Mutational Landscape in Myeloproliferative Neoplasms (MPN) and Eosinophilia: Diagnostic and Treatment – Section 12

Mutational Landscape in Myeloproliferative Neoplasms (MPN) With Eosinophilia: Diagnosis and Treatment

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Take-home messages:

- Clonality-associated eosinophilia is established through the finding of cytogenetic aberrations, tyrosine kinase fusion genes and point mutations.
- PDGFRα and PDGFRβ fusion genes are exquisitely sensitive to imatinib, conferring an excellent prognosis.
- New tyrosine kinase inhibitors are promising for MPN in association with FGFR1 (pemigatinib) and JAK2 (ruxolitinib) fusion genes but allogeneic stem cell transplantation remains an important treatment option.

Establishment of clonality by genetic techniques in patients with unexplained eosinophilia has important prognostic and therapeutic implications, ranging between watch and wait and rapid allogeneic hematopoietic stem cell transplantation (HSCT).1,2

The most frequent molecular aberration is the cytogenetically cryptic FIP1L1-PDGFRα tyrosine kinase (TK) fusion gene, which is usually identified by RT-PCR or FISH analysis, for which cells from peripheral blood are sufficient. We consider RT-PCR as the gold standard, because of several FISH-negative/RT-PCR-positive cases but not vice versa. In contrast, the vast majority of related but rare TK fusion genes with rearrangement of PDGFRβ (most frequently ET6-PDGFRβ or CDC88C-PDGFRβ), FGFR1 (eg, ZMYM2-FGFR1), JAK2 (eg, PCMI-JAK2), ABL1 (eg, ET6-ABL1) or FLT3 (eg, ET6-FLT3) are usually identified through cytogenetic analysis of cells derived from a bone marrow aspirate.3 Distinct reciprocal translocations, most frequently (5;12) (q31-q33;p13) or (8;13)(p11;q12), which imply involvement of PDGFRβ at 5q32 and FGFR1 at 8p11, guide the confirmation of the fusion gene by RTPCR/sequencing analysis, which is essential for molecular follow-up of response to therapy. Another recurrent fusion, ET6-ABL1, is created through a more complex rearrangement but can also be cytogenetically cryptic. Due to its strong association with eosinophilia, it should be included in the WHO subcategory of myeloid/lymphoid neoplasms with eosinophilia (MLN-eo) and associated TK fusion genes.4 Some cytogenetically cryptic fusion genes, mainly due to inversions or small deletions, for example, ZMYM2-FLT3 or DIAHIP1-PDGFRβ,5 have been identified through RNA sequencing, which should become a routine diagnostic tool in the near future.

Besides eosinophilia, recurrent non-genetic characteristics of TK fusion gene driven MLN-eo include (a) elevated serum levels of tryptase, vitamin B12, and LDH, (b) cytopenias and monocytosis, (c) hepatosplenomegaly and lymphadenopathy, and (d) variable levels of fibrosis and increased numbers of spindle-shaped and loosely scattered, CD25+ positive neoplastic mast cells in the bone marrow. Of note, eosinophilia can be absent, for example, in association with involvement of FGFR1 or PDGFRβ fusion genes, which may at least in part depend on the partner gene, for example, BCR. Special attention should be paid to the bone marrow biopsy which should always include an aspirate for standard morphology, cytogenetics and FACS (eg, T-cells, blasts) and a core biopsy. The proportion of missed or incorrect diagnoses whilst differentiating between clonal and reactive eosinophilia is a concern and most prominent is the oversight of systemic mastocytosis.6,7 Particularly important is the evaluation of proliferation and dysplasia of non-eosinophilic lineages, fiber staining and immunohistochemistry of megakaryocytes, monocytes, mast cells and blasts.8 Unexpected molecular genetic results should prompt a re-evaluation and final diagnosis should consider both morphology and genetic profile (Fig. 1).

The FIP1L1-PDGFRα fusion gene is exquisitely sensitive to low-dose imatinib, for example, 100 mg/day following diagnosis and 3 × 100 mg/week as maintenance dose after achievement of complete molecular remission (CMR).9–12 Imatinib 100 mg/day has also been successfully used in patients with PDGFRβ fusion genes.13 Rarely, patients are diagnosed in primary lymphoid or myeloid blast phase, which is often present at extramedullary sites.
in terms of T-cell, rarely B-cell lymphoma, or myeloid sarcoma. Without evidence from in vitro data or clinical trials, we recommend treating patients in blast phase with imatinib 400 mg/day and to only consider dose reduction to 100 mg/day after achievement of sustained CMR and the availability of frequent sensitive molecular monitoring. Recent data have suggested that imatinib can be interrupted/stopped in FIP1L1-PDGFRA positive patients in a similar way as in BCR-ABL1 positive CML. In FIP1L1-PDGFRA positive patients, we have not yet observed primary resistance while the secondary resistance may occasionally be caused by point mutations, for example, T674I or D842V. Despite encouraging in vitro data, potential second-generation inhibitors, for example, nilotinib, have not been effective and most patients reported have died within 12 months of emergence of imatinib-resistance. Potentially new drugs are either off-label, for example, midostaurin (T674I24,27) or ponatinib (T674I and D842V22,23), or only available in clinical trials, for example, pemigatinib or avapritinib (D842V). Due to the poor prognosis, rapid HSCT should be considered in eligible patients. ETV6-ABL1 positive patients can achieve complete and durable remissions on ABL1-inhibitors with a better outcome with nilotinib or dasatinib compared to imatinib.24 The situation is different for patients with FGRF1 and JAK2 fusion genes.25 Primary or secondary blast phase in bone marrow or at extramedullary sites is frequent and rapidly emerging. Patients may therefore receive primary treatment with intensive chemotherapy but only rarely achieve durable remissions because of primary resistance or early relapse. This may change through the availability of ruxolitinib (JAK224,26,27) and pemigatinib (FGFR1).28 Patients can achieve complete remissions, but the long-term benefit is yet unknown and (early) allogeneic HSCT should always remain an option in every eligible patient.

The diagnostic criteria of chronic eosinophilic leukemia, not otherwise specified (CEL, NOS) include a cytogenetic or molecular genetic abnormality (with exception of an eosinophilia-associated TK fusion gene) or blast cells ≥2% in the peripheral blood or >5% in the BM. However, cytogenetic abnormalities other than those being associated with TK fusion genes or increased numbers of blast cells occur very rarely. Recent data have highlighted the presence of additional somatic mutations which are either defining specific subtypes of myeloid neoplasms, for example, KIT D816V or JAK2 V617F24,26,30 or which are otherwise known to be of prognostic relevance in myeloid neoplasms. Because significant eosinophilia is present in 20% to 30% of patients with KIT D816V positive advanced systemic mastocytosis, KIT D816V represents in fact the second most common eosinophilia-associated molecular aberration after FIP1L1-PDGFRA. Clinical markers indicating KIT D816V positive advSM include cytopenia(s), monocytosis, elevated tryptase and alkaline phosphatase in serum, signs of portal hypertension and malabsorption.29,30 Other recurrent mutations include STAT5B N642H and JAK2 ex13InDel.31,32 Extended molecular profiling of STAT5B N642H and KIT D816V positive patients has revealed that the prognosis is predominantly determined by presence and number of additional somatic mutations, for example, SRSF2, ASXL1, RUNX1. Besides the specific use of KIT- (eg, midostaurin, avapritinib) or JAK-inhibitors (eg, ruxolitinib), these patients may be candidates for treatment with hydroxyurea or interferon-alpha. Overall, all patients should be carefully checked upon eligibility of HSCT because of the association of eosinophilia with additional somatic mutations and consequently adverse prognosis.

References


Concise overview on myeloid neoplasms with eosinophilia.


Concise overview on diagnostic criteria and classification of eosinophilia-associated disorders.


New patient cohort and literature review on treatment-free remission in FIP1L1-PDGFRα-positive myeloid/lymphoid neoplasms with eosinophilia after imatinib discontinuation.


Systemic mastocytosis is an important differential diagnostic work-up of eosinophilia.


New recurrent point mutation in myeloid neoplasms with eosinophilia.