Management of Relapsed Mantle Cell Lymphoma: Still a Treatment Challenge

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Mantle cell lymphoma (MCL) is a distinct subtype of non-Hodgkin lymphoma that occurs most commonly in older patients with advanced-stage disease.

Mantle cell lymphoma (MCL) is a distinct subtype of non-Hodgkin lymphoma that occurs most commonly in older patients with advanced-stage disease. The typical clinical course is characterized by frequent relapse after initial therapy, with a reported median survival of 5 years. Median failure-free survival has been reported as approximately 8 to 20 months with upfront standard therapies such as CHOP-like regimens (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone),[1-3] although longer progression-free survival (PFS) has been reported with high-intensity chemotherapy, such as the hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin [Adriamycin], dexamethasone), with or without autologous stem-cell transplantation (ASCT).[4,5] The relative merits of these approaches are difficult to fully appreciate due to the differences in eligible patient populations and limited randomized comparative data.

**THE ISSUES**

- Mantle cell lymphoma (MCL) is relatively uncommon, and despite recent therapeutic advances, survival data for salvage regimens are limited by the low patient numbers and enrollment on clinical studies.
- Most MCL patients are older, and may be less able to tolerate more aggressive therapy due to age or comorbid illnesses.

Management of recurrent disease is an expected yet difficult clinical problem in MCL due to both disease and patient factors. MCL is a relatively uncommon entity that accounts for roughly 5% to 8% of all lymphomas.[6,7] Despite many important therapeutic advances in the past decade, there remains a paucity of evidence demonstrating relative survival advantages of various salvage regimens, partially limited by the low patient numbers and enrollment on clinical studies. Most MCL patients are older, and may be less able to tolerate more aggressive therapy due to age or comorbid illnesses. The major therapeutic goal in MCL management is to extend survival and improve quality of life whenever possible. Thus, an individualized treatment approach should be devised after reviewing options, taking into consideration the clinical characteristics of the disease such as MCL-related symptoms and pace of disease, and the patient’s performance status and preferences, with an emphasis on clinical trial participation.

**Treatment Options**

A growing list of novel regimens for MCL has been introduced to the clinic in the past 2 decades. In a retrospective survival analysis of two historical patient cohorts followed in Germany 20 years apart, Herrmann and colleagues reported a median overall survival (OS) of 2.7 years for the earlier Kiel Lymphoma Study Group patients as compared with 4.8 years for the contemporary German Low Grade Lymphoma Study Group (GLSG) patients.[8] The longer median overall survival in the later cohort is likely largely due to improvements in therapy, perhaps mostly in the second-line setting, in recent decades. This review will discuss agents and combinations with utility in the recurrent disease setting.
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Intensive Chemotherapy-Based Approach

- Intensive chemotherapy
- Hematopoietic stem cell transplantation
- Biologic and targeted agents
- Metronomic therapy
- Other novel agents

**Second-Line Chemotherapy**—For younger patients with aggressive disease, outside of clinical trials there are several commonly employed chemotherapeutic options including R-ICE (rituximab [Rituxan], ifosfamide, carboplatin, etoposide), R-DICE (rituximab, dexamethasone, ifosfamide, cisplatin, etoposide), R-DHAP (rituximab, dexamethasone, high-dose cytarabine [Ara-C], cisplatin [Platinol]), R-ESHAP (rituximab, etoposide, methylprednisolone [SoluMedrol], high-dose cytarabine, cisplatin) or R-hyperCVAD (rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin [Adriamycin], dexamethasone, alternating with high-dose methotrexate and cytarabine). Based on clinical factors, including prior treatments and their effect and tolerability, patients who have not received intensive treatment initially sometimes receive high-dose therapy with ASCT. While comparisons are limited, this group as well as those who were previously treated intensively upfront (including stem cell transplant) may also receive chemotherapy followed by allogeneic nonmyeloablative stem cell transplantation (NSCT).

**Hematopoietic Stem Cell Transplantation**—Both ASCT and NSCT have been studied in relapsed MCL. Compared with ASCT in first remission, inferior outcomes have generally been reported in the relapsed setting—but treatment responsiveness in any setting is greater upfront vs in recurrence, and no study has randomized patients to early vs late ASCT in MCL. An estimated 4-year disease-free survival of 31% was reported in a Dana-Farber Cancer Center series with 20 relapsed MCL patients receiving purged autologous bone marrow graft.[9] Gopal and colleagues reported apparently more successful outcomes (3-year OS of 93% and PFS of 61%) combining the high-dose iodine-131–labeled anti-CD20 antibody tositumomab (Bexxar) with etoposide and cyclophosphamide followed by ASCT.[10]

In a recent report from M.D. Anderson Cancer Center on high-dose therapy from 1990 to 2007, 36 patients (aged 42–76) received ASCT with conditioning regimens including high-dose cyclophosphamide and total-body irradiation (Cy/TBI), R-Cy/TBI and R-BEAM (carmustine [BCNU], etoposide, cytarabine, melphalan), and 35 patients (aged 43–68) received NSCT with conditioning regimens of either PFA (cisplatin, fludarabine, cytarabine) or FCR (fludarabine, cyclophosphamide, rituximab).[11] For the ASCT patients, the median PFS and OS were 27 and 52 months, and transplant-related mortality rates were 8% at 3 months and 1 year. Inclusion of rituximab in the treatment regimen was not associated with an improved outcome. For the NSCT patients, the median PFS duration was 60 months and the median OS has not been reached, with a median follow-up of 56 months. In contrast to the ASCT patients, plateaus in the survival curves were observed for both PFS and OS in nine NSCT patients followed between 63 and 110 months. The transplant-related mortality rates were 0% at 3 months and 9% at 1 year. The actuarial risk of acute graft-vs-host disease (GVHD) was 37%, and chronic GVHD risk was 60%.

Other studies using variations of conditioning regimens have reported variable clinical outcomes, and patient selection is clearly a major factor in results.[12,13] Nevertheless, reduced-intensity allogeneic SCT represents a promising salvage strategy that warrants continued and cautious investigation.

**Biologic and Targeted Agents**

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<td><strong>Targeted Therapy in Relapsed Mantle Cell Lymphoma</strong></td>
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For many patients with relapsed MCL, intensive salvage and high-dose therapy are not options because of either comorbidities or personal preferences. Several novel compounds have shown meaningful clinical activities as single agents, and in some cases have demonstrated durable disease control when used in rational combinations while preserving quality of life (Table 1). Given the array of options and unanswered questions in this area, we believe that patients with MCL should be encouraged to participate in clinical trials whenever possible.

**Monoclonal Antibody-Based Therapies**—Rituximab, a chimeric antibody directed against the CD20 antigen, has been widely employed in B-cell malignancies. In mantle cell lymphoma, the standard regimen of four weekly infusions of 375 mg/m²/wk has been demonstrated to have modest...
activity, with an overall response rate (ORR) of 37% in the relapsed setting, and a median duration of response of 1.2 years.[14] Ghielmini and colleagues reported that prolonged treatment with rituximab did not significantly improve response rate, duration of response, or event-free survival after induction with rituximab alone.[15]

Other results from a randomized study by the GLSG showed that maintenance rituximab led to a statistically significant prolongation of response duration after second-line therapy with R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone; \( P = .049 \)).[16] After a median observation of 26 months, median response duration was slightly prolonged by rituximab maintenance (14 vs 12 months) but with a significantly higher proportion of patients with ongoing remission beyond 2 years (45% vs 9%). The bottom line is that rituximab is commonly included in MCL treatment regimens, but its impact as a single agent, in combinations, and for maintenance seems to be more limited than that in other lymphoma histologies.

**REFERENCE GUIDE**

### Therapeutic Agents Mentioned in This Article

- Bevacizumab (Avastin)
- Bortezomib (Velcade)
- Carboplatin
- Carmustine (BCNU)
- Cisplatin
- Cyclophosphamide
- Cytarabine
- Dexamethasone
- Doxorubicin
- Etoposide
• **Bortezomib**—Bortezomib (Velcade), a dipeptidyl boronic acid derivative, selectively inhibits the 26S proteasome, which is essential in the degradation of intracellular proteins including p53, nuclear factor kappa B (NFkB), bcl-2, and cyclin-dependent kinase (CDK) inhibitors such as p21 and p27. Inhibition of the ubiquitin-proteasome pathway in tumor cells in part hinders tumor growth by inducing cell-cycle arrest, apoptosis, and inhibition of tumor metastasis and angiogenesis. Results from multiple phase II reports demonstrate that bortezomib is an active agent in relapsed and refractory mantle cell lymphoma, producing ORRs of 33% to 50%, and complete response (CR) rates of 4% to 8%. When given at 1.3 mg/m² on days 1, 4, 8, and 11 of a 21-day cycle, bortezomib demonstrated an ORR of 33%, including 8% CR/unconfirmed CR, with a median duration of response of 9.2 months and time to progression of 6.2 months in a multicenter pivotal phase II trial, leading to US Food and Drug Administration (FDA) approval of bortezomib for this indication. The most common grade 3/4 adverse events were peripheral neuropathy, fatigue, and thrombocytopenia. Currently, multiple trials are ongoing to further examine the efficacy of bortezomib either as a single agent or in combination with other active regimens including rituximab or CHOP plus rituximab (R-CHOP) in non-Hodgkin lymphoma.

• **Bendamustine**—Bendamustine is a novel agent consisting of a mechlorethamine group, a benzimidazole ring, and a butyric acid side chain. Bendamustine causes direct DNA damage and apoptosis, inhibition of mitotic checkpoints, and induction of mitotic catastrophe. Phase II studies of the combination of rituximab plus bendamustine have shown marked clinical responses. Bendamustine was given at a dose of 90 mg/m² on days 1 and 2, combined with rituximab at 375 mg/m² on day 1, given every 4 weeks for a maximum of four cycles. Rummel and colleagues reported an ORR of 75% with a CR rate of 50% in 16 patients with recurrent MCL. The median PFS for MCL patients was 18 months. A recent international phase II study included 12 patients with MCL. Rituximab was administered on day 1, and bendamustine on days 2 and 3 of each 28-day cycle for a total of 4-6 cycles. An additional dose of rituximab was administered 1 week before the first cycle and 4 weeks after the last cycle. The investigators reported an ORR of 92%, CR of 42%, and CRu of 17% for the MCL patients, with a median duration of response of 19 months. Similar clinical activities were reported for the combination of bendamustine with mitoxantrone and rituximab. In general, bendamustine regimens were well tolerated, with primary toxicities of myelosuppression including grade 3/4 neutropenia and thrombocytopenia.

• **IMiDs**—Immunomodulatory drugs (IMiDs) are a series of synthetic compounds that have been developed based on the glutamate-derivative backbone of the prototype drug thalidomide (Thalomid). Thalidomide has wide-ranging functions including anti-inflammatory, immunomodulatory, antiangiogenic, and direct anticancer activities. The second-generation compound lenalidomide (Revlimid) has enhanced immunologic and anticancer properties with fewer side effects. Drach and colleagues have reported clinical activity of thalidomide and rituximab in a small clinical study for patients with relapsed/refractory MCL. Of 16 evaluable subjects, 13 demonstrated objective responses (5 CR, 8 partial response [PR], ORR of 81%, and CR rate of 31%) while taking thalidomide at 200 to 400 mg daily in combination with rituximab, with median time to progression at 20 months. The main toxicities of thalidomide include fatigue, somnolence, neuropathy and thromboembolic events. Lenalidomide has demonstrated significant clinical activity either as a single agent or in combination with rituximab in MCL. Single-agent lenalidomide given at 25 mg orally daily on days 1 to 21 every 28 days in relapsed aggressive lymphoma subtypes demonstrated an ORR of 35%, including 53% ORR for 15 MCL patients. An international study of lenalidomide in aggressive non-Hodgkin lymphoma subtypes by Czuczman and colleagues reported a 28% ORR, with 36% ORR for 22 MCL patients, and identified low tumor burden and longer duration from prior rituximab as two favorable predictive factors. Wang and colleagues explored the combination of lenalidomide and rituximab in a phase I/II study in patients with relapsed/refractory MCL. At a 20-mg daily dose of lenalidomide (on days 1–21 of a 28-day cycle), five out of six patients achieved responses including one CR, one PR, and one case of progressive disease, following two cycles of treatment. Longer follow-up with additional patients will
Fatigue and myelosuppression with thrombocytopenia and neutropenia are the most common adverse effects of lenalidomide therapy. Coleman and colleagues from our center have reported preliminary clinical experience on the THRIL regimen, which includes alternating daily thalidomide at 50 mg with lenalidomide at 10 mg on a continuous basis in combination with maintenance rituximab every 6 months to minimize cytopenias. In three patients with MCL, two achieved CR and one PR.[30]

**mTOR Inhibitor Temsirolimus**—The mammalian target of rapamycin (mTOR) is a serine/threonine kinase downstream of the PI3-kinase/AKT pathway.[31] mTOR-mediated phosphorylation activates downstream targets that are essential in the regulation of cell growth, proliferation, and survival.[32] Selective mTOR inhibitors have shown antiangiogenic activities by inhibiting hypoxia-inducible factor (HIF)-1–mediated vascular endothelial growth factor (VEGF) production downstream of the PI3-kinase/AKT/mTOR pathway, as well as a direct inhibitory effect on endothelial cell proliferation.[33,34]

Witzig and colleagues reported the first phase II trial of the mTOR inhibitor temsirolimus (CCI-779, Torisel) in patients with relapsed mantle cell lymphoma. Temsirolimus was given at 250 mg intravenously every week as a single agent. A 38% response rate was observed in 34 evaluable patients, with a median time to progression of 6.5 months. Thrombocytopenia was dose-limiting, but of short duration.[35] A subsequent randomized, open-label phase III study compared the antitumor activity of temsirolimus with an investigator’s choice of therapy in patients with relapsed MCL. Patients were randomly assigned to one of two schedules of IV temsirolimus, 175 mg three times weekly followed by either 75 mg (175/75 mg) or 25 mg (175/25 mg) weekly, or the investigator’s choice of therapy. Treatment with the temsirolimus 175/75 mg arm resulted in significant improvement in PFS (4.8 months vs 1.9 months, \( P = .0009 \)), objective response rate (22% vs 2%, \( P = .0019 \)), and a trend toward longer OS (10.9 months vs 5.8 months, \( P = .0714 \)), compared with the investigator’s choice. The most common grade 3/4 adverse events were cytopenias.[36]

**Metronomic Therapy**

**Case Report: A Man With a Cecal Mass**

Mr. D. is a 70-year-old man who was initially diagnosed with mantle cell lymphoma after presenting with gastrointestinal complaint and lethargy. A colonoscopy revealed a 6-cm cecal mass. Staging workup was consistent with stage IV disease. He was initially treated with six cycles of R-CHOP chemotherapy and achieved an overall partial response. Six months later, he began to have worsening abdominal bloating, and scan documented progression of disease. He was treated with bortezomib at 1.3 mg/m\(^2\) for three cycles and achieved stable disease.

The patient now presents with a 10-cm cecal mass which is causing significant abdominal discomfort. Mr. D. runs a small business, and prefers the therapy that would take the least amount of time from work.

What are the salvage therapy options for this patient?

1. Salvage chemotherapy followed by autologous stem cell transplant for consolidation
2. Debulking surgery to relieve impending bowel obstruction, followed by systemic therapy
3. Participation in a clinical study

Indeed, any of the above options could be considered, depending on the patient's comorbidity and preference. The authors would recommend participation in a clinical trial. In fact, the patient had the large cecal mass removed, and enrolled in a phase II clinical study that combines metronomic therapy of PEPC (prednisone, etoposide, procarbazine, and cyclophosphamide) with thalidomide and rituximab. He achieved a complete response, and has been in remission for 4 years, enjoying excellent quality of life.

Metronomic chemotherapy refers to the administration of low doses of medications on a frequent or continuous schedule without extended drug-free breaks. The main targets of metronomic therapy are the endothelial cells of the growing tumor vasculature.[37] An effective, convenient, and well-tolerated therapy in relapsed MCL that has been used by our group is the PEPC (C3) regimen.[38] PEPC consists of low-dose prednisone (20 mg), etoposide (50 mg), procarbazine (Matulane, 50 mg), and cyclophosphamide (50 mg) administered orally, with dosing frequency titrated to hematologic parameters (ie, absolute neutrophil count > 1,000/µL). In 22 patients with...
relapsed MCL, an ORR of 82% and a CR of 46% were observed with this regimen.
We have further combined the PEPC regimen with two agents that are active against MCL—rituximab and thalidomide[39]—to comprise the RT-PEPC regimen, in order to further improve the therapeutic index of metronomic therapy for relapsed/refractory MCL in an ongoing study.[40]

Other Novel Agents

• **Cyclin-Dependent Kinase Inhibitors**—The overexpression of cyclin D1 in mantle-cell lymphoma makes cell-cycle inhibition an attractive therapeutic target. Flavopiridol, a synthetic N-methylpiperidinyl, chlorophenyl flavone compound, can induce cell-cycle arrest by direct inhibition of CDKs. Modest activity was observed for single-agent flavopiridol in a phase II study, which demonstrated an 11% PR rate, 71% stable disease rate, and a median duration of response of 3.3 months.[41] Other doses, schedules, and combinations of flavopiridol are under active investigation by several groups.

A pilot study of PD 0332991, a specific and potent CDK4/6 inhibitor, also showed modest activity as a single agent in relapsed MCL (50% stable disease in 16 patients),[42] while clearly demonstrating inhibitory effects on cell-cycle pathways in translational assays. Additional studies of other CDKs with rational dosing schedules and in combination with agents with potentially synergistic activities are ongoing.

• **Anti-VEGF Agents**—Stopeck and the Southwest Oncology Group (SWOG) reported prolonged stabilization of disease in a significant subset (25%) of patients with relapsed aggressive NHL subtypes (including 15 patients with relapsed MCL) treated with single-agent bevacizumab (Avastin) at 10 mg/kg every 2 weeks on the SWOG S0108 study.[43] Combinations with chemoimmunotherapy such as R-CHOP and other antiangiogenic compounds are in various stages of clinical development.

**Recommendations**

- Management of relapsed disease requires an individualized approach.
- Promising regimens include bendamustine/rituximab combinations, bortezomib, lenalidomide, temsirolimus, and metronomic therapy.
- Patients should be encouraged to participate in clinical trials, where available.
- For rapidly progressive disease, a chemotherapy-based approach is appropriate. Once a response is achieved, stem cell transplant options may be considered.
- Allogeneic approaches seem to have greater potential than autologous options in the relapsed setting.
- For elderly patients or those with comorbidities, less aggressive approaches are more appropriate.

MCL is recognized as one of the most challenging forms of lymphoma, with emergence of resistance to chemotherapy and a relatively rapid clinical progression in the majority of cases. Traditional CHOP-based chemotherapy affords moderate response rates, but relapse is expected within 1 to 3 years. Addition of the monoclonal anti-CD20 antibody rituximab improves response rates; however, the benefit cannot clearly be translated into a progression-free or overall survival advantage. More intensive regimens such as hyper-CVAD are largely prohibitive for many patients because of treatment-related toxicities, although in selected patients, rates of complete response and time to progression appear superior to those achieved with other regimens. Whether this regimen and/or autologous stem cell transplant improve overall survival remains debatable. For most MCL patients, recurrent/resistant disease is ultimately expected, and further strategies are needed.

Management of relapsed disease is a challenging task that requires a thoughtful and individualized approach. The good news is that we are providing our MCL patients with improved therapeutic and supportive care regimens, which will likely translate into better overall survival. Importantly, we now have a growing list of biologic agents that target tumor cells and the tumor microenvironment in various stages of clinical development and maturity. Rational application of these compounds, either
alone or in combination, has brought about durable disease control with minimal toxicities in selected MCL patients. Particularly promising regimens include the bendamustine/rituximab combination, bortezomib, lenalidomide, temsirolimus, and schedules based on metronomic therapy. Limitations are the lack of clear evidence demonstrating relative survival advantages of various treatments, and the lack of routinely available clinicopathologic biomarkers to guide selection of a particular regimen.

In our practice, we have adapted an individualized treatment strategy by placing great emphasis on clinical trial participation. Without an available suitable clinical study, treatment can be chosen based on the clinical setting. For patients with extensive, rapidly progressive disease, a chemotherapy-based approach is appropriate in order to achieve a rapid response. After response is achieved, depending on previous treatments, expectations regarding response durability, and comorbid illnesses, stem cell transplant options may be considered. Generally speaking, allogeneic approaches seem to have greater potential than autologous options in the relapsed setting. In our experience, for many patients who are elderly or have comorbidities, less aggressive approaches are more appropriate in relapse. These patients typically cycle through the array of lower-intensity options, including metronomic approaches and novel biologic agents, with the choice in part based on the goal of achieving meaningful disease control and preservation of quality of life. While these clinical situations always require time and thoughtful consideration, there is reason for optimism that the availability of new approaches will further improve outcomes for MCL patients in the coming years.

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