New Hematological Indications for Imatinib

a report by

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Chronic myeloid leukemia (CML) is the only molecularly defined myeloid disorder to date and is distinguished by a unique chromosomal abnormality—the Philadelphia (Ph) chromosome—and expression of the BCR-ABL fusion oncoprotein.\(^1\) The treatment of CML was transformed by innovative molecularly targeted therapy, tyrosine kinase inhibitors (TKIs), namely imatinib mesylate (Gleevec\(^\text{®}\), Novartis). In addition to its inhibitory effect against cell proliferation induced by the constitutively active BCR-ABL TK in CML patients, imatinib is also an inhibitor of the KIT, ARG, and platelet-derived growth factor receptor (PDGFR) TKs. Imatinib is also indicated for the treatment of gastrointestinal stromal tumors that are associated with the mutated KIT TK; imatinib inhibits cell proliferation and induces apoptosis in the malignant cells. Some TKs, such as PDGFR, are active in disease pathways that underlie a number of rare hematological diseases. In October 2006, imatinib was approved for the treatment of five additional disorders, marking the first time that a single medicine has been approved for multiple indications simultaneously. The newly approved indications for rare and potentially life-threatening hematological diseases are listed in Table 1; these indications are based on a series of small clinical trials and multiple case studies presenting the efficacy of imatinib in the treatment of these diseases. Imatinib has been linked by its mechanism of action to the disease pathways of these rare hematological diseases; it is this connection and the discovery of shared molecular dysregulation that has made drug treatment with TKIs such as imatinib possible. The focus of this short article will be to address the rationale and the clinical evidence of efficacy for imatinib in the rare blood disorders myelodysplastic syndromes (MDS)/myeloproliferative diseases (MPDs), hypereosinophilic syndrome (HES)/chronic eosinophilic leukemia (CEL), and aggressive systemic mastocytosis (ASM).

Myelodysplastic Syndromes/Myeloproliferative Diseases

MDS and MPDs are distinct disorders. However, in certain cases, there can be an overlap of clinical and/or morphological features that are traditionally associated with either MDS or MPD alone, thus diagnosis may be more challenging. This overlap led to World Health Organization (WHO) reclassification of hematopoietic and lymphoid neoplasms and the recognition of a new separate category of MDS/MPD,\(^2\) which includes chronic myelomonocytic leukemia (CMML), atypical CML (aCML), juvenile myelomonocytic leukemia (JML), and MDS/MPD unclassifiable (MDS/MPD-U). MDS/MPD is a heterogeneous group of clonal hematopoietic stem cell disorders characterized by the overproduction of certain myeloid cells in the bone marrow that are abnormal in appearance, ‘out of shape,’ or dysplastic. Of all the chromosomal abnormalities detected in MDS/MPD patients, over half are due to deletions in chromosomes 5, 7, 11, 12, 13, and 20.\(^3\) A small proportion of MDS/MPD patients have a chromosomal breakpoint on chromosome 5 (5q33), causing constitutive activation of the PDGFR\(β\) gene coding for a PDGFR\(β\) TK.\(^4\) Others may have a chromosomal breakpoint on chromosome 4 (4q12), causing activation of a gene for PDGFR\(α\) TK. It is believed that these TKs are responsible for the disease in these patients, and they are particularly sensitive to imatinib. Cytogenetic testing is mandatory for all patients with MDS/MPD.\(^3\) Additionally, since MDS/MPD may be associated with high eosinophil levels, cytogenic testing may help to distinguish MDS/MPD from HES.

**Diagnosis**

CMML is distinguished from CML by the absence of the Ph chromosome and the BCR-ABL transcript.\(^4\) Under the new WHO classification, CMML is divided into two subcategories—CMML-1 and CMML-2—based on number of blast cells in the blood and bone marrow, because of the relationship between blast-cell number and prognosis.\(^5\) The median age at diagnosis is 73 years and survival is dependent on disease severity, with a median survival time of 12–24 months.\(^5\) Abnormal clonal myeloid proliferation in CMML often progresses to acute myeloid leukemia (AML). The symptoms of aCML are similar to those of CML; however, aCML patients are Ph-chromosome-negative. Furthermore, aCML is associated with granulocyte and multilineage dysplasia, which is not found in CML. aCML can be distinguished from CMML by the presence of a higher percentage (>15%) of circulating immature granulocytes. The disease is very aggressive and median survival time is 11–18 months.\(^6\)

**Current Treatment Options**

Currently, allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative therapy for CMML; however, many patients with CMML are not eligible for HSCT due to advanced age or comorbid conditions. CMML can also be treated with standard chemotherapy of hydroxyurea with supportive care. Topotecan and cytarabine have also been found to be effective in generating hematological and cytogenetic responses in patients with CMML.\(^7\) Hematopoietic growth factors, particularly erythropoietin, may be of benefit for some CMML patients.\(^7\) aCML can also be treated with standard chemotherapy of hydroxyurea, interferon-\(α\), and busulfan; however, this regimen is associated with poor outcome. In comparison, allogeneic HSCT has an estimated survival rate of 89% for patients with aCML.\(^8\)

**Rationale and Clinical Evidence for Imatinib**

Imatinib has been approved for the treatment of adults with forms of MDS/MPD associated with PDGFR gene rearrangements. PDGFR gene
rearrangements result from translocations involving chromosome 5q33
and 4q12; therefore, confirmation of these translocations should support
the use of imatinib in MDS/MPD patients. CMML and aCML are two
MDS/MPD disorders associated with specific PDGFR gene rearrangements
that lead to aberrant PDGFR signaling and hematopoietic transformation.
Translocations involving the PDGFRβ gene on chromosome 5 have been
associated with MDS/MPD, and many fusion partners have been
identified to date.11 In these patients, the PDGFRβ gene has served as a
distinct marker in predicting response to imatinib therapy.12 Imatinib
induces durable clinical responses in MPDs associated with PDGFRβ.13–15
One of the larger studies showed that with imatinib therapy blood
counts underwent rapid normalization in 11 of 12 patients.16 Several case
studies have confirmed the therapeutic benefits of imatinib therapy in
PDGFRβ-rearranged MPD regardless of the fusion gene partner.16,17 The
data presented to the US Food and Drug Administration (FDA) include a
phase II study of seven MDS/MPD patients and an additional 24 patients
from a number of case reports and clinical studies treating patients with
400mg imatinib daily. Complete hematologic and major cytogenetic
response was achieved in 14 (45%) and 12 (39%) of these 31 patients,
respectively; 10 patients achieved a complete cytogenetic response.
All 17 patients found to possess a PDGFR gene rearrangement responded
hematologically, and 13 (81%) had a complete hematologic response.
None of the 14 patients lacking a PDGFR gene rearrangement responded
cytogenetically, although one (7%) achieved a complete hematologic response.20
The recommended dosage for adult patients with
MDS/MPD is 400mg imatinib daily, but responses to lower doses have
been observed.21

Hypereosinophilic Syndrome/
Chronic Eosinophilic Leukemia
HES refers to a group of myeloproliferative disorders characterized by the
persistent overproduction and elevated levels of eosinophils in blood
(>1,500 cells/µl) with symptoms of organ involvement, including valvular
disease, cardiomyopathy, sensorimotor isolated central nervous system
(CNS) vasculitis, optic neuritis, pulmonary infiltrates, gastroenteritis,
sclerosing cholangitis, cytopenias, bone marrow fibrosis, and thrombotic
angiopathy.22–24 Primarily affecting males, HES has a reported 10-year
survival rate of less than 50%.25 Patients previously diagnosed with
idiopathic HES can be divided into at least three distinct subgroups. The
first are those patients reclassified as having ‘clonal’ eosinophilia (CEL)
because of the identification of the FIP1L1-PDGFRα fusion transcript.27–29
Second, there are patients with HES in whom no evidence of clonality can
be demonstrated; these patients must be considered idiopathic and may
have disease that ultimately evolves into acute leukemia or aggressive
forms of MPDs.30 The third subset of patients carry an abnormal T-cell
population (helper Th2 lymphocytes) that produces interleukin-5 (IL-5), a
cytokine required for the growth and differentiation of eosinophils.31

Diagnosis
Diagnosis of HES is based on sustained eosinophilia (>1,500 cells/µl) for
more than six months in the absence of other causes of eosinophilia such as
parasitic infections and allergies.26 HES patients with a deletion in
chromosome 4, which fuses the FIP1-like-1 gene (FIP1L1) to the PDGFRα
gene, are now reclassified as CEL, as the resulting FIP1L1-PDGFRα
rearrangement gene has become a marker of disease clonality.27–29 The
new fusion gene leads to constitutive activation of the PDGFRα TK.30 This

can be effectively negated through treatment with imatinib, the
treatment of choice for these patients. Proper testing for the FIP1L1-
PDGFRα rearrangement is highly recommended in all patients with
suspected HES/CEL. Other patients with HES/CEL may have a
chromosomal abnormality with a breakpoint at a site where genes for
PDGFR TKs are found (4q12 and 5q33 for PDGFRα and β, respectively).
These TKs are constitutively active in these cases and are sensitive to
imatinib therapy. Cytogenetic testing is highly recommended for patients
with suspected HES/CEL.

Current Treatment Options
Asymptomatic HES patients lacking evidence of organ damage are closely
monitored in lieu of treatment, although there is no general consensus on
how to treat them.24 The first-line treatment of HES has traditionally
been prednisone, with a response rate of nearly 70%.25 However, relapses often occur upon cessation of therapy, requiring the patient to
seek alternative drug options, such as interferon-α or hydroxyurea,
considered now to be the second-line drugs of choice.25

Rationale and Clinical Evidence for Imatinib
Among the recent FDA approvals was the indication of imatinib for the
treatment of adults with HES/CEL associated with FIP1L1-PDGFRα fusion
kinase—identified by mutational analysis or fluorescence in situ
hybridization (FISH) demonstration of CHIC2 allele deletion—and for
patients with HES/CEL who are FIP1L1-PDGFRα fusion kinase-negative or
unknown. The incidence of the FIP1L1-PDGFRα fusion kinase mutation
has not been firmly established, and may be less common than initially
anticipated. The prevalence has been conveyed in multiple reports to
range anywhere between 3 and 56%, with most studies reporting a
frequency of 10–15%.34,35 The fusion gene also has a distinct male
preponderance.36,37 Cases of HES/CEL with the FIP1L1-PDGFRα
rearrangement have been established to have high sensitivity to imatinib,
with an overall rate of complete hematological remission of over 95%
across 73 reported cases.17,32,38–44 Patients expressing the FIP1L1-PDGFRα
fusion gene experienced rapid complete hematological remission within
three months in 100% of patients (15/15). Complete molecular
remission, defined as a negative nested reverse transcriptase polymerase
chain reaction (RT-PCR) for FIP1L1-PDGFRα fusion transcripts in
peripheral blood, was seen within six months in 83% (10/12) of FIP1L1-
PDGFRα-positive patients.45 In contrast, of the 14 patients lacking this

<table>
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<td>Unresected, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP)</td>
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<td>Relapsed/refractory Philadelphia-chromosome-positive acute lymphoblastic leukemia (Ph+ ALL)</td>
<td>45</td>
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<td>Myelodysplastic syndromes/myeloproliferative disorders (MDS/MPD) (certain forms associated with PDGFR gene rearrangements)</td>
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<td>Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase-negative or unknown</td>
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<td>Aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown</td>
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Hematological Cancer

marker, only three (21%) responded to imatinib, while six (43%) achieved partial or complete clinical and hematological responses.6 HES/CEL patients have shown durable remission of up to five years when treated with imatinib (100–400mg daily).28 Twenty-one FIP1L1-PDGFRα-positive HES/CEL patients achieved a complete hematological response in less than one month.28 All of these patients remained in complete hematological remission with a median follow-up of 28 months (range 13–67).28 Other studies have documented complete hematological responses in at least 13 of 69 patients (19%) lacking the fusion gene.12,26–42 It appears that although imatinib is less effective in HES without the FIP1L1-PDGFRα marker, the drug may also have a non-specific myelosuppressive effect.25 With this in mind, HES patients should be analyzed for the presence of the FIP1L1-PDGFRα rearrangement prior to commencing therapy to assess the efficacy of ensuing imatinib treatment. The recommended dosage of imatinib in HES/CEL patients is 400mg daily. However, a daily starting dosage of 100mg imatinib is recommended for HES/CEL patients with the FIP1L1-PDGFRα rearrangement, with the possibility of increasing dosage to 400mg daily in the absence of adverse effects or insufficient response to drug therapy.28

Aggressive Systemic Mastocytosis
SM is a heterogeneous group of disorders characterized by clonal expansion of mast cells and their excessive accumulation in various organs such as skin, bone marrow, gastrointestinal tract, lymph nodes, liver, and spleen. The clinical course can range from no/minimal symptoms to diffuse systemic involvement with a multitude of symptoms. When the involvement of an organ with the disease affects its function, the disease is considered to be aggressive, or ASM, and prognosis is poor. KIT is a receptor for stem cell factor that is expressed by mast cells at varying developmental stages; its deregulation is thought to play a role in mast cell proliferation.18,40

Diagnosis
A great majority of SM patients exhibit a mutation in the c-kit oncogene, resulting in ligand-independent mast cell growth through auto-phosphorylation of the KIT TK. The D816V mutation is the most common KIT mutation, but is insensitive to imatinib. Sporadic cases of alternative KIT mutations have been described, which are usually imatinib-sensitive.20 Proper testing for KIT mutational status in patients suspected of having SM is highly suggested; positive results help to confirm the diagnosis (it is part of the diagnostic criteria) and may help the physician to select proper therapy. A subgroup of patients, usually those with associated eosinophilia, has also been found to express the imatinib-sensitive FIP1L1-PDGFRα rearrangement gene.28 Patients with ASM and associated eosinophilia should undergo proper testing to document the presence of the FIP1L1-PDGFRα rearrangement.

Current Treatment Options
Interferon-α and cladribine have traditionally been the first-line therapeutic agents used in the treatment of ASM. Though reported to improve symptoms of ASM, interferon-α has a low response rate—ranging from 30 to 50%—and multiple adverse effects. Cladribine has shown therapeutic activity in ASM as well, but myelosuppression occurs in approximately one-third of cases.23

Rationale and Clinical Evidence for Imatinib
Imatinib is approved for the treatment of adults with ASM who either lack the D816V KIT mutation or are of unknown KIT mutational status. The D816V mutation, responsible for function activity in the KIT TK, has been reported to be present in over 90% of ASM cases,29 while another study has shown a much lower incidence of the mutation (31%).32 Although imatinib can inhibit wild-type KIT through binding, it is unable to interact with mast cell lines expressing the D816V variant.31,32 However, ASM patients with mutations elsewhere in c-kit have shown clinical responses to imatinib.44,51 SM may be accompanied by clonal eosinophilia, and half of these patients have the FIP1L1-PDGFRα fusion kinase. These patients have been shown to obtain complete clinical responses under imatinib therapy.42–45 Case studies and phase II clinical data involving 28 patients with ASM receiving 100–400mg imatinib daily were presented to the FDA. Only one of the four patients carrying the D816V mutation responded to imatinib treatment with a complete hematological response, but this patient also had concomitant CML. The two patients with juxtamembrane mutations in KIT experienced a partial hematological response, while only seven of 15 patients (44%) of unknown KIT mutational status displayed this response. Of the seven patients carrying the FIP1L1-PDGFRα rearrangement, all were found to achieve complete hematological response.56 The recommended dosage of imatinib is 400mg daily. A starting dosage of 100mg daily is recommended for patients with ASM associated with eosinophilia, with the possibility of increasing dosage to 400mg daily in the absence of adverse effects or insufficient response to drug therapy.43

The use of tyrosine kinase inhibitors in chronic and acute leukemias has led to the discovery of new targets in other diseases, such as the platelet-derived growth factor receptor gene rearrangements.

Conclusions
Molecularly targeted therapies have been successful in treating myeloid disorders, largely through the activities of TKIs. Through potent inhibition of a number of TKs, imatinib has been newly indicated for the treatment of PDGFR-rearranged MDS/MPD, HES/CEL, and ASM without the D816V c-kit mutation or with unknown mutational status. The success of this targeted drug therapy in the aforementioned rare hematological diseases was possible only through increasing knowledge of disease pathways. The multi-
indication approval for imatinib has immense implications in the development of disease treatment. The use of TKIs in chronic and acute leukemias has led to the discovery of new targets in other diseases, such as the PDGFRA gene rearrangements. The efficacy of imatinib against multiple diseases stems from the drug’s ability to act against common molecular pathways and emphasizes a new approach to drug development, as cancers with diseases varying with origins and locations can respond similarly to certain drug treatments due to shared disease pathways. The continued search for novel targets and ever-expanding knowledge about the molecular pathogenesis of hematological malignancies will likely lead to growth in the area of molecularly targeted therapy.

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