



## **aCML - Atypical chronic myeloid leukemia, *BCR-ABL1*-negative**

Continuous research and targeted examinations of blood and bone marrow result in various diagnostic recommendations for patients with atypical chronic myeloid leukemia (aCML).

### **Diagnostic recommendation**

Method	Anticoagulant	Empfehlung
Cytomorphology	EDTA	mandatory
Immunophenotyping	EDTA or Heparin	optional
Chromosome analysis	Heparin	mandatory
FISH	EDTA or Heparin	no
Molecular genetics	EDTA or Heparin	mandatory



## Status: April 2020

### aCML - Definition

BCR-ABL1-negative atypical chronic myeloid leukemia (aCML) is a rare entity from the overlapping area of myelodysplastic and myeloproliferative diseases.

### aCML - Classification

According to the WHO classification 2017, aCML is a leukemic disorder with myelodysplastic as well myeloproliferative features (MDS/MPN).

#### aCML WHO Classification 2017 (Swerdlow et al. 2017)

#### Myelodysplastic/myeloproliferative neoplasia Atypical chronic myeloid leukaemia (aCML), BCR-ABL1-negative

##### Diagnostic criteria according to WHO 2017:

- ☑ Peripheral blood leukocytosis  $\geq 13 \times 10^9/L$ , due to increased numbers of neutrophils and their precursors (i.e. promyelocytes, myelocytes and metamyelocytes), with neutrophil precursors constituting  $> 10\%$  of the leukocytes
- ☑ Dysgranulopoiesis, which may include abnormal chromatin clumping
- ☑ No or minimal basophilia; basophils constitute  $< 2\%$  of the peripheral blood leukocytes
- ☑ No or minimal monocytosis; monocytes constitute  $< 10\%$  of the peripheral blood leukocytes
- ☑ Hypercellular bone marrow with granulocyte proliferation and granulocytic dysplasia, with or without dysplasia in the erythroid and megakaryocytic lineages
- ☑  $< 20\%$  blasts in the blood and bone marrow
- ☑ No evidence of *PDGFRA*, *PDGFRB* or *FGFR1* rearrangement, or of *PCM1-JAK2*
- ☑ WHO criteria for BCR-ABL1-positive CML, PMF, PV or ET are not met

### Diagnostics of aCML

#### Cytomorphology

Cytomorphology serves to differentiate the disease from other myeloproliferative diseases (MPN), CMML and myelodysplastic syndrome (MDS) and to secure the diagnosis. It is also required for classification according to WHO.

#### Chromosome analysis

Chromosomal changes have been detected in about 40% of patients with aCML (Meggendorfer et al. 2018). The changes known from MPN and MDS occur. Most frequently an increase of chromosome 8 was observed, less frequently among others a monosomy 7 or 7q deletion, an isochromosome 17q or a complex karyotype (Wang et al. 2014). However, these changes are not specific for aCML.

#### Molecular genetics

##### Recurrent mutations in aCML

Mutations in the *SETBP1* gene ("set binding protein 1") have been described in about 25-30% of all cases (Piazza et al. 2013, Meggendorfer et al. 2013). Mutations in the *ETNK1* gene ("ethanolamine kinase 1") were detected in 3-9% of aCML patients (Gambacorti-Passerini et al. 2014, Meggendorfer et al. 2018).

Furthermore, mutations in the genes *ASXL1* (60%), *TET2* (approx. 45%) and *SRSF2* (approx. 35%) are found (Meggendorfer et al. 2018). However, these mutations are also found in other myeloid diseases. They can be used as clonal markers to differentiate aCML from reactive processes and for course diagnosis.

In contrast to chronic neutrophil leukemia (CNL), in which mutations in the *CSF3R* gene ("receptor for colony stimulating factor 3") have been frequently observed, they occur in only about 3% of patients with aCML (Meggendorfer et al. 2014).

In addition, low frequency mutations in *CBL*, *RUNX1*, *NRAS* and *KRAS*, among others, have been described in patients with aCML (Meggendorfer et al. 2018). At 9%, there are hardly any mutations in the JAK-STAT signalling pathway (*JAK2*, *CALR*, *MPL*), while the RAS signalling pathway (*NRAS*, *KRAS*, *CBL*) is more frequently affected at 37% (Meggendorfer et al. 2018).

It should be noted that according to WHO 2017, within the framework of differential diagnoses, a CNL should be morphologically excluded in the case of detection of a *CSF3R* mutation. Likewise, MPN should be excluded if a *JAK2*, *CALR* or *MPL* mutation is detected. In contrast, according to WHO 2017, the presence of a *SETBP1* or *ETNK1* mutation supports the diagnosis of atypical CML.

### Prognosis of aCML

A leukocyte count of  $> 50 \times 10^9/L$  has been described in several studies as a prognostically negative parameter for aCML (Onida et al. 2002, Breccia et al. 2006, Wang et al. 2014). In some of these studies, an age  $> 65$  years, female sex and a hemoglobin level of  $< 10$  g/dL were also prognostically



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unfavourable. Furthermore, a negative influence of a *SETBP1* mutation was shown (Piazza et al. 2013). 30-40% of patients with aCML show a transformation into AML (Wang et al. 2014).



#### aCML - Recommendation

It should be noted that according to WHO 2017, within the framework of differential diagnoses, a CNL should be morphologically excluded if a *CSF3R* mutation is detected. Similarly, in the case of detection of a *JAK2*, *CALR* or *MPL* mutation, an accelerated phase of an MPN should be excluded based on the history.

In contrast, according to WHO 2017, the presence of a *SETBP1* or *ETNK1* mutation supports the diagnosis of atypical CML.

#### Referenzen

Die zugehörigen Referenzen finden Sie hier:

<https://www.mll.com/en/agnostic-offer/myelodysplastic-myeloproliferative-neoplasms/atypical-chronic-myeloid-leukemia-acml.html#referenzen>