New Strategies in the Treatment of Mantle Cell Lymphoma

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Abstract

Mantle cell lymphoma (MCL) is a rare type of non-Hodgkin lymphoma that traditionally has been thought to possess the poor-risk features of both indolent lymphoma, with its incurability, and aggressive lymphoma, with its ability to proliferate rapidly. Although there is considerable debate as to whether MCL can be cured, a number of retrospective studies are beginning to suggest an improvement in overall survival over the past decade, likely coinciding with the introduction of rituximab, more intensive chemotherapy, and the increasing use of autologous stem cell transplant (ASCT) in first remission. At present, intensive induction chemotherapy regimens consistently produce a response rate of >90%, sometimes even 100% in the first-line setting, and consolidation with ASCT in first remission can improve the complete response rate to 90%. The emergence of a more sophisticated understanding of the underlying pathogenesis, coupled with a host of new agents and targets, has again created new opportunities to improve the care of our patients with MCL. Here, we discuss many of these developments and how they may potentially affect the natural history of this disease. Clin Cancer Res; 18(13): 3499–508. ©2012 AACR.

Background

In the past decade, we have made much progress in elucidating the biology of mantle cell lymphoma (MCL), and our understanding of this biology has evolved from one based on morphology to one based on its underlying molecular features (1). It is now clear that MCL is characterized by gross dysregulation of cell-cycle control. The hallmark of MCL is aberrant cyclin D1 control and regulation (2–6), as depicted in Fig. 1. On a molecular level, the pathognomonic chromosomal translocation t (11, 14) (q13;q32) places cyclin D1 downstream of the highly active immunoglobulin H enhancer (7). Subsequently, the mRNA of cyclin D1 undergoes alternative splicing to produce 2 transcripts: cyclin D1a, whose role in MCL pathology is well characterized (8, 9), and cyclin D1b, whose expression in MCL is more variable and role is less well defined (10). Deletion or mutation of the cyclin D1a mRNA tail region produces a truncated version of cyclin D1a mRNA, which is 6 times more stable than the wild-type full-length cyclin D1a mRNA (10). At the translation level, cyclin D1a is downregulated by microRNAs (miRNA), specifically mir16-1. Mutation of the tail region on the cyclin D1a mRNA in MCL cells eliminates the binding site of miR16-1, resulting in abundantly translated cyclin D1 protein (11). At the posttranslational level, cyclin D1 is known to be phosphorylated by GSK3β, and phosphorylated cyclin D1 undergoes polyubiquitination by the E3 ligase FBX4, subsequently becoming a substrate for proteasome degradation (12–14). Phosphorylation of cyclin D1 can be prevented by phosphorylation and inactivation of GSK3β, achieved via aberrantly activated AKT in MCL cells (15), whereas polyubiquitination and degradation of cyclin D1 are prevented by mutation of the E3 ligase FBX4 (16). Collectively, these overlapping mechanisms of cyclin D1 regulation ensure high levels of cyclin D1 protein in MCL.

Overexpressed cyclin D1 enables cells to bypass the normal pathways involved in cell-cycle control (17, 18), which can be compounded by a variety of other dysregulated mechanisms (Fig. 1). Cyclin D1 interacts with CDK4 or CDK6 to promote cell-cycle progression through the G1–S checkpoint (19–21). CDK4 is frequently overexpressed or amplified in MCL (22, 23). In contrast, the CDK inhibitors p16 and p27 are either absent or present at very low levels in many patients with MCL (24–26). Deletion of p16 has been found in approximately half of all patients with MCL, where the gene is subject to point mutations and silencing by promoter hypermethylation (24, 27). In addition, the protein level of p27 in MCL is regulated by proteasome-mediated degradation, though the mechanisms are not fully understood. The p27 specific F-box protein, Skp2, is inducible and overexpressed in some MCL patients with aggressive disease, and mediates the degradation of p27 (28–30). Collectively, overexpression of cyclin D1 and CDK4/6 provides the drive, and loss of p16 and p27 removes the brakes, for MCL cells to bypass normal cell-cycle control and checkpoints (Fig. 1).

Many lines of evidence suggest that cyclin D1 is critical for the pathogenesis of MCL. Patients with the truncated version of the mRNA of cyclin D1a, the more stable form, are known to be associated with aggressive or blastoid histology.
Overexpression and gene amplification

**Figure 1.** MCL is characterized by loss of cell-cycle control through multiple mechanisms, including overexpression of cyclin D1, loss of p27 activity, and overexpression of CDKs.

(a) t (11;14) enhances transcription
(b) Tail truncation stabilizes mRNA
(c) Tail mutation prevents miRNA-mediated translational inhibition
(d) mTOR prevents GSK3β-dependent ubiquitination and degradation

Overexpression and gene amplification

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(31) and a shorter overall survival (OS) of only 1.38 years, compared with 3.28 years for patients with full-length and unstable mRNA (10). On the other hand, high-level p27 expression is associated with better survival (26, 32), again supporting the notion that MCL is a disease characterized by gross cell-cycle dysregulation at a variety of levels, and that the level of dysregulation correlates with prognosis. Finally, direct inhibition of the expression of cyclin D1 can be achieved in the laboratory by short-hairpin RNA targeting cyclin D1, and has been shown to reduce proliferation and clonogenic survival of MCL cells (8, 33, 34).

**Clinical Perspectives of MCL**

Historically, MCL has been treated like most other forms of B-cell non-Hodgkin lymphoma (NHL), with CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone)–like regimens. However, early retrospective studies in the United States and Europe showed that MCL patients treated with CHOP-based regimens had an OS of <3 years, which is much worse than that observed for other indolent lymphomas (35, 36). Addition of the anti-CD20 antibody rituximab to CHOP improved the overall response rate (ORR) from 75% to 94%, and the complete response (CR) rate from 7% to 34% (37). A 5-year update of this dataset showed that the median response duration was prolonged from 18 months for CHOP to 29 months for R-CHOP ($P = 0.0052$), and the 5-year OS rate was 59% for R-CHOP compared with 46% for CHOP ($P = 0.27$ [38]). A recent retrospective study suggested that the addition of rituximab to chemotherapy as first-line therapy improved the survival of elderly patients from 27 months to 37 months ($P < 0.001$ [39]). Rituximab has become an essential component of all MCL treatment regimens.

Because CHOP-like regimens failed to prolong OS, more aggressive treatment regimens have been investigated. A prospective trial at The University of Texas MD Anderson Cancer Center (Houston, TX) reported a high CR rate (up to 68%) for elderly patients with aggressive MCL treated with fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (hyper-CVAD) alternated with high-dose methotrexate and cytarabine [MA (40)]. The regimen was subsequently modified to include rituximab (R-hyperCVAD/R-MA) with increased doses of cytarabine (41), which produced an improved CR (87%) and OS (82% at 3 years) in this patient group. At the 10-year follow-up, the OS rate was 64%, which compares favorably with other treatment regimens, including those that incorporate stem-cell rescue (42). However, there remain substantial uncertainties regarding this regimen because patients in this study (at least those who provided adequate samples for analysis) appeared to be enriched for low Ki-67. Furthermore, the regimen was associated with substantial toxicity, including an 8% treatment-related mortality. In a multi-institution European trial using the same regimen, the majority of patients were unable to complete their planned treatment courses, due primarily to hematologic toxicities (43).

**On the Horizon**

**Autologous stem-cell transplantation in first remission**

Given the inability to produce protracted progression-free survival (PFS) and improved OS for patients with MCL treated with standard combination chemotherapy in the upfront setting, and the significant toxicities associated with aggressive or intensified chemotherapy, researchers have investigated the efficacy of autologous stem-cell transplantation (ASCT) extensively. Early small studies suggested that patients who received ASCT in first remission experienced better OS, disease-free survival, and event-free survival (EFS) compared with those receiving ASCT after relapse (44–46). Vandenbergh and colleagues (47) conducted a retrospective analysis of 340 MCL patients who had received ASCT and were identified from the European Blood and Bone Marrow Transplant Registry or the Autologous Blood and Marrow Transplant Registry. The 2-year and 5-year PFS rates were 55% and 33%, respectively. Of importance, patients who had undergone a transplant for relapsed MCL
were 2.99 times more likely to die (95% CI, 1.66–5.38; \( P < 0.001 \)) than patients who had undergone a transplant in first remission.

More definitive evidence supporting transplantation in first remission was provided by a randomized trial conducted by Dreyling and colleagues (48) from the European MCL Network. In this trial, previously untreated patients with advanced-stage MCL received CHOP-like chemotherapy for induction. Patients who achieved a partial response (PR) or CR were then randomized to receive either myeloablative radiochemotherapy followed by ASCT (arm A), or 2 more cycles of CHOP-like consolidation followed by IFN-\( \alpha \) maintenance and ASCT at relapse (arm B). After a median follow-up of 25 months, patients in arm A, who received ASCT in first remission, exhibited a median PFS of 39 months, compared with 17 months for patients in arm B, who received salvage chemotherapy and ASCT at relapse. With a relatively short follow-up of only 34 months, there was no difference in OS between arms A and B. In conclusion, although the results for ASCT in MCL patients with relapsed disease generally have been disappointing, ASCT in first remission may represent an optimal approach when considering myeloablative chemotherapy for those patients who are suitable candidates, as discussed below in further detail.

Recent clinical studies of upfront treatment of MCL have focused on ASCT in first remission using more effective induction regimens. These studies typically incorporated rituximab and high-dose cytarabine into the induction regimens, and produced marked improvements in CR rate and encouraging OS (49, 50). Most notably, the Nordic Lymphoma Group evaluated the treatment of newly diagnosed MCL patients with dose-intensified CHOP (maxi-CHOP) alternated with high-dose cytarabine followed by ASCT in the MCL-2 trial. Maxi-CHOP was highly effective, producing an ORR of 96% and a CR rate of 54% after induction, which increased to 97% and 90%, respectively, after consolidation with high-dose chemotherapy and ASCT. The OS at 6 years was a remarkable 70% for patients enrolled in MCL-2, with a PFS of 66% at 6 years and a 4-year EFS rate of 63% (51). Of importance, the Nordic MCL-2 trial reported marked improvement of clinical outcomes compared with an earlier MCL-1 trial that was conducted in a similar population of patients who received maxi-CHOP and ASCT [i.e., no cytarabine and no rituximab (52)]. The patients in the MCL-1 trial experienced an ORR of 76% and CR rate of 29%, which eventually translated into 4-year OS, failure-free survival, and EFS rates of 51%, 15%, and 18%, respectively.

**Targeting underlying cell-cycle dysregulation in MCL: CDK inhibitors**

Considering the critical importance of cyclin D1 in the pathogenesis of MCL, inhibition of cyclin D1 would seem to be a logical strategy to treat MCL. Currently, however, no specific inhibitor of cyclin D1 is available for patients. Alternatively, the function of cyclin D1 can be inhibited through inhibition of its catalytic partners, CDK4 and CDK6. In this regard, on the basis of results from an anticancer drug-screening program of the National Cancer Institute, flavopiridol was found to be a potent inhibitor of cell cycle and a pan-CDK inhibitor (53, 54). Flavopiridol is well tolerated in patients and has been studied in numerous phase I and II clinical trials. In MCL, flavopiridol as a single agent produced stable disease and minor responses (55, 56). Ongoing clinical trials are exploring combinations of flavopiridol with histone deacetylase inhibitors, proteasome inhibitors, lenalidomide, and conventional cancer drugs. More specific or potent CDK inhibitors have also entered clinical evaluation. PD0332991 is a specific inhibitor of CDK4 and CDK6, is generally well tolerated, and has shown clinical activity (57–60). SCH727963 (dinaciclib), a novel inhibitor of CDK1, -2, -5, and -9, showed superior activity and an improved therapeutic index compared with flavopiridol in laboratory models of solid and hematologic malignancies (61, 62) and was the subject of intense investigation in numerous clinical trials (63–65). However, preliminary data did not show a dramatic response to these CDK inhibitors, suggesting that other deregulated pathways are contributing to the growth and survival advantages of aggressive MCL cells compared with normal cells (8, 33, 34).

**B-cell receptor signaling pathway: targeting Bruton tyrosine kinase and Syk**

A recent proteomic screen of phosphorylated proteins in MCL cells indicated that proteins connecting the B-cell receptor (BCR) signaling network were among the most abundant proteins found, and active BCR signaling in MCL cells was confirmed by flow cytometry (66). As depicted in Fig. 2, B-cell lymphocytes are activated via antigen binding and oligomerization of the BCR, composed of surface immunoglobulin and Ig/\( \gamma \) heterodimers, leading to phosphorylation of the Src-family tyrosine kinases Lyn and Syk, which in turn leads to transphosphorylation and autophosphorylation of Bruton tyrosine kinase [BTK (67)]. Activated BTK binds to the scaffold protein BLNK, leading to phosphorylation of PLC-\( \gamma \)-2, calcium mobilization, and activation of transcription factors such as NF-xB, NF-AT, and the mitogen-activated protein kinase pathway (68). The BCR signaling pathway is emerging as a promising target for many lymphomas, including MCL.

**BTK inhibitors.** BTK is critical for B-cell development. Patients with loss-of-function mutations of BTK develop X-linked agammaglobulinemia and lack circulating B-cell lymphocytes (69). MCL cell lines were shown to possess overexpressed and constitutively autophosphorylated BTK, and to be sensitive to BTK inhibition (70). PCI-32765 is an orally selective irreversible inhibitor of BTK that induces B-cell selective apoptosis and inhibits downstream pathway activation (71–73). In a phase I study with PCI-32765 as monotherapy in patients with relapsed aggressive NHL, an objective response rate of 25% (1/4) was reported in patients with MCL (74). Preliminary data from a phase II study of PCI-32765 as single agent in relapsed or refractory patients with MCL showed an ORR of 58% (7/12) in bortezomib-naïve patients, and 75% (9/12) in...
bortezomib-exposed patients (75). The most common grade I/II side effects were fatigue, diarrhea, dizziness, and peripheral edema, and grade III/IV adverse effects (diarrhea, rash, neutropenic fever, and abdominal pain) occurred in 11% of the patients [4/39 (75)]. In most patients with MCL treated with PCI-32765, a reduction in lymphadenopathy was associated with a transient increase in the absolute lymphocyte count, most of which were CD19+/CD5+ and CXCRlow/CD38low cells (76). In addition, in vitro studies of MCL cell lines treated with PCI-32765 showed that PCI-32765 inhibited chemokine-induced adhesion and reduced migration of MCL cells, suggesting that inhibition of BTK may disrupt the interaction of MCL and its microenvironment niche (76).

**Syk inhibitors.** Syk is a tyrosine kinase in the BCR-BTK pathway that has also been investigated in MCL. Studies of MCL cell lines by comparative genomic hybridization, gene expression profiling, and fluorescence in situ hybridization revealed genomic amplification of Syk (77). In addition, in vitro studies of MCL cell lines treated with PCI-32765 showed that PCI-32765 inhibited chemokine-induced adhesion and reduced migration of MCL cells, suggesting that inhibition of BTK may disrupt the interaction of MCL and its microenvironment niche (76).

A study that used gene expression profiling and real-time quantitative reverse transcription PCR to compare MCL cells from peripheral blood of patients with naif B-cells from tonsils revealed upregulation of several genes in the PI3K/AKT pathway in MCL, including PIK3CA and AKT1 (81). In MCL cell lines, the PI3K/Akt and mTOR pathways are constitutively activated, and inhibition of those pathways with Ly294002 (inhibitor of PI3K) and rapamycin (inhibitor of mTOR) resulted in reduced proliferation, G0–G1 cell-cycle arrest, and downregulation of cyclin D1 in vitro (15). In addition, inhibition of PI3K with Ly294002 induced apoptosis in primary MCL cells from patients.

Inhibitors of several components of the PI3K/AKT and mTOR pathways are in clinical trials in MCL. A phase I trial of CAL-101/GS1101, an oral isoform-selective inhibitor of PI3Kδ, in relapsed or refractory NHL, showed an ORR of 62% (10/16) in patients with MCL, with <10% grade III cytopenias (82). A phase III trial comparing temsirolimus, an oral specific inhibitor of the mTOR kinase, versus investigator’s choice of chemotherapy (e.g., gemcitabine, fludarabine, chlorambucil, or cladribine) in relapsed or refractory MCL resulted in improved PFS (4.8 months vs. 1.9 months).
but no difference in OS (83). These results led to the approval of temsirolimus in Europe. The most common grade III/IV adverse events for temsirolimus were thrombocytopenia, anemia, neutropenia, and asthenia. These studies show that inhibitors of the PI3K/mTOR pathway are well tolerated and are active in MCL.

Bendamustine

Bendamustine is a nitrogen mustard compound with alkylating and antimetabolite properties that consists of a 2-chloroethylamine alkylating group, a benzimidazole ring, and a butyric acid side chain (84). First synthesized in the early 1960s in then East Germany as a less toxic alkylating drug, bendamustine does not share strong cross-resistance with other alkylating drugs. It shows a distinct pattern of activity and is highly active against various lymphoma, myeloma, leukemia, and breast cancer cells that are refractory to other alkylating drugs (84, 85). In the United States, bendamustine is approved for the treatment of patients with indolent B-cell NHL progressing after rituximab-based therapy, as well as patients with chronic lymphocytic leukemia. Several studies have shown that bendamustine is effective in MCL either alone or in combination with other agents. In a Japanese multicenter phase II study of bendamustine in relapsed or refractory indolent B-cell lymphoma, a group of 11 patients with MCL was shown to have an ORR of 100%, CR of 64%, PR of 27%, and DFS at 1 year follow-up of 90% (86). Similarly, a multicenter phase II study of bendamustine and rituximab in patients with relapsed indolent B-cell NHL included 12 patients with MCL. In the group of patients with MCL, 42% achieved a CR, 33% had a PR, and 92% showed an ORR, with a median duration of response of 19 months (87). The combination was well tolerated, with the most significant grade III and IV toxicities being leukopenia (30%), neutropenia (37%), and thrombocytopenia (10% (87)). Another phase II study that used a combination of bendamustine, bortezomib, and rituximab in relapsed or refractory B-cell lymphomas included 7 patients with MCL, and this group achieved an ORR of 71% (88). One Italian study evaluated a combination of bendamustine, rituximab, and cytarabine in both untreated and relapsed or refractory patients with MCL (89). Preliminary results showed that the combination was well tolerated, with CR rates of 82% for the untreated population and 67% for the relapsed or refractory population, and 1-year PFS of 87% and 62%, respectively. These nonrandomized phase II studies demonstrate that bendamustine is highly active and well tolerated in MCL, for both untreated and relapsed or refractory patients. How this agent can be optimally incorporated into existing therapies is an area of intense investigation. Numerous phase I and II studies are investigating the effects of combining bendamustine with rituximab, lenalidomide (NCT00963534), cytarabine (NCT00992134), and temsirolimus (NCT01078142), to name just a few. Of importance, SWOG is conducting a randomized phase II study to compare bendamustine with combination chemotherapy comprised of cyclophosphamide, doxorubicin, vincristine, dexamethasone, methotrexate, and cytarabine as the induction therapy for newly diagnosed patients with MCL who are eligible for stem-cell transplant. Patients in both arms of the study also receive rituximab.

Proteasome inhibitors

Proteasomes are important regulators of cellular function and cell fate, because many proteins that are involved in regulating the cell cycle, proliferation, and survival (notably p53 and NF-kB) are regulated by ubiquitin-mediated proteasome degradation (90). Bortezomib is a proteasome inhibitor that forms a covalent and reversible complex with the chymotrypsin-like site in 20S proteasome and induces cell-cycle arrest and apoptosis in MCL cells in vitro (91, 92). Several studies have shown activity of bortezomib as a single agent in refractory or relapsed MCL, with ORR ranging from 29% to 46%, CR from 0% to 21%, and PR from 21% to 42% (93–97). On the basis of these results, the U.S. Food and Drug Administration (FDA) has approved bortezomib for relapsed patients with MCL. However, up to 54% of patients experienced grade III/IV peripheral neuropathy in earlier experiences. Although early detection and dose adjustment of bortezomib markedly reduced the incidence of grade III/IV peripheral neuropathy in later studies because of concerns about compromised patient response due to dose adjustment, several approaches are being used to minimize bortezomib-induced neuropathy. In an analysis of gene expression in the HOVON-65/GMMG-HD4 trial of newly diagnosed multiple myeloma, upregulation of genes RHOB/BL2 (involved in drug-induced apoptosis), CPT1C (mitochondrial dysfunction), and SOX8 (peripheral nervous system development) in the myeloma samples was associated with early-onset bortezomib-induced neuropathy, whereas upregulation of SOD2 and MYO5A (involved in nervous system development) was associated with late-onset bortezomib-induced neuropathy (98). Similarly, a genetic analysis of peripheral blood from these patients revealed that significant single-nucleotide polymorphisms in the genes caspase 9, ALOX12, and IGF1R were associated with early-onset neuropathy, whereas MBL2, PPARD, ERCC3, and ERCC4 were associated with late-onset neuropathy. These interesting findings need to be validated in patients with MCL and in prospective or randomized trials, but they may aid in tailoring bortezomib treatment to individual patients based on their diseases and genetic makeup. In addition, a phase III trial of relapsed multiple myeloma patients in which s.c. and i.v. administration of bortezomib were compared resulted in less peripheral neuropathy (38% vs. 53% for any neuropathy, and 6% vs. 16% for grade III/IV neuropathy), with no difference in ORR, PFS, or OS (99). A newer generation of proteasome inhibitors is also being developed. For example, carfilzomib is a second-generation proteasome inhibitor that irreversibly and preferentially targets the chymotrypsin-like activity of the 20S core proteasome and immunoproteasome (100). Carfilzomib was able to achieve an ORR ranging from 50% to 60% as a single agent in patients with relapsed multiple myeloma, with minimal neuropathy (101–103). Data on the clinical activity of carfilzomib in MCL are very limited at
present (104). Clinical trials are being conducted to investigate the activity of carfilzomib in combination with the histone deacetylase inhibitor vorinostat in B-cell and T-cell lymphomas based on the strong synergy of these drugs in MCL in preclinical studies (105). Bortezomib is also increasingly being investigated in combination with other drugs for MCL. In previously untreated patients with MCL, bortezomib plus R-CHOP resulted in an ORR of 81%, CR of 64%, and PR of 17%, with median PFS of 23 months and median OS not reached at median follow-up of 34 months (106). Another study that incorporated bortezomib into modified R-hyperCVAD in untreated patients with MCL resulted in an ORR of 90%, CR of 77%, and PR of 13%, with 3-year PFS and OS of 63% and 86%, respectively (107).

**Targeting the MCL microenvironment**

The tumor microenvironment has emerged as an important mechanism of drug resistance and a promising therapeutic target in hematologic malignancies (108, 109). DNA microarray and immunohistochemistry of MCL tissue revealed overexpression of chemokines CCL4, CCL5, and 4-1BB ligand, which are normally involved in immune regulation by promoting T-cell recruitment and B-cell activation (110). MCL cell lines have also been shown to overexpress CXCR4 and CXCR5 chemokine receptors and VLA-4 adhesion molecules. Furthermore, a CXCR4 antagonist, plerixafor, was able to block the migration of MCL cells beneath bone marrow stromal cells (111). Another CXCR4 antagonist, BKT140, was found to target lymphoma cells effectively in the bone marrow microenvironment and to synergize with rituximab (112).

Drugs targeting the lymphoma/leukemia microenvironment are in various stages of clinical development. Plerixafor is a CXCR4 antagonist that has been approved by the FDA for stem-cell mobilization and is being studied in combination with lenalidomide for the treatment of chronic lymphocytic leukemia. Lenalidomide has been shown to have antiproliferative and antiangiogenic properties, and to augment both adaptive and innate immune systems and overcome the tumor-promoting effects of the tumor microenvironment in preclinical models of multiple myeloma and lymphomas (113). An analysis of bone marrow from patients with MCL receiving lenalidomide treatment showed that lenalidomide induced an increase in microvessel density and activation of macrophage and natural killer cells, supporting an immunomodulatory effect of lenalidomide on the tumor microenvironment (114). Furthermore, lenalidomide has been shown to enhance rituximab-induced, antibody-dependent cellular cytotoxicity in MCL cell lines in vitro (115).

Lenalidomide is approved by the FDA for the treatment of myelodysplastic syndrome with the 5q– syndrome and for multiple myeloma, and has shown significant activities for NHL including MCL, with ORR typically up to 50% for relapsed MCL (116–118). In a large phase II trial in patients with relapsed and refractory NHL, the ORR of lenalidomide for 57 patients with MCL was 42% (119). In another phase II study, patients with relapsed or refractory MCL not eligible for ASCT responded well to a combination of lenalidomide and dexamethasone, producing an ORR and CR rate of 52% and 24%, respectively, with a median PFS of 12 months in a population of 33 patients (114). A registration-directed study of lenalidomide in >100 patients with relapsed or refractory MCL has now completed accrual. Lenalidomide in combination with rituximab was well tolerated in a recently completed phase II clinical study of 46 patients with relapsed and refractory MCL (120). In this study, the ORR was 58%, with a CR rate of 33%. Preliminary results from a phase I trial incorporating lenalidomide with rituximab and bendamustine as front-line therapy in elderly patients (>65 years) with MCL showed an ORR of 100% (10/10), although with significant toxicity, including cutaneous and allergic reactions (121). The effects of lenalidomide on the host immune system and the tumor microenvironment suggest that this agent may be an excellent modality for maintenance therapy in MCL.

In Europe, 2 clinical trials, the MCL0208 trial for previously untreated MCL and the R2-B trial for relapsed refractory MCL, are being planned to evaluate the efficacy of lenalidomide as a maintenance treatment after chemotherapy (122).

**Conclusions**

With our increased understanding of the biology of MCL, improvement in OS and prolonged disease control may be beginning to emerge. The introduction of rituximab as part of induction therapy and purging during ASCT has improved the outcomes of patients with MCL. Intensification of chemotherapy followed by ASCT, especially when given in first remission, is also associated with improved PFS and contributes to improvement in OS. Novel drugs targeting dysregulated pathways in MCL, particularly BCR and deregulated cell-cycle control, will likely emerge as important components in next-generation combination therapies. These novel targeted drugs, as well as drugs currently approved for other hematologic malignancies (e.g., bendamustine and 2-CDA), may provide abundant opportunities for patients with relapsed MCL. A major challenge will be to design studies that will allow us to define the incremental benefit of integrating these new drugs into existing treatment paradigms.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**Development of methodology:** C. Deng, O.A. O’Connor

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** C. Deng, O.A. O’Connor

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New Strategies in Mantle Cell Lymphoma


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New Strategies in the Treatment of Mantle Cell Lymphoma

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