Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology November 2013

Unmet Needs in the Treatment of Mantle Cell Lymphoma

Moderator

Steven T. Rosen, MD
Director, Robert H. Lurie Comprehensive Cancer Center
Genevieve E. Teuton Professor of Medicine
Professor in Medicine—Hematology/Oncology
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Discussants

Brian K. Link, MD
Professor
University of Iowa Hospitals & Clinics
Iowa City, Iowa

Nathan H. Fowler, MD
Co-Director of Clinical and Translational Research
Lead, Phase I and Indolent Research Groups
Department of Lymphoma/Myeloma
MD Anderson Cancer Center
Houston, Texas

Abstract: Mantle cell lymphoma is one of the most challenging hematologic malignancies, owing to an aggressive disease course, a high rate of relapse, and lack of standard of care. In the United States, mantle cell lymphoma accounts for approximately 6% of all newly diagnosed cases of non-Hodgkin lymphoma. Because most patients are initially diagnosed with advanced-stage disease, they are often symptomatic at presentation. Common features include widespread lymphadenopathy and splenomegaly, as well as bone marrow infiltration. Leukemic involvement is found in 20% to 30% of patients. The disease course can be highly variable. Some patients may have very aggressive disease, whereas others may have a much more indolent course. The optimal frontline therapy remains undefined. Strategies include chemotherapy, immunotherapy, radioimmunotherapy, stem cell transplantation, and novel biologic agents. Although mantle cell lymphoma often responds well to frontline chemotherapy, the responses are not durable and often of relatively short duration. Effective treatment options in the frontline setting have included the addition of rituximab to bendamustine. Once mantle cell lymphoma has entered the relapsed/refractory stage, it becomes more difficult to treat. Bortezomib and lenalidomide are approved for treatment of relapsed/refractory mantle cell lymphoma. The novel Bruton's tyrosine kinase inhibitor ibrutinib appears to be highly active in relapsed/refractory mantle cell lymphoma. Other agents in clinical trials include cladribine, idelalisib, and IPI-145.

Supported through funding from Pharmacyclics Inc.

Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

Table of Contents

Unmet Needs in Mantle Cell Lymphoma: Introduction

Steven T. Rosen, MD

Mantle cell lymphoma (MCL) is an aggressive B-cell subtype of non-Hodgkin lymphoma (NHL) that typically affects adults who are middle-aged or older. Generally, MCL arises from naive, pre–germinal center lymphocytes. MCL characteristically exhibits small-to-medium–sized tumor cells that can infiltrate the lymph nodes, spleen, bone marrow, blood, and gastrointestinal system (Figure 1). Although new treatment strategies are on the horizon, MCL remains one of the most challenging hematologic malignancies, owing to an aggressive disease course, a high rate of relapse, and lack of standard of care.

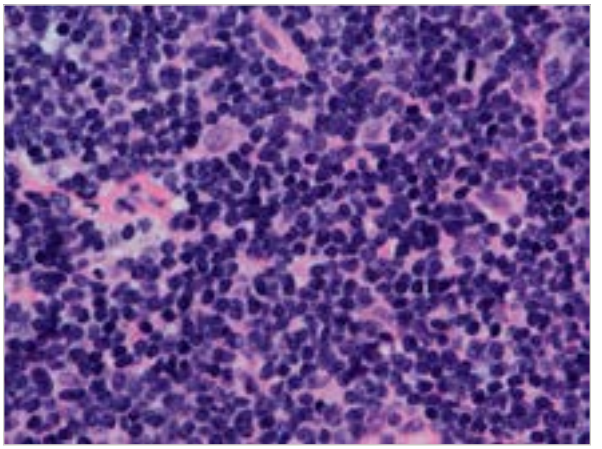


Figure 1. This high-power view of nodular mantle cell lymphoma shows irregular nuclear contours of medium-sized lymphoma cells and the presence of a pink histiocyte. Image from Gabriel Caponetti, MD.

Epidemiology

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

The SEER registry analysis identified other demographic characteristics of MCL.[4] Men are disproportionately affected, with an incidence rate that was more than doubled compared with women (0.84 cases per 100,000 vs 0.34 cases per 100,000, respectively); the relative risk of MCL in men vs women was 2.48 (95% CI, 2.28-2.70). The overall median age at diagnosis was 68 years; this age was 67 years in men and 70 years in women. Risk of MCL was higher in whites (0.61 cases per 100,000 person-years) than African Americans (0.32 cases per 100,000 person-years). The relative risk was 2.25 (95% CI, 1.89-2.71) in whites vs 1.17 in other ethnicities (95% CI, 0.90-1.52). Approximately three-quarters of patients were diagnosed with later stage disease (Ann Arbor stage III or IV [Table 1]).

Histologic, Immunologic, and Molecular Characteristics

Three patterns of tumor infiltration are characteristic of MCL: diffuse replacement of the entire lymph node, infiltration into the expanded mantle zone, and vague nodular patterns. The MCL tumor cells typically appear as a monomorphic population of small-to-medium–sized cells that resemble centrocytes, with scant cytoplasm and cleaved, slightly irregular nuclei.[5,6] The nuclei have condensed chromatin and no nucleoli. Often, prominent vascular hyalinization is present, as are scattered epithelioid histiocytes.

Several cytologic subtypes of MCL were identified in a pathologic study of 304 MCL patients.[5] The classical subtype was present in 87.5% of cases. Less frequent subtypes included small cell (3.6%), pleomorphic (5.9%), and blastic (2.6%). Notably, the small cell variant may resemble small lymphocytic leukemia, the pleomorphic

Table 1. Modified Ann Arbor Staging of Mantle Cell Lymphoma*

Stage I	Involvement of single lymph node region or localized extranodal site†
Stage II	Involvement of 2 or more lymph node regions or localized extranodal sites,† or both, on the same side of the diaphragm
Stage III	Involvement of lymph node regions or localized extranodal sites,† or both, on both sides of the diaphragm
Stage IV	Diffuse or disseminated involvement of 1 or more extralymphatic organs, with or without associated lymph node involvement. Involvement of liver or bone marrow is considered stage IV

*Subsets A and B are designated by the absence (A) or presence (B) of systemic symptoms (night sweats, weight loss of at least 10% of body weight, or unexplained fever).

†Designated by the suffix E (eg, stage IIE).

Data from McKay P et al. *Br J Haematol*. 2012;159(4):405-426.[6]

variant may resemble diffuse large B-cell lymphoma, and the blastic variant may resemble lymphoblastic leukemia. Additionally, 2 new subtypes were identified: 1 containing a mixture of cells from the classical and pleomorphic subtypes (1.6%), and 1 containing cells that are transitioning between the classical and pleomorphic subtypes (1.6%).

The highly proliferative, blastic variant may be suspected based on findings from positron emission tomography with computed tomography (PET-CT).[7] The blastic variant of MCL can also be identified by expression of histone deacetylase (HDAC) 11, which has a 15-fold to 20-fold higher expression in this variant.[8,9]

MCL is readily identifiable, owing to characteristic histologic, immunologic, and molecular phenotypes (Table 2). The immunohistochemistry profile of MCL typically consists of CD5-positive, CD20-positive, CD43-positive, and cyclin D1–positive cells. CD10 and CD23 may be positive or negative. However, this profile is not necessary for a diagnosis of MCL. Indeed, MCL cases with aberrant immunophenotype profiles have been described. For example, CD5-negativity may be present in 5% to 10% of MCL cases.[10-13]

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

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

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

Clinical Presentation and Disease Course

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

Table 2. The Immunophenotype of Mantle Cell Lymphoma

By Immunohistochemistry						
CD20	CD5	CD10	CD23	Cyclin D1	BCL6	BCL2
+	+	–	–	+	–	+
By Flow Cytometry						
CD19	CD20	CD5	CD10	FMC7	CD23	Surface Ig
+	+	+	–	+	–	+(bright)

Ig, immunoglobulin.

Data from McKay P et al. *Br J Haematol*. 2012;159(4):405-426.[6]

central nervous system involvement was 26% (95% CI, 10%-42%), and the median time from diagnosis to the development of neurologic symptoms was 25 months.[28]

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

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

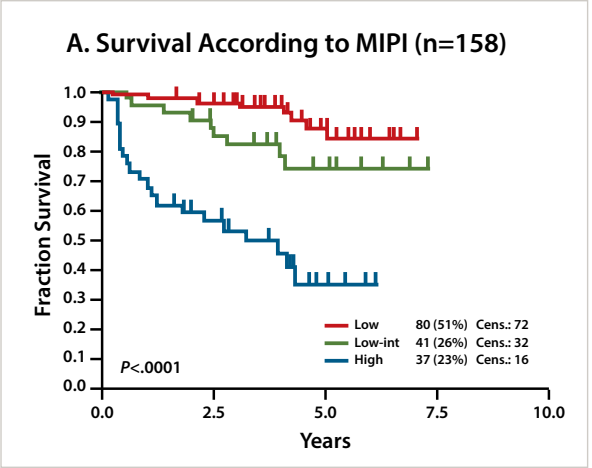
A separate subset of patients, representing between 15% and 30% of MCL cases, has a more indolent course and an even longer median survival.[31,32] These patients typically have an indolent presentation and no acute symptoms. Because they have no immediate need for therapy, treatment can be delayed without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

Several tumor-specific and patient-specific factors are known to have a significant effect on prognosis in MCL. Proliferative activity, as assessed by the Ki67 proliferation index, is the most important of these factors in routine clinical practice. A high proliferation rate is associated with a shorter overall survival, as was observed in a study of 304 MCL patients.[5] Median overall survival steadily decreased from 42 months in patients with a Ki67 proliferation index of less than 10%, to 30 months in patients with an index of 11% to 40%, to as low as 15 months in patients with an index of more than 40% (*P*<.0001). However, the Ki67 proliferation index is subject to interobserver variability, and according to the NCCN guidelines, it should not be used to guide treatment decisions.[14]

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

The immunoglobulin heavy chain (IgHV) gene can be mutated or unmutated in MCL. In contrast to CLL, the prognostic role of this phenotype remains undefined in MCL.

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



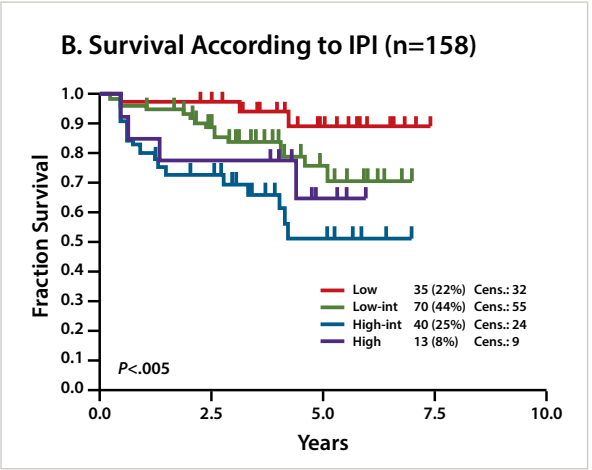


Figure 2. Among patients from the Nordic MCL2 trial, the MIPI was found to predict survival following first-line treatment (**A**) significantly better than the traditional IPI (**B**). IPI, International Prognostic Index; MCL, Mantle Cell Lymphoma International Prognostic Index. Adapted from Geisler CH et al. *Blood*. 2010;115(8):1530-1533.[36]

Acknowledgment

Dr Rosen is a consultant for Teva Pharmaceuticals, Cell Therapeutics, Genentech, Genzyme, Merck, Seattle Genetics, Therakos, and Celgene. He has received grants for clinical trials and research from Amgen, Berlex Laboratories, Biogen IDEC, Cytogen Corp, Millennium & ILEX Partners, Pharmacyclics, and Wyeth-Ayerst Research. He is on the speakers bureaus of Cephalon and Teva. He is on the advisory boards of Abbott Laboratories, Celgene, NanoSphere, MedNet Solutions, and Genentech.

References

1. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenberger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood*. 2006;107(1):265-276.
2. Swerdlow SH, Campo E, Seto M, Müller-Hermelink HK. Mantle cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: International Agency for Research on Cancer; 2008:229-232.
3. Smedby KE, Hjalgrim H. Epidemiology and etiology of mantle cell lymphoma and other non-Hodgkin lymphoma subtypes. *Semin Cancer Biol*. 2011;21(5):293-298.
4. Zhou Y, Wang H, Fang W, et al. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. *Cancer*. 2008;113(4):791-798.
5. Tiemann M, Schrader C, Klapper W, et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. *Br J Haematol*. 2005;131(1):29-38.
6. McKay P, Leach M, Jackson R, Cook G, Rule S. Guidelines for the investigation and management of mantle cell lymphoma. *Br J Haematol*. 2012;159(4):405-426.
7. Brepoels L, Stroobants S, De Wever W, et al. Positron emission tomography in mantle cell lymphoma. *Leuk Lymphoma*. 2008;49(9):1693-16701.
8. Shah BD, Villagra A, Merino O, et al. HDAC profiling in mantle cell lymphoma unveils HDAC11 and HDAC10 as potential molecular targets [ASH abstract 2505]. *Blood*. 2010;116(suppl 21)
9. Sahakian E, Shah BD, Powers J, et al. The opposing role of histone deacetylase 10 (HDAC10) and HDAC11 in proliferation/survival of mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) [ASH abstract 1363]. *Blood*. 2011;118(suppl 21).
10. Wlodarska I, Pittaluga S, Hagemeijer A, De Wolf-Peeters C, Van Den Berghe H. Secondary chromosome changes in mantle cell lymphoma. *Haematologica*. 1999;84(7):594-599.
11. Zanetto U, Dong H, Huang Y, et al. Mantle cell lymphoma with aberrant expression of CD10. *Histopathology*. 2008;53(1):20-29.
12. Espinet B, Salaverria I, Beà S, et al. Incidence and prognostic impact of secondary cytogenetic aberrations in a series of 145 patients with mantle cell lymphoma. *Genes Chromosomes Cancer*. 2010;49(5):439-451.
13. Gualco G, Weiss LM, Harrington WJ Jr, Bacchi CE. BCL6, MUM1, and CD10 expression in mantle cell lymphoma. *Appl Immunohistochem Mol Morphol*. 2010;18(2):103-108.
14. Non-Hodgkin's lymphomas. Version 2.2013. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf. Accessed October 17, 2013.
15. Fu K, Weisenburger DD, Greiner TC, et al. Cyclin D1-negative mantle cell lymphoma: a clinicopathologic study based on gene expression profiling. *Blood*. 2005;106(13):4315-4321.
16. Herens C, Lambert F, Quintanilla-Martinez L, Bisig B, Deusings C, de Leval L. Cyclin D1-negative mantle cell lymphoma with cryptic t(12;14)(p13;q32) and cyclin D2 overexpression. *Blood*. 2008;111(3):1745-1746.
17. Quintanilla-Martinez L, Slotta-Huspenina J, Koch I, et al. Differential diagnosis of cyclin D2+ mantle cell lymphoma based on fluorescence in situ hybridization and quantitative real-time-PCR. *Haematologica*. 2009;94(11):1595-1598.
18. Ek S, Dictor M, Jerkeman M, Jirström K, Borrebaeck CA. Nuclear expression of the non B-cell lineage Sox11 transcription factor identifies mantle cell lymphoma. *Blood*. 2008;111(2):800-805.
19. Dictor M, Ek S, Sundberg M, et al. Strong lymphoid nuclear expression of SOX11 transcription factor defines lymphoblastic neoplasms, mantle cell lymphoma and Burkitt's lymphoma. *Haematologica*. 2009;94(11):1563-1568.
20. Mozos A, Royo C, Hartmann E, et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. *Haematologica*. 2009;94(11):1555-1562.
21. Wang X, Asplund AC, Porwit A, et al. The subcellular Sox11 distribution pattern identifies subsets of mantle cell lymphoma: correlation to overall survival. *Br J Haematol*. 2008;143(2):248-252.
22. Xu W, Li JY. SOX11 expression in mantle cell lymphoma. *Leuk Lymphoma*. 2010;51(11):1962-1967.
23. Nygren L, Baumgartner Wennerholm S, Klimkowska M, Christensson B, Kimby E, Sander B. Prognostic role of SOX11 in a population-based cohort of mantle cell lymphoma. *Blood*. 2012;119(18):4215-4223.
24. Pérez-Galán P, Dreyling M, Wiestner A. Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. *Blood*. 2011;117(1):26-38.
25. Ghielmini M, Zucca E. How I treat mantle cell lymphoma. *Blood*. 2009;114(8):1469-1476.
26. Dreyling M, Hiddemann W; European MCL Network. Current treatment standards and emerging strategies in mantle cell lymphoma. *Hematology (Am Soc Hematol Educ Program)*. 2009:542-551.
27. Jares P, Campo E. Advances in the understanding of mantle cell lymphoma. *Br J Haematol*. 2008;142(2):149-165.
28. Ferrer A, Bosch F, Villamor N, et al. Central nervous system involvement in mantle cell lymphoma. *Ann Oncol*. 2008;19(1):135-141.

29. Mantle cell lymphoma facts. July 2012. Leukemia & Lymphoma Society. http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/lymphoma/pdf/mantlecelllymphoma.pdf. Accessed September 9, 2013.
30. Bernard M, Gressin R, Lefrère F, et al. Blastic variant of mantle cell lymphoma: a rare but highly aggressive subtype. *Leukemia*. 2001;15(11):1785-1791.
31. Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. *J Clin Oncol*. 2009;27:1209-1213.
32. Martin P, Leonard J. Is there a role for "watch and wait" in patients with mantle cell lymphoma? *Semin Hematol*. 2011;48(3):189-193.
33. Fernàndez V, Salamero O, Espinet B, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. *Cancer Res*. 2010;70(4):1408-1418.
34. Hoster E, Dreyling M, Klapper W, et al; German Low Grade Lymphoma Study Group (GLSG); European Mantle Cell Lymphoma Network. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood*. 2008;111(2):558-565.
35. Hoster E. Prognostic relevance of clinical risk factors in mantle cell lymphoma. *Semin Hematol*. 2011;48(3):185-188.
36. Geisler CH, Kolstad A, Laurell A, et al. The Mantle Cell Lymphoma International Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive first-line immunochemotherapy and autologous stem cell transplantation (ASCT). *Blood*. 2010;115(8):1530-1533.

Current Treatment Approaches to Mantle Cell Lymphoma

Brian K. Link, MD

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

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

The second major factor to consider when deciding on a course of therapy is the goals of treatment. A cure is typically thought to be elusive in MCL. Thus, reasonable goals of treatment for MCL patients may include long-term survival, symptom control (if needed), or durable event-free survival. For younger, fitter patients who are potential candidates to proceed to autologous stem cell transplantation (ASCT), the goal of chemotherapy induction should be to obtain as deep a remission as possible.[1]

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

Once these factors have been considered, the next step in the decision plan is to ascertain which therapeutic options are realistically available and appropriate for the individual patient (Figure 3). For initial treatment, the 2 primary areas of focus when determining the suitability of a particular regimen are the intensity of the induction therapy and the choice of postinduction management. Initially, the knowledge that informs these choices was limited because it was based primarily on data from retrospective series. However, more recent data from prospective and/or randomized phase 2 or 3 clinical trials has allowed greater confidence in the choice of therapy.[2-6]

Frontline Therapy

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

Few patients present with localized stage I or II MCL, and data regarding treatment of these patients are limited. In one retrospective study, progression-free survival was increased in patients who received radiotherapy (with or without chemotherapy) as part of their frontline treatment regimen.[7]

In certain patients, it may be appropriate to defer therapy and instead rely on an initial observational approach, as discussed in the previous article. In a small retrospective study that evaluated the outcomes of MCL patients who deferred initial therapy, patients who underwent observation exhibited a statistically superior median survival compared with patients who underwent immediate treatment (not reached vs 64 months; P=.004).[8] However, some patients may be hesitant to postpone therapy. For these patients, single-agent rituximab may be a good treatment choice, as suggested by 2 studies in which it had moderate activity. A study from the Swiss Group for Clinical Cancer Research found that single-agent rituximab was associated with a clinical response rate of 27%

Table 3. Phase 3 Trials in the Initial Treatment of Mantle Cell Lymphoma

Compared Arms		N	Primary Endpoint	Best Arm	Secondary Endpoint	Best Arm	Reference
CVP	CHOP	63	CR	No difference	OS	No difference	Meusers 1989[43]
CHOP→ ASCT	CHOP→IFN	122	PFS	ASCT	OS	No difference	Lenz 2004[44]
CHOP	R-CHOP	122	OR and CR	R-CHOP	PFS	No difference	Lenz 2005[13]
CHOP	MCP	86	OR	No difference	PFS and OS	No difference	Nickenig 2006[45]
R-CHOP	R-FC	485	CR	No difference	PFS and OS	R-CHOP	Kluin-Nelemans 2012[3]
R-CHOP	R-B	94	PFS	R-B	CR	R-B	Rummel 2013[2]
R-CHOP →ASCT	R-CHOP→ R-DHAP→ASCT	497	TTF	R-CHOP→ R-DHAP→ASCT	OS	R-CHOP→ R-DHAP→ ASCT	Hermine 2012[46]

ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; CR, complete response unconfirmed; CVP, cyclophosphamide, vincristine, and prednisone; IFN, interferon; PFS, progression-free survival; R-B, rituximab, bendamustine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin.

in newly diagnosed MCL patients.[9] A European phase 2 trial demonstrated a 38% response rate with single-agent rituximab in newly diagnosed MCL.[10]

Overall, rituximab seems to have less robust activity as a single agent in MCL as compared with other B-cell lymphomas such as follicular lymphoma and diffuse large B-cell lymphoma.[1] However, it has a significant role when added to other chemotherapy drugs. A systematic review and meta-analysis of chemotherapy alone vs rituximab plus chemotherapy in MCL concluded that the latter may result in a superior overall survival (hazard ratio, 0.60; 95% CI, 0.37-0.98).[11] However, this conclusion was limited by the availability of only a small number of randomized clinical trials for the analysis.

By itself, the combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is associated with only minimal activity in MCL patients. The addition of rituximab greatly improves response. In a phase 2 study of 40 patients, the combination of rituximab plus CHOP (R-CHOP) was associated with high response rates: 48% of patients achieved a complete response, and 48% achieved a partial response.[12] However, owing to a high rate of relapse, this response rate was not predictive of progression-free survival, despite a lack of PCR-detectable disease in a number of patients.

Similarly, in a prospective, randomized phase 3 trial from the German Low Grade Lymphoma Study Group (GLSG), the addition of rituximab to CHOP significantly improved rates of overall response (75% vs 94%; *P*=.0054), complete response (7% vs 34%; *P*=.00024), and median time to treatment failure (14 vs 21 months; *P*=.0131) compared with CHOP alone.[13] However, these benefits did not translate into an improvement in either progression-free survival or overall survival.

Another effective treatment option in the frontline setting is the addition of rituximab to bendamustine. In a recently updated, prospective, randomized, multicenter, open-label, noninferiority trial from the German Study Group of Indolent Lymphomas (StiL), the combination of rituximab plus bendamustine was compared with R-CHOP as frontline therapy in patients with indolent lymphomas or MCL (comprising approximately 18% of patients).[2,14] After a median follow-up of 45 months, the median progression-free survival was significantly increased among all patients treated with rituximab plus bendamustine compared with R-CHOP (69.5 vs 31.2 months; hazard ratio, 0.58; 95% CI, 0.44-0.74; *P*<.0001). This benefit in progression-free survival was also evident among MCL patients alone (35.4 vs 22.1 months; hazard ratio, 0.49; 95% CI, 0.28-0.79; *P*=.0044; Figure 4). The overall response rate was similar between the treatment groups, but the rates of complete response were higher with rituximab plus bendamustine (40%) compared with R-CHOP (31%). Interestingly, rituximab plus bendamustine seemed to be associated with superior progression-free survival independent of the quality of response. The median progression-free survival for patients who achieved a complete response was not reached for those treated with rituximab plus bendamustine and 54 months for those treated with R-CHOP (*P*=.02). Similarly, for patients who achieved a partial response, the median progression-free survival was 57 months for patients treated with rituximab plus bendamustine and 31 months for patients treated with R-CHOP (*P*=.0002). Importantly, patients were better able to tolerate the rituximab plus bendamustine

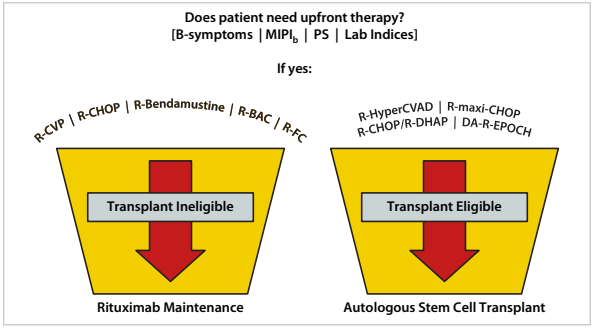


Figure 3. The mantle cell lymphoma "funnels" treatment paradigm. DA-R-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab; MIPI, Mantle Cell Lymphoma International Prognostic Index; PS, performance status, R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; R-FC, rituximab, fludarabine, cyclophosphamide. Courtesy of J. Deutsch, MD.

combination, with lower frequencies of alopecia, hematologic toxicities, infections, peripheral neuropathy, and stomatitis. The addition of cytarabine to bendamustine and rituximab resulted in very high response rates in a recent phase 2 Italian study of 40 elderly patients, and this regimen deserves further study.[5] Cladribine has been evaluated both as a single agent and in combination with rituximab in the frontline setting.[15] In 26 previously untreated MCL patients, the overall response rate to single-agent cladribine was 81%, with 42% of patients achieving a complete response. The median progression-free survival was 13.6 months, and the 2-year overall survival rate was 81%. Among 29 previously untreated MCL patients who received a combination of cladribine and rituximab, the overall response rate was 66%, and the complete response rate was 52%. More recently, a retrospective chart review was published that attributed an overall response rate of 87% and a complete response rate of 61% to the combination of cladribine plus rituximab.[16] Notably, the majority of responding patients had also received rituximab as maintenance therapy.

In randomized trials, fludarabine inductions perform less well, and there may be a role for cytarabine. Some of the alternatives to anthracycline-based immunochemotherapy regimens in elderly patients should be considered with caution, as a recent study demonstrated that rituximab plus fludarabine and cyclophosphamide (R-FC) was associated with worse outcomes compared with R-CHOP in elderly MCL patients.[3,17] In this double-randomized, open-label, multicenter trial, R-FC induction had a complete response rate that was comparable to that of R-CHOP (40% vs 34%; *P*=.10). However, disease progression occurred more frequently in patients randomized to R-FC compared with R-CHOP (14% vs 5%), and the 4-year overall survival rate was significantly lower with R-FC compared with R-CHOP (47% vs 62%; *P*=.005).

Because of the relatively poor prognosis and low survival rates associated with MCL, many physicians and patients have opted for more aggressive frontline treatment strategies. For example, 3-year overall survival rates exceeding 80% have been reported in small studies evaluating rituximab plus a regimen of cyclophosphamide, vincristine, doxorubicin, and dexamethasone, with alternating high-dose methotrexate and cytarabine (hyper-CVAD), or with ASCT.[18] Long-term (10-year) follow-up of patients treated with this dose-intense R–hyper-CVAD regimen showed that the median overall survival had not been reached, and the median time-to-treatment failure was 4.6 years.[19] However, a retrospective analysis of 181 MCL patients found that more intensive regimens did not significantly improve overall survival as compared with R-CHOP or rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP).[20] It should be noted that both the 3-year overall survival rate (86%) and median overall survival (7.1 years) both exceeded what is typically reported following frontline treatment of MCL patients.

There are additional data suggesting that dose-intensive regimens may not have a significant benefit in MCL. The recent phase 2 multicenter Southwest Oncology Group (SWOG) 0213 study demonstrated that the combination of rituximab plus hyper-CVAD was associated with a median progression-free survival of 4.8 years and a median overall survival of 6.8 years. Although the response rates associated with this treatment were high, they proved not to be durable.[4,21] This regimen was associated with a continuous rate of relapse over time, coupled with marked hematologic toxicity.[4,21]

More recently, an analysis from the NCCN NHL database was performed to ascertain the benefit of more aggressive frontline regimens in younger (<65 years) MCL patients.[22] Data were evaluated from patients treated with a number of regimens, including rituximab fractionated CVAD (RHCVAD), R-CHOP plus high-dose therapy with autologous stem cell rescue, RHCVAD plus high-dose therapy with autologous stem cell rescue, and R-CHOP. There was no significant difference in progression-free survival among the aggressive regimens (*P*>.57). Importantly, however, progression-free survival was significantly increased with any one of the aggressive regimens compared with treatment with R-CHOP (*P*<.004; Figure 5). Cytarabine has again attracted interest as a treatment for younger MCL patients based on a phase 2 study of R-CHOP followed by rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) and consolidation with ASCT, in which R-DHAP led to a complete response rate of 57% and a median event-free survival of 83 months.[6]

Thus, taken together, these data suggest that dose-intensive frontline therapy may be an appropriate choice

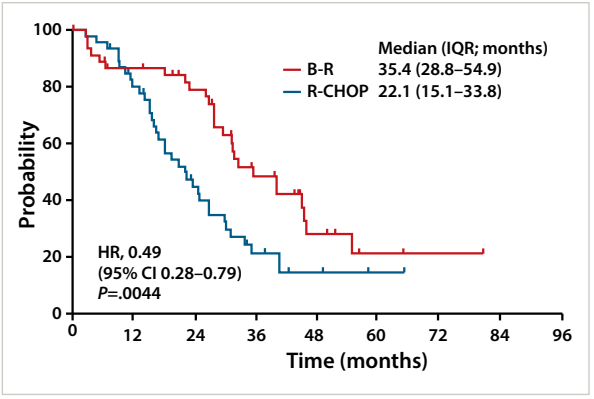


Figure 4. In a trial from the German Study Group of Indolent Lymphomas, rituximab plus bendamustine improved median progression-free survival over R-CHOP among the cohort with mantle cell lymphoma. B-R, bendamustine, rituximab; HR, hazard ratio; IQR, interquartile range; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. Adapted from Rummel MJ et al. *Lancet*. 2013;381(9873):1203-1210.[2]

in certain MCL patients.[23] In cases where the MCL patient is younger and presents with intermediate- or high-risk MCL, aggressive therapy may be considered. For older MCL patients with intermediate- or high-risk disease, a regimen consisting of rituximab added to combination chemotherapy (such as R-CHOP, R-CVP, or rituximab plus bendamustine) may be more appropriate. Cytarabine is currently a drug of active study in both scenarios.

Postremission Therapy

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

Role of Stem Cell Transplant

Patients who are fit and achieve a very good remission in response to initial therapy should be considered for consolidation with high-dose chemotherapy and ASCT. In prospective studies, this approach improved rates of event-free survival and, in some cases, overall survival as compared with historical controls.[24] Disease status at the time of transplantation appears to be the most significant factor affecting survival following HDT/ASCR. Patients who remain in their first remission (either a complete response or a partial response) at the time of transplant achieve the best survival outcomes as compared with patients who have relapsed or refractory disease at the time of transplant.[25,26] The only randomized study in this setting compared consolidation with myeloablative radiochemotherapy followed by ASCT vs maintenance therapy with interferon-α (both after achieving a complete or partial response with a CHOP-like induction therapy).[27] There was a significantly prolonged median progression-free survival in the ASCT arm (39 vs 17 months; *P*=.0108).[27] Although there was a trend toward an improved 3-year overall survival rate with ASCT (83% vs 77%), this difference did not achieve statistical significance (*P*=.18), and longer follow-up is needed.

In the nonrandomized phase 2 multicenter Nordic Lymphoma Group MCL2 trial, 160 previously untreated MCL patients (<66 years) underwent dose-intensified induction therapy, alternating between R-maxi-CHOP and rituximab plus high-dose cytarabine.[28] Responding patients subsequently received high-dose chemotherapy with either carmustine, etoposide, cytarabine, melphalan (BEAM) or high-dose carmustine, etoposide, Ara-C and cyclophosphamide (BEAC), supported by in vivo rituximab-purged autologous stem cells. The 6-year overall and event-free survival rates following treatment were 70% and 56%, respectively, with no patient showing evidence of a relapse throughout 5 years of follow-up. However, in longer follow-up (median 6.5 years), 6 patients experienced a late relapse.[29] The overall results remain encouraging, with a median overall survival exceeding 10 years and a median event-free survival of 7.4 years.

Role of Maintenance Therapy

For the majority of MCL patients who are not candidates for an aggressive consolidation strategy, postinduction maintenance treatment with rituximab may be an effective alternative.[3] When older (≥60 years of age) MCL patients who had responded to initial induction therapy with either R-CHOP or R-FC were rerandomized to maintenance therapy with either single-agent rituximab or interferon-α (each administered until disease progression), rituximab was associated with a 45% decrease in the risk of progression or death (hazard ratio, 0.55; 95% CI, 0.36-0.87; *P*=.01). For patients who had responded to R-CHOP induction therapy, maintenance rituximab significantly improved the 4-year overall survival rate vs maintenance with interferon-α (87% vs 63%; *P*=.005). Maintenance therapy with newer agents demonstrating activity in MCL, such as lenalidomide or ibrutinib, is currently under investigation.

Management of Relapsed/Refractory Disease

Once MCL has entered the relapsed/refractory stage, it becomes even more difficult to treat and exhibits even

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

Therapy	N	Primary Endpoint	Result	Secondary Endpoint	Result	Reference
Fludarabine	6	OR	16%	Treatment failure	6 months	Tobinai 2006[47]
	15	OR	33%	CR	0%	Decaudin 1998[48]
Cladribine	24	OR	46%	PFS	5 months	Inwards 2008[15]
Rituximab	40	OR	37%	Response duration	1.2 years	Foran 2000[10]
	54	OR	28%	CR	2%	Ghielmini 2005[9]
Bortezomib	155	OR	33%	CR/CRu	8%	Fisher 2006[31]
	24	OR	29%	CR	4%	Strauss 2006[49]
	40	OR	43%	CR	12%	O'Connor 2009[33]
Lenalidomide	134	OR	28%	CR	7%	Goy 2013[38]
	15	OR	53%	CR	20%	Habermann 2009[50]
	57	OR	42%	CR	21%	Witzig 2011[51]
	26	OR	31%	PFS	3.9 months	Eve 2012[52]
Temsirolimus	34	OR	38%	CR	3%	Witzig 2005[53]
	28	OR	41%	CR	1%	Ansell 2008[54]
	108	PFS	4+ months	OR	22%	Hess 2009 (phase 3)[36]

CR, complete response; CRu, complete response, unconfirmed; OR, overall response; PFS, progression-free survival.

less sensitivity to treatment, with response rates to single agents generally less than 50% (Table 4).[30] Even with combination therapy, complete response rates seldom exceed 30%.[29] The NCCN guidelines recommend various treatment options for relapsed/refractory patients, and 2 agents have gained approval from the US Food and Drug Administration (FDA) in this setting.

The reversible proteasome inhibitor bortezomib received FDA approval in December 2006 for treatment of MCL patients who have relapsed after at least 1 prior therapy. This approval was based primarily on the pivotal phase 2 PINNACLE (Multicenter Phase II Study of Bortezomib in Patients With Relapsed or Refractory Mantle Cell Lymphoma) trial, in which single-agent bortezomib was administered to 155 relapsed or refractory MCL patients who had received a median of 1 prior therapy (range, 1-3).[31] The response rate was 33%, with 8% of patients achieving a complete response or unconfirmed complete response. Responses were relatively durable, with a median duration of response of 9.2 months and a median time to progression of 6.2 months. At the initial median follow-up of 13.4 months, a median overall survival had not been reached. In an updated analysis with a longer follow-up (median, 26.4 months), the median overall survival was 23.5 months.[32] Among patients who had initially responded to single-agent bortezomib, the median time-to-progression was 12.4 months, and the median overall survival was 35.4 months. The 1-year overall survival rate was also improved among responding patients (91%) as compared with the overall treated population (69%). Notably, bortezomib appeared to be active even in patients who had relapsed following high-intensity treatment. A separately reported phase 2 trial provided further evidence of bortezomib's activity in this setting, with even heavily pretreated MCL patients exhibiting a 47% overall response rate.[33]

Subsequent studies have evaluated bortezomib in combination with rituximab for the treatment of relapsed/refractory MCL, with promising results. In one such phase 2 trial, the overall response rate among 14 MCL patients was 29%.[34] In a second study, when bortezomib was combined with rituximab and dexamethasone, the overall response rate among 16 heavily pretreated MCL patients was 81.3%, including a 43.8% rate of complete response.[35] The median progression-free survival was 12.1 months, and the median overall survival was 38.6 months, although neither survival endpoint had been reached in patients who had achieved a complete response with this combination.

The class of drugs known to inhibit the mammalian target of rapamycin (mTOR) is also active in relapsed MCL. Temsirolimus is approved for relapsed and/or refractory MCL in the European Union and several other countries outside of the United States on the basis of a randomized phase 3 trial demonstrating a benefit in progression-free survival (4.8 months) compared with investigator choice (1.9 months).[36] The orally available mTOR inhibitor everolimus demonstrated similar activity in a phase 2 trial, with an overall response rate of 20% and a median progression-free survival of 5.5 months.[37]

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

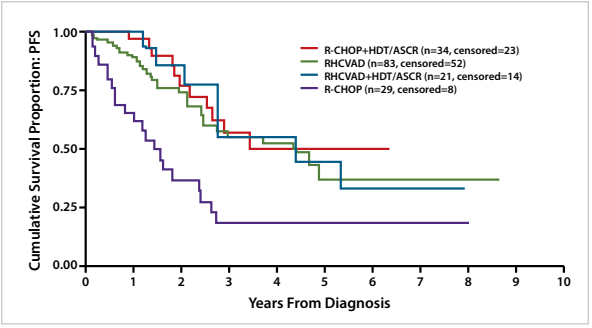


Figure 5. In an analysis from the National Comprehensive Cancer Network Non-Hodgkin Lymphoma database of aggressive frontline regimens in younger mantle cell lymphoma patients, PFS was significantly increased with any one of the aggressive regimens compared to treatment with R-CHOP. HDT/ASCR, high-dose therapy/autologous stem cell rescue; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; RHCVAD, rituximab fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone. Adapted from LaCasce AS et al. *Blood*. 2012;119(9):2093-2099.[22]

MCL-001 EMERGE (Study to Determine the Efficacy and Safety of Lenalidomide in Patients With Mantle Cell NHL Who Have Relapsed or Progressed After Treatment With Bortezomib or Are Refractory to Bortezomib) trial, which included 134 MCL patients who had either relapsed after therapy with bortezomib or were refractory to bortezomib (or a bortezomib-based regimen).[38] These patients were heavily pretreated, with 60% having bortezomib-refractory disease. Patients had received a median of 4 prior therapies. An overall response rate of 28% was reported, with a 7.5% rate of complete response or unconfirmed complete response. Responses were rapid (median time to response, 2.2 months) and durable (median duration of response, 16.6 months; Figure 5).[39] The median progression-free survival was 4.0 months, and the median overall survival was 19.0 months.

Fludarabine-based regimens, either with or without rituximab, show promising activity in relapsed/refractory MCL patients. Among 66 MCL patients enrolled in a randomized, prospective phase 3 study, improved outcomes were observed when rituximab was combined with fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) compared with fludarabine, cyclophosphamide, and mitoxantrone alone.[40,41] These outcomes included higher overall response rates (58% vs 46%) and complete response rates (29% vs 0%). Additionally, among those patients who had responded to R-FCM induction therapy, rituximab maintenance therapy led to a higher rate of 2-year remission compared with observation alone (45% vs 9%; *P*=.049). The combination of fludarabine plus rituximab was compared against bendamustine plus rituximab in a phase 3 randomized trial from the StiL group.[42] The study included 208 patients with relapsed/refractory follicular or indolent lymphoma or MCL (approximately 20% of patients had MCL histology).[39] The overall response rate to fludarabine plus rituximab was 52.5%, and the complete response rate was 16%, both of which were significantly inferior to the rates achieved with bendamustine plus rituximab (83.5% and 38.5%, respectively). Although there was no apparent difference in overall survival between the 2 treatment arms, fludarabine plus rituximab was associated with a significantly shorter median progression-free survival compared with bendamustine plus rituximab (11 vs 30 months; *P*<.0001).

Single-agent cladribine has also been investigated in the relapsed/refractory MCL patient setting. Among 25 patients with recurrent MCL, the overall response rate was 46%, the complete response rate was 21%, and the median progression-free survival was 5 months.[15] Future studies will likely evaluate cladribine combined with rituximab for relapsed/refractory MCL patients.

Acknowledgment

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

References

1. McKay P, Leach M, Jackson R, et al. Guidelines for the investigation and management of mantle cell lymphoma. *Br J Haematol*. 2012;159(4):405-426.
2. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-1210.
3. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med*. 2012;367(6):520-531.
4. Bernstein SH, Epner E, Unger JM, et al. A phase II multicenter trial of hyper-CVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213. *Ann Oncol*. 2013;24(6):1587-1593.
5. Visco C, Finotto S, Zambello R, et al. Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation. *J Clin Oncol*. 2013;31(11):1442-1449.
6. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. *Blood*. 2013;121(1):48-53.
7. Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited-stage mantle-cell lymphoma. *Ann Oncol*. 2003;14(10):1555-1561.
8. Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. *J Clin Oncol*. 2009;27(8):1209-1213.
9. Ghielmini M, Schmitz SF, Cogliatti S, et al. Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK). *J Clin Oncol*. 2005;23(4):705-711.
10. Foran JM, Rohatiner AZ, Cunningham D, et al. European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. *J Clin Oncol*. 2000;18(2):317-324.
11. Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2007;99(9):706-714.
12. Howard OM, Gribben JG, Neuberg DS, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. *J Clin Oncol*. 2002;20(5):1288-1294.
13. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly

improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *J Clin Oncol*. 2005;23(9):1984-1992.
14. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany) [ASH abstract 405]. *Blood*. 2009;114(suppl 22).
15. Inwards DJ, Fishkin PA, Hillman DW, et al. Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. *Cancer*. 2008;113(1):108-116.
16. Spurgeon SE, Pindyck T, Okada C, et al. Cladribine plus rituximab is an effective therapy for newly diagnosed mantle cell lymphoma. *Leuk Lymphoma*. 2011;52(8):1488-1494.
17. Kluin-Nelemans JC, Hoster E, Walewski J, et al. R-CHOP versus R-FC followed by maintenance with rituximab versus interferon-alfa: outcome of the first randomized trial for elderly patients with mantle cell lymphoma [ASH abstract 439]. *Blood*. 2011;118(suppl 21).
18. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. *J Clin Oncol*. 2005;23(28):7013-7023.
19. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with rituximab-hyperCVAD alternating with rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. *Br J Haematol*. 2010;150(2):200-208.
20. Martin P, Chadburn A, Christos P, et al. Intensive treatment strategies may not provide superior outcomes in mantle cell lymphoma: overall survival exceeding 7 years with standard therapies. *Ann Oncol*. 2008;19(7):1327-1330.
21. Epner EM, Unger J, Miller T, et al. A multicenter trial of hyperCVAD + Rituxan in patients with newly diagnosed mantle cell lymphoma [ASH abstract 387]. *Blood*. 2007;110(suppl 11).
22. LaCasce AS, Vandergrift JL, Rodriguez MA, et al. Comparative outcome of initial therapy for younger patients with mantle cell lymphoma: an analysis from the NCCN NHL Database. *Blood*. 2012;119(9):2093-2099.
23. Vose JM. Mantle cell lymphoma: 2012 update on diagnosis, risk-stratification, and clinical management. *Am J Hematol*. 2012;87(6):604-609.
24. Ghielmini M, Zucca E. How I treat mantle cell lymphoma. *Blood*. 2009;114(8):1469-1476.
25. Till BG, Gooley TA, Crawford N, et al. Effect of remission status and induction chemotherapy regimen on outcome of autologous stem cell transplantation for mantle cell lymphoma. *Leuk Lymphoma*. 2008;49(6):1062-1073.
26. Vandenberghe E, Ruiz de Elvira C, Loberiza FR, et al. Outcome of autologous transplantation for mantle cell lymphoma: a study by the European Blood and Bone Marrow Transplant and Autologous Blood and Marrow Transplant Registries. *Br J Haematol*. 2003;120(5):793-800.
27. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. *Blood*. 2005;105(7):2677-2684.
28. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood*. 2008;112(7):2687-2693.
29. Geisler CH, Kolstad A, Laurell A, et al. Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur. *Br J Haematol*. 2012;158(3):355-362.
30. Non-Hodgkin's lymphomas. Version 2.2013. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf. Accessed October 17, 2013.
31. Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol*. 2006;24(30):4867-4874.
32. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. *Ann Oncol*. 2009;20(3):520-525.
33. O'Connor OA, Moskowitz C, Portlock C, et al. Patients with chemotherapy-refractory mantle cell lymphoma experience high response rates and identical progression-free survivals compared with patients with relapsed disease following treatment with single agent bortezomib: results of a multicentre phase 2 clinical trial. *Br J Haematol*. 2009;145(1):34-39.
34. Baiocchi RA, Alinari L, Lustberg ME, et al. Phase 2 trial of rituximab and bortezomib in patients with relapsed or refractory mantle cell and follicular lymphoma. *Cancer*. 2011;117(11):2442-2451.
35. Lamm W, Kaufmann H, Raderer M, et al. Bortezomib combined with rituximab and dexamethasone is an active regimen for patients with relapsed and chemotherapy-refractory mantle cell lymphoma. *Haematologica*. 2011;96(7):1008-1014.
36. Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. *J Clin Oncol*. 2009;27(23):3822-3829.
37. Renner C, Zinzani PL, Gressin R, et al. A multicenter phase II trial (SAKK 36/06) of single-agent everolimus (RAD001) in patients with relapsed or refractory mantle cell lymphoma. *Haematologica*. 2012;97(7):1085-1091.
38. Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. *J Clin Oncol*. 2013;31(29):3688-3695.
39. Williams ME, Goy A, Sinha R, et al. Lenalidomide in relapsed/refractory mantle cell lymphoma post-bortezomib: subgroup analysis of the MCL-001 study [ASCO abstract 8534]. *J Clin Oncol*. 2013;31(15 suppl).
40. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2004;104(10):3064-3071.
41. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). *Blood*. 2006;108(13):4003-4008.
42. Rummel MJ, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent, and mantle cell lymphomas—final results of the randomized phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany) [ASH abstract 856]. *Blood*. 2010;116(suppl 21).
43. Meusers P, Engelhard M, Bartels H, et al. Multicentre randomized therapeutic trial for advanced centrocytic lymphoma: anthracycline does not improve the prognosis. *Hematol Oncol*. 1989;7(5):365-380.
44. Lenz G, Dreyling M, Schiegnitz E, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). *Blood*. 2004;104:2667-2674.
45. Nickenig C, Dreyling M, Hoster E, et al. Combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) improves response rates but not survival and has lower hematologic toxicity compared with combined mitoxantrone, chlorambucil, and prednisone (MCP) in follicular and mantle cell lymphomas: results of a prospective randomized trial of the German Low-Grade Lymphoma Study Group. *Cancer.* 2006;107(5):1014-1022.
46. Hermine O, Hoster E, Walewski J, et al. Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) increases overall survival when compared to 6 courses of CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: final analysis of the MCL younger trial of the European Mantle Cell Lymphoma Network (MCL net) [ASH abstract 151]. *Blood*. 2012;119(suppl 21).
47. Tobinai K, Watanabe T, Ogura M, et al. Phase II study of oral fludarabine phosphate in relapsed indolent B-Cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2006;24(1):174-180.
48. Decaudin D, Bosq J, Tertian G, et al. Phase II trial of fludarabine monophosphate in patients with mantle-cell lymphomas. *J Clin Oncol*. 1998;16(2):579-583.
49. Strauss SJ, Maharaj L, Hoare S, et al. Bortezomib therapy in patients with relapsed or refractory lymphoma: potential correlation of in vitro sensitivity and tumor necrosis factor alpha response with clinical activity. *J Clin Oncol*. 2006;24(13):2105-2112.
50. Habermann TM, Lossos IS, Justice G, et al. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma. *Br J Haematol*. 2009;145(3):344-349.
51. Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. *Ann Oncol*. 2011;22(7):1622-1627.

52. Eve HE, Carey S, Richardson SJ, et al. Single-agent lenalidomide in relapsed/refractory mantle cell lymphoma: results from a UK phase II study suggest activity and possible gender differences. *Br J Haematol*. 2012;159(2):154-163.
53. Witzig TE, Geyer SM, Ghobrial I, et al. Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. *J Clin Oncol*. 2005;23(23):5347-5356.
54. Ansell SM, Inwards DJ, Rowland KM Jr, et al. Low-dose, single-agent temsirolimus for relapsed mantle cell lymphoma: a phase 2 trial in the North Central Cancer Treatment Group. *Cancer*. 2008;113(3):508-514.

Novel Treatment Approaches to Mantle Cell Lymphoma

Nathan H. Fowler, MD

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

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

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

Improving Existing Regimens

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

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

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

A phase 2 trial evaluated the combination of bendamustine and rituximab with cytarabine for the treatment

of older MCL patients (≥65 years) who were ineligible for intensive chemotherapy regimens or ASCT.[7] Both previously untreated and relapsed/refractory patients were included. The overall response rate was 100%; the complete response rates were 95% for previously untreated patients and 70% for relapsed/refractory patients. The 2-year progression-free survival rate was 95% for previously untreated patients and 70% for relapsed/refractory patients.

Agents Targeting the Microenvironment

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

Another recent report regarding the efficacy of lenalidomide in this setting was a subgroup analysis of the MCL-001 study. MCL-001 found an overall response rate of 28% with lenalidomide in heavily pretreated MCL patients.[9] The subgroup analysis analyzed the efficacy of lenalidomide specifically among those patients who had previously received bortezomib.[10] In these patients, the overall response rate was 28% by central review (32% by investigator review). The median duration of response was 16.6 months by central review and 18.5 months by investigator review.

Combining lenalidomide with CD20-targeted therapies is an intriguing possibility to achieve greater efficacy in MCL patients. This combination was recently tested in a single-arm, open-label, phase 1/2 trial, with promising results.[11] Relapsed/refractory MCL patients who had received between 1 and 4 prior therapies were included; 14 patients were enrolled in the phase 1 dose-finding portion, and 44 patients (including 6 who had received the maximal tolerated dose in the phase 1 portion) were enrolled in the phase 2 study. An overall response was achieved in 57% of patients, of whom 36% achieved a complete response. Importantly, 5 of the patients who achieved an overall response had previously been treated with bortezomib. The median duration of response was 18.9 months, the median progression-free survival was 11.1 months, and the median overall survival was 24.3 months. This combination appeared to be well-tolerated; grade 3/4 adverse events included neutropenia, lymphopenia, leukopenia, and thrombocytopenia.

Novel Antibody Therapies

Building on the importance of rituximab in the treatment of MCL, current studies are integrating novel antibody therapies into treatment regimens for MCL. ^{90}Y-ibritumomab-tiuxetan is a novel radioimmunotherapy agent that was evaluated in the phase 2 multicenter GELTAMO (Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea) trial.[12] In this study, previously untreated MCL patients underwent frontline induction therapy with R-hyper-CVAD alternating with rituximab, methotrexate, and cytarabine, followed by consolidation with ^{90}Y-ibritumomab-tiuxetan. Among patients who had responded to induction therapy and underwent consolidation therapy, the failure-free survival rate was 55%, and the overall survival rate was 87%. However, this regimen was associated with significant toxicities.

Obinutuzumab (GA-101) is a glycoengineered, humanized anti-CD20 antibody that was evaluated in a phase 1 trial that included patients with a number of different B-cell lymphomas, including 4 patients with MCL.[13] Of these 4 patients, 1 experienced a short-lived improvement in tumor load that progressed immediately after ending treatment, and 1 had a durable stable disease lasting up to 1 year after study entry.

Agents Targeting Specific Cellular Pathways in MCL

Novel agents targeting specific pathways within MCL represent one of the most promising avenues for improving patient survival. Proximal inhibitors of the B-cell receptor (BCR) pathway have recently been explored in MCL with exciting results. The BCR pathway is essential for the development of normal B cells, and it is maintained in most B-cell malignancies. During lymphomagenesis, the malignant phenotype becomes dependent, or "addicted," to tonic or chronic signaling through the BCR pathway, and hence, key kinases in the pathway represent an attractive target for lymphoma therapy. Several strategies to inhibit the BCR pathway have been tested in MCL.

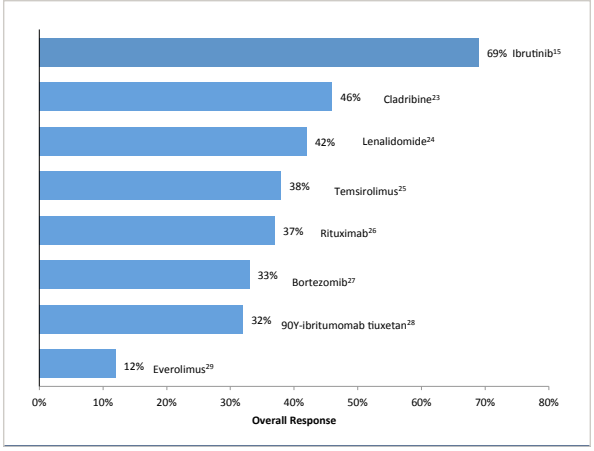


Figure 6. Novel and targeted agents may provide one means by which long-term patient outcomes can be significantly improved in mantle cell lymphoma.

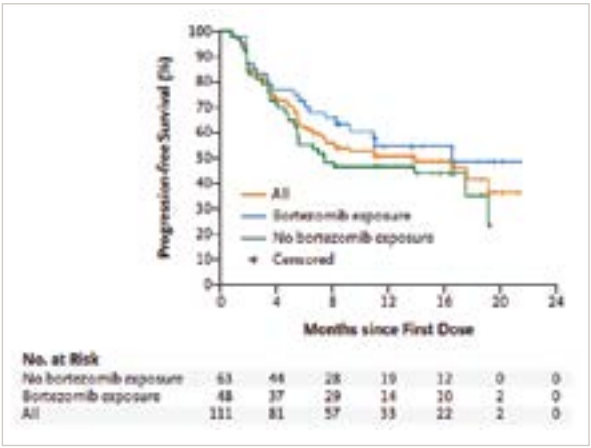


Figure 7. Progression-free survival in a phase 2 trial of single-agent ibrutinib in patients with relapsed/refractory mantle cell lymphoma. Adapted from Wang ML et al. *N Engl J Med*. 2013;369(6):507-516.[14]

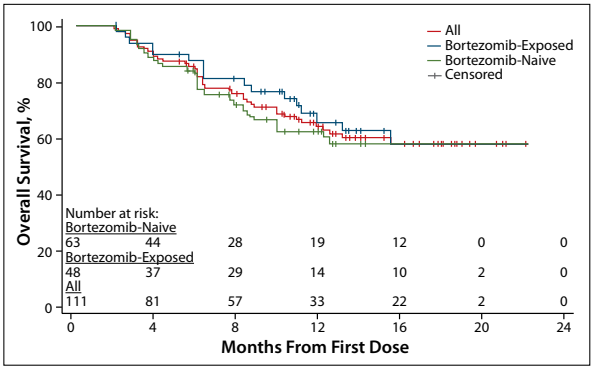


Figure 8. In a phase 2 trial evaluating ibrutinib in patients with relapsed or refractory. the median overall survival was not reached. Adapted from Wang ML et al. *N Engl J Med*. 2013;369(6):507-516.[14]

Ibrutinib was one of the first BCR pathway inhibitors to enter clinical development. Ibrutinib targets Bruton's tyrosine kinase (BTK) for inhibition. In a recently reported phase 2 trial, ibrutinib was administered as a single agent to 111 patients with relapsed/refractory MCL; patients had received a median of 3 prior therapies.[14] Prior to treatment, patients were divided into 2 groups: those who had previously received at least 2 complete cycles of bortezomib therapy and those who had received 1 or no cycles of bortezomib. Ibrutinib appeared to be highly active in all of these patients, with an overall response rate of 68% and a complete response rate of 22%. Importantly, the degree of prior bortezomib exposure did not affect the response rate. After a median follow-up of 15.3 months, the estimated median duration of response was 17.5 months, the estimated median progression-free survival was 13.9 months (Figure 7), and the median overall survival was not reached (Figure 8). The estimated 18-month overall survival rate was 58%. Interestingly, the response rate improved with longer drug exposure. An initial presentation of this study reported a complete response rate of 16%,[15] whereas longer follow-up (and longer ibrutinib exposure) was associated with a rate of 39%.[16] After treatment was initiated, there was a significant incidence of lymphocytosis, which was associated with a dramatic reduction in tumor volume.

Idelalisib is a selective inhibitor of phosphoinositide-3 kinase P110δ (PI3Kδ), a protein known to be critical in the proliferation and survival of B cells and that may also be important in the pathogenesis of some B-cell malignancies. Idelalisib was recently investigated in a phase 1 trial of 40 patients with relapsed/refractory MCL.[17] Patients were heavily pretreated, with a median range of 4 prior therapies. The overall response rate to idelalisib was 40%, including a 7.5% complete response rate. Importantly, among patients who were treated with a dose of 150 mg or higher, the overall response rate was increased to 67%, compared with 29% in patients treated with less than 150 mg. The median duration of response was 2.7 months. The 1-year progression-free survival rate was 22%, which is inferior to that of ibrutinib.

Idelalisib is also being studied in a phase 1 study in which it is combined with everolimus, bortezomib, or bendamustine plus rituximab in patients with relapsed MCL.[18] In a preliminary report, the overall response rates were 39% for idelalisib plus everolimus, 45% for idelalisib plus bortezomib, and 100% for idelalisib plus bendamustine and rituximab. Complete response rates were 11%, 0%, and 50%, respectively. Among all patients, the overall response rate was 49%, the complete response rate was 12%, and the median progression-free survival was 8.1 months.

IPI-145 is an investigational agent that is a potent inhibitor of PI3Kδ, as well as PI3Kγ. Preliminary results from an ongoing phase 1 trial demonstrated a 67% rate of overall response in relapsed/refractory MCL patients.[19] An update of this study's results is expected in the near future.

The mTOR inhibitor temsirolimus is approved in Europe for treatment of relapsed/refractory MCL. However, it is associated with rapid progression after treatment is ceased, and therefore its use requires continuous administration.[20] When 2 doses of temsirolimus were compared with treatment of the physician's choice in a randomized study of relapsed/refractory MCL patients, the higher dose was associated with a significantly prolonged progression-free survival and a higher rate of overall response compared with the investigator's choice of therapy (22% vs 2%).[21,22] Although the same trend was apparent with the lower temsirolimus dose, the differences did not reach statistical significance. Median overall survival was 12.8 months in the high-dose temsirolimus arm compared with 9.7 months in the investigator's choice arm.

Acknowledgment

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

References

1. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany) [ASH abstract 405]. *Blood*. 2009;114(suppl 22).
2. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-1210.
3. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med*. 2012;367(6):520-531.
4. Rummel MJ, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent, and mantle cell lymphomas – final results of the randomized phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany) [ASH abstract 856]. *Blood*. 2010;116(suppl 21).
5. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26(27):4473-4479.
6. Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. *Blood*. 2011;117(10):2807-2812.
7. Visco C, Finotto S, Zambello R, et al. Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation. *J Clin Oncol*. 2013;31(11):1442-1449.
8. Witzig TE, Vose J, Zinzani PL, et al. Combined analysis of single-agent lenalidomide in relapsed/refractory mantle cell lymphoma [ASCO abstract 8533]. *J Clin Oncol*. 2013;31(15 suppl).
9. Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. *J Clin Oncol*. 2013;31(29):3688-3695.
10. Williams ME, Goy A, Sinha R, et al. Lenalidomide in relapsed/refractory mantle cell lymphoma post-bortezomib: subgroup analysis of the MCL-001 study [ASCO abstract 8534]. *J Clin Oncol*. 2013;31(15 suppl).
11. Wang M, Fayad L, Wagner-Bartak N, Zhang L, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. *Lancet Oncol*. 2012;13:716-723.
12. Arranz R, García-Noblejas A, Grande C, et al. First line treatment with rituximab-hyper-CVAD alternating with rituximab-methotrexate-cytarabine and followed by consolidation with 90Y-ibritumomab-tiuxetan in patients with mantle cell lymphoma. Results of a phase 2 pilot multicenter trial from the GELTAMO group. *Haematologica*. 2013 Oct;98(10):1563-1570.
13. Salles G, Morschhauser F, Lamy T, et al. Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. *Blood*. 2012;119(22):5126-5132.
14. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2013;369(6):507-516.
15. Wang L, Martin P, Blum KA, et al. The Bruton's tyrosine kinase inhibitor PCI-32765 is highly active as single-agent therapy in previously-treated mantle cell lymphoma (MCL): preliminary results of a phase II trial [ASH abstract 442]. *Blood*. 2011;118(suppl 21).
16. Wang M, Rule SA, Martin P, et al. Interim results of an international, multicenter, phase 2 study of Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765), in relapsed or refractory mantle cell lymphoma (MCL): durable efficacy and tolerability with longer follow-up [ASH abstract 904]. *Blood*. 2012;119(suppl 21).
17. Spurgeon SEF, Wagner-Johnston ND, Furman RR, et al. Final results of a phase I study of idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase P110γ (PI3Kγ), in patients with relapsed or refractory mantle cell lymphoma (MCL) [ASCO abstract 8519]. *J Clin Oncol*. 2013;31(15 suppl).
18. Wagner-Johnston ND, De Vos S, Leonard J, et al. Preliminary results of PI3Kγ inhibitor idelalisib (GS-1101) treatment in combination with everolimus, bortezomib, or bendamustine/rituximab in patients with previously treated mantle cell lymphoma (MCL) [ASCO abstract 8501]. *J Clin Oncol*. 2013;31(15 suppl).
19. Horwitz SM, Flinn I, Patel MR, et al. Preliminary safety and efficacy of IPI-145, a potent inhibitor of phosphoinositide-3-kinase-γ-δ, in patients with relapsed/refractory lymphoma [ASCO abstract 8518]. *J Clin Oncol*. 2013;31(15 suppl).
20. McKay P, Leach M, Jackson R, Cook G, Rule S. Guidelines for the investigation and management of mantle cell lymphoma. *Br J Haematol*. 2012;159(4):405-426.
21. Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. *J Clin Oncol*. 2009;27(23):3822-3829.
22. Hess G, Smith SM, Berkenblit A, Coiffier B. Temsirolimus in mantle cell lymphoma and other non-Hodgkin lymphoma subtypes. *Semin Oncol*. 2009;36(suppl 3):S37-S45.
23. Inwards DJ, Fishkin PA, Hillman DW, et al. Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. *Cancer*. 2008;113(1):108-116.
24. Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. *Ann Oncol*. 2011 Jul;22:1622-1627.
25. Witzig TE, Geyer SM, Ghobrial I, et al. Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. *J Clin Oncol*. 2005;23(23):5347-5356.
26. Foran JM, Rohatiner AZ, Cunningham D, et al. European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. *J Clin Oncol*. 2000;18(2):317-324.
27. Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol*. 2006;24(30):4867-4874.
28. Wang M, Oki Y, Pro B, et al. Phase II study of yttrium-90-ibritumomab tiuxetan in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol*. 2009;27(31):5213-5218.
30. O'Connor OA, MD, Popplewell L, Winter JN, et al. PILLAR-1: preliminary results of a phase II study of mTOR inhibitor everolimus in patients with mantle cell lymphoma (MCL) who are refractory or intolerant to bortezomib [ASH abstract 3963]. *Blood*. 2010;116(suppl 21).

Unmet Needs in Mantle Cell Lymphoma: General Discussion

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

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

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

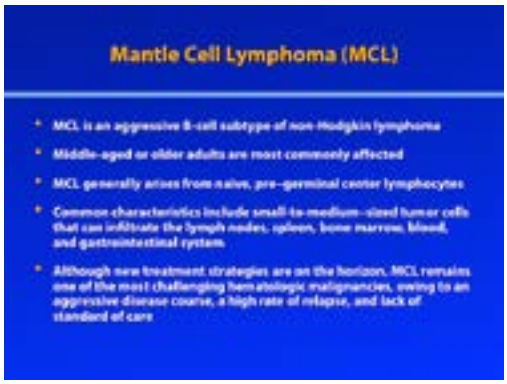
Steven T. Rosen, MD That is fascinating. What are some areas of unmet need, and how are they being addressed?

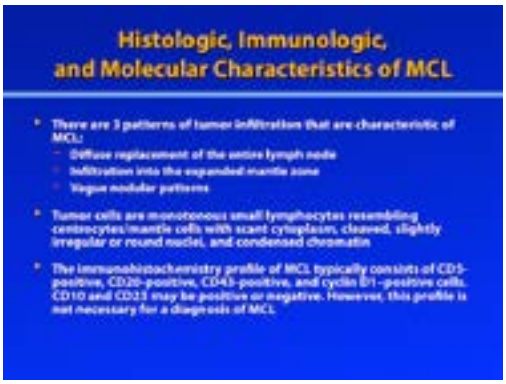
Brian K. Link, MD I had been looking forward to hearing results from the SWOG study that is evaluating how aggressive the optimal induction regimen should be. The clinical design was such that young MCL patients were randomized to either bendamustine-based induction therapy or R-hyper-CVAD alternating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

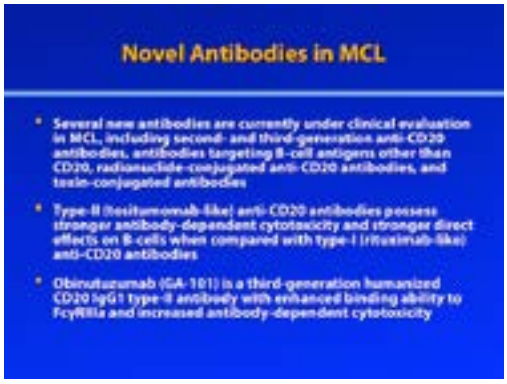
Acknowledgments

Dr Rosen is a consultant for Teva Pharmaceuticals, Cell Therapeutics, Genentech, Genzyme, Merck, Seattle Genetics, Therakos, and Celgene. He has received grants for clinical trials and research from Amgen, Berlex Laboratories, Biogen IDEC, Cytogen Corp, Millennium & ILEX Partners, Pharmacyclics, and Wyeth-Ayerst Research. He is on the speakers bureaus of Cephalon and Teva. He is on the advisory boards of Abbott Laboratories, Celgene, NanoSphere, MedNet Solutions, and Genentech. Dr Link is a consultant for Genentech/Roche, Celgene, and Pharmacyclics.

Slide Library







For a free electronic download of these slides, please direct your browser to the following web address:

http://www.hematologyandoncology.net