

Chronic Eosinophilic Leukemias and the Myeloproliferative Variant of the Hypereosinophilic Syndrome

Barbara J. Bain, MBBS, FRACP, FRCPath*,
Sarah H. Fletcher, MBBChir, MRCP

*Department of Haematology, St Mary's Hospital Campus of Imperial College Faculty
of Medicine, St Mary's Hospital, Praed Street, London, W2 1NY, UK*

Eosinophilia can be primary or secondary. Most cases of primary eosinophilia represent a hematological neoplasm; a minority, for example familial eosinophilia, do not. Secondary or reactive eosinophilia can result from a multitude of underlying conditions. In addition to cases of eosinophilia identifiable as primary or secondary, there are patients in whom the cause cannot be discovered and in whom the eosinophilia is therefore referred to as “idiopathic.” Among idiopathic cases, a syndrome of persistent unexplained eosinophilia leading to tissue damage has been designated the “idiopathic hypereosinophilic syndrome.”

For several decades following Chusid and colleagues’ [1] formulation of criteria for the diagnosis of the idiopathic hypereosinophilic syndrome in 1975, the true nature of this condition remained mysterious. Although there were no disease features that identified the condition as “leukemia,” there was always a suspicion that in at least some cases the disease represented a hematological neoplasm. A proportion of patients subsequently developed granulocytic sarcoma or acute myeloid leukemia, suggesting that the chronic eosinophilia actually represented a chronic eosinophilic leukemia with the subsequent development of acute myeloid leukemia (AML) representing clonal evolution [2–4], analogous to the acute transformation that can occur in chronic myelogenous leukemia and less often in polycythemia vera and essential thrombocythemia. There have been at least 11 instances of patients with a diagnosis of idiopathic hypereosinophilic syndrome subsequently developing AML, with the time interval being as long as 24 years [4]. There

* Corresponding author.

E-mail address: b.bain@ic.ac.uk (B.J. Bain).

appear to be some common disease characteristics with 8 of 11 patients having developed a granulocytic sarcoma and 7 of 8 developing central nervous system (CNS) disease. Of four of these patients who were demonstrated to have normal cytogenetic analysis initially, three were restudied at the time of transformation and two of three had become abnormal [3,4].

In the past decade evidence has emerged that suggests that some patients with what would once have been called the idiopathic hypereosinophilic syndrome have a reactive condition and others have a hematological neoplasm.

In some patients with reactive eosinophilia, the cause, eg, parasitic infection, allergic disease, or lymphoma, is readily apparent. In others in whom there is no apparent primary causative condition, subsequent investigation discloses a population of cytokine-secreting T lymphocytes that are driving the eosinophilia [5,6]. The term "lymphocytic variant of hypereosinophilic syndrome" has been used to describe such cases. Sometimes an overt lymphoproliferative disorder subsequently becomes apparent.

***FIP1L1-PDGFR α* –associated chronic eosinophilic leukemia**

An important subset of patients with eosinophilia that would otherwise be unexplained have recently been found to have eosinophilic leukemia, this diagnosis being based on the demonstration of a fusion gene that is a marker of a neoplastic clone of myeloid cells [7]. The term "myeloproliferative variant of hypereosinophilic syndrome" has been used for this condition. The neoplastic nature of the condition in these patients remained undiscovered for a considerable time because most patients had normal chromosomes on conventional cytogenetic analysis. The index patient, who drew attention to the cryptic deletion at 4q12, had t(1;4)(q44;q12) and was found to have an *FIP1L1-PDGFR α* fusion gene. A small number of other patients have had a different translocation with a 4q12 breakpoint, eg, a t(4;10)(q21;p11) in a Japanese man [8] and a few have had an unrelated chromosomal abnormality, such as add(2)(q),del(6)(q),+8,+19 [7] and add(17)(q25) [9]; both of these groups of patients, ie, those with related and those with unrelated clonal chromosomal abnormalities, can be diagnosed as having eosinophilic leukemia using conventional criteria. However, most patients with a normal karyotype could not be recognized as having leukemia before the discovery of the fusion gene and the introduction of tests for its detection.

The *FIP1L1-PDGFR α* fusion gene encodes an aberrant, constitutively activated tyrosine kinase that drives the eosinophil proliferation without the need for external growth stimuli. The responsible mutation occurs in a pluripotent lymphoid-myeloid hemopoietic stem cell, able to give rise (at least in some patients) to eosinophils, neutrophils, monocytes, mast cells, B lymphocytes, and T lymphocytes [10]. However, generally abnormal

proliferation is confined to eosinophil, mast cell, and, to a lesser extent, neutrophil lineages.

This syndrome has characteristic clinical and pathological features that aid in its recognition. It is predominantly a disease of males with the observed male:female ratio being about 17:1. The age range is wide, from 7 to 77 years, with most patients being between 25 and 55 years [11,12]. Clinical features may be those characteristically associated with leukemia or may be the result of tissue damage attributable to the release of eosinophil granule contents. Leukemia-related disease features include weight loss, fatigue, hepatomegaly, splenomegaly, pruritis, pallor, and bruising. Other patients present with cardiac, respiratory, cutaneous, or gastrointestinal symptoms and signs. The most serious tissue damage is cardiac, with the myocardium, endocardium, and cardiac valves being particularly affected. Other patients suffer from thromboembolic events, both venous and arterial. Respiratory symptoms include dyspnea and cough. Lung disease is usually mainly restrictive but sometimes there is also an obstructive element. Gastrointestinal symptoms often include diarrhea.

The importance of the discovery of the *FIP1L1-PDGFR* fusion gene is that its aberrant product is a constitutively activated tyrosine kinase, which drives the abnormal proliferation and which can be inhibited by imatinib. Imatinib has already revolutionized the management of chronic myelogenous leukemia. It is now set to revolutionize the management of eosinophilic leukemia resulting from this fusion gene. In fact the *FIP1L1-PDGFR* protein is much more readily inhibited than the *BCR-ABL1* protein of chronic myelogenous leukemia. Although the same imatinib dose, 400 mg daily, is often used it is also possible to use a dose of 100 mg daily as long as molecular monitoring is possible, thus reducing both the side effects and the cost of treatment.

Timely diagnosis is important because some patients with long-established disease have died from cardiac complications despite effective treatment of the malignancy. Since the fusion gene can be detected in peripheral blood cells, molecular analysis can be performed quite early in the diagnostic process.

FIP1L1-PDGFR fusion can be identified by the polymerase chain reaction (PCR), the greater sensitivity of nested PCR often being required for detection. It can also be identified by fluorescence in situ hybridization (FISH) analysis, looking for deletion of the *CHIC2* gene (which is located between *FIP1L1* and *PDGFR* and is lost when this interstitial deletion occurs) or looking for fusion of upstream and downstream signals that are normally separate. The commercial availability of suitable probes means that such analysis is likely to become much more widely available than it has been until now. The detection of a clonal chromosomal abnormality (other than the specific ones described below) is *not* a reason to refrain from *FIP1L1-PDGFR* analysis; molecular analysis is not needed to establish the diagnosis of chronic eosinophilic leukemia in patients with a clonal

karyotypic abnormality but it is still required to identify this particular syndrome and direct therapy.

Patients with *FIPILI-PDGFR*A-associated chronic eosinophilic leukemia may have cytologically abnormal eosinophils in the blood (eg, hypogranular, hypolobulated, hyperlobulated, or immature with granules having basophilic staining characteristics); however, such abnormalities are neither always present nor specific for the syndrome. The bone marrow aspirate and trephine biopsy may be more helpful. In addition to a marked increase of eosinophils and their precursors, the majority of patients also have an increase of mast cells. These may be scattered and form loose clusters but in some patients there are cohesive clusters of spindle-shaped mast cells, which resemble those of systemic mastocytosis. There is an associated increase in serum mast cell tryptase; this is not usually as high as in systemic mastocytosis but there is some overlap. To avoid misdiagnosis of systemic mastocytosis it is important to look for the fusion gene in such patients. Such misdiagnosis is to be avoided as systemic mastocytosis associated with a *KIT* mutation is rarely responsive to imatinib. Analysis for mutation of the *KIT* gene is best performed on a bone marrow aspirate or needle biopsy specimen since peripheral blood analysis is considerably less sensitive.

The peripheral blood and bone marrow aspirate in *FIPILI-PDGFR*A-associated chronic eosinophilic leukemia do not usually show any increase of blast cells. If such is found, it is likely to indicate impending transformation. Treatment with imatinib is still appropriate but careful hematological and molecular observation of the response is needed.

Less often *PDGFR*A contributes to other fusion genes. A man with imatinib-responsive chronic eosinophilic leukemia and a complex chromosomal abnormality involving chromosomes 3, 4, and 10 was found to have a *KIF5B-PDGFR*A fusion gene [13] and a woman with ins(9;4)(q33;q12q25) was found to have a *CDK5RAP2-PDGFR*A fusion gene [14].

Two patients (males aged 3 and 37 years) with t(4;22)(q12;q11) and a *BCR-PDGFR*A fusion gene had a myeloproliferative disorder resembling chronic myelogenous leukemia but in both cases eosinophilia was unusually prominent [15]; one of these patients had a T-lymphoblastic transformation and the other developed accelerated phase disease. Imatinib responsiveness, although less than that associated with *FIPILI-PDGFR*A was subsequently shown in a cell line [16]. Two further patients were subsequently described with t(4;22)(q12;q11), *BCR-PDGFR*A fusion, and chronic myeloid leukemia, one of whom developed B-lymphoblastic transformation; both of these patients were responsive to imatinib [17,18]. One of them did not have peripheral blood eosinophilia but had 13% eosinophils in the bone marrow [18]. This syndrome has disease characteristics intermediate between those of *FIPILI-PDGFR*A-associated eosinophilic leukemia and those of *BCR-ABL*1-positive chronic myelogenous leukemia; eosinophilia may or may not be prominent.

Other eosinophilic leukemias

There are other forms of eosinophilic leukemia including several specific syndromes that need to be distinguished from other causes of hypereosinophilia. The most important of these is chronic eosinophilic leukemia associated with *ETV6-PDGFRB* or other rearrangements of the *PDGFRB* gene. The importance of this syndrome is that, like *FIP1L1-PDGFR α* -associated chronic eosinophilic leukemia, it is responsive to imatinib.

t(5;12)(q31-33;p12-13) with ETV6-PDGFRB or other PDGFRB rearrangement

This syndrome was first reported by Keene and colleagues [19] in 1987 with Golub and colleagues [20] subsequently demonstrating the presence of an *ETV6-PDGFRB* fusion gene (previously known as *TEL-PDGFRB*). The clinical and hematological features are heterogeneous. The age range is wide but the median age is fairly low and there is a remarkable male predominance. Some patients have splenomegaly, hepatomegaly being less frequent. Cardiac damage leading to cardiac failure can occur [21,22]. Skin infiltration is sometimes seen. The hematological features are quite variable. In the current WHO classification [23], some patients with these rearrangements are classified as having a myeloproliferative disorder (MPD), specifically chronic eosinophilic leukemia. Others are classified as having a myeloproliferative/myelodysplastic syndrome (MPD/MDS), either chronic myelomonocytic leukemia (CMML) or atypical Philadelphia-negative chronic myeloid leukemia (aCML) or even juvenile myelomonocytic leukemia (JMML) [24]. Eosinophilia is usual but not invariable [25]. There may be anemia and thrombocytopenia. In addition to the usual prominent eosinophilia, monocytosis is common and sometimes there is neutrophilia or basophilia. Rarely the hematological features are those of chronic basophilic leukemia [22]. Mast cell infiltration of the bone marrow has been reported and the mast cells can be spindle shaped [22,26] and immunophenotypically abnormal, resembling those of systemic mastocytosis in that they express CD2 and CD25 [22]. Serum tryptase can also be mildly or moderately elevated [22]. As for *FIP1L1-PDGFR α* -associated chronic eosinophilic leukemia, designation as systemic mastocytosis is better avoided despite the probable mast cell involvement, since this condition is quite distinct from systemic mastocytosis with *KIT* mutation. Trephine biopsy may show reticulin fibrosis [22]. Acute transformation can occur after a variable period of time (9 months to 12 years being reported [25]).

Most patients have *t(5;12)(q31-33;p12-13)* with *ETV6-PDGFRB*. The same fusion gene in one patient resulted from *ins(2;12)(p21;q?13q?22)* [27]. Other translocations resulting in different fusion genes should be recognized; at least 14 are known (Table 1) [20–22,25–40]. All cases so far described have had a relevant abnormality on standard cytogenetic analysis. The molecular changes can be confirmed by break-apart FISH or, in the case of

Table 1
Cytogenetic abnormalities and fusion genes in chronic myeloproliferative and myeloproliferative/myelodysplastic disorders with t(5;12)(q31-33;p12-13) or related translocations resulting in rearrangement of *PDGFRB* gene

Translocation	Fusion gene	Imatinib response	Reference
Usually t(5;12)(q31~33;p13)	<i>ETV6-PDGFRB</i>	Yes	[20,25]
Rarely t(1;3;5)(p36;p21;q33)	<i>WDR48-PDGFRB</i>	Yes	[28]
Rarely der(1)t(1;5)(p34;q33), der(5)t(1;5)(p34;q15),der(11) (ins(11;5)(p12;q15q33)	<i>GPIAP1-PDGFRB</i>	Yes	[22]
Rarely t(1;5)(q21;q33)	<i>TPM3-PDGFRB</i>	Yes	[29]
Rarely t(1;5)(q23;q33)	<i>PDE4DIP-PDGFRB</i>	Yes	[30]
Rarely t(3;5)(p21;q31)	<i>PDGFRB</i> rearranged	Yes	[27]
Rarely t(4;5)(q21.3;q33)	<i>PDGFRB</i> rearranged	Yes	[26]
Rarely t(4;5;5)(q23;q31;q33)	<i>PRKG2-PDGFRB</i>	Yes	[22]
Rarely t(3;5)(p21-25;q31-35)	<i>GOLGA4-PDGFRB</i>	Yes	[28]
Rarely t(5;7)(q33;q11.2)	<i>HIP1-PDGFRB</i>	Likely	[31]
Rarely t(5;10)(q33;q21)	<i>CCDC6(H4/D10S170)-PDGFRB</i>	Likely	[32,33]
Rarely t(5;12)(q33;q13)	<i>PDGFRB</i> rearranged	Yes	[34]
Rarely t(5;12)(q31-33;q24)	<i>GIT2-PDGFRB</i>	Yes	[22]
Rarely t(5;14)(q33;q24)	<i>NIN-PDGFRB</i>	Yes	[35]
Rarely t(5;14)(q33;q32)	<i>KIAA1509-PDGFRB</i>	Yes	[36]
Rarely t(5;14)(q33;q22) ^a	<i>TRIP11(CEV14)-PDGFRB^a</i>	Not known	[37]
Rarely t(5;15)(q33;q22)	<i>TP53BP1-PDGFRB</i>	Yes (transient)	[27,38]
Rarely t(5;16)(q33;p13)	<i>NDE1-PDGFRB</i>	Yes	[39]
Rarely t(5;17)(q33;p13)	<i>RABEP1 (RAB5)-PDGFRB</i>	Yes	[40]
Rarely t(5;17)(q33;p11.2)	<i>SPECC1(HCMOGT1)-PDGFRB</i>	Likely	[24]

^a New abnormality after relapse of acute myeloid leukemia, associated with appearance of eosinophilia [37].

ETV6-PDGFRB, reverse transcriptase PCR (RT-PCR). Other reported patients have had a translocation with a 5q31 or 5q33 breakpoint and with *PDGFRB* being rearranged but without the fusion partner having been identified (see Table 1).

This diagnosis has major therapeutic relevance because of the imatinib sensitivity and because the median survival was less than 2 years in the pre-imatinib era. Imatinib responsiveness has been demonstrated for the majority of fusion products (see Table 1) and it is predicted that this would also be so for the other variant fusion products. In a series of 12 imatinib-treated patients the median survival was 65 months with 10 of 12 patients being alive at the time of reporting [27].

This syndrome is also responsive to nilotinib [41] and a mouse model has shown sensitivity to the investigational agent, SU11657 [42].

The 8p11 stem cell syndrome

This rare syndrome arises through a mutation in a pluripotent stem cell capable of differentiating into myeloid, T lymphoid, and B lymphoid cells.

Most cases are associated with t(8;13)(p11-12;q12) and a *ZNF198-FGFR1* fusion gene but there are also variant translocations leading to other fusion genes involving *FGFR1* (Table 2) [43–52]. Trisomy 21 is common as a secondary cytogenetic abnormality.

Patients can present in chronic phase with a myeloproliferative disorder with increased neutrophils and neutrophil precursors but usually without any increase in basophils. About 90% of patients have peripheral blood or bone marrow eosinophilia with eosinophil counts up to $40 \times 10^9/\text{L}$. Occasional patients have monocytosis. Within a relatively short period of time there is myeloid, T lymphoblastic, or B lymphoblastic transformation. Other patients present with the disease already transformed to acute leukemia or lymphoblastic lymphoma, particularly of T lineage. A single patient may suffer both a lymphoid and a myeloid transformation. Among the patients who present with, or have transformation to, acute myeloid leukemia, granulocytic sarcoma is relatively common.

This condition is resistant to imatinib but other tyrosine kinase inhibitors, eg, PKC412 [53], are under active evaluation and it is likely that a reasonably specific treatment will be developed. Until such time, allogeneic hemopoietic stem cell transplantation is often indicated, as this syndrome otherwise has a very poor prognosis.

Other eosinophilic leukemias

Other patients who present with hypereosinophilia can be recognized as having eosinophilic leukemia on the basis of a clonal molecular or cytogenetic abnormality, more often the latter. Demonstration of clonality by study of X-linked polymorphisms, eg, HUMARA analysis, can indicate that the correct diagnosis is eosinophilic leukemia; however, such analysis is possible only in women. A small number of patients have been found to have the *JAK2* V617F mutation that is more characteristic of polycythemia vera and other classical MPD. A range of cytogenetic abnormalities,

Table 2

Chromosomal rearrangements associated with the 8p11 stem cell syndrome and *FGFR1* rearrangement (previous gene names are in brackets)

Cytogenetics	Molecular genetics
Most often t(8;13)(p11;q12)	<i>ZNF198-FGFR1</i> [43,44]
Sometimes t(6;8)(q27;p11-12)	<i>FGFR1OP1(FOP)-FGFR1</i> [45]
Sometimes t(7;8)(q34;p11)	<i>TRIM24(TIF1)-FGFR1</i> [46]
Sometimes t(8;9)(p11;q33)	<i>CEP1(CEP110)-FGFR1</i> [47]
Sometimes t(8;11)(p11;p15)	<i>FGFR1</i> rearranged [48]
Sometimes t(8;12)(p11;q15)	<i>FGFR1</i> rearranged [48]
Sometimes t(8;17)(p11;q23)	<i>MYO18A-FGFR1</i> [49]
Sometimes t(8;17)(p11;q25)	<i>FGFR1</i> rearranged [48]
Sometimes t(8;19)(p12;q13.3)	<i>HERVK-FGFR1</i> [50]
Sometimes t(8;22)(p11;q11)	<i>BCR-FGFR1</i> [51]
Sometimes ins(12;8)(p11p11p22)	<i>FGFR1OP2-FGFR1</i> [52]

including some such as trisomy 8 and 20q- that are characteristic of myeloid neoplasms in general, have been recognized in eosinophilic leukemia. Chronic myeloid leukemia associated with *ETV6-ABL1* fusion sometimes has more marked eosinophilic differentiation than is usual in chronic myelogenous leukemia [54,55] and cardiac damage can result from the hypereosinophilia [55].

Investigation of possible eosinophilic leukemia

Any patient with hypereosinophilia and signs of severe tissue damage should be investigated promptly so that specific treatment can be started. In the absence of signs or symptoms of tissue damage, investigation of unexplained hypereosinophilia can proceed in a systematic manner, investigating first the possibilities that appear most probable from the clinical circumstances. If preliminary assessment discloses no reason to suspect allergy or parasitic disease, investigation is needed for an abnormal T-cell population, eosinophilic leukemia, and systemic mastocytosis.

The investigation of hypereosinophilic patients where there is a possibility of eosinophilic leukemia requires a careful history, including a travel history and a drug history; the drug history should elicit any exposure to alternative medications. Symptoms that may be complained of by patients with eosinophilic leukemia include cough, dyspnea, ankle swelling, diarrhea, weight loss, and pruritis. A careful physical examination is equally necessary with lymphadenopathy, hepatomegaly, splenomegaly, rash, or skin infiltration being particularly relevant. When the cause of eosinophilia is not apparent from history, examination, and preliminary investigation, more specific investigations are indicated. These include a CT scan of the chest and abdomen, a bone marrow aspirate and trephine biopsy, cytogenetic analysis on the bone marrow aspirate, peripheral blood analysis for the *FIP1L1-PDGFR*A gene, and peripheral blood immunophenotyping to identify any abnormal T-cell population. Depending on the clinical features, skin biopsy or lymph node biopsy will be indicated in some patients.

The relationship of eosinophilic leukemia to the idiopathic hypereosinophilic syndrome

These diagnoses “eosinophilic leukemia” and “idiopathic hypereosinophilic syndrome” are mutually exclusive [56]. A diagnosis of idiopathic hypereosinophilic syndrome should only be made when a patient has been adequately investigated to exclude not only aberrant T cells but also eosinophilic leukemia. At a minimum, this requires bone marrow aspiration and trephine biopsy, cytogenetic analysis of bone marrow cells, and molecular analysis of peripheral blood cells to demonstrate or exclude *FIP1L1-PDGFR*A-associated chronic eosinophilic leukemia. Use of the term “hypereosinophilic syndrome” should be discouraged since this term reveals

nothing of the true nature of the condition. It is more likely to indicate either an imprecise use of language or that the patient has not been adequately investigated. Correct, precise diagnosis and classification are not merely of academic interest but are critical for appropriate management of the patient.

When full investigation reveals no cause for eosinophilia and the patient meets the criteria of Chusid and colleagues [1], a diagnosis of idiopathic hypereosinophilic syndrome remains appropriate. Some patients in whom this diagnosis is legitimately made will have features suggestive, but not diagnostic, of a myeloproliferative/leukemic disorder such as splenomegaly, hypercellularity of the bone marrow, increased serum tryptase, and increased serum B₁₂. When clonality cannot be demonstrated, the true nature of the condition will be revealed only with careful follow-up and perhaps not even then.

The idiopathic hypereosinophilic syndrome has traditionally been managed with corticosteroids, hydroxycarbamide (previously known as hydroxyurea) and interferon. The question now arises as to whether imatinib or other targeted therapy is appropriate in the absence of a demonstrable relevant genetic abnormality. This question is particularly relevant to patients whose clinical and laboratory features suggest a myeloproliferative disorder. In such patients a trial of imatinib is justified if circumstances permit. Data on file by Novartis, the manufacturer of imatinib, based on published and unpublished cases, shows that all of 61 patients with a *FIP1L1-PDGFR*A fusion had a complete hematological response on imatinib [57]. However 12 of 56 patients (21%) with no demonstrable fusion gene also had a complete hematological response and 7 (12%) a partial response. Some responses probably represent patients in whom a fusion gene was present but was not demonstrated because of inadequacy of the techniques applied. Others are likely to represent a response in a patient genuinely lacking the fusion gene. In general, those without *FIP1L1-PDGFR*A fusion are likely to respond less well and need a higher dose of imatinib. If financial constraints limit drug availability, it is desirable to at least give a trial of imatinib in a dose of 100 mg daily for 2 to 4 weeks. This is particularly important if the patient has myeloproliferative features or if there is already cardiac damage. A brief trial of low-dose therapy will serve to identify patients with the fusion gene for whom this therapy is of critical importance.

Other therapeutic measures available or under assessment for the idiopathic hypereosinophilic syndrome include interferon alpha, mepolizumab, and alemtuzumab.

Summary

The precise diagnosis of the myeloproliferative variant of hypereosinophilic syndrome is increasingly important as highly effective targeted therapies become available for a subset of these patients in whom eosinophilic leukemia is the result of a fusion gene encoding an aberrant tyrosine kinase.

References

- [1] Chusid ML, Dale DC, West BC, et al. The hypereosinophilic syndrome. *Medicine* 1975;54: 1–27.
- [2] Bain BJ. Eosinophilic leukaemias and the idiopathic hypereosinophilic syndrome. *Br J Haematol* 1996;95:2–9.
- [3] Yoo TJ, Orman SV, Patil SR, et al. Evolution to eosinophilic leukemia with a t(5;11) translocation in a patient with idiopathic hypereosinophilic syndrome. *Cancer Genet Cytogenet* 1984;11:389–94.
- [4] Doorduijn JK, van Lom K, Löwenberg B. Eosinophilia and granulocyte dysplasia terminating in acute myeloid leukaemia after 24 years. *Br J Haematol* 1996;95:531–4.
- [5] Roufosse F, Schandene L, Sibille C, et al. T-cell receptor-independent activation of clonal Th2 cells associated with chronic hypereosinophilia. *Blood* 1999;94:994–1002.
- [6] Simon HU, Plötz SG, Dummer R, et al. Abnormal clones of interleukin-5-producing T cells in idiopathic eosinophilia. *N Engl J Med* 1999;341:1112–20.
- [7] Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by the 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.
- [8] Tashiro H, Shirasaki R, Noguchi M, et al. Molecular analysis of chronic eosinophilic leukemia with t(4;10) showing good response to imatinib mesylate. *Int J Hematol* 2006; 83:433–8.
- [9] Rotoli B, Catalano L, Galderisi M, et al. Rapid reversion of Loeffler's endocarditis by imatinib in early stage clonal hypereosinophilic syndrome. *Leuk Lymphoma* 2004;45: 2503–7.
- [10] Robyn J, Lemery S, McCoy JP, et al. Multilineage involvement of the fusion gene in patients with *FIP1L1/PDGFR*A-positive hypereosinophilic syndrome. *Br J Haematol* 2006;132: 286–92.
- [11] Rives S, Alcorta I, Toll T, et al. Idiopathic hypereosinophilic syndrome in children: report of a 7-year-old boy with *FIP1L1-PDGFR*A rearrangement. *J Pediatr Hematol Oncol* 2005;27: 663–5.
- [12] 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.
- [13] Score J, Curtis C, Waghorn K, et al. Identification of a novel imatinib responsive *KIF5B-PDGFR*A fusion gene following screening for *PDGFR*A overexpression in patients with hypereosinophilia. *Leukemia* 2006;20:827–32.
- [14] Walz C, Curtis C, Schnittger S, et al. Transient response to imatinib in a chronic eosinophilic leukemia associated with ins(9;4)(q33;q12q25) and a *CDK5RAP2-PDGFR*A fusion gene. *Genes Chromosomes Cancer* 2006;45:950–6.
- [15] Baxter EJ, Hochhaus A, Bolufer P, et al. The t(4;22)(q12;q11) in atypical chronic myeloid leukaemia fuses *BCR* to *PDGFR*A. *Hum Mol Genet* 2002;11:1391–7.
- [16] Gavrilescu LC, Cross NCP, Van Etten RA. Distinct leukemogenic activity and imatinib responsiveness of a *BCR-PDGFR*α fusion tyrosine kinase. *Blood* 2006;108:3634 [abstract].
- [17] Trempat P, Villalba C, Laurent G, et al. Chronic myeloproliferative disorders with rearrangement of the platelet-derived growth factor alpha receptor: a new clinical target for STI571/Glivec. *Oncogene* 2003;22:5702–6.
- [18] Saffley AM, Sebastian S, Collins TS, et al. Molecular and cytogenetic characterization of a novel translocation t(4;22) involving the breakpoint cluster region and platelet-derived growth factor receptor-alpha genes in a patient with atypical chronic myeloid leukaemia. *Genes Chromosomes Cancer* 2004;40:44–50.
- [19] Keene P, Mendelow B, Pinto MR, et al. Abnormalities of chromosome 12p13 and malignant proliferation of eosinophils: a nonrandom association. *Br J Haematol* 1987;67:25–31.

- [20] Golub TR, Barker GF, Lovett M, et al. Fusion of PDGF receptor beta to a novel ets-like gene, tel, in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. *Cell* 1994;77:307–16.
- [21] Wittman B, Horan J, Baxter J, et al. A 2-year-old with atypical CML with a t(5;12)(q33;p13) treated successfully with imatinib mesylate. *Leuk Res* 2004;28(Suppl 1):S65–9.
- [22] Walz C, Metzgeroth G, Haferlach C, et al. Characterization of three new imatinib-responsive fusion genes in chronic myeloproliferative disorders generated by disruption of the platelet-derived growth factor receptor beta gene. *Haematologica* 2007;92:163–9.
- [23] Jaffe ES, Harris NL, Stein H, et al, editors. World Health Organization Classification of Tumours: pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2001.
- [24] Morerio C, Aquila M, Rosanda C, et al. HCMOGT-1 Is a novel fusion partner to PDGFRB in juvenile myelomonocytic leukemia with t(5;17)(q33;p11.2). *Cancer Res* 2004;64:2649–51.
- [25] Steer EJ, Cross NCP. Myeloproliferative disorders with translocations of chromosome 5q31-35: role of the platelet-derived growth factor receptor beta. *Acta Haematol* 2002;107:113–22.
- [26] Dalal BI, Horsman DE, Bruyere H, et al. Imatinib mesylate responsiveness in aggressive systemic mastocytosis: novel association with a platelet derived growth factor receptor beta mutation. *Am J Hematol* 2006;82:77–9.
- [27] David M, 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.
- [28] Curtis C, Apperley JF, Dang R, et al. The platelet derived growth factor receptor beta fuses to two distinct loci at 3p21 in imatinib responsive chronic eosinophilic leukemia. *Blood* 2005;106:909a.
- [29] Rosati R, La Starza R, Luciano L, et al. TPM3/PDGFRB fusion transcript and its reciprocal in chronic eosinophilic leukemia. *Leukemia* 2006;20:1623–4.
- [30] Wilkinson K, Velloso ERP, Lopes LF, et al. Cloning of the t(1;5)(q23;q33) in a myeloproliferative disorder associated with eosinophilia: involvement of PDGFRB and response to imatinib. *Blood* 2003;102:4187–90.
- [31] Ross TS, Bernard OA, Berger R, et al. Fusion of Huntingtin Interacting Protein 1 to platelet-derived growth factor β receptor (PDGFR β) in chronic myelomonocytic leukemia with t(5;7)(q33;q11.2). *Blood* 1998;91:4419–26.
- [32] Kulkarni S, Heath C, Parker S, et al. Fusion of H4/D10S170 to the platelet-derived growth factor receptor B in BCR-ABL negative myeloproliferative disorders with a t(5;10)(q33;q21). *Cancer Res* 2000;60:3592–8.
- [33] Schwaller J, Anastasiadou E, Cain D, et al. H4(D10S170), a gene frequently rearranged in papillary thyroid carcinoma, is fused to the platelet-derived growth factor receptor β gene in atypical chronic myeloid leukemia with t(5;10)(q33;q22). *Blood* 2007;97:3910–8.
- [34] Apperley JF, Gardenbas M, Melo JV, et al. Chronic myeloproliferative diseases involving rearrangements of the platelet derived growth factor receptor beta (PDGFRB) showing rapid responses to the tyrosine kinase inhibitor STI571 (imatinib mesylate). *N Engl J Med* 2002;347:481–7.
- [35] Vizmanos JL, Novo FJ, Roman JP, et al. NIN, a gene encoding a CEP110-like centrosomal protein, is fused to PDGFRB in a patient with a t(5;14)(q33;q24) and an imatinib-responsive myeloproliferative disorder. *Cancer Res* 2004;64:2673–6.
- [36] Levine RL, Wadleigh M, Sternberg DW, et al. KIAA1509 is a novel PDGFRB fusion partner in imatinib-responsive myeloproliferative disease associated with a t(5;14)(q33;q32). *Leukemia* 2005;19:27–30.
- [37] Abe A, Tanimoto M, Towatari M, et al. Acute myeloblastic leukemia (M2) with translocation followed by marked eosinophilia and additional abnormalities of chromosome 5. *Cancer Genet Cytogenet* 1995;37:37–41.

- [38] Grand FH, Burgstaller S, Kühr T, et al. p53-Binding protein 1 is fused to the platelet-derived growth factor receptor β in a patient with a t(5;15)(q33;q22) and an imatinib-responsive eosinophilic myeloproliferative disorder. *Cancer Res* 2004;64:7216–9.
- [39] Rosati R, La Starza R, Bardi A, et al. PDGFRB fuses to TPM3 in the t(1;5)(q23;q33) of chronic eosinophilic leukemia and to NDE1 in the t(5;16)(q33;p13) of chronic myelomonocytic leukemia. *Haematologica* 2006;91(Suppl 1):214.
- [40] Magnusson MK, Meade KE, Brown KE, et al. Rabaptin-5 is a novel fusion partner to platelet-derived growth factor receptor in chronic myelomonocytic leukemia. *Blood* 2001;98:2518–25.
- [41] Stover EH, Chen J, Lee BH, et al. The small molecule tyrosine kinase inhibitor AMN107 inhibits TEL-PDGFR β and FIP1L1-PDGFR α in vitro and in vivo. *Blood* 2005;106:3206–13.
- [42] Cain JA, Grisolan JL, Laird AD, et al. Complete remission of TEL-PDGFRB-induced myeloproliferative disease in mice by receptor tyrosine kinase inhibitor SU11657. *Blood* 2004;104:561–4.
- [43] Xiao S, Nalbolu SR, Aster JC, et al. FGFR1 is fused with a novel zinc-finger gene, ZNF198, in the t(8;13) leukaemia/lymphoma syndrome. *Nat Genet* 1998;18:84–7.
- [44] Macdonald D, Reiter A, Cross NCP. The 8p11 myeloproliferative syndrome: a distinct clinical entity caused by constitutive activation of FGFR1. *Acta Haematol* 2002;107:101–7.
- [45] Popovici C, Zhang B, Grégoire M-J, et al. The t(6;8)(q27;p11) translocation in a stem cell myeloproliferative disorder fuses a novel gene, FOP, to fibroblast growth factor receptor 1. *Blood* 1999;93:1381–9.
- [46] Belloni E, Trubia M, Gasparini P, et al. 8p11 myeloproliferative syndrome with a novel t(7;8) translocation leading to fusion of the FGFR1 and TIF1 genes. *Genes Chromosomes Cancer* 2005;42:320–5.
- [47] Guasch G, Mack GJ, Popovici C, et al. FGFR1 is fused to the centrosome-associated protein CEP110 in the 8p12 stem cell myeloproliferative disorder with t(8;9)(p12;q33). *Blood* 2000;95:1788–96.
- [48] Sohal J, Chase A, Mould S, et al. Identification of four new translocations involving FGFR1 in myeloid disorders. *Genes Chromosomes Cancer* 2001;32:155–63.
- [49] Walz C, Chase A, Schoch C, et al. The t(8;17)(p11;q23) in the 8p11 myeloproliferative syndrome fuses MYO18A to FGFR1. *Leukemia* 2005;19:1005–9.
- [50] Guasch G, Popovici C, Mugneret F, et al. Endogenous retroviral sequence is fused to FGFR1 kinase in the 8p12 stem-cell myeloproliferative disorder with t(8;19)(p12;q13.3). *Blood* 2003;101:286–8.
- [51] Fioretos T, Panagopoulos J, Larsen C, et al. Fusion of the *BCR* and the fibroblast growth factor receptor-1 (*FGFR1*) genes as a result of t(8;22)(p11;q11) in a myeloproliferative disorder: the first fusion gene with *BCR* but not *ABL*. *Genes Chromosomes Cancer* 2001;32:302–10.
- [52] Grand EK, Grand FH, Chase AJ, et al. Identification of a novel gene, FGFR1OP2, fused to FGFR1 in 8p11 myeloproliferative syndrome. *Genes Chromosomes Cancer* 2004;40:78–83.
- [53] Chen J, DeAngelo DJ, Kutok JL, et al. PKC412 inhibits the zinc finger 198-fibroblast growth factor receptor 1 fusion tyrosine kinase and is active in treatment of stem cell myeloproliferative disorder. *Proc Natl Acad Sci USA* 2004;101:14479–84.
- [54] Van Limbergen H, Beverloo HB, van Drunen E, et al. Molecular cytogenetic and clinical findings in ETV6/ABL1-positive leukaemia. *Genes Chromosomes Cancer* 2001;30:274–82.
- [55] Keung YK, Beaty M, Steward W, et al. Chronic myelocytic leukemia with eosinophilia, t(9;12)(q34;p13), and ETV6-ABL gene rearrangement: case report and review of the literature. *Cancer Genet Cytogenet* 2002;138:139–42.
- [56] Bain BJ. Eosinophilic leukemia and idiopathic hypereosinophilic syndrome are mutually exclusive diagnoses. *Blood* 2004;104:3836–7.
- [57] NOVARTIS Pharmaceuticals USA. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf. Accessed April 30, 2007.