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’s lymphoma (NHL) traditionally thought to possess the poor risk features of both indolent lymphoma, with its incurability, and aggressive lymphoma, with its ability to proliferate rapidly. While there is considerable debate as to whether MCL can be cured or not, 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 greater than 90%, sometimes even 100% in the frontline setting, while 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. We will discuss many of these developments and how they may potentially impact the natural history of this disease.

Background

Molecular Pathogenesis of MCL. Much progress has been made in the past decade in our understanding of the biology of mantle cell lymphoma (MCL), which has evolved from one based on morphology to one based on its underlying molecular features (1). What is clear now is 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 Figure 1. On a molecular level, the pathognomonic chromosomal translocation t(11;14)(q13;q32) places cyclin D1 downstream of the highly active IgH enhancer (7). Subsequently, the mRNA of cyclin D1 undergoes alternative splicing to produce two transcripts: cyclin D1a, whose role in MCL pathology has
have been well established; and cyclin D1b, whose expression in MCL is more variable and its role less well defined (8, 9). Deletion or mutation of the cyclin D1a mRNA tail region produces a truncated version of cyclin D1a mRNA, which is six times more stable than the wild-type full-length cyclin D1a mRNA (10). At the translation level, cyclin D1a is down-regulated by microRNAs, 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), while polyubiquitination and degradation of cyclin D1 is 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 (Figure 1). Cyclin D1 interacts with CDK4 or CDK6 to promote cell cycle progression through the G1-S check point (19-21). CDK4 is frequently overexpressed or amplified in MCL (22, 23). In contrast, the levels of the CDK inhibitors p16 and p27 are either absent or severely decreased in many MCL patients (24-26). Deletion of p16 has been found in approximately half of all MCL patients, 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, while loss of p16 and p27 removes the brakes, for MCL cells to bypass normal cell cycle control and checkpoints (Figure 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 (31), and a shorter overall survival (OS) of only 1.38 years, compared to 3.28 years for patients with the 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 shRNA targeting cyclin D1, and has been shown to reduce proliferation and clonogenic survival of MCL cells (8, 33, 34).

Clinical Perspectives of MCL. Mantle cell lymphoma has been historically treated like most other forms of B-cell non-Hodgkin's lymphoma (NHL), with CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone) like regimens. However, early retrospective studies in the U.S. and Europe demonstrated that MCL patients treated with CHOP based regimens had an OS of less than 3 years, much worse than other indolent lymphomas (35, 36). The addition of the anti-CD20 antibody rituximab to CHOP improved the ORR from 75% to 94%, while the CR rate improved from 7% to 34% (37). A 5 year update of this dataset demonstrated that the median response duration was prolonged from 18 months for CHOP to 29 months for R-CHOP (p = 0.0052), and the 5-years OS rate was 59% for R-CHOP, compared to 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 < .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 MD Anderson Cancer Center (MDACC) reported high a CR rate, up to 68%, for elderly patients with aggressive MCL treated with fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (hyperCVAD) alternating 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 survival (82% at 3 years) in this patient group. At 10 years follow up, the OS rate was 64%, which compared favorably with other treatment regimens, including those incorporating stem cell rescue (42). However, there remain significant uncertainties regarding this regimen, as patients in this study appeared to be enriched for low Ki-67, at least among those patients who had adequate samples for the analysis. 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 to primarily to hematologic toxicities (43).

On the Horizon

**Autologous Stem Cell Transplant (ASCT) 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, the efficacy of ASCT has been investigated extensively. Early small studies suggested that patients who received ASCT in first remission experienced better OS, disease free survival, and event free survival compared to those receiving ASCT after relapse (44-46). Vandenberghhe and colleagues conducted a retrospective analysis of 340 MCL patients who received ASCT
identified from the European Blood and Bone Marrow Transplant (EBMT) Registry or Autologous Blood and Marrow Transplant Registry (ABMTR) (47). The 2-year and 5-year progression free survival rates were 55% and 33% respectively. Importantly, patients transplanted for relapsed MCL were 2.99 times (95% CI: 1.66–5.38, P < 0.001) more likely to die compared to patients transplanted in first remission.

More definitive evidence supporting transplant in first remission was provided by a randomized trial conducted by Dreyling and colleagues from the European MCL Network (48). In this trial, previously untreated advanced stage MCL patients received CHOP like chemotherapy for induction. Patients achieving 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 interferon-α 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 to 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 is no difference in OS between arms A and B. In conclusion, while the role of ASCT for MCL patients with relapsed disease has been generally disappointing, ASCT in first remission may represent the optimal place to consider 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 have 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) alternating 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 the 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 event free survival (EFS) rate of 63% (51). Importantly, the Nordic MCL-2 trial reported marked improvement of clinical outcomes compared to an earlier MCL-1 trial, conducted in a similar patient population that 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, FFS, 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 is a logical strategy to treat MCL. However, there is currently no specific inhibitor of cyclin D1 available for patients. Alternatively, the function of cyclin D1 can be inhibited through inhibition of its catalytic partners, CDK4 and CDK6. In this regard, flavopiridol was found to be a potent inhibitor of cell cycle and a pan-CDK inhibitor based on an anticancer drug-screening program of the National Cancer Institute (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 the 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). SCH727965 (dinaciclib) is a novel inhibitor of CDK1, 2, 5 and 9, with superior activity and an improved therapeutic index compared to flavopiridol in laboratory models of solid and hematological malignancies (61, 62), and is the subject of intense investigation in numerous clinical trials (63-65). Preliminary data did not demonstrate dramatic response to these CDK inhibitors, suggesting other deregulated...
pathways are contributing to the growth and survival advantages of aggressive MCL cells compared to the normal cells (8, 33, 34).

**B-Cell Receptor (BCR) Signaling Pathway: Targeting Bruton Tyrosine Kinase and Syk**

A recent proteomic screen of phosphorylated proteins in MCL cells indicated that proteins connecting the BCR signaling network were among the most abundant signals found, and active BCR signaling in MCL cells was confirmed by flow cytometry (66). As depicted in Figure 2, B-cell lymphocytes are activated via antigen binding and oligomerization of the B-cell receptor, composed of surface immunoglobulin and Igα/Igβ heterodimers, leading to phosphorylation of Src-family tyrosine kinases Lyn and Syk, which in turn leads to transphosphorylation and autophosphorylation of Bruton’s tyrosine kinase (BTK) (67). Activated BTK binds to the scaffold protein BLNK, leading to phosphorylation of PLC-γ2, calcium mobilization, and activation of transcription factors including NF-kappaB, NF-AT, and MAP 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 have been shown to possess overexpressed and constitutively autophosphorylated BTK, and were 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 non-Hodgkin lymphoma, 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 MCL patients resulted in 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 occurred in 11% (4/39), which were diarrhea, rash, neutropenic fever, and abdominal pain (75). In most MCL patients 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 CXCRloCD38lo cells (76). In addition, in vitro studies of MCL cell lines treated with PCI-32765 show that PCI-32765 inhibits chemokine-induced adhesion, and reduces 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, eight out of ten MCL samples from patients in that study also showed Syk overexpression by immunohistochemistry. Treatment of the MCL cell line Jeko-1 with picetannol, a Syk inhibitor, resulted in growth inhibition and apoptosis in vitro, suggesting Syk is a potential therapeutic target in MCL (77). A phase I/II clinical trial of fostamatinib sodium, an oral SyK inhibitor, in non-Hogkin lymphoma and CLL included 9 patients with MCL. The ORR was 11% in patients with MCL (1/9 patients), while the dose-limiting toxicity was neutropenia, diarrhea, and thrombocytopenia (78). Further studies are needed to establish inhibition of Syk as a clinically important therapeutic target in MCL.

**PI3K/mTOR/AKT inhibitors**

The PI3K/mTOR/AKT pathway has been shown to be an important regulator of cell growth, proliferation, and survival, and has been investigated as a potential therapeutic target in hematologic malignancies (79). Briefly, various receptor tyrosine kinases are activated by antigens or growth factors, leading to activation of phosphatidylinostitol 3-kinase (PI3K), as shown in Figure 2. PI3K converts phosphatidylinositol-4,5-biphosphate to phosphatidylinositol-
3,4,5-triphosphate (PIP3), leading to recruitment of AKT protein kinase to the plasma membrane and phosphorylation. Activated AKT leads to phosphorylation of a variety of substrates, including tuberous sclerosis complex 2, leading to activation of mammalian Target of Rapamycin (mTOR) kinase (80). mTOR regulates mRNA translation of many genes, including cyclin D1 and p27Kip1, and is an important regulator of cell cycle, survival, and proliferation (79).

A gene expression profiling and real time quantitative reverse transcription PCR comparing MCL cells from peripheral blood of patients with naïve B-cells from tonsils revealed up-regulation of several genes in the PI3K/AKT1 pathway in MCL, including PIK3CA and AKT1 (81). In MCL cell lines, 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 down-regulation of cyclin D1 in vitro (82). In addition, inhibition of PI3K with Ly294002 induced apoptosis in primary MCL cells from patients (82).

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 overall response rate of 62% (10/16) in patients with MCL, with less than 10% grade III cytopenias (83). A phase III trial comparing temsirolimus, an oral specific inhibitor of the mTOR kinase, versus investigator’s choice (gemcitabine, fludarabine, chlorambucil, cladribine, among others) of chemotherapy in relapsed or refractory MCL resulted in improved progression free survival (4.8 months versus 1.9 months), although overall survival was not different (84). 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 PI3K/mTOR pathway are well-tolerated and are active in MCL.
Bendamustine

Bendamustine is a nitrogen mustard compound with alkylating and anti-metabolite properties, comprising of a 2-chloroethylamine alkylating group, a benzimidazole ring, and a butyric acid side chain (85). 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 and demonstrate a distinct pattern of activity, and is highly active against various lymphoma, myeloma, leukemia, and breast cancer cells refractory to other alkylating drugs (85, 86). In the United States, bendamustine is approved for the treatment of patients with indolent B-cell NHL progressing after rituximab-based therapy and in patients with chronic lymphocytic leukemia. Several studies have shown that bendamustine is effective in mantle cell lymphoma 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, 11 patients with mantle cell lymphoma were shown to have an ORR of 100%, with CR of 64%, PR of 27%; and the PFS at one year follow-up was 90% (87). Similarly, a multicenter phase II study of bendamustine and rituximab in patients with relapsed indolent B-cell non-Hodgkin lymphoma included 12 patients with mantle cell lymphoma; in the mantle cell lymphoma patients, 42% achieved CR, 33% PR, and 92% ORR, with median duration of response of 19 months (88). The combination was well tolerated, with most significant grade III and IV toxicities being leukopenia (30%), neutropenia (37%), and thrombocytopenia (10%) (88). Another phase II study utilizing combination of bendamustine, bortezomib, and rituximab in relapsed or refractory B-cell lymphomas included 7 mantle cell lymphoma patients, who achieved ORR of 71% (89) One Italian study evaluated combination of bendamustine, rituximab, and cytarabine in both untreated and relapsed or refractory mantle cell lymphoma patients; preliminary results show that the combination was well tolerated, with complete response rates of 82% for untreated and 67% for relapse or refractory patients, with one year progression-free survival of 87% and 62%, respectively (90). These non-randomized
phase II studies demonstrate that bendamustine is highly active and well-tolerated in mantle cell lymphoma, for both untreated and relapsed/refractory patients; how it 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), temsirolimus (NCT01078142), to name just a few. Importantly, SWOG is conducting a randomized phase II study that compares bendamustine with combination chemotherapy comprised of cyclophosphamide, doxorubicin, vincristine, dexamethasone, methotrexate, and cytarabine as the induction therapy for newly diagnosed MCL patients eligible for stem cell transplant. Both arms also receive rituximab.

Proteasome inhibitors

Proteasomes are important regulators of cellular function and cell fate, as many proteins involved in regulating cell cycle, proliferation, and survival are regulated by ubiquitin-mediated proteasome degradation, notable examples being p53 and NF-kappaB (91). Bortezomib is a proteasome inhibitor that forms covalent and reversible complex with the chymotrypsin-like site in 20S proteasome and induces cell cycle arrest and apoptosis in mantle cell lymphoma cells in vitro (92, 93). Several studies have shown activity of bortezomib as a single agent in refractory or relapsed mantle cell lymphoma, with ORR ranging from 29% to 46%, CR from 0% to 21%, and PR from 21% to 42% (94-98). Based on these results, the FDA has approved bortezomib for relapsed MCL patients. However, up to 54% of patients experienced grade III/IV peripheral neuropathy in earlier experiences. Although early detection and dose adjustment of bortezomib have markedly reduced the incidence of grade III-IV peripheral neuropathy in later studies, the concern of compromised patient response due to dose adjustment has led to several approaches to minimize bortezomib-induced neuropathy. In an analysis of gene expression in the HOVON-65/GMMG-HD4 trial of newly diagnosed multiple myeloma, up-regulation of genes RHOBTB2 (involved in drug-induced apoptosis), CPT1C (mitochondrial dysfunction), and
SOX8 (peripheral nervous system development) in the myeloma samples were associated with early-onset bortezomib-induced neuropathy, while up-regulation of SOD2 and MYO5A, involved in development of nervous system, were associated with late-onset bortezomib-induced neuropathy (99). Similarly, genetic analysis of peripheral blood from these patients revealed that significant single nucleotide polymorphisms (SNP) in the genes caspase 9, ALOX12, and IGF1R were associated with early-onset neuropathy, while MBL2, PPARD, ERCC3, and ERCC4 were associated with late-onset neuropathy. These interesting findings need to be validated in MCL patients and in prospective or randomized trials, but promise to tailor bortezomib to individual patients based on their diseases and genetic makeup. In addition, a phase III trial of relapsed multiple myeloma patients comparing subcutaneous versus intravenous administration of bortezomib resulted in less peripheral neuropathy (38% versus 53% for any neuropathy, and 6% versus 16% for grade III/IV neuropathy), with no difference in response rate, PFS, and OS (100). Newer generation of proteasome inhibitors are also being developed. For example, carfilzomib is a 2nd generation proteasome inhibitor, which irreversibly and preferentially targets the chymotrypsin-like (CT-L) activity of the 20S core proteasome and immunoproteasome (101). Carfilzomib is able to achieve an ORR ranging from 50% to 60% as a single agent in relapsed multiple myeloma patients with minimal neuroapathy (102-104). Data on the clinical activity of carfilzomib in MCL are very limited at present (105); clinical trials are being conducted to investigate the activity of carfilzomib in combination with the histone deacetylase inhibitor vorinostat in B- and T-cell lymphomas based on strong synergy of these drugs in MCL in preclinical studies (106). Bortezomib is also increasingly investigated in combination with other drugs for MCL. In previously untreated mantle cell lymphoma patients, bortezomib plus R-CHOP resulted in ORR of 81%, CR of 64%, PR of 17%, with median PFS of 23 months, and median OS not reached at median follow-up of 34 months (107). Another study incorporating bortezomib into modified R-hyperCVAD in untreated mantle cell lymphoma
patients resulted in ORR of 90%, CR of 77%, and PR 13%, with 3 year PFS and OS of 63% and 86%, respectively (108).

**Targeting MCL Microenvironment**

Tumor microenvironment has emerged as an important mechanism of drug resistance, and a promising therapeutic target in hematologic malignancies (109, 110). 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 (111). 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 the bone marrow stromal cells *in vitro*. As the stromal cells were protective for the MCL cells against chemotherapy, disrupting CXCR4 dependent interaction with the tumor microenvironment may overcome chemo-resistance provided by the microenvironment (112). Another CXCR4 antagonist, BKT140, was found to effectively target lymphoma cells in the bone marrow microenvironment, and synergized with rituximab (113).

Drugs targeting the lymphoma / leukemia microenvironment are in various stages of clinical development. Plerixafor is a CXCR4 antagonist approved for stem cell mobilization, and is studied in combination with lenalidomide for the treatment of CLL. Lenalidomide has demonstrated antiproliferative and anti-angiogenic properties, and is able to augment adaptive and innate immune system, and overcome the tumor promoting effects of tumor microenvironment in preclinical models of multiple myeloma and lymphomas (114). Analysis of bone marrow from MCL patients receiving lenalidomide treatment showed lenalidomide induced an increase in micro-vessel density, and activation of macrophage and NK cells, supporting immunomodulatory effect of lenalidomide on the tumor microenvironment (115). Furthermore,
lenalidomide has been shown to enhance rituximab-induced antibody-dependent cellular cytotoxicity in MCL cell lines in vitro (116).

Lenalidomide is approved for the treatment of myelodysplastic syndrome with 5q- syndrome and for multiple myeloma, and has demonstrated significant activities for NHL including MCL, with ORR typically up to 50% for relapsed MCL (117-119). In a large phase II trial of relapsed and refractory NHL patients, the ORR of lenalidomide for 57 MCL patients was 42% (120). In another phase II study, patients with relapsed or refractory MCL not eligible for ASCT responded well to the combination of lenalidomide and dexamethasone, producing ORR and CR rate of 52% and 24%, respectively, with a median PFS of 12 months among 33 patients (121). A registration directed study of lenalidomide in over 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 (122). 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 (>65 years) with MCL show ORR 100% (10/10), although with significant toxicity, including cutaneous and allergic reactions (123). The effects of lenalidomide on the host immune system and the tumor microenvironment suggest that it may be an excellent modality for maintenance therapy in MCL. Two clinical trials, the MCL0208 trial for previously untreated MCL and R2-B trial for relapsed or refractory MCL, are planned in Europe to evaluate the efficacy of lenalidomide as a maintenance treatment after chemotherapy (124).

**Conclusion**

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 MCL patients. Intensification
of chemotherapy followed by ASCT, especially given to those 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 therapy. For patients with relapsed MCL, there are abundant opportunities using these novel targeted drugs, as well as drugs currently approved for other hematological malignancies, including bendamustine and 2-CDA. 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.

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Figure legends

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

**Figure 2.** BCR and PI3K are two interconnected pathways that share both upstream and downstream signals. Together they promote the growth, proliferation, and survival of MCL cells.
Skp2 mediated protein degradation

- Overexpression and gene amplification
- Deregulated cell cycle progression, manifested by high Ki-67

- Cyclin D1
- CDK4
- mTOR prevents GSK3β-dependent ubiquitination and degradation

Cyclin D1
CDK4
mTOR
GSK3β

(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
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