Clinical Roundtable Monograph

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Recent Advances in the Treatment of Mantle Cell Lymphoma: A Post–ASH 2009 Discussion

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Abstract

Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin lymphoma characterized by CD5 expression and a t(11;14) cytogenetic translocation that results in overexpression of the cyclin D1 gene. Currently, there is no standard of care for the treatment of MCL, and patient prognosis is poor. Traditional treatments for MCL rely on conventional chemotherapy agents, including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The addition of the immunotherapeutic agent rituximab to this regimen (CHOP-R) has helped to improve patient response to treatment. These treatments often provide good initial responses that are difficult to sustain. Therefore, a number of newer agents and combinations have been investigated to produce more durable benefit. Several of these advances were reported at the 51st American Society of Hematology (ASH) Annual Meeting and Exposition, held December 5–8, 2009 in New Orleans, Louisiana. In this clinical roundtable monograph, new strategies in the treatment of MCL are discussed. Some of the drug classes examined here are proteasome inhibitors, inhibitors of the protein mammalian target of rapamycin (mTOR), the unique alkylating agent bendamustine, and immunomodulatory agents.

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Target Audience

This clinical roundtable monograph is specifically designed for practicing clinicians, medical oncologists, hematologists, hematologist/oncologists, and oncology nurses who wish to review and update their knowledge of contemporary treatment of hematologic malignancies, including emerging strategies in mantle cell lymphoma.

Statement of Need/Program Overview

Mantle cell lymphoma (MCL) is an aggressive non-Hodgkin lymphoma that is incurable with current chemotherapeutic approaches. It comprises 4–6% of all cases of non-Hodgkin lymphoma and is clinically heterogeneous. Despite response rates of 50–70% with many regimens, all patients have disease progression after chemotherapy, and median survival is approximately 4–5 years. There is no clear standard of care for MCL. The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has improved patient response. Recent clinical trials have examined incorporation of newer agents, such as proteasome inhibitors, inhibitors of the protein mammalian target of rapamycin (mTOR), the unique alkylating agent bendamustine, and immunomodulatory agents, into MCL therapy. It is imperative that clinicians be informed of the latest study data in order to properly diagnose patients with MCL and implement appropriate treatment strategies.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the importance of existing and emerging agents in the natural history of mantle cell lymphoma (MCL) and the potential role of novel treatment approaches in the management of MCL.
- Discuss the clinical implications of the results of pivotal clinical trials, including early phase trials that have the potential to impact the use of novel therapies in the treatment of MCL.
- Identify future research directions for emerging agents in the treatment of MCL.

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This supplement was authored by an independent medical writer based on presentations and discussions by Myron S. Czuczman, MD, John P. Leonard, MD, and Michael E. Williams, MD.

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Inhibitors of the Proteasome and mTOR

John P. Leonard, MD

Proteasome inhibitors—in particular, bortezomib—are the only targeted therapies that have been clinically proven to be effective for the treatment of mantle cell lymphoma (MCL). Physicians who treat MCL patients should be very familiar with the safety and efficacy of these agents in this disease. Current research involving bortezomib in lymphoma has focused on 2 areas: its efficacy and safety in combination regimens, and clarification of the exact tumor histologies that are the most sensitive to bortezomib's effects.

The proteasome is a barrel-shaped complex comprised of several protein subunits, which together are responsible for the elimination of unneeded, damaged, or misfolded proteins within the cell.[1] These proteins are marked for degradation by the binding of small proteins—ubiquitin—that are recognized by the proteasome. Because multiple proteins are targets for ubiquitination and are thereby marked for proteasomal degradation, proteasome inhibitors can affect many different proteins. Thus, although proteasome inhibitors themselves are targeted agents in that they selectively inhibit the proteasome complex, their effects are much broader. The proteasome is a major mechanism by which the cell maintains particular proteins in "balance," including those involved in cellular growth and proliferation.[2] Many cancer cells, including MCL cells, rely on the proteasome pathway to maintain cellular homeostasis. Therefore, proteasome inhibitors can disrupt this source of regulation, and cancer cells are more profoundly affected by these agents than are normal cells.[3] In addition to inducing cell death, proteasome inhibitors may also sensitize malignant cells to chemotherapy.[4]

The prototype proteasome inhibitor bortezomib is indicated for the treatment of multiple myeloma and previously treated MCL.[5] The approval of bortezomib for previously treated MCL was based on results of a phase II single-arm, multicenter trial in 155 patients (median age, 65 years) with relapsed MCL.[6] Patients had progressive disease, and 77% were diagnosed with stage IV MCL. All patients had received at least 1 prior treatment regimen, and the majority (91%) had received all 3 of the primary agents used in the treatment of MCL: anthracycline, cyclophosphamide, and rituximab. Patients were treated with bortezomib (1.3 mg/m^2 intravenous bolus) on days 1, 4, 8, and 11 every 21 days for up to 12 months. The overall response rate (ORR) was 33%; of these, 8% were complete responses (CR) or unconfirmed CR (CRu). The median duration of response was 9.2 months, and the median time to progression was 6.2 months. The toxicity profile of bortezomib in this study was found to be similar to that previously found in patients with multiple myeloma. The most common grade 3 or higher adverse events reported included peripheral neuropathy (13%), fatigue (12%), and thrombocytopenia (11%). Together, these findings were deemed to be a clinically meaningful response, thus resulting in the approval of bortezomib in this setting.[7]

Because of its activity as a single agent in MCL, bortezomib has also been investigated for its role in combination regimens. Several studies reported at the 2009 American Society of Hematology (ASH) meeting focused on the combination of bortezomib with other therapies for the treatment of MCL.

Several studies are currently investigating the safety and efficacy of the addition of bortezomib to chemotherapy in different lymphoma subtypes. Ruan and colleagues reported data from a phase I/II trial evaluating bortezomib in combination with standard cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (CHOP-R) among previously untreated MCL patients.[8] This study included 36 patients who each received 6 standard 21-day cycles of CHOP-R plus dose-escalated bortezomib (4 patients received 1.0 mg/m^2 and 32 patients received 1.3 mg/m^2) on days 1 and 4 of each cycle. The median patient age was 66 years (range, 45–80 years), and most patients were male. Most patients (94%) had stage III or IV MCL. Overall, the combination treatment was well tolerated, although several patients experienced grade 3/4 hematologic adverse events, including neutropenia (23%), thrombocytopenia (14%), and anemia (11%). Both bortezomib and vincristine are associated with neuropathy, and in this study, 56% of patients experienced peripheral neuropathy.[9] Most of these cases were grade 1/2, and the toxicity was considered manageable. Among evaluable patients (n=32), the ORR was 91%; 72% of patients experienced a CR/CRu. In the intent-to-treat population, the median progression-free survival (PFS) was 21 months (95% confidence interval [CI], 17–29 months), and the 2-year overall survival (OS) rate was 86% (95% CI, 69–94%). Notably, this improvement in PFS was modest compared to what has previously been shown with initial CHOP-R treatment alone (16.6 months).[10] However, a larger randomized trial is required to

confirm any PFS benefit for the combination of bortezomib plus CHOP-R compared with CHOP-R alone for the initial treatment of MCL.

Two other studies presented at ASH investigated bortezomib plus bendamustine and rituximab, a combination based on evidence that bendamustine plus rituximab was highly active in MCL.[11] These trials, conducted by 2 different groups, evaluated this combination in patients with relapsed MCL. Friedberg and colleagues reported results from a multicenter phase II trial that included 7 MCL patients for a total of 31 patients.[12] Of these 7 patients, 5 responded to treatment with six 28-day therapy cycles (90 mg/m^2 bendamustine on day 1 and 4,375 mg/m^2 rituximab on day 1, and 1.3 mg/m^2 bortezomib on days 1, 4, 8, and 11.) In the second trial, the phase II study VERTICAL (A Phase II Study of VELCADE [Bortezomib] in Combination With Bendamustine and Rituximab in Subjects With Relapsed or Refractory Follicular Lymphoma), Fowler and colleagues reported that this combination (with a slightly higher bortezomib dosage of 1.6 mg/m^2 on days 1, 8, 15, and 22) was active in a population of heavily pretreated patients with follicular lymphoma.[13] Bortezomib has less overlying toxicity with bendamustine, which is not associated with peripheral neuropathy, and both studies showed this combination was well tolerated. Again, a randomized study is needed in order to more conclusively determine if the addition of bortezomib improved upon the activity of bendamustine plus rituximab in patients with relapsed MCL.

Second-Generation Proteasome Inhibitors

Because of the success of bortezomib in the treatment of MCL and multiple myeloma, as well as its putative success in clinical trials for a number of other tumors, several research groups are pursuing second-generation proteasome inhibitors. Unlike bortezomib, which is a reversible inhibitor of the proteasome, these newer agents act as irreversible proteasome inhibitors.[14] These agents are being evaluated in diseases for which bortezomib has already proven to be active, including MCL, multiple myeloma, and indolent lymphoma subtypes.

One of these, carfilzomib (PR-171), was recently studied in a phase I dose-escalation study in patients with various subtypes of relapsed/refractory hematologic malignancies, including MCL.[15] As a single agent, carfilzomib was found to be tolerable, and clinical activity was suggested in this study. Several studies investigating carfilzomib were reported at ASH, many of which focused on the safety and tolerability of this agent.[16-18] In the future, comparative trials may provide insight into whether carfilzomib is superior to bortezomib or other treatment options.

Another second-generation proteasome inhibitor, salinosporamide A (NPI-0052), is currently in phase I clinical trials for multiple myeloma along with other malignancies.[19] Preliminary results of a phase I clinical trial of salinosporamide A in patients with relapsed/refractory multiple myeloma were presented at ASH.[20] Interestingly, no cases of peripheral neuropathy or thrombocytopenia—2 adverse events associated with bortezomib—were reported for salinosporamide A.

Targeting the PI3K/Akt/mTOR Pathway

One of the most significant cellular signaling pathways that has been targeted for cancer drug development is the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. This pathway, normally triggered by growth, nutrients, or energy signals, is dysregulated in a number of malignancies, leading to overactivation.[21] This pathway has been targeted specifically in MCL due to its characteristic overexpression of cyclin D1, a protein that is regulated by mTOR signaling.[22] A variety of drugs targeting different components of this pathway are under investigation in MCL. For example, the PI3K inhibitor CAL-101 is currently being studied in a phase I dose-escalation study for patients with relapsed/refractory hematologic malignancies. Similarly, several Akt-specific inhibitors are also being studied in clinical trials. However, agents targeting the mTOR protein are the furthest along in development for MCL.

The mTOR inhibitor temsirolimus was first shown to be active as a single-agent in MCL in 2 phase II clinical trials, producing ORRs of 38% and 41%.[23,24] A subsequent randomized phase III trial of 162 patients with heavily pretreated relapsed/refractory MCL compared 2 dosing regimens of temsirolimus with investigator's choice of therapy.[25] This trial showed that temsirolimus (175 mg weekly for 3 weeks followed by 75 mg weekly) significantly improved PFS compared with investigator's choice of therapy (median PFS, 4.8 vs 1.9 months, respectively; hazard ratio, 0.44; P=.0009). The ORR was also significantly improved among patients who received this dosage of temsirolimus compared with investigator's choice of therapy (22% vs 2%; P=.0019). Because previous research has shown that rituximab addition can enhance the efficacy of chemotherapy in MCL, Ansell and colleagues presented results at ASH of a phase II study of temsirolimus in combination with rituximab for the treatment of relapsed/refractory MCL.[26] A total of 71 patients were enrolled in this study. The ORR was 48%; 20% were CR. These results, combined with evidence of tolerability, prompted the investigators to conclude that further studies of this combination were warranted.

A newer mTOR inhibitor, everolimus, has also been investigated in MCL. For example, a phase I/II study of 27 patients with hematologic malignancies (4 patients with MCL) showed that a daily dose of 10 mg was well tolerated, with no dose-limiting toxicities apparent.[27] A separate

study performed exclusively in MCL cell lines found that everolimus successfully inhibited in vitro cell growth both alone and in combination with doxorubicin, vincristine, or rituximab, suggesting a possible synergy for the treatment of MCL patients.[28] A small phase I trial, reported at ASH, evaluated everolimus in 13 patients with relapsed/refractory non-Hodgkin lymphoma (NHL; 2 patients had MCL).[29] Everolimus was found to be well tolerated in this patient population, although specific activity in MCL was not reported.

Overall, agents targeting the PI3K/Akt/mTOR pathway are in development as possible therapeutic alternatives for MCL, and among these, mTOR inhibitors are particularly promising. A major step in the development of these agents is to establish their efficacy and safety in combination with other agents, such as proteasome inhibitors. Many of these cellular pathways are linked, providing a biologic rationale for the combination of many of these targeted agents. Additionally, because they are generally well tolerated as single agents, it is likely that the combination of these therapies will also be well tolerated.

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Bendamustine Alone and in Combination Regimens

Myron S. Czuczman, MD

First developed in the German Democratic Republic, the chemotherapeutic agent bendamustine was intended to be a nitrogen mustard compound that was less toxic but as effective as other nitrogen mustard agents.[1] Recently, a study that profiled bendamustine using the National Cancer Institute in vitro antitumor screen provided a deeper understanding of the mechanism of action of this agent, showing it to be unique compared with other DNA alkylating agents such as chlorambucil and phosphoramide mustard.[2] Several mechanisms of action were attributed to bendamustine, including inhibition of mitotic checkpoints, induction of mitotic catastrophe, activation of a base excision DNA repair pathway, and activation of DNA-damage stress response and apoptosis. Bendamustine is unique in that although it shares structural similarities with both alkylating agents and antimetabolites, it is not cross-resistant with other alkylating agents.[3] Thus, even patients who have prior alkylating agent or purine analogue exposure still have a high response rate to bendamustine.

Bendamustine is currently indicated for the treatment of chronic lymphocytic leukemia (CLL) as well as for patients with indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.[4] Its approval in CLL was based on favorable results in a phase III, randomized European study that compared single-agent bendamustine with chlorambucil as first-line therapy for CLL, finding bendamustine to be superior in this setting.[5] Soon after its approval for CLL, bendamustine was approved in patients with indolent B-cell NHL that progressed following treatment with rituximab. This approval was based on a single-arm, multicenter study that reported an ORR of 75% among patients with rituximab-refractory indolent B-cell NHL.[6]

Bendamustine in MCL

One of the first major trials suggesting that bendamustine could have a role in the treatment of MCL was a phase II study of bendamustine plus rituximab in patients with relapsed indolent B-cell lymphoma and MCL.[7] A total of 67 patients (18% MCL) were enrolled in the trial. All patients received 4–6 cycles (28-day cycles) of rituximab (375 mg/m^2 on day 1) and bendamustine (90 mg/m^2 on days 2 and 3). The ORR among patients with MCL was 92% (the same as in the overall population), and the rate of CR/CRu among MCL patients was 59% (55% among the overall population). The median duration of response among MCL patients was 9 months (95% CI, 12–24 months). Importantly, when patients were analyzed by prior rituximab exposure, those who had previously received rituximab (n=37) still achieved a high ORR (87%), although not quite as high as the ORR of those patients (n=29) who had no prior exposure (100%). Thus, this study made it very clear that bendamustine plus rituximab had a high level of activity even among patients with relapsed disease. Overall, the combination was well tolerated, with hematologic toxicities being the most common grade 3/4 adverse events reported (36% neutropenia, 9% thrombocytopenia). Based on these results, the dosages of bendamustine and rituximab used in this trial are now considered as standard starting doses for this combination therapy.

This study mirrored the results of a slightly earlier study that also evaluated the bendamustine and rituximab combination in 63 patients with either MCL (n=16; 25%) or low-grade lymphoma.[8] All patients had relapsed/refractory disease. The combination again resulted in a high rate of ORR and CR among both MCL patients (75% and 50%, respectively) and the overall population (90% and 60%, respectively). The median PFS for MCL patients was 18 months, compared with 24 months for the entire patient population.

Although both of these prior studies evaluated this combination in patients with relapsed/refractory disease, Rummel and colleagues reported the final results of a phase III study of the StiL (Study Group Indolent Lymphomas, Germany) trial, which evaluated this combination as front-line therapy.[9] This randomized trial compared bendamustine (90 mg/m^2 on days 1 and 2) plus rituximab (375 mg/m^2 on day 1) given every 28 days versus standard CHOP-R therapy given every 21 days. A total of 549 patients were enrolled, and histologies were distributed evenly between both treatment arms (among MCL patients, 18% received bendamustine/rituximab and 19% received CHOP-R). The ORR was similar between the bendamustine/rituximab and CHOP-R groups (93.8% and 93.5%, respectively). However, the rate of CR was significantly higher among patients who received bendamustine/rituximab compared with CHOP-R (40.1% vs 30.8%; *P*=.0323). The median PFS was also significantly improved with bendamustine/rituximab therapy compared with CHOP-R (54.8 vs

34.8 months; *P*=.0002; hazard ratio, 0.5765; 95% CI, 0.4292–0.7683). Similarly, event-free survival and time to next treatment were also significantly improved. At the time of this report, OS was not significantly different between the 2 treatment arms. Importantly, patients in the CHOP-R group experienced a higher frequency of serious adverse events compared with patients in the bendamustine/rituximab group (74 vs 49 events, respectively). Compared with CHOP-R, bendamustine/rituximab was associated with significantly less grade 3/4 neutropenia (46.5% vs 10.7%; *P*<.0001) and grade 3/4 leukopenia (38.2% vs 12.1%; *P*<.0001). The bendamustine/rituximab regimen was also associated with significantly lower rates of alopecia, infectious complications, peripheral neuropathy, and stomatitis. The only adverse event reported with increased frequency in patients who received bendamustine/rituximab was drug-associated erythematous skin reactions (*P*=.0122).

An ongoing phase II clinical trial is now being conducted to more fully explore the bendamustine plus rituximab combination in a patient population with MCL.[10] This study is enrolling only patients with relapsed/refractory MCL.

Novel Bendamustine-Based Combinations

Because of the successful results attributed to the combination of bendamustine and rituximab in both newly diagnosed and relapsed/refractory disease, other bendamustine-based combinations have also been explored. For example, bortezomib plus bendamustine was evaluated as weekly treatment for patients with refractory, indolent NHL.[11] At ASH, Friedberg and colleagues presented initial results of a multicenter phase II trial that tested bendamustine (90 mg/m^2 on day 1) plus rituximab (375 mg/m^2 on day 1) and bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11) in 31 patients with relapsed/refractory indolent NHL and MCL (n=7).[12] A total of 25 of 31 patients were evaluable for response, providing an ORR of 84%. Importantly, 5 of the 7 MCL patients achieved a response. The addition of bortezomib to the bendamustine/rituximab combination resulted in a higher frequency of adverse events. Another novel combination explored was bendamustine plus vincristine and prednisone (BOP) versus cyclophosphamide plus vincristine and prednisone (COP). These combinations were compared in a phase III trial of 164 patients with advanced indolent NHL or MCL.[13] In the overall patient population, the rate of CR was similar between both BOP and COP (22% and 20%, respectively). However, BOP resulted in a higher projected 5-year survival rate compared with COP (61% vs 46%). The 5-year survival advantage with BOP versus COP nearly reached statistical significance (74% vs 56%; *P*=.05), and it did reach significance among patients who did not receive interferon maintenance therapy (70% vs 47%; *P*=.03).

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IMiDs and the Tumor Microenvironment

Michael E. Williams, MD

Mounting evidence suggests that a tumor microenvironment permissive to crosstalk with accessory stromal cells promotes the growth of B-cell malignancies by supporting tumor cell proliferation, inhibiting apoptosis, and mediating treatment resistance.[1] Furthermore, this microenvironment may, in conjunction with chemokines and adhesion molecules, allow homing and retention of malignant cells within stromal niches to provide a reservoir of cells that persist and survive systemic therapy and then later lead to relapse. In fact, this function may be a primary mechanism by which these malignancies remain difficult to cure. Thus, the tumor microenvironment represents an attractive therapeutic target, wherein future treatment strategies may combine cytotoxic drugs targeting malignant cells with agents that interfere with the microenvironment. One such agent under active clinical investigation is the immunomodulatory drug (IMiD) lenalidomide.

IMiDs represent a novel class of agents that are largely structural and functional analogues of thalidomide. Compared with thalidomide, IMiDs exhibit higher potency and reduced toxicity, thus making them attractive anticancer drugs.[2] The rationale for lenalidomide therapy in MCL and other lymphomas is based in part on disruption of the tumor microenvironment. Preclinical models suggest that lenalidomide can inhibit the interactions between the tumor cells and stromal cells. Further, IMiDs like lenalidomide can stimulate effector T-cells and natural killer (NK) cells. Recent data also show that lenalidomide enhances the immunologic synapse that forms between the lymphoma cell and the effector T- or NK-cells, an effect that is enhanced by the addition of rituximab.[3] Finally, lenalidomide has direct antiproliferative effects on the tumor cell.

Lenalidomide in MCL

The IMiD lenalidomide is currently approved in combination with dexamethasone for the treatment of relapsed multiple myeloma,[4] and it is being explored as a therapeutic alternative in CLL and NHLs, including MCL.

Two different studies in CLL reported ORRs of 32% and 47%, with lower rates of CR (7% and 9%), depending on the dosage administered (10 mg/day and 25 mg/day, respectively, for 21 days of a 28-day cycle).[5,6] These patients were largely refractory to other therapies, suggesting a unique mechanism of action for lenalidomide in CLL. However, a separate report in 4 CLL patients found that the higher dose of lenalidomide (25 mg/day for 21 days of a 28-day cycle) was associated with severe adverse events, including tumor flare in 3 patients.[7] Two of the 3 patients who developed a tumor flare required hospitalization, and 1 died. A fourth patient developed sepsis and renal failure.

Similarly to CLL, lenalidomide has shown activity in both indolent and aggressive NHL. A study of 43 patients with indolent NHL reported an ORR of 23%, whereas another study of 49 patients with aggressive subtypes (15 patients with MCL) found an ORR of 35% (53% among MCL patients).[8,9] Several important studies evaluating lenalidomide in the treatment of NHL were presented at ASH. In addition to lenalidomide, other IMiDs have been developed that are of interest for NHL therapy, including pomalidomide.

Witzig and colleagues reported results from an international phase II trial that investigated the safety and efficacy of lenalidomide for the treatment of patients with relapsed/refractory aggressive NHL subtypes.[10] Patients, all of whom had at least 1 prior therapy, received lenalidomide (25 mg daily on days 1–21 of a 28-day cycle) until evidence of disease progression or unacceptable toxicity. Of the 217 patients enrolled in the study, 57 had MCL. The ORR among the MCL patients was 42% (35% among all histologies), and the median PFS was 5.7 months (3.5 months among all histologies). At the time of this report, the median duration of response had not been reached for MCL patients. The most frequent adverse event experienced by patients overall was reversible myelosuppression, including grade 3/4 neutropenia (24.5%), thrombocytopenia (18.4%), leukopenia (8.2%), and anemia (2%). Nearly half of all patients (44%) required dose modifications or interruptions, and 22% discontinued treatment.

Vose and colleagues presented results of a study that evaluated single-agent lenalidomide (25 mg daily on days 1–21 of a 28-day cycle) in patients with relapsed/refractory aggressive NHL who had previously received a stem cell transplant.[11] A total of 87 patients were enrolled in this study, all of whom were pooled from 2 phase II studies. Of these patients, 19 were diagnosed with MCL. The ORR among MCL patients was 63% (39% among all

histologies), and the CR/CRu rate was 26% (13% among all histologies). This response was shown to be durable, with a median duration of response of 9.7 months. Nearly one-quarter of patients (21%) had to discontinue treatment due to an adverse event.

Wang and colleagues provided results of a phase I/II study of lenalidomide in combination with rituximab in patients with relapsed/refractory MCL.[12] This study first determined that the maximally tolerated dose of lenalidomide within this combination was 20 mg/day on days 1–21 of a 28-day cycle. Patients were also treated with rituximab (375 mg/m^2 weekly) for 4 doses during the first cycle only. Notably, all patients had previously been treated with rituximab, and the study included patients resistant to rituximab. Among the 36 patients evaluable for response, the rate of ORR was 53%, and the CR rate was 31%. Importantly, no patients who received lower doses of lenalidomide (10–15 mg daily) achieved a response. The median time to response was 2 months (range, 2–8 months), and median PFS was 14 months (range, 1–32 months). The most frequently occurring grade 3/4 hematologic toxicities included neutropenia and thrombocytopenia. The investigators concluded that the combination of lenalidomide and rituximab was active, even in a patient population that included rituximab-resistant patients, and was associated with a reasonable safety profile.

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Question and Answer Forum

Should MCL be included with other lymphoma histologies in clinical trials?

Dr. John P. Leonard MCL is a relatively rare disease, and therefore MCL patients are often included with other NHL patients in order to increase the patient size of a clinical trial. When the purpose of the trial is to screen a novel agent or combination for activity, it is wise to use a broad patient population that includes a number of lymphoma histologies, in order to ensure that drug efficacy in a particular histology will be apparent. Once the activity and tolerability of an agent or drug combination has been shown, it is then necessary to further explore its safety and efficacy in a specific histology, such as MCL. Even when patient enrollment is restricted to a particular histology, it is now becoming increasingly apparent that each is comprised of distinct subtypes that may respond differently to treatment. As our understanding of these within-histology subtypes deepens, their importance in clinical trial design and enrollment will increase. This approach will allow us to move towards more specific therapies for individual histological subtypes over time.

Does the grade of MCL affect its response to bendamustine?

Dr. Myron S. Czuczman The studies to date that have investigated bendamustine for the treatment of MCL have not distinguished patient responses according to the particular grade of their disease. It is important to note that most studies evaluating bendamustine in relapsed/refractory disease likely did not include patients with blastoid variant MCL, a poor prognostic histological subtype, which may occur de novo or as a transformation of previously treated disease.

What should physicians consider about bendamustine as they begin to incorporate it into their everyday practice?

MC There is a definite learning curve for physicians as they begin to become more familiar with bendamustine. One important point when considering bendamustine usage is the dosage. The typical starting dose used in clinical trials is 90 mg/m^2 for 2 days of a 28-day cycle. However, not all patients will tolerate this dose equally, and their blood cell counts should be monitored closely to determine if the dosage should be lowered. Additionally, some patients may require growth factor support during therapy.

Adverse events are another important consideration when choosing to treat a patient with bendamustine. Especially of note are skin reactions, some of which may become serious. Although there is some evidence that these skin reactions are associated with bendamustine, it is also possible that they are due to the bendamustine/rituximab combination. These skin reactions are typically self-limiting and reversible, and patients should be monitored for their presence. Patients should also be instructed to watch for the development of skin reactions and to call their physician if necessary.

How will MCL treatment change in the future?

Dr. Michael E. Williams Currently, there is no standard of care for the treatment of MCL. Traditionally, patients have been treated with the CHOP regimen, the efficacy of which was increased with the addition of rituximab. Although CHOP-R results in a high rate of response, it is generally not sustainable over time. One possibility is that using a targeted therapy with a unique mechanism of action as a maintenance or consolidation strategy may help to destroy cells that were able to survive the initial chemotherapy. In the near future, incorporation of newer agents into the initial treatment regimens followed by a targeted therapy–based maintenance strategy may improve the durability of responses.

How will our knowledge of the pathobiology of MCL impact advances in treatment?

MW As our understanding of the pathobiology of MCL has increased, it has become apparent that the disease arises from several factors that converge to trigger the malignancy: dysregulated cell cycle pathways, defects in the cellular response to DNA damage, and altered cell survival and apoptosis pathways. Recently, epigenetic alterations affecting micro RNA and histone acetylation have been identified, adding to the biologic complexity of the disease but providing important new insights into aberrant gene expression and MCL pathogenesis.[1] In this era of targeted therapy, knowledge of these factors has allowed more rational design and development of a number of agents that show promise

for MCL. Although previously this disease had been associated with a poor prognosis, the availability of new treatment options and the development of these targeted agents now offer hope for increased survival and improved quality of life for MCL patients.

Which HDAC inhibitors are currently being evaluated in MCL?

JL It is believed that in hematologic malignancies, histone deacetylase (HDAC) enzymes may repress the transcription of cellular differentiation genes. Therefore, HDAC inhibitors (especially vorinostat) are under investigation to determine their efficacy in MCL. The only study evaluating HDAC inhibitors presented at ASH was a phase I study by Budde and colleagues.[2] This study tested the HDAC inhibitor vorinostat in combination with rituximab, ifosfamide, carboplatin, and etoposide in patients with relapsed/refractory lymphoid malignancies and untreated T-cell lymphoma or MCL. The initial results reported at ASH indicated that the combination was relatively safe and modestly active.

Recently, results of a phase I study were published by Watanabe and colleagues, showing that vorinostat was well tolerated up to 200 mg.[3] One of the 2 MCL patients included in this study achieved a CRu. Several clinical trials are currently recruiting participants to investigate HDAC inhibitors in MCL. One of these is a phase II study testing bortezomib and vorinostat in patients with recurrent MCL or refractory/recurrent diffuse large B-cell lymphoma.

Are angiogenesis inhibitors being explored in MCL?

MC To date, only 1 study (by Stopeck and colleagues[4]) has been reported that investigated the anti-angiogenic monoclonal antibody bevacizumab in MCL. In that study, a total of 52 patients with relapsed, aggressive NHL were treated with single-agent bevacizumab. Treatment was well tolerated, and no unexpected toxicities occurred. The authors reported a 6-month PFS of 16%, indicating a modest response to bevacizumab.

Currently, a phase II clinical trial of bevacizumab plus R-CHOP is recruiting patients with untreated MCL.[5] The study has an estimated enrollment of 36 patients, and the primary outcomes planned are response rate and time to disease progression.

What other new agents for MCL were reported on at ASH?

MC The radioimmunologic agent ^{90}Y-ibritumomab tiuxetan is comprised of the radioactive Yttrium-^{90} isotope attached to an anti-CD20 antibody. ^{90}Y-ibritumomab tiuxetan was evaluated in a study of 148 MCL patients with previously untreated disease, reported by Kolstad and colleagues.[6] Patients were first treated with dose-intensive immunochemotherapy; those who achieved a CR then received stem cell transplant, which was preceded by 1 week with 90Y-ibritumomab tiuxetan plus rituximab. The post-transplant CR/CRu rate was 91%.

The nucleoside analogue gemcitabine was tested in combination with bortezomib in a phase I study reported by Kirschbaum and colleagues.[7] Of the 28 patients enrolled with relapsed/refractory NHL, 3 patients had MCL. This combination was effective in the study, prompting its continued evaluation in a phase II study. In addition, as discussed in detail earlier in this monograph, single-agent lenalidomide[8] and bendamustine plus rituximab combination therapy[9] demonstrated significant activity against MCL in the relapsed and upfront setting, respectively.

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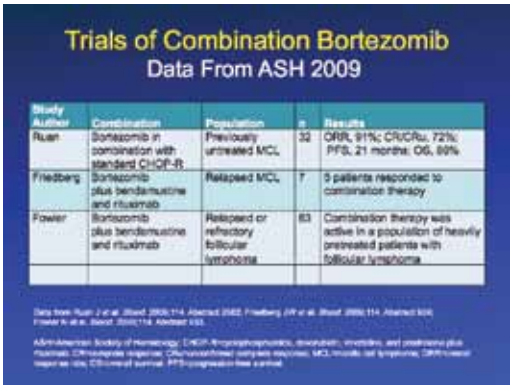

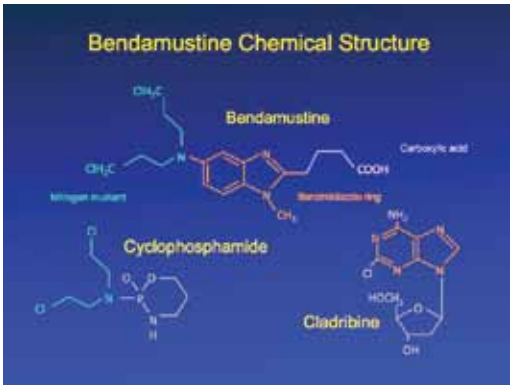

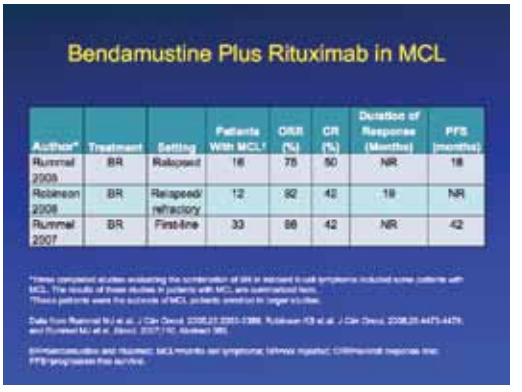

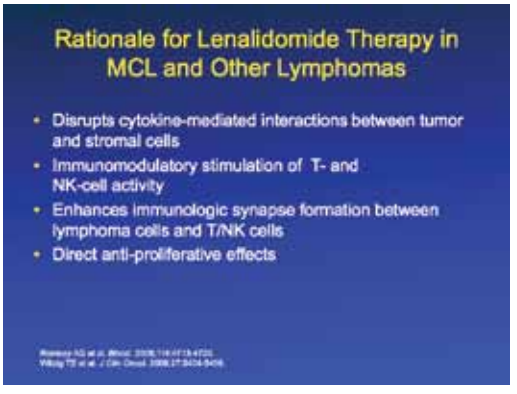

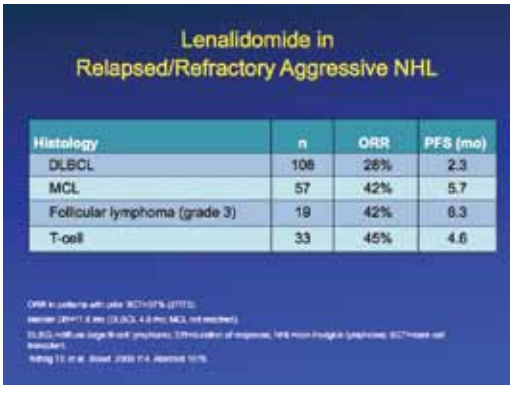

Single-Agent Lenalidomide for Relapsed/Refractory Aggressive NHL Patients With Prior SCT

	n	ORR	CR/CRu
DLBCL	52	15 (29%)	5 (10%)
MCL	19	12 (63%)	5 (26%)
Transformed	10	6 (60%)	1 (10%)

Lenalidomide Plus Rituximab in Relapsed/Refractory MCL

- Phase I/II study
- Lenalidomide maximum tolerated dose: 20 mg/d x 21 d
- Rituximab 375 mg/m^2 weekly x 4 doses during cycle 1 only
  - All patients had received previous rituximab therapy, including those who were rituximab-resistant
- ORR 53% (19/36); CR 31% (11/36)
  - No responses at 10-15 mg dose levels (ph I)
- Median time to response: 2 months
- Median PFS: 14 months
- Toxicity: Cytopenias, non-heme as for each agent
- Conclusion: Active regimen with favorable toxicity

Novel mAbs in Clinical Trials

- GA101 (anti-CD20)
  - Type II: Increased ADCC, decreased CDC
- Ofatumumab (anti-CD20; approved for CLL)
- Veltuzumab (anti-CD20)
- PRO131921 (anti-CD20)
- Inotuzumab ozogamicin (CMC-544, anti-CD22)
- SAR3419 (anti-CD19)
  - Maytansinoid immunoconjugate (tubulin inhibitor)
- Dacetuzumab (SGN-40, anti-CD40)
- Blinatumomab (BiTE mAb)
  - Single-chain bispecific anti-CD19 and anti-CD3
- Brentuximab (SGN-35, anti-CD35)
- Conatumumab (TRAIL/death receptor agonist)
- IPH101 (γδ T-cell agonist)

Selected Novel Agents for Lymphoma

- IMID
  - Lenalidomide
- Angiogenesis and TK Inhibitors
  - Sunitinib (VEGF receptor), bevacizumab (VEGF)
  - Sorafenib (multikinase inhibitor)
- mTOR Inhibitors
  - Temsirolimus, everolimus
- HDAC Inhibitors
  - Vorinostat, penobinostat, romidepsin, PCI-2478
- PI3K Inhibitor
  - CAL-101
- HSP90 Inhibitor
  - 17-AAG

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Recent Advances in the Treatment of Mantle Cell Lymphoma: A Post–ASH 2009 Discussion

CME Post-Test: *Circle the correct answer for each question below.*

1. In a study of single-agent bortezomib for previously treated MCL, approximately how many patients responded to treatment?

   a. One-fourth
   b. One-third
   c. One-half
   d. Two-thirds

2. In a study presented at ASH by Friedberg and colleagues that evaluated bortezomib plus bendamustine and rituximab, which of the following was true?

   a. Bortezomib plus bendamustine and rituximab was associated with a high rate of peripheral neuropathy
   b. Bortezomib plus bendamustine and rituximab produced no response in patients with MCL
   c. Bortezomib plus bendamustine and rituximab was associated with a high rate of toxicity
   d. Bortezomib plus bendamustine and rituximab was associated with a low rate of toxicity

3. In a phase II trial presented by Ansell and colleagues at ASH, the combination of temsirolimus with rituximab in relapsed/refractory MCL produced what ORR?

   a. 15%
   b. 24%
   c. 48%
   d. 92%

4. Which of the following is a mechanism of action attributed to bendamustine?

   a. Inhibition of the proteasome
   b. Induction of mitotic catastrophe
   c. Inhibition of mTOR
   d. Inhibition of angiogenesis

5. In the phase III study of the StiL trial that evaluated bendamustine plus rituximab, all of the following were true EXCEPT:

   a. The ORR was similar between the bendamustine/rituximab and CHOP-R groups
   b. The rate of CR was significantly higher among patients who received bendamustine/rituximab compared with CHOP
   c. The rate of CR was similar among patients who received bendamustine/rituximab compared with CHOP
   d. The median PFS was also significantly improved with bendamustine/rituximab therapy compared with CHOP-R

6. Which of the following is NOT a characteristic of the tumor microenvironment?

   a. Produces cancer-fighting cytokines that help to fight off malignant cells to prevent their spread
   b. Works in conjunction with chemokines and adhesion molecules to allow homing and retention of malignant cells within stromal niches
   c. Provides a reservoir of cells that persist and survive systemic therapy and then later lead to relapse
   d. Promotes the growth of B-cell malignancies by supporting tumor cell proliferation, inhibiting apoptosis, and mediating treatment resistance

7. In a phase II trial conducted by Friedberg and colleagues, initial results of the bendamustine plus rituximab plus bortezomib combination showed what ORR?

   a. 12%
   b. 30%
   c. 55%
   d. 84%

8. In a phase III trial that compared BOP (bendamustine plus vincristine and prednisone) versus COP (cyclophosphamide plus vincristine and prednisone), which regimen produced a significantly higher CR rate?

   a. BOP
   b. COP
   c. Rate was similar between both regimens

9. In a phase II trial by Witzig and colleagues presented at ASH, what was the most frequent adverse event experienced with lenalidomide?

   a. Neutropenia
   b. Thrombocytopenia
   c. Leucopenia
   d. Alopecia

10. True or False? In a phase I/II study presented at ASH by Wang and colleagues examining lenalidomide in combination with rituximab in patients with relapsed/refractory MCL, rituximab-resistant patients benefited from treatment.

    a. True
    b. False

Evaluation Form: Recent Advances in the Treatment of Mantle Cell Lymphoma: A Post–ASH 2009 Discussion

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives
After participating in this activity, I am now better able to:

1. Describe the importance of existing and emerging agents in the natural history of mantle cell lymphoma (MCL) and the potential role of novel treatment approaches in the management of MCL.	1 2 3 4 5
2. Discuss the clinical implications of the results of pivotal clinical trials, including early phase trials that have the potential to impact the use of novel therapies in the treatment of MCL.	1 2 3 4 5
3. Identify future research directions for emerging agents in the treatment of MCL.	1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice? _____

What barriers do you see to making a change in your practice? _____

Which of the following best describes the impact of this activity on your performance?
❒ I will implement the information in my area of practice.
❒ I need more information before I can change my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

The content presented:

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5

Would you be willing to participate in a post-activity follow-up survey? ❒ Yes ❒ No

Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities: _____

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by project ID 7117. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit

Name _____ Degree _____
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Signature _____ Date _____

For Physicians Only: I certify my actual time spent to complete this educational activity to be: _____
❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.