

# Acute myeloid leukemia (AML)

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

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DGHO Deutsche Gesellschaft für Hämatologie und  
Medizinische Onkologie e.V.  
Bauhofstr. 12  
D-10117 Berlin

Executive chairman: Prof. Dr. med. Andreas Hochhaus

Phone: +49 (0)30 27 87 60 89 - 0

[info@dgho.de](mailto:info@dgho.de)

[www.dgho.de](http://www.dgho.de)

## **Contact person**

Prof. Dr. med. Bernhard Wörmann  
Medical superintendent

## **Source**

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# Acute myeloid leukemia (AML)

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- [Conflict of interests](#)

**Authors:** Christoph Röllig, Francis Ayuketang Ayuk, Jan Braess, Michael Heuser, Markus G. Manz, Jakob Passweg, Dirk Reinhardt, Richard F. Schlenk, Armin Zebisch

English translation: Christoph Röllig

**Previous authors:** Dietrich Wilhelm Beelen, Thomas Büchner, Richard Greil, Dietger Niederwieser, Markus Schaich

## 1 Summary

Acute myeloid leukemia (AML) is a biologically heterogeneous disease that leads to death in a short time if left untreated. The incidence increases with age. AML is subdivided according to the WHO classification based on cytomorphologic, cytogenetic, and molecular genetic characteristics. Therapeutic decisions are based on disease biology, comorbidity, and the therapeutic goals of the individual patient. The therapeutic approach is curative in younger and in older fit patients.

## 2 Basics

### 2.1 Definition and basic information

Acute Myeloid Leukemia (AML) is a neoplasia of myelopoiesis with variable involvement of myeloid cell lineages.

Before the availability of effective drugs, the natural history of AML resulted in death in half of patients 5 months after the first symptoms and in all patients within one year [78].

Only after the introduction of daunorubicin and cytarabine were complete remissions and long-term success possible [21]. The prognosis of AML has steadily improved since the 1970s. This has been demonstrated in two registry-based studies from the USA and the UK. Therapeutic advances have mainly benefited young patients, while the prognosis of older patients over 70-75 years of age has remained poor [76, 82].

### 2.2 Epidemiology

The incidence is approximately 3.7 cases per 100,000 population per year and increases with age with age-specific incidences exceeding 100 cases per 100,000 population in patients older than 70 years. The median age was 72 years in a Swedish registry of adult patients [36].

### 2.3 Pathophysiology

The origin is the pathological proliferation of clonal myeloid cells, which immunophenotypically belong mostly to the highly proliferative progenitor pool (i.e. CD34+/CD38+) or more rarely to the stem cell pool (i.e. CD34+/CD38-). This proliferating clone overgrows the healthy bone marrow and leads to depletion of healthy hematopoiesis with the resulting clinical consequences of

granulocytopenia (infections, sepsis), thrombocytopenia (bleeding), and anemia (dyspnea, decreased performance). With the beginning of cytogenetic diagnostics in the 1980s, it became clear that - in contrast to CML - quite different cytogenetic aberrations can be observed. Besides gene translocations such as the translocations t(8;21), t(15;17) or the inversion inv(16), numerical alterations such as trisomy 8, monosomy 7 or complex alterations with more than three recurrent chromosomal aberrations were found in one clone. Later it could be shown that these alterations play a very important prognostic role (see Chapter 5.4). With the introduction of modern molecular techniques, especially Next Generation Sequencing (NGS), it became apparent that even within individual patients the disease may consist of genetically different subclones and the proportion of different clones may change over the course of the disease (clonal diversification/evolution). NGS analysis of 200 AML patients revealed an average of 5 recurrent mutations per patient; the most frequent mutations were found in the known genes FLT3, NPM1, DNMT3A, and IDH1 or IDH2, each of which was mutated in at least 20% of patients. Nearly all patients had at least one mutation in one of 9 functional groups critical for transformation. These mutations can be divided into nine classes:

1. activating mutations of signal transduction (FLT3, KIT, KRAS, NRAS, etc.)
2. mutations of myeloid transcription factors (RUNX1, CEBPA, etc.)
3. fusions of transcription factor genes (PML-RARA, MYH11-CBFB and others)
4. mutations of chromatin modifiers (MLL-PTD, ASXL1 et al.)
5. mutations in the cohesin complex (SMC1S and others)
6. spliceosome mutations
7. mutations in tumor suppressor genes (TP53, WT1 et al.)
8. NPM1 mutations
9. mutations in DNA methylation genes (TET1, TET2, IDH1, IDH2, DNMT3B, DNMT1, DNMT3A).

Further investigations showed that in about 50% of the patients at least one additional subclone was detectable besides the dominant main clone; in individual patients up to three additional leukemia clones were present. This clonal heterogeneity could have a significant impact on the response to therapy or on the development of relapse [60].

## 2.4 Risk factors

Risk factors for AML include exposure to radioactive radiation (based on Japanese data from survivors of the atomic bombs on Hiroshima and Nagasaki), benzenes, tobacco, petroleum products, paints, ethylene oxides, herbicides, and pesticides. Radiotherapy and cytostatic agents are among the causative agents, typically alkylating agents with onset of leukemia 4-6 years after application and with aberrations on chromosomes 5 and/or 7, and topoisomerase II inhibitors (anthracyclines, anthraquinones, epipodophyllotoxins) with onset of leukemia 1-3 years after exposure and often associated chromosomal aberrations of chromosome 11 band q23 but also of the balanced translocation t(1,17). Younger age at the time of diagnosis of the primary tumor, therapy with intercalating agents (anthracyclines, anthraquinones), and topoisomerase II inhibitors were associated with a short latency period to the onset of secondary AML in a large meta-analysis [42]. In a large meta-analysis of 23 epidemiologic studies involving 7,746 AML cases, a clear association between smoking and AML development was demonstrated. The risk of AML is increased by 40% in active smokers and 25% in former smokers compared to non-smokers ( $p < 0.001$ ), the risk furthermore correlates with the pack years and affects both sexes equally [32].

AML is not infrequently associated with myelodysplastic syndromes (MDS), such as a history of MDS or MDS-typical morphology or typical cytogenetics [86]. In particular, patients in the genetically defined subgroups with chromatin spliceosome mutations are more likely to have a history of MDS or typical morphological changes [70].

Age-associated clonal hematopoiesis of indeterminate potential (ARCH/clonal hematopoiesis of indeterminate potential, CHIP) is a risk factor for the development of AML. Mutations in the following genes were found more frequently in CHIP carriers who later developed AML than in CHIP carriers who did not develop AML: DNMT3A, TET2, SRSF2, ASXL1, TP53, U2AF1, JAK2, RUNX1, and IDH2 [1]. Similarly, a higher variant allele frequency and a higher number of CHIP mutations are associated with a higher risk of developing AML. Depending on the constellation, the 10-year AML risk increases 2-12.5-fold [1]. In case of familial clustering of myeloid neoplasms, suggestive cytogenetic findings or mutations of suggestive genes (e.g. CEBPA or RUNX1), a familial germline mutation should be evaluated as a cause of AML [22].

### **3 Prevention and early detection**

There is no evidence for effective prevention and early detection measures.

## **4 Clinical picture**

### **4.1 Symptoms**

The clinical presentation of AML is determined by progressive hematopoietic insufficiency due to blastic bone marrow infiltration and by nonspecific general symptoms.

Often, the symptoms are initially nonspecific and later prove to be expressions of anemia (fatigue, decreased performance, pallor, etc.), neutropenia (especially bacterial infections of the lungs, pharynx, and skin, as well as systemic mycoses), and thrombocytopenia (petechiae, ecchymoses, menorrhagia, or epistaxis). However, an increased bleeding tendency is also possible due to disseminated intravascular coagulation and hyperfibrinolysis. In the blood, leukocytosis is found in about 60% of patients, and leukemic blasts are found regardless of the leukocyte count. If the leukocytosis exceeds a value of about 100,000/ $\mu$ l, there is a risk of leukostasis with hypoxia, pulmonary shadowing, retinal hemorrhage and neurological symptoms. Leukostasis represents a hematologic emergency and requires rapid lowering of the peripheral leukocyte count by chemotherapy and, in exceptional cases, by the combination of chemotherapy and leukapheresis. Less frequently, aleukemic courses with normal or even decreased leukocyte counts are observed. These are frequently found in secondary or therapy-associated AML and in older patients. In myelomonocytic/monoblastic differentiated AML, extramedullary manifestations such as skin infiltrates, meningeosis leukaemica, gingival hyperplasia and infiltration of spleen and liver are observed with above-average frequency.

## **5 Diagnosis**

### **5.2 Diagnosis**

#### **5.2.1 Initial diagnosis**

Disease-defining is a blast percentage of >20% in peripheral blood or bone marrow or other tissues (myelosarcoma), or detection of the AML-defining genetic aberrations t(8;21)(q22;q22.1) RUNX1-RUNX1T1, inv(16)/t(16;16)(p13.1;q22) CBFB-MYH11 or t(15;17)(q22;q12) PML-RARA,

see WHO classification [4]. Investigations to confirm the diagnosis as well as complementary investigations to assess health status and to plan therapy are summarized in Table 1.

**Table 1: Diagnostic tests for suspected acute myeloid leukemia**

| Aim                                 | Diagnostics   |
|-------------------------------------|---|
| Confirmation of diagnosis           | <p>Medical history and physical examination findings<br/> Blood count and differential blood count<br/> Bone marrow cytology and cytochemistry<br/> Bone marrow biopsy (mandatory in case of punctio sicca)<br/> Immunophenotyping (including CD33 on blasts, CD4, CD56, CD123 and TCL1 for differentiation of a BPDCN; MPO on lineage affiliation)<br/> Cytogenetics<br/> FISH; if cytogenetic analysis is unsuccessful: Detection of translocations such as RUNX1-RUNX1T1, CBFB-MYH11, KMT2A (MLL), and EVI1; or loss of chromosome 5q, 7q, or 17p.<br/> Molecular genetics (at least the following mutations)</p> <ul style="list-style-type: none"> <li>• NPM1</li> <li>• CEBPA</li> <li>• RUNX1</li> <li>• FLT3 (internal tandem duplications (ITD), mutant-wild type quotient)</li> <li>• FLT3 TKD (codon D835 and I836)</li> <li>• IDH1</li> <li>• IDH2</li> <li>• TP53</li> <li>• ASXL1</li> </ul> <p>Molecular genetics (translocations)</p> <ul style="list-style-type: none"> <li>• PML-RARA</li> <li>• CBFB-MYH11</li> <li>• RUNX1-RUNX1T1</li> <li>• BCR-ABL1</li> <li>• KMT2A (MLL) fusions</li> <li>• DEK-NUP214</li> <li>• GATA2 MECOM</li> <li>• RBM15-MKL1</li> </ul> |
| Ergänzende Untersuchungen/Maßnahmen | <p>Supplementary examinations/measures General condition (ECOG/WHO score)<br/> Evaluation of comorbidities (e.g. HCT-CI Score)<br/> Clinical chemistry, coagulation, urinalysis<br/> Pregnancy test<br/> Gene panel sequencing (in case of clinical consequences)<br/> HLA typing (if necessary also of siblings, parents, children) + CMV status (in patients suitable for allogeneic stem cell transplantation)<br/> Hepatitis and HIV serology<br/> Chest X-ray<br/> ECG<br/> Echocardiography, lung function</p>  |

### 5.2.2 Disease progression

The following remission criteria apply:

#### **Complete remission**

##### **Morphological complete remission (CR)**

- Blasts in bone marrow <5%
- Absence of Auer rods and extramedullary manifestations.
- Neutrophils  $\geq 1000/\mu\text{l}$  and platelets  $\geq 100,000/\mu\text{l}$
- No blasts in peripheral blood

##### **Morphologic complete remission with incomplete hematologic regeneration (CRi)**

- Blasts in bone marrow <5%
- Absence of Auer rods and extramedullary manifestations.



- Only one of the following parameters present: neutrophils  $\geq 1000/\mu\text{l}$  or platelets  $\geq 100,000/\mu\text{l}$
- No blasts in the peripheral blood

### **Cytogenetic complete remission (CRc)**

- CR with absence of cytogenetic change detectable at initial diagnosis.

### **Molecular complete remission (CRm)**

- CR with absence of molecular change detectable at initial diagnosis

### **Complete remission with partial hematologic regeneration (CRh)**

- Blasts in bone marrow  $< 5\%$
- Absence of Auer rods and extramedullary manifestations
- Neutrophils  $\geq 500/\mu\text{l}$  and platelets  $\geq 50,000/\mu\text{l}$
- No blasts in the peripheral blood

This remission category describes a state of morphologic leukemia freedom without adequate blood count regeneration, filling a gap between morphologic leukemia free state (MLFS) and CR with incomplete regeneration of neutrophils or platelets (CRi). The CRh category recognizes that, in the presence of adequate response, prognosis may be favorably influenced by continuation of therapy before full CR is achieved rather than by regeneration-related delay [8].

### **Morphologically leukemia-free state (MLFS)**

- Blasts in bone marrow  $< 5\%$ .
- Absence of Auer rods and extramedullary manifestations
- no blasts in peripheral blood
- neutrophils  $< 500/\mu\text{l}$  AND platelets  $< 50,000/\mu\text{l}$

Retrospective analyses suggest a different prognostic value of the different CR qualities. Accordingly, CRi/CRp/CRh are all associated with a worse prognosis than CR/CRc/m, whereas MLFS only indicates a response to prior chemotherapy.

### **Partial remission (PR)**

- Reduction of blasts in bone marrow to 5-25% AND decrease of blasts by at least 50% compared to diagnosis time point.
- Neutrophils  $\geq 1000/\mu\text{l}$  and platelets  $\geq 100,000/\mu\text{l}$ .
- No blasts in peripheral blood

### **Relapse after CR**

- Increase in bone marrow blasts to  $\geq 5\%$  or peripheral blood blasts not explainable by reactive hematopoietic regeneration or
- extramedullary AML manifestation.

## 5.3 Classification

### 5.3.1 Overview

The improved understanding of the molecular pathogenesis of AML is reflected in the current WHO classification, which includes several balanced translocations or inversions as separate entities [t(15;17), t(8;21), inv(16), t(9;11), inv(3)/t(3;3), t(6;9), t(1;22)] as well as two molecularly defined entities (AML with NPM1 mutation and AML with CEBPA double mutation) and one provisional molecularly defined entity (RUNX1 mutation). Another subgroup of AML is defined by genetic alterations. This is AML with myelodysplasia-associated cytogenetic alterations, which includes a whole range of unbalanced and balanced aberrations (see 5.3.1). Overall, based on this classification, well over 50% of patients with AML are now classifiable by cytogenetic and molecular genetic characteristics. Thus, the new classification offers a significant advance in objectivity and reproducibility compared to the previously used, predominantly morphological criteria of the FAB classification [4], see [Table 2](#).

### 5.3.2 AML with Myelodysplasia Related Changes (MRC)

The reason for the creation of this WHO subgroup was the different prognosis from other AMLs, which could be explained by the biological proximity to AMLs from pre-existing MDS. The diagnostic criteria of this subgroup are complex and have been without immediate therapeutic consequence until recently. However, when approving CPX-351, the FDA and EMA linked the indication area for the compound to the presence of AML MRC according to WHO in order to assign the heterogeneous patient population of the pivotal study to a standardized diagnostic group. Thus, the knowledge of the MRC subgroup after approval of CPX-351 by the EMA has immediate therapeutic consequences, as corresponding patients can be treated with the substance.

An AML-MRC according to WHO is defined as  $\geq 20\%$  myeloblasts in bone marrow (BM) BM or PB, if at least one of the following criteria is fulfilled:

- History of MDS or MDS/MPN.
- Myelodysplasia-associated cytogenetic alterations (see below).
- Multilineage dysplasia in BM at initial AML diagnosis ( $\geq 50\%$  dysplasia in  $\geq 2$  hematopoietic lineages) in the absence of genetic markers from the WHO entity "Acute Myeloid Leukemia with recurrent genetic aberrations".

The following cytogenetic alterations are considered myelodysplasia-associated according to WHO:

- Complex karyotype (defined as 3 or more chromosomal aberrations without concomitant presence of any of the genetic markers from the WHO entity "Acute Myeloid Leukemia with recurrent genetic aberrations").
- Unbalanced aberrations: -7 or del(7q); -5 or del(5q); i(17q) or t(17p); -13 or del(13q); del(11q); del(12p) or t(12p); idic(X)(q13)
- Balanced aberrations: t(11;16) (q23.3;p13.3); t(3;21)(q26.2;q22.1); t(1;3) (p36.3;q21.2); t(2;11)(p21;q23.3); t(5;12) (q32;p13.2); t(5;7)(q32;q11.2); t(5;17) (q32;p13.2); t(5;10) (q32;q21.2); t(3;5) (q25.3;q35.1)

### **5.3.3 Therapy-related myeloid neoplasia (tAML)**

The WHO defines any myeloid neoplasia that has occurred after previous cytotoxic therapy as therapy-associated [4]. There are no restrictions on agents used or radiation modalities and doses, and no definition for the timing of AML to past therapy. The distinction between "alkylating agent related" and "topoisomerase II-inhibitor related" was already omitted in the WHO-2008 classification. Like AML-MRC, the subgroup of tAML has a therapeutic implication by definition in the FDA and EMA approval of CPX-351.

In addition, numerous patients with tAML have been shown to have germline alterations associated with the development of malignancies. Therefore, a detailed family history is particularly important in these patients.

**Table 2: WHO classification of AML [4]**

| Subgruppe  | Spezifikation  |
|--|--|
| Acute Myeloid Leukemia with recurrent genetic aberrations  | AML with t(8;21)(q22;q22); RUNX1-RUNX1T1   |
|  | AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11                          |
|  | APL with t(15;17)(q22;q12); PML-RARA   |
|  | AML with t(9;11)(p22;q23); MLLT3-KMT2A   |
|  | AML with t(6;9)(p23;q34); DEK-NUP214   |
|  | AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); GATA2, MECOM                           |
|  | AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1                               |
|  | Provisional entity: AML with BCR-ABL1  |
|  | AML with mutated NPM1  |
|  | AML with biallelic mutations of CEBPA  |
|  | Provisional entity: AML with mutated RUNX1   |
| Acute myeloid leukemia with myelodysplasia-related changes | see Chapter 5.3.1.   |
| Therapy-related myeloid neoplasms                          | see Chapter 5.3.2.   |
| Acute myeloid leukemia, not otherwise specified (NOS)      | Acute myeloid leukemia with minimal differentiation                                    |
|  | Acute myeloid leukemia without maturation  |
|  | Acute myeloid leukemia with maturation   |
|  | Acute myelomonocytic leukemia  |
|  | Acute monoblastic/monocytic leukemia   |
|  | Pure erythroid leukemia  |
|  | Erythroleukemia, erythroid/myeloid   |
|  | Acute megakaryoblastic leukemia  |
|  | Acute basophilic leukemia  |
|  | Acute panmyelosis with myelofibrosis (syn.: acute myelofibrosis; acute myelosclerosis) |
| Myeloid sarcoma  |  |
| Blastic plasmacytoid dendritic neoplasm                    |  |
| Myeloid proliferations related to Down-syndrome            | Myeloid leukemia associated with Down syndrome   |
|  | Transient abnormal myelopoiesis (syn.: transient myeloproliferative disorder)          |
| Acute leukemias of ambiguous lineage                       | Acute undifferentiated leukemia  |
|  | Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL1                       |
|  | Mixed phenotype acute leukemia with t(v;11q23); MLL rearranged/KMT2A                   |
|  | Mixed phenotype acute leukemia, B/myeloid, NOS   |
|  | Mixed phenotype acute leukemia, T/myeloid, NOS   |

## 5.4 Prognostic factors

Age and molecular or cytogenetic changes have the strongest influence on prognosis. With increasing age, the chance of achieving a complete remission decreases, while at the same time the risk of recurrence increases. In the Swedish registry (first diagnosis date from 1997 to 2006), 5-year survival rates were 60% in patients younger than 30 years, 43% in patients 45-54 years, 23% between 55-64 years, and decreased further at older ages [29]. The molecular cytogenetic alterations at initial diagnosis are classified into three groups according to the 2017 ELN classification [22], see Table 3. However, the prognostic value of the FLT3-ITD mutant-wild-type ratio is controversial, especially since FLT3 inhibitors have become therapeutically available, see Chapter 6. 1. 1. 1. 2. 1. In contrast to the ELN risk groups, unfavorable genetic alterations are grouped as unfavorable in the presence of a concomitant NPM1 mutation [2].

**Table 3: Molecular cytogenetic risk groups according to the European LeukemiaNet ELN classification [27]**

| ELN Risk Group | Aberrations   |
|----------------|---|
| Favorable      | t(8;21)(q22;q22); <i>RUNX1-RUNX1T1</i><br>inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i><br>Mutated <i>NPM1</i> without <i>FLT3</i> -ITD or without <i>FLT3</i> -ITD <sup>low*</sup><br>Biallelic mutation in <i>CEBPA</i>  |
| Intermediate   | Mutated <i>NPM1</i> with <i>FLT3</i> -ITD <sup>high*</sup><br>Wildtype <i>NPM1</i> without <i>FLT3</i> -ITD or with <i>FLT3</i> -ITD <sup>low*</sup> (without unfavorable genetic aberrations)<br>t(9;11)(p22;q23); <i>MLL3-KMT2A</i> <sup>§</sup><br>Cytogenetic aberrations that were not classified as favorable or unfavorable  |
| Unfavorable    | t(6;9)(p23;q34); <i>DEK-NUP214</i><br>t(v;11)(v;q23); <i>KMT2A</i> -gene rearrangement<br>t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i><br>inv(3)(q21q26.2) or t(3;3)(q21;q26.2); <i>GATA2, MECOM (EVI1)</i><br>-5 or del(5q); -7; -17/abn(17p)<br>Complex karyotype (≥3 Aberrations <sup>†</sup> )<br>Monosomal karyotype (one monosomy associated with at least one other monosomy or other structural chromosomal aberration (other than CBF-AML))<br>Wildtype <i>NPM1</i> with <i>FLT3</i> -ITD <sup>high*</sup><br>Mutated <i>RUNX1</i> <sup>‡</sup><br>Mutated <i>ASXL1</i> <sup>‡</sup><br>Mutated <i>TP53</i> |

Legend:

\* *FLT3*-ITD<sup>low</sup> = mutant-wild-type allele quotient <0.5; *FLT3*-ITD<sup>high</sup> = mutant-wild-type allele quotient ≥0.5. Determined via semi-quantitative measurement of *FLT3*-ITD allele quotient by DNA fragment analysis as the quotient of the AUC for *FLT3*-ITD divided by the AUC for *FLT3*-wild-type.

§ in the presence of rarer aberrations classified as unfavorable, the t(9;11) "overrules," i.e., it tips the scales for classification in the intermediate risk group

† only applicable if one of the WHO-defined AML-typical aberrations is not simultaneously present (i.e., t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*).

‡ to be classified as unfavorable only in the absence of aberrations classified as favorable, i.e., in the presence of favorable alterations, these tip the scales in favorable risk group classification.

Other risk factors are a high LDH and leukocyte count at initial diagnosis.

Acute promyelocytic leukemia (APL) has a special position and needs to be distinguished from all other non-APL AMLs. Its prognosis is the best among all AML diseases, with a long-term survival rate of over 80% if the acute initial coagulation derailment and resulting life-threatening complications can be effectively controlled. For diagnosis and treatment of APL, please refer to the [Onkopedia Acute Promyelocytic Leukemia](#) (German guideline). To be distinguished from AML is Blastic Plasmacytoid Dendritic Cell Neoplasia, which is different in terms of prognosis and therapy, see [Onkopedia BPDCN](#) (German guideline).

## 5.5 Differential diagnosis

By combining morphology, cytochemistry, immunophenotyping, cyto- and molecular genetics, the diagnosis of "acute myeloid leukemia" can usually be made without doubt. Table 4 shows some possible differential diagnoses and the corresponding diagnostic procedures.

**Table 4: Differential diagnosis of suspected acute myeloid leukemia**

| Disease   | Investigations   |
|---|--|
| Acute lymphoblastic leukemia                            | Bone marrow cytochemistry (peroxidase or esterase positivity)<br>Immunophenotyping<br>Cyto- and molecular genetics   |
| Acute leukemia of unclear lineage                       | Bone marrow cytochemistry (pox or esterase positivity)<br>Immunophenotyping<br>Cyto- and molecular genetics  |
| viral infections (e.g. parvovirus B19, EBV, CMV or HIV) | virus detection (PCR, Ag or serological)<br><br>Absence of blast detection in PB or BM immunophenotyping   |
| Myelodysplastic syndromes                               | < 20% blasts in bone marrow and/or peripheral blood.<br>Cyto- and molecular genetics   |
| Vitamin B12/folic acid deficiency                       | history<br>Vitamin B12 and folic acid levels<br>BM morphology (megaloblasts)   |
| Aplastic anemia   | BM morphology (aplasia)<br>Cytogenetics  |
| Leukemic lymphoma                                       | absent detection of myeloid blasts in PB or BM<br>Immunophenotyping<br>soluble interleukin-2 receptor, if applicable   |
| Myeloproliferative syndromes                            | < 20% blasts in BM (exception: blast crisis of CML)<br>often no anemia or thrombocytopenia<br>Cytogenetics (t(9;22))<br>Molecular genetics (BCR-ABL, JAK2 mutation, CALR mutation, MPL mutation) |

## 6 Therapy

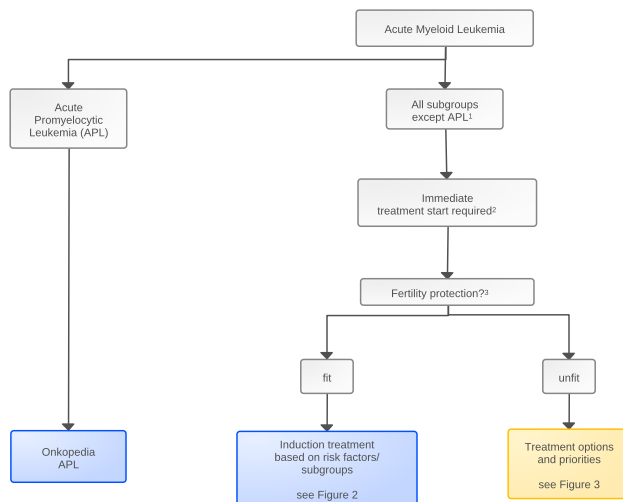
### 6.1 Therapy structure

Therapy of AML should be performed at a hematologic oncology center and in the context of a clinical trial. Since the 1980s, several AML study groups and multicenter studies have been formed in Germany: AML-CG ([https://www.kompetenznetz-leukaemie.de/content/studien/studiengruppen/amlcg\\_muenchen/kontakt/](https://www.kompetenznetz-leukaemie.de/content/studien/studiengruppen/amlcg_muenchen/kontakt/)), AMLSG (<https://www.amlsg.de/>), OSHO (<https://osho-studiengruppe.de/>), SAL (<https://www.sal-aml.org/>).

For centers not integrated in an AML study group, therapy following a valid study protocol is recommended.

Immediately upon initial diagnosis, a decision must be made regarding the urgency of initiating therapy, see Figure 1.

**Figure 1: Algorithm for the initiation of therapy**



Legend:

■ - curative therapy intention; ■ non-curative treatment intention ;

1 APL - Acute Promyelocytic Leukemia

2 Leukostasis or tumor lysis syndrome or derailed coagulation.

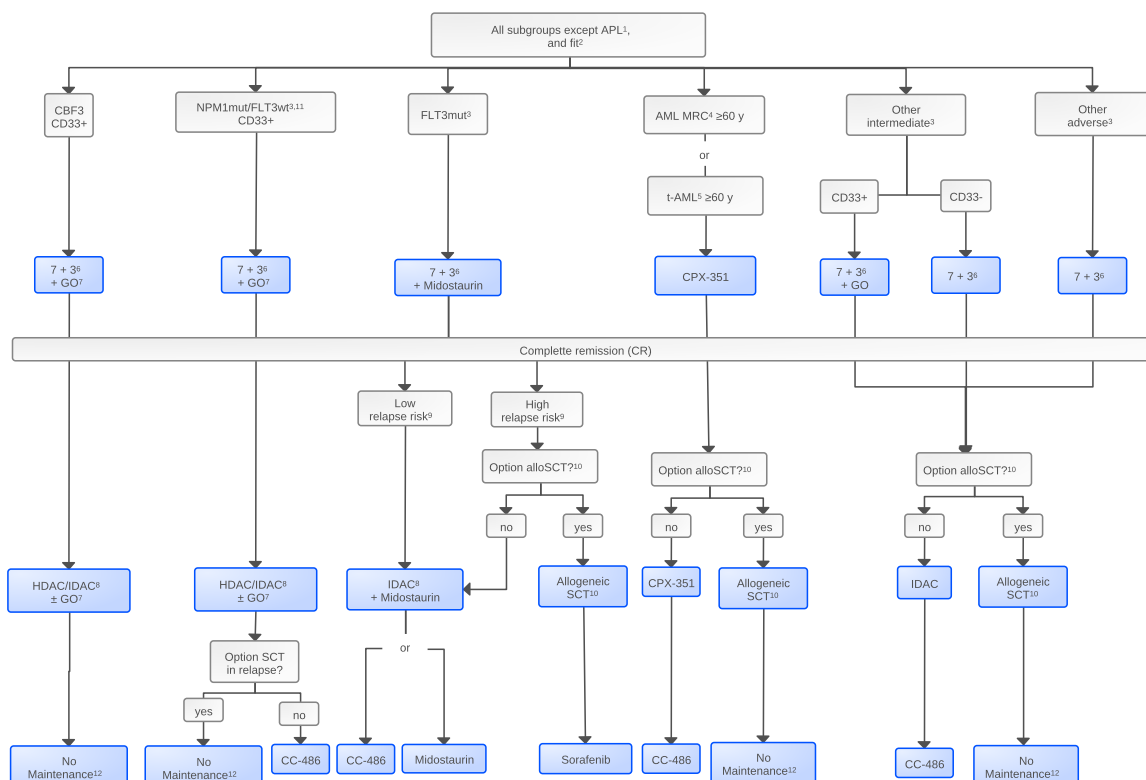
3 [https://www.dgho.de/publikationen/schriftenreihen/fertilitaetserhalt/dgho\\_gpsr\\_xi\\_de\\_0971\\_web](https://www.dgho.de/publikationen/schriftenreihen/fertilitaetserhalt/dgho_gpsr_xi_de_0971_web)

4 Based on ECOG status and comorbidity

In case of suggestive morphologic findings or cytogenetic (t(15;17)) or molecular biological (PML-RARA) evidence of acute promyelocytic leukemia (APL, FAB M3), therapy with all-trans retinoic acid (ATRA) must be initiated immediately, followed by APL-specific cytostatic therapy, see [Onkopedia guidelines on Acute Promyelocytic Leukemia](#). (in German)

Since comprehensive diagnostics including genetic analysis form the basis of modern subgroup-specific therapy, initiation of therapy is not advised until these data are obtained [67], see [Figure 2](#). An immediate start of intensive therapy should be made in patients with signs of leukostasis syndrome with or without hyperleukocytosis and/or tumor lysis syndrome or derailed coagulation.

**Figure 2: Therapy - Algorithm for the initial decision at first diagnosis.**



**Legend:**

  curative intent;

1 APL - Acute Promyelocytic Leukemia excluded.

2 fit for intensive therapy, based on ECOG status and comorbidity.

3 see Table 3 [27]

4 AML MRC - AML with myelodysplastic changes (Myelodysplasia - Related Changes), incl. MDS in history.

5 t-AML - therapy-associated AML

6 7+3 - therapy regimen with Ara-C on 7 days, daunorubicin on 3 days

7 GO - gemtuzumab ozogamicin

8 7+3 - HDAC - high-dose Ara-C; IDAC - intermediate-dose Ara-C;

9 Low risk of recurrence: FLT3-ITDlow + NPM1mut without relevant MRD (measurable residual disease) or FLT3-TKD + NPM1mut without relevant MRD. High risk of recurrence: FLT3-ITDlow+NPM1mut with relevant MRD or FLT3-TKD+NPM1mut with relevant MRD or FLT3-ITDhigh+NPM1mut or FLT3-ITD+NPM1wt or FLT3-TKD+NPM1wt.

10 allo SCT - allogeneic stem cell transplantation

11 This recommendation includes biallelic CEBPA mutated patients.

12 MRD monitoring if possible

In general, intensive curative intentional therapy of AML is divided into induction therapy with the goal of complete remission (CR) and post-remission therapy to maintain CR. The chance of achieving CR after intensive induction therapy is mainly determined by the genetic background of AML and to a smaller degree by patient age [71]. CR rates are >80-90% in patients with favorable cyto- or molecular genetic aberration (including t(8;21), in(16), NPM1-mut, CEBPAdm) versus <30% in patients with unfavorable aberrations (including TP53 mutation, monosomal karyotype). Therefore, cyto- and molecular genetic findings are indispensable in the selection of initial therapy.

The use of new therapeutics can increase the CR rate in some cases even in patients who are not suitable for intensive chemotherapy.

In general, the results of randomized trials of midostaurin, gemtuzumab ozogamicin and CPX-351 show a significant improvement in prognosis in certain patient groups. Since these agents are generally used immediately at the beginning of the standard induction therapy (midostaurin from day 8, GO from day 1) or CPX-351 is used instead of the standard induction with DA/7+3, a diagnostic assignment to the relevant subgroups is necessary before the start of induction therapy in view of the therapeutic advantage for the patients concerned. Specifically, this means that for correct assignment, the result of the genetic analyses in combination



with the phenotypic and morphological findings must be awaited to enable the important assignment to the most appropriate therapeutic subgroup. The flow cytometric CD33 determination is available within a few hours; the findings on fusion transcripts as well as gene mutations are available within a few days (by means of molecular biological methods and/or FISH), whereas the classical cytogenetic chromosome analysis usually requires at least one week of processing time.

Treatment decisions based on the specific diagnosis represent a therapeutic paradigm shift, since until now the immediate induction initiation at diagnosis was the therapeutic standard [75]. Meanwhile, results of two retrospective analyses show that prognosis in clinically stable situations is not associated with the time between diagnosis and initiation of therapy [7, 67].

Patients with signs of leukostasis syndrome with or without hyperleukocytosis and/or tumor lysis syndrome or derailed coagulation are excluded from such a recommendation. In the presence of this constellation, there is an immediate need for treatment at diagnosis, since the life-threatening conditions mentioned are caused by AML and immediate cytostatic therapy is therefore indicated. Therapy then consists of administration of hydroxyurea and, if necessary, cytarabine if symptom control cannot be achieved. It should be noted that effective therapy of hyperleukocytosis ( $>50\text{-}100 \times 10^9/\text{L}$ ) may require a dosage of hydroxyurea of 4-5 g per day. Cytarabine may be administered as a pre-phase or as part of a 7+3 regimen. Anthracyclines should not be started until the leukocyte count has dropped below 30 Gpt/l to avoid adversely affecting the rheologic properties of the blood [48]

If waiting for results was planned initially based on a clinically stable situation and the patient develops the above-mentioned life-threatening clinical symptoms before receipt of the findings, intensive therapy should be determined on the basis of the findings available to date and started immediately.

Another special constellation at initial diagnosis is the suspected presence of acute promyelocytic leukemia (APL, FAB M3) with suggestive morphology and/or signs of coagulation activation. Already in case of clinical suspicion, therapy with all-trans retinoic acid should be started before confirmation of a corresponding genetic alteration (t(15;17)/PML-RARA) and, if necessary, stopped again after exclusion of APL. For further therapy of a confirmed APL, see [Onkopedia Acute Promyelocytic Leukemia](#) (German guideline).

Elderly patients with a biological age beyond 75 years and/or with significant comorbidities should not be offered intensive curative therapy in view of high toxicity and early mortality with a chance of only about 10% of long-term remission [38]. The goal of therapy is to prolong life with as good a quality of life as possible. The basis for this is supportive therapy (Best Supportive Care, BSC) with the addition of potentially life-prolonging cytostatic treatment, see Chapter 6.1. 1. 3.

### **6.1.1 First-line therapy**

#### **6.1.1.1 Intensively treatable patients with curative therapy intention ("fit")**

Patients with a biological age up to 75 years and no or few comorbidities are assigned to this group.

Depending on the urgency of the therapy, the possibility of fertility-preserving measures should be considered for young patients who wish to have children or have not yet completed their family planning.

### 6.1.1.1.1 Induction therapy

#### 6.1.1.1.1.1 7+3

This therapy is used for patients who cannot be assigned to any of the following subgroups or who have an immediate indication for therapy at initial diagnosis and the results of genetic diagnostics are not yet available.

Standard induction therapy (3+7 regimen) includes the combination of 3 days of anthracycline/anthracenedione (e.g. daunorubicin 60 mg/m<sup>2</sup>, idarubicin 10-12 mg/m<sup>2</sup>, or mitoxantrone 10-12 mg/m<sup>2</sup>) and 7 days of cytarabine (100-200 mg/m<sup>2</sup> continuous).

An alternative induction regimen is recommended when classified into the following subgroups:

- Patients with CD33-positive core-binding factor AML (CBF-AML), patients with CD33-positive NPM1 mutation in FLT3wt and with CD33-positive AML and biallelic CEBPA mutation.
- Patients with FLT3 mutation
- Patients with AML-MRC and patients with therapy-associated AML (tAML) and FLT3wt
- Patients with CD33-positive intermediate-risk AML and FLT3wt.

#### 6.1.1.1.1.2 Patients with CD33-positive core-binding factor AML (CBF-AML), patients with CD33-positive NPM1 mutation and FLT3wt and patients with CD33-positive AML and biallelic CEBPA mutation

For patients in this subgroup, the addition of gemtuzumab ozogamicin (GO) to the first cycle of standard 7+3 induction therapy is recommended. Gemtuzumab ozogamicin (GO), a conjugate of CD33 antibody and cytotoxin calicheamicin, was approved by the EMA in 2018 for first-line therapy in combination with standard chemotherapy based on the published trial results of the French ALFA-0701 trial and other randomized trials and their meta-analysis [35, 50]. CD33 positivity is a prerequisite for the use of this agent. Meta-analysis of randomized intervention trials indicates a significant advantage in overall survival for the patient group of CBF-AMLs by adding GO to standard induction with DA (HR 0.5; 5-year survival 77.5% versus 55%) [35]. The advantage does not appear to arise from an increase in CR rates [35, 73], but rather from a greater reduction in leukemic burden in CR patients (deeper remission of CR or higher remission quality) and a resulting reduced risk of recurrence [49].

In the randomized AMLSG 09-09 trial, this was also shown for NPM1-mutated patients. CR rates were similar with and without GO, but recurrence-free survival was significantly and clinically relevantly prolonged in patients in CR, based on a greater reduction in MRD by GO [40]. In patients aged >70 years, the rate of induction death was increased, and therefore the primary endpoint EFS was not improved by GO. The cause of the increased early mortality is most likely increased toxicity of the combination due to the addition of etoposide to 7+3/DA. In the ALFA-0701 trial, early mortality was not significantly different, but the upper patient age was limited to 70 years.

Based on review of the data, GO is recommended in NPM1-positive AML due to its clear antileukemic effect; potential use in patients over 70 years of age should be weighed up against possible toxicity.

The majority of patients for the abovementioned meta-analysis were from the MRC/NCRI AML15 and AML16 trials and received GO at a dose of 3 mg/m<sup>2</sup> as a single dose. Based on the greater effect size for recurrence risk, EFS/RFS, and OS in the three-dose administration in the ALFA trial, as well as the greater MRD reductions demonstrated by GO in the ALFA and AMLSG trials, the three-dose administration is recommended in accordance with the approval. According to

the label, GO should only be administered in the first, not in a possible second induction therapy. The value of GO during consolidation therapy is less clearly established [11], but within the scope of the marketing authorization its use is possible.

#### 6.1.1.1.1.3 Patients with FLT3 mutation

Patients with FLT3-ITD or FLT3-TKD mutation should receive midostaurin from day 8-21 of induction therapy. According to data from a randomized placebo-controlled trial, midostaurin in combination with standard chemotherapy can significantly prolong both EFS, RFS, and OS in FLT3-mutated AML patients up to 60 years of age [80]. Based on this study, midostaurin was approved by the EMA in 2017 for combination with standard induction chemotherapy, chemoconsolidation, and as maintenance therapy for twelve 28-day cycles in patients with newly diagnosed FLT3-mutated AML, see Drug Evaluation Midostaurin.

Deviating from the study population (age 18-59 years), approval was granted without an upper age restriction. Data for patients aged 60-70 years are available from a phase II study [74]. In patients for whom hematopoietic stem cell transplantation is planned, midostaurin should be discontinued 48 hours prior to conditioning therapy. When used concomitantly with strong inhibitors of CYP3A4 (e.g., ketoconazole, posaconazole, voriconazole, ritonavir, or clarithromycin), increased attention should be paid to toxicities, especially in patients aged >60 years, because of the risk of midostaurin level elevations [74]. Strong CYP3A4 inducers (e.g., carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's wort) should not be given concomitantly because of the decrease in levels of midostaurin.

#### 6.1.1.1.1.4 Patients with AML-MRC and patients with therapy-associated AML (tAML)

For this subgroup, the use of CPX-351 (a liposomal formulation of cytarabine and daunorubicin in fixed molar ratio) is approved as a replacement for the classic combination of cytarabine and anthracycline in induction therapy. Approval was based on a significant survival benefit of 9.6 months versus 5.9 months at 7+3 in the pivotal randomized trial (HR 0.69) [51]. Included patients were aged 60 - 75 and belonged to the following different subgroups.

- Prior MDS (47%) or CMML (7.5%).
- de novo AML with MDS karyotype (25%)
- tAML (20%)

In deviation from the study population, approval was granted for patients with AML-MRC (including patients with multilineal dysplasia) and tAML and for all ages  $\geq 18$  years. Due to the lack of evidence for younger patient groups and in light of retrospective real-world data including younger patients showing no superiority of CPX-351-based induction over standard intensive chemotherapy, its use is recommended only in patients aged 60 years and older [6, 14].

It should be noted that the liposomal formulation is associated with higher bone marrow toxicity, manifested by an approximately 7-day prolonged posttherapeutic cytopenic phase. This did not result in an increase in infectious complications, but in 15% more bleeding events in the CPX-351 arm. Among the study patients, the survival benefit from the use of CPX-351 was greatest in those with consolidating allogeneic stem cell transplantation [51], see Chapter 6.1.1.1.

#### 6.1.1.1.1.5 Patients with CD33-positive intermediate-risk AML and FLT3wt

For patients with intermediate cytogenetic risk, the meta-analysis on the effect of GO in combination with standard chemotherapy also demonstrated a survival benefit, with NPM1 mutated patients included in the intermediate risk group. The CR rate was not significantly increased by GO (OR 0.91), but overall survival was prolonged; the corresponding hazard ratio was 0.85. The corresponding 15% risk reduction or increase in 5-year survival from 35.5% to 40.7% is thus

significantly lower than for patients with a favorable genetic constellation (see above). In the overall view of the data, GO is therefore recommended as optional in this patient group.

#### 6.1.1.1.1.6 Patients not assigned to the above subgroups

Patients who cannot be assigned to any of the above subgroups according to the available specific diagnostics or for whom an immediate start of therapy is necessary at initial diagnosis before the results of the genetic diagnostics are available, will receive the standard induction therapy with 7+3.

Patients who do not respond to one or two cycles of induction therapy are considered primary refractory and are further treated with salvage chemotherapy, see Chapter 6. 1. 2.

#### 6.1.1.1.2 Post-remission therapy

Patients who achieve CR require consolidation therapy, otherwise a rapid relapse of AML is to be expected. Consolidation therapy can generally be performed with higher-dose cytarabine or allogeneic hematopoietic stem cell transplantation. The choice of consolidation therapy is based on the risk profile or the corresponding subgroup of AML and the general condition of the patient.

High-dose cytarabine (HDAC) is associated with a significantly prolonged RFS compared with intermediate-dose cytarabine (IDAC) in the group of CBF-AMLs, whereas it does not confer an RFS advantage over IDAC in intermediate and unfavorable cytogenetic risk and generally makes no difference in OS [55].

High-dose myeloablative chemotherapy with autologous transplantation has a similarly low treatment-associated mortality as higher-dose cytarabine and is occasionally used as an alternative consolidation option. However, the risk of recurrence is significantly increased compared with allogeneic transplantation, and superiority in overall survival compared with higher-dose cytarabine has not yet been demonstrated. However, this therapeutic principle seems to be of value especially in low-risk patients (CEBPAdm, CBF-AML) [72].

##### 6.1.1.1.2.1 Patients with CD33-positive core-binding factor AML (CBF-AML) and patients with CD33-positive NPM1 mutation and FLT3wt

The risk of relapse in these subgroups is comparatively low at 20-40% [15, 70]; therefore, post-remission therapy with high-dose cytarabine results in a relatively high proportion of long-term remissions. Outside of trials, patients with cytogenetically favorable risk, i.e., t(8;21) or inv(16) should therefore receive chemoconsolidation with high-dose cytarabine (HDAC) [46]. This is also true for patients with AML and normal karyotype and NPM1 mutation without concomitant FLT3-ITD mutation [27]. Disease in these patients can be monitored by measuring minimal/measurable residual disease (MRD) using mutant NPM1 [77] and, in the event of molecular relapse or molecular persistence, can be directed to a salvage approach, including allogeneic stem cell transplantation if possible.

A possible standard chemotherapy for younger patients outside of trials is the adapted CALGB protocol [56] with high cytarabine doses of 3 g/m<sup>2</sup> twice daily for 3 days. Since cytarabine is associated with high toxicity in the elderly patient group, intermediate-dose cytarabine is used for better tolerability in elderly patients.

The role of GO in post-remission therapy is unclear, as randomized trials either used GO only in induction or in all patients who received GO during induction; the approval status includes the

administration of GO in two post-remission regimens. Two randomized trials failed to show a benefit of GO in postremission therapy [74].

For patients with FLT3-ITD<sub>low</sub> and NPM1 mutation, the MRD status at the time of first CR after induction therapy can be included in the decision on postremission therapy. The prognostic relevance of NPM1 MRD thresholds of 1-2% has only been demonstrated after the end of consolidation therapy [46, 77]. Application after induction therapy carries the risk of categorizing a higher number of patients as prognostically unfavorable. Since there are no standardized uniform thresholds for the prognostic value of flow cytometric MRD measurement methods and NGS-based approaches, the guideline refers to the local laboratory-based thresholds and their interpretation by the phrase "relevant MRD".

Accordingly, patients without relevant MRD in CR1 may receive cytarabine-based chemoconsolidation with midostaurin after intensive induction therapy, whereas allogeneic hematopoietic stem cell transplantation should be pursued for patients with relevant MRD.

Due to lack of efficacy data and low risk of relapse in CBF AMLs, maintenance therapy with oral azacitidine (CC-486) is not recommended in this patient population.

In NPM1-mutated AML, maintenance therapy with oral azacitidine (CC-486) is effective and resulted in a prolongation of median overall survival from 26.2 to 48.6 months in MRD-negative patients and from 10.3 to 39.4 months in MRD-positive patients according to subgroup analyses of the pivotal study [29]. Based on these data, maintenance therapy with oral azacitidine is recommended for patients who are already unsuitable for allogeneic transplantation in primary therapy or who would refuse it even in relapse. All remaining patients with NPM1-mutated AML and the option of allogeneic SCT in relapse should receive close NPM1 monitoring in lieu of CC-486 maintenance in order to promptly receive allogeneic SCT in the event of molecular relapse [5].

#### 6.1.1.1.2.2 Patients with FLT3 mutation - consolidation

For patients with FLT3-ITD or FLT3-TKD mutation and cytarabine-based chemoconsolidation, they should receive midostaurin from day 8-21 of consolidation therapy if midostaurin was used in induction.

Two approved options are available for maintenance therapy after completion of chemoconsolidation: Midostaurin and oral azacitidine (CC-486). In the pivotal trial for midostaurin, midostaurin maintenance was only used in patients who had already received midostaurin in induction and consolidation, i.e., they were not re-randomized after completion of chemotherapy. A landmark analysis from the time of maintenance failed to demonstrate a significant effect of midostaurin maintenance on disease-free or overall survival [52]. In the pivotal trial of oral azacitidine, patients were randomized to placebo or oral azacitidine at the start of maintenance therapy. The FLT3-mutated subgroup was small with 63 patients. Maintenance with CC-486 significantly prolonged median relapse-free survival from 4.6 to 23.6 months, whereas median overall survival was non-significantly prolonged from 9.7 to 28.2 months [28]. It is important to note, as a limitation, that the efficacy data for CC-486 were collected in a collective of older patients aged 55 years and older, whereas the midostaurin data were obtained from patients aged 18 to 60 years.

Based on these data, maintenance therapy with oral azacitidine until disease progression, or, in case of intolerability or contraindication, alternatively with midostaurin for 12 cycles of 28 days each, is recommended for patients without the option of transplantation after completion of chemoconsolidation.

For patients with the option of allogeneic transplantation, despite allogeneic stem cell transplantation, the risk of relapse is increased in FLT3-ITD AML. In the randomized placebo-controlled SORMAIN trial, maintenance therapy with sorafenib significantly reduced the risk of relapse or death by 61% and prolonged overall survival (HR 0.52) in FLT3-ITD-positive patients who underwent first CR allogeneic stem cell transplantation [9]. Other publications support the significant antileukemic effect of sorafenib after allogeneic SCT [13, 87].

Although the above data were collected in patients without midostaurin primary therapy/off-label sorafenib maintenance for 2 years, starting between day +60 and +100 after transplantation, is recommended in FLT3-ITD patients after allogeneic SCT. Attention should be paid to toxicities and dose reductions should be made if necessary.

Non-randomized data suggest that other FLT3 inhibitors after allogeneic stem cell transplantation may also favorably affect prognosis.

#### 6.1.1.1.2.3 Patients with AML-MRC and patients with therapy-associated AML (tAML) - consolidation

Patients with AML-MRC have a high risk of relapse, therefore in suitable patients in remission after CPX-351 or 7+3 standard induction and available donor, allogeneic stem cell transplantation is recommended as post-remission therapy. In the absence of a transplant option, CPX-351 is also available for consolidation, but its place in the pivotal trial has not been compared against the usual standard high-dose cytarabine, but against 7+3, which is uncommon in consolidation [51]. For patients without a transplant option, maintenance therapy with oral azacitidine is recommended after chemoconsolidation.

The prognosis of patients with t(AML) depends on the genetic profile, so the best post-remission therapy should be selected according to the grouping in the ELN risk strata.

#### 6.1.1.1.2.4 Patients with intermediate or unfavorable prognosis

Due to the relevant risk of relapse, allogeneic SCT is recommended as post-remission therapy for both subgroups if the patient is suitable and a suitable donor is available [3, 15]. Since transplantation outcomes depend on disease risk, transplantation risk, and concomitant diseases, these patients should be presented early to a transplant center, even with reduced general condition or concomitant diseases, in order to allow shared decision making together with the transplant team.

Even in patients with intermediate cytogenetic risk, allogeneic SCT should be sought outside of studies if an HLA-identical sibling or HLA-identical unrelated donor is available. Alternatively, in fit patients without an HLA-identical donor, allogeneic stem cell transplantation with an HLA-haploidentical familial donor should be considered, see [Onkopedia Allogeneic Stem Cell Transplantation - Indications](#) (German guideline).

In older fit patients without t(8;21) or inv(16) who have achieved CR after induction therapy, allogeneic SCT after dose-reduced conditioning should be pursued whenever possible [59], as long-term remissions of 30% can be achieved in this setting, even in the presence of a mismatch [69]. This also applies to patients who were not suitable for intensive induction at initial diagnosis due to leukemia-related physical impairment and have been successfully treated with hypomethylating agents, low-dose cytarabine and venetoclax and have reached a physical state in remission that allows SCT.

Patients without donors, with significant comorbidities or poor clinical condition should receive chemoconsolidation with 2-3 cycles of intermediate-dose cytarabine when possible [56]. For these patients, maintenance therapy with oral azacitidine is recommended after chemoconsolidation. Data are based on the results of the QUAZAR randomized pivotal trial. Elderly patients



≥55 years of age with intermediate or unfavorable genetic risk with CR/CRi after intensive induction therapy with or without prior consolidation therapy but who were not suitable for allogeneic stem cell transplantation were treated with the oral azacitidine formulation CC-486 versus placebo until disease progression, death, or intolerable toxicity. CC-486 significantly prolonged median overall survival to 24.7 months versus 14.8 months with placebo (HR 0.69;  $p=0.0009$ ) [84]. After 3 years, 37.4% of patients were still alive in the CC-486 arm, compared to 27.9% in the placebo arm [85].

#### **6.1.1.2 Elderly fit patients**

Patients with a biological age above 65 years and no or few comorbidities are assigned to this group. Since both remission rates and long-term remissions decrease with increasing age and the risk of therapy-associated complications increases at the same time [36, 58, 78], chances and risks in this age group must be weighed up particularly thoroughly and discussed with the patient. In this context, an estimation of the individual CR probability and early mortality risk based on scores, e.g., [www.amlcompositemodel.org](http://www.amlcompositemodel.org) [47] and the genetic risk constellation [71], can be helpful. The Multistage Prediction Tool includes genetic information in addition to clinical characteristics in risk prediction and compares outcome with and without allogeneic stem cell transplantation (<https://cancer.sanger.ac.uk/aml-multistage/> ).

To assess the optimal treatment strategy, newly diagnosed AML patients should be presented to an experienced treatment center.

In the following constellation a palliative therapy with cytoreductive outpatient chemotherapy (see Chapter 6. 1. 1. 3) or Best Supportive Care (BSC) should rather be considered, because the expected complications of an intensive therapy exceed a possible benefit:

- biological age >75 years
- comorbidities
  - severe diabetic organ manifestations
  - severe liver or kidney disease
  - congestive heart failure (EF <30%).
- ECOG ≥3
- Low chance of cure, high risk of early mortality under induction.

All remaining patients should be evaluated for intensive curative intentional therapy. Therapy is not fundamentally different from that of younger patients and is described in Chapter 6.1.1.1. Modifications between younger (usually up to a biological age of 65 years) and older fit patients only concern the missing recommendation for a double induction (instead evaluation of the bone marrow with regenerated blood count after one induction cycle) and the reduced cytarabine dose in the consolidation therapy.

#### **6.1.1.3 Elderly patients without intensive therapy options**

In patients with a biological age over 75 years or with significant comorbidities such as late-stage diabetic syndrome, liver or kidney disease, congestive heart failure (EF <30%), ECOG ≥3 or low chances of cure due to unfavorable cytogenetics (unfit, fragile or frail), the therapeutic goal is to prolong life while maximizing quality of life [58]. In addition to BSC, these patients should be offered cytoreductive outpatient chemotherapy. In addition to a purely symptomatic administration of hydroxyurea to lower the leukocyte count, the hypomethylating agents (HMA)

5-azacitidine and decitabine are recommended because they can induce higher response rates and prolong survival compared to the historical standard of low-dose cytarabine [30, 39].

Due to the mechanism of action of HMA, there may be a delayed response with HMA monotherapy, so that an efficacy assessment is not recommended until 3-4 months [63]. Therapy should be administered every four weeks until progression, as relapses occur rapidly after discontinuation [12]. Although randomized direct comparisons of the two agents are lacking, their efficacy can be considered equivalent [88]. Thus, their use is also guided by practical considerations.

In two randomized placebo-controlled trials, the combination of 5-azacitidine or LDAC with the bcl2 inhibitor venetoclax resulted in a significant increase in remission rates (CR/CRi) from 28.3% to 66.4% with azacitidine and from 13% to 48% with LDAC, respectively. Venetoclax significantly prolonged overall survival in combination with azacitidine from 9.6 to 14.7 months. This beneficial effect was demonstrated in all genetic subgroups [25, 83]. The predefined primary endpoint analysis in the combination study with venetoclax and LDAC after 12 months of median follow-up showed a survival difference of 7.2 versus 4.1 months, which did not reach statistical significance. Only after an additional 6 months and a difference in overall survival of 8.4 versus 4.1 was statistical significance achieved. On the basis of the above data, the EMA did not grant approval to the combination of LDAC plus venetoclax.

Approval for the combination of venetoclax with a hypomethylating agent was granted by the EMA in 2021. Based on data, this combination is recommended as the first priority treatment standard in first-line therapy of patients ineligible for intensive chemotherapy. The evidence is more robust for azacitidine, but similar efficacy can be assumed for decitabine as a combination partner [24].

Clinical management for combination therapy with venetoclax differs significantly from that for monotherapy with HMA:

To reduce the risk of tumor lysis, venetoclax combination should be started only when the leukocyte count is less than 25,000/ $\mu$ l, dose-ramp up should be performed over 4 days, and supportive measures should be taken to prevent tumor lysis. In addition, drug interactions have to be considered. We recommend:

- Cycle 1 should be started under in-patient conditions.
- Venetoclax dosing must be adjusted when co-medicating with CYP3A inhibitors.
- The more pronounced cytopenia compared with HMA monotherapy, combined with a higher likelihood of infectious complications, requires close monitoring including bone marrow diagnostics already after cycle 1 (between days 21 and 28) and prompt dose adjustments depending on remission status and blood count. After achieving blast clearance, G-CSF can be used if regeneration is delayed, although there is no firm evidence of benefit from the growth factor.
- Dose adjustment of venetoclax with concomitant administration of ciprofloxacin or macrolides.
- Reduction of venetoclax dose by 75% with concomitant administration of posaconazole.

As another option for combination with LDAC in unresectable patients, the hedgehog inhibitor glasdegib was approved in June 2020, resulting in an increase in CR/CRi rates from 5.3% to 24.3% and a median significant increase in survival from 4.3 to 8.3 months compared with LDAC monotherapy in a randomized non-placebo-controlled trial [16]. To date, there is no direct comparison of this combination to the efficacy of LDAC plus venetoclax.

Alternatively, low-dose cytarabine (LDAC) can be used in case of contraindications to HMA or progressive disease. LDAC has a higher efficacy than hydroxyurea in this situation [10].

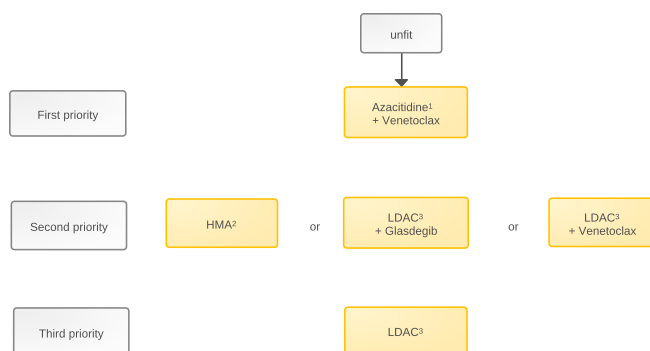


For a summary of the therapeutic options for first-line treatment of unfit patients and their prioritization, see [Figure 3](#).

A small proportion of newly diagnosed patients may be so impaired by leukemia-related organ impairment (e.g., leukemic infiltration of the liver), neutropenic infectious complications, or B symptoms that intensive therapy is not possible or justifiable at initial diagnosis. Successful treatment of AML with HMA or LDAC, possibly in combination with venetoclax, may improve the condition such that SCT appears feasible and can be successfully performed.

Due to the far-reaching prognostic consequences for or against intensive curative or palliative cytoreductive therapy, newly diagnosed AML patients should be presented to an experienced therapy center for assessment of the optimal treatment strategy.

**Figure 3: Therapy options for the primary therapy of unfit patients**



**Legend:**

non-curative intended therapy;

<sup>1</sup> in case of contraindications to azacitidine, decitabine can be used.

<sup>2</sup> HMA - hypomethylating agents

<sup>3</sup> LDAC - low-dose Ara-C;

## 6.1.2 Relapse treatment

In fit patients who are to be treated in relapse with curative intent, allogeneic stem cell transplantation remains the only procedure with the possibility of long-term remission. If neither an HLA-identical family donor nor an unrelated donor is available, alternative donors, especially HLA-haploidentical family donors, can be used, see [Onkopedia Allogeneic Stem Cell Transplantation Donor Selection](#) (German guideline).

Outside of trials, re-induction with the goal of obtaining a second CR is considered best for long-term remission after allogeneic SCT. There are no prospective controlled studies on the superiority of a defined therapeutic strategy in relapsed AML. However, the general consensus is to perform remission-inducing reinduction therapy that includes intermediate- or high-dose cytarabine. Alternatively, venetoclax-based or GO-based combinations may be considered [55]. The efficacy of direct transplantation without prior, potentially complication-prone salvage chemotherapy is currently being investigated as an alternative strategy in a randomized trial.

With approval of the second-generation type I FLT3 inhibitor gilteritinib for monotherapy of relapsed/refractory AML with FLT3 mutation, an additional third route to allogeneic SCT is opening up. In the 2:1 randomized-controlled pivotal trial, relapsed/refractory FLT3-mutated AML patients were treated with either predetermined standard therapy (60.5% intensive and 39.5% non-intensive) versus gilteritinib as oral monotherapy. Remission rates were higher in the gilteritinib arm (CR 21.1% versus 10.5%, CR/CRi 25.5% versus 11.3%, CR/CRh 34% versus 15.3%). In the gilteritinib arm, 63/247 (25.5%) patients underwent allogeneic stem cell transplantation, compared with 19/124 (15.3%) in the standard arm. Patients in the gilteritinib arm were eligible to receive the drug after allogeneic SCT as maintenance therapy until progression. Including

allogeneically transplanted patients, median overall survival in the gilteritinib arm was 9.3 versus 5.6 months in the control arm (HR 0.64;  $p < 0.001$ ); after censoring transplanted patients at the time of allogeneic SCT, the difference was 8.3 versus 5.3 months (HR 0.58). In terms of both response and median overall survival, the results of gilteritinib were superior to those of standard intensive relapse chemotherapy (CR 24.8% versus 16.0%, median survival 10.5 versus 6.9 months) [62]. Therefore, in patients with relapsed/refractory disease and FLT3 mutation, gilteritinib is recommended as first-line relapse therapy, even if the patient is eligible for intensive salvage therapy and allogeneic SCT is planned. If gilteritinib fails, standard intensive salvage therapy may be considered.

In case of relapse after allogeneic SCT, repeat SCT may be considered in individual patients with chemosensitive disease [31]. Donor lymphocyte administration (DLI) in relapse is associated with similar efficacy as a second allogeneic SCT [43]. Combining DLI with HMA may increase efficacy [89].

Relapsed patients with FLT3 mutation who are not suitable for intensive salvage therapy should be treated with gilteritinib. FLT3 wild-type patients who have not previously received HMA ("HMA-naïve") can be treated with HMA.

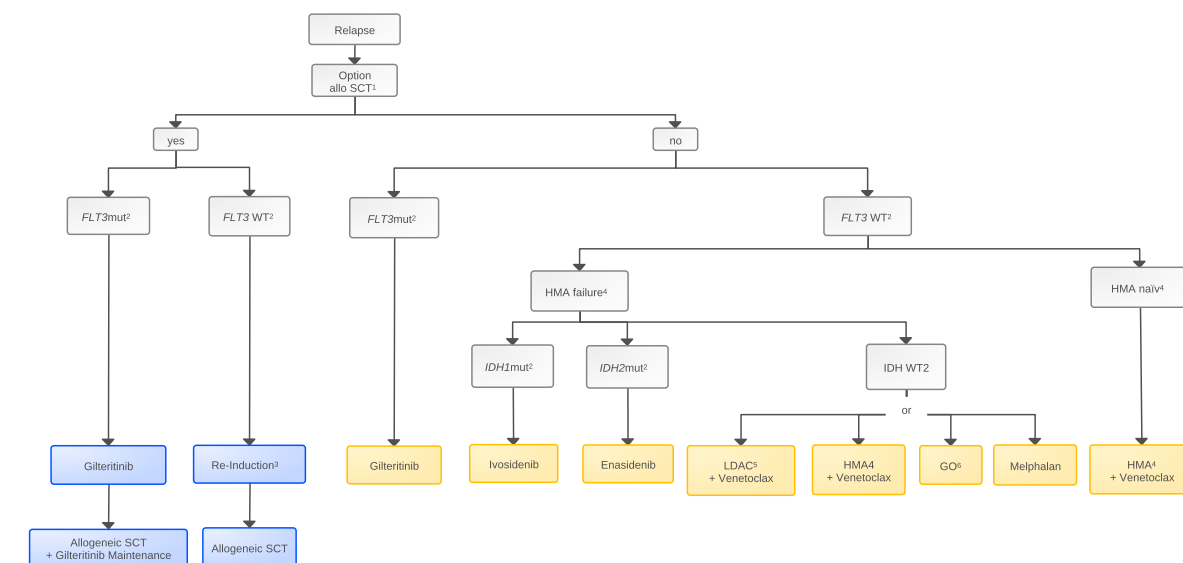
After previous HMA therapy ("HMA-failure"), the response to any salvage therapy is poor and the prognosis is short with a median overall survival of 3-4 months [57, 64]. In relapse after HMA failure, patients should therefore be treated preferentially in clinical trials. The combination of venetoclax with LDAC or HMA (approved by the FDA for first-line therapy) is associated with CR rates around 40%, but experience to date is limited to small case series [26, 65].

A mutation in the IDH1 or IDH2 gene is found in 10-20% of AML patients at initial diagnosis. The mutation product leads to the reduction of alpha-keto-glutarate to 2-hydroxy-glutarate (2-HG). 2-HG promotes hypermethylation of the genome, thereby leading to inhibition of cell differentiation and contributing to leukemogenesis. The antileukemic effect achieved by inhibiting mutant IDH formed the basis for the development of the IDH inhibitors ivosidenib (IDH1) and enasidenib (IDH2) [79]. In relapse with an IDH1 mutation, CR/CRi rates of 35% and median overall survival of approximately 9 months can be expected for ivosidenib [23], and CR/CRi rates of 27% and median survival also around 9 months for enasidenib in the presence of an IDH2 mutation [79]. Based on these data from nonrandomized trials, the FDA approved the drug in 2017 for the treatment of relapsed or refractory AML with confirmed IDH1/2 mutations. Due to a lack of survival benefit in a randomized trial of enasidenib versus azacitidine, LDAC, IDAC, or BSC in a very difficult-to-treat patient population (patients aged  $>60$  years in 2nd or 3rd relapse), EMA approval is not expected for monotherapy in relapse.

GO is also approved in the US as monotherapy for CD33-positive AML relapses. Remission rates around 30-40% have been described for monotherapy in first relapse [68, 81]. Due to the risk of VOD, GO is not recommended in relapse after allogeneic SCT [17]. Alternatively, classical cytostatics such as LDAC or melphalan can be used in HMA failure.

For a summary of therapeutic options in relapse and their prioritization, see Figure 4.

**Figure 4: Therapeutic algorithm for recurrence therapy.**



**Legend:**

█ curative intention; █ non-curative treatment intention;

1 SCT - stem cell transplantation

2 mut - mutated; WT - wild-type;

3 re-induction - re-induction with cytostatic drugs.

4 HMA - hypomethylating agents

5 LDAC - low dose Ara-C

6 GO - gemtuzumab ozogamicin

### 6.1.3 Supportive care

The prognosis of newly diagnosed AML patients has improved significantly over the last decades, especially in the younger patient population. Given the marginal changes in cytostatic therapy - the combination of cytarabine plus anthracycline has been used since the 1970s, the 7+3 regimen dates from the early 1980s, and high-dose cytarabine consolidation from the mid-1990s - this improvement in prognosis is due in no small part to improvements in supportive therapy [59, 61, 76, 82]. Essential components of supportive therapy are infection prophylaxis and transfusions, antiemesis and therapy of gastrointestinal complications. For concrete implementation, please refer to the separate guidelines on supportive therapy (<https://www.onkopedia.com/onkopedia/guidelines>) and the hygiene requirements for immunosuppressed patients of the Robert Koch Institute ([http://www.rki.de/Content/Infekt/Krankenhaushygiene/Kommission/Downloads/Immunsuppr\\_Rili.html](http://www.rki.de/Content/Infekt/Krankenhaushygiene/Kommission/Downloads/Immunsuppr_Rili.html)).

## 6.3 Children and adolescents

### 6.3.1 Basic principles

Although the chances of survival for children and adolescents with AML have improved in recent decades from a disease that was almost always fatal to more than 70% survival today, AML remains one of the most threatening diagnoses. With an incidence of 7 per 1,000,000 children, approximately 100 to 120 children and adolescents develop the disease annually in Germany [37].

The treatment of pediatric AML has been continuously developed over the past 40 years through population-based optimization studies. In Germany, Austria, Switzerland, the Czech Republic, and Slovakia, this was done by the AML-BFM study group. Internationally, various European (NOPHO, Scandinavia; AIOEP, Italy; LAME, France; MRC- UK), American (COG; St.

Jude) or even the Japanese study group have contributed to the further development of therapy as well as to the identification of prognostic factors [19].

Only a small proportion of pediatric AML is based on a genetic predisposition, most notably trisomy 21 or Fanconi anemia. In children, the origin of leukemic development may begin prenatally [33] - leukemia-associated aberration could already be detected in the metabolic screening cards of newborns [34].

A particular model is myeloid leukemia in children with trisomy 21. The predisposition initially leads to relatively increased megakaryopoiesis (trisomy 21 ~ 70% vs. normal ~30%) in fetal hematopoiesis in utero. During the 2nd trimester, increased GATA1 (hematopoietic transcription factor) mutant megakaryoblastic clones then become detectable, which apparently can become dominant in fetal hematopoiesis in association with other trisomy 21-related dispositions. This proliferation is then diagnosed as transient leukemia (TL) in 5-10% of newborns. As yet unexplained are factors that lead to myeloid leukemia in Down syndrome (ML-DS) in more than 20% of children within the first 4 years of life. This phenotypically also megakaryoblastic leukemia (AMKL) almost always has the identical GATA1 mutation as TL [44]. In other subgroups, disposition, either by novel mutations, polymorphisms or even by predisposing germline mutations could also play a relevant role.

### 6.3.2 Clinical picture

The symptoms of AML in children and adolescents are nonspecific and is mainly explained by the displacement of normal hematopoiesis in the bone marrow or directly by high blast concentrations. Most obvious are anemia-related pallor, increased hematomas and petechiae in thrombocytopenia, or infections due to neutro- and lymphopenia. High blast counts may cause viscosity problems, often beginning with pulmonary symptoms, or severe bleeding in case of coagulation disorders.

Multiple skin infiltrations may be seen, particularly in monoblastic leukemias. Hyperplasia of the gingiva should also prompt further hematologic diagnosis. Further extramedullary manifestations may be present as a space-occupying lesion in the orbit, especially in AML associated with translocation 8;21, but also as a so-called myelosarcoma or chloroma at any other site.

### 6.3.3 Children and adolescents

The diagnosis of AML is primarily made in the bone marrow, i.e. by analysis of the bone marrow aspirate, see also Table 1. In AML with associated myelofibrosis, a bone marrow biopsy may also be required. In cases of very high leukocyte counts with a high risk of bleeding, diagnosis is initially made from peripheral blood. The same applies to the initially obligatory lumbar puncture to exclude or detect involvement of the central nervous system.

Despite advances in molecular genetic methods, primary morphologic and immunophenotypic assessment retains its high initial value because it allows rapid lineage assignment as AML. However, it is also particularly relevant for the immediate identification of acute promyeloblastic leukemia (APL, AML FAB M3) or monoblastic leukemia (here, especially in differentiation from ALL). Both AML subtypes should be considered emergencies requiring direct intervention.

APL has a significantly higher incidence among children of Mediterranean/Asian origin than in Northern Europeans (>20% vs. 5%), see also Onkopedia Acute Promyelocytic Leukemia. Older children and adolescents are more frequently affected. Due to the very high risk of bleeding (including fatal cerebral hemorrhage) in the initial phase, APL is an emergency, especially if the leukocyte count is above 10,000/ $\mu$ l. In this case, immediate therapy with differentiating all-trans-retinoic acid (ATRA) is required.

In monoclastic leukemia and the frequently accompanying hyperleukocytosis, rapid measures to inhibit proliferation (e.g., cytarabine therapy) must be initiated together with supportive therapy (rasburicase, hydration, correction of coagulopathy) [20, 53].

#### **6.3.4 Prognostic factors and risk groups**

Stratification into risk groups as favorable, intermediate, and unfavorable is internationally established. The current ELN classification is summarized in Table 4 [4]. In most study groups, allocation is based on genetic characteristics of the leukemic blasts. This is supplemented by determination of response to therapy by morphology and immunophenotyping.

#### **6.3.5 Therapy**

##### **6.3.5.1 Chemotherapy**

Treatment of AML is based on intensive polychemotherapy, the main components of which are cytarabine and anthracyclines. The improvements of the last decades were mainly based on the intensification of treatment in the induction phase. The prerequisite for this was above all an improved supportive therapy in order to be able to control the severe side effects and high infection frequency, see also Chapter 6.1.3.

Due to the cardiotoxicity of anthracyclines, a liposomal formulation of daunorubicin is used in the AML-BFM studies in Germany, Austria, the Czech Republic, Switzerland and Slovakia. The formulation is intended to reduce the cardiac damaging effect [18].

In addition to the two substances, etoposide, mitoxantrone or thioguanine are used as further cytostatics in the therapy of AML.

In recent years, additional substances have been introduced into the treatment of pediatric AML to achieve targeted therapy or therapy aimed at specific mechanisms [66, 90]. Both the American COG and the AML-BFM study group recommend the additional administration of sorafenib in the interval of chemotherapy blocks in AML with a FLT3-ITD.

##### **6.3.5.2 Allogeneic stem cell transplantation**

In addition to chemotherapy, allogeneic stem cell therapy can be given after remission of AML. The results of allogeneic stem cell transplantation have improved significantly in recent years. Nevertheless, SCT remains reserved for high-risk AML [45].

##### **6.3.5.3 Relapse**

Therapy of relapse of AML is performed with re-induction therapy. In a worldwide study in 20 countries and 200 centers, the International AML Study Group was able to achieve survival rates from relapse of 38% in all cases where SCT was indicated in the 2nd remission. CBL-AML even had survival rates after relapse of about 60% [41]. All patients with a quantifiable genetic marker are continuously monitored after remission to detect early molecular relapse (increase >1 log level). Since molecular relapse always progresses to overt relapse if left untreated, ongoing studies are investigating whether early intervention can save therapy toxicity prior to the need for stem cell transplantation.

#### **6.3.5.4 Myeloid leukemia with trisomy 21**

Children with trisomy 21 have a high risk of developing AML with the mutation of GATA1 in the first 4 years of life see Chapter 6. 3. 1. In contrast to other AML, in these children, due to increased susceptibility to toxicities, reduction and adjustment of therapy intensity resulted in improved survival rates of about 90%.

#### **6.3.5.5 Acute Promyelocytic Leukemia (APL)**

Once the initial phase with the very high risk of bleeding was overcome, APL already had a very good prognosis in the past [19]. The current recommendation includes the combination of ATRA and arsenic trioxide as in adults, see also [Onkopedia Acute Promyelocytic Leukemia](#) (German guideline).

#### **6.3.5.6 Therapy-associated AML**

AML is the most common second malignancy following prior radio- or chemotherapy. Myelomonoblastic AML is most common, usually associated with t(9;11). Overall, the prognosis of therapy-associated AML remains unfavorable. The experience of the last decades shows that remission or at least blast freedom (morphologically) should be achieved with one or two induction blocks, followed by allogeneic SCT. With this approach of limited chemotherapy, a survival of 30-40% could be achieved.

#### **6.3.6 Late toxicity**

Severe late sequelae in children and adolescents with AML manifest themselves in the form of second malignancies, cardiotoxicities and as consequences of stem cell transplantation as chronic GvHD. The cumulative second malignancy rate after 20 years is approximately <2%. Overall, however, about half of all long-term survivors report chronic health problems. Severe, life-threatening diseases are about 3 times more common than in the reference population. Late cardiotoxicity can be expected in about 5% of patients, but only half of them is symptomatic. Statements about fertility are difficult to make. In girls who have only received chemotherapy, 14% show a significant reduction in anti-Müllerian hormone as a sign of impaired fertility [18, 54].

#### **6.3.7 Outlook**

With the exception of APL, the newer molecularly active agents alone have not been able to cure AML. Only in a few cases the therapeutic results seem to be improved by combination with conventional chemotherapy. Therefore, there is a need for optimization of current therapy standards. This concerns risk stratification, supportive therapy, chemotherapy and stem cell transplantation.

At the same time, research on the mechanisms of development and more targeted drugs with fewer side effects or alternative options such as immunotherapies and cellular therapies must be intensified in order to make AML curable in all children and adolescents in the future.

## 8 Follow-up and aftercare

### 8.1 Monitoring

During ongoing therapy, remission control is generally performed at the following time points:

- - two weeks after the start of induction I ("early control")
- - after the end of induction therapy when the blood count is regenerated
- - before the start of each consolidation therapy
- - after the end of post-remission therapy

### 8.2 Follow-up

AML patients should be followed up clinically and hematologically to detect relapse as early as possible. This requires regular clinical presentations, as well as blood counts and bone marrow checks. If there is a clinical suspicion of recurrence or abnormal blood work, a bone marrow examination must be performed. Since the majority of relapses occur within 18-24 months of achieving remission, blood counts are recommended every 1-3 months within the first two years, then every 3-6 months for years 3-5.

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## 15 Experts' Affiliations

### **Prof. Dr. med. Francis Ayuketang Ayuk**

Universitätsklinikum Hamburg-Eppendorf  
Klinik für Stammzelltransplantation  
Martinistr. 52  
20246 Hamburg  
[ayuketang@uke.de](mailto:ayuketang@uke.de)

### **Prof. Dr. med. Jan Braess**

Krankenhaus der Barmherzigen Brüder Regensburg  
Onkologisches Zentrum  
Prüfeninger Str. 86  
93049 Regensburg  
[jan.braess@barmherzige-regensburg.de](mailto:jan.braess@barmherzige-regensburg.de)

### **Prof. Dr. med. Michael Heuser**

Medizinische Hochschule Hannover  
Klinik für Hämatologie,  
Hämostaseologie, Onkologie &  
Stammzelltransplantation  
Carl-Neuberg-Str. 1  
30625 Hannover  
[heuser.michael@mh-hannover.de](mailto:heuser.michael@mh-hannover.de)

**Prof. Dr. med. Markus G. Manz**

Universitätsspital Zürich  
Zentrum für Hämatologie und Onkologie USZ  
Rämistr. 100  
CH-8091 Zürich  
[Markus.Manz@usz.ch](mailto:Markus.Manz@usz.ch)

**Prof. Dr. med. Jakob Passweg**

Universitätsspital Basel  
Hämatologie  
Petersgraben 4  
CH-4031 Basel  
[jakob.passweg@usb.ch](mailto:jakob.passweg@usb.ch)

**Prof. Dr. med. Dirk Reinhardt**

Universitätsklinikum Essen  
Klinik für Kinderheilkunde III  
Hufelandstr. 55  
45122 Essen  
[dirk.reinhardt@uk-essen.de](mailto:dirk.reinhardt@uk-essen.de)

**Prof. Dr. med. Christoph Röllig**

Universitätsklinikum Dresden  
Medizinische Klinik und Poliklinik I  
Fetscherstr. 74  
01307 Dresden  
[christoph.roellig@uniklinikum-dresden.de](mailto:christoph.roellig@uniklinikum-dresden.de)

**Prof. Dr. Richard F. Schlenk**

Nationales Centrum für Tumorerkrankungen (NCT)  
Marsilius Arkaden  
Turm West 9 Stock  
Im Neuenheimer Feld 330.3  
69120 Heidelberg  
[richard.schlenk@nct-heidelberg.de](mailto:richard.schlenk@nct-heidelberg.de)

**Prof. Dr. med. Armin Zebisch**

Abteilung für Hämatologie und Otto Loewi Forschungszentrum  
Medizinische Universität  
Auenbruggerplatz 38  
A-8036 Graz  
[armin.zebisch@medunigraz.at](mailto:armin.zebisch@medunigraz.at)

## **16 Disclosure of Potential Conflicts of Interest**

according to the rules of the responsible Medical Societies.