Myeloid / lymphoid neoplasms with eosinophilia and rearrangement of *PPDGFRA, PDGFRB or FGFR1, or with PCM1-JAK2* (MLN-Eo with TK fusion)

Stand: February 2021

Diagnostic Recommendation

Method	Anticoagulant	Recommendation
Cytomorphology	EDTA	mandatory
Immunophenotyping	EDTA or Heparin	optional
Chromosome analysis	Heparin	mandatory
FISH	EDTA or Heparin	mandatory
Molecular genetics	EDTA or Heparin	mandatory

Definition and characteristics

Myeloid/lymphoid neoplasms with eosinophilia (MLN-Eo) and rearrangements involving the tyrosine kinases (TK) *PDGFRA*, *PDGFRB*, *FGFR1* or presence of a *PCM1-JAK2* fusion are rare specific diseases. Clinical and hematologic manifestation is influenced by the partner gene involved in the rearrangement. Eosinophilia is characteristic but not necessarily present.

Classification

The neoplasms with eosinophilia and *PDGFRA* (4q12), *PDGFRB* (5q31-33), *FGFR1* (8p11), or *PCM1-JAK2* rearrangement are grouped as a separate entity in the 2017 WHO classification, with MLN-Eo with *PCM1-JAK2* rearrangement t(8;9)(p22;p24.1) defined as a new provisional entity.

All share constitutive activation of a tyrosine kinase with a highly heterogeneous clinical presentation. While *PDGFRA*, *PDGFRB*, *FGFR1* rearrangements involve activation of a receptor tyrosine kinase, the *PCM1-JAK2* rearrangement involves constitutive activation of Janus kinase 2 (*JAK2*), a non-receptor tyrosine kinase. Other rearrangements involving *JAK2* (e.g., *ETV6-JAK2* and *BCR-JAK2*) do not currently lead to classification into this specific entity according to WHO.

Essentially, two phases of disease can be distinguished for myeloid/lymphoid neoplasms with eosinophilia and TK fusion: the chronic phase and the blast phase. In the chronic phase, the disease usually presents as MPN or MDS/MPN. In the blast phase, it presents as an acute leukemia (**AML**, **ALL**, or MPAL (Mixed-Phenotype Acute Leukemia)) and/or extramedullary disease (e.g., myeloid sarcoma, lymphoma) (Gerds et al. 2020). In contrast, the term accelerated phase is not clearly defined in MLN-Eo with TK fusion (Gerds et al. 2020).

WHO classification 2017
(Swerdlow et al. 2017)

Myeloid/lymphoid neoplasms with eosinophilia and PDGFRA, PDGFRB, FGFR1 rearrangement or with PCM1-JAK2.
- Myeloid/lymphoid neoplasm with *PDGFRA* rearrangement
- Myeloid/lymphoid neoplasm with *PDGFRB* rearrangement
- Myeloid/lymphoid neoplasm with von *FGFR1* rearrangement
- Provisional entity: myeloid/lymphoid neoplasm with *PCM1-JAK2*

Overview of MLN-Eo with TK fusion

Table 1: Overview of genetic alterations, clinical presentation and treatment options in myeloid and lymphoid neoplasms with eosinophilia and tyrosine kinase fusion according to Arber et al. 2016, updated data on fusion partners according to Reiter & Gotlib 2017, Wang et al. 2020 and Atlas of Genetics and Cytogenetics in Oncology and Haematology.

Disease	Presentation	Genetics	Treatment
PDGFRA	• Eosinophilia • ↑ Serum-Tryptase • ↑ Mast cells in bone marrow	cryptic deletion of 4q12-*FIP1L1-PDGFRA*, at least 18 known partner genes	Response to TKI
PDGFRB	• Eosinophila • Monocytosis, imitatesCMML	t(5;12)(q33;p13); *ETV6-PDGFRB*, > 30 known partner genes	Response to TKI
FGFR1	• Eosinophilia • Frequent presentation as T-ALL orAML	8p11-Translocation *FGFR1*-known partner genes, 15 described so far	Poor prognosis; no response to TKI
PCM1-JAK2	• Eosinophilia • Rare Presentation as T-LBL or B-ALL • Bone marrow mit left shifted erythroid predominance and lymphatic aggregatesn	t(8;9)(p22;p24.1); *PCM1-JAK2*	Possible response to *JAK2*-inhibition

Common: *PDGFRA* and *PDGFRB* rearrangements
The most common *PDGFRA* rearrangement observed is the *FIP1L1-PDGFRA* rearrangement, which results from a submicroscopic deletion in the long arm of chromosome 4, del(4)(q12q12) (Cools et al. 2003). This change is not visible in chromosome band analysis. However, deletion of the *CHIC2* gene can be detected by FISH and the resulting *FIP1L1-PDGFRA* rearrangement by PCR (Gotlib et al. 2004). Rarely, *PDGFRA* rearrangements with another partner gene occur. These cases, as well as rarely occurring activating *PDGFRA* mutations, are also encompassed by the WHO category (Swerdlow et al. 2017).

Several fusion partners have been described in the literature for *PDGFRB*. The most common translocation occurs at t(5;12)(q33;p13), where the oncogene *ETV6* fuses with *PDGFRB* (Cross & Reiter 2002). *ETV6-PDGFRB* rearrangements can be detected by FISH and RT-PCR. Screening for rare *PDGFRB* rearrangements is possible by FISH, although chromosome band analysis is usually required for accurate partner determination. RNA sequencing has also recently become available to search for partner genes. Excluded from this WHO entity are Philadelphia-like ALL associated fusions such as *EBF1-PDGFRB*, *SSBP2-PDGFRB*, *TNIP1-PDGFRB*, *ZEB2-PDGFRB*, *ATF7IP-PDGFRB* (Swerdlow et al. 2017).

***FGFR1* rearrangement (8p11 syndrome)**
FGFR1 rearrangements result from a fusion of the *FGFR1* gene (in chromosomal band 8p11, hence the name "8p11 syndrome") with a variety of fusion partners, 15 are known to date (Wang et al. 2020). The 8p11 syndrome is clinically characterized by eosinophilia and an association with T-

lymphoblastic lymphomas as well as a high transformation rate to acute leukemias. Cytogenetically, a translocation t(8;13)(p11;q12) is usually found, which leads to a *ZNF198-FGFR1* rearrangement at the molecular level (Cross & Reiter 2002). These diseases show no response to 1st- and 2nd-generation tyrosine kinase inhibitors, but in vitro data suggest inhibition of chimeric *FGFR1* fusion kinases by ponatinib (Ren et al. 2013). One patient with *BCR-FGFR1*-positive mixed-phenotype acute leukemia (MPAL) achieved a response to combination therapy consisting of chemotherapy followed by ponatinib administration (Khodadoust et al. 2016). Currently, a **Phase II trial (Fight-203)** is evaluating monotherapy with the FGFR inhibitor pemigatinib. Initial interim results show good response rates. Among the 10 patients with at least one treatment response study, a clinical response (complete or partial remission) was observed in 8 of the 10 patients, this was accompanied by a complete or partial cytogenetic response (Verstovsek et al. 2018). The study is still in the recruitment phase (see also Therapy).

Rare: *PCM1-JAK2* rearrangements and other fusions.
Myeloid and lymphoid neoplasms with eosinophilia and *PCM1-JAK2* rearrangement occur rather rarely. The translocation t(8;9)(p22;p24) is the cause here (Reiter et al. 2005). Other rare rearrangements involving *JAK2* as well as *ABL1* and *FLT3* have been described in MLN-Eo but are not included in the WHO definition (Gerds et al. 2020). Differential diagnosis for rare *JAK2* fusions as well as *ABL1* fusions should include Philadelphia-like ALL (Swerdlow et al. 2017, Gerds et al. 2020). In patients with *PCM1-JAK2* or *JAK2*, *ABL1*, and *FLT3* fusions, consideration should be given to treatment with a directed tyrosine kinase inhibitor (Gerds et al. 2020, Schwaab et al. 2020). For example, patients with chronic eosinophil leukemia (CEL) and *PCM1-JAK2* rearrangement have already shown a response to treatment with ruxolitinib (Reiter et al. 2005, Liermann et al. 2012, Patterer et al. 2013, Rumi et al. 2013 & 2015). Recent data on ruxolitinib therapy in 9 patients with *JAK2* fusion show a response (at least complete hematologic remission (CHR)) in 5 of 9 patients. Based on current data, the response appears to be transient, with only one patient achieving a long-lasting (>24 months) CHR. However, ruxolitinib treatment should be considered as a bridge to allogeneic stem cell transplantation (Schwaab et al. 2015 & 2020).

Diagnostics

Cytomorphology

Especially in view of the great heterogeneity of the appearance (see also Table 1), cytomorphology is of essential importance in the morphological characterization. It is important for the exclusion of secondary and reactive causes of eosinophilia and, in conjunction with other diagnostic disciplines, for the differential diagnosis of diseases that may also be associated with eosinophilia (Shomali & Gotlib 2019). Follow-up examinations are important for the assessment of hematologic response and for the exclusion or detection of leukemic transformation.

Immunophenotyping

Immunophenotyping plays a minor role when cases present as myeloproliferative neoplasm in the chronic phase. When cases present as acute leukemia or leukemic transformation, immunophenotyping is important for lineage determination.

Chromosome analysis

Chromosome analysis plays an important role in the diagnosis of myeloid/lymphoid neoplasms with tyrosine kinase fusion. With the exception of the cytogenetically cryptic *FIP1L1-PDGFRA* rearrangement, all other rearrangements involving *PRDGFRA*, *PDGFRB* and *FGFR1*, as well as the *PCM1-JAK2* fusion, can usually be detected by chromosome analysis. Chromosome analysis is also suitable to identify both fusion partners.

FISH

The *FIP1L1-PDGFRA* rearrangement as the most common cause of myeloid/lymphoid neoplasm with tyrosine kinase fusion can be detected very well by FISH. The ~800 kB deletion on chromosome 4q12 is detected with a probe directed against the *CHIC2* gene, which is located in the deleted region.

In addition, probes are available in modern FISH diagnostics that allow screening for possible abnormalities of 4q12 (*PDGFRA*), 5q32-33 (*PDGFRB*), 8p11 (*FGFR1*), 9p24 (*JAK2*) as well as 12p13 (*ETV6*) with a short turn-around time. Fusion partners can be identified in a further step by chromosomal analysis or molecular genetic characterization.

Molecular genetics

Molecular genetics can significantly aid in the diagnosis of these diseases. Thus, the most common rearrangements can be detected by RT-PCR, such as *FIP1L1-PDGFRA*, *ETV6-PDGFRB*, *ZNF198-FGFR1*, and *PCM1-JAK2*. In addition to FISH, *FIP1L1-PDGFRA* RT-PCR offers another possibility to detect the cytogenetically cryptic rearrangement.

The method of RNA sequencing offers the possibility to identify fusion partners and might in the future improve the delineation between MLN-Eo with rare rearrangements of *PDGFRA/B* or *JAK2* and Philadelphia-like ALL. The latter is defined by its *BCR-ABL1*-like gene expression profile (Swerdlow et al. 2017).

For patients with rearrangements of *PDGFRA* and *PDGFRB*, molecular remissions are achieved with imatinib therapy, and RT-PCR provides the sensitivity needed to monitor treatment response in this setting. In very rare cases, resistance to imatinib occurs due to a *PDGFRA* T674I or D842V mutation; these can be detected by sequencing (Gerds et al. 2020). An isolated case report described imatinib resistance in a patient with MPN and *PDGFRB* rearrangement; an indirect resistance mechanism was suspected as the cause (Bastie et al. 2004).

Little is known about the mutational landscape of MLN-Eo with TK fusion compared with other myeloid neoplasms. In an initial study for which all four subtypes of MLN-Eo with TK fusion were molecularly characterized, at least one mutation was detectable in 23% of 61 patients. The only recurrent mutations were in *RUNX1*. These showed a strong association with MLN-Eo with *FGFR1* rearrangement, so *RUNX1* mutations occurred as an isolated mutation in 5 of the 6 patients with this rearrangement. Among the cases with *PDGFRA* rearrangement (n=35), with *PDGFRB* rearrangement (n=13), and with *PCM1-JAK2* fusion (n=7), 9 of the 14 mutations found were in the class of epigenetic regulators (*ASXL1*, *BCOR*, *DNMT3A*, and *TET2*) (Baer et al. 2018).

Prognosis

Good therapeutic response in neoplasms with eosinophilia and *PDGFRA* and *PDGFRB* rearrangements.
Regardless of the partner gene, the detection of *PDGFRA* rearrangements is of great importance from a therapeutic point of view, as these usually show a good response to treatment with tyrosine kinase inhibitors (Cools et al. 2003). In particular, for *FIP1L1-PDGFRA* rearrangement, it has been shown that deep molecular and long-lasting remissions are achieved in a large proportion of patients (>90-95%) (Onkopedia Guideline Myeloid Neoplasms with Eosinophilia 2020). Initial, mostly retrospective, studies are currently evaluating whether, analogous to a TKI stop in **CML**, discontinuation of imatinib treatment is possible (Klion et al. 2007, Gerds et al. 2020, Metzgeroth et al. 2020). Imatinib stop has been described in the literature in a total of 42 patients, 21 of whom experienced molecular or hematologic relapse (Metzgeroth et al. 2020). Re-initiation of imatinib treatment rapidly restored remission in the vast majority of patients (Metzgeroth et al. 2020).

A similarly good therapeutic response to tyrosine kinase inhibitors and long-term remissions were observed in patients with *PDGFRB* rearrangements (Cheah et al. 2014). No data are currently available on TKI stop in this patient group (Gerds et al. 2020, Onkopedia Guideline Myeloid Neoplasms with Eosinophilia 2020).

Study on the use of the FGFR inhibitor pemigatinib in neoplasms with eosinophilia and FGFR1 rearrangement.
For patients with MLN-Eo and *FGFR1* rearrangement, treatment with the *FGFR1* inhibitor pemigatinib may be available in a phase II trial. Initial interim results showed a response in 80% of patients (Verstovsek et al. 2018). Further information on study design, inclusion criteria, and study protocol is available at **ClinicalTrials.gov** and on the homepage of the **Leukemia Competence Network**. An overview of participating German study centers and contact information can be found **here**.

High transformation rate to AML in *PCM1-JAK2* rearrangement and 8p11 syndrome
Myeloid and lymphoid neoplasms with eosinophilia and *PCM1-JAK2* rearrangement or *FGFR1* rearrangement (8p11 syndrome) show a high transformation rate to acute leukemias.

Recommendation

In case of clinical and cytomorphological suspicion of myeloid/lymphoid neoplasms with eosinophilia and *PDGFRA*, *PDGFRB*, *FGFR1* or *PCM1-JAK2* rearrangement, comprehensive screening by cytogenetics and molecular genetics should be performed for diagnosis both for classification according to WHO and because of the immense therapeutic consequences.

Due to the rarity of these disorders, inclusion in the **Registry of Patients with Rare Myeloid Neoplasms (German language)** may be recommended.

References

You can find the corresponding references here:
https://www.mll.com/en/diagnostic-offer/hypereosinophilic-syndromes-and-mastocytosis/pdgfra-pdgfrb-fgfr1-rearrangements.html#referenzen