Ibrutinib: a strong candidate for the future of mantle cell lymphoma treatment

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"Targeting tumor and its microenvironment: oral single-agent ibrutinib, a Bruton's tyrosine kinase inhibitor, has unprecedented anti-tumor activity in patients with mantle cell lymphoma."

Mantle cell lymphoma (MCL) is a well-defined pathologic and clinical entity classified as a subtype of B-cell lymphoma derived from $CD5^+$ B cells within the mantle zone that surrounds normal germinal center follicles. The major genetic feature of MCL is the t(11;14) chromosomal translocation that results in overexpression of cyclin D1 [1]. Early symptoms of MCL usually include fever, night sweats and unexplained weight loss. MCL thrives in the tumor microenvironment and presents as swelling of the lymph node and/or splenomegaly (occurring in 40% of patients). Notably, gastrointestinal involvement is frequently detected by endoscopy and random biopsies, although fewer patients complain of gastrointestinal symptoms. MCL is detected in the bone marrow in 92% of patients; although in some cases, the marrow infiltration is scarce and needs to be confirmed by repeated bone marrow biopsy and cytogenetic fluorescence *in situ* hybridization analysis [2].

The frontline therapy for MCL includes rituximab plus cyclophosphamide, vincristine, doxorubicin and dexamethasone [3]. This intensive immunochemotherapy with or without hematopoietic stem cell transplantation significantly improves the outcome of patients; however, most patients eventually have disease relapse [3]. In addition, the majority of MCL patients are older (median age at diagnosis is 65 years) and often unable to tolerate intensively cytoreductive chemotherapy [4]. However, in recent years novel targeted agents with more tolerable side-effect profiles have begun to emerge. Therapies targeting constitutively active cell survival pathways, such as PI3K/AKT/mTOR and STAT3, as well as the proteasome, have shown promise in relapsed/refractory MCL. Bortezomib, a first-in-class reversible proteasome inhibitor and the only targeted agent approved by the US FDA for the treatment of MCL, has been shown to produce a 31–50% response rate as a single-agent therapy [5]. Carfilzomib, a second-generation proteasome inhibitor that selectively disables the chymotrypsin-like activity of the proteasome, is currently being tested in MCL in Phase II clinical trials. Temsirolimus, an mTOR inhibitor, has been shown to produce a 38% response rate [6]. The promise of a cure for MCL lies in the burgeoning area of novel high efficiency but low toxicity agents specifically targeting key proteins dominantly expressed in MCL.

"Btk has a well-defined role in the constitutive activation of B-cell receptor-mediated signals in mantle cell lymphoma."

B-cell receptor (BCR)-mediated signals play a key role in B-cell differentiation and development, and they are constitutively activated in MCL [7]. BCR-associated kinases include spleen tyrosine kinase, Btk and PKC-β. Btk is a key kinase in BCR-mediated signals essential for normal B-cell development. It plays a crucial role in B-cell maturation and its absence at the

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early stages of development causes X-linked agammaglobulinemia. Patients with X-linked agammaglobulinemia present normal pre-B cells in bone marrow but lack mature B cells in both tissues and peripheral blood. In malignant B cells, Btk is a potential therapeutic target. As a member of the Tec family of nonreceptor protein tyrosine kinases, Btk has a well-defined role in the constitutive activation of BCR-mediated signals in MCL. Inhibition of Btk induces growth inhibition and apoptosis of MCL cells [8].

> "...the most important observation from clinical study of ibrutinib is the compartmental shift phenomenon. Treatment with ibrutinib was associated with a transient increase in peripheral lymphocyte count."

Ibrutinib, an orally administered inhibitor of Btk, inactivates Btk by selectively interacting with the ATP-binding site in the tyrosine kinase domain and preventing phosphorylation. Moreover, downstream signals for B-cell activation are blocked completely and irreversibly. Ibrutinib has shown clinical success before a full picture of its mechanism of action has been elucidated. Ibrutinib induces a higher rate of objective responses in patients with relapsed or refractory MCL than other B-cell malignancies [9]. These results suggest that Btk inhibition is a novel therapeutic approach in MCL. In an international study of single-agent ibrutinib in patients with MCL, 115 subjects (65 bortezomib-naive and 50 bortezomib-exposed) were enrolled. The overall response rate (ORR) was more than 69% in both bortezomib-naive and bortezomib-exposed patients. The median time on treatment was 6.0 months (0.7–16.6 months), and most subjects remain on treatment without significant toxicities. 12-month progression-free survival was 53%. Of note, the quality of response to ibrutinib increased with longer duration of treatment. When the median time on study treatment increased from 3.8 to 11.3 months, the ORR increased from 69 to 74.5% and complete responses increased from 16 to 35.3%. More importantly, data from the longer follow-up demonstrate the durability of responses and confirm the unprecedented single-agent activity of ibrutinib in relapsed or refractory MCL. All clinical trials conducted to date have shown that ibrutinib is well tolerated without significant toxicity. Moreover, no cumulative toxicity was found thus far even after continuous ibrutinib treatment at 560-mg daily [10].

Furthermore, the most important observation from clinical study of ibrutinib is the compartmental shift phenomenon. Treatment with ibrutinib was associated with a transient increase in peripheral lymphocyte count, representing a shift of MCL cells from local tumor compartment to peripheral blood. These data demonstrate that ibrutinib not only directly kills MCL cells but also disrupts the interactions between MCL cells and the tumor microenvironment. However, the mechanism(s) by which ibrutinib exerts its effects on the tumor microenvironment are unclear. Therefore, the priority in basic research is to elucidate the mechanism of ibrutinib-mediated compartmental shift using a reliable mouse model. Our group has created a human primary MCL mouse model that mimics the natural history of human MCL growth, propagation and metastasis and is the ideal platform for investigation of the ibrutinib-mediated compartmental shift of the MCL cell *in vivo* [11].

Tumor growth is critically influenced by its microenvironment, which includes accessory cells, such as stromal cells, myeloid cells, and some other immunocytes that secrete cytokines, chemokines or other soluble molecules associated with tumor survival, proliferation and metastasis. Btk is not only expressed in normal and malignant B cells but also in monocytes, macrophages and neutrophils [12]. Typically, Btk plays an important role in macrophages, and inhibition of Btk abolishes FcγRIII-induced TNF-α, IL-1β and IL-6 production [13]. Furthermore, Btk-deficient macrophages did not show activation of PI3K, AKT and MAPK, showed inactivation of NF-κB, IRF3 and AP-1, and failed to stimulate the secretion of inflammatory cytokines [14]. Of note, IL-6 is a very important cytokine for MCL growth and survival. Importantly, macrophages and bone marrow stromal cells secrete tenfold more IL-6 than MCL cells themselves, providing a rich source of IL-6 in the tumor microenvironment [15]. Furthermore, *in vivo* studies show that Btk deficiency primarily led to loss of macrophages, suggesting a role for Btk in regulating the life span of macrophages [16]. Therefore, Btk is involved in constitutive activation of B-cell lymphoma and is crucial for overexpression of inflammatory factors involved in B-cell lymphoma survival. These actions can be triggered by circulating antigens or immune complexes. Taken together, these findings suggest that the small-molecule Btk inhibitor ibrutinib displays a dual mechanism of action against MCL. First, ibrutinib inhibits BCR-dependent MCL proliferation; second, ibrutinib suppresses myeloid cell-derived inflammatory cytokines that support the growth and proliferation of MCL in its microenvironment. Another open question is whether or not Btk is expressed in other myeloid-derived cells, such as myeloid dendritic cell and myeloid-derived suppressor cells (MDSCs). It has been reported that Btk plays a negative regulatory role in the maturation and T-cell stimulatory function of dendritic cells. In Btk-deficient mice, the enhancement of Th1- and Th2-dominant immune responses was observed [17]. However, to date, there are no data published investigating the expression of Btk in MDSCs. MDSCs are a heterogeneous family of myeloid cells that suppress immunity in the tumor microenvironment. If Btk is expressed in MDSCs and is involved in regulating the function and lifespan of MDSCs as well as macrophages and dendritic cells, then inhibition of Btk in MDSCs would liberate T cells and other immune effector cells from MDSC-mediated immune suppression in the tumor microenvironment.

> "The ibrutinib-induced compartmental shift is associated with inhibition of the production of chemokines and their receptors."

Chemokines and their receptor interactions are crucial for homeostasis of T cells or B cells in hematopoietic or lymphoid organs [18]. In the tumor microenvironment, interaction between tumor cells and accessory cells (macrophages, stromal cells or

some other immunocytes) is mediated by chemokine receptors and adhesion molecules. The ibrutinib-induced compartmental shift is associated with inhibition of the production of chemokines and their receptors. In early research, CCL19 and CXCL12 (SDF-1) were taken as the chemoattractants and confirmed to induce MCL cell adhesion and migration in a transwell study *in vitro*. Therefore, the receptors, CCR7 and CXCR4, may play a key role in tumor cell migration and homing [19]. Recent research has shown that bone marrow stromal cells attracted MCL cells via the G protein-coupled chemokine receptors (CXCR4, CXCR5) and the adhesion molecules, CD44, VLA-4 and CD62L [20].

In summary, ibrutinib, a selective and irreversible Btk inhibitor, has achieved higher ORRs in patients with MCL than other B-cell lymphomas [9,10]. These clinical results indicate that MCL is the optimal model for elucidating the mechanism of action and therapeutic effect of ibrutinib. Our current knowledge suggests a dual mechanism of action for ibrutinib in MCL: direct targeting of B-cell signaling in MCL cells and targeting of myeloid-derived cells, including macrophages and others, in the tumor microenvironment. Because ibrutinib shifts MCL cells from the local tumor compartment to peripheral blood, its combination with other chemo- or immuno-therapeutic drugs is an attractive strategy to fully eradicate MCL cells in patients.

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