Mantle Cell Lymphoma: State of the Art

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Abstract: Mantle cell lymphoma (MCL) accounts for approximately 6% of all non-Hodgkin lymphomas (NHLs). The median age at diagnosis is 60 to 70 years, although MCL may occur in younger patients. Between 75% and 80% of patients are males. MCL usually presents as stage III/IV disease, and extranodal involvement is quite common, particularly in the bone marrow, blood, and gastrointestinal tract. Until recently, MCL was considered a disease with an overall poor prognosis. With the introduction of more aggressive induction chemotherapy regimens (especially those incorporating high-dose cytarabine), the anti-CD20 monoclonal antibody rituximab, and the more widespread use of consolidation with high-dose therapy and autologous stem cell rescue, outcomes have significantly improved. Some patients have even experienced long-term remissions. New insights into the biology of MCL, most prominently the role of the B-cell receptor pathway, have shed new light on treatment approaches for this disease. In this article, we will review current therapeutic approaches for MCL, as well as experimental ones.

Keywords
B-cell receptor pathway, bortezomib, ibrutinib, lenalidomide, mantle cell lymphoma

Introduction

Mantle cell lymphoma (MCL) accounts for approximately 6% of all non-Hodgkin lymphomas (NHLs). The median age at diagnosis is 60 to 70 years, although MCL may occur in younger patients. The majority of patients (75% to 80%) are males. MCL usually presents as stage III/IV disease, and extranodal involvement is quite common, particularly in the bone marrow, blood, and gastrointestinal tract. Until recently, MCL was considered a disease with an overall poor prognosis. Outcomes have significantly improved, however, with the introduction of more aggressive induction chemotherapy regimens (especially those incorporating high-dose cytarabine), the anti-CD20 monoclonal antibody rituximab (Rituxan, Genentech/Biogen Idec), and the more widespread use of consolidation with high-dose therapy and autologous stem cell rescue. Some patients even experience long-term remission.

Conventional immunochemotherapy has improved both objective response rates (ORRs) and complete response (CR) rates, but usually does not cure MCL, making its management challenging.

Although treatment responses are similar to those for indolent NHLs, patients with MCL typically relapse and often develop chemoresistance over time. Because of the high rate of relapse and resistance, treatment for MCL has shifted to more intensive immunochemotherapy regimens, with the aim of achieving prolonged remission. Many patients present at an older age, however, making intensive regimens not easily feasible.

New insights into the biology of MCL—most prominently the role of the B-cell receptor (BCR) pathway—have shed new light on treatment approaches for this disease. In this article, we will review current therapeutic approaches for MCL, as well as experimental ones.

Pathogenesis

MCLs are characterized by the chromosomal translocation t(11;14)(q13;q32), placing the *BCL1* gene locus on chromosome 11 adjacent to the immunoglobulin heavy chain gene on chromosome 14, and deregulating expression of cyclin D1.[1,2] The cyclin family of proteins is responsible for regulating progression through the cell cycle. The D-type cyclins (cyclin D1, D2, and D3) regulate the transition from G1 to S phase in cell division, acting in conjunction with cyclin-dependent kinases (CDKs). This cyclin D/CDK complex tightly regulates phosphorylation of the retinoblastoma (RB) protein, which is responsible for controlling entrance into the cell cycle through regulation of the E2F family of proteins.[3] Cyclin D1 expression varies during the normal cell cycle, including in hematopoietic cells, and is highly regulated. Most lymphomas show persistent overexpression of cyclin D1, though at a much lower level than what is seen in MCL. When cyclin D1 is assembled with CDK4 and CDK6, this complex forms an active kinase that phosphorylates RB, removing its repressive function on cell cycle progression.[4] Intranuclear localization of cyclin D1 seems to be an important factor for cell transformation and lymphomagenesis. Nuclear cyclin D1 staining is found in the majority of MCLs, and its presence may lead to genomic instability by activating DNA damage checkpoints and allowing uncontrolled DNA replication. The kinase ATM may also increase genetic instability, and cyclin D1 mutations that prevent its degradation are associated with tumorigenesis. In a study using transgenic mice, expression of a constitutive nuclear cyclin D1 was sufficient to cause B-cell lymphomagenesis; however, those lymphomas were not necessarily MCL, pointing to the possibility that cyclin D1 mutation may be necessary, but not sufficient, for MCL development.[5] Though a small fraction of MCLs have been reported as negative for cyclin D1, they typically express cyclin D2 or cyclin D3—reflecting the importance of cell cycle deregulation in MCL—and carry otherwise similar clinical features and outcome.[6]

More recently, aberrant expression of *SOX11* has been described as an oncogenic step in the pathogenesis of MCL. This occurs by downstream upregulation of PAX5, a transcription factor necessary for establishment of B-cell identity and a suppressor of plasma cell differentiation.[7]

Prognostic Factors

MCL is a biologically heterogeneous disease, making treatment choice difficult. The MCL International Prognostic Index (MIPI) serves as an attempt to further stratify disease risk by taking into account clinical and laboratory characteristics such as age, performance status, lactate dehydrogenase levels, and white blood cell count. MIPI scores divide patients into three risk groups: low (median overall survival [OS] not reached; 5-year OS, 60%), intermediate (median OS, 51 months), and high (median OS, 29 months).[8]

Additional biological prognostic factors include blastoid morphology, which often shows *TP53* deletion or mutation and is associated with poorer OS (14.5 vs 53 months for the nonblastoid variant)[9,10]; and altered β_2-microglobulin levels.[11] The gene expression profile signature revealed the importance of the proliferation signature in MCL, and identified patient subsets for whom median OS may differ by more than 5 years.[12]

Ki67 has been used as surrogate marker of proliferation signature with a cutoff of 30%, though this carries limitations. Ki67 levels are determined by immunohistochemistry with semiquantitative visual analysis, and most patients have low to very low Ki67 at diagnosis. Ki67 was added to MIPI (MIPIb), which helped further stratify patients retrospectively.[13] A number of other biological factors have been reported, such as truncation of the CCND1 3' untranslated region, complexity of karyotype (frequent secondary abnormalities), miRNAs, and methylation signatures, among others.[14]

Though MCL is a spectrum of disease, a subset of patients present with indolent-type disease with high white blood cell count, splenomegaly, and little or few lymphadenopathy. The proliferation rate typically is low by Ki67, and SOX11 often is negative.[15] These patients also carry somatic mutations, their disease is more stable genetically over time, and they likely should be managed differently than other patients. CNS involvement in MCL is not frequent at baseline, but it might occur more frequently in the future as patient survival continues to improve.[16,17]

Frontline Therapy for MCL

There is no single standard chemotherapy for MCL.[18] High response rates may be achieved with standard lymphoma immunochemotherapy, but these generally are not durable. Intensification of therapy clearly has improved

progression-free survival (PFS), as presented below. However, intensification of therapy is not always feasible in practice, so decisions typically are based on age and comorbidities at presentation.

Frontline Therapy for Younger, Fit Patients

For many years, the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen was the standard of care for untreated MCL. Response rates to this regimen are usually high (ORR, 94%; CR, 34%), but the duration of response is low, averaging approximately 1.5 years.[19] This has led to either intensifying frontline therapy with more aggressive regimens, or consolidating first remission with high-dose therapy followed by autologous stem cell rescue (HDT/ASCR).

Several trials have incorporated HDT/ASCR into the initial treatment strategy for MCL, and outcomes were better than otherwise expected with immunochemotherapy alone. However, most patients participating in these trials were younger than the median age at presentation, and usually healthier, so selection bias may play an important role. Therefore, the results should be interpreted with caution.[20-22]

To date, there has been only 1 randomized study testing the value of HDT/ASCR as a part of frontline therapy for MCL. In this study, 122 patients 65 years of age or younger with MCL who had responded to CHOP were randomized either to HDT (total body irradiation plus cyclophosphamide) in combination with ASCR, or to maintenance interferon-α (IFN-α).[23] Patients receiving HDT/ASCR had a significantly longer PFS (39 vs 17 months), though no plateau in OS has been observed. It is valid to note in this trial that: (1) induction was performed with a regimen that did not incorporate rituximab, (2) it currently is known that other combination regimens are superior to CHOP (ie, rituximab + hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [R-hyperCVAD] and bendamustine/rituximab, as discussed below) for this patient population, and (3) the comparator arm involved maintenance with IFN-α, which historically has been used as a consolidation approach, but does not translate well to the current clinical paradigm.

More recently, studies have incorporated high-dose cytarabine (HiDAC) into induction, reporting longer PFS (60%-90% at 3 years) and suggesting an important role for this approach.[24,25] A randomized trial compared 6 cycles of R-CHOP (arm A) with alternating R-CHOP × 3 and rituximab, dexamethasone, HiDAC, and cisplatin (R-DHAP) × 3 (arm B), with each arm followed by a different protocol for HDT/ASCR. This study showed that the inclusion of cytarabine led to earlier, deeper clinical and molecular remissions and improved overall outcome, including OS. The overall response rate was 90% after R-CHOP and 95% after R-CHOP/R-DHAP, with a 25% CR rate in the R-CHOP arm and a 36% CR rate in the R-CHOP/R-DHAP arm (CR/unconfirmed CR [CRu] rates of 40% for arm A and 54% for arm B). At a median follow-up of 53 months, the median time to treatment failure (TTF) was 46 months in the R-CHOP arm vs 88 months in the R-CHOP/R-DHAP arm. At the time of final analysis, OS was superior in arm B (not reached in arm B vs 82 months for arm A; P=.045).[26] In this trial, molecular remission was more frequent in the cytarabine-containing arm (73%) than in the standard R-CHOP arm (32%). Achievement of molecular remission correlated with improved duration of remission (DOR) (89% in arm B vs 74% in arm A at 24 months).[27] A phase 2 trial studied 3 cycles of R-CHOP followed by 3 cycles of R-DHAP, followed by consolidation with HDT/ASCR using either carmustine, etoposide, cytarabine, and melphalan (BEAM) or total body irradiation, cytarabine, and melphalan (TAM6). This study showed a high rate of conversion to CR after the inclusion of HiDAC. The objective response rate after R-CHOP was 93%; however, only 12% achieved CR. After R-DHAP, the CR rate increased to 57%. With a median follow-up of 67 months, median event-free survival (EFS) was 83 months, and median OS was not reached. The 5-year OS rate was 75%.[28] The LyMa trial studied induction with 4 cycles of R-DHAP alone and reported interim data of 76% CR/CRu prior to HDT/ASCR.[29]

The Nordic Lymphoma Group has reported on an induction regimen of maxi-CHOP (cyclophosphamide 1200 mg/m², doxorubicin 75 mg/m², vincristine 2 mg, prednisone 100 mg × 5 days) alternating with HiDAC for a total of 6 cycles, with the incorporation of rituximab after the fourth cycle. In this phase 2 trial, those patients who responded to this induction regimen received consolidation with BEAM or carmustine, etoposide, cytarabine, and cyclophosphamide (BEAC) followed by autologous stem cell rescue.[30] Of the 160 patients included in this trial, 74 had primers available for monitoring of minimal residual disease by polymerase chain reaction of t(11;14) or clonal immunoglobulin heavy chain gene rearrangement. Those patients who presented solely with molecular relapse after transplant—not considered failures—were then offered preemptive therapy with 4 weekly doses of rituximab. With a median observation time of 6.5 years, the intent-to-treat population achieved a projected 10-year EFS and OS of 43% and 58%, respectively. Several patients in this trial had response durations of more than 10 years, though late relapses occurred beyond 5 years.

The MCL3 trial from the same group used a similar induction regimen (R-maxi-CHOP alternating with HiDAC). But, for those patients not in CR after 6 cycles of chemotherapy, the radioimmunoconjugate ^{90}Y-ibritumomab

tiuxetan (Zevalin, Biogen Idec/Spectrum) was added, achieving a pretransplant ORR of 97%. Outcomes for OS and PFS, however, were not different than those found in the MCL2 trial, with patients who received ^{90}Y-ibritumomab tiuxetan (ie, patients not in CR with chemotherapy alone) having a shorter duration of response.[31]

The MD Anderson group reported on a regimen of rituximab with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with rituximab, methotrexate, and cytarabine (R-hyperCVAD/MA), which is now commonly used for treatment of fit patients with MCL. The initial phase 2 trial included 97 patients with good performance status (ECOG ≤1) and achieved an ORR of 97%, with 87% CR/CRu. With a 10-year follow-up, the median TTF was 4.6 years and the median OS had not been reached. Eight-year TTF and OS rates were significantly higher in patients 65 years of age or younger (46% and 68%, respectively) when compared with older patients (16% and 33%, *P*=.003 and *P*=.0007, respectively). The investigators have suggested that there was no benefit to HDT/ASCR for patients in remission following 6 to 8 cycles of R-hyperCVAD/MA.[11,32]

Retrospective data from the National Comprehensive Cancer Network (NCCN) suggested similar outcomes for 6 to 8 cycles of R-hyperCVAD/MA, for less than 6 cycles of R-hyperCVAD/MA followed by HDT/ASCR, or for 6 to 8 cycles of R-CHOP followed by HDT/ASCR. The same data, however, suggested worse outcomes for patients treated with 6 to 8 cycles of R-CHOP without consolidation with HDT/ASCR.[33] Patients receiving R-CHOP had poorer OS when compared with R-hyperCVAD/MA (HR, 2.5; 95% CI, 1.0-6.2; *P*=.04). The difference between R-CHOP and R-CHOP+HDT/ASCR was not statistically significant (HR, 1.9; 95% CI, 0.6-5.7; *P*=.27). By pooling patients in the 3 intensive therapy groups, they found that both OS (HR, 0.4; 95% CI, 0.2-0.8; *P*=.02) and PFS (HR, 0.3; 95% CI, 0.2-0.6; *P*<.001) were significantly improved vs patients receiving R-CHOP alone.

For those patients who received HDT/ASCR as consolidation of response, the role of preemptive rituximab is under scrutiny. Data from some groups suggest that monitoring minimal residual disease following HDT/ASCR may detect disease relapse prior to clinical relapse, and may be effectively treated with rituximab. Further studies are warranted to advocate this strategy.[30,34]

Frontline Therapy for Older, Less Fit Patients

The median age of presentation for patients with MCL is 68 years, and is currently increasing.[16] With aging, patients find themselves at a worse risk stratification category, as defined by MIPI, with an increase in relative risk of 1.04 per year of age.[8] In addition, comorbidities and age-related changes in chemotherapy pharmacokinetics and tolerance make treatment selection for MCL in the older, less fit population challenging.

There are data that support the use of initial observation for older patients presenting with low-risk disease, which does not appear to affect OS. In particular, observation may be reasonable for elderly patients who are asymptomatic, have low-bulk disease, and have low Ki67 levels.[35]

When treatment is required, R-CHOP traditionally was the "go-to" regimen in this patient population, although recent data have helped change this paradigm. A European MCL Network trial randomized 560 patients older than 60 years (median age, 70 years) to receive either 8 cycles of R-CHOP every 21 days or 6 cycles of rituximab, fludarabine, and cyclophosphamide (R-FC) every 28 days. Median OS was inferior with R-FC (40 vs 64 months; *P*=.0072), and toxicities were more common. Patients with an initial response to treatment were re-randomized to either maintenance treatment with rituximab or IFN-α. Rituximab reduced the risk of progression or death by 45% compared with IFN-α (in remission after 4 years, 58% vs 29%; HR for progression or death, 0.55). For the subset of patients whose disease responded to R-CHOP induction and who were maintained on rituximab until disease progression, the 4-year OS was 87%; whereas for the same population receiving IFN maintenance, the OS rate was 63% (*P*=.005).[36] These results solidified the advantage of prolonged rituximab maintenance. Although maintenance was studied after response to R-CHOP, given the disease kinetics, these results may be generalizable to those responding to other induction regimens.

Cladribine, a purine analogue, has been used in combination with rituximab as frontline therapy for MCL in elderly patients. Few data are available to substantiate this practice. A retrospective analysis of 31 patients who received R-cladribine frontline therapy revealed an overall response rate of 87%, with 61% of patients achieving CR. The estimated median follow-up was 32.5 months, the median PFS was 37.5 months, and the median OS was 85.2 months, although most patients in this analysis received rituximab maintenance.[37]

Bendamustine (Treanda, Teva) is a novel agent with significant activity against MCL. The randomized STiL (German Study Group for Indolent Lymphoma) trial compared frontline therapy with bendamustine in combination with rituximab (BR) vs R-CHOP for patients with indolent NHL, including 93 patients with MCL.[38,39] For this patient population, with a median age of 70 years, BR led to a significantly longer PFS than R-CHOP (69.5 vs 31.2 months; HR, 0.58; 95% CI, 0.44-0.74; *P*<.0001), and was better tolerated. However, there was no difference in OS. The BRIGHT trial compared BR with prespecified cyclophosphamide, vincristine, and

prednisolone (R-CVP) or R-CHOP. Complete response in BR was noninferior to R-CVP/R-CHOP, and BR had a more tolerable toxicity profile.[40] Based on these data, BR is a reasonable option for the treatment of elderly patients with MCL, especially those in whom doxorubicin cardiotoxicity is a concern.

In a recent report, 40 patients with MCL (including 20 newly diagnosed or previously untreated patients) were treated with a combination of BR and cytarabine (R-BAC). The achieved ORR and CR rates were 100% and 95%, respectively, in newly diagnosed or previously untreated patients, and 80% and 70%, respectively, in patients with relapsed or refractory (R/R) disease. The 2-year PFS rate was 95% for patients with untreated disease and 70% for patients with R/R MCL.[41]

A prospective phase 2 trial tested the rituximab, bendamustine, bortezomib (Velcade, Millennium Pharmaceuticals), and dexamethasone (RiBVD) regimen in previously untreated MCL in elderly (>65 years old) patients, or those not eligible for HDT/ASCR. Preliminary results showed an ORR of 87%, with a 60% CR/CRu rate. Despite having 6% toxic deaths, toxicities seemed acceptable and manageable.[42]

Three randomized trials are currently comparing BR induction to other regimens: BR ± bortezomib in patients 60 years of age or older (ECOG-E1411; NCT01415752), followed by maintenance rituximab ± lenalidomide (Revlimid, Celgene); BR vs R-hyperCVAD/MA induction followed by HDT/ASCR in each arm for those less than 65 years of age (S1106; NCT01412879); and BR ± ibrutinib (Imbruvica, Pharmacyclics/Janssen Biotech) for patients older than 65 years of age with previously untreated disease (the SHINE trial; NCT01776840).

A recent report on preliminary results of the LYM-3002 trial of R-CHOP vs rituximab, bortezomib, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) for newly diagnosed patients with MCL who are ineligible for HDT/ASCR, yielded improved PFS in the VR-CAP arm (24.7 months) when compared with R-CHOP (14.4 months). Complete response rates were also improved (44% vs 34%, respectively). This trial led to the recent US Food and Drug Administration (FDA) approval of bortezomib for patients with previously untreated MCL.[43]

Therapy for Relapsed MCL and Strategies to Adapt Such Therapies to the Frontline Setting

Unfortunately, most patients relapse over time even after intensive dose therapy and HDT/ASCR strategies. Using standard approved therapy, the DOR remains short and OS remains disappointing, eliciting a pressing need for novel therapies. Currently, 3 drugs are approved in the US for the treatment of relapsed MCL.

Bortezomib

Bortezomib, an inhibitor of the ubiquitin-proteasome pathway, is approved in the United States for the treatment of relapsed MCL. The multicenter PINNACLE study reported on the activity of bortezomib as a treatment for relapsed MCL.[44,45] This phase 2 study had 155 patients receiving single-agent bortezomib on a standard twice-weekly schedule (1.5 mg/m² on days 1, 4, 8, and 11) for 2 of every 3 weeks. Achieved ORR was 33% (CR/CRu, 8%), with a median OS of almost 2 years, and a median time to disease progression (TTP) of 6.7 months. For patients who responded to therapy with bortezomib, the median TTP was 12.4 months and the median OS was 35.4 months. This has triggered interest in combining bortezomib with other agents. A phase 2 trial studied the combination of bortezomib, rituximab, and dexamethasone.[46] For 16 patients with R/R disease, they reported an ORR of 81% and a CR rate of 44%. A more recent trial combined bortezomib with R-CHOP for patients with newly diagnosed MCL, and achieved an ORR of 81% and CR/CRu rate of 64%, with 2-year PFS and OS rates of 44% and 86%, respectively.[47] A multicenter phase 2 trial led by the Eastern Cooperative Oncology Group (ECOG) studied the combination of bortezomib and modified R-hyperCVAD (VcR-CVAD) followed by maintenance rituximab in patients with newly diagnosed MCL. The reported ORR was 97%, with a CR rate of 68%. The 3-year PFS and OS were 72% and 88%, respectively. Transplant-eligible patients had the option of autologous stem cell transplantation consolidation instead of maintenance rituximab. No significant differences in outcome were observed between these strategies, though this was not a randomized trial.[48,49]

One phase 2 trial looked at frontline treatment with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin with rituximab (DA-EPOCH-R) plus bortezomib followed by maintenance bortezomib vs observation in 43 patients aged 41 to 75 years. A recent preliminary report of this study found 4-year PFS and OS rates of 50% and 80%, respectively, without any difference in PFS between the bortezomib maintenance and observation groups. This regimen was well tolerated overall, but more than 50% of patients developed neuropathy of grade 2 or higher.[50]

Bortezomib is being studied as maintenance in the post-HDT/ASCR setting. A phase 2 trial randomly assigned patients who received induction with R-CHOP + methotrexate (with cyclophosphamide dosed at 2 g/m²) followed by HDT/ASCR with cyclophosphamide, carmustine, and etoposide (CBV) conditioning and 2 doses of rituximab after transplant, to either 4 cycles of consolidation with bortezomib (1.3 mg/m² on days 1, 4, 8, and 11) or 18 months of maintenance with bortezomib

(1.6 mg/m^2 on days 1, 8, 15, and 22, given on alternate months). A preliminary report of this study showed a 2-year PFS of 89% for the consolidation arm and 84% for the maintenance arm. When compared with historical controls using the same induction and transplant backbone, previously reported in the CALGB 59909 trial, 3-year PFS from time of transplant for patients who received bortezomib after transplant (overall) was 67%, whereas for controls it was 59% (P=.0086).[51]

Lenalidomide

Lenalidomide is an immunomodulatory agent that enhances the antitumor activity of natural killer cells and T cells, and is currently approved in the United States for treatment of R/R MCL. The initial phase 2 trial of lenalidomide (25 mg daily for 21 days of a 28-day cycle) in patients with R/R aggressive NHL included 15 MCL patients. The reported ORR was 53%.[52] A follow-up confirmatory trial (NHL-003) with 39 patients having R/R MCL reported an ORR of 41% (CR, 13%). For those patients who previously received bortezomib, the pooled data analysis from these 2 trials revealed an ORR of 57% (CR/CRu, 21%).[53] A more recent prospective phase 2 trial of single-agent lenalidomide in 134 patients with MCL whose disease relapsed after treatment with bortezomib reported an ORR of 28% (CR/CRu, 8%), regardless of the number of prior therapies, and the median DOR was longer than 16 months.[54]

Preclinical data pointed to synergistic activity of lenalidomide and dexamethasone in MCL cell lines,[55,56] leading to a trial combining lenalidomide with dexamethasone (Len/Dex) for patients with R/R MCL. For the 33 patients who received Len/Dex, ORR was 53% (24% CR/CRu) with a median PFS of 12 months.[55] Rituximab, when combined with lenalidomide, further enhances the antitumor activity of natural killer cells, warranting the study of a lenalidomide/rituximab (R^2) regimen. In a phase 2 trial, 44 patients with relapsed MCL were treated with the R^2 regimen. ORR was 57%, with a 36% CR rate. Median OS and PFS were 24.9 and 11.1 months, respectively.[57] Another study tested R^2 as frontline therapy for MCL. Lenalidomide was administered at 20 mg daily on days 1 through 21 of a 28-day cycle for a total of 12 cycles (dose escalation to 25 mg daily if tolerated). Rituximab was administered at a dose of 375 mg/m^2 weekly × 4 during cycle 1, then once every other cycle, for a total of 9 doses. This was followed by a maintenance phase, starting with cycle 13. Lenalidomide was then administered at 15 mg daily on days 1 through 21 of a 28-day cycle, with rituximab maintenance once every other cycle until progression of disease. At a median follow-up of 12 months, the preliminary ORR for evaluable patients was 77%, with 40% CR/CRu. Median PFS and DOR have not been reached.[58] A phase 1/2 study combined lenalidomide (15 mg) with BR (LENA-BERIT trial) in elderly patients with newly diagnosed MCL, achieving an ORR of 97%, CR/CRu rate of 79%, estimated PFS at 2 years of 74%, and OS at 2 years of 87%.[59,60]

Ibrutinib

Proper functioning of the BCR signaling pathway is essential for normal B-cell development and function. Components of this pathway are constitutively activated in MCL cell lines, contributing to tumor proliferation and survival, and making it a rational target for novel therapies.[61] The Bruton's tyrosine kinase (BTK) is crucial to BCR signaling, and its blockade arrests B-cell maturation. Ibrutinib is a potent oral BTK inhibitor. The initial phase 1 trial in patients with indolent lymphomas included 9 patients with MCL, 7 of whom responded to ibrutinib, and 3 with CRs.[62] In this patient population, toxicities were minimal—mainly nausea, fatigue, and diarrhea. The international phase 2 trial of ibrutinib, at a dose of 560 mg daily, studied this drug in patients with R/R MCL, and found an ORR of 68% and CR rate of 21%. Previous exposure to bortezomib did not affect outcomes in this population. The median PFS was 13.9 months, and the median OS has not yet been reached.[63]

Multiple trials are underway that combine ibrutinib with other agents. The international, placebo-controlled, phase 3 SHINE trial is combining BR ± ibrutinib for patients older than 65 years of age with previously untreated disease. Another phase 1 trial is combining ibrutinib with R-CHOP, while other trials are combining ibrutinib with lenalidomide or rituximab, or comparing ibrutinib with temsirolimus (Torisel, Wyeth).

Novel Agents in Mantle Cell Lymphoma

Agents Targeting the BCR Activation Pathway

With the success of ibrutinib in patients with relapsed MCL, much interest has been placed in developing therapies that target different steps in the BCR activation pathway (see the Table).

Spleen tyrosine kinase (Syk), a component of the BCR pathway, is highly phosphorylated in some MCL cell lines, and its inhibition can induce growth arrest in these cells.[64] Fostamatinib, a Syk inhibitor, was tested in patients with R/R NHL or chronic lymphocytic leukemia (CLL). Of 63 studied patients, 9 had MCL, with 1 achieving a partial response (PR) and 4 having stable disease (SD). The median PFS in this study was 3.8 months.[65]

Phosphoinositide 3-kinase (PI3K) is activated by Syk and is a critical controller of B-cell activation and proliferation. Idelalisib (Zydelig, Gilead Sciences) is an orally available inhibitor of PI3Kδ, which recently was approved

by the FDA as treatment for relapsed CLL, small lymphocytic lymphoma, and follicular lymphoma. The phase 1 trial for patients with R/R MCL revealed an ORR of 40%, with CR in 2 of 40 patients (5%). The median duration of response was 2.7 months, the median PFS was 3.7 months, and 1-year PFS was 22%.[66] Common adverse events included nausea, vomiting, diarrhea, and fatigue. Preliminary results of a phase 1 study of idelalisib plus everolimus (Afinitor, Novartis), bortezomib, or BR in patients with R/R MCL revealed an ORR of 49% and a CR rate of 12% for all patients. For those patients in the idelalisib plus BR arm, the ORR and CR rates were 100% and 50%, respectively. Median PFS for all patients was 8.1 months.[67] Idelalisib is currently being investigated in combination with rituximab and lenalidomide, and in combination with the oral Syk inhibitor GS-9973 for patients with R/R MCL.

Protein kinase C β (PKCβ) is involved in angiogenesis through modulation of the vascular endothelial growth factor (VEGF), but also is part of the BCR pathway. High levels of VEGF receptor have been associated with poor prognosis in patients with MCL.[68] Enzastaurin, a selective inhibitor of PKCβ, was tested in patients with relapsed MCL. No objective responses were achieved, but 10% of patients had stable disease for over 6 months.[69]

Agents Targeting the mTOR Pathway

The mammalian target of rapamycin (mTOR) sits downstream from PI3K/Akt and integrates information regarding cell status to control cell growth and division. Upregulation of the PI3K/Akt/mTOR pathway is important in MCL pathogenesis. Therefore, blocking mTOR activity in MCL cells may lead to antiproliferative effects and cell death.[70] The mTOR inhibitor temsirolimus was studied in patients with R/R MCL, initially at a dose of 250 mg weekly, yielding an ORR of 38% and a median DOR of 6.9 months.[71] Temsirolimus was then studied at a lower dose of 25 mg weekly, which yielded similar efficacy (ORR, 41%; TTP, 6 months) but less toxicity.[72] A phase 3 randomized trial compared 2 different dosing schedules of temsirolimus against investigator's choice of single-agent therapy in patients with R/R MCL. This study found an ORR of 22%, 6%, and 2%, with median PFS of 4.8, 3.4, and 1.9 months for the higher-dose temsirolimus, lower-dose temsirolimus, and investigator's choice groups, respectively.[73] A phase 2 trial of everolimus, an orally available mTOR inhibitor, for relapsed aggressive lymphoma included 19 patients with MCL, with an ORR of 32% (CR, 2%).[74] The PILLAR-1 trial evaluating single-agent everolimus in MCL patients with disease refractory to bortezomib reported an ORR of 8.6%, no CRs, and a median PFS and OS of 4.4 months and 16.9 months, respectively.[75] The study combining temsirolimus with rituximab in patients with relapsed MCL yielded an ORR of 59% (19% CR).[76] Ongoing trials are combining temsirolimus with BR and everolimus with lenalidomide for patients with relapsed MCL.

Monoclonal Antibodies

Rituximab, an anti-CD20 monoclonal antibody, has been successfully used across subtypes of NHL, although some of its efficacy may be hampered by the way some patients—especially older men—metabolize it, by the CD20 epitope it targets, or by genetic polymorphisms. To overcome some of the aforementioned issues, new anti-CD20 monoclonal antibodies are being engineered to enhance either antibody-dependent cell-mediated cytotoxicity (ADCC)[77] or complement activation,[78] to bind to a different epitope of CD20, or to not require translocation into lipid rafts.

Obinutuzumab (Gazyva, Genentech), the first glycoengineered type 2 antibody, can induce cell death and ADCC more potently than type 1 antibodies (rituximab and ofatumumab [Arzerra, GlaxoSmithKline]), without activating complement-dependent cytotoxicity. In contrast with type 1 anti-CD20 antibodies, type 2 antibodies do not induce redistribution of CD20 into detergent-resistant lipid rafts, but instead form strong homotypic adhesions and cause actin-dependent lysosome-mediated cell death.[79] The phase 2 GAUGUIN study reported on obinutuzumab monotherapy for patients with R/R diffuse large B-cell lymphoma and MCL. Out of 15 patients with heavily pretreated MCL, 4 had an objective response.[80]

Ofatumumab is a fully humanized monoclonal antibody engineered to target a unique CD20 epitope and has shown better complement-dependent cytotoxicity when compared with rituximab. Ofatumumab has been studied in combination with bendamustine and dexamethasone for older patients (60 years or older) with newly diagnosed MCL. Preliminary results from this phase 1/2 study reported an ORR and CR rate of 94% and 90%, respectively.[81] Additional trials are studying ofatumumab plus bendamustine in patients who are ineligible for HDT/ASCR (NCT01437709) or in combination with hyper-CVAD/MA as frontline therapy for younger patients with MCL (NCT01527149).

CD79b is expressed by nearly all B-cell malignancies, and is a component of the BCR. DCDS4501A (polatuzumab vedotin) is an antibody-drug conjugate that combines an anti-CD79b monoclonal antibody to the tubulin disrupting agent monomethyl auristatin E (MMAE). In preliminary results of a phase 1 trial of 33 patients with R/R B-cell NHLs, 4 had MCL and 1 of these had a PR.[82] An updated report of this trial included an expanded cohort of patients, with 9 patients receiving a combination of DCDS4501A and rituximab. Five of these patients had indolent NHL; however, the abstract

Table. Novel Agents for Mantle Cell Lymphoma

Agent[a]	Mechanism of Action	Number of Patients With MCL in Trial	Response Rates for Patients With MCL	Outcomes for Patients With MCL
Fostamatinib[65]	Syk inhibitor	9	1 PR; 4 SD	PFS 3.8 mo
Idelalisib[66]	PI3K inhibitor	40	ORR 40%; CR 5%	DOR 2.7 mo; 1-y PFS 22%
Idelalisib + everolimus vs idelalisib + bortezomib vs idelalisib + BR[67]	PI3K inhibitor mTOR inhibitor Proteasome inhibitor	22	Id+E ORR 25%; CR 0% Id+Bor ORR 50%; CR 0% Id+BR ORR 100%; CR 50%	DOR for whole cohort, 2.5 mo; For Id+BR arm median DOR and PFS not reached
Enzastaurin[69]	PKCβ inhibitor	60	ORR 0%	SD>6 mo 10%
Temsirolimus 25 mg[72]	mTOR inhibitor	29	ORR 41%; CR 3.7%	TTP 6 mo; DOR 6 mo
Everolimus[74]	mTOR inhibitor	19	ORR 32%; CR 2%	DOR 5.7 mo
Everolimus for patients refractory to bortezomib[75]	mTOR inhibitor	58	ORR 8.6%; CR 0%	PFS 4.4 mo; OS 16.9 mo
Temsirolimus + rituximab[76]	mTOR inhibitor + anti-CD20 mAb	71	ORR 59%; CR 19%	DOR 10.6 mo; OS 29.5 mo; TTP 9.7 mo
Obinutuzumab[80]	Type 2 anti-CD20 mAb	15	ORR 26%	NA
Ofatumumab + bendamustine + dexamethasone[81] (1st line setting)	Type 1 anti-CD20 mAb (ofatumumab)	36 (19 evaluable for response)	ORR 94%; CR 90%	NA
DCDS4501A[82]	Anti-CD79b antibody-drug conjugate	4	1 PR	NA
Dacetuzumab[85]	Anti-CD40 mAb	10	1 PR	NA
Vorinostat[90]	Histone deacetylase inhibitor	9	1 SD >26 mo	NA
Flavopiridol + fludarabine + rituximab[94]	CDK1 inhibitor (flavopiridol)	10	CR 70%; PR 10%	PFS 21.9 mo
Alisertib[95]	AAK inhibitor	13	ORR 27%	NA
ABT-199[96]	BCL2 inhibitor	12	8 PRs; 1 CR	NA

[a] All were tested in the relapsed or refractory setting, except where noted.

AAK, aurora A kinase; Bor, bortezomib; BR, bendamustine plus rituximab; CDK, cyclin-dependent kinase; CR, complete response; DOR, duration of response; E, everolimus; Id, idelalisib; mo, months; mAb, monoclonal antibody; MCL, mantle cell lymphoma; mTOR, mammalian target of rapamycin; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PKCβ, protein kinase C β; PR, partial response; SD, stable disease; Syk, spleen tyrosine kinase; TTP, time to progression; y, year/years.

does not specify histology. The study found a 100% ORR and a 40% CR rate.[83]

Milatuzumab is a humanized monoclonal antibody targeted to CD74, a pan-B marker that can activate the PI3K/mTOR/Akt pathway. Preclinical data suggest that milatuzumab has antilymphoma activity when combined with rituximab.[84]

Dacetuzumab is a humanized antibody targeted to CD40, which is present on activated B-cells, monocytes, and dendritic cells. Dacetuzumab has been studied in a phase 1 trial for patients with R/R NHL, which found a PR for 1 in 10 patients with MCL.[85]

Radioimmunotherapy (RIT) is a therapeutic modality that uses monoclonal antibodies linked to a radioactive agent to deliver radiation directly to the target cell and immediate surroundings while minimizing systemic radiation exposure. RIT has been studied as frontline therapy for MCL, with first-line ^{131}I-tositumomab yielding an

ORR of 83% (CR/CRu, 46%). Patients in this study received CHOP after RIT, with a median EFS of only 1.4 years.[86] A phase 2 trial of RIT with ^{90}Y-ibritumomab tiuxetan in relapsed MCL reported a 31% ORR and a median EFS of 6 months.[87] Considering that RIT may work better with low-burden disease, the E1499 trial used ^{90}Y-ibritumomab tiuxetan as consolidation after 4 cycles of R-CHOP in 57 patients with newly diagnosed MCL. The ORR was 82% (55% CR/CRu), with a median TTF of 34 months and an estimated 5-year OS of 73% (79% for patients ≤65 years old vs 62% for patients >65 years old).[88] A more recent phase 2 trial used ^{90}Y-ibritumomab tiuxetan as consolidation following induction with R-hyperCVAD/R-MA as frontline treatment, but toxicities were unacceptable.[89]

Other Novel Agents

Histone deacetylases (HDACs) are involved in the control of gene expression and also have post-translational modifying effects on tumor suppressor genes, such as *PTEN*, or transcription factors, such as NF-κB. Vorinostat (Zolinza, Merck), an oral HDAC inhibitor approved for use in cutaneous T-cell lymphoma, was studied in patients with refractory lymphoma, including 9 patients with MCL.[90] Only 1 MCL patient had a prolonged stable disease for 26 months; the others did not respond. Preclinical data suggest that vorinostat and temsirolimus in combination have synergistic activity against MCL cell lines.[91] Panobinostat is being tested in combination with everolimus in patients with relapsed lymphoma and shows promising activity.[92] Belinostat (Beleodaq, Spectrum Pharmaceuticals) and romidepsin (Istodax, Celgene) have been found to have synergistic activity in vitro against MCL cell lines when combined with bortezomib.[93]

CDK inhibition is an obvious target of drug development, because the interactions between cyclin D1 and CDK are in the genesis of MCL. Flavopiridol is a CDK1 inhibitor that induces apoptosis in MCL cell lines. A phase 1 trial of flavopiridol in combination with fludarabine and rituximab included 10 patients with R/R MCL. Of these patients, 7 achieved CR and 1 had a PR. For MCL patients, the median PFS was 21.9 months. The main side effect was significant myelosuppression.[94]

Aurora kinases are important in cell cycle regulation. Inhibition of aurora A kinase (AAK) may lead to cell cycle arrest and ultimately to cell death. Alisertib, a specific inhibitor of AAK, was tested in a phase 2 trial for patients with aggressive lymphoma. Thirteen patients with R/R MCL were included, achieving a 27% ORR.[95]

ABT-199 is an orally bioavailable, second-generation BCL2 inhibitor that has been studied in patients with NHL. In a phase 1 study that included 12 patients with R/R MCL, 8 had a PR and 1 had a CR.[96] There is an ongoing study combining ABT-199 with bendamustine and rituximab in patients with R/R NHL.

The Role of Allogeneic Stem Cell Transplantation

Compared with HDT/ASCR, there is a paucity of data for the role of allogeneic stem cell transplantation (allo-SCT) in the treatment of MCL. A number of single-center prospective and retrospective studies have been reported, but the data are conflicting in regard to both toxicity and efficacy. Most patients in these studies received an allo-SCT in the setting of relapsed disease following HDT/ASCR, making them heavily treated patients. Reduced intensity conditioning (RIC) may decrease toxicity and transplant-related mortality, making allo-SCT an option in this largely elderly population. There are not sufficient data to suggest that allo-SCT as frontline consolidation is better than HDT/ASCR. In fact, a recent report from the Center for International Blood and Marrow Transplant Research (CIBMTR) investigated a retrospective cohort of outcomes for HDT/ASCR and RIC allo-SCT. For patients receiving 1 of these transplant modalities in first PR/CR with no more than 2 lines of therapy, the OS rate was similar (5-year OS, 61% HDAT/ASCR vs 62% RIC allo-SCT; P=.951).[97] For patients receiving transplant after later lines of therapy (second PR/CR or >2 lines of therapy), survival also was similar (5-year OS, 44% HDT/ASCR vs 31% RIC allo-SCT; P= .202). In both cohorts, the risk of relapse was lower and nonrelapse mortality was higher in the RIC allo-SCT group. OS and PFS were highest in patients who underwent HDT/ASCR in first CR. Multivariate analysis of survival from diagnosis identified a survival benefit favoring early transplant for both HDT/ASCR and RIC allo-SCT. Nevertheless, RIC allo-SCT may still be an effective therapeutic choice for patients with relapsed disease after HDT/ASCR who are responding to chemotherapy, as some patients achieved prolonged remissions. For the more aggressive blastoid subtype of MCL, frontline consolidation with RIC allo-SCT may be an interesting option, though more studies are needed to justify this approach.

Adoptive T-Cell Therapy

Genetically modified autologous T cells, incorporating a chimeric receptor that targets a tumor antigen and induces antigen-specific T-cell activation, proliferation, and killing (CAR T cells), are an emerging therapeutic alternative for hematologic malignancies. The proof-of-concept clinical trial for patients with R/R indolent B-cell lymphoma included 1 patient with MCL.[98] Patients received CD20-specific CAR T cells. Two of the 7 included patients

achieved a CR with cytoreductive chemotherapy administered before the T-cell infusions, and remained disease-free 3 months and 13 months after T-cell infusions. Another patient attained an objective PR lasting 3 months after treatment with T-cell infusion plus interleukin 2. Four patients exhibited stable disease for 3, 5, 6, and 12 months. The 1 patient with MCL, however, did not receive a T-cell infusion, owing to an inability to achieve a preestablished cell dose collection. Currently, CD19-specific CAR T cells are being studied in patients with MCL after frontline induction chemotherapy followed by autologous stem cell transplantation, or as salvage in the relapsed setting.

Summary

MCL is a biologically and clinically heterogeneous disease for which treatment remains challenging, especially for older patients. Advances have been made with the incorporation of frontline chemoimmunotherapy in combination with intensive chemotherapy regimens, followed by consolidation with HDT/ASCR for younger patients. Novel agents, particularly those targeting the BCR pathway, pose an interesting paradigm for treatment of older or heavily pretreated patients. Although the role of HDT/ASCR is well established, RIC allo-SCT may be an effective therapy for highly selected cases, including the more aggressive blastoid variant. Future research in MCL should incorporate novel targeted agents with multiagent intensive chemotherapy in the frontline setting. The role of adoptive T-cell therapy with CD19-chimeric antigen receptor (CD19-CAR) T cells is being studied for MCL, particularly as consolidation after HDT/ASCR in the frontline setting, which is an interesting and very promising approach.

Disclosures

Dr Skarbnik has no conflicts of interest to disclose. Dr Goy has disclosed advisory board participation with Celgene, Takeda, Janssen, and Pharmacyclics; consultancy for Celgene; honoraria for Celgene; being on the speakers bureau for Takeda, Janssen, and Pharmacyclics; and institutional clinical research funding from Celgene.

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Erratum

An article in the November 2014 issue, "Development of a platform for systemic antiangiogenesis therapy for advanced cervical cancer" by Krishnansu S. Tewari, MD, and Bradley J. Monk, MD, contained incorrect labeling in Figure 3 because of a production error. The dark blue circle should read "GOG 204" instead of "GOG 169," and the dark green circle should read "GOG 240" instead of "GOG 169." Readers are advised to download the corrected version at www.hematologyandoncology.net.