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REVIEW ARTICLE

Myeloid/lymphoid neoplasms with eosinophilia: clinical picture and therapeutic approaches

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Abstract

Myeloid/lymphoid neoplasms with eosinophilia (M/L_{eo}) and tyrosine kinase (TK) fusion genes constitute a separate category within the 2016 World Health Organization (WHO) classification. All these are characterized by blood or tissue eosinophilia and the presence of a unique genetic abnormality. M/L_{eo} may have diverse clinical manifestations with variable response to TK inhibitors (TKI). *PDGFRA*-rearranged neoplasms (usually with detectable *FIP1L1-PDGFRA*) are found to be extremely sensitive to low dose of imatinib (IM at 100 mg daily) with nearly 100% hematological complete response rate. Moreover, >90% of IM treated patients may achieve long-term molecular response. IM discontinuation may result in sustained remission in c.50–60% of patients. An excellent response to IM (but at 400 mg/day) was also demonstrated for patients with *PDGFRB* rearrangements, but trials on IM cessation were not attempted. The *FGFR1*-rearranged neoplasms are associated with an aggressive disease course and allogeneic stem cell transplantation (allo-SCT) is the only potentially curative approach. Participation in clinical trials should be recommended. Recently, pemigatinib was found to be effective in a proportion of *FGFR1*-rearranged individuals. An aggressive outcome with rapid blast transformation is also characteristic for the *JAK2*-rearranged neoplasms. These patients should be included in clinical trials or attempted with ruxolitinib or fedratinib as a 'bridge' to allo-SCT. A new category of neoplasms with eosinophilia and *FLT3* and *ABL1* rearrangements has not yet been incorporated into the WHO 2016 classification. The prognosis is poor with a tendency to evolve into resistant acute leukemia. The treatment includes TKI with known activity against *FLT3/ABL1* followed by allo-SCT.

Key words: myeloid, lymphoid, neoplasms, eosinophilia, *PDGFRA, PDGFRB, FGFR1, JAK2, FLT3, ABL1*, imatinib, treatment

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Introduction

Hypereosinophilic syndromes (HES) constitute a group of rare disorders presenting with blood or tissue hypereosinophilia (HE) associated with eosinophilia-attributable organ damage/dysfunction [1]. Rapid development in molecular findings within HES has led to the discovery of several dysregulated tyrosine kinase (TK) fusion genes which were then incorporated into the 2016 World Health Organization (WHO) classification of tumors. These neoplasms created a new category of 'myeloid/lymphoid neoplasms with eosinophilia and gene rearrangements of platelet derived growth factor receptor alpha/beta (*PDGFRA/B*), fibroblast growth factor receptor 1 (*FGFR1*) and with *PCM-JAK2*' [2] (Table I). Moreover, two novel rearrangements of *FLT3* and *ABL1* (both commonly partnered by *ETV6*) are still under investigation and have not yet been added to the WHO classification [3]. All these abovementioned entities may

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Table I. World Health Organization classification of myeloid/lymphoid neoplasms with eosinophilia (modified from [2])

Category	Presentation and characteristic findings
PDGFRA-rearranged neoplasm	1) CEL, MPN or AML, rarely T-LBL or myeloid sarcoma; eosinophilia common, but can be absent 2) Presence of *FIP1L1/PDGFRA* fusion gene (by FISH or RT-PCR) or with other fusions of *PDGFRA* gene
PDGFRB-rearranged neoplasm	1) CMML, MPN/MDS, MPN; monocytosis; eosinophilia is not invariably present 2) Presence of t(5;12) or a variant translocation or demonstration of an *ETV6-PDGFRB* fusion gene or other fusions of *PDGFRB* gene
FGFR1-rearranged neoplasm	1) MPN, MDS/MPN, AML or T-/B-cell LBL with eosinophilia (not invariably present) and/or neutrophilia and/or monocytosis and 2) Presence of t(8;13) or a variant translocation leading to *FGFR1* rearrangement
JAK2-rearranged neoplasm	1) MPN with eosinophilia (not invariably present), AML, T-cell LBL/ALL or MPAL 2) Presence of t(8;9) or a variant translocation leading to *JAK2* rearrangement

ALL — acute lymphoblastic leukemia; AML — acute myeloid leukemia; CEL — chronic eosinophilic leukemia; CMML — chronic myelomonocytic leukemia; FISH — fluorescence *in situ* hybridization; LBL — lymphoblastic lymphoma; MDS — myelodysplastic syndromes; MPAL — mixed phenotype acute leukemia; MPN — myeloproliferative neoplasms; RT-PCR — reverse transcriptase polymerase chain reaction

clinically present in the chronic phase, most commonly as chronic eosinophilic leukemia (CEL) or other myeloproliferative neoplasms (MPN) or at *de novo* blast phase with aggressive disease course and poor response to therapy (clinically as acute leukemia/lymphoma). Of interest, not all these neoplasms have prominent blood eosinophilia. The sensitivity to TK inhibitors (TKI) is variable; from remarkable responses in cases with *PDGFRA/B* rearrangements, to poor in the remaining neoplasms [4].

The characteristics of myeloid/lymphoid neoplasms with eosinophilia are set out in Table I.

PDGFRA-rearranged neoplasms

Epidemiology: male predominance, age 20–50 years, single cases reported in females and children. Incidence in developed countries: 10–20% in patients with unexplained HE. The most common partner gene of *PDGFRA* is *FIP1L1* (F/P); other fusions rarely detected.

Manifestation: skin involvement in 57%, spleen (52%), lungs (45%) and heart (35%).

Clinical presentation: CEL, acute myeloid leukemia (AML) with eosinophilia, T-cell lymphoblastic leukemia/lymphoma (T-cell ALL/LBL), extramedullary disease (EMD).

Typical findings in blood: HE, but normal eosinophil count can rarely be present. Blast cells rarely observed, but may occur. Marked elevation of serum vitamin B_{12} and tryptase is common.

Typical findings in bone marrow: in chronic phase (CP) — hypercellular with increased number of eosinophil precursors, loosely distributed spindle-shaped mast cells, reticulin fibrosis. In blast phase (BP) — depending on type of leukemia/lymphoma

Diagnosis: F/P fusion is not visible on conventional cytogenetics. It results from deletion in chromosome 4q12. Diagnosis can be set up by fluorescence *in situ* hybridization (FISH) and/or reverse transcriptase polymerase chain reaction (RT-PCR). Both peripheral blood and bone marrow can be used for assessment. RT-PCR detects most breakpoints within *PDGFRA* and *FIP1L1* but misses rare cases of *PDGFRA*-associated neoplasms with alternate fusion partners.

Treatment: in CP — imatinib (IM) 100 mg daily with concurrent use of corticosteroids in patients with cardiac involvement. Complete hematological response (CHR) expected within days, complete molecular response (CMR) within weeks or months. CHR and CMR rates ~100% and >90% respectively. IM 100 mg daily to 100 mg weekly as response maintenance. In BP — IM 100–400 mg daily plus chemotherapy.

Response assessment: RT-PCR or FISH every 3 months for the first 3 years, then every 3–6 months. Imaging studies for extramedullary presentation. In IM resistance, screen for *PDGFRA* T674I or D842V acquired mutations.

Imatinib discontinuation: IM cessation may lead to durable remissions. Molecular relapse-free survival (MRS) survival was 91% at 12 months and 65% at 24 months after stopping IM. Dose and duration of IM treatment as well as CMR duration did not impact on MRS. Twenty out of 46 patients (57%) relapsed after median 45 months in a recent report. Time to IM initiation and duration of IM administration were independent factors of relapse.

Prognosis: Excellent in CP, variable, but usually favorable in BP [4–16].

PDGFRB-rearranged neoplasms

Epidemiology: male predominance, median age 49 years (range 20–80). Single cases reported in children. Incidence is low (<2% of all MPN). More than 30 gene partners of *PDGFRB* have been identified, but *ETV6-PDGFRB* resulting from t(5;12)(q32;p13.2) is the commonest.

Manifestation: most patients have splenomegaly, but hepatomegaly can also be observed. Dermatological manifestation is rare.

Clinical presentation: chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), CEL, MPN or AML. EMD can also be present.

Typical findings in blood: eosinophilia is common (58%), most patients show moderate anemia or thrombocytopenia. Cases without eosinophilia have been reported.

Typical findings in bone marrow: in CP — hypercellular due to neutrophilic and eosinophilic proliferation. Spindle-shaped mast cells can be present. In BP — depending on type of leukemia/lymphoma.

Diagnosis: standard cytogenetics on bone marrow/peripheral blood cells remains preferred method to confirm diagnosis. Cytogenetic analysis usually shows t(5;12)(q32;p13.2). Breakpoints of *PDGFRB* are located in chromosomal region 5q31~q33, but rare cases harboring *PDGFRB* rearrangements may reveal normal karyotype. FISH can be used to demonstrate all *PDGFRB* rearrangements, but cannot identify partner fusion genes. RT-PCR can detect small clones, complex and/or cryptic cases not evident on cytogenetics. RT-PCR useless outside of *ETV6-PDGFRB*.

Treatment: IM 400 mg daily in CP and combined with chemotherapy in BP. CHR and complete cytogenetic remission (CCR) rates for CP are 100% and 86%, respectively. After IM duration of 7 years, six-year progression-free survival rate of 88%. CHR is usually achieved by 1 month and CCR by 3 months of IM treatment. Reduction of IM to 100 mg daily can be considered after CHR/CCR.

Response assessment: standard cytogenetics and/or FISH every three months during the first 3 years, then every 3–6 months. RT-PCR can be used to document molecular response (in patients with known fusion genes). Imaging studies for extramedullary presentation. In resistant cases, screen for C843G mutation.

Imatinib discontinuation: single reports with variable outcome.

Prognosis: excellent in CP, variable but usually favorable in BP [4, 17–22].

FGFR1-rearranged neoplasms

Epidemiology: moderate male predominance. Median age 32 years, but this neoplasm can occur in children and older people (7–84 years). Incidence is low (<1% of all MPN). To date, 15 partner genes of *FGFR1* have been detected. Common rearrangements include: 1) t(8;13)(p11;q12) which results in the fusion of *ZMYM2* with *FGFR1*; 2) t(8;9)(p11;q33) leading to *CNTRL/FGFR1*; and 3) t(6;8)(q27;p11) with *FGFR1OP/FGFR1* fusion.

Manifestation: in CP — splenomegaly and hepatomegaly, mediastinal lymphadenopathy is usually absent. In BP — depends on clinical presentation (*see below*).

Clinical presentation: CEL, AML, T-cell LBL [mainly in association with t(8;13) fusion gene], CML [t(8;22)], CMML [t(6;8) and t(8;9)], mixed phenotype acute leukemia (MPAL).

Typical findings in blood: eosinophilia, neutrophilia, occasionally monocytosis.

Typical findings in bone marrow: MPN-like with eosinophilia and considerable variability in CP, blast infiltrations in acute leukemias/lymphomas.

Diagnosis: standard cytogenetics identifies *FGFR1*-related translocations which can be confirmed by FISH and/or RT-PCR.

Treatment: in CP — clinical trial or TKI with activity against *FGFR*: pemigatinib or midostaurin or ponatinib. In BP — treatment depends on clinical presentation: chemotherapy (AML/ALL-like) plus TKI. Imatinib, nilotinib and dasatinib are ineffective. Allogeneic stem cell transplantation (allo-SCT) is only curative therapeutic approach and should be considered early in eligible patients.

Response assessment: PB/BM including conventional cytogenetics/FISH and RT-PCR (if available). Imaging studies for extramedullary presentation.

Imatinib discontinuation: not applicable.

Prognosis: aggressive clinical course with poor prognosis, rapid transformation of CP to BL (within 1–2 years of diagnosis) [3, 4, 19, 23, 24].

JAK2-rearranged neoplasms

Epidemiology: marked male predominance, median age 47 years (range 12–75). Incidence is low (<1% of all MPN). Commonly includes cases with t(8;9)(p22;p24.1) resulting in fusion of *PCM1-JAK2*. Alternative partners of *JAK2* may contain t(9;12)(p24.1;p13.2) and t(9;22)(p24.1;q11.2) with fusions of *ETV6-JAK2* and *BCR-JAK2*, respectively.

Manifestation: hepatosplenomegaly.

Clinical presentation: atypical CML, CEL, primary myelofibrosis (PMF), MPN/MDS, AML, B/T-cell LBL.

Typical findings in blood: eosinophilia (not commonly observed), neutrophil precursors.

Typical findings in bone marrow: in CP — eosinophilia, dyserythropoiesis and dysgranulopoiesis (MPN/MDS), increased fibrosis (PMF) is frequent. BP — depending on clinical presentation.

Diagnosis: standard cytogenetics identifies *JAK2*-related translocations which can be confirmed by FISH and/or RT-PCR.

Treatment: In CP — clinical trial or TKI with activity against *JAK2*: ruxolitinib or fedratinib. In BP — treatment depends on clinical presentation: chemotherapy (AML/ALL-like) plus TKI. Imatinib, nilotinib and dasatinib are ineffective. Allo-SCT is only curative therapeutic approach, and should be considered early in eligible patients.

Response assessment: PB/BM including conventional cytogenetics/FISH and RT-PCR (if available). Imaging studies for extramedullary presentation.

Imatinib discontinuation: not applicable.

Prognosis: highly variable from weeks (BP) to years (CP) [3, 4, 19, 25–27].

ETV6-FLT3 and *ETV6-ABL1* gene fusions

These fusion genes constitute 'provisional' categories which have not yet been added to the WHO 2016 classification. The cases with *FLT3* fusions occur extremely rarely, and usually involve t(12;13)(p13;q12) leading to fusion with *ETV6*. To date, 17 cases and seven genes have been identified as partners of *FLT3*. Clinically present as CEL, T-cell LBL or peripheral T-cell lymphoma. Rearrangement can be detected by standard cytogenetics but FISH and RT-PCR are useful. Clinical course is aggressive. Patients should be recommended to participate in a clinical trial or receive TKI with activity against *FLT3*: midostaurin, sorafenib, sunitinib or gilteritinib. In BP — chemotherapy with TKI. Allo-SCT should be considered as soon as possible [3, 4, 28, 29].

ALL remains the most common presentation in *ABL1*-rearranged neoplasms, however various clinical phenotypes have been reported. Eosinophilia is not invariably present (in all MPN/AML, but in a minority of ALL). The common abnormality includes t(9;12)(q34;p13) resulting in *ETV6-ABL1* fusion. Rearrangement can be detected by standard cytogenetics, but FISH and RT-PCR are highly recommended. This neoplasm is characterized by an aggressive disease course with poor response to therapy. Patient should be treated within clinical trials or receive TKI with activity against *ABL1*. In BP — chemotherapy plus TKI. Early recommendation to allo-SCT [3, 4, 30].

Step-by-step algorithms with treatment options for myeloid/lymphoid neoplasms with eosinophilia are summarized in Figure 1 [31].

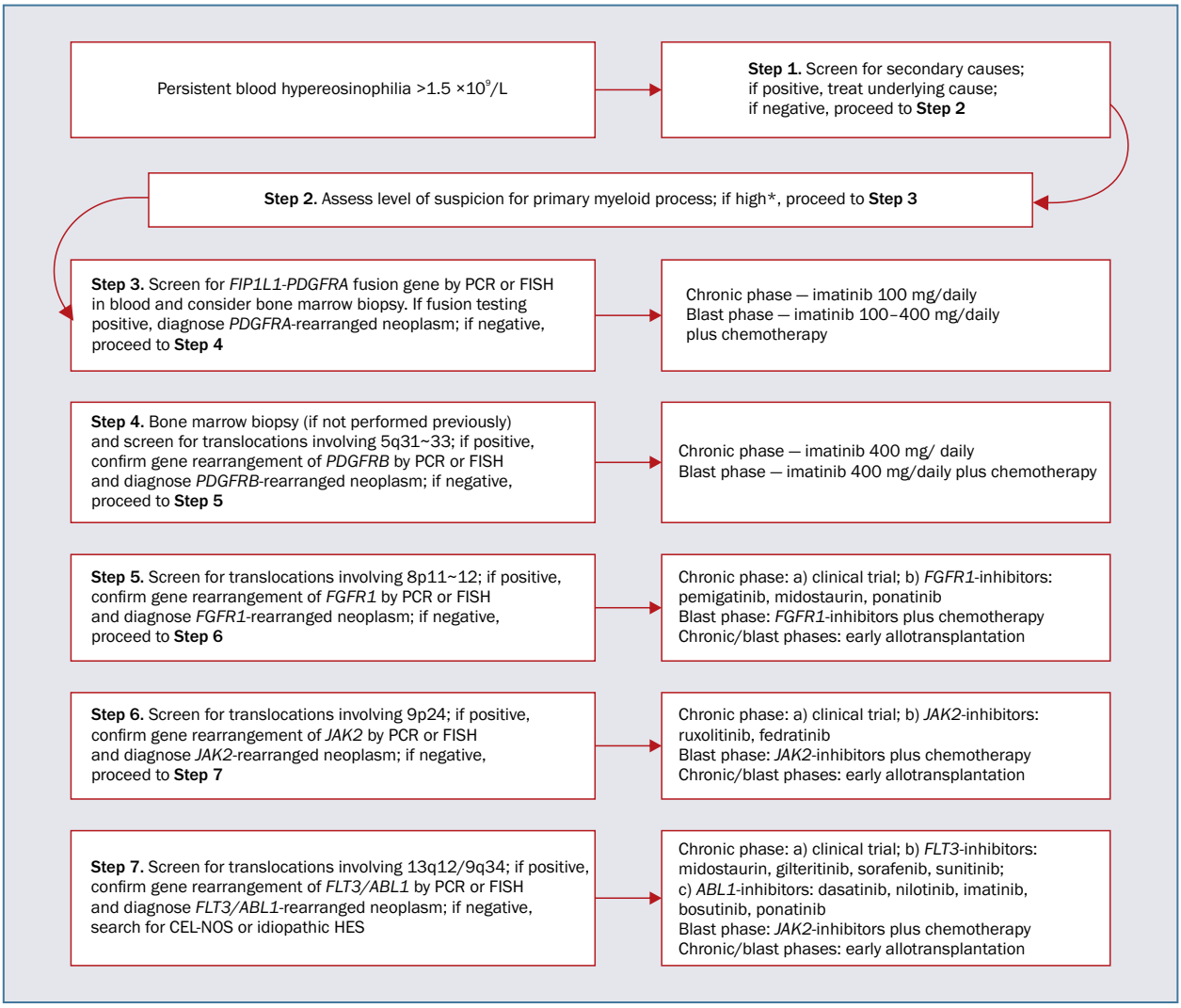

Figure 1. Step-by-step diagnostic ladder with therapeutic options (modified from [31]); *including elevated serum B_{12} or tryptase, splenomegaly, dysplastic eosinophils or blasts in peripheral blood, unexplained anemia/thrombocytopenia, or known steroid-refractory eosinophilia); PCR — polymerase chain reaction; FISH — fluorescence *in situ* hybridization; CEL-NOS — chronic eosinophilic leukemia-not otherwise specified; HES — hypereosinophilic syndromes

Conclusions

Molecular findings have led to the discovery of several novel mutations involving dysregulated tyrosine kinase genes. These findings have resulted in better characteristics of several myeloid and lymphoid neoplasms with eosinophilia which has created a separate category within the WHO classification. The results of molecular profiling will enable more targeted therapy and precise monitoring.

Author's contributions

GH — sole author.

Conflicts of interest

Advisory board: Novartis, Abbvie. Speaker's fee: Novartis.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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