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New Kinase Inhibitors for the Treatment of Chronic Hematological Neoplasms-Editorial

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Protein kinases (PKs) and lipid kinases (LKs) are good targets for signal transduction therapy, as these enzymes are involved in signaling pathways, and are often related to the pathogenesis of myeloid and lymphoid malignancies. The attractiveness of PKs and LKs as druggable targets is enhanced by the fact that they are enzymes whose biological activity can be turned off by drugs that block their catalytic site. In the last few years, small molecular kinase inhibitors (KIs) have been synthesized and become available for preclinical studies and clinical trials. At present, thirteen kinase inhibitors have been approved in the United States, all for oncological indications. The first KI, introduced into clinical practice in 1998, was the tyrosine kinase inhibitor (TKI) imatinib mesylate, which became the first choice drug in chronic myeloid leukemia (CML) [1,2]. Subsequently, the second-generation TKIs, dasatinib and nilotinib, have been successfully used in the treatment of patients with CML, especially in cases refractory to imatinib [3,4]. Dasatinib and nilotinib have shown promising results in imatinib-resistant or intolerant CML patients, but they are not active against CML clones with a highly resistant T315I mutation [5]. Bosutinib is a third-generation TKI which has been studied in a first line setting in patients with CML and the results look very promising [6]. Nilotinib, dasatinib and bosutinib demonstrate increased potency over imatinib and inhibit most imatinib-resistant mutants, except T315I [7,8].

Despite very good results of current CML treatment, there is still room for improvement. In the last few years, several drugs with an inhibitory action towards the Aurora kinase family have been developed. Currently, a number of Aurora kinase inhibitors with different isoform selectivities are being evaluated in the clinic. The first Aurora kinase inhibitor to enter clinical trials is tozasertib (MK-0457, VX-680) [9]. This molecule inhibits multiple kinases, including Flt-3, and potently inhibits Abl and the T315I mutant [10,11]. Danusertib (PHA-739358) is another inhibitor of Bcr-Abl and Aurora kinases. In a Phase I clinical trial, a response occurred in 6 of 14 subjects with CML and Ph+ ALL [12]. The other Aurora kinase inhibitors with known activity against wild-type and mutated BCR-ABL are XL228 and AT9283. Both compounds have shown activity in CML patients in phase I clinical trials [13,14].

The Janus family kinases (JAKs), JAK1, JAK2, JAK3, and TYK2, are involved in cell growth and the survival, development, and differentiation of a variety of cells, particularly immune cells and hematopoietic cells. Mutations of each of the JAKs are associated with malignant transformations [15]. The most common are mutations of JAK2 in polycythemia vera (PV) and other myeloproliferative neoplasms (MPN). Identification of the V617F mutation of the JAK2 gene (JAK2 V617F) led to an important breakthrough in the understanding of MPN disease pathogenesis. Several JAK inhibitors in a range of chemical classes have been recently developed. Some of them, such as ruxolitinib, CYT387, TG101348, INCB018424, AZD1480, CEP-701, lestaurtinib, SB1518 and pacritinib are in clinical development. Recently, JAK2 inhibitor ruxolitinib has been evaluated as a new treatment option in idiopathic myelofibrosis (MF) [16]. Ruxolitinib is the first JAK2 inhibitor approved by the Food and Drug Administration (FDA) for the therapy of intermediate and high-risk MF, including primary MF (PMF), post-polycythemia vera (PV) myelofibrosis, and post- essential thrombocythemia (ET) myelofibrosis. Ruxolitinib is currently undergoing evaluation in a Phase II clinical trial in patients with MF in combination with lenalidomide (ClinicalTrials.gov Identifier: NCT01375140) and in a Phase I clinical trial in combination with panobinostat (ClinicalTrials.gov Identifier: NCT01433445).

SAR302503 (TG101348) is another JAK2-selective inhibitor created by structure-based drug design. This compound has been found to be a potent inhibitor of JAK2V617F and MPLW515L/K mutations commonly associated with PV and primary MF [17]. A reduction in palpable spleen size of more than 50% has been observed in 39% and 47% of patients after 6 and 12 cycles of therapy, respectively [18]. SAR302503 improved constitutional symptoms like fatigue, night sweats, pruritus and cough. Moreover, drug administration resulted in a significant decrease in the JAK2 V617F allele burden after 6 and 12 cycles of treatment, which is quite a unique ability among small molecule inhibitors of the JAK-STAT pathway. SAR302503 is currently recruiting for a Phase III multicenter, randomized study in patients with primary MF, post-PV MF, or post-ET MF with splenomegaly (JAKARTA study; ClinicalTrials.gov Identifier: NCT01437787).

In addition, several multi-targeted TKIs can suppress JAK/STAT signaling through specific JAK2 inhibition, in addition to broad therapeutic activity. Lestauritinib (CEP-701) targets both wild-type and mutated JAK2 in MPN and has FLT-3 and Trk-A inhibiting activity. The results of a Phase II study conducted in 22 JAK2 V617F -positive MF patients showed an overall response rate of 27% [19,20]. Lestauritinib is currently undergoing Phase I/II studies in other MPN patients (ClinicalTrials.gov Identifier: NCT00668421). Many other JAK2 inhibitors such as SB1518, CEP701 and LY2784544 are now under investigation for MPN development. However, definitive data from ongoing and future preclinical and clinical trials will aid in better defining the status of these drugs in the treatment of these diseases.

Recently, several KIs have been developed to target the proximal B-cell receptor (BCR) signaling pathway. BCR inhibitors such as spleen tyrosine kinase (Syk) inhibitors and Bruton's tyrosine kinase (Btk) inhibitors are highly active and well tolerated in non Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) patients, irrespective of high-risk genomic abnormalities and suggest that these drugs may be an important new targeted treatment approach for these disorders. The most interesting Btk inhibitors in clinical trials are

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ibrutinib (PCI-32765) and AVL-292. Ibrutinib shows encouraging clinical activity in patients with CLL and NHL [21]. Recently, O'Brien et al. reported the results of a multicenter trial on 61 patients with CLL and small lymphocytic lymphoma (SLL) [22]. After a median follow-up time of 10.2 months for a 420 mg cohort, and 6.5 months for an 840 mg cohort, 82% of patients remained on ibrutinib and only 8% of patients were found to have progressive disease. This data indicates that ibrutinib is a highly active drug in CLL/SLL patients and suggests that this agent may be an important new treatment in indolent lymphoid malignancies.

Syk plays a crucial role in the coordination of immune recognition receptors and orchestrates multiple downstream signaling pathways in hematopoietic cells. BCR-mediated signaling through Syk occurs to a greater degree, and for a longer duration, in neoplastic B cells than in nonmalignant B cells [23]. Fostamatinib is the first oral Syk inhibitor in development as a novel therapeutic approach for the treatment of B-cell lymphoid malignancies. In patients with SLL/CLL, treated in Phase I/II studies, the response rate was 55% and the median PFS was 4.2 months [24].

Phosphatidylinositol 3-kinases (PI3K) are a family of lipid kinases which mediate signals from cell surface receptors [25]. CAL-101 (GS-1101) is an oral PI3Kδ-specific inhibitor which has shown preclinical and clinical activity against CLL, NHL and Hodgkins lymphoma [26]. The interim results of the Phase I trial of CAL-101 involving patients with relapsed or refractory hematological malignancies have been recently presented [27]. Objective response was noted in 4 out of 17 patients with CLL. In addition, 91% of the patients achieved a lymph node response. CAL-101 was also evaluated in combination with rituximab and/or bendamustine in patients with previously treated NHL [28]. An evaluable overall response rate of >65% was observed. Other PI3K inhibitors, including NVP-BKM120, GDC-0941, SF1126, NVP-BEZ235 and XL147, also exhibit excellent potency in treating lymphoid malignancies, and demonstrate promising activity in preclinical studies. However, the relevant clinical studies have yet to bear fruit [29].

Cyclin-dependent kinases (Cdks) are a family of serine/threonine kinases which are activated through binding to regulatory subunits called cyclins. They are key positive regulators of cell cycle progression and attractive targets in the treatment of lymphoid malignancies. In recent years, several Cdk inhibitors have been developed and are being evaluated in preclinical studies and clinical trials [30]. Flavopiridol is a pan cyclin-dependent kinase inhibitor that induces apoptosis by down-regulating the expression of critical antiapoptotic proteins such as Mcl-1 and X–linked inactivator of apoptosis (XIAP) [31]. Flavopiridol was the first Cdk inhibitor to enter clinical trial and has been shown to be effective in patients with relapsed and refractory CLL, including those refractory to fludarabine and with del (17p) [32]. Another pan-specific CDK is dinacilb. In a Phase I trial including 33 CLL patients, 8 patients achieved a partial response among the 23 patients ready for response assessment [33]. In some studies, dinacilib exhibited superior activity than flavopiridol, with an improved therapeutic index [34].

The development of new KIs remains vital to success in fighting leukemias and other hematological neoplasms. The opportunity for improved therapies with KIs remains an open area for future preclinical studies. Ongoing studies will help to define the role of these new agents in the standard therapy of this disease.

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