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| Clinical Utility of Molecular Testing in  MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE GENE FUSIONS  Diagnostic utility   * Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions are a family of diseases with varied clinical presentations that may resemble myeloproliferative neoplasms, myelodysplastic/myeloproliferative neoplasms, systemic mastocytosis, or de novo or secondary acute leukaemias/lymphomas of B-cell, T-cell, myeloid, mixed or ambiguous phenotype1. The phenotype may change throughout the disease course. Eosinophilia is a common feature, but not invariably so. * Specifically defined entities under this category include gene rearrangements of *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *FLT3* and the *ETV6*::*ABL1* fusion. * Rarer entity defining fusion genes reported include *ETV6*::*FGFR2*, *ETV6*::*LYN*, *ETV6*::*NTRK3*, *RANBP2*::*ALK*, *BCR*::*RET* and *FGFR1OP*::*RET*. Other rare fusion genes with potentially novel partners are possible. * Several *PDGFRB* and *JAK2* fusions have been described in *BCR::ABL1*-like B-lymphoblastic leukaemia (B-ALL). *De novo* cases without eosinophilia and monocytosis that otherwise have typical morphological and immunophenotypic features of B-ALL may best be classified as *BCR::ABL1*-like B-ALL1.   Prognostic UTILITY   * Myeloid/lymphoid neoplasms with *PDGFRA* or *PDGFRB* rearrangement generally have a good prognosis with tyrosine kinase inhibitor treatment, especially when in chronic phase2,3. * The prognosis for myeloid/lymphoid neoplasms with other gene fusions is generally less favourable but also depends partly on the disease phase at presentation4. * Somatic gene mutations (e.g *ASXL1, RUNX1)* may be detected in addition to the disease-defining tyrosine kinase gene fusion5,6. There are limited studies addressing the prognostic effects of additional mutations in this context7.   BIOMARKERS OF RESPONSE TO THERAPY   * Myeloid/lymphoid neoplasms with *PDGFRA* or *PDGFRB* rearrangement are especially responsive to tyrosine kinase inhibitors such as imatinib3,8. * Nested or quantitative RT-PCR may be used for molecular monitoring of measurable residual disease during and after therapy7. * Acquired resistance to tyrosine kinase inhibitors in myeloid/lymphoid neoplasms with *PDGFRA* rearrangement is rare but has been reported. Resistance has been associated with mutations in the ATP-binding domain of *PDGFRA* (e.g. Thr674Ile and Asp842Val)7,9*.* * Other fusions involving *FGFR1*, *ABL1, JAK2* and *FLT3* may be more sensitive to inhibitors with higher activity against these tyrosine kinases or multi-kinase inhibitors7.   References  **1.** WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. Lyon (France): International Agency for Research on Cancer; forthcoming. (WHO classification of tumours series, 5th ed.; vol. 11). https://publications.iarc.fr. **2.** Rohmer J, et al. Epidemiology, clinical picture and long-term outcomes of FIP1L1-PDGFRA-positive myeloid neoplasm with eosinophilia: Data from 151 patients. *Am J Hematol* 2020; **95**(11): 1314-23. **3.** Cheah CY, et al. Patients with myeloid malignancies bearing PDGFRB fusion genes achieve durable long-term remissions with imatinib. *Blood* 2014; **123**(23): 3574-7. **4.** Metzgeroth G, et al. Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions: reevaluation of the defining characteristics in a registry-based cohort. *Leukemia* 2023; **37**(9): 1860-7. **5.** Baer C, et al. Molecular genetic characterization of myeloid/lymphoid neoplasms associated with eosinophilia and rearrangement of PDGFRA, PDGFRB, FGFR1 or PCM1-JAK2. *Haematologica* 2018; **103**(8): e348-e50. **6.** Tang G, et al. Myeloid/lymphoid neoplasms with FLT3 rearrangement. *Mod Pathol* 2021; **34**(9): 1673-85. **7.** Reiter A, et al. How I (Diagnose and) Treat Myeloid / Lymphoid Neoplasms with Tyrosine Kinase Gene Fusions. *Blood* 2024. **8.** Cools 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**(13): 1201-14. **9.** Lierman 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**(5): 845-51. |