Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*

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The 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues introduced a new category for myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*.[1] Many of these cases present as a myeloproliferative neoplasm, usually with eosinophilia. However, neoplasms associated with rearrangement of *PDGFRA* can present as acute myeloid leukemia or as T lymphoblastic lymphoma with eosinophilia.[2] Neoplasms associated with rearrangement of *FGFR1* even more frequently present as acute myeloid leukemia or T lymphoblastic lymphoma, in both instances with eosinophilia, and both T lymphoblastic and B lymphoblastic transformation of chronic eosinophilic leukemia have also been described.[3-5] Because of the prominent lymphoid component these disorders have been assigned, in the WHO classification, to a specific category rather than being categorized as a myeloproliferative neoplasm. However, it should be noted that *BCR-ABL1*-positive chronic myelogenous leukemia is accepted as a *bona fide* myeloproliferative neoplasm and yet it too can undergo lymphoblastic transformation and even present as acute lymphoblastic leukemia with the underlying chronic myelogenous leukemia being revealed only after remission has been achieved.

Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA

The discovery by Cools and colleagues[6] that many examples of what had previously been categorized as idiopathic hypereosinophilic syndrome were actually chronic eosinophilic leukemia was a major advance in this field. Their demonstration of a *FIP1L1-PDGFRA* fusion gene, usually resulting from a cryptic deletion at 4q12, was important for two reasons. Firstly it was a scientific advance, since it clarified the nature of many examples of a condition that many had long suspected was myeloproliferative in nature. Secondly, because of the exquisite sensitivity to tyrosine kinase inhibitors, recognition of this condition became important to patients.

Eosinophilia appears to be an invariable part of this syndrome. In addition there may be neutrophilia and an increase of bone marrow mast cells, which can be immunophenotypically abnormal. Serum vitamin B_{12} and serum tryptase may be increased. An unexplained curious feature is a very striking male predominance.

Occasional patients, including the index patient of Cools *et al.*, have had a chromosomal rearrangement with a 4q12 breakpoint, such as t(1;4)(q44;q12)[6] or t(4;10)(q12;p11).[7] However in the great majority of cases the fusion gene results from a cryptic deletion so that diagnosis must necessarily be molecular. Standard single step reverse transcriptase polymerase chain reaction will not detect all cases and it is usually necessary to use nested polymerase chain reaction.[6] Probes are also available to permit diagnosis by fluorescence *in situ* hybridization (FISH).

Since the discovery of the *FIP1L1-PDGFRA* fusion gene, a small number of patients have been described with other rearrangements of *PDGFRA*. These are summarized in Table 1.[8]

There are technical difficulties in detecting all cases with *PDGFRA* rearrangement. These may be circumvented by the generic quantitative polymerase chain reaction reported in this issue of Haematologica by Erben and colleagues.[9] This screening test is based on detection of overexpression of a 3′ region of *PDGFRA* or a 3′ region of *PDGFRB* which is a possible indicator of an underlying

Table 1. Chronic eosinophilic leukemia and related conditions associated with rearrangement of *PDGFRA* (reproduced with permission from reference 8).

Chromosomal abnormality	Fusion gene	Number of cases	Hematologic manifestations
Usually normal with cryptic deletion at 4q12; occasionally translocation with 4q12 breakpoint	*FIP1L1-PDGFRA*	The great majority of cases	CEL, often with neutrophilia and abnormal bone marrow mast cells; T lymphoid and acute myeloid transformations can occur; acute myeloid leukemia with eosinophilia
t(4;22)(q12;q11)	*BCR-PDGFRA*	5	Intermediate features between CEL and Ph-positive CGL; T and B lymphoid transformation can occur
Complex involving chromosomes 3, 4, 10 and probably 13	*KIF5B-PDGFRA*	1	CEL
ins(9;4)(q33;q12q25)	*CDK5RAP2-PDGFRA*	1	CEL
t(2;4)(p24;q12)	*STRN-PDGFRA*	1	CEL
t(4;12)(q12;p13)	*ETV6-PDGFRA*	1	CEL

CEL, chronic eosinophilic leukemia.

fusion gene. All 51 patients with a total of five different *PDGFRA* fusion partners were detected. The specificity of the test was 88.4%. Some patients who had over-expression without a detectable fusion gene were found to have a point mutation in *PDGFRA* leading to constitutive activation.[10]

Because of the therapeutic implications, it is desirable to screen for *PDGFRA* rearrangement not only in patients who present with eosinophilic leukemia but also in those who present with acute myeloid leukemia and eosinophilia without a *CBFB-MYH11* fusion gene[11] and in those who present with T lymphoblastic lymphoma with eosinophilia.[2]

Given the striking sensitivity to imatinib, a dose of 100 mg daily is sufficient.[12] Chronic eosinophilic leukemia with *FIP1L1-PDGFRA* is likely to be responsive also to dasatinib, nilotinib, sorafenib and midostaurin (PKC412).[13] Resistance to imatinib, associated with refractory disease or the emergence of acute myeloid leukemia, can occur as the result of a further mutation, such as T674I or D842V. The T674I mutation confers resistance also to dasatinib but retained sensitivity has been demonstrated, either *in vitro* or *in vivo*, to sorafenib, nilotinib and midostaurin.[13,14] The D842V mutation confers resistance at tolerated doses, either *in vitro* or *in vivo*, to imatinib, dasatinib, sorafenib and midostaurin and possibly also to nilotinib.[13] A further patient has been described in whom resistance to imatinib was associated with the appearance of both S601P and L629P mutations; the former of these was shown *in vitro* to confer resistance to sorafenib.[15] Interferon-α may be a therapeutic option in patients with imatinib-refractory disease.

The optimal treatment of this group of disorders requires not only the use of a tyrosine kinase inhibitor but also consideration of whether the eosinophil count should initially be lowered with corticosteroids. This is indicated in patients who already have cardiac damage evident clinically or on echocardiography or who have an elevated level of serum troponin.

Myeloid neoplasms with eosinophilia and abnormalities of PDGFRB

Myeloid neoplasms with rearrangement of *PDGFRB* are phenotypically and genotypically even more diverse than the neoplasms associated with *PDGFRA* rearrangement. Phenotypically they include cases that have been categorized as chronic eosinophilic leukemia, chronic myelomonocytic leukemia (usually with eosinophilia), atypical chronic myeloid leukemia (usually with eosinophilia), primary myelofibrosis, juvenile myelomonocytic leukemia with eosinophilia, acute myeloid leukemia (without eosinophilia) and even chronic basophilic leukemia. Genetically they are equally heterogeneous with at least 23 fusion genes having been described, to which Erben[8,16] and colleagues have now added a *SART3-PDGFRB* fusion.

The fusion genes involving *PDGFRB* described to date have been associated with cytogenetically detectable translocations. However sometimes the causative chromosomal rearrangements are complex and cytogenetic analysis may fail to yield metaphases. FISH analysis has also occasionally failed to detect the abnormality. The screening technique reported by Erben and colleagues is, therefore, an advance in the detection of these rearrangements. All patients known to have a *PDGFRB* rearrangement (seven patients with five different fusion genes) were detected. In addition, a patient with a myeloproliferative neoplasm with eosinophilia with non-informative cytogenetic analysis (only four analyzable metaphases as a result of myelofibrosis), who had positive results on the screening test, was found to have a *SART3-PDGFRB* fusion that had not been previously described. The specificity of the test was 94%.

Like neoplasms associated with *PDGFRA* rearrangement, myeloid neoplasms associated with rearrangement of *PDGFRB* are responsive to imatinib. Usually a dose of 400 mg daily is given. Sorafenib is also a potent inhibitor of the *ETV6-PDGFRB* fusion product.[18] Since the median survival pre-imatinib was of the order of 2 years, the discovery of the sensitivity of this group of disorders to tyrosine kinase inhibitors has been a major advance.

As pointed out by Erben and colleagues, there are some patients with hypereosinophilia who have imatinib-responsive disease but have no detectable rearrangement of *PDGFRB* and who have normal results with this screening test. It is, therefore, possible to justify a trial of imatinib even in patients with a negative result. However, there is more probability of being able to obtain the drug for a patient if *in vitro* tests predict that it will be efficacious.

Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of FGFR1

Myeloid and lymphoid neoplasms associated with rearrangement of *FGFR1* are hematologically and genetically heterogeneous but share common features. Eosinophilia is a prominent feature. The most frequent presentation is as a myeloproliferative neoplasm with eosinophilia or as T lymphoblastic lymphoma with eosinophilia. Less often they present as acute myeloid leukemia. In one patient the relevant translocation, the fusion gene and the eosinophilia occurred at the time of transformation of refractory anemia with excess of blasts into acute myeloid leukemia.[19] Patients who present with a myeloproliferative neoplasm may subsequently suffer myeloid or lymphoblastic transformation, or even both. Myeloid transformations include myeloid sarcoma. Lymphoblastic transformations can be B or T. Eosinophils, myeloblasts, T lymphoblasts and B lymphoblasts are all part of the neoplastic clone.

There is also genetic heterogeneity. Most cases are associated with t(8;13)(p11;q12), t(8;9)(p11;q33) or t(6;8)(q27;p11-12) with the fusion genes being respectively *ZNF198-FGFR1*, *CEP110-FGFR1* and *FGFR1OP1-FGFR1*. However, at least seven other fusion partners have been recognized.[1,19,20] There is a specific association of cases of this syndrome with t(6;8)(q27;p11-12) with polycythemia vera, four cases having been described; one of these patients also had a *JAK2* mutation.[21]

Although *FGFR1* encodes a tyrosine kinase there is, as yet, no recognized effective targeted treatment for this group of neoplasms. There is a report on one patient who responded partially to midostaurin (PKC412)[22] but further reports are awaited. Other inhibitors have shown good

activity *in vitro* but are not yet available for general clinical use.[23] Because patients are usually young (the median age of reported cases is in the early 30s), early allogeneic hematopoietic stem cell transplantation should be considered.

Relationship to systemic mastocytosis

It should be noted that neoplasms associated with rearrangement of *PDGFRA* or *PDGFRB* share some characteristics with systemic mastocytosis. Serum tryptase may be elevated and bone marrow mast cells may be increased. Sometimes the mast cells are immunophenotypically abnormal. Nevertheless these are quite distinct neoplasms, which should not be confused.

Conclusion

Hematologic neoplasms associated with rearrangement of *PDGFRA* or *PDGFRB* are rare but nevertheless important to diagnose because of their responsiveness to imatinib. Their recognition can be difficult so that the generic quantitative polymerase chain reaction developed by Erben and colleagues is a diagnostic advance. The diagnosis of hematologic neoplasia associated with *FGFR1* rearrangement is also important since only a trial of midostaurin or an allogeneic transplant offers the hope of avoiding an early death.

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