Tyrosine Kinase Inhibitors in the Treatment of Eosinophilic Neoplasms and Systemic Mastocytosis

Jason Gotlib, MD, MS

KEYWORDS

• Systemic mastocytosis • Hypereosinophilic syndrome • Tyrosine kinase inhibitor • *FIP1L1-PDGFRA* • *FGFR1* • *JAK2* • Imatinib • Midostaurin

KEY POINTS

- Evaluation of eosinophilia-associated neoplasms and systemic mastocytosis requires diagnostic testing for rearrangements or point mutations involving tyrosine kinase genes.
- Imatinib is a highly effective, first-line therapy for myeloid/lymphoid neoplasms with eosinophilia characterized by *PDGFRA* or *PDGFRB* gene fusions.
- An unmet need exists for treatment of *FGFR1*-rearranged and *JAK2*-rearranged eosinophilic myeloid/lymphoid neoplasms in which currently available tyrosine kinase inhibitors demonstrate suboptimal efficacy.
- Novel agents with potent inhibitory activity against KIT D816V have demonstrated significant clinical benefit and reductions of bone marrow mast cell burden in patients with advanced systemic mastocytosis.

INTRODUCTION

Constitutive activation of tyrosine kinases (TKs) is a common theme among myeloproliferative neoplasms (MPNs), and typically occurs via point mutations or rearrangements. Well-known examples include *BCR-ABL1*, which operationally defines chronic myeloid leukemia (CML), and Janus kinase 2 (*JAK2*) V617F, which is a highly recurrent mutation among the classic Philadelphia chromosome–negative MPNs polycythemia vera, essential thrombocythemia, and primary myelofibrosis.[1] Among the primary (clonal)

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Division of Hematology, Stanford Cancer Institute/Stanford University School of Medicine, 875 Blake Wilbur Drive, Room 2324, Stanford, CA 94305-5821, USA
E-mail address: jason.gotlib@stanford.edu

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eosinophilias, a subset of patients belongs to the 2016 World Health Organization (WHO) category entitled, "Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*."[1] In addition to these TK genes, eosinophilic neoplasms may rarely be associated with rearrangement of FMS-like tyrosine kinase 3 (*FLT3*) and *ABL1* (**Table 1**). In systemic mastocytosis (SM), the aspartate to valine mutation in codon 816 (D816 V) in the gene encoding the KIT receptor tyrosine kinase can be identified in approximately 80% to 90% of patients and is a primary driver of disease pathogenesis.[1,2]

Although imatinib treatment of *FIP1L1-PDGFRA*–positive (and *PDGFRB*-rearranged) myeloid neoplasms with eosinophilia has recapitulated the success observed in CML, therapy of other eosinophilic diseases has been more challenging due to the limited potency and selectivity of current of TK inhibitors (TKIs) and disease heterogeneity (**Table 2**). Recently, agents such as midostaurin, a multikinase/KIT inhibitor, have demonstrated encouraging efficacy in patients with advanced SM.[3] In this article, I review the current landscape and challenges of TKI therapy in eosinophilic neoplasms and advanced mast cell disease, and discuss emerging opportunities for progress.

EOSINOPHILIC NEOPLASMS

Imatinib in Patients with PDGFRA/B Fusion Genes

Imatinib's profound benefits in CML led to its empiric use in patients with hypereosinophilia who exhibited myeloproliferative features. In 2001 to 2002, several reports highlighted rapid and complete hematologic responses with imatinib 100 to 400 mg daily in patients with hypereosinophilic syndrome.[4–6] The fusion oncoprotein FIP1L1-PDGFRα, generated by a cytogenetically occult 800-kilobase interstitial deletion on chromosome 4q12, was identified as the target of imatinib.[7,8] The deleted segment contains the *CHIC2* gene, which is the basis for the fluorescence in situ hybridization (FISH) test used to diagnose of *FIP1L1-PDGFRA* disease[9]; FISH and reverse-transcriptase polymerase chain reaction (PCR) can be used for diagnosis, and both assays have been used to monitor cytogenetic and molecular response to imatinib (see **Table 1**). Although *FIP1L1-PDGFRA*–positive disease usually presents as a chronic myeloid neoplasm with eosinophilia, it may be diagnosed in the blastic phase of an MPN, or as an eosinophilia-associated acute myeloid leukemia (AML) or T-cell lymphoblastic lymphoma.[10]

The durable hematologic and molecular remissions induced by imatinib in *FIP1L1-PDGFRA*–positive myeloid neoplasms have been corroborated by many studies (see **Table 2**).[7,11–16] Molecular remissions were first reported by the National Institutes of Health group in 5 of 6 *FIP1L1-PDGFRA*–positive patients after 1 to 12 months of imatinib therapy.[13] Although 100 mg daily may be sufficient to achieve a molecular remission in many patients, others may require higher maintenance doses in the range of 300 to 400 mg daily. Dosing of 100 to 200 mg weekly may be sufficient to maintain long-term molecular remissions in some patients.[17] In a French Eosinophil Network series, a complete hematologic response was achieved in all patients, and complete molecular response (CMR) in 95% of patients (average starting imatinib dose, 165 mg/d).[16]

The disease course of imatinib-treated *FIP1L1-PDGFRA*–positive myeloid neoplasms was studied in a prospective Italian cohort of 27 patients with a median follow-up period of 25 months (range 15–60 months).[12] Patients were dose escalated from an initial dose of 100 mg daily to a final dose of 400 mg daily. Complete hematologic remission was achieved in all patients within 1 month, and all patients became PCR-negative for *FIP1L1-PDGFRA* after a median of 3 months of treatment. Patients continuing imatinib remained PCR-negative during a median follow-up period of