in patients with relapsed MCL. In a preliminary report, the overall response rates were 39% for idelalisib plus everolimus, 45% for idelalisib plus bortezomib, and 100% for idelalisib plus bendamustine and rituximab. Complete response rates were 11%, 0%, and 50%, respectively. Among all patients, the overall response rate was 49%, the complete response rate was 12%, and the median progression-free survival was 8.1 months.

**Figure 6.** Novel and targeted agents may provide one means by which long-term patient outcomes can be significantly improved in mantle cell lymphoma.

**Figure 7.** Progression-free survival in a phase 2 trial of single-agent ibrutinib in patients with relapsed/refractory mantle cell lymphoma. Adapted from Wang ML et al. *N Engl J Med.* 2013;369(6):507-516.

**Figure 8.** In a phase 2 trial evaluating ibrutinib in patients with relapsed or refractory, the median overall survival was not reached. Adapted from Wang ML et al. *N Engl J Med.* 2013;369(6):507-516.
IPI-145 is an investigational agent that is a potent inhibitor of PI3Kδ, as well as PI3Kγ. Preliminary results from an ongoing phase 1 trial demonstrated a 67% rate of overall response in relapsed/refractory MCL patients. An update of this study's results is expected in the near future.

The mTOR inhibitor temsirolimus is approved in Europe for treatment of relapsed/refractory MCL. However, it is associated with rapid progression after treatment is ceased, and therefore its use requires continuous administration. When 2 doses of temsirolimus were compared with the investigator's choice of therapy (22% vs 2%), although the same trend was apparent with the lower temsirolimus dose, the differences did not reach statistical significance. Median overall survival was 12.8 months in the high-dose temsirolimus arm compared with 9.7 months in the investigator's choice arm.

Acknowledgment
Dr Fowler has served on scientific advisory boards for Pharmacyclics, Janssen, Celgene, and Roche. He currently receives research funding or serves as principal investigator for studies from Pharmacyclics, Janssen, Roche, Celgene, and Gilead.

References
Unmet Needs in Mantle Cell Lymphoma: General Discussion

Steven T. Rosen, MD I recently saw a patient with an uncommon manifestation of MCL. The patient presented with an isolated lymph node that had been partially resected. All of the clinical investigations that had been performed, including PET scans, bone marrow studies, and gastrointestinal evaluation, were unremarkable. Through this case, I became aware of the existing literature on the use of radiation in the rare patient who presents with stage I disease. Surprisingly, there appears to be a true “cure” rate in some of these patients, who show continued survival over many years without relapse. Based on this finding, instead of treating with systemic chemotherapy as I had been contemplating, I used radiotherapy. The patient is currently doing well, and we continue to monitor her.

Brian K. Link, MD That is an interesting observation. Two points come to mind regarding patients in this setting. With some frequency, I have had patients referred to me with this specific presentation—that is, a patient found to have an isolated lymph node and unremarkable staging scans, often including PET scan. We consider radiotherapy as an option in these cases. However, I think it is important to note that before choosing this option, I usually recommend that patients undergo routine endoscopic evaluation of their bowel because this seems to be a relatively frequent form of surreptitious disease that is not often picked up by routine staging. Ruling out occult gastrointestinal involvement is important prior to undertaking a potential curative strategy.

Last month, I was visited by a patient who has been in follow-up since 1992. She had been treated with radiation therapy for localized disease. Throughout this entire time, she had never shown any evidence of disease relapse. However, most recently, we found that she developed biopsy-proven multifocal skin disease. This case is a reminder that even after 2 decades, patients cannot be considered cured.

Steven T. Rosen, MD That is fascinating. What are some areas of unmet need, and how are they being addressed?

Brian K. Link, MD I had been looking forward to hearing results from the SWOG study that is evaluating how aggressive the optimal induction regimen should be. The clinical design was such that young MCL patients were randomized to either bendamustine-based induction therapy or R-hyper-CVAD alternating with methotrexate and cytarabine induction therapy. All patients were then to be consolidated with ASCT. However, my understanding is that this trial has now been closed to accrual owing to triggering a toxicity threshold in the R-hyper-CVAD arm. I am also anxious to learn more about the role for chronic suppressive therapy as tested in the ECOG 1411 and European MCL Network MCL R2 protocols, where following induction therapy, patients are randomized to maintenance rituximab vs rituximab and lenalidomide.

Acknowledgments
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**Mantle Cell Lymphoma (MCL)**
- MCL is an aggressive B-cell subtype of non-Hodgkin lymphoma
- Middle-aged or older adults are most commonly affected
- MCL generally arises from naïve, pre-germinal center lymphocytes
- Common characteristics include small- to medium-sized tumor cells that can infiltrate the lymph nodes, spleen, bone marrow, blood, and gastrointestinal system
- Although new treatment strategies are on the horizon, MCL remains one of the most challenging hematologic malignancies, owing to an aggressive disease course, high rate of relapse, and lack of standard of care

**Histologic, Immunologic, and Molecular Characteristics of MCL**
- There are 3 patterns of tumor infiltration that are characteristic of MCL:
  - Diffuse replacement of the entire lymph node
  - Infiltration into the expanded mantle zone
  - vaguely nodular patterns
- Tumor cells are monomorphic small lymphocytes resembling centrocytes/centroblasts with scant cytoplasm, cleaved, slightly irregular or round nuclei, and condensed chromatin.
- The immunophenotypic profile of MCL typically consists of CD3+, CD5+, CD23+, and CD10−. CD10 and CD23 may be positive or negative. However, this profile is not necessary for a diagnosis of MCL.

**Frontline Treatment Strategies in MCL**
- The optimal frontline therapy remains undefined
- Although MCL often responds well to frontline chemotherapy, the responses are not durable and are often of relatively short duration
- Effective treatment options in the frontline setting have included the addition of rituximab to bendamustine

**Management of Relapsed/Refractory Disease**
- Once MCL has entered the relapsed/refractory stage, it becomes more difficult to treat
- Bortezomib and lenalidomide are approved for treatment of relapsed/refractory MCL

**Novel Antibodies in MCL**
- Several new antibodies are currently under clinical evaluation in MCL, including second- and third-generation anti-CD20 antibodies, antibodies targeting B-cell antigens other than CD20 (including BRN-05, BFL-1, and anti-DNA antibodies), and toxin-conjugated antibodies
- Type II (rituximab-like) anti-CD20 antibodies possess longer antibody-dependent cytotoxicity and stronger direct effects on B-cells when compared with type I (rituximab-like) anti-CD20 antibodies
- Obinutuzumab (GA101) is a third-generation humanized CD20 IgG1 type II antibody with enhanced binding ability to FcγRIIIa and increased antibody-dependent cytotoxicity

**Agents Targeting Specific Cellular Pathways in MCL**
- Novel agents targeting specific pathways within MCL represent one of the most exciting possibilities for improving patient outcomes
- Bortezomib was one of the first BCR pathway inhibitors to enter clinical development. Bortezomib targets Bryant’s tyrosine kinase (BTK) for inhibition
- Melphalan is a selective inhibitor of phosphatase and tensin homolog (PTEN), a protein known to be critical in the proliferation and survival of B cells and may also be important in the pathogenesis of some B-cell malignancies
- IPI-145 is an investigational agent that is a potent inhibitor of PI3K, as well as PTEN

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