Chronic myelomonocytic leukemia (CMML)

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Learn important information about the classification, diagnosis and prognosis of CMML.

Diagnostic Recommendation

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

CMML: Definition and characteristics

CMML (chronic myelomonocytic leukemia) is a clonal hematopoietic malignancy with features of both a myeloproliferative neoplasm (MNP) and a myelodysplastic syndrome (MDS). The incidence of CMML is about 0.4/100,000 per year, with the highest incidence of about 4/100,000 in the group of >80 years of age (Dinmohamed et al. 2015). The median age of onset of the disease is 70-72 years (Germing et al. 1998).

CMML - Classification

According to the WHO classification 2017, CMML is one of the myelodysplastic/myeloproliferative neoplasms.

Diagnostic criteria
- persistent peripheral blood monocytosis (≥1x10^9/L)
- Monocytes accounting for ≥10% of the leukocytes
- WHO criteria for BCR-ABL1-positive chronic myeloid leukemia, primary myelofibrosis, polycythemia vera and essential thrombocythemia are not met
- No rearrangement of *PDGFRA*, *PDGFRB* or *FGFR1* and no *PCM1*-JAK2
- Blast constitute < 20% of the cells in the peripheral blood and bone marrow
- Dysplasia involving > 1 myeloid lineages classically dysplasia in one or more myeloid lines or

If myelodysplasia is absent or minimal, criteria 1-4 are met and:
- An acquired, clonal cytogenetic or molecular genetic abnormality is present in hematopoietic cells

or
- The monocytosis has persisted for > 3 months and all other causes of monocytosis (e.g. malignancy, infection, and inflammation) have been excluded.

(Swerdlow et al. 2017).

The detection of an acquired cytogenetic or molecular genetic alteration thus represents a diagnostic criterion according to WHO 2017. The presence of mutations in genes such as *TET2*, *SRSF2*, *ASXL1* or *SETPB1*, which are often associated with CMML, can support the diagnosis of CMML in a suitable clinical context. However, mutations in these genes may also be age-associated (clonal haematopoiesis of indeterminate potential, CHIP), so that interpretation in conjunction with the other diagnostic criteria is required.

CMML WHO Classification 2017
(Swerdlow et al. 2017)

Myelodysplastic/myeloproliferative neoplasms
Chronic myelomonocytic leukemia (CMML)

Furthermore, the CMML is subdivided into three categories, defined by the percentage of blasts and promonocytes in the peripheral blood and bone marrow (Swerdlow et al. 2017):

CMML-0

<2% blasts in the blood and <5% blasts in bone marrow, no Auer rods

CMML-1

2-4% blasts in the blood or 5-9% blasts in bone marrow, no Auer rods

CMML-2

5-19% blasts in the blood, 10-19% blasts in bone marrow or Auer rods are present; < 20% blasts in the bone marrow and blood

Facts

In over
90%

of patients with NGS (Next Generation Sequencing)
one or more mutations are found (oncopedia
guideline CMML)

Diagnostics of CMML

Cytomorphology

Characteristic for CMML is a peripheral blood monocytosis with a monocyte count ≥1x10^9/L, it is usually 2-5x10^9/L, but can also exceed >80x10^9/L. Depending on the total leukocyte count, CMML is divided into two variants: the so-called dysplastic form (total leukocyte count <13x10^9/L) and the proliferative form (total leukocyte count ≥13x10^9/L).

In general, the monocytes are mature and have unremarkable morphology, but they can exhibit unusual nuclear segmentation or chromatin patterns and abnormal granulation. The proportion of promonocytes and (mono-) blasts together must be less than 20%. Dysgranulopoiesis is present in most cases. Cytochemical staining is strongly recommended, especially myeloperoxidase and in particular the unspecific esterase, for assessing the monocytic components.

Immunophenotyping

Immunophenotyping is helpful to distinguish CMML from benign reactive monocytosis. It has been shown that a proportion of ≥94% of so-called classical monocytes (MO1: $CD14^+$, $CD16^-$) in peripheral blood with a specificity and sensitivity of more than 90% each distinguishes a CMML from reactive monocytosis (Selimoglu-Buet et al. 2015). The information obtained by immunophenotyping can also be used to track minimal residual disease under therapy.

Chromosome analysis

Chromosome analysis should be performed in the presence of CMML. Chromosomal changes are present in 20-40% of all cases (Swerdlow et al. 2017). The aberration rate is higher for blasts in the sense of CMML-2 (Such et al. 2011). In most scoring systems (see **Prognosis of CMML**) chromosomal abnormalities play a decisive role, so that chromosomal analysis is required to assess the prognosis here. Common cytogenetic changes are trisomy 8, monosomy 7 or 7q deletion, loss of the Y chromosome, 20q deletion or trisomy 21. A complex aberrant karyotype (defined as at least three aberrations) has been described in 3-6% of cases (Valent et al. 2019). However, these abnormalities are not specific for CMML, but are also observed in other - mainly myeloid - haematological neoplasms.

FISH

In addition to chromosome analysis or with regard to individual typical alterations, FISH can be performed on interphases or for further clarification of the karyotype on metaphases. On its own, this method is not necessary for the diagnosis or prognosis of CMML. FISH can make a contribution to follow-up examinations and the determination of residual disease after therapy. In addition, FISH can detect cytogenetic cryptic changes (*TET2* deletion, *NF1* deletion, *ETV6* deletion), which are present in 2-10% of cases (Valent et al. 2019).

Molecular genetics

Majority of patients show molecular mutations

Since the majority of patients have a normal karyotype, extensive studies have been carried out in recent years to investigate the molecular basis of CMML. In these studies it could be shown that more than 90% of CMML patients have at least one molecular mutation, some of which has prognostic relevance (Patnaik et al. 2018). Table 1 summarises common mutations.

Table 1: Common mutations in CMML

TET2	Encoding an epigenetic regulator. TET2 is mutated in about 60% of all CMML patients and is therefore the most frequently mutated gene in CMML.
SRSF2	Affecting the splicing machinery, splicing of pre-mRNA. SRSF2 mutations are present in about 50% of CMML patients.
ASXL1	Encoding a chromatin binding protein and thus also plays a role in epigenetic modifications (histone modification). Mutations in this gene occur with an incidence of about 40%. ASXL1 mutations are associated with a poor prognosis, shorter survival and transformation to AML (Gelsi-Boyer et al. 2010).
RUNX1	Encoding a transcription factor. Mutations in this gene often lead to a differentiation stop, depending on the type of mutation. RUNX1 mutations occur in about 15% of CMML patients
RAS	Both NRAS and KRAS, two cytoplasmic proteins of the RAS signalling pathway, can carry activating mutations. NRAS and KRAS mutations are found in approximately 15% and 10% of CMML patients, respectively.
SETBP1	Coding for SET-binding protein 1, for which mutations have recently been detected in various MDS/MPN overlap entities. In CMML patients, SETBP1 mutations are found in approximately 15% of CMML patients, respectively.

Other rarer gene mutations in CMML are with an incidence of about 1-20%: ***BCOR, CBL, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, NF1, NPM1*** and genes of the spliceosome (***SF3B1, U2AF1, ZRSR2***) (Yoshida et al. 2011, Patnaik et al. 2018). The analysis of these and the more frequently mutated genes listed in Table 1 by means of NGS is recommended by the EHA/ELN (Itzykson et al. 2018).

Prognosis of CMML

The median survival time of patients with CMML is 20-40 months, 15-30% of patients show progression to AML (Swerdlow et al. 2017).

For mutations in the genes *ASXL1*, *NRAS*, *RUNX1* and *SETBP1* a prognostically unfavourable significance was proven, which is taken into account in the calculation of the prognosis score according to Elena et al. (2016) (see below). A prognostically negative influence was also shown for *SRSF2* mutations (Itzykson et al. 2013), which, however, could not be demonstrated in another study (Meggendorfer et al. 2012). For *TET2* mutations no negative effect on survival could be shown (Meggendorfer et al. 2012; Itzykson et al. 2013).

Prognostic scoring systems for the risk classification of patients
According to Such et al (2011), CMML can be divided cytogenetically into three prognostic groups.
- **Favourable:** normal karyotype or loss of the Y chromosome; approx. in 80% of all patients
- **Adverse**: Trisomy 8, aberrations affecting chromosome 7 or complex aberrant karyotype (≥ 3 aberrations)
- **Intermediary**: all other abnormalities

Based on this cytogenetic risk classification as well as the parameters CMML subtype according to WHO and FAB and transfusion dependence, the CPSS score according to Such et al (2013) is calculated.

The scoring system according to Itzykson et al. (2013) includes for risk classification purposes not only age, leucocytes, platelets and anemia but also a molecular genetic mutation, namely the *ASXL1* mutation status (see Table 2). With these parameters a patient can be classified into the prognostic groups favourable (0-4 points), intermediate (5-7 points) and unfavourable (8-12 points).

Table 2: Prognostic scoring system according to Itzykson et al. (2013)

Prognostic variable	Scoring-Points
Age > 65 Years	2
WBC > $15x10^9$/L	3
Anemia (hemoglobin <10g/dL in women and < 11g/dL in men)	2
Platelets < $100x10^9$/L	2
ASXL1 mutated	2

With the scoring system according to Elena et al. (2016), CMML patients are classified into different risk groups by means of cyto- and molecular genetic parameters. Based on the cytogenetic risk classification according to Such et al. (2011) and the detection of mutations in *ASXL1*, *NRAS*, *RUNX1* and/or *SETBP1*, a patient can be prognostically classified into the groups favourable (0 points), intermediate-1 (1 point), intermediate-2 (2 points) or unfavourable (≥3 points) (see Table 3).

Table 3: Prognostic scoring system (genetic risk group) according to Elena et al (2016)

	CPSS cytogenetic risk group*	*ASXL1*	*NRAS*	*RUNX1*	*SETBP1*
Variable Score					
0	Low	Unmutated	Unmutated	Unmutated	Unmutated
1	Intermediate	Mutated	Mutated	-	Mutated
2	High	-	-	Mutated	-

Genetic risk group	Score
Low	0
Intermediate-1	1
Intermediate-2	2
High	≥3

– not applicable

*Cytogenetic risk groups are defined according to Such et al: low, normal, and isolated –Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7.

In addition to the genetic risk group thus determined, the calculation of the CPSS mol takes into account the proportion of blasts in the bone marrow, leucocytes and transfusion dependency.

Calculation of prognosis
Here you can access the prognosis calculation of the CPSS-Mol-Score.

References

You can find the corresponding references here:
https://www.mll.com/en/diagnostic-offer/myelodysplastic-myeloproliferative-neoplasms/cmml-chronic-myelomonocytic-leukemia.html#references