Novel Therapies in Mantle Cell Lymphoma: A Pathway to Chemotherapy-Free Strategies

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This review will cover innovative therapeutic approaches in relapsed or refractory MCL, many of which have the potential to alter treatment paradigms toward the development of strategies that do not involve conventional chemotherapy agents.

Introduction

Mantle cell lymphoma (MCL) is an uncommon but distinct subtype of non-Hodgkin lymphoma (NHL) associated with a poor prognosis.[1] The incidence of MCL has increased over the past decade, a change that may in part reflect development of more sensitive diagnostic technologies that have resulted in improvements in classification over the same period. However, the rising incidence of MCL in elderly persons, particularly white men, remains unexplained.[2] Typically, patients present in their late 60s with advanced-stage disease, and they often have concomitant extranodal involvement.[3,4]

With the introduction of high-dose cytarabine, intensification of induction therapy, and consolidation with autologous transplant, responses and disease-free intervals have improved for patients with previously untreated MCL.[5-10] Despite these advances, most patients eventually relapse and die from MCL or related complications. In addition, this disease affects elderly patients, many of whom may not be candidates for intensive therapy. Therefore, more effective therapies for this patient population are needed. This review will cover innovative therapeutic approaches in relapsed or refractory MCL, many of which have the potential to alter treatment paradigms toward the development of strategies that do not involve conventional chemotherapy agents.

Molecular Targets in Mantle Cell Lymphoma

MCL is characterized by overexpression of cyclin D1, a cell cycle regulator that promotes cellular proliferation. Secondary genetic events that enhance cell growth, activate cell survival pathways, inhibit apoptosis, and promote interactions with the tumor microenvironment also serve as potential targetable mechanisms of lymphomagenesis.[11-13] More specifically, evidence that MCL pathogenesis is antigen-dependent[14] and that these tumors exhibit constitutive B-cell receptor (BCR) activation[15] posits the BCR signaling pathway as a rational prospect for drug development. Several key components of this pathway have been explored as potential targets in MCL therapy. Spleen tyrosine kinase (SYK) is amplified in some patients with MCL, and its inhibition leads to the arrest of cell proliferation and apoptosis.[11] Acting downstream of SYK, Bruton tyrosine kinase (BTK) is a promising target in a variety of B-cell malignancies, including MCL.[16,17] In addition, BCR ligation activates the prosurvival phosphoinositide-3 kinase (PI3K) pathway via AKT, which itself has been implicated in MCL pathogenesis.[12,18,19] The development of specific tyrosine kinase inhibitors that target elements in these pathways has allowed molecularly driven clinical investigation in MCL.

Inhibition of cyclin D1

Cyclin D1 overexpression is the distinguishing aberrancy in MCL. The broad cyclin-dependent kinase (CDK) inhibitor flavopiridol leads to downregulation of cyclin D1 and induces apoptosis of malignant lymphocytes in vitro and in murine lymphoma models.[20] In a phase I study of flavopiridol, 7 of 46 patients had relapsed MCL; of these, 2 achieved a partial response (PR).[21] Hematologic toxicity was common, with grade 3/4 leukopenia observed in 60% of patients, but infection was infrequent. Common nonhematologic toxicities included diarrhea and fatigue. Biochemical tumor lysis was observed in two patients, but neither required hemodialysis.
Flavopiridol has also shown activity in combination with fludarabine and rituximab or bortezomib in phase I clinical trials.[22,23] A direct CDK 4/6 inhibitor, PD0332991, demonstrated clinical benefit in 17 patients with MCL; 5 patients achieved progression-free survival (PFS) of > 1 year, with 1 complete response (CR) and 2 PRs (overall response rate [ORR] = 18%).[24] Despite the promise of direct CDK inhibition for a disease characterized by cyclin overexpression, CDK inhibitors have had little clinical impact in MCL to date.

**Targeting the B-cell receptor signaling pathway**

Recent clinical research has targeted the BCR signaling pathway. BCR activation engages the prosurvival nuclear factor kappa B (NF-kB) pathway.[25] Bortezomib, a proteasome inhibitor that inhibits NF-kB, received approval from the US Food and Drug Administration (FDA) for use in the setting of relapsed MCL based on results of the phase II multicenter PINNACLE study.[26,27] with additional supporting data from smaller single-center and multicenter phase II studies.[28,29] The PINNACLE study included 155 patients with relapsed or refractory MCL who had received one to three previous lines of therapy. Bortezomib was associated with an ORR of 32% (8% CR or complete response/unconfirmed [CRu]), median response duration of 9.2 months, median time to progression of 6.7 months, and median overall survival (OS) of 23.5 months. In patients who achieved a CR, median response duration and time to progression were not reached after a median follow-up of 26.4 months, with median OS of 36 months. The most common grade ≥ 3 adverse events were peripheral neuropathy, fatigue, and thrombocytopenia. Single-agent bortezomib was associated with remarkable survival in patients with relapsed or refractory MCL, given that 98% of patients had previously received multiagent therapy involving an anthracycline. Immunohistochemical analyses of archival tumor specimens (N = 73) used in preplanned exploratory analyses of candidate biomarkers of bortezomib activity indicated that elevated NF-kB p65 demonstrated a trend for better response and longer OS, elucidating the role of NF-kB pathway inhibition in MCL treatment.[30] Other proteasome inhibitors are now available that can also be explored in MCL.

Because constitutive BCR signaling plays a role in NF-kB activation in MCL and other lymphoma subtypes, upstream inhibition of the BCR signaling pathway has also been explored. Ibrutinib is an orally available, highly selective, irreversible inhibitor of BTK that provides more direct targeting of the BCR signaling pathway upstream. Early clinical studies involving ibrutinib have demonstrated activity in several B-cell malignancies.[17,31,32] A recent phase II international study investigated the efficacy and safety of ibrutinib in patients with relapsed or refractory MCL.[16] A total of 115 patients were enrolled (111 received study drug) and were classified as bortezomib-exposed (≥ 2 cycles of bortezomib) or bortezomib-naïve (no prior exposure or < 2 cycles of bortezomib). The median age of patients was 68 years; 77% were male; 49% had a high Mantle Cell Lymphoma International Prognostic Index (MIPI) score; median number of prior therapies was three (including 11% who had undergone stem cell transplant); and 45% had refractory disease. With a median follow-up of just over 15 months, the ORR in patients who received ibrutinib was 68%, with a CR in 21% and a PR in 47%. Response did not vary according to baseline characteristics or prior therapy, and responses improved over time with continued therapy. Estimated median response duration was 17.5 months, median time to response was 1.9 months, and median time to CR was 5.5 months. The estimated median PFS among treated patients was 13.9 months. The median OS for this study was not reached (estimated OS rate was 58% at 18 months). Grade 3/4 adverse events were uncommon; the most frequent treatment-related effects were mild or moderate diarrhea, fatigue, and nausea. Grade 3/4 hematologic adverse events included neutropenia in 16% of patients, thrombocytopenia in 11%, and anemia in 10%. The authors concluded that ibrutinib demonstrates efficacy as a single agent in patients with relapsed or refractory MCL and is associated with a favorable toxicity profile. The phase I/II clinical trial investigating the oral SYK inhibitor fostamatinib in relapsed NHL and chronic lymphocytic leukemia (CLL) enrolled 3 MCL patients in the phase I cohort and 9 MCL patients in the phase II cohorts.[32] The most common grade 3/4 adverse events were neutropenia and anemia in 18% and 7% of patients, respectively. Of the MCL patients in the phase II portion of the trial, one achieved a PR and four demonstrated stable disease, with median PFS of 3.8 months. This clinical trial was one of the first to demonstrate that disruption of the BCR signaling pathway represents a novel and active therapeutic approach for NHL, but the efficacy of SYK inhibition in MCL remains unclear.

Protein kinase C beta (PKCβ) acts downstream of SYK as the major PKC isoform involved in BCR signaling. PKCβ is an important modulator of the angiogenic activity of vascular endothelial growth factor (VEGF). Notably, elevated baseline levels of VEGF and increased vascularity are associated with poor prognosis in NHL patients, including those with MCL.[34] Enzastaurin is an oral inhibitor of
signaling through the PKCβ/PI3K/AKT pathways. A phase II trial of enzastaurin enrolled 60 patients (median age = 66 years) with relapsed or refractory MCL.[35] Although no objective tumor responses occurred, 22 patients (37%) were free from progression for ≥ 3 cycles (one cycle = 28 days), with 6 free from progression for > 6 months. The most common toxicity was fatigue; no grade 4 toxicities were reported.

As mentioned earlier, BCR ligation activates the PI3K signaling pathway. In fact, constitutive activation of BCR signaling independent of receptor ligation appears to be mediated by class 1 isoforms (α, β, δ, γ) of PI3K, with the p110δ isoform highly expressed in cells of hematopoietic origin and strongly upregulated in various hematologic malignancies.[36] Idelalisib is an orally available selective inhibitor of the p110δ isoform of PI3K. A phase I study investigating idelalisib includes 18 patients with MCL; preliminary results were presented in 2010.[37] Grade ≥ 3 hematologic adverse events included neutropenia (9%), lymphopenia (5%), and thrombocytopenia (5%). Two to 8 weeks after initiation of the study drug, about one-third of patients had a grade 3 elevation in liver enzymes, which resolved 2 to 4 weeks after drug interruption. After liver enzyme abnormalities resolved, most patients were rechallenged with idelalisib at either initial or reduced dose, and the majority were able to resume treatment without recurrence of transaminase elevations. In evaluable MCL patients, 62% achieved a PR. The median duration of response in MCL patients was 3 months. The authors concluded that targeting the PI3Kδ isoform in relapsed NHL remains promising and has an acceptable safety profile.

Mammalian target of rapamycin (mTOR) kinase is a key downstream component of the PI3K/AKT pathway. Temsirolimus, a specific inhibitor of mTOR kinase, was compared with standard chemotherapeutic single agents in an open-label, randomized phase III study of patients with relapsed or refractory MCL, and was associated with significant improvement in PFS (4.8 months vs 1.9 months, respectively) and in objective response rates (22% vs 2%, respectively).[38] However, there was no significant difference in median OS between the temsirolimus 175/75 mg group and the investigator’s choice group: 12.8 months vs 9.7 months, respectively (P = .3519). The most frequent grade 3/4 adverse events in the temsirolimus groups were thrombocytopenia, anemia, neutropenia, and asthenia. Based on this study, temsirolimus is approved for relapsed MCL in Europe.

Regulators of Apoptosis

The Bcl family of proteins are key regulators of apoptosis, making them attractive targets in many hematologic malignancies. The anti-apoptotic protein Bcl-2 is often constitutively overexpressed in MCL, which may contribute to resistance to apoptosis.[39] A phase I study is evaluating the selective Bcl-2 inhibitor ABT-199 in patients with relapsed or refractory NHL; preliminary results have been presented.[40] In the 31 patients enrolled as of January 11, 2013, the median age was 68 years, the median number of prior therapies was 3, and 13 (42%) and 4 (13%) patients had bulky disease (> 5 and > 10 cm, respectively). The most common adverse events were nausea (36%), diarrhea (26%), dyspepsia, vomiting, fatigue, pyrexia, and cough (16% each). Grade 3/4 adverse events were anemia (13%), neutropenia (13%), febrile neutropenia (6%), and thrombocytopenia (10%). Grade 3 tumor lysis occurred after the initial dose in one patient with bulky adenopathy (> 10 cm). With a median follow-up of 5 months, ORR was 55% in the 29 evaluable patients, with 1 CR (in a patient with diffuse large B-cell lymphoma) and 15 PRs (52%). Of note, 8/8 MCL patients achieved a PR. Additional follow-up and further studies are planned.

Immunomodulatory Drugs in MCL

Although the precise mechanisms of action of lenalidomide, an analog of thalidomide, are unknown, its efficacy has been attributed to targeting the tumor microenvironment by enhancing the proliferative and functional capacity of T cells and increasing natural killer cell–mediated antibody-dependent cell cytotoxicity.[41-44] Preliminary results of a multicenter phase II study of single-agent lenalidomide in 134 MCL patients who had relapsed after or were refractory to bortezomib therapy led to FDA approval of lenalidomide in this setting.[45] Median age was 67 years (≥ 65 years in two-thirds), and the median number of prior therapies was 4. ORR was 28% (CR or CRu, 8%), median duration of response was 16.6 months, median PFS was 4 months, and median OS was 19 months. The most common grade 3/4 adverse events were neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (8%), and fatigue (7%). Other adverse events (any grade) included tumor flare reaction (10%), deep venous thrombosis (4%), pulmonary embolism (2%), and invasive second primary malignancies (2%). In this heavily pretreated population, lenalidomide was associated with durable efficacy and with the expected toxicity profile.
Disruption of Adhesion and Chemotaxis of MCL cells

An interesting observation in early clinical trials investigating drugs that disrupt the BCR signaling pathway (e.g., ibrutinib) was that rapid lymphocytosis often occurred concomitantly with marked reductions in lymphadenopathy following initiation of the study drug. This phenomenon was noted in both CLL and MCL.[17,31] In a phase II study of ibrutinib in MCL, 34% of patients had a transient increase in lymphocytosis; the peak occurred at a median of 4 weeks after initiation of treatment and substantially tapered off during cycle 4 or 5.[16] Peripheral blood samples from patients enrolled in phase I and II trials of ibrutinib have been analyzed[16,31]; CD19+CD5+ cells were found to have significant reduction in the expression of CXCR4, CD38, and Ki67 after 7 days of treatment.[46] In addition, plasma chemokines CCL22, CCL4, and CXCL13 were reduced 40% to 60% after treatment. This suggests a role for BCR signaling in chemokine-mediated adhesion and chemotaxis of MCL. Therapeutically, this has interesting implications and may affect how clinicians monitor and assess treatment response.

Conclusions

MCL is a subtype of NHL that remains a clinical challenge: with standard chemotherapeutic approaches, it is incurable, and most patients will succumb to the disease. Clearly, this disease warrants novel therapies with tolerable side effect profiles. Biologically, the known genetic aberrancies in MCL afford researchers the opportunity to investigate molecularly targeted therapy. We have summarized innovative single-agent therapies (Table) that hold promise in relapsed MCL, although many questions remain. How can the therapeutic efficacy of these targeted approaches be maximized? Will targeting multiple pathways simultaneously ward off resistance, or should single agents be used sequentially or in conjunction with multidrug chemoimmunotherapy instead? How will these innovative approaches be incorporated into front-line therapy? The future of lymphoma clinical research is at once full of hope and full of complexity. We will need to be adaptive in our approach in order to overcome the intricate mechanisms underlying mantle cell lymphomagenesis, but these promising agents provide the foundation for constructing treatment strategies for MCL that avoid or limit the use of chemotherapy.

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Table: Clinical Trials of Novel Single-Agent Approaches in Relapsed MCL

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