TREATMENT UPDATE

New Options for the Treatment of Relapsed Mantle Cell Lymphoma

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This activity is intended for physicians, registered nurses, and other healthcare professionals who wish to expand their knowledge of the evolving treatment paradigm and optimal patient management of mantle cell lymphoma.

PURPOSE

The purpose of this activity is to provide clinicians with the latest clinical advances and practical applications for managing patients with mantle cell lymphoma.

LEARNING OBJECTIVES

- Apply proteasome inhibitors in the clinical management of patients with relapsed/refractory mantle cell lymphoma
- Contrast stem cell transplantation strategies in the treatment of relapsed/refractory mantle cell lymphoma
- Discuss current data on second-line treatment strategies for patients with relapsed/refractory mantle cell lymphoma
- Interpret results of clinical trials that evaluate the use of investigational agents for the treatment of mantle cell lymphoma

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New Options for the Treatment of Relapsed Mantle Cell Lymphoma

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Introduction

During the past 10 years, significant progress has been made in the treatment of patients with mantle cell lymphoma (MCL). A recent retrospective comparison found that overall survival (OS) has increased from 2.7 years to 4.8 years ($P < .0001$).[1] Because randomized trials do not yet clearly support the hypothesis that survival improvements are the result of changes in first-line therapies,[2] the changes in MCL therapeutic outcomes are likely in part, a result of improved second-, third-, and fourth-line therapies. Therefore, although cures remain elusive, better control of the disease after relapse has been obtained.[3]

The National Comprehensive Cancer Network (NCCN) currently recommends the following regimens for second-line therapy of MCL[2]:

- Bendustamine with or without rituximab
- Bortezomib
- Cladribine
- Fludarabine, cyclophosphamide (FC) with or without rituximab
- Fludarabine, cyclophosphamide, mitoxantrone, rituximab (FCMR)
- Fludarabine, mitoxantrone, rituximab (FMR)
- Lenalidomide
- Pentostatin, cyclophosphamide, rituximab (PCR)
- Prednisone, etoposide, procarbazine, cyclophosphamide (PEP-C) with or without rituximab
- Temsirolimus
- Thalidomide plus rituximab
- *Second-line consolidation:*
    - High-dose therapy with allogeneic stem cell rescue (nonmyeloablative or myeloablative)

This module examines the newer and best-supported options for second-line therapy of MCL.

Single-Agent Bortezomib in the Treatment of Mantle Cell Lymphoma

Bortezomib is a first-in-class proteasome inhibitor approved in the United States for the treatment of multiple myeloma and for the treatment of patients with MCL who have received at least 1 previous therapy. The efficacy of bortezomib in MCL has been demonstrated in the PINNACLE trial.[4,5]

Proteasome Biology

The proteasome is the organelle responsible for the degradation of nuclear and cytoplasmic proteins.[6] Structurally, the proteasome is arranged as a central barrel (core particle), where multiple protease activities are contained, with 2 caps (regulatory particles) at either end. The regulatory particles serve as the gatekeepers for entry into the degradative process and bind to polyubiquitin chains or to denatured/misfolded proteins. Upon recognition of a protein slated for destruction, the regulatory particle opens the proteolytic vault of the core particle and feeds the protein in. Ubiquitin chains are added to proteins by the activity of a cascade of 3 enzymes. The initial ubiquitin is added to the epsilon amino group on a lysine (or, more rarely, onto the N-terminal amino group of the protein). When a sufficiently long chain of ubiquitin molecules has been added, the regulatory particle of the proteasome is able to bind the chain and proceed with the degradative process.

The regulation of degradation is managed at the level of ubiquitin addition. The 3 ubiquitin-adding enzymes are E_1, E_2, and E_3. E_1 exists as a single subtype, activates ubiquitin for binding in the presence of E_2 and ATP, and interacts with all 5 E_2 subtypes. E_2 in turn interacts with E_3,

the specific ubiquitin-protein ligase that adds the ubiquitin to the protein substrate. There are at least 7 different E_3 subtypes, each of which interacts with specific E_2 subtypes and with different classes of protein substrates. The E_3 subtypes play a key role in the ubiquitin-mediated proteolytic cascade, serving as the specific recognition factor of the system. The result of the specificity of the ubiquitin addition cascade is that different proteins are regulated so to have different rates of turnover, with half-lives that vary from a few minutes (eg, p53 and many regulatory proteins) to several days (eg, actin or myosin) or even years (lens protein). The proteasome itself, however, appears to play a passive role in the regulatory process, simply degrading what it can bind to.[6] Therefore, bortezomib, as a reversible inhibitor of the chymotrypsin activity of the proteasome has multiple biological effects, such as inhibiting constitutive nuclear factor–kappaB (NF-kB) and cyclin D1 expression and to upregulating the proapoptotic Noxa protein, leading to apoptosis of MCL cells.[7]

Bortezomib was studied in the multicenter, prospective, single-arm, phase II PINNACLE trial—the largest prospective study to date in patients with relapsed/refractory MCL (N = 155).[4,5] Mantle cell lymphoma was pathologically confirmed, by demonstration of overexpression of cyclin D1 or evidence of the t(11;14) translocation, and patients had documented relapse or progression after 1-2 previous lines of antineoplastic therapy (including an anthracycline or mitoxantrone, and rituximab). The median time from diagnosis to bortezomib treatment was 2.3 years (range: 0.2-11.2); the median age was 65 years; 46% of patients had received 2 or more previous lines of therapy; and 77% had stage IV disease. Bortezomib at 1.3 mg/m^2 was administered on Days 1, 4, 8 and 11 of a 21-day cycle. Treatment continued for up to 17 cycles, or 4 cycles beyond initial reporting of complete response (CR) or unconfirmed CR (CRu) or until discontinuation due to progressive disease or toxicity.

In total, 141 assessable patients were followed for a median of 63.7 months.[5] The overall response rate (ORR) was 32% (n = 45), of which 8% (n = 11) were CR/CRu. The median time to first response was 1.4 months. The median duration of response for all responders was 9.2 months, 6.7 months for patients attaining a partial response (PR), and not reached (at 720 days) for patients with CR/CRu. There was no correlation between the time to response and the response duration. The median time to progression was 6.7 months for all patients, 12.4 months for responders, and not reached for patients with CR/Cru (Figure 1). The median OS after bortezomib treatment was 23.5 months and 35.4 months for responders. Median OS from time of MCL diagnosis was 61.1 months (Figure 2).

Figure 1. Median time to progression.[5]

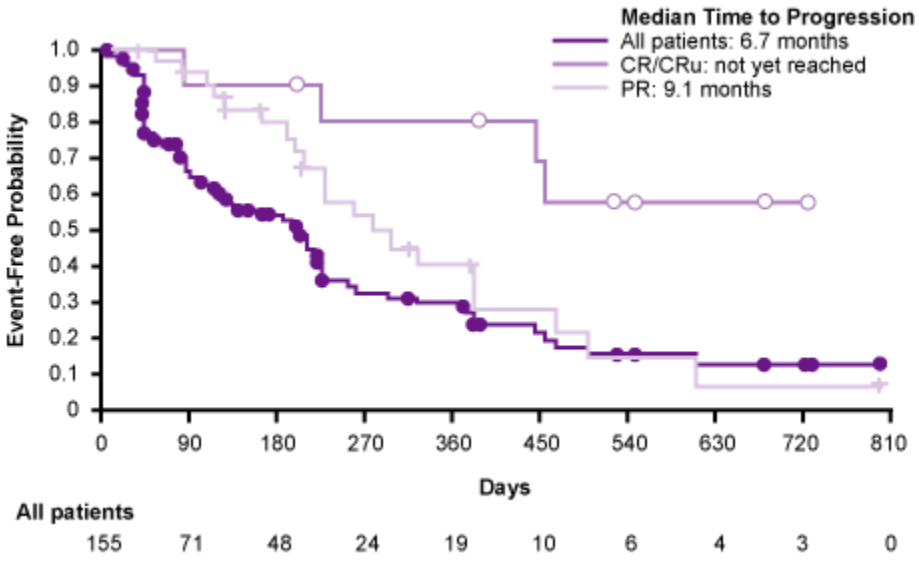
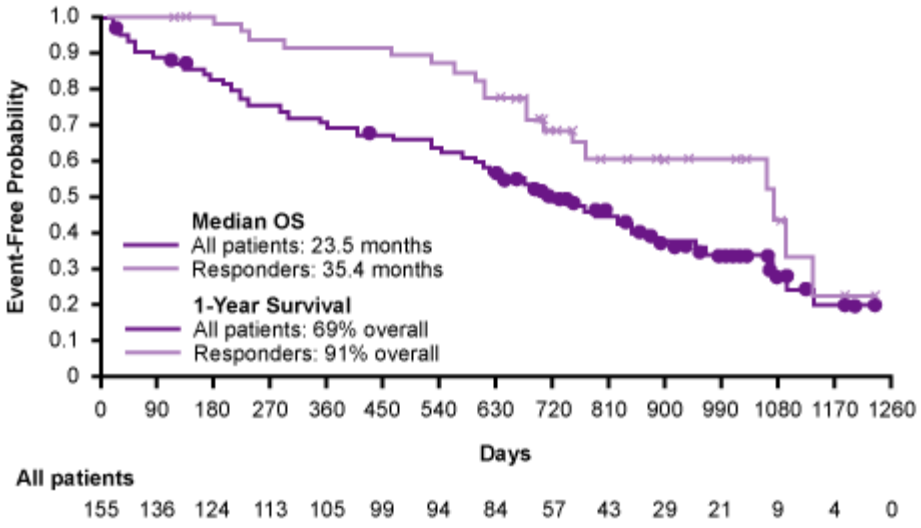


Figure 2. Median overall survival.[5]



In this trial, bortezomib was effective in both patients with refractory MCL (n = 51) and those who relapsed following previous high-intensity therapy (n = 52) (some patients met both conditions). Responses were similar to those of the overall treatment group.

For all patients, the most common grade 3 or higher nonhematologic adverse event was peripheral neuropathy, seen in 13% (n = 20) of patients, with a median time to onset (any grade) of 4 cycles. Grade 3 or higher lymphopenia was seen in 34% (n = 52) of patients; by the end of treatment visit (typically 30 days after the last dose of bortezomib), of these patients, 9 had recovered and 29 had improved at least one grade on the National Cancer Institute Common Terminology Criteria for Adverse Events scale. There were 12 deaths, 4 of which were considered related to treatment (3 nonneutropenic sepsis, 1 respiratory failure). Studies of bortezomib treatment for multiple myeloma indicate the peripheral neuropathy seen is usually reversible; these data were not collected in PINNACLE.

O'Connor and colleagues[8] conducted a smaller multicenter phase II trial of single-agent bortezomib in relapsed/refractory MCL patients. The ORR was 47% in 40 patients with heavily pretreated MCL, including a CR rate of 13%. Relapsed and refractory patients had ORR and time to progression rates similar to the group as a whole. A single-center Canadian trial of single-agent bortezomib treatment showed a similar ORR of 46.7% (7.0% CRu) in 15 previously treated MCL patients.[9]

The PINNACLE data, in conjunction with results from these smaller phase II trials, were key to the US Food and Drug Administration (FDA) approval of bortezomib in 2006 for the second-line treatment of MCL, and as such, we now have another effective agent for the treatment of patients with MCL. However, clinicians now using bortezomib need to closely follow their patients for the development of neuropathy and make the appropriate dose modifications based on the grade of toxicity.

Bendamustine in the Treatment of Mantle Cell Lymphoma

Bendamustine is a novel alkylating agent consisting of a nitrogen mustard (mechlorethamine) attached to a benzimidazole ring (which might also function as a purine analogue and provide better access to DNA) with a butyric acid side chain.[10] Bendamustine is chemically related to chlorambucil and to cyclophosphamide but has mechanistic differences these and other alkylating agents.[11] Although approved in the United States in 2008 (for rituximab-refractory

indolent B-cell non-Hodgkin's lymphoma [NHL]), it has been used in Germany since 1971 for the treatment of several hematologic malignancies.[10]

An open-label phase II trial examining the combination of bendamustine and rituximab for low-grade NHL included 16 patients with MCL, 7 of whom were refractory to previous treatment.[12] Following rituximab 375 mg/m^2 on Day 1, bendamustine 90 mg/m^2 was given on Days 2 and 3, combined with 375 mg/m^2 rituximab on Day 1, for a maximum of 4 cycles every 4 weeks. The ORR was 75%, with CR obtained in 50%. The median progression-free survival (PFS) time for MCL patients was 18 months, with 6 patients still in remission at a median follow-up of 20 months. There were no treatment-related deaths, and nonhematologic toxicity was generally mild (World Health Organization [WHO] grade 1/2). Leukopenia was the most common adverse effect, with grade 3/4 events occurring in 35 (16%) of 216 cycles (all patients).

Further evidence for the efficacy of bendamustine plus rituximab comes from a multicenter phase II trial by Robinson and colleagues[13] of 12 patients with relapsed MCL (n = 12) or indolent B-cell lymphoma (n = 54). Nearly all (97%) of the patients had received previous chemotherapy (median: 1 regimen), and 44% were rituximab naive. The median time from diagnosis was 3.4 years, and 82% of patients had stage III/IV disease. Patients received rituximab 375 mg/m^2 on Day 1, followed by bendamustine 90 mg/m^2 on Days 2 and 3 every 28 days for 4 cycles. Additional doses of rituximab were administered 7 days before the first cycle and 28 days after the last cycle. The median follow-up was 20 months. In the MCL patients (n = 12), the ORR was 92%, including 42% CR, 17% CRu, and 33% PR. There was no significant difference in the ORR with or without previous exposure to rituximab. The median duration of response was 19 months. These results were similar to those seen in the other NHL patients.

Of the 66 patients (both MCL and indolent B cell), 61 patients (92%) received at least 4 cycles of treatment. The primary toxicity was reversible myelosuppression; grade 3/4 neutropenia was reported in 24 patients (36%), including 4 (6%) with febrile neutropenia. Other grade 3/4 hematologic toxicities included thrombocytopenia (9%) and anemia (2%).

Given the single agent activity of bendamustine, as well as the activity of bendamustine in combination with rituximab, investigators have begun to study bendamustine in combination with other chemotherapy agents. For example, one question that is being addressed is whether bendamustine can substitute for cyclophosphamide in the COP (cyclophosphamide, vincristine, prednisone) regimen. In a prospective trial,[14] 164 patients with follicular lymphoma, MCL, or lymphoplasmacytic lymphoma were treated with vincristine 2 mg (Day 1) and prednisone 100 mg/m^2 (Days 1-5) and randomly assigned to either bendamustine 60 mg/m^2 (BOP) or cyclophosphamide 400 mg/m^2 (COP) on Days 1-5. A total of eight 21-day cycles were administered. The CR rate was similar between groups—22% with BOP and 20% with COP—but the projected 5-year survival rates were 61% vs 46%, respectively. These data suggest the possibility that in some cases, bendamustine may be able to replace cyclophosphamide.

Another study evaluated the efficacy and feasibility of adding the topoisomerase inhibitor mitoxantrone to the bendamustine and rituximab regimen. This was examined in a phase II study of patients with stage III/IV relapsed/refractory indolent lymphomas (n = 39) and MCL (n = 18).[15] Treatment consisted of bendamustine 90 mg/m^2 on Days 1 and 2, mitoxantrone 10 mg/m^2 on Day 1, and rituximab 375 mg/m^2 on Day 8. Treatment was repeated on Day 29 for a total of 4 cycles. After a median observation time of 27 months, the estimated median PFS for all patients was 19 months. The 2-year OS rate was 60% for MCL patients. However, 4% of patients were unexpectedly hospitalized because of toxic effects, and 78% developed WHO grade 3/4 leukopenia. The addition of mitoxantrone appeared to contribute to hematologic toxicity and did not seem to improve the overall efficacy compared with historic efficacy data of the bendamustine plus rituximab regimen.

These data indicate that bendamustine is an active agent in MCL. The challenge remains as to optimally incorporate this agent into treatment algorithms for patients with MCL. In this regard, phase II clinical trials are under way with bendamustine as a single agent,[16] with rituximab,[17] and with bortezomib and rituximab.[18]

Stem Cell Transplantation in Relapsed Mantle Cell Lymphoma

Since conventional chemotherapy does not yet offer a cure for MCL, both autologous and allogeneic stem cell transplantation (SCT) are being examined for their potential benefits. Both procedures involve rigorous induction therapies and are associated with short-term morbidity. Autologous transplantation has the advantage of avoiding graft-vs-host disease (GVHD).

Although autologous SCT may have a role in the upfront treatment of patients with MCL, its efficacy for patients with relapsed/refractory MCL is questionable, in contrast to the benefit seen with autologous SCT for patients with relapsed diffuse large cell lymphoma, as well as follicular lymphoma. Autologous SCT is not as effective for patients with relapsed/refractory MCL. Till and colleagues[20] conducted a single-center review of outcomes of 56 consecutive MCL patients who received high-dose therapy plus autologous SCT. The estimated OS rate at 3 years in cases where autologous SCT was given in first CR or PR (CR1/PR1) was 93% (n = 36) compared with 46% (n = 20) in patients with relapsed/refractory disease. Estimated 3-year PFS rates were 63% and 36%, respectively. The hazard of mortality among patients transplanted with relapsed/refractory disease was 6.09 times that of patients transplanted in CR1/PR1 (P = .006).

Similarly, an analysis of data from the European Blood and Bone Marrow Transplant registry and the Autologous Blood and Marrow Transplant Registry of MCL patients receiving autologous SCT (1988-1998) found that the disease status at transplantation was the most significant factor affecting survival.[20] Patients with chemosensitive disease but not in CR1 were 2.99 times (P < .001) more likely to die than patients transplanted in CR1.

In an attempt to improve upon the outcome of ASCT for patients with relapsed/refractory MCL, investigators have added radioimmunotherapy to the transplant regimen. For example, the addition of yttrium-90 (^{90}Y)-ibritumomab tiuxetan to a conditioning regimen of rituximab and carmustine, etoposide, cytarabine, melphalan (BEAM) showed promising results in a phase II trial by Krishnan and colleagues.[21] The patients had CD20+ follicular lymphoma, diffuse large B-cell lymphoma, transformed lymphoma, or poor-risk MCL (ie, requiring at least 2 induction regimens to achieve PR/CR; n = 13). The median age was 59.6 years, and 73% had stage III/IV disease. On Day -21, patients were given rituximab 250 mg/m^2, and on Day -14, the same dose of rituximab was administered with ^{90}Y-ibritumomab 14.8 MBq/kg (capped at 40 mCi), which was followed BEAM (carmustine 150 mg/m^2 on Days -7 and -6, etoposide 100 mg/m^2 and cytarabine 100 mg/m^2 twice daily on Days -5 through -2, and melphalan 140 mg/m^2 on Day -1). Autologous SCT was performed on Day 0.

At a median follow-up of 18.4 months, the estimated 2-year OS and PFS rates in MCL patients were 84.6% and 68.4%, respectively. Transplantation-related mortality was 0% at 100 days. The addition of radioimmunotherapy did not appear to add to the toxicity of the BEAM conditioning regimen, which was tolerated well in this largely older population. Thus, the incorporation of radioimmunotherapy into the ASCT transplant paradigm is an interesting experimental approach and phase II trials examining the ability of rituximab, ^{90}Y-ibritumomab, and other CD20-specific ablating treatments to improve outcomes following autologous SCT are in progress.[22-25]

To date, the therapeutic approach for patients with MCL that offers the greatest chance for “cure” is that of allogeneic transplantation. The potential of cure is likely offered by the proposed

“graft versus lymphoma effect.” However, the graft versus host disease (GVHD) seen with allogeneic transplant, as well as the need for immunosuppression to control GVHD, significantly increases the morbidity and nonrelapse mortality of this approach. In an attempt to decrease some of the acute treatment related toxicity of allogeneic transplantation, and to increase the feasibility of allogeneic transplantation for older patients, most recent studies exploring this approach for patients with MCL are using reduced intensity allogeneic transplants.

One of the largest series to date of reduced-intensity conditioning (RIC) in MCL was reported by Maris and colleagues[26] in 33 relapsed/refractory MCL patients (median age: 53.5 years). The median number of previous treatment regimens received was 4 (range: 1-10), and 42% of patients had failed previous high-dose autologous SCT. The RIC regimen comprised fludarabine 30 mg/m^2 on Days -4, -3, and -2 before SCT, and 2 Gy of total body irradiation on the day of transplantation. Cyclosporine and mycophenolate mofetil were given as GVHD prophylaxis. Transplantation occurred when the patient was in CR for 39%, in PR for 15%, and 46% were relapsed/refractory at the time of allogeneic SCT; altogether, 61% showed signs of disease. The median follow-up was 24.6 months. At 2 years, the OS rate was 64%, and the PFS rate was 60%. Nonprogression-related mortality was 24% at 2 years. Four (12%) patients died from complications from acute and chronic GVHD.

As allogeneic transplant is the only therapy to date with the potential of cure, it should at least be considered in appropriate patients. It must also be considered that in addition to the relapse and nonrelapse mortality of this approach described above, chronic GVHD can impair the quality of life of surviving patients. Indeed, the incidence of chronic GVHD was 64% in the study of Maris and colleagues.

Immunomodulation With Thalidomide and Lenalidomide in Relapsed Mantle Cell Lymphoma

Thalidomide

Thalidomide has a wide range of pharmacologic effects. As an antiemetic, it was marketed to pregnant women for several years in the late 1950s before its teratogenic effects became evident. As its teratogenic effects may in part have been due to its effect on angiogenesis, interest in this agent as an anticancer drug increased as tumor angiogenesis began to be appreciated as a target of cancer therapy. It has been used to treat erythema nodosum leprosum, a painful complication of leprosy, first as a sedative and later as an antiinflammatory therapy, and was approved by the FDA for this indication in 1998. Indeed, its ability to inhibit the inflammatory cytokine tumor necrosis factor–alpha, as well as inhibit angiogenesis led to its investigation in the treatment of numerous diseases, particularly cancers. The FDA approved thalidomide for the treatment of multiple myeloma in 2006 following demonstration of efficacy in a phase II study of patients with refractory myeloma.[27]

It is likely the anticancer activity of thalidomide is due to multiple mechanisms. For example, thalidomide can directly suppress the growth and survival of myeloma cells, and it may also directly kill them[28]; these effects may be because of thalidomide-associated changes in the composition of the extracellular milieu that allows myeloma cells to attach and grow within the bone marrow.[29] Thalidomide also can alter the production and activity of cytokines involved in the growth and survival of myeloma cells. Thalidomide can inhibit the angiogenesis that the tumor cells need to grow and survive, and it might activate the targeting of tumor cells by the immune system. A serious adverse event of thalidomide is venous thromboembolism, which occurs in 1% to 3% of patients receiving single-agent thalidomide, rising to 10% to 15% when thalidomide is combined with dexamethasone, and to 25% when thalidomide is administered with other cytotoxic agents, particularly doxorubicin.[30]

A phase II trial of single-agent thalidomide by the Cancer and Leukemia Group B examined the outcomes of 24 evaluable patients with relapsed/refractory indolent lymphomas who were treated with thalidomide 200 mg daily, with escalation by 100 mg daily every 1-2 weeks to a maximum of 800 mg daily.[31] Patients had received a median of 2 previous regimens (range: 1-4). The ORR of 12.5% comprised CR in 8.0% (n = 2) and PR in 4% (n = 1). In this small group, there were 4 thromboembolic events. Although there is evidence that thalidomide, alone or in conjunction with rituximab, has activity against MCL,[32,33] the low response rate together with the high rate of adverse events has shifted attention away from thalidomide and to a next-generation immunomodulator, lenalidomide.

Lenalidomide

Lenalidomide is a derivative of thalidomide with enhanced anti tumor necrosis factor–alpha activity, greatly reduced teratogenic potential, and comparable antiangiogenic activity.[34] Lenalidomide was FDA approved in 2006, in combination with dexamethasone, for the treatment of multiple myeloma patients who have received at least 1 previous therapy. Lenalidomide has a better safety profile than thalidomide and does not cause significant somnolence, constipation, or peripheral neuropathy.[30] However, myelosuppression can be a serious problem. Both lenalidomide and thalidomide have comparable incidences of venous thrombotic disease, manifesting as deep vein thrombosis or pulmonary embolism. The antitumor mechanism of action of lenalidomide is being intensely studied and is likely to be similar to that of thalidomide.

A recent phase II multicenter trial, conducted by Wiernik and colleagues,[35] evaluated lenalidomide monotherapy in 49 patients with relapsed/refractory NHL (grade 3 follicular lymphoma, diffuse large B-cell lymphoma, MCL, or transformed low-grade lymphoma). Oral lenalidomide 25 mg/day was given on Days 1-21 of a 28-day cycle for up to 52 weeks or until disease progression or intolerance. At a median follow-up time of 3.7 months, the ORR was 35%, including 4% CR, 8% CRu, and 22% PR.

A subgroup analysis of the MCL patients enrolled in this study was conducted by Habermann and colleagues.[36] These patients (n = 15) had a median age of 66 years, and a median time from diagnosis of 5.1 years. Most (73%) had received previous treatment with anthracyclines, alkylating agents with and without rituximab; 33% had undergone previous autologous SCT, 33% had been treated with bortezomib, and the median number of previous treatment regimens was 4 (range: 2-7).

The ORR in MCL patients was 53% 20% CR and 33% PR); stable disease was found in 13%. Patients who were refractory to their previous treatment were found to have a lower likelihood of responding to lenalidomide. A response was seen in 80% of those that underwent prior autologous SCT, and 40% of those that previously received bortezomib. The median duration of response was 13.7 months (not reached for the 3 CR patients), and the median PFS time was 5.6 months. Partial responders had a median response duration of 4 months. Grade 3 neutropenia was seen in 40% of patients; grade 3/4 thrombocytopenia was reported in 33% of patients. Eight patients (53%) had dose reductions because of adverse events—most often for neutropenia. In this difficult-to-treat population, the early response rate to lenalidomide is encouraging, especially given that lenalidomide is an oral therapy that appears adequately tolerated. Longer-term outcome data will enable a better evaluation of lenalidomide's full potential.

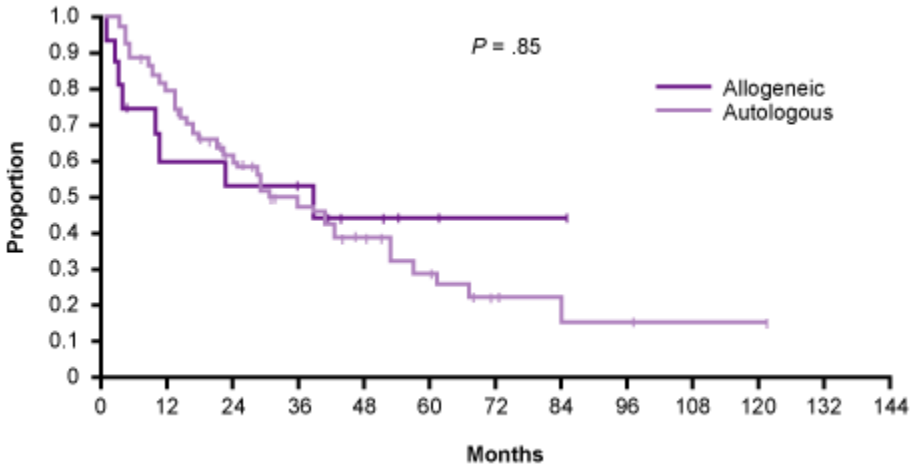
mTOR Inhibition With Temsirolimus

The mammalian target of rapamycin (mTOR) is a large and highly conserved kinase that integrates cellular signals regulating growth, energy, and nutrient availability, and that regulates the translation of proteins responsible for cellular growth and proliferation in conjunction with the

enzymes PI3K and AKT.[37] It was discovered to be the mediator through which sirolimus (rapamycin) and tacrolimus mediate their antirejection activity in organ transplantation.[38] As mTOR levels are elevated in many cancers, including MCL, there has been much interest in evaluating the efficacy of mTOR inhibitors in cancer.

Temsirolimus is a dihydroester of rapamycin that inhibits mTOR activity and, thereby, inhibits mTOR-regulated downstream activities including angiogenesis (Figure 3). Temsirolimus has recently been FDA approved for the treatment of renal cell carcinoma.[39] As a hallmark of MCL cells is the characteristic overexpression of cyclin D1, which is under the translational control of the PI3K signal transduction pathway and is downstream of mTOR,[40] there has been interest in studying this agent in MCL. Indeed, in that in MCL cell lines in vitro, the silencing of mTOR expression induces cell cycle arrest and apoptosis, indicating the mTOR signaling pathway is activated in MCL and, thereby, contributes to cell cycle progression and tumor cell survival.

Figure 3. The mTOR signaling pathway.



A phase II trial evaluated intravenous temsirolimus (250 mg/week) in 35 patients with relapsed MCL.[41] The ORR was 38%, including 3% CR and 35% PR. However, 71% of the patients experienced grade 3 hematologic toxicity, and 9% experienced grade 4 hematologic toxicity. Subsequent to that trial, temsirolimus was FDA approved in 2007 for the treatment of renal cell carcinoma at a dose of 25 mg/week, based on phase III data showing significantly improved OS compared with interferon alfa alone (P = .008).[42]

The observation that renal cell carcinoma could be treated with temsirolimus at a dose 10% of that used in this previous phase II MCL trial led to the initiation of a second phase II trial, evaluating the reduced dose in relapsed MCL.[43] This study enrolled 28 relapsed/refractory MCL patients (median age: 69 years) with stage III/IV disease (97%), had received a median of 4 previous chemotherapy treatments (range: 1-9). Temsirolimus was given as an infusion (25 mg/week) on a 4-week cycle. The dose was withheld in the event of hematologic toxicity until it resolved. The median follow-up was 30 months. The ORR was 41%, including 4% CR and 37% PR. Of interest, there were no responses in the patients (11%) with blastoid morphology. The median OS was 14 months, and the median time to progression was 6 months. The primary toxicity was reversible myelosuppression. There was 1 case (4%) of grade 4 anemia and 2 cases (7%) of grade 4 fatigue, with the most common drug-related adverse event being grade 3 thrombocytopenia, seen in 39% of patients. Grade 3 neutropenia was seen in 18% of patients and grade 3 anemia in 11%. Most of the adverse events resolved with cessation or reduction of the temsirolimus dose. Therefore, temsirolimus was shown to have single-agent efficacy against MCL.

Ridaforolimus (formerly known as deforolimus) is another mTOR inhibitor that has been evaluated in early-stage clinical trials. In one treatment cohort of patients with MCL embedded in a larger trial of relapsed/refractory patients with hematologic cancers, ridaforolimus 12.5 mg daily for 5 days every 2 weeks resulted in a PR in 3 out of 9 patients.[44] Mouth sores, fatigue, nausea, and thrombocytopenia were the most common adverse events among all patients.

Other Treatment Approaches for Mantle Cell Lymphoma

Purine Analogues: Cladribine

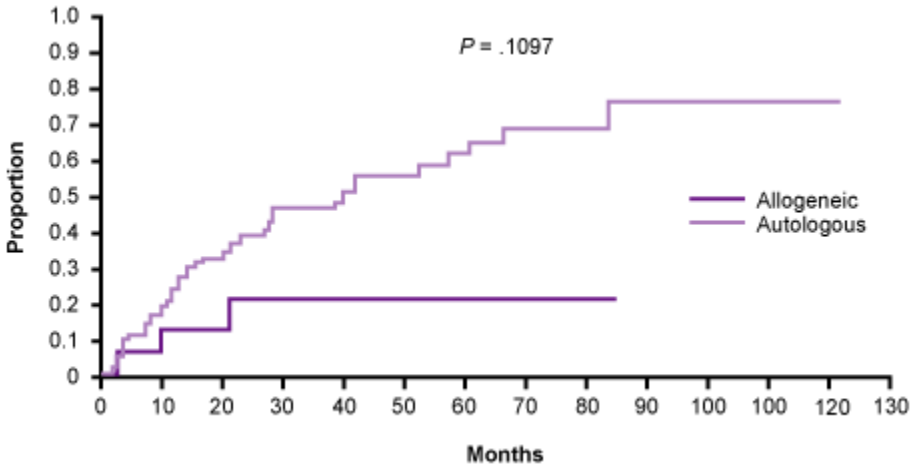
Cladribine (2-CDA) is a purine analogue and as such is in the same general class as fludarabine and pentostatin. Cladribine is a prodrug that specifically targets mononuclear cells that have the combination of a relative abundance of deoxycytidine kinase, the enzyme that phosphorylates cladribine to its active cytotoxic metabolite (cladribine monophosphate) and relatively low concentrations of nucleotidases that degrade the phosphorylated cladribine.[45] The accumulation of phosphorylated cladribine in lymphoid tissue causes DNA strand breaks, depletion of intracellular nicotinamide-adenine dinucleotide stores, and subsequent cell death by apoptosis. The toxicity of cladribine in nonlymphoid tissues is relatively low because the relative abundance of nucleotidases in these cells degrades the cladribine metabolites.

Inwards and colleagues[46] reported on the long-term follow-up (median: 6.3 years) of 24 patients with recurrent MCL given single-agent cladribine (5 mg/m^2 intravenously on Days 1-5 every 28 days, for up to 6 cycles). The ORR was 46%, including 21% CR and 25% PR. The median PFS time was 5.4 months, the 2-year OS rate was 36%, and the median OS was 1.9 years. Grade 3 neutropenia was seen in 29% of patients and grade 4 neutropenia in 21%; 13% had grade 3 thrombocytopenia and 4% had grade 4 thrombocytopenia. The elderly patients studied in this trial appeared to tolerate cladribine well, and the response rate is sufficient to allow consideration of cladribine for this population.

Microtubule Stabilizers: Single-Agent Ixabepilone

Ixabepilone is an epothilone, a class of microtubule stabilizers that has a mechanism of action similar to that of the taxanes (binding to the α,β-tubulin dimer) but whose chemical structure is very different than that of the taxanes (Figure 4).[47] One consequence is that the epothilones have the ability to overcome drug-resistant disease and can be used in patients who are refractory to treatment by anthracyclines or taxanes.[48] The epothilones are also more potent inhibitors than paclitaxel. Ixabepilone was approved in 2007 for the treatment of patients with metastatic breast cancer refractory to anthracyclines, taxanes, and capecitabine and is currently being investigated for its applicability to a wide range of metastatic diseases.[48]

Figure 4. Ixabepilone (BMS-247550)



O'Connor and colleagues[49] investigated single-agent ixabepilone in patients with indolent lymphomas (including MCL in 54% of patients) in a multicenter phase II study. Patients (n = 22) had a median age of 65 years, received a median of 3 previous cytotoxic therapies (range: 1-4), and a median time from diagnosis of 50 months. The patients had received a wide range of alkylator-based (100%), purine-analgoue (68%), and biological-based regimens. All patients had received previous rituximab. Ixabepilone 25 mg/m^2/week was given for 3 consecutive weeks on a 4-week cycle for a median of 2 cycles. The dosage was reduced in the event of adverse events (4 patients). Only 21% of patients received more than 2 cycles—or more than 6 doses—and responders and nonresponders received statistically indistinguishable amounts of therapy.

Of the 15 MCL patients treated, 11 were evaluable for efficacy. The ORR was 27% (all PRs) with a median duration of response of 2 months. Stable disease was seen in 46%, and disease progression in 27%. Four patients with MCL were not assessed for response because of: 1) asthenia after 3 doses in 1 patient, 2) transformation of MCL to rapidly progressing Burkitt lymphoma in 1 patient, 3) rapid progression of leukemic MCL in another, and 4) cellulitis in a patient who attained a PR. For all patients, 57% experienced grade 3/4 neutropenia, and 22% had grade 3/4 thrombocytopenia. Neurotoxicity is of particular concern regarding microtubule inhibitors, and in this trial, 7% of patients experienced grade 3 neuropathy. It is possible that the incidence of neuropathy might be reduced by a longer time of infusion (3 hours is now indicated; 1 hour was used in this trial).[47]

PEP-C

Another recent novel approach to cancer therapy, especially for elderly patients with refractory disease is low-dose metronomic chemotherapy, which is the close, regular administration of low-dose cytotoxic drugs over prolonged periods with minimal or no drug-free breaks. Coleman and colleagues[50] recently reported the results of a retrospective analysis of metronomic therapy with PEP-C, an oral regimen comprising prednisone 20 mg after breakfast; cyclophosphamide 50 mg after lunch; etoposide 50 mg after dinner, and procarbazine 50 mg at bedtime with an antiemetic such as ondansetron. This regimen was administered daily until the development of leukopenia (< 3.0 x 10^9 cells/L), at which time treatment was withheld until recovery of the leukocyte count. After recovery, the regimen was resumed with the same dosages at a variable frequency, titrated to maintain a white blood cell count of at least 3.0 x 10^9 cells/L.

This study enrolled 22 MCL patients with recurrent disease who were treated with PEP-C over 16 years at a single institution. Most patients were older than 60 years of age (64%), 81% of whom had received 2 or more previous regimens including 41% who had received at least 3 previous treatments, and 41% were chemoresistant. Eighty-two percent achieved an objective response comprising CRs in 46% and PRs in 36%. In patients who were resistant to previous therapy, the CR and PR rates were both 33% (n = 3 each). The median time on therapy was 17 months and was longer for patients in CR (mean: 21 months) than PR (mean: 7 months). Six patients were removed from therapy for alternative approaches (eg, observation after response), and 7 patients relapsed. The time on therapy was used as a surrogate measure for OS, which was not measured. Based on these findings, however, a more comprehensive phase II trial of PEP-C plus rituximab and thalidomide in relapsed MCL patients is under way.[51] The potential advantage of this regimen is that it is well tolerated, and the results of the ongoing phase II trial will be of interest.

Gemcitabine, Mitoxantrone, Rituximab (GMR)

The GMR regimen comprises gemcitabine, a nucleoside analogue that interferes with DNA synthesis; mitoxantrone, an anthracenedione that inhibits topoisomerase and, therefore, inhibits DNA synthesis and repair; and rituximab, an antibody directed against CD20. Each has been previously investigated as single agents in phase II trials. Garbo and colleagues[52] conducted a prospective phase II trial that combined these agents for the first time in the second-line treatment of MCL. All 16 patients (median age: 74 years) had stage III/IV disease (88% stage

IV) and had received previous chemotherapy. On Day 1, patients received gemcitabine 900 mg/m^2 followed by mitoxantrone 10 mg/m^2 followed by rituximab 375 mg/m^2. On Day 8, gemcitabine 900 mg/m^2 was administered again. This was repeated on a 21-day cycle for a maximum of 8 cycles. Patients were treated until there was evidence of a CR, progressive disease, or intolerable toxicity.

In 15 evaluable patients, the ORR was 47%, with 20% attaining a CR. The median response duration was 7.9 months. At a median follow-up of 10.7 months, the median survival and PFS had not been reached, and the 1-year OS and PFS rates were estimated at 57% and 54%, respectively. All deaths were because of disease progression. The most common grade 3/4 toxicities were neutropenia (100%), thrombocytopenia (67%), leukopenia (53%), and anemia (33%). Four patients (25%) discontinued study treatment because of asthenia, neutropenia, and convulsion. The study was discontinued because of slow accrual, as well as the concurrent approval of bortezomib for MCL. Whether bortezomib will live up to its early promise and whether there might yet be a place for the GMR regimen will be determined by future trials.

Rituximab, HyperCVAD, and Methotrexate-Cytarabine

As described in the section in the upfront treatment of patients with MCL, rituximab-hyperCVAD/methotrexate/cytarabine is one option for initial treatment. Wang and colleagues[53] also studied this in a prospective phase II trial enrolled 31 patients with relapsed/refractory MCL (median age: 63 years), of whom 29 were evaluable. The median number of previous regimens was 1 (range: 1-5). Four patients had been treated with rituximab plus hyperCVAD alternating with rituximab plus methotrexate/cytarabine, and 5 had previous autologous SCT.

Patients received a median of 5 cycles, with an ORR of 93% that included CR/CRu in 45% (n = 13). Nine patients underwent consolidation therapy with nonmyeloablative SCT; those who did not receive SCT did not do so for a variety of reasons, primarily age. At a median follow-up time of 40 months, the OS was 19 months and the median failure-free survival time was 11 months. No pretreatment variable appeared to predict failure-free survival. The rates of grade 4 neutropenia and grade 4 thrombocytopenia were 60% and 54%, respectively. The incidence of neutropenic fever was 11%, and 13% of patients stopped therapy because of toxicity.

This is an intensive regimen that is associated with a significant degree of toxicity and its role in the salvage setting needs further evaluation.

Conclusion

This review was meant to provide the reader with an understanding of the ever increasing therapeutic approaches for patients with relapse and refractory MCL. To date, however, there is no standard approach for such patients and as such, all patients should go on a clinical trial. It is only through the context of clinical trials that we can further increase the survival rate and hopefully the cure rate of our patients that suffer from this disease. Indeed, a listing of available clinical trials can be obtained from the National Institutes of Health (www.ClinicalTrials.gov), the National Cancer Institute (www.cancer.gov/clinicaltrials), or from the Mantle Cell Lymphoma Research Initiative and Consortium (www.mantlecelllymphoma.org).

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1. Which of the following was NOT reported from the phase II PINNACLE trial of bortezomib in the treatment of relapsed/refractory mantle cell lymphoma (MCL)?

A. A 32% overall response rate (ORR)
B. A longer median overall survival (OS) time for responders
C. Efficacy in both patients with refractory MCL and those who relapsed after previous high-intensity therapy
D. A correlation between time to response and response duration

2. The mammalian target of rapamycin inhibitor temsirolimus has been shown in a phase II study to produce a response in more than 40% of relapsed/refractory MCL patients using which of the following doses?

A. 250 mg/week
B. 25 mg/week

3. Which of the following comparisons between epothilones and taxanes is/are accurate?

A. Epothilones have a similar mechanism of action to that of the taxanes
B. Epothilones have a similar chemical structure as that of the taxanes
C. Epothilones are less potent than paclitaxel
D. All of the above are correct
E. A and B are correct
F. B and C are correct

4. The gemcitabine/mitoxantrone/rituximab (GMR) regimen was evaluated as second-line therapy for MCL in a phase II trial. Although a 47% ORR was reported, grade 3/4 toxicity was very common, including which of the following reported in 100% of patients?

A. Neutropenia
B. Thrombocytopenia
C. Leukopenia
D. Anemia

5. Wiernik and colleagues conducted a phase II study of lenalidomide monotherapy for the treatment of relapsed/refractory non-Hodgkin's lymphoma. Which of the following results were NOT seen in a subgroup analysis of the 15 MCL patients enrolled in this study?

A. Patients who were refractory to their last treatment were more likely to be refractory to lenalidomide
B. Higher overall and complete response (CR) rates vs the overall study cohort
C. Grade 3/4 thrombocytopenia
D. No adverse event–related dose reductions

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