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Novel therapies for relapsed/refractory mantle cell lymphoma

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ABSTRACT

Mantle cell lymphoma is an aggressive Non-Hodgkin's lymphoma that is considered incurable with standard therapies. Most patients treated with frontline immunochemotherapy relapse within a few years and do not usually respond to salvage chemotherapy. Persistent activation of the B-cell receptor pathway is critical to the pathogenesis of mantle cell lymphoma. Inhibition of Bruton's tyrosine kinase, an essential B-cell receptor pathway component with ibrutinib has shown clinical activity and has changed how MCL is treated in the relapsed/refractory setting. However, resistance to ibrutinib is common and response is limited. Novel agents targeting the B-cell receptor pathway along with therapies outside of the pathway will be reviewed in this article. Ongoing and future studies will better define how these agents should be utilized in the ever-changing treatment landscape of mantle cell lymphoma.

Mantle cell lymphoma (MCL) is a type of Non-Hodgkin lymphoma (NHL) characterized by the translocation of the immunoglobulin heavy chain on chromosome 14 to cyclin D1 on chromosome 11, resulting in over-expression of cyclin D1. Though a small number of patients have the indolent form where observation is reasonable [1] the majority of patients have an aggressive clinical course that requires treatment. MCL is currently considered incurable [2], though younger patients can have a 75% 5-year survival when treated aggressively [3]. However, with median age at diagnosis of 67 years [4,5], the majority of patients are not candidates for aggressive therapy and current standard of care results in a PFS of 2–3 years [6,7]. Front line treatments for older and younger patients are discussed in other reviews in this issue. This article will review the novel, targeted therapies that are changing the landscape of MCL in the relapsed, refractory setting. The B-cell Receptor (BCR) signaling pathway plays a vital role in the proliferation and survival of MCL [8] and targeting this pathway is crucial to help achieve a more durable response. Targets of this pathway are at the forefront of treatment for patients failing chemotherapy.

1. B-cell receptor pathway

The BCR is a surface receptor complex on B-cells and signals through the spleen tyrosine kinase (SYC), Bruton's tyrosine kinase (BTK), phosphoinositide-3-kinase (PI3K), and protein kinase C-beta (PKCβ). These signals ultimately lead to NF-κB and AKT activation, which promote survival and proliferation of normal and malignant B-cells [8]. Persistent activation of the BCR pathway has been found to be a major contributor to the pathogenesis of MCL. Rinaldi et al. showed the *syc* RNA and SYC protein were overexpressed in a subset of primary MCL cells and BTK, LYN, and SYC were noted to be the most abundant

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tyrosine phosphorylated proteins in the MCL cell lines [9]. Furthermore, when BTK activity of MCL primary tumors cells were compared to B-cells from healthy donors, levels of phosphorylated BTK was significantly higher in primary MCL cells [10,11].

2. BTK inhibitors

Ibrutinib emerged as an effective targeted therapy for B-cell malignancies that rely on the BCR signaling pathway. Ibrutinib is an oral, irreversible BTK inhibitor that binds cysteine 481 in the phosphorylation site of BTK [10] and is approved for MCL in those who have received at least one prior therapy based on a phase 2 trial demonstrating 68% response rate (RR) and median progression free survival (PFS) of 13.9 months [12]. These included high-risk patients per the MCL International Prognostic Index (MIPI) and those who previously were heavily pretreated, (median of three prior therapies). The median time to response was 1.9 months and the time to complete response (CR) was 5.5 months, indicating that response tends to improve with prolonged exposure. With a median of 2 year follow up, 31% remained free from progression and 47% were still alive [13]. Dreyling et al. demonstrated that ibrutinib is better tolerated and associated with an improved PFS when compared to temsirolimus [14]. Ibrutinib has also been found to be safe and effective outside of a clinical trial setting as studied in a recent retrospective, observational study looking at those who received ibrutinib through compassionate use in Italy [15] and has been shown to be effective in those with central nervous system involvement [16,17] and in the setting of bridge to transplant [18].

Epperla et al. reported a retrospective study of relapsed or refractory MCL patients on ibrutinib ($n = 97$) and demonstrated similar results to the prospective studies. Overall response rate (ORR) was 65% with duration of response (DOR) of 17 months. PFS was 15 months and median overall survival (OS) was 22 months. This study also assessed factors predictive of response, PFS, and OS. Only a lack of primary refractory disease was a predictor of ibrutinib response [19].

Most recently, a pooled analysis of the three open-label studies of ibrutinib in MCL, PCYC-1104, SPARK, and RAY revealed a similar ORR (68%, 63%, 72%), median PFS (22.5 months, 25.4 months, and not reached), and OS at 18 months (58%, 61%, 58%) between the three trials [20]. This analysis also demonstrated that PFS and OS are dependent on baseline disease characteristics. Multiple lines of prior therapy, blastoid histology, poor ECOG performance status, higher simplified MIPI score, and bulky disease were identified as poor prognostic markers [20].

The side effect profile of ibrutinib is tolerable however in the most recent pooled analysis of 370 patients, adverse events are universal with 98.4% ($n = 364$) of patients experiencing an adverse event. Diarrhea (39.5%, $n = 146$), fatigue (34.9%, $n = 129$) and cough (21.9%, $n = 81$) were the most common. Grade 3 atrial fibrillation occurred in a minority of patients (4.6%, $n = 17$) along with major bleeding (4.9%, $n = 18$) [20]. However another retrospective study had shown the risk of bleeding increases when ibrutinib is combined with anticoagulant therapy (9.9% 7/71 patients) [21]. A recent retrospective study looking at ibrutinib associated infections in various NHLs, including 28 MCL patients, found risk of infections, specifically airway infections, to be a concern [22].

Unfortunately, treatment with ibrutinib is not durable and the majority of patients do not achieve a long-term remission. Primary resistance to ibrutinib occurs in a third of patients and acquired resistance is common with a median response duration of slightly over 1.5 years [13]. A multi-institution retrospective study by Martin et al. looked at 114 patients with MCL who experienced disease progression while on ibrutinib. Overall median duration of ibrutinib was 4.7 months and 8.6 months among responders. The investigator-reported best RR was 55% (43% PR, 12% CR) and the median OS after cessation of ibrutinib was 2.9 months ($n = 107$). For those who did not receive subsequent treatment after ibrutinib failure, median OS was only 0.8 months [23].

In the previously mentioned study by Epperla et al., 50.4% (49/97) of patients either did not respond, developed toxicity, or relapsed on ibrutinib with an OS of 2.5 months after failure was identified. For those who received post-ibrutinib therapies, an ORR of 48% was seen with a median DOR of only 3 months with no specific therapy showing superior activity in this setting [19]. Previous studies have shown those who fail ibrutinib are not likely to respond to salvage chemotherapy [24] thus underscoring the importance of utilizing novel targeted therapies to improve durability of response and overcome ibrutinib resistance.

There have been several proposed primary and secondary mechanisms for ibrutinib resistance. A BTK C4815 mutation was discovered by Chiron et al. [25] in those who progressed on ibrutinib with CLL which has since also been identified in the bone marrow and spleen from those who relapsed with MCL [26]. However, there are likely to be alternative mechanisms of resistance unrelated to BTK mutations as they are not identified in the majority of relapses [27]. In the MCL 3001 (RAY) study comparing ibrutinib to temsirolimus, next generation sequencing was performed on patient samples and no BTK C4815 mutations were identified. Rather, they found mutations in the NF-κB pathway bypassing BTK to be a common mechanism of resistance [28]. PIK3-AKT activity has been implicated as an etiology for resistance as the pathway was inactivated in those responding to ibrutinib and activated in those not responding [27]. The alternative NF-κB pathway has also been found to be upregulated in ibrutinib resistant MCL cell lines [29,30]. Hence relapse to ibrutinib does not appear to be due to ineffective ibrutinib inhibition but rather sustained parallel or distal BCR signaling.

Other BTK inhibitors thought to be more selective and potent are also being developed and have shown promising results. Acalabrutinib (ACP-196) is an oral novel irreversible second-generation BTK inhibitor that has shown promising activity in CLL [31] and now is being studied in comparison to ibrutinib in relapsed, refractory MCL (NCT02735876). Acalabrutinib is thought to have less bleeding and atrial fibrillation toxicities, both considered on-target effects of inhibition of the TEK family

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