

# Mast Cells and Eosinophils in Mastocytosis, Chronic Eosinophilic Leukemia, and Non-clonal Disorders

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Mast cells and eosinophils often travel in the same biologic circles. In non-clonal states, such as allergic and inflammatory conditions, cell-to-cell contact and the pleiotropic actions of multiple cytokines and chemokines, derived from local tissues or mast cells themselves, foster the co-recruitment of these cells to the same geographic cellular niche. While eosinophils and mast cells serve critical roles as part of the host immune response and in maintenance of normal homeostasis, these cell types can undergo neoplastic transformation due to the development of clonal molecular abnormalities that arise in early hematopoietic progenitors. The dysregulated tyrosine kinases, D816V KIT and FIP1L1-PDGFR $\alpha$ , are the prototypic oncogenic lesions resulting in systemic mastocytosis (SM) and chronic eosinophilic leukemia, respectively. We review the pathobiology of these myeloproliferative neoplasms (MPNs) with a focus on the relationship between mast cells and eosinophils, and discuss murine models, which further elucidate how the phenotype of these diseases can be influenced by stem cell factor (SCF) and expression of the potent eosinophilopoietic cytokine, interleukin-5 (IL-5). Therapy of SM and FIP1L1-PDGFR $\alpha$ -positive disease and the prognostic relevance of increased peripheral blood and tissue mast cells in hematolymphoid malignancies will also be addressed.

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While the exact roles of eosinophils and mast cells in maintenance of a healthy homeostasis are still debated, they are often found together in tissues in a variety of inflammatory and neoplastic diseases.<sup>1</sup> In most cases, mast cells and eosinophils produced normally in a non-clonal fashion from bone marrow progenitors are recruited into the inflamed tissue by the action of chemokines generated by the inflammatory cells. In hematopoietic neoplasms, such as mastocytosis and chronic eosinophilic leukemia, they are generated from the same progenitor cell

carrying the same clonal markers. Once in the tissue, they can interact with each other through secretion of soluble mediators or via membrane contact mechanisms. These interactions involve potential mechanisms to enhance or suppress proliferation or activation of these cells.

Mast cells and eosinophils are derived from the pluripotent hematopoietic cells residing within the CD34<sup>+</sup> population in the bone marrow. While eosinophils and basophils are thought to share a common bipotential progenitor,<sup>2</sup> there is no evidence for a similar progenitor that only gives rise to eosinophils and mast cells.<sup>3</sup> The primary growth and differentiation factor for mast cells is stem cell factor (SCF).<sup>3,4</sup> This cytokine, through binding its cognate receptor KIT, mediates proliferation and differentiation of mast cells and contributes to their chemotaxis and activation. Other cytokines such as interleukin (IL)-3, IL-4, IL-5, IL-6, and IL-9 enhance the mast cell growth promoting effect of SCF but are not sufficient to drive mast cell differentiation in the absence of SCF. Mature mast cells are rich sources of a variety of biologically active molecules, including vasoactive amines (histamine), proteoglycans (heparin), arachidonic acid metabolites (PGD2 and cysLTs), proteases (tryptase, chymase, carboxypeptidase), cytokines (tumor necrosis factor [TNF]), and chemokines (RANTES), which

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can affect various aspects of eosinophil growth, differentiation, chemotaxis, and activation.<sup>5</sup>

Eosinophil-committed hematopoietic progenitors are identified within the CD34<sup>+</sup> progenitor population as IL5R<sup>+</sup>/CCR3<sup>+</sup> cells.<sup>6,7</sup> Eosinophil development is promoted by IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) and is controlled by the transcription factors GATA-1, GATA-2, and C/EBP.<sup>8</sup> After entering the circulation under the influence of IL-5, mature eosinophils migrate to inflamed tissues via the action of a variety of chemotactic factors, including eotaxins (CCL11, 24, 26), VCAM-1, PAF, LTD2, and RANTES (CCL5). Mature eosinophil mediators include MBP, EDN, ECN, EPO galectin 10, and lipid mediators, including LTC<sub>4</sub>, PGE<sub>2</sub>, and PAF, as well as a variety of cytokines and chemokines, including SCF, transforming growth factor  $\beta$  (TGF $\beta$ ), TNF, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, and nerve growth factor (NGF).<sup>8</sup>

Mast cells and eosinophils typically coexist in atopic disorders such as allergic rhinitis, atopic dermatitis, and asthma.<sup>9</sup> Mast cells, which normally reside in mucosal tissues and at interfaces with allergen interaction, provide the immediate stimuli upon activation to initiate the allergic inflammatory cascade, resulting in eosinophil recruitment during the later phases following the allergen encounter. Mast cells and eosinophils have been demonstrated in increased numbers in other non-allergic inflammatory and neoplastic conditions including eosinophilic esophagitis,<sup>10</sup> chronic gastritis,<sup>11</sup> gastrointestinal neoplasms,<sup>12</sup> parasitic infections,<sup>13</sup> and inflammatory bowel disease.<sup>14</sup> Both mast cells and eosinophils express CCR3 and respond to eotaxins and RANTES (CCL5), leading to recruitment of both cell types into inflamed tissue. Mast cell-derived heparin can bind and stabilize eotaxins.<sup>15</sup> Mast cells and eosinophils can interact with each other through soluble mediators or direct cell-to-cell contact (Table 1). Mast cells can also be induced to produce IL-3 and IL-5, which can potentiate eosinophil longevity in the tissue.<sup>16</sup> Mast cell proteases appear to have dual action on eosinophil functions. Mast cell-derived chymase suppresses eosinophil apoptosis and induces release of IL-6, CXCL8, CCL2, and CXCL1 from eosinophils.<sup>17,18</sup> Beta-tryptase, on the other hand, can cleave eotaxin and RANTES and can potentially limit eosinophil chemotaxis.<sup>19</sup> Eosinophils in turn produce SCF, which can attract more mast cells into the tissue and protect them from apoptosis.<sup>20</sup> Simultaneous down-regulation of eosinophil and mast cell activation can be regulated by inhibitory surface molecules, such as CD300a<sup>9</sup> and Siglec 8,<sup>21</sup> which are expressed by both cell types. Mature forms of both mast cells and eosinophils express Siglec 8, a cell surface marker with lectin activity. Siglec-8 induces eosinophil apoptosis<sup>22</sup> and inhibits IgE-mediated mast cell activation,<sup>23</sup> thereby providing a common mechanism to limit inflammation caused by the coexistence of both cell types.

**Table 1. Selected Mast Cell Products and Surface Molecules and Their Potential Interactions With Eosinophils**

| Mast Cell Product | Biologic Effect                                                                                            |
|-------------------|------------------------------------------------------------------------------------------------------------|
| CCL5 (RANTES)     | Eosinophil and mast cell chemotaxis                                                                        |
| Tryptase          | Inactivation of eotaxins                                                                                   |
| Chymase           | Suppress eosinophil apoptosis                                                                              |
| TNF               | Support eosinophil survival and chemotaxis                                                                 |
| IL-3              | Support eosinophil proliferation                                                                           |
| IL-5              | Enhance eosinophil proliferation and survival                                                              |
| Histamine         | Modulate eosinophil chemotaxis, inhibit activation                                                         |
| Heparin           | Stabilize eotaxins                                                                                         |
| PGD <sub>2</sub>  | Eosinophil chemotaxis                                                                                      |
| CD48              | Adhesion and activation of eosinophil via CD244                                                            |
| CD54 (ICAM-1)     | Adhesion to eosinophil via LFA-1                                                                           |
| CD226 (DNAM-1)    | Adhesion to eosinophil via CD112 (Nectin-2)                                                                |
| CD117 (Kit)       | Interact with eosinophil derived SCF to induce differentiation, proliferation and activation of mast cells |

Mast cell and eosinophil couples have been observed in allergic inflammatory tissue, gastric cancers, and chronic gastritis, leading to the hypothesis that cell-to-cell contact is involved in cross talk between these cells.<sup>9,24</sup> This physical contact could be replicated in tissue culture using human peripheral blood eosinophils and cord blood-derived mast cells, and was shown to result in transfer of mediators between the two cell types. Potential surface molecules mediating this contact include CD112/Nectin-2, CD244, and LFA-1 on eosinophils binding to CD226/DNAM-1, CD48, and ICAM-1/CD54, respectively, on the surface of the mast cells.<sup>9,24</sup>

Mast cells and eosinophils can also be found in increased numbers in hematologic neoplastic disorders such as Hodgkin lymphoma (HL)<sup>25</sup> and primary myeloproliferative disorders of the bone marrow. In contrast to the inflammatory conditions mentioned above, the mechanism of the increased numbers of mast cells and eosinophils in myeloproliferative disorders involves a primary defect in a tyrosine kinase gene resulting in uncontrolled proliferation and dysregulated ap-

optosis. Two such disorders, which are particularly associated with increased numbers of both cell types, are systemic mastocytosis (SM; usually associated with the gain of function D816V *KIT* mutation) and chronic eosinophilic leukemia (CEL) (associated with the *FIP1L1-PDGFR*A fusion).

### ***FIP1L1-PDGFR*A-POSITIVE DISEASE: EOSINOPHILIC-MYELOID NEOPLASM WITH INCREASED MARROW MAST CELLS OR SYSTEMIC MASTOCYTOSIS WITH EOSINOPHILIA?**

In 2003, the *FIP1L1-PDGFR*A fusion was identified in patients with idiopathic hypereosinophilic syndrome.<sup>26</sup> This clonal abnormality is not visible by standard chromosome analysis and its detection requires either use of reverse-transcriptase polymerase chain reaction (RT-PCR) or fluorescent in situ hybridization (FISH).<sup>26,27</sup> Because this genetic lesion results from an interstitial 800-kb deletion on chromosome 4q12, which removes a segment of DNA involving the *CHIC2* gene, a common clinically available method for detecting this abnormality has been referred to as “FISH for the *CHIC2* deletion.” The presence of this clonal genetic marker re-defines such patients as having a neoplasm instead of idiopathic hypereosinophilic syndrome.<sup>28,29</sup> The frequency of this molecular abnormality in patients presenting with idiopathic hypereosinophilia in developed countries is approximately 10%, despite earlier reports suggesting a considerably higher prevalence, which reflected a highly selected subgroup of eosinophilic patients.<sup>30</sup> Before the discovery of *FIP1L1-PDGFR*A, these patients historically carried a poor prognosis due to early cardiac death in the absence of effective treatment.<sup>31–35</sup> However, with identification of this fusion tyrosine kinase as a therapeutic target of imatinib, it quickly became evident that these patients exhibit dramatic hematologic responses with this agent.<sup>26,36,37</sup>

Patients with *FIP1L1-PDGFR*A-associated eosinophilia present with features of a myeloproliferative disorder: splenomegaly, hypercellular bone marrows, and clinicopathologic characteristics that overlap with systemic mast cell disease, including increased numbers of abnormal-appearing bone marrow mast cells, marrow fibrosis, and elevated serum tryptase levels.<sup>38</sup> Soon after discovery of the fusion, a debate arose regarding whether *FIP1L1-PDGFR*A-positive disease represents a subtype of SM rather than a primary eosinophilic neoplasm. In an analysis by the Mayo Clinic, the bone marrow biopsies of these patients demonstrated less dense clusters (eg, an interstitial pattern) of mast cells by tryptase immunostaining compared to the typical multifocal aggregates observed in D816V *KIT*-positive SM.<sup>39</sup> In some cases, the mast cells exhibited spindle-shaped morphology and aberrant surface expression of CD25, both minor criteria for SM according to the

**Table 2. WHO Diagnostic Criteria for Systemic Mastocytosis**

**Major:**

Presence of multifocal mast cell aggregates (each with >15 mast cells) in involved organs (most commonly bone marrow)

**Minor:**

1. Morphologic abnormalities in mast cells (spindle-shaped, hypogranulated)
2. Detection of a codon 816 c-kit mutation
3. CD25 expression by mast cells (by immunohistochemistry or flow cytometry)
4. Tryptase >20 ng/mL (not applicable if another associated hematologic neoplasm is present)

NOTE. Diagnosis of systemic mastocytosis requires one major plus one minor criteria or three minor criteria.

World Health Organization (WHO) criteria. In the 2008 revised WHO classification, the presence of one major plus one minor criteria or three minor criteria (Table 2) can fulfill the diagnosis of SM.<sup>40</sup> Thus, even in the absence of the major criterion of multifocal mast cell aggregates, the finding of atypical (spindle-shaped) mast cells, mast cell expression of CD25, and a serum tryptase level >20 ng/mL (a common finding in patients with the *FIP1L1-PDGFR*A fusion) makes the rationale for calling such cases SM understandable. However, in the revised 2008 WHO semi-molecular scheme of myeloid neoplasms, *FIP1L1-PDGFR*A-positive disease is not considered a subtype of SM. Instead, such cases are included in the major new category designated “myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFR*A, *PDGFRB*, or *FGFR1*.”<sup>28</sup> Conversely, mastocytosis is now re-categorized as a subtype of myeloproliferative neoplasm (MPN) rather than its own major WHO disease category.

Patients with SM may exhibit an associated hematologic non-mast cell disease (eg, myelodysplastic syndrome [MDS], MDS/MPN overlap, acute myelogenous leukemia, hypereosinophilic syndrome [HES] or CEL, or more rarely myeloma or lymphoma).<sup>40,41</sup> SM-HES and SM-CEL with the D816V *KIT* mutation have been described, and techniques such as single-cell laser microdissection can detect this mutation in both the SM and associated hematologic non-mast cell disorder (AHNMD) component.<sup>42</sup> Similar to cases of SM-HES or SM-CEL characterized by oncogenic D816V *KIT*, it is likely that *FIP1L1-PDGFR*A is a pathogenetic driver of the co-existent eosinophilic and abnormal mast cell proliferations. In support of this, the *FIP1L1-PDGFR*A rearrangement has been found in a variety of myeloid cell types (neutrophils, monocytes, eosinophils), including

**Table 3. Clinicopathologic Features of Eosinophilia-Associated *FIP1L1-PDGFR*A-Rearranged Myeloid Neoplasms Versus D816V *KIT*-Positive Systemic Mastocytosis**

|                                  | <i>PDGFR</i> A-Rearranged   | D816V <i>KIT</i> -Positive                                   |
|----------------------------------|-----------------------------|--------------------------------------------------------------|
| Gender                           | Overwhelmingly male         | Less gender skewing                                          |
| Bone marrow mast cell aggregates | Loose clusters/interstitial | Dense aggregates                                             |
| AEC/tryptase ratio               | >100                        | ≤100                                                         |
| Treatment                        | Imatinib-sensitive          | Imatinib-resistant; second-generation TKIs (eg, midostaurin) |
| Symptom profile                  | Cardiac/pulmonary           | Gastrointestinal/urticaria pigmentosa/vascular               |
| Vitamin B <sub>12</sub> level    | Elevated                    | Normal                                                       |

Abbreviations: AEC, absolute eosinophil count; TKIs, tyrosine kinase inhibitors.

mast cells, consistent with a mutational origin in a multipotent hematopoietic progenitor.<sup>43</sup> The relative penetrance of eosinophil versus mast cell signs and symptoms of illness may reflect host or disease related factors that are not yet well understood.

The *FIP1L1-PDGFR*A fusion and D816V *KIT* mutation appear to be mutually exclusive oncogenic lesions. Investigators generated a set of clinical and laboratory features that could reliably distinguish patients with *KIT* D816V-positive SM with eosinophilia from individuals with the *FIP1L1-PDGFR*A-positive myeloid neoplasms with eosinophilia.<sup>44</sup> In the D816V *KIT*-positive group, gastrointestinal symptoms, urticaria pigmentosa, thrombocytosis, median serum tryptase value, and the presence of dense mast cell aggregates in the bone marrow were statistically significantly increased or more frequently represented compared to *FIP1L1-PDGFR*A-positive patients. Conversely, male sex, cardiac and pulmonary symptoms, median peak absolute eosinophil count, the eosinophil to tryptase ratio, and elevated serum B<sub>12</sub> levels were higher or more common in the *FIP1L1-PDGFR*A-positive group. A scoring system incorporating these clinical and laboratory parameters could reliably predict whether patients with peripheral eosinophilia and increased marrow mast cell burden carried the D816V *KIT* mutation versus *FIP1L1-PDGFR*A, which is important for guiding treatment decisions (Table 3).<sup>44</sup>

## MURINE MODELS EVALUATING THE DEVELOPMENT OF EOSINOPHILIA AND MASTOCYTOSIS

*FIP1L1-PDGFR*α can promote the proliferation and survival of the eosinophils through activation of several signaling pathways such as phosphoinositol 3-kinase, ERK1/2, and STAT5.<sup>26,45</sup> The exact mechanism by which *FIP1L1-PDGFR*α preferentially affects eosinophils remains unclear. In one murine model, expression of the *FIP1L1-PDGFR*A fusion in bone marrow cells was not sufficient to cause eosinophilia, but only

a general myeloproliferative disease.<sup>46</sup> However, in another murine model, expression of *FIP1L1-PDGFR*A together with overexpression of IL-5, the most potent eosinophilopoietic cytokine, mimicked more typical features of HES, such as tissue infiltration of eosinophils.<sup>47</sup> In an analysis of polymorphic variation at the IL5 receptor alpha (*IL5RA*) gene, an association was identified between a single nucleotide polymorphism in the 5' untranslated region of *IL5RA* and the eosinophil count (and eosinophilic infiltration of tissues) in *FIP1L1-PDGFR*A-positive patients.<sup>48</sup>

The development of mastocytosis and eosinophilia was evaluated in another murine model by introducing *FIP1L1-PDGFR*A into hematopoietic stem cells (HSCs) and progenitors with T-cell overexpression of IL-5.<sup>49</sup> These mice exhibited increased mast cell infiltration of the bone marrow and extramedullary organs such as the spleen, skin, and small intestine compared to control mice that received a transplant of IL-5 transgenic HSCs or progenitor cells alone. Injection of a neutralizing antibody against KIT decreased mast cell infiltration of the intestine induced by expression of *FIP1L1-PDGFR*A. SCF increased migration of *FIP1L1-PDGFR*A-expressing mast cells compared to mock vector-transduced mast cells and also contributed to increased survival of mast cells. These preclinical data indicate that in response to SCF, *FIP1L1-PDGFR*A can synergistically promote the development, activation, and survival of mast cells, and recapitulate aspects of coexistent eosinophil and mast cell proliferations observed in human disease.

## PROGNOSTIC RELEVANCE OF EOSINOPHILIA IN SYSTEMIC MASTOCYTOSIS AND OTHER HEMATOLYMPHOID NEOPLASMS

In WHO-defined myeloid malignancies, the prognostic relevance of concurrent eosinophilia has been studied in a limited number of diseases. In a series of 123 patients with SM, eosinophilia was prevalent in 34% of cases, but was prognostically neutral and not affected

by exclusion of *FIP1L1-PDGfra*-positive cases.<sup>50</sup> In another study of 63 patients, SM with eosinophilia was associated with a significantly reduced probability of overall and event-free survival (EFS) compared to SM without eosinophilia.<sup>51</sup> In approximately 1,000 patients with de novo MDS, eosinophilia (and basophilia) predicted a significantly reduced survival without having a significant impact on leukemia-free survival.<sup>52</sup> A retrospective analysis of 288 newly diagnosed MDS subjects revealed that a significantly higher number of patients with eosinophilia or basophilia (compared to patients with neither) exhibited a karyotype with an intermediate or poor prognosis.<sup>53</sup> In addition, the overall survival rate was lower, and rate of evolution to acute myeloid leukemia (AML) was higher.

The prognostic value of eosinophilia has also been evaluated in lymphocytic leukemias and lymphomas. In patients with acute T-lymphoblastic leukemia (ATLL), blood eosinophilia was identified as an independent and significant unfavorable prognostic factor for overall survival.<sup>54</sup> The same group previously showed a correlation between high IL-5 levels and eosinophilia in ATLL, and that high serum IL-5 was similarly an adverse prognostic factor in these patients.<sup>55</sup> In 26 patients with primary cutaneous T-cell lymphomas, tissue eosinophils were found in 22 of 26 cases. The density and activation of tissue eosinophils were significantly related to disease progression.<sup>56</sup>

Increased blood and tissue eosinophils and higher numbers of tumor-associated mast cells can be associated with (HLs) and non-Hodgkin lymphomas (NHLs) and demonstrate prognostic utility. In HL, CD30L-bearing mast cells can activate CD30<sup>+</sup> Reed-Sternberg cells through a CD30L-CD30 interaction.<sup>57</sup> Mast cells may additionally be recruited to the tumor by chemokines produced by Reed-Sternberg cells, such as CCL5 (RANTES).<sup>58</sup> In a study of 123 HL patients, higher mast cell infiltration of tumor specimens was associated with worse relapse-free survival and nodular sclerosis histology.<sup>59</sup> In a retrospective study of 59 patients with classical HL, mast cells were significantly higher in cases of refractory disease or early relapse compared to responders.<sup>60</sup> Histologic analysis of 1,511 diagnostic biopsy specimens from HL patients treated by the German Hodgkin's Lymphoma Study Group between 1988 and 1994 revealed marked eosinophilia in 38% of cases.<sup>61</sup> In a multivariate analysis, tissue eosinophilia was the strongest prognostic factor for freedom from treatment failure and overall survival. Another study similarly revealed that heavy eosinophilic infiltration of tumor specimens from 140 cases of HL was the most important prognostic factor for determining disease-free survival in all patients, regardless of age.<sup>62</sup>

In contrast to the HL experience, in patients with diffuse large B-cell lymphoma, higher numbers of tumor-infiltrating mast cells were associated with better EFS in both germinal center and non-germinal center

subtypes.<sup>63</sup> In follicular lymphoma (FL), in addition to the validated Follicular Lymphoma International Prognostic Index (FLIPI), tumor-infiltrating cytotoxic and regulatory T cells, and macrophages have prognostic value in patients who have been treated with chemotherapy.<sup>64</sup> In a study of FL patients treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), immunohistochemical analysis revealed that high tissue mast cell content was associated with a significant negative impact on progression-free survival. This effect on prognosis was independent of FLIPI and the presence of tumor-associated macrophages (TAMs); in addition, the high tissue mast cell count eliminated the favorable prognostic value of TAMs.<sup>64</sup>

These contrasting prognostic correlations between tumor-infiltrating mast cells and prognosis in different lymphoma subtypes (favorable in diffuse large B-cell lymphoma and unfavorable in HL and FL) highlight that mast cells play a key role in the host inflammatory response, but their exact contribution to the complex biological interplay between tumor and the local microenvironment remains poorly understood.

#### **THERAPY IN SYSTEMIC MASTOCYTOSIS AND MYELOID NEOPLASMS WITH EOSINOPHILIA AND REARRANGEMENT OF *PDGFRA/B* AND *FGFR1***

Because of the potential for phenotypic overlap between WHO-defined SM with an eosinophilia-related AHNMD (eg, SM-HES or SM-CEL, not otherwise specified) and myeloid neoplasms with rearrangement of *PDGFRA*, molecular determination of *KIT* and *FIP1L1-PDGfra* mutation status is critical to guide therapeutic options. The vast majority of advanced SM patients in whom cytoreductive therapy is being considered carry the D816V *KIT* mutation (frequency ~80%),<sup>65,66</sup> which is imatinib-resistant.<sup>67,68</sup> Conversely, rare SM patients who exhibit a juxtamembrane *KIT* mutation (<5%) are likely to respond to imatinib.<sup>69</sup> Patients with the D816V *KIT* mutation may be responsive to second-generation tyrosine kinase inhibitors, including investigational midostaurin (PKC412),<sup>70</sup> or to dasatinib (currently approved only for Philadelphia chromosome-positive chronic myelogenous leukemia and acute lymphoblastic leukemia).<sup>71</sup> Of interest, some patients with D816V *KIT*-positive SM with HES- or CEL-not otherwise specified have demonstrated rapid and complete normalization of severe peripheral eosinophilia with midostaurin treatment.<sup>70</sup> It is unknown whether this is due to (1) a preferential effect of the drug on eosinophil-specific signaling, (2) increased sensitivity of eosinophils to inhibition of constitutive D816V *KIT* signaling, or (3) reduction of reactive eosinophilia related to cytoreduction of mast cells which elaborate eosinophilopoietic cytokines. Interferon-alpha with or without corticoste-

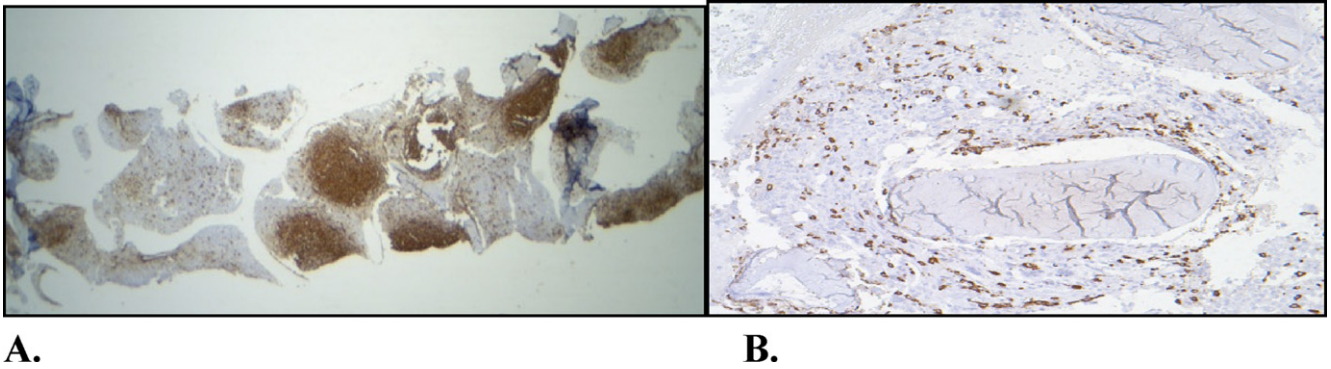


**Figure 1.** (A) Immunohistochemistry for mast cell tryptase demonstrates multifocal mast cell aggregates in a core bone marrow biopsy from a patient with *KIT* D816V-positive systemic mastocytosis. (B) Immunohistochemistry for mast cell tryptase reveals an interstitial pattern of mast cell infiltration in a core bone marrow biopsy from a patient with *FGFR1*-rearranged myeloid neoplasm with eosinophilia. The patient also had a concurrent T-cell lymphoblastic lymphoma. Photomicrographs courtesy of Dr Tracy George, Stanford University School of Medicine, Department of Pathology.

roids<sup>72-76,82</sup> and 2-chlorodeoxyadenosine<sup>77-82</sup> are active agents for advanced SM; however, overall response rates are in the range of 40% to 50%, and most responses are partial in nature.

As previously noted, identification of the *FIP1L1-PDGFR*A fusion in patients with eosinophilia (even in the presence of increased bone marrow mast cells) is an indication for treatment with imatinib, regardless of the presence of organ dysfunction. Imatinib can elicit hematologic remissions within 4 weeks at doses of 100 to 400 mg daily.<sup>26,27,30,83,84</sup> A standard dose has not been recommended, as some patients require higher doses to achieve more in-depth remissions. Cytogenetic remissions (using FISH for the *CHIC2* deletion) or in-depth molecular remissions have been achieved in a period as soon as 1 month and have been maintained with long-term follow-up.<sup>83-85</sup> Maintenance imatinib therapy with doses as low as 100 to 200 mg weekly is sufficient to achieve or sustain a molecular remission; however, patients in whom imatinib therapy has been held or discontinued may demonstrate cytogenetic/molecular relapses, and loss of hematologic remission within a period of several months.<sup>86,87</sup> With the treatment experience in *FIP1L1-PDGFR*A-positive disease now reaching more than 9 years, the natural history and long-term prognosis of these patients treated with imatinib is outstanding. Fewer than 10 cases of imatinib-resistance with documented mutations within *PDGFR*A have been reported (eg, secondary resistance mutations T674I and D842V in advanced/blast-crisis phases of disease, and primary resistance mutations S601P and L629P in the chronic phase).<sup>26,88-91</sup> Second-generation tyrosine kinase inhibitors (eg, sorafenib, sunitinib) with in vitro activity against these mutants have been used in patients but usually with short-lived clinical benefit.<sup>92-94</sup>

Whereas the *FIP1L1-PDGFR*A molecular abnormality is occult by standard cytogenetic analysis, patients

with rearrangement of *PDGFRB* exhibit a reciprocal translocation involving chromosome segment 5q31-33. In such cases, FISH or PCR can be used to identify the fusion partner of *PDGFRB*, with more than 20 partners now described. Patients with *PDGFRB* rearrangements typically present with an overlap MDS/MPN neoplasm such as chronic myelomonocytic leukemia, often associated with eosinophilia. Patients with *PDGFRB* rearrangements demonstrate sensitivity to imatinib similar to *FIP1L1-PDGFR*A.<sup>95</sup> The recommended dose is 400 mg daily, which has resulted in excellent outcomes.

Rare patients have been described with reciprocal translocations involving the fibroblast growth factor receptor 1 (*FGFR1*) gene, with more than 10 fusion partners described (most commonly *ZNF198*) and approximately 65 patients reported in the literature.<sup>96</sup> *FGFR1* rearrangements are associated with the t(8p11-13) chromosomal breakpoint and clinically present with a B- or T-cell lymphoblastic lymphoma and a myeloproliferative disorder with eosinophilia. These mixed lineage neoplasms are derived from an early hematopoietic progenitor and thus have been referred to as “stem cell leukemias/lymphomas.” The disease often terminates in AML in less than 2 years. Intensive chemotherapy (with AML or acute lymphocytic leukemia type induction regimens) followed by early allogeneic transplantation is recommended, but prognosis is dismal despite these interventions. *FGFR1* is not a therapeutic target of imatinib, but *FGFR1* inhibitors are currently in development. In addition to the more common presentation of eosinophilia, cases of *PDGFRB*- and *FGFR1*-rearranged neoplasms associated with SM have been observed,<sup>97,98</sup> indicating that genetic alterations involving these tyrosine kinases can develop in early hematopoietic clones that can give rise to either eosinophils or mast cells. Figure 1 demonstrates the typical multifocal mast cell aggregates observed in *KIT*

D816V<sup>+</sup> SM versus the loose, interstitial pattern of mast cells that are more commonly observed in myeloid neoplasms associated with eosinophilia and rearrangement of *PDGFRA/B* or *FGFR1*.

## CONCLUSION

Mast cells and eosinophils are important effectors cells of allergic inflammation, but are often found together in other inflammatory, infectious, and neoplastic disorders. CCR3 expressed by both cell types allows a common mechanism for recruitment into tissues. Once in the tissue, mast cells can interact with and modulate eosinophil activation, survival, and apoptosis through a number of soluble mediators and cell-to-cell contact. Mast cells and eosinophils are derived from CD34<sup>+</sup> hematopoietic progenitor cells and clonally expanded in myeloproliferative disorders, particularly SM and chronic eosinophilic leukemia. While mast cells in these disorders share certain pathologic features, such as aberrant mast cell morphology and CD25 expression, they are associated with distinct molecular defects and have different clinical presentations, prognosis, and response to therapy with tyrosine kinase inhibitors. Therefore, accurate diagnosis of a patient presenting with increased tissue and bone marrow mast cells and eosinophils is crucial in appropriate management and counseling for prognosis.

## REFERENCES

1. Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol*. 2010;125: S73–80.
2. Denburg JA, Telizyn S, Messner H, et al. Heterogeneity of human peripheral blood eosinophil-type colonies: evidence for a common basophil-eosinophil progenitor. *Blood*. 1985;66:312–8.
3. Kitamura Y, Oboki K, Ito A. Molecular mechanisms of mast cell development. *Immunol Allergy Clin North Am*. 2006;26:387–405.
4. Kirshenbaum AS, Goff JP, Kessler SW, Mican JM, Zsebo KM, Metcalfe DD. Effect of IL-3 and stem cell factor on the appearance of human basophils and mast cells from CD34<sup>+</sup> pluripotent progenitor cells. *J Immunol*. 1992; 148:772–7.
5. Metcalfe DD. Mast cells and mastocytosis. *Blood*. 2008; 112:946–56.
6. Gauvreau GM, Ellis AK, Denburg JA. Haemopoietic processes in allergic disease: eosinophil/basophil development. *Clin Exp Allergy*. 2009;39:1297–306.
7. Lamkhieoued B, Abdelilah SG, Hamid Q, Mansour N, Deslespesse G, Renzi PM. The CCR3 receptor is involved in eosinophil differentiation and is up-regulated by Th2 cytokines in CD34<sup>+</sup> progenitor cells. *J Immunol*. 2003; 170:537–47.
8. Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol*. 2006;24:147–74.
9. Minai-Fleminger Y, Levi-Schaffer F. Mast cells and eosinophils: the two key effector cells in allergic inflammation. *Inflamm Res*. 2009;58:631–8.
10. Abonia JP, Blanchard C, Butz BB, et al. Involvement of mast cells in eosinophilic esophagitis. *J Allergy Clin Immunol*. 2010;126:140–9.
11. Piazzuelo MB, Camargo MC, Mera RM, et al. Eosinophils and mast cells in chronic gastritis: possible implications in carcinogenesis. *Hum Pathol*. 2008;39:1360–9.
12. Caruso RA, Fedele F, Zuccala V, Fracassi MG, Venuti A. Mast cell and eosinophil interaction in gastric carcinomas: ultrastructural observations. *Anticancer Res*. 2007; 27:391–4.
13. Anthony RM, Rutitzky LI, Urban JF, Jr, Stadecker MJ, Gause WC. Protective immune mechanisms in helminth infection. *Nat Rev Immunol*. 2007;7:975–87.
14. Jeziorska M, Haboubi N, Schofield P, Woolley DE. Distribution and activation of eosinophils in inflammatory bowel disease using an improved immunohistochemical technique. *J Pathol*. 2001;194:484–92.
15. Ellyard JI, Simson L, Bezos A, Johnston K, Freeman C, Parish CR. Eotaxin selectively binds heparin. An interaction that protects eotaxin from proteolysis and potentiates chemotactic activity in vivo. *J Biol Chem*. 2007;282:15238–47.
16. Shakoory B, Fitzgerald SM, Lee SA, Chi DS, Krishnaswamy G. The role of human mast cell-derived cytokines in eosinophil biology. *J Interferon Cytokine Res*. 2004; 24:271–81.
17. Takafuji S, Tadokoro K, Ito K, Nakagawa T. Release of granule proteins from human eosinophils stimulated with mast-cell mediators. *Allergy*. 1998;53:951–6.
18. Wong CK, Ng SS, Lun SW, Cao J, Lam CW. Signalling mechanisms regulating the activation of human eosinophils by mast-cell-derived chymase: implications for mast cell-eosinophil interaction in allergic inflammation. *Immunology*. 2009;126:579–87.
19. Pang L, Nie M, Corbett L, Sutcliffe A, Knox AJ. Mast cell beta-tryptase selectively cleaves eotaxin and RANTES and abrogates their eosinophil chemotactic activities. *J Immunol*. 2006;176:3788–95.
20. Hartman M, Piliponsky AM, Temkin V, Levi-Schaffer F. Human peripheral blood eosinophils express stem cell factor. *Blood*. 2001;97:1086–91.
21. Hudson SA, Herrmann H, Du J, et al. Developmental, malignancy-related, and cross-species analysis of eosinophil, mast cell, and basophil siglec-8 expression. *J Clin Immunol*. 2011;31:1045–53.
22. Nutku E, Aizawa H, Hudson SA, Bochner BS. Ligation of Siglec-8: a selective mechanism for induction of human eosinophil apoptosis. *Blood*. 2003;101:5014–20.
23. Yokoi H, Choi OH, Hubbard W, et al. Inhibition of FcεpsilonRI-dependent mediator release and calcium flux from human mast cells by sialic acid-binding immunoglobulin-like lectin 8 engagement. *J Allergy Clin Immunol*. 2008;121:499–505.
24. Minai-Fleminger Y, Elishmereni M, Vita F, et al. Ultrastructural evidence for human mast cell-eosinophil interactions in vitro. *Cell Tissue Res*. 2010;341:405–15.
25. Glimelius I, Rubin J, Rostgaard K, et al. Predictors of histology, tissue eosinophilia and mast cell infiltration in Hodgkin's lymphoma—a population-based study. *Eur J Haematol*. 2011;87:208–16.
26. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase

- created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med.* 2003;348:1201-14.
27. Pardanani A, Ketterling RP, Brockman SR, et al. CHIC2 deletion, a surrogate for FIP1L1-PDGFR fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. *Blood.* 2003;102:3093-6.
28. Bain BJ, Gilliland DG, Horny H-P, et al. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1. In: Swerdlow S, Harris NL, Stein H, Jaffe ES, Theil J, Vardiman JW (eds). *World Health Organization classification of tumours. pathology and genetics of tumours of haematopoietic and lymphoid tissues.* Lyon, France: IARC Press; 2008:68-73.
29. Chusid MJ, Dale DC, West BC, et al. The hypereosinophilic syndrome. Analysis of fourteen cases with review of the literature. *Medicine.* 1975;54:1-27.
30. Gotlib J, Cools J. Five years since the discovery of the FIP1L1-PDGFR: what we have learned about the fusion and other molecularly defined eosinophilias. *Leukemia.* 2008;22:1999-2010.
31. Spry CJ, Davies J, Tai PC, et al. Clinical features of fifteen patients with the hypereosinophilic syndrome. *Q J Med.* 1983;52:1-22.
32. Lefebvre C, Bletry O, Degoulet P, et al. Prognostic factors of hypereosinophilic syndrome. Study of 40 cases. *Ann Med Interne (Paris).* 1989;140:253-7.
33. Flaum MA, Schooley RT, Fauci AS, et al. A clinicopathologic correlation of the idiopathic hypereosinophilic syndrome. *Blood.* 1981;58:1012-20.
34. Fauci AS, Harley JB, Roberts WC, et al. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. *Ann Intern Med.* 1982;97:78-92.
35. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. *Blood.* 1994;83:2759-79.
36. Schaller JL, Burkland GA. Case report: rapid and complete control of idiopathic hypereosinophilia with imatinib mesylate. *MedGenMed.* 2001;7:3-9.
37. Gleich GJ, Leiferman KM, Pardanani A, et al. Treatment of hypereosinophilic syndrome with imatinib mesilate. *Lancet.* 2002;359:1577-8.
38. Klion AD, Noel P, Akin C, et al. Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood.* 2003;101:4660-6.
39. Pardanani A, Brockman SR, Paternoster SF, et al. FIP1L1-PDGFR fusion: prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia. *Blood.* 2004;104:3038-45.
40. Horny HP, Akin C, Metcalfe DD, et al. Mastocytosis. In: Swerdlow S, Campo E, Lee Harris N, et al (eds). *WHO classification of tumours of haematopoietic and lymphoid tissues.* Lyon, France: IARC Press; 2008:53-63.
41. Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: Consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest.* 2007;37:435-53.
42. Sotlar K, Fridrich C, Mall A, et al. Detection of c-kit point mutation Asp-816 Val in microdissected pooled single mast cells and leukemic cells in a patient with systemic mastocytosis and concomitant chronic myelomonocytic leukemia. *Leuk Res.* 2002;26:979-84.
43. Robyn J, Lemery S, McCoy JP, et al. Multilineage involvement of the fusion gene in patients with FIP1L1/PDGFR-positive hypereosinophilic syndrome. *Br J Haematol.* 2006;132:286-92.
44. Maric I, Robyn J, Metcalfe DD, et al. KIT D816V-associated systemic mastocytosis with eosinophilia and FIP1L1/PDGFR-associated chronic eosinophilic leukemia are distinct entities. *J Allergy Clin Immunol.* 2007;120:680-7.
45. Buitenhuis M, Verhagen LP, Cools J, Coffey PJ. Molecular mechanisms underlying FIP1L1-PDGFR-mediated myeloproliferation. *Cancer Res.* 2007;67:3759-66.
46. Cools J, Stover EH, Boulton CL, et al. PKC412 overcomes resistance to imatinib in a murine model of FIP1L1-PDGFR $\alpha$ -induced myeloproliferative disease. *Cancer Cell.* 2003;3:459-69.
47. Yamada Y, Rothenberg ME, Lee AW, et al. The FIP1L1-PDGFR fusion gene cooperates with IL-5 to induce murine hypereosinophilic syndrome (HES)/chronic eosinophilic leukemia (CEL)-like disease. *Blood.* 2006;107:4071-9.
48. Burgstaller S, Kreil S, Waghorn K, Metzgeroth G, Preudhomme C, Zoi K, et al. The severity of FIP1L1-PDGFR-positive chronic eosinophilic leukaemia is associated with polymorphic variation at the IL5RA locus. *Leukemia.* 2007;21:2428-32.
49. Yamada Y, Sanchez-Aguilera A, Brandt EB, et al. FIP1L1/PDGFR $\alpha$  synergizes with SCF to induce systemic mastocytosis in a murine model of chronic eosinophilic leukemia/hypereosinophilic syndrome. *Blood.* 2008;112:2500-7.
50. Pardanani A, Lim KH, Lasho TL, et al. Prognostically relevant breakdown of 123 patients with systemic mastocytosis associated with other myeloid malignancies. *Blood.* 2009;114:3769-72.
51. Böhm A, Födinger M, Wimazal F, et al. Eosinophilia in systemic mastocytosis: clinical and molecular correlates and prognostic significance. *J Allergy Clin Immunol.* 2007;120:192-9.
52. Wimazal F, Germing U, Kundi M, et al. Evaluation of the prognostic significance of eosinophilia and basophilia in a larger cohort of patients with myelodysplastic syndromes. *Cancer.* 2010;116:2372-81.
53. Matsushima T, Handa H, Yokohama A, et al. Prevalence and clinical characteristics of myelodysplastic syndrome with bone marrow eosinophilia or basophilia. *Blood.* 2003;101:3386-90.
54. Utsunomiya A, Ishida T, Inagaki A, et al. Clinical significance of a blood eosinophilia in adult T-cell leukemia/lymphoma: a blood eosinophilia is a significant unfavorable prognostic factor. *Leuk Res.* 2007;31:915-20.
55. Inagaki A, Ishida T, Ishii T, et al. Clinical significance of serum Th1-, Th2- and regulatory T cells-associated cytokines in adult T-cell leukemia/lymphoma: high interleukin-5 and -10 levels are significant unfavorable prognostic factors. *Int J Cancer.* 2006;118:3054-61.
56. Ionescu MA, Rivet J, Daneshpouy M, et al. In situ eosinophil activation in 26 primary cutaneous T-cell lympho-

- mas with blood eosinophilia. *J Am Acad Dermatol*. 2005;5:32-9.
57. Molin D, Fischer M, Xiang Z, et al. Mast cells express functional CD30 ligand and are the predominant CD30L-positive cells in Hodgkin's disease. *Br J Haematol*. 2001;11:616-23.
  58. Fischer M, Juremalm M, Olsson N, et al. Expression of CCL5/rantes by Hodgkin and Reed-Sternberg cells and its possible role in the recruitment of mast cells into lymphomatous tissue. *Int J Cancer*. 2003;107:197-201.
  59. Molin D, Edström A, Glimelius I, et al. Mast cell infiltration correlates with poor prognosis in Hodgkin's lymphoma. *Br J Haematol*. 2002;119:122-4.
  60. Canioni D, Deau-Fischer B, Taupin P, et al. Prognostic significance of new immunohistochemical markers in refractory classical Hodgkin lymphoma: a study of 59 cases. *PLoS One*. 2009;4:e6341.
  61. von Wasielewski R, Seth S, Franklin J, et al. Tissue eosinophilia correlates strongly with poor prognosis in nodular sclerosing Hodgkin's disease, allowing for known prognostic factors. *Blood*. 2000;95:1207-13.
  62. Enblad G, Sundstrom C, Glimelius B. Infiltration of eosinophils in Hodgkin's disease involved lymph nodes predicts prognosis. *Hematol Oncol*. 1993;11:187-93.
  63. Hedström G, Berglund M, Molin D, et al. Mast cell infiltration is a favourable prognostic factor in diffuse large B-cell lymphoma. *Br J Haematol*. 2007;138:68-71.
  64. Taskinen M, Karjalainen-Lindsberg ML, Leppä S. Prognostic influence of tumor-infiltrating mast cells in patients with follicular lymphoma treated with rituximab and CHOP. *Blood*. 2008;111:4664-7.
  65. Longley BJ, Tyrrell L, Lu SZ, et al. Somatic c-KIT activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. *Nat Genet*. 1996;12:312-4.
  66. Longley BJ Jr, Metcalfe DD, Tharp M, et al. Activating and dominant inactivating c-KIT catalytic domain mutations in distinct clinical forms of human mastocytosis. *Proc Natl Acad Sci USA*. 1999;96:1609-14.
  67. Akin C, Brockow K, D'Ambrosio C, et al. Effects of tyrosine kinase inhibitor STI571 on human mast cells bearing wild-type or mutated c-kit. *Exp Hematol*. 2003;31:686-92.
  68. Zermati Y, De Sepulveda P, Feger F, et al. Effect of tyrosine kinase inhibitor STI571 on the kinase activity of wild-type and various mutated c-kit receptors found in mast cell neoplasms. *Oncogene*. 2003;22:660-4.
  69. Akin C, Fumo G, Yavuz AS, et al. A novel form of mastocytosis associated with a transmembrane c-kit mutation and response to imatinib. *Blood*. 2004;103:3222-5.
  70. Gotlib J, DeAngelo DJ, George TI, et al. (2010). KIT inhibitor Midostaurin exhibits a high rate of clinically meaningful and durable responses in advanced systemic mastocytosis: report of a fully accrued phase II trial. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:316.
  71. Verstovsek S, Tefferi A, Cortes J, et al. Phase II study of dasatinib in Philadelphia chromosome-negative acute and chronic myeloid diseases, including systemic mastocytosis. *Clin Cancer Res*. 2008;14:3906-15.
  72. Kluin-Nelemans HC, Jansen JH, Breukelman H, et al. Response to interferon a-2b in a patient with systemic mastocytosis. *N Engl J Med*. 1992;326:619-23.
  73. Worobec AS, Kirshenbaum AS, Schwartz LB, Metcalfe DD. Treatment of three patients with systemic mastocytosis with interferon alfa-2b. *Leuk Lymphoma*. 1996;22:501-8.
  74. Butterfield JH. Response of severe systemic mastocytosis to interferon alpha. *Br J Dermatol*. 1998;138:489-95.
  75. Casassus P, Caillat-Vigneron N, Martin A, et al. Treatment of adult systemic mastocytosis with interferon- $\alpha$ : Results of a multicentre phase II trial on 20 patients. *Br J Haematol*. 2002;119:1090-7.
  76. Hauswirth AW, Simonitsch-Klupp I, Uffmann M, et al. Response to therapy with interferon a-2b and prednisolone in aggressive systemic mastocytosis: report of five cases and review of the literature. *Leuk Res*. 2004;28:249-57.
  77. Tefferi A, Li CY, Butterfield JH, et al. Treatment of systemic mast-cell disease with cladribine. *N Engl J Med*. 2001;344:307-9.
  78. Kluin-Nelemans HC, Oldhoff JM, Van Doormaal JJ, et al. Cladribine therapy for systemic mastocytosis. *Blood*. 2003;102:427-6.
  79. Lortholary O, Vargaftig J, Feger F, et al. Efficacy and safety of cladribine in adult systemic mastocytosis: a French multicenter study of 33 patients. *Blood (ASH Annual Meeting Abstracts)*. 2004;104:661.
  80. Pardanani A, Hoffbrand AV, Butterfield JH, et al. Treatment of systemic mast cell disease with 2-chlorodeoxyadenosine. *Leuk Res*. 2004;28:127-31.
  81. Hermine O, Hirsh I, Damaj G, et al. Long term efficacy and safety of cladribine in adult systemic mastocytosis: a French multicenter study of 44 patients. *ASH Annual Meeting Abstracts*. 2010;116:1982.
  82. Lim KH, Pardanani A, Butterfield JH, Li CY, Tefferi A. Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. *Am J Hematol*. 2009;84:790-4.
  83. Baccarani M, Cilloni D, Rondoni M, et al. The efficacy of imatinib mesylate in patients with FIP1L1-PDGFRalpha-positive hypereosinophilic syndrome. Results of a multicenter prospective study. *Haematologica*. 2007;92:1173-9.
  84. Jovanovic JV, Score J, Waghorn K, et al. Low-dose imatinib mesylate leads to rapid induction of major molecular responses and achievement of complete molecular remission in FIP1L1-PDGFRa-positive chronic eosinophilic leukemia. *Blood*. 2007;109:4635-40.
  85. Klion AD, Robyn J, Akin C, et al. Molecular remission and reversal of myelofibrosis in response to imatinib mesylate treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome. *Blood* 2004;103:473-8.
  86. Helbig G, Stella-Holowiecka B, Majewski M, et al. A single weekly dose of imatinib is sufficient to induce and maintain remission of chronic eosinophilic leukaemia in FIP1L1-PDGFRa-expressing patients. *Br J Haematol*. 2008;141:200-4.
  87. Klion AD, Robyn J, Maric I, et al. Relapse following discontinuation of imatinib mesylate therapy for FIP1L1/PDGFRa-

- positive chronic eosinophilic leukemia: implications for optimal dosing. *Blood*. 2007;110:3552–6.
88. Von Bubnoff N, Sandherr M, Schlimok G, et al. Myeloid blast crisis evolving during imatinib treatment of an FIP1L1-PDGFRalpha-positive chronic myeloproliferative disease with prominent eosinophilia. *Leukemia*. 2004; 19:286–7.
89. Ohnishi H, Kandabashi K, Maeda Y, et al. Chronic eosinophilic leukaemia with FIP1L1-PDGFRα fusion and T674I mutation that evolved from Langerhans cell histiocytosis with eosinophilia after chemotherapy. *Br J Haematol*. 2006;134:547–9.
90. Lierman E, Michaux L, Beullens E, et al. FIP1L1-PDGFRalpha D842V, a novel panresistant mutant, emerging after treatment of FIP1L1-PDGFRalpha T674I eosinophilic leukemia with single agent sorafenib. *Leukemia*. 2009; 23:845–51.
91. Simon D, Salemi S, Yousefi S, et al. Primary resistance to imatinib in Fip1-like 1-platelet-derived growth factor receptor alpha-positive eosinophilic leukemia. *J Allergy Clin Immunol* 2008;121:1054–6.
92. Lierman E, Folens C, Stover EH, et al. Sorafenib is a potent inhibitor of FIP1L1-PDGFRalpha and the imatinib-resistant FIP1L1-PDGFRalpha T674I mutant. *Blood*. 2006;108:1374–6.
93. Stover EH, Chen J, Lee BH, et al. The small molecule tyrosine kinase inhibitor AMN107 inhibits TEL-PDGFR-beta and FIP1L1-PDGFRalpha in vitro and in vivo. *Blood*. 2005;106:3206–13.
94. von Bubnoff N, Gorantla SP, Thone S, et al. The FIP1L1-PDGFRα T674I mutation can be inhibited by the tyrosine kinase inhibitor AMN107 (nilotinib). *Blood*. 2006;107: 4970–1.
95. Cross DM, Cross NC, Burgstaller S, et al. Durable responses to imatinib in patients with PDGFRB fusion gene-positive and BCR-ABL-negative chronic myeloproliferative disorders. *Blood*. 2007;109:61–4.
96. Jackson CC, Medeiros LJ, Miranda RN. 8p11 myeloproliferative syndrome: a review. *Hum Pathol*. 2010;41:461–76.
97. Mayeur-Rousse C, Sorel N, Voldoire M, et al. Unique association of systemic mastocytosis and myeloid/lymphoid neoplasm in blast crisis with abnormality of *FGFR1* gene. *Leuk Res*. 2012;36:377–81.
98. Lahortiga I, Akin C, Cools J, et al. Activity of imatinib in systemic mastocytosis with chronic basophilic leukemia and a PRKG2-PDGFRB fusion. *Haematologica*. 2008;93: 49–56.