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Chronic Myelomonocytic Leukemia (CMML)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Chronic Myelomonocytic Leukemia (CMML)

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1 Summary

Diagnosis of chronic myelomonocytic leukemia (CMML) is based on the detection of monocytes in the blood associated with dysplasia in the bone marrow. Exclusion of reactive monocytosis is mandatory. Additional cytogenetic and molecular evaluations are essential. CMML may present like myelodysplastic neoplasms (MDS) with concomitant monocytosis (leukocytes <13,000/µl) or like myeloproliferative neoplasms (MPN) (leukocytes ≥13.000/µl). Risk scores such as the CPSS and the CPSS-molecular allow estimation of the prognosis of patients in terms of overall survival and risk of progression to acute myeloid leukemia (AML). CMML is mainly a disease of advanced age. Patients with dysplastic CMML usually suffer from the consequences of hematopoietic insufficiency, whereas patients with proliferative CMML more often have constitutional symptoms and organomegaly.

Improving quality of life and prolongation of life expectancy are the main goals of therapy. The mode of therapy should always be adapted individually. Supportive measures are of utmost importantance and cytoreduction is recommended in cases with high leucocyte counts. The only curative therapy is allogeneic stem cell transplantation (SCT), which is only applicable in a minority of patients due to age and frequent comorbidities. Azacitidine is approved for patients with high-risk dysplastic CMML who are ineligible for SCT, and some patients benefit from the response to the drug. Other agents are not approved to date.

2 Basics

2.2 Epidemiology

Chronic myelomonocytic leukemias (CMML), like all myeloid/myelodysplastic neoplasms, are rare diseases. With a proportion of about 20% of MDS, the incidence is around 0.5-1.0 per 100,000 per year. More men than women are affected (ratio about 2:1) with a median age at diagnosis around 76 years. With the current changes in population structure, this results in an increasing prevalence and higher incidence at advanced ages [1].

2.3 Pathogenesis

CMML are malignant diseases characterized by clonal hematopoiesis in the bone marrow. In more than 90% of patients, one or more somatic mutations are detectable by NGS (next generation sequencing). The mutations are devided into four categories:

- epigenetic regulator genes, such as EZH2, ASXL1, TET2, DNMT3A, IDH1, and IDH2,
- mutations in the spliceosome such as SF3B1, SRSF2, U2AF1 and others,

- mutations affecting DNA repair mechanisms (TP53),
- mutations affecting tyrosine kinases and transcription factors such as JAK2, KRAS, NRAS, RUNX1.

It is likely that multiple mutations occur in a staggered fashion, with the first mutations often found in the TET2 or the ASXL1 gene. Subsequently.second and probably more additional events occur, which then trigger the development of the disease. The most common mutations found in CMML are TET2 (60%), SRSF2 (50%), ASXL1 (40%) and RAS (10-30%). Regarding the phenotype of CMML with always associated monocytosis, one theory is that immature dysplastic granulocytes of the CMML clone produce α-defensin protein, which then inhibit macrophage colony-stimulating factor-induced differentiation of monocytic cells, leading to the presence of immature monocytes [2, 3].

2.4 Risk factors

Risk factors include exposure to organic solvents, prior radiation therapy, radioiodine therapy, and chemotherapy. Benzene were no proved risk factor in a cohort study, but this remains controversial. Notably, in cigarette smoking, the risk factor benzene accumulates as a major product. If relevant occupational exposure to organic solvents is suspected, a report should be made to the respective professional association [4, 5, 6].

3 Prevention and early detection

There is no possibility of prevention for CMML. Measures for early detection of CMML are not available. In general, noxious agents (chemotherapy, radiotherapy), that are indicated because of another serious disease cannot be avoided because of their potential of inducing CMML as a second neoplasm, after years.

3.2 Early detection

3.2.1 Individuals at-risk

CMML are diseases of the elderly, which mostly manifest after the age of 60 years. Only 3% of CMML patients are under 50 years of age, so age per se is a risk factor for developing CMML. For unknown reasons, men develop the disease about twice as often as women. About 10% of CMML cases are therapy-associated (t-CMML) and are associated with high-risk cytogenetics and poor prognosis, comparable to therapy-associated MDS. There is a median of 6 years between exposure and initial diagnosis of t-CMML. Secondary CMML that develops from preexisting MDS is rare. CMML without evidence of diasease-inducing factors is classified as primary CMML. Possible effects of environmental factors on the development of CMML have not extensively been investigated. However, due to the similarity to MDS, CMML is supposed to have similar risk factors as MDS. These include exposure to solvents (benzene), cytotoxic substances (especially alkylants, topoisomerase II inhibitors) or radioactive radiation. Furthermore, chronic inflammation (e.g. autoimmune diseases such as polymyalgia rheumatica) seems to support the development of CMML. Smokers and former smokers appear to be at higher risk for CMML compared with nonsmokers. There is no known hereditary cause of adult CMML, although there are rare germline mutations that may be associated with CMML [7, 8]. Especially, DDX41, a rare germline mutation favors the development of CMML [9].

4 Clinical manifestation

4.1 Symptoms

In a large proportion of patients, CMML is diagnosed incidentally by an otherwise indicated blood test. Only a small proportion of patients have clinical symptoms that lead to diagnostis. General symptoms such as night sweats, weight loss, fatigue, and a reduced general condition are usual. The clinical symptoms of CMML are most fequently caused by the hematopoietic insufficiency. The clinical presentation is more similar to MDS or chronic MPN, with one of the two components becoming more prominent in the individual case. Patients with an MDS phenotype (MD-CMML) (leukocytes <13,000 µl) often have cytopenia in the peripheral blood with associated sequelae, such as neutropenia-related infections, thrombocytopenia with associated bleeding, and anemia requiring transfusion. At diagnosis, severe bleeding caused by thrombocytopenia is uncommon; petechiae, gingival bleeding, and a tendency to hematoma are more frequent. In the proliferative phenotype (MP-CMML) (leukocytes ≥13,000 /µl), splenomegaly, mostly asymptomatic, is present in approximately 50% of cases, hepatomegaly and lymphadenopathy are less frequent. Infiltration of myelomonocytic cells in the skin, pleura, and peritoneum may occur, particularly with leukocyte counts of ≥13000/µl in the peripheral blood. In a proportion of patients, CMML transforms into acute myeloid leukemia (AML), with a frequency of 15-30%. An increase of monocytes in the blood per se is not sufficient to postulate a progression of CMML, as infecions can also cause higher monocyte counts, which regress under successful treatment.

CMML is associated with autoimmune diseases more frequently than MDS. An autoimmune disease is present in approximately 20% of cases in CMML. Vasculitis, idiopathic thrombocytopenia (ITP), psoriasis, rheumatoid polyarthritis, and neutrophilic dermatosis (Sweet syndrome) are most common. Autoimmune phenomena may precede the initial diagnosis of CMML by years [10].

4.2 Incidental findings

Due to the tendency of monocytes to migrate into various tissues, monocytic organ infiltrations are not rare in CMML and are mostly associated with high peripheral leukocyte counts. Meningeosis leukaemica occurs very rarely and usually reflects a transition to acute leukemia. Gingival hyperplasia, which is frequent in monocytic differentiated acute leukemias, can rarely occur in CMML and is usually combined with an increase of leukocytes in the peripheral blood.

Thrombocytopenia in patients with CMML does not necessarily reflect dysplastic bone marrow insufficiency or infiltration by leukemic cells, but may rarely be due to classic ITP, which may occur years after the diagnosis of CMML [8, 9]. Usually, these patients show a good response to steroids.

4.3 General condition and comorbidity

CMML is a disease of older and therefore more frequently multimorbid patients. In recent years, it has become evident for a number of chronic hematological diseases (MDS, CLL, CML, Hodgkin's lymphoma) that comorbidity is an independent prognostic factor, which significantly influences overall survival. After diagnosis and assessment of prognosis, the therapy of CMML depends in particular on the age, general condition and comorbidities of the respective patient. Mild and asymptomatic cytopenias do not initially require therapy. Only when symptoms appear or proliferation increases therapy is required. Mild therapy with e.g. hydroxyucarbamide or demethylating substances is frequently possible in patients of limited general condition and with comorbidities after benefit-risk assessment. However, the application of these drugs may

be difficult in very bad general condition and especially in high Charlson comorbidity index or MDS-CI [11]. For patients scheduled for SCT, the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) is suitable to estimate overall survival and risk of non-relapse-related mortality after allogeneic SCT.

5 Diagnosis

5.1 Diagnostic criteria

CMML is usually dignosed when the causes of unclear leukocytosis, monocytosis or cytopenia are investigated. First clinical signs of CMML in older patients may be general symptoms (B symptoms), symptoms of splenomegaly or clinical consequences of cytopenias (anemia, bleeding, infection). Cytopenia, but also leukocytosis (in about 50% of cases) with monocytosis (average around 4.3 G/l) and increased blast counts are possible in the peripheral blood. By definition, CMML presents with persistent monocytosis of >500/µl in the blood, accounting for at least 10% of the leukocyte count, if a genetic aberrant marker is present; if there is lack of a genetic marker, persistent monocytosis of >1000/ µl is mandatory. In addition, 1 to 3 cell lineages in the bone marrow have dysplasia signs. Dysplasias of megakaryopoiesis and granulopoiesis are usually more prominent than of erythropoiesis. Due to monocytic/granulocytic hyperplasia in the bone marrow, erythropoiesis typically accounts for only about 15% of nucleated cells. Esterase staining allows visualizing variable degrees of monocytes in the bone marrow. The blast percentage (including promonocytes) in blood and bone marrow is by definition between 0 and 19%. The abnormal partitioning of peripheral blood monocyte subsets is a supportive criterion for the diagnosis of CMML.

According to the peripheral and medullary blast percentage, **two types** are distinguished: CMML 1 with peripheral blast percentage <5% and medullary blast percentage <10% and CMML 2 with peripheral blast percentage 5-19% and medullary blast percentage 10-19%. If peripheral and/or medullary blast percentage are ≥20%, a diagnosis of acute leukemia is made. The former CMML 0 subgroup was included into CMML 1 because the prognosis is similar to CMML 1, whereas CMML 2 has an indisputably worse prognosis.

Chromosome analysis is an obligatory part of the diagnosis of CMML. Approximately 80% of patients with CMML have a normal karyotype. Among chromosomal aberrations, loss of genetic material from chromosome 7 and trisomy 8 are more common. Molecular markers such as mutations of ASXL1, TP53, and of other genes are sometimes the only way to identify the clonal nature of the disease. In addition to **WHO subgroups** 0, 1, and 2, CMML is further classified according to leukocyte count into a dysplastic variant (leukocytes <13,000/µl) (MD-CMML) and a proliferative variant (leukocytes ≥13,000/µl) MP-CMML. The proliferative variant is usually associated with activated RAS pathway and has a worse prognosis. This classification is important from a prognostic point of view, furthermore it reflects the different clinical presentation.

The diagnosis CMML is based on peripheral blood counts and bone marrow aspiration. In Table 1, the diagnostic criteria according to WHO 2022 are represented. Some patients with MDS and concomitant monocytosis formally develop CMML during the diesease course by exceeding 500 or 1000 monocytes/µl. These cases exhibit clinical and molecular characteristics of CMML already at initial diagnosis and are then classified as "oligomonocytic CMML" if they have a chromosomal or molecular genetic abnormality typical of CMML [12, 17]. A consensus group has developed the minimal diagnostic criteria for CMML in an expanded and more precise form [18]. To avoid misdiagnosis of an underlying systemic mastocytosis with monocytosis, a test for KIT D816V mutation should be included.

Table 1: CMML diagnostic criteria according to WHO 2022 [19]

Criterion	Note
1) Prerequisite criteria 1. persistent monocytosis in peripheral blood (>500/µl over 3 months comprising >10% of leukocytes, with genetically aberrant marker or >1000/ µl comprising >10% of leukocytes, without genetic marker).	no consideration of the monocyte count in the bone marrow
2. <20% blasts incl. promonocytes in blood and bone marrow.	
3. exclusion of BCR::ABL1 positive CML, PMF, PV and ET.	
4. no evidence of myeloid/lymphoid neoplasia with tyrosine kinase fusion.	should be excluded in cases with eosinophilia (cave: MLN-TK without eosinophilia).
2) Supporting criteria	
1. dysplasia of one or more myeloid lineages (>10% each) 2. acquired clonal cytogenetic or molecular abnormality (TET2, SRSF2, ASXL1, SETBP1). 3. abnormal monocyte population in flow cytometry. from peripheral blood.	
3) Requirements for diagnosis Prerequisite criteria must be present in all cases	
If monocytes >1000/µl: one or more supporting criteria must be met. If monocytes >500/µl and <1000/µl: supporting criteria 1 and 2 must be met.	

5.2 Diagnostics

5.2.1 Initial diagnosis

The cytomorphology from peripheral blood and bone marrow including cytochemistry is diagnostically relevant and therefore mandatory. Iron and esterase staining are helpful, desirable are also POX, and PAS staining. Signs of dysplasia, the percentage of blasts (blast equivalent = myeloblasts, monoblasts and promonocytes), monocytic cells and ring sideroblasts are determined. Furthermore, bone marrow histology (fibrosis?, cellularity?) and obligatory oncogenomics (banding cytogenetics, screening for somatic mutations, supplemented or replaced by FISH, if necessary) are highly recommended, as well as imaging for evaluation of spleen size. Immunophenotyping can also be helpful to distinguish between clonal and nonclonal monocytoses by means of co-expression of CD14 and CD16. An increase of monocytes with CD14+/ CD16- phenotype (cut off 94%) is highly specific and sensitive for the presence of CMML in contrast to secondary/reactive monocytoses [17]. Molecular genetic testing is mandatory to exclude other diseases (see Table 1), but it is also important with regard to modern prognostic systems and therapy recommendations. The determination of RUNX1, NRAS, SETBP1 and ASXL1 mutations is recommended with regard to their prognostic significance and it is always obligatory if no other prove of diagnosis is present [18]. The extent of mutation screening should be adapted individually and should be targeted and moderate. In most cases, NGS gene analysis panels with the simultaneous analysis of >50 genes are available. The synopsis of the findings frequently enables diagnosis and classification. The diagnostic steps are shown in Table 2.

Table 2: Diagnostics of CMML

Method	Criteria	Importance
Peripheral blood	• assessment of dysplasia of granulocytes and platelets • quantification of cell counts, incl. monocytes and blasts	obligatory
Bone marrow smear	• quantification of the blast fraction • esterase staining for estimation of monocyte percentage • iron staining for the detection of ring sideroblasts • assessment of dysplasia of erythropoiesis, granulopoiesis and megakaryopoiesis	obligatory
Bone marrow biopsy	• determination of cellularity and fibrosis	recommended
Cytogenetics	• recognition of acquired aberrations	obligatory
FISH	• in case of insufficient banding analysis detection of typical chromosomal aberrations	obligatory, if conventional cytogenetics not possible
Mutation analysis of genes	• detection of somatic mutations • diagnostic: BCR::ABL1, PDGFR α and β, FGFR1, PCM1::JAK2 (exclusion), SRSF2, KIT D816V (exclusion). • prognostic: NRAS, RUNX1, ASXL1, SETBP1, SRSF2	obligatory, if diagnostics with other methods are inconclusive, recommended in other cases
Immunophenotyping	• CD14+/CD16 - Population	recommended, but obligatory if relevant as additional criterion for diagnosis

5.2.2 Disease progression

CMML is a chronic disorder. Median survival is between 12 and 36 months. Regular checks of blood counts and of spleen size are mandatory. During therapy or in case of suspected progression (e.g. transition to acute leukemia), the bone marrow examination including the genetic findings have to be re-evaluated. Response criteria have not yet been defined lacking reliable data, but a first proposal has been published [16]. The need for further specific diagnostic measures may arise from individual clinical problems (infections, splenic infarction, extramedullary manifestations).

5.2.3 Rare complications

CMML is more frequently associated with various autoimmune diseases as compared to other myeloid neoplasms.

5.3 Classification

In principle, two different **subtypes are distinguished**, the dysplastic subtype (more MDS-typical with more cytopenias, dysplasias as well as more frequent cytogenetic aberrations) and the proliferative subtype (more similarity to myeloproliferative neoplasms with more frequent splenomegaly, higher leukocyte counts with left shift and extramedullary manifestations such as skin infiltrates or effusions). Regarding the leukocyte count, the diagnositc cutoff is <13 G/L for dysplastic CMML and ≥13 G/l for proliferative CMML.

The WHO classification 2022 further distinguishes between two CMML **subgroups** taking into account the blast content (see Table 3). The description of rare CMML variants, such as oligomonocytic CMML, CMML with associated systemic mastocytosis, CMML with concomitant myeloid/lymphoid neoplasia is available in a consensus paper referring to the details [18]. In

parallel to WHO, an "International Consensus Classification" was proposed by another working group, which differs only marginally from the WHO proposals.

Table 3: CMML subgroups by WHO classification (2022): [19]

Subgroup	Blood	Bone marrow
Chronic Myelomonocytic Leukemia I (CMML I)	≤4% blasts uni- or bicytopenia, persistent monocytosis in peripheral blood: >500/µl over 3 months, comprising >10% of leukocytes, with genetically aberrant marker or >1000/ µl, comprising >10% of leukocytes, without genetic marker (see also complete diagnostic criteria Table 1), no Auer rods	≤9% blasts, dysplasias in >10% of cells in 1-3 rows, no Auer rods, no BCR::ABL1, PDGFR α or β, FGFR1, PCM1::JAK2, no MLN-TK.
Chronic Myelomonocytic Leukemia II (CMML II)	5-19% blasts, uni- or bicytopenia, persistent monocytosis in peripheral blood: (>500/µl over 3 months, comprising >10% of leukocytes, with genetically aberrant marker or >1000/ µl, comprising >10% of leukocytes, without genetic marker (see also complete diagnostic criteria Table 1). Auer rods possible	10-19% blasts, dysplasias in >10% of cells in 1-3 rows, Auer rods possible. No BCR::ABL1, PDGFR α or β, FGFR1, PCM1::JAK2, no MLN-TK.

5.4 Prognostic factors

Important prognostic parameters for patients with CMML are patient-specific parameters such as age, gender and concomitant diseases and disease-specific parameters such as peripheral and medullary blast percentage, the extent of cytopenia, need for erythrocyte transfusion, chromosomal and molecular findings. MDS-specific prognosis scores are of limited value in assessment of prognosis because parameters important for MDS are rarely present in CMML. The best prognostic tools to date are the CPSS (CMML-specific prognostic scoring system, Table 4 and the CPSS-molecular, Table 5).

The CPSS includes the following parameters as risk factors to define 4 risk groups: a leukocyte count of >13,000/µl, a medullary blast percentage of ≥10%, regular transfusion requirements, and cytogenetic findings (Table 4). Molecular markers were added to the CPSS, and the blast threshold was lowered to >5%. This score (CPSS-M) also defines 4 risk groups and is especially appropriate for the identification of low-risk and high-risk patients (Table 5).

In absence of cytogenetic and molecular genetic data, the prognosis of patients with CMML can also be estimated using the Düsseldorf score [20, 24]. This score identifies a small group of low-risk patients and a small group of high-risk patients, whereas a large proportion of cases are assigned to the intermediate group.

Table 4: CPSS [23].

Variable	**score points**		
	0	**1**	**2**
WHO type	CMML1	CMML2	
FAB type (leukocyte count)		>13,000/µl	
Cytogenetics	low	intermediate	high
Transfusion requirements*	no	yes	
Cytogenetic risk group			
Low:	normal, -Y		
Intermediate:	other anomalies		
High:	+8, complex karyotype and abnormalities of chromosome 7		
CPSS risk group	**score points**		
Low	**0**		
Intermediate 1	**1**		
Intermediate 2	**2-3**		
High	**4-5**		

Legend:
**Transfusion requirement defined as ≥2 erythrocyte concentrates (EC) every 8 weeks for 4 months.*

Table 5: CPSS molecular [24].

Score points	cytogenetic risk group	ASXL1	NRAS	RUNX1	SETBP1
0	low	unmutated	unmutated	unmutated	unmutated
1	intermediate	mutated	mutated		mutated
2	high			mutated	
Cytogenetic risk group					
Low:	normal, -Y				
Intermediary:	other abnomalities				
High:	+8, complex karyotype and abnormalities of chromosome 7				
Genetic score risk groups	**score points**				
Low	0				
Intermediate 1	1				
Intermediate 2	2				
High	≥3				
Score points	**genetic risk group**	**bone marrow blasts**	**leukocytes**	**transfusion requirements**	
0	low	<5%	<13,000/µl	no	
1	intermediate1	≥5%	≥13,000/µl	yes	
2	intermediate 2				
3	high				
				Transfusion requirements defined as >2 ECs every 8 weeks for 4 months.	
CPSS molecular risk groups	**score points**				
Low:	0				
Intermediate 1	1				
Intermediate 2	2-3				
High	≥4				

5.5 Differential diagnosis

It is essential to exclude other clonal myeloproliferative disorders, as well as reactive causes of splenomegaly, leukocytosis, monocytosis, and cytopenia. Similar, but reactive blood count changes, especially monocytosis, may appear during acute infections, sepsis, chronic infections, TBC, and rheumatic and autoimmune diseases. Other non-hematologic diseases, which can cause splenomegaly (liver and systemic diseases, infections, congenital storage diseases), are a matter of exclusion.

Clonal hematological neoplasms that may be relevant for differential diagnosis of CMML include other forms of MDS and MPN, in particular MPN with neutrophilia (formerly atypical CML) and PMF. Very rare but therapeutically relevant differential diagnoses of monocytosis are myeloid/ lymphoid neoplasms with eosinophilia (PDGFRα or β rearrangement), with tyrosine kinase fusion genes (MLN-TK), hairy cell leukemia (splenomegaly and pancytopenia), or LGL leukemias. Monocytosis can also occur in the transformation from MDS or MPN to AML M4 or M5 and in systemic mastocytosis (*KIT* D816V mutation) (see Onkopedia guideline systemic mastocytosis (German Version)). However, there are also patients with CMML who acquire a KIT D816V mutation during the course of the disease. Differential diagnoses and appropriate diagnostic procedures are shown in Table 6.

Table 6: Differential diagnosis of CMML.

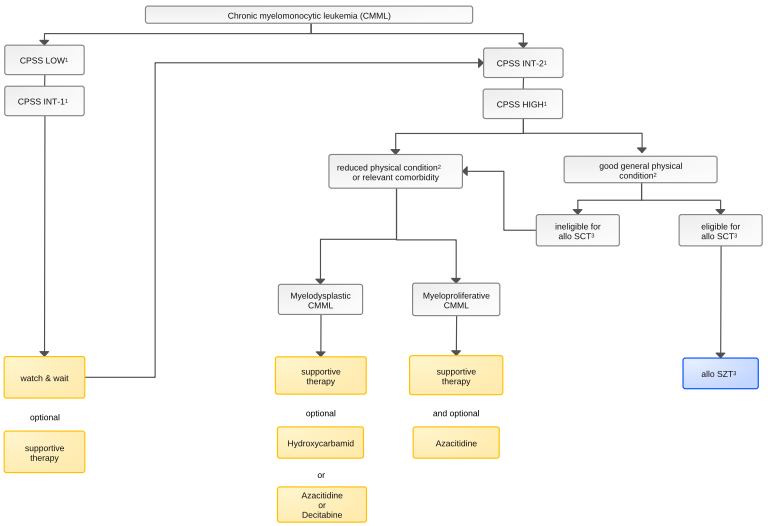
Differential diagnosis	diagnostic procedure
Reactive bone marrow changes (sepsis, HIV, chronic infections, TBC, auto-immune diseases, etc.).	cytology, anamnesis, laboratory
Monocytosis of other cause	medical history, laboratory
Immune thrombocytopenia	cytology, anamnesis, disease course
Hypersplenic syndrome, congenital storage disease	medical history/ clinical picture/ splenomegaly
Acute leukemias (M4, M5)	cytology
Myeloproliferative disorders (esspecially PMF, MPN-U, systemic mastocytosis with associated clonal hematologic neoplasia (SM-AHN), CGL, chronic eosinophil leukemia/hypereosinophilia)	histology, cytogenetics, molecular genetics
Hairy cell leukemia, LGL	cytology, immunophenotyping
Other myelodysplastic/myeloproliferative neoplasms (JMML, MDS/MPN-U, MPN with neutrophilia, MLN-TK)	histology, cytogenetics, molecular genetics

6 Therapy

6.1 General principles of therapy

For the almost elderly patients, maintaining or improving quality of life and autonomy is the main goal of therapeutic efforts. In many asymptomatic CMML patients with mild cytopenia and lack of symptoms, a watch and wait strategy is appropriate. The indication for disease-specific therapy is depending on the stage of disease, age and clinical condition of the patient. In **low-risk CMML patients (CPSS LOW and CPSS INT-1),** therapy is mostly not indicated, which is in part due to the lack of validated therapeutic interventions. Patients with **high-risk CMML (CPSS INT-2 and CPSS HIGH**) should be treated cytoreductively, if necessary, also with the intention of delaying progression to AML [25, 33]. A treatment algorithm is shown in Figure 1.

Figure 1: Therapy of Chronic Myelomonocytic Leukemia.



Legend:
curative therapy; palliative therapy;
[1] CPSS - CMML-Specific Prognostic Scoring System, see chapter 5.4
[2] allo SCT - allogeneic stem cell transplantation

6.2 Therapy modalities

6.2.1 Operation

There are no surgical measures specific to CMML.

6.2.2 Irradiation

In exceptional cases, splenic irradiation may be considered for extremely enlarged spleens causing clinical problems.

6.2.3 Therapy of symptomatic or advanced CMML

In CMML requiring therapy, the basis of any treatment is a good supportive therapy, which includes erythrocyte transfusions as well as sufficient treatment of concomitant diseases. In a significant proportion of patients, thrombocytopenia is the most frequent indication for starting therapy. Anemia, especially in older patients, leads to fatigue, increased incidence of falls with risk of fractures, and reduced cognition and quality of life. Clinically relevant neutropenia is rare. A large multicenter retrospective analysis including over 900 cases describes the results of first-line therapy with azacytidine compared to hydroxycarbamid [34]. This study showed a median survival of 20.7 months with azacytidine compared with 15.6 months with hydroxycarbamid. Of course, because this was a retrospective analysis, it cannot be ruled out that there were generally more patients with less severe concomitant disease and a selection bias for azacytidine therapy. A prospective phase 3 study in MP-CMML patients compared hydroxycarbamid with decitabine, here no survival advantage and no advantage in event-free survival could be found [35].

6.2.4 Supportive therapy

6.2.4.1 Transfusions

The main component of supportive therapy is the transfusion of red blood cells depending on the clinical condition of the individual patient (not depending on a defined Hb threshold; exception: in severe coronary artery disease and/or other severe concomitant diseases, the Hb value should be kept above 9 g/dl).

Clinically significant bleeding is to be expected mainly above a threshold of <10 G/l platelets, although CMML patients may experience bleeding complications even with higher platelet counts. If possible, platelet concentrate substitution should not be prophylactic (exception: high fever, severe infection) but should only be used in case of clinical bleeding signs (risk of alloimmunization). In each case, the therapy decision must be individually adapted to the situation of the patient and the facility providing care (practice, special outpatient clinic with emergency care, etc.).

6.2.4.2 Antibiotics and vaccinations

The use of antibiotics in case of infections (also trivial infections) should be generous, especially in neutropenic patients, whereas routine antibiotic prophylaxis is not indicated. However, the general recommendation of vaccination against pneumococci (STIKO recommendation above the age of 65), COVID-19 and influenza should be followed.

Treatment of concomitant diseases (lung disease, heart disease, etc.) is an important part of the overall therapy.

6.2.5 Iron chelators

Polytransfused patients are at risk for concomitant secondary hemochromatosis (especially cardiomyopathy). Therefore, therapy with iron chelators may be considered in patients with a life expectancy of more than 2 years who receive at least 20 red cell concentrates or have a serum ferritin level of >1000 ng/ml (strength of evidence IIa, recommendation grade D).

6.2.6 Hematopoietic growth factors

Therapy with erythropoiesis stimulating factors (ESF, classical: erythropoietin 150-300 U/kg of body weight, 3 times/week s.c., or 500 U/kg weekly s.c.; delay erythropoietin: 150 µg or 300 µg weekly s.c.) should be considered in the following anemic patients (strength of evidence Ib, grade of recommendation A) [15, 16, 27].

- erythropoietin level <200 IU/ml
- low transfusion dependency (maximum 2 EC in 8 weeks)
- blast cells not >10%
- dysplastic variant of CMML

The response is to be expected after 6 months of therapy at the latest. If the patient fails to respond, treatment should be discontinued. The availability of thrombopoietic growth factors (romiplostim, eltrombopag) offers the possibility of treating severe thrombocytopenia in low-risk CMML. However, these drugs are not approved for CMML and can therefore only be used off-label or within clinical trials.

6.2.7 Special therapies

6.2.7.1 Intensive chemotherapy

Intensive chemotherapy analogous to AML is not an established treatment option for mostly elderly CMML patients outside of trials and especially without subsequent allogeneic SCT. Whether intensive chemotherapy is useful in individual cases (e.g., for remission induction before planned allogeneic SCT) can only be decided on an individual basis, taking into account the risk-benefit ratio.

6.2.7.2 Non-intensive chemotherapy

For many patients with proliferative CMML, **hydroxycarbamide is** the preferred standard therapy to control proliferation including splenomegaly. The first randomized trial [33] demonstrated a survival benefit over etoposide. Other non-intensive chemotherapy such as low-dose **cytarabine** (20 mg/m²/day from day 1 to 14) or low-dose **melphalan** (2 mg/day) has been used in the absence of better therapeutic alternatives in advanced CMML. The availability of **demethylating agents** may offer another therapeutic option.

6.2.7.3 Epigenetic therapy

Azacytidine and **decitabine** are pyrimidine analogs that are incorporated into DNA instead of cytosine. Both agents have a direct cytotoxic effect on proliferating cells. In addition, they prevent the methylation of CpG segments (so-called CpG) in DNA by irreversibly binding and thus inhibiting the enzyme DNA methyltransferase (DNMT-1). Both substances have been evaluated in phase II and randomized phase III studies.

In two randomized trials in patients with MDS (and in some patients with MD-CMML), treatment with 5-azacytidine was shown to have an advantage over supportive therapy alone. Other phase II trials with homogeneous cohorts of CMML patients (dysplastic and proliferative) showed comparable efficacy to MDS patients. However, the only related randomized trial in MP-CMML comparing hydroxycarbamide and decitabine was negative and did not show a survival benefit or better EFS with decitabine [35]. No prospective randomized data are available on the use of azacytidine specifically for CMML. According to the approval of azacytidine, blast excess and CMML with <13,000/µl leukocytes (dysplastic variant) can be treated with this agent when allogeneic SCT is not possible (strength of evidence Ib, recommendation grade A). The standard AZA-7 regimen is given subcutaneously or intravenously at 75 mg/m^2 for 7 days. Cycles are repeated at 28-day intervals. Because the effect of epigenetic modulation occurs almost slowly, at least 6 cycles of azacitidine should be administered before an assessment of response can be made. If there is a response (at least improvement in peripheral blood counts), therapy should be continued. The optimal number of cycles has not yet been defined. It can be assumed that patients who respond will also benefit from continuation of therapy. Predictive factors for response to azacytidine have not been established. In the course of treatment with a demethylating therapy, resistance usually develops. In this case, switching to the other available demethylating drug (i.e. from azacytidine to decitabine or vice versa) is not officially recommended, but may induce a new response in individual cases.

6.2.8 Ruxolitinib

The oral JAK1/2 inhibitor ruxolitinib is approved for the treatment of primary myelofibrosis (PMF), post-PV/post-ET myelofibrosis and polycythaemia vera. Ruxolitinib positively affects disease-associated symptoms (by reducing the production of inflammatory cytokines) and

splenomegaly in particular in these diseases. Small case series [36, 37] suggest that ruxolitinib may also have a positive effect on these symptoms in CMML (off-label use).

6.2.9 Allogeneic stem cell transplantation

At present, allogeneic SCT remains the only curative treatment option for CMML. This therapy is applicable less frequently with increasing age. Therefore, a bias must be taken into account when comparing the survival of the transplanted patients with non-transplanted patients, as transplanted patients are younger and with better general health, which both have a significant influence on overall survival. At this time, there is no study randomizing patients to a transplant arm versus a different type of therapy. Therefore, the possible advantages of allogeneic SCT in CMML must be weighed against the known disadvantages of this treatment approach.

There are studies on allogeneic SCT in CMML, but no prospectively controlled studies. Compared to other myeloid neoplasms, the results with allogeneic SCT are disappointing. A study by Liu et al [28] of 209 allogeneic transplanted CMML patients showed a long-term survival of 26% in the low-risk groups and 14% in the high-risk groups. Another relatively large study of 513 patients was conducted by the EBMT. This study showed a 4-year overall survival of about 30%, which was dependend on the chosen conditioning regimen [29]. The French study group also published a study on allogeneic SCT in CMML in 2013. Seventy-three patients were studied, and the 3-year survival was 30%, similar to other studies [30]. The negative outcome after allogeneic SCT is approximately half due to recurrences of the underlying disease and half due to SCT-related problems such as GvHD, toxicity, etc. It is presently a matter of discussion, whether overall survival improves, if complete remission was achieved prior to allogeneic SCT. Some retrospective study results suggest a better outcome of transplantation in CMML patients, if they have been previously treated with hypomethylating agents compared to cytotoxic chemotherapy [31]. In summary, for younger patients in good clinical condition and at higher risk, allogeneic SCT remains the therapy of choice. However, a clear defintion of this “higher risk” is currently pending.

6.2.10 Autologous stem cell transplantation

Autologous SCT is not a treatment option for patients with CMML.

6.2.11 Therapeutic options in the presence of CMML with concomitant mastocytosis

For patients with CMML and concomitant mastocytosis approved agents as avapritinib and midostaurin are available. For details, see Oncopedia: Mastocytosis (German Version only). Avapritinib was recently approved by the FDA in SM-AHN including CMML [40, 41].

6.3 Summary of therapy options

Most patients with CMML are in advanced age. For these patients non-intensive therapies and good supportive care represent the basis of therapy. In younger patients with high-risk CMML, the possibility of allogeneic SCT has always to be considered first. High-risk CMML patients with dysplastic variant who do not qualify for this procedure may receive treatment with azacytidine. Patients with proliferative variant, should primarily treated with hydroxycarbamide, although azacytidine or decitabine may be effective, but are not approved [42]. As mentioned above, there was no advantage to using decitabine compared with hydroxycarbamide in a randomized trial of decitabine. Therefore, if applicable, its use should be considered only in cases of progression to AML (≥20% blasts). In cases of progression on standard treatment and high-

risk constellations, patients should be included in ongoing clinical trials when possible. Further information is available from the Acute and Chronic Leukemia Competence Network, the Düsseldorf MDS Registry, and the German MDS Study Group. A European guideline summarizes the essential diagnostic and therapeutic procedures. The Austrian CMML Biodatabase [43] will help to provide sufficient material from CMML patients with appropriate data set (see links in chapter 14).

7 Follow-up

7.1 Progress control

Clinical examination of spleen size and, if necessary, abdominal sonography are useful once a year. The intervals of the examination of blood count including differential blood picture and clinical chemistry depend on the individual course of the disease and the respective form and phase of therapy. In the initial phase of therapy, the controls should be more frequent. In case of reaching a stable phase, control intervals up to a quarter of a year or longer may be possible. Follow-up examinations of the bone marrow to detect transformation to acute leukemia are required according to the individual course. If there is evidence of progression (increasing anemia or thrombocytopenia, blasts in the peripheral blood, etc.), a follow-up examination of the bone marrow should be considered. Follow-up examinations of somatic mutations and karyotype are indicated if therapeutic consequences arise. Expansion of the present genetic aberrations or evolution with appearance of further genetic aberrations can occur. Both can influence the prognosis and the course of the disease.

The follow-up of CMML after allogeneic SCT does not differ significantly from the follow-up of other transplanted hemopathies. Center-specific guidelines should be followed, which often include quarterly follow-up in the first year, four-monthly follow-up in the second year, and six-monthly follow-up in subsequent years. This should include chimerism analysis, cytology, histology, and MRD tracking of CMML specific initial changes (cytometry of abnormal monocytes and blasts, karyotype abnormalities, mutations in NGS and molecular biology) in order to detect molecular relapse as early as possible and to be able to counteract it before morphological relapse. This can be done, for example, by withdrawal of immunosuppression, transfusion of donor lymphocytes, and hypomethylating therapy. Regular dermatologic, cardiologic, and gynecologic (in women) examinations should be performed after allogeneic transplantation to detect secondary malignancies early after allogeneic SCT. Even if it is assumed that a patient is cured, differential blood counts should be performed regularly, at least annually, to detect early relapse, secondary MDS, or secondary leukemia. Densitometry in regular intervals is also indicated.

Table 7: Follow-up examinations in CMML

Question	Investigations
Organomegaly	Clinical examination, abdominal sonography if necessary.
Hematopoietic insufficiency/ proliferation.	Blood count and differential blood count
Increased cell turnover	LDH
Clonal evolution	Cytogenetics, somatic mutations in the course, if applicable.
After allogeneic stem cell transplantation	Chimerism, bone marrow cytology/histology, cytogenetics, somatic mutations in progression if applicable.

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10 Active studies

Currently, there is no specific study for CMML patients in the German-speaking area

14 Links

Multicenter and international open-access teaching and learning program with lectures, case reports on diagnostics and therapy of MDS and CMML, and virtual microscopy with commentary where appropriate.
www.mdsdiagnosis.com

Overview of clinical trials administered by EMSCO
www.emsco.eu

Homepage of the German MDS Study Group
www.D-MDS.de

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16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License[4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
Blum, Sabine	Centre Hospitalier Universitaire Vaudois, Lausanne, Schweiz	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Germing, Ulrich	Uniklinik Düsseldorf	**Yes** BMS	**No**	**No**	**Yes** Novartis, BMS, Janssen	**Yes** BMS, Abbvie, Novartis	**No**	**No**
Lübbert, Michael	Univ.-Klinik Freiburg	**Yes** Ad.boards: AbbVie, Astex Pharmaceuticals, Hexal, Janssen, Otsuka, Pfizer, Syros	**No**	**No**	**No**	**Yes** Finanzierung eines Forschungsvorhabens: Janssen-Cilag Studienware: Cheplapharm, Janssen, Aristopharm, TEVA	**No**	**No**
Metzgeroth, Georgia	III. Medizinische Klinik Universitätsmedizin Mannheim	**Yes** GSK, Vifor	**No**	**No**	**Yes** GSK,Vifor, Novartis, Celgene, BMS, Roche	**No**	**No**	**No**
Pfeilstöcker, Michael	Hanusch Krankenhaus der Österreichischen Gesundheitskasse H.Collinstr 30 1140 Wien Österreich	**Yes** Abbvie, BMS, Jazz, Sobi	**No**	**No**	**Yes** Abbvie, BMS, Novartis	**Yes** BMS: projektbezogene Finanzierung statistische Auswertungen	**Yes** Reisekostenerstattung BMS,	**No**
Platzbecker, Uwe	Universitätsklinikum Leipzig	**Yes** BMS, Janssen, Geron, Amgen, Abbvie, Novartis, Jazz	**No**	**No**	**Yes** BMS, Janssen, Geron, Amgen, Abbvie, Novartis, Jazz	**Yes** BMS, Janssen, Geron, Amgen, Abbvie, Novartis, Jazz	**No**	**No**

Legend:

[1] - Current employer, relevant previous employers in the last 3 years (institution/location).

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