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Burton's Tyrosine Kinase Inhibition by Ibrutinib: Current Status

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Editorial

Burton's tyrosine kinase (BTK) is a nonreceptor/cytoplasmic tyrosine kinase that modulates the downstream signaling pathway of B-cell receptor (BCR) [1]. Aberrant BCR signaling including up-regulation of tyrosine kinases i.e. Lyn, Syk and Btk is a common feature in lymphoid malignancies such as Chronic Lymphocytic Leukemia (CLL), Mantle Cell Lymphoma (MCL) and other Non-Hodgkin's Lymphoma (NHL) [2]. Therefore, inhibition of tyrosine kinases is an attractive treatment option in these lymphoid malignancies. Ibrutinib (formerly PCI-32765) is a first-in-human, orally bioavailable small molecule inhibitor of BTK that has shown potent clinical activity in majority of CD20 positive B-cell malignancies. Based on high response rate, tolerability and safety data, Imbruvica/Ibrutinib has recently been approved by Food and Drug Administration (FDA) for the treatment of MCL (in November 2013) and CLL (in February 2014) with at least one prior therapy. It is now under evaluation as front line therapy in other subtypes of NHL and is explored for combination with other drugs.

Ibrutinib showed a response rate of 68% (75 patients) with a complete response rate of 21% and a partial response rate of 47% in a phase II study of 111 patients with relapsed or refractory mantle cell lymphoma [3]. Previous therapy to these patients had no effect on overall survival. Updated results presented in American society of hematology (Ash) meeting 2014 demonstrated the durability of response and sustained single agent activity of ibrutinib in an international multicenter phase II study of refractory MCL [4]. In another study on previously treated CLL, ibrutinib showed an 71% overall response rate and updated results after 3 years of follow up verify the durability of responses, probably on account of lower toxicity of ibrutinib in CLL and SLL [5]. Results from other recent studies also supports ibrutinib as first line or second treatment option in refractory cases [6]. A survival benefit with ibrutinib, together with sustained improvements in hematologic endpoints and PRO suggest that it enhances quality of life, while prolonging survival in CLL including with p17 deletion [7].

Further, treatment of ibrutinib is under evaluation for other tumors such as Follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and Multiple myeloma (MM). Early results of various studies showed promise of using it as a single agent treatment in relapsed/refractory lymphomas and myeloma. Although, ibrutinib appears less active in FL than in MCL and CLL but it may be a good option for refractory FL [8]. Recent study with multiple myeloma in heavily pre-treated patient population also showed evidence of anti-tumor activity with treatment of ibrutinib, as a single agent and in combination with dexamethasone, as the treatment was well tolerated with manageable toxicities [9]. In addition, several drug combinations of ibrutinib with other drugs are under evaluation. Initial results from recent studies have also shown that ibrutinib can be successfully combined with rituximab, bortezomib, bendamustine, lenalidomide, ABT-199, ofatumumab or newly developed anti-CD20 antibodies Ublituximab (UTX) or Obinutuzumab (GA101) in different clinical protocols for MCL and CLL [10-14]. The success of ibrutinib also come from its ability to target tumor microenvironment, chemokines SDF1/CXCR4 mediated migration. Ibrutinib inhibits concomitant TLR and BCR- driven proliferation of CLL cells and overrides the supportive survival-promoting effects of microenvironmental signals [15].

Inspite of a broad clinical activity of ibrutinib, several of patients with B-cell malignancies progressed after treatment with ibrutinib. Few studies undertaken so far, attributes the resistance to ibrutinib with mutations in B-cell receptor (BCR) signaling proteins such as BTK C481S, PLCg2 [16,17]. In addition, mutations in MLL2, CREBBP, PIM1 and ERBB4 kinase were also attributed to resistance mechanisms to ibrutinib [18]. Interestingly, treatment with ibrutinib, vincristine, or doxorubicin could induce cell death in MCL cells, but could not reduce the percentage of MCL-initiating cells (MCL-ICs) in a co-culture MCL model [19]. Therefore, it is important to understand the mechanisms underlying the activity of ibrutinib. However, advanced studies have shown that treatment with other targeting agents such as inhibitors of SYK, another downstream mediator of BCR signaling or ABT-199, a Bcl2 inhibitor have potential to sensitize ibrutinib resistant MCL and CLL cells [20]. Pretreatment of DLBCL cells with SYK inhibitors (e.g. R406) re-sensitized resistant B-lymphoma cells with either C481S BTK or R665W PLCG2 mutations to ibrutinib. Ibrutinib in combination with BCL-2 or SYK inhibitors, inhibiting cell growth, IgM-induced calcium flux, cell adhesion or migration in mutation containing cells [21]. Further, other drugs such as Duvelisib (IPI-145), a Phosphoinositide-3-Kinase-δ,γ Inhibitor or RP6530, a Dual PI3Kδ/γ Inhibitor and newer generation HSP90 inhibitors (AUY922) have been shown to have clinical activity in patients progressed after ibrutinib treatment [22-24].

Pre-clinical reports suggests that ibrutinib antagonizes rituximab-dependent NK-cell mediated cytotoxicity (ADCC) due to its secondary irreversible binding to interleukin-2 inducible tyrosine kinase (ITK), which is required for FcR-stimulated NK cell function including calcium mobilization, granule release, and overall ADCC [25]. Therefore, new BTK inhibitors, BTK-InhA (ACP-196), BTK-InhB (BGB-3111), and CGI-1746 (GDC-0834) [26,27] have been synthesized with lower ITK binding, which may preserve NK cell function and therefore synergize rather than antagonize rituximab. Preclinical studies showed that the efficacy of therapeutics which do not inhibit NK cell function, including three novel BTK inhibitors, is superior to ibrutinib [26,28]. Further, clinical investigation with newer inhibitors is needed to determine the impact of this finding on patients with lymphoma receiving rituximab.

In conclusion, ibrutinib has a broad clinical activity in all B-cell malignancies and provided a good treatment option for

chemorefractory MCL, and CLL. More mechanistic insights into its function, resistance mechanisms will clearly help understand its clinical activity and its possible use in other leukemia, indolent and other types of lymphomas.

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