REVIEW ARTICLE

Allogeneic Stem Cell Transplantation in Acute Myeloid Leukemia

Establishment of Indications on the Basis of Individual Risk Stratification

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SUMMARY

Introduction: Acute myeloid leukemia (AML) is a heterogeneous disorder with subtypes that differ considerably in morphology and in their underlying chromosomal and molecular aberrations, which, in turn, determine their prognosis. The establishment of the indications for allogeneic stem cell transplantation (SCT) therefore requires individualized risk stratification based on a combination of multiple diagnostic methods, including cytogenetic and molecular genetic studies, and immunophenotyping, as well as the sensitivity of the disease to chemotherapy.

Methods: This article surveys the current strategies for establishing the indications for SCT in AML on the basis of a selective review of the relevant literature in the Medline database.

Results: In patients with a high risk constellation—e.g., chromosome 7 anomalies, complex aberrations, or FLT3-length mutations—there is an indication for SCT in first remission. The balanced translocations t(15;17) and t(8;21), and the inversion inv(16) are prognostically favorable and are thus not considered an indication for SCT in first remission. The establishment of indications for stem cell transplantation also depends on the residual leukemic cell burden (minimal residual disease, MRD) as determined by the quantitative polymerase chain reaction or by flow cytometry, as well as an insufficient response to induction chemotherapy. Reduced-dose conditioning, a new technique that lessens acute toxicity, has been found to be associated with a 30% to over 50% two-year survival rate when used in the treatment of chemotherapeutically unresponsive or relapsing AML.

Discussion: The indications for allogeneic SCT in AML should be further refined by more investigation in large studies.

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Acute myeloid leukemia (AML) occurs with an annual incidence of 4 per 100 000 persons in the western world. The median age at disease onset is 63 years with an increase in the incidence to about 15 per 100 000 in over 65-year-olds. Five-year survival is 25% to 35% in all patients, but diverges considerably depending on genetic subgroup and further risk factors (1). Intensive chemotherapy is sufficient for some patients; if there is a high risk of relapse, the indication for allogeneic stem cell transplantation (SCT)—from bone marrow, peripheral stem cells, or meanwhile also cord blood—is established.

The indication for allogeneic transplantation in acute leukemia is currently the subject of sometimes contentious debate following publication of a report by the Institute for Quality and Efficiency in Health Care (IQWiG). The present authors, who work in the field of allogeneic stem cell transplantation, take a critical view of some aspects of this report and, taking AML as an example, would like to describe in the form of an overview how complex the decision process for transplantation is and what criteria are relevant. A further aim is to present the impulses provided by molecular research for optimizing this indication.

Further changes have arisen through the concept of dose-reduced conditioning which both significantly reduces the toxicity of allogeneic SCT and allows its use in elderly patients or when concomitant diseases are present (1). A lower degree of tumor reduction is accepted in attenuated conditioning chemotherapy/radiotherapy, with higher priority being assigned to the immune effect of the transplantation against the leukemia.

To understand the complexity of establishing the indication for allogeneic transplantation in AML, it is first necessary to describe the heterogeneity of this condition on the basis of very different, genetically defined subgroups (1). 55% of the patients have a wide variety of aberrations at the chromosomal level. These range from structural changes such as balanced translocations, to numerical changes. Each of these is associated with a different relapse rate. For example, 5-year survival in acute promyelocytic leukemia (APL) with the translocation t(15;17)(q22;q21) characterized by fusion of the PML (promyelocytic leukemia) and RARA (retinoic acid receptor alpha) genes is more than 80%, in contrast to scally significant mutations are also identifiable by molecular studies in more than 80% of cases in the 45% of patients without chromosomal aberrations (e2).

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The detection of the genetically determined risk constellations in all patients with acute myeloid leukemia is only possible thanks to the further development and use of a broad range of hematological diagnostic techniques. Cytomorphology, immunophenotyping, as well as cytogenetics and molecular genetics are some examples. Sensitive detection of the residual leukemia cell burden below the microscopic detection limit (minimal residual disease diagnosis) with the polymerase chain reaction (PCR) and flow cytometry allows early detection of relapse (2–5). Further biological factors are of importance: The prognosis is better in *de novo* AML (i.e., without previous chemotherapy or hematological disease) than in secondary AML after myelodysplastic syndrome (MDS) or in therapy-associated AML after chemo-/radiotherapy.

Numerous factors therefore influence survival and relapse probability in AML. An improved understanding of these prognostic factors—i.e., of the parameters relevant for the therapeutic outcomes under clinical or hematological diagnostic aspects—makes it possible to adapt the intensity of therapy to the individual risk constellation: In patients with a high risk of relapse according to the genetic analysis findings, allogeneic transplantation proved significantly superior to all other therapeutic strategies in all large studies (6). Even when there is inadequate response to therapy or an increase in the MRD (minimal residual disease) parameters which represent the residual leukemic cell burden, an allogeneic stem cell transplantation from a related or unrelated donor is attempted in order to utilize the "graft-versus-leukemia effect" additively to the cytotoxic therapy. On the other hand, "overtherapy" is to be avoided in patients with a favorable prognosis (7)—great importance attaches to this aspect in view of the morbidity and mortality associated with allogeneic SCT. Furthermore, numerous other factors, such as the patient's general condition or donor-recipient compatibility, are considered when establishing the indication.

When establishing the indication for allogeneic SCT in AML, therefore, numerous individual factors have to be considered, from whose combination conclusions can be drawn regarding the individual risk profile. This results in complex requirements for leukemia diagnostics (8).

Study topic and methods

This article provides an overview of the strategies currently employed in establishing the indication for allogeneic SCT for AML in adults. It further indicates which criteria are to be regarded as relevant for this decision, especially in relation to the various methods of hematological diagnosis and the disease stage. This survey was based on controlled studies (when available) with larger case numbers which evaluated SCT outcomes as a function of the respective risk profiles (*table 1*). Moreover, emphasis was placed on studies performed to assess the indication for SCT in relation to the individual hematological diagnostic methods. However, the scope of this review article

does not allow a complete presentation of the relevant literature (*box 1*).

Results

Indication for SCT based on cytogenetics

The karyotype as the strongest prognostic factor in AML allows patients to be classified into 3 risk groups (9, e3): The prognostically most favorable group comprises acute promyelocyte leukemia with balanced translocation t(15; 17) or the PML-RA-RA fusion and the balanced translocations t(8;21)/AML1-ETO and inversion inv(16)/CBFB-MYH11. The intermediate prognostic group contains patients with normal karyotype or, for example, trisomy 8.

The third prognostically unfavorable group includes, among others, unbalanced karyotypes as well as anomalies of chromosomes 3 or 7. Complex changes with at least 3 chromosomal aberrations in about 15% of all cases can almost never be brought to stable remission with conventional therapy (8, e4). Also included are 11q23/MLL rearrangements (e5), which occur with an increased incidence after treatment with topoisomerase II inhibitors like the cytostatic agent etoposide. All these prognostically unfavorable changes show high relapse rates—in some cases >80%—and therefore represent an indication for allogeneic SCT (8).

In these prognostically unfavorable risk groups, a significant improvement in survival due to allogeneic SCT was observed across all study samples; no negative influence was observed in any large study. For example, in one prospective study performed by two European research teams (EORTC/GIMEMA), leukemia-free survival of patients from cytogenetically unfavorable prognostic groups that underwent allogeneic transplantation was 43%. For patients who received high-dose chemotherapy with autologous stem cell transplantation, leukemia-free survival was 18% (6). It should be taken into account, however, that in this case ultimately only a small group of patients could be evaluated and that the principle of "biological randomization" applied in this case did not go uncriticized: Patients with a suitable related donor underwent allogeneic stem cell transplantation, whereas patients without a related donor received high-dose therapy with autologous stem cell transplantation. The mean follow-up in this study was 4 years after transplantation.

In therapy-induced or secondary AML, for example after myelodysplastic syndrome (MDS), prognostically unfavorable karyotypes are in relative terms more frequent than in *de novo* AML (10, 11, e6). In a retrospective analysis, patients with advanced MDS or secondary AML were found to have a 3-year survival of 31% and a disease-free survival of 28%, although with a high transplantation-associated mortality of 52% (12). Nevertheless, the prognosis in these patient populations is extremely unfavorable, and these outcomes are therefore to be regarded as a success. Newer concepts with dose-reduced conditioning which are currently in the trial stage (13, e7–8) are hoped to provide further improvements in terms of transplantation-related mortality.

TABLE 1

Selected studies for risk stratification and results of allogeneic stem cell transplantation in AML

	Source	Study group	Study type	Patients	Results
Cytogenetic risk groups of AML	Slovak et al. 2000 (e28)	Southwest Oncology Group/ Eastern Cooperative Oncology Group Study	Biologically randomized study to compare allo-SCT in HLA-identical related donor vs consolidation/autologous SCT	609 patients <56 years with AML	AML classified into three cytogenetic prognostic groups: favorable (n=121); intermediate (n=278); unfavorable (n=184) (not classifiable: n=26) significant superiority of allo-SCT in prognostically unfavorable karyotype (n=38)
	Byrd et al. 2002 (9)	Cancer and Leukemia Group B (CALGB 8461)	Randomized study to compare different conventional consolidation strategies	1213 patients with de novo AML	Classification of AML into three cytogenetic prognostic groups: favorable, medium, unfavorable prognostic group
	Haferlach et al. 2003 (e29)	German AML Cooperative Group (AMLCG)	Randomized study to compare different conventional postremission strategies (2nd consolidation vs maintenance)	614 patients with de novo AML	Morphological dysplasia not an independent prognostic parameter Independent prognostic parameters: cytogenetic prognostic group, age, LDH
	Buchner et al. 2004 (8)	German AML Cooperative Group (AMLCG)	Randomized study to compare different conventional induction strategies and postremission strategies (2nd consolidation vs maintenance)	Two sequential analyses: 832 and 1094 patients (16–81 years) with de novo or s-AML	Independent risk factors: cytogenetic prognostic group, age, LDH, bone marrow blasts on day 16 after start of therapy
Molecular risk groups of AML	Falini et al. 2005 (15)	Perugia University, Italy	Retrospective analysis	591 patients (15–60 years) with de novo AML	<i>NPM1</i> mutations: – 35% of all de novo AML cases – good response to therapy
	Baldus et al. 2003 (19)	Cancer and Leukemia Group B (CALGB9621)	Retrospective analysis	86 patients with de novo AML and normal karyotype	<i>BAALC</i> expression: high expression: negative prognostic factor with poorer survival with normal karyotype
	Döhner et al. 2002 (e30)	Acute Myeloid Leukemia Study Group Ulm (AMLSG)	Retrospective analysis	525 patients with AML	<i>MLL</i> -PTD: – incidence: 8% of all patients – significantly inferior survival
	Yanada et al. 2005 (14)	Nagoya University, Japan	Meta-analysis of 4 larger studies 2001–2003	1160 patients with AML	Mutation in <i>FT3</i> gene: – significantly inferior survival
Allogeneic SCT in certain molecular risk groups	Bornhauser et al. 2007 (16)	German Study Initiative AML (DSIL)	Biologically randomized study to compare allo-SCT in HLA-identical related donor vs autologous SCT/conventional consolidation therapy	999 patients with AML ≤60 years	Comparison allogeneic/autologous SCT vs chemotherapy alone in 175 patients with AML/ <i>FLT3</i> -LM/ITD: both allogeneic and autologous SCT significantly superior to conventional therapy (4-year survival: 46% vs 21%)
Allogeneic/autologous SCT in certain cytogenetic risk groups	Suciu et al. 2003 (6)	EORTC/GIMEMA	Biologically randomized study to compare allo-SCT in HLA-identical related donor vs autologous SCT	734 patients <46 years in first remission of AML	Comparison allogeneic/autologous SCT: cytogenetically unfavorable risk groups (n=158): leukemia-free survival 43% after allogeneic SCT; 18% after autologous SCT
Allogeneic/autologous SCT in MDS/s-AML	de Witte et al. 2000 (12)	European Group for Blood and Marrow Transplantation (EBMT)	Retrospective analysis to compare the results of allogeneic SCT from related and unrelated donor and autologous SCT	1378 patients with advanced MDS/s-AML	Comparison allogeneic SCT (n=1180)/autologous SCT (n=173) Allogeneic SCT: 3-year survival: 31%; disease-free survival: 28 % Autologous SCT: relapse rate: 55%
Allogeneic SCT with dose-reduced conditioning in MDS/s-AML	Kröger et al. 2003 (13)	German Cooperative Transplant Study Group	Retrospective analysis	37 patients with MDS/s-AML	Allogeneic SCT with dose-reduced conditioning: – 3-year survival: 39% – disease-free survival: 38%
	Platzbecker et al. 2006 (21)	Dresden University	Prospective analysis	26 patients with AML with unfavorable karyotype/nonresponders	Allo-SCT with dose-reduced conditioning at median interval of only 40 days after diagnosis of AML >3-year survival 61%
	Marks et al. 2008 (e31)	Freiburg and Regensburg Universities	Prospective analysis	81 patients with AML and MDS	Allo-SCT with dose-reduced conditioning (fludarabine, BCNU, melphalan): 3-year survival 42% in 61 patients with refractory AML
Allogeneic SCT in therapy refractory AML	Schmid et al. 2006 (20)	Ludwig-Maximilians-University Munich	Prospective analysis	103 patients with therapy refractory AML	Allo-SCT with dose-reduced conditioning after sequential chemotherapy in therapy refractory AML >1-year survival 54%
AML relapse	Breems et al. 2005 (23)	Dutch-Belgian Hemato-Oncology Cooperative Group; Swiss Group for Clinical Cancer Research Collaborative Group	Retrospective analysis to compare different salvage therapy strategies in AML relapse (chemotherapy/autologous SCT/allogeneic SCT/donor lymphocytes/immune therapy)	667 patients in AML relapse	Risk stratification in relapse: prognosis depending on interval since first diagnosis, karyotype, age, previous SCT; Allogeneic SCT as salvage strategy in 109 patients >5-year survival 26% vs 6% to 9% for autologous SCT/chemotherapy in the unfavorable risk group; 88% vs 33% to 55% in the favorable risk group

SCT, stem cell transplantation; AML, acute myeloid leukemia; s-AML, secondary AML; MDS, myelodysplastic syndrome; PCR, polymerase chain reaction; *NPM1*, nucleophosmin gene; *BAALC*, brain and acute leukemia, cytoplasmic gene; *MLL*-PTD, partial tandem duplication in the mixed lineage leukemia gene; de novo AML, without therapy association or previous hematological disease; LDH, lactate dehydrogenase

BOX 1

Literature search method

- Basis of literature search: Medline database
- Search terms: "acute myeloid leukemia" (AML), "allogeneic stem cell transplantation" (SCT), "prognosis," "risk stratification," "cytogenetics," "karyotype," "molecular genetics," "polymerase chain reaction" (PCR), "immunophenotyping," "multiparameter flow cytometry," "mutation," "minimal residual disease" (MRD), "remission," "dose reduced conditioning" (RIC), "clinical trial," "relapse," "refractory."
- Emphasis of selective literature review:
 - Selection of studies evaluating the indication for stem cell transplantation in dependence on the different hematological diagnostic methods (cytomorphology, cytogenetics, molecular genetics, and immune phenotyping) and minimal residual disease (MRD) (detection of residual leukemia burden during the disease course).
 - Selection of multicenter studies with large case numbers or selection of studies with the largest possible sample sizes for highly specific research topics.

BOX 2

Chromosomal anomalies in hematological neoplasias

Numerical aberration:

Gain or loss of one or more whole chromosomes

Structural aberration:

Gain or loss of chromosome portions

Inversion:

Rotation of a chromosome segment within a chromosome by 180°

Balanced translocation:

Exchange of segments between two chromosomes without loss or gain of material

Reciprocal gene fusion:

Correlate of a balanced translocation at the molecular level by fusion of not usually adjacent gene portions

In contrast, in the aforementioned prognostically favorable balanced translocations—t(8;21), inv(16) and APL—in first remission SCT provides no advantages compared to conventional therapy, so that allogeneic SCT therapy is performed only in relapse cases (4, 7, 14) (*box 2, table 2*).

Indication for SCT based on molecular mutations

45% of all AML patients show no anomalies at the chromosomal level. This large prognostically intermediate subgroup with normal karyotype, however, is very heterogeneous as regards clinical course. Molecular studies now make it possible to obtain a more accurate classification in at least 80% of these cases (*box 2*): Length

mutations in the FLT3 gene (FLT3-LM; FLT3-ITDs) which lead to increased cell proliferation are found in about 40% of all patients with normal karyotype. They are associated with poor therapeutic response and high relapse rates (e9, e10). Prognostically favorable are mutations in the nucleophosmin (NPM1) gene. This mutation blocks the function of the NPM1 protein in a tumor suppressor pathway (15) which plays a regulatory role for cell proliferation.

In future, molecular studies in the normal karyotype subgroup may allow a more differentiated decision regarding stem cell transplantation. For example, patients with an FLT3 length mutation appear to benefit from an allogeneic stem cell transplantation because the prognosis is otherwise so unfavorable (16). If no FLT3 length mutation is present, and if an NPM1 mutation is detectable, then the prognosis is so favorable that SCT need not be performed in primary therapy. The same applies for isolated mutations in the CEBPA gene which are also to be regarded as prognostically favorable (17).

The combination of different molecular markers is also relevant. For example, the prognosis with simultaneous detection of NPM1 and FLT3 length mutations is much more unfavorable than with an isolated NPM1 mutation (17).

Nevertheless, the indication for allogeneic stem cell transplantation in FLT3-positive AML should be researched further in prospective studies, because it remains a matter of controversy in some quarters (18).

Other mutations are also of importance when there is a normal karyotype. High expression of the BAALC (brain and acute leukemia, cytoplasmic) gene (19, e 11) and mutations in the MLL gene (MLL-PTD) (e12) are also prognostically unfavorable (*box 3*).

Indication for SCT based on therapeutic response and age

In about 15% of all AML patients up to 60 years of age and in more than 50% of patients above 60 years of age, induction chemotherapy is ineffective (therapy refractoriness). In this situation, allogeneic SCT is therefore the only option offering a curative approach based on the graft-versus-leukemia effect. In the refractory situation, prospective controlled studies use the approach of dose-reduced conditioning, which achieved a 2-year survival of about 30% (20). Whether the results could be improved even further by the later administration of lymphocytes from the same donor (donor lymphocyte infusions) to reinforce the immune effect will have to be defined in controlled studies (20, e13). Performing the transplantation at an early stage, at the latest 2.5 months after the diagnosis, is another promising approach for refractory situations (21).

It is further to be considered that the prognosis for AML patients over 60 years of age is much less promising than in younger patients because of the more frequent presence of prognostically unfavorable cytogenetic and molecular aberrations and because of the poorer response to chemotherapy. The modification of the allogeneic therapeutic procedures, including the introduction of dose-reduced conditioning in combination with improved

TABLE 2

Classification of acute myeloid leukemia into prognostic groups based on cytogenetics and molecular mutations

Prognostic group	Genetic subgroup
Favorable prognostic group	<ul style="list-style-type: none"> ● t(15; 17)/<i>PML-RARA</i> ● t(8; 21)/<i>AML-ETO</i> ● inv(16)/<i>CBFB-MYH11</i> ● isolated <i>NPM1</i> mutations (normal karyotype) ● isolated <i>CEPBA</i> mutations (normal karyotype)
Intermediate prognostic group	<ul style="list-style-type: none"> ● normal karyotype ● trisomy 8
Unfavorable prognostic group	<ul style="list-style-type: none"> ● complex aberrations (≥ 3 chrom. anomalies) ● monosomy 7 ● anomalies on chromosome 3 ● <i>FLT3</i> length mutations (<i>FLT3-LM/FLT3-ITD</i>) ● <i>MLL-PTD</i>

GvHD (graft-versus-host disease) prophylactic strategies, also allow successful SCT in elderly patients (22).

Increase in minimal residual disease parameters

Quantitative PCR offers the highest possible sensitivity for MRD diagnosis during the disease course. Examples include the prognostically favorable balanced changes t(15;17), t(8;21), and inv(16), whose fusion transcripts can be quantified with molecular methods based on the polymerase chain reaction (PCR) (e14, e15, 4, 5). Persisting evidence after therapy (4) and a smaller decrease in the fusion transcript (5) correlate significantly ($p < 0.0001$) with a higher relapse rate. An increase in the corresponding molecular markers may precede the clinically overt relapse by 3 to 6 months and should therefore prompt the clinician to consider allogeneic SCT. However, quantitative PCR has so far only been established for some of the mutations, and validation as MRD parameter is not yet complete.

In about 95% of all AML patients, flow cytometry can detect a leukemia-associated aberrant immune phenotype with good suitability for MRD diagnosis (2). It has been demonstrated in numerous studies that persistence or repeat detection of the aberrant immune phenotype after therapy correlates with an unfavorable prognosis. The value of MRD diagnosis based on immune phenotyping for therapy planning, however, certainly requires further study-based evaluation (3, e16, e17).

Overt relapse

Although the prognosis is generally poorer in relapse than for de novo AML, the karyotype also has an independent prognostic significance in this situation. For example, balanced changes such as t(8;21) are also prognostically more favorable in this case than complex changes (23). The velocity of relapse development is also significant: Early relapses after less than 12 months are particularly unfavorable; second relapses are more critical than first relapses. Permanent remissions can rarely be achieved by purely conventional therapy in relapse, which is why allogeneic SCT should always be attempted. In relapse, this leads to a significant improvement in sur-

vival compared to other options (23), even if the results are poorer because of higher transplant-related mortality (TRM) or higher relapse rates compared to transplantation in first remission (24).

Discussion

A steady increase in allogeneic transplantations has been observed in AML over the last 20 years. The basis for this development was created by dose-reduced conditioning (e18) and improved supportive therapeutic resources, as well as the extension of HLA typing by the use of molecular methods, the increased use of peripheral blood stem cells (e19, e20), and the expansion of voluntary donor databases.

On the other hand, improved genetic subclassification and the more sensitive MRD diagnosis also make it possible to define the prognosis more reliably and recognize relapses earlier (e21–25). In this prognostically favorable—admittedly numerically small—subgroup allogeneic SCT is not performed anymore in first complete remission, without thereby worsening the therapeutic outcome (7). In second remission—i.e., after relapse of the disease—allogeneic transplantation is, however, the only curative therapeutic alternative regardless of the initial risk status of the leukemia. The results of transplantation from unrelated donors are equivalent to those of sibling donors (e26).

This balancing act between achieving the greatest possible safety for patients with a high relapse risk by allogeneic SCT and identifying the patients who have an adequate curative chance on conventional therapy is only successful when the individual risk profile is closely considered. The results of cytogenetics and molecular genetics and MRD diagnosis after PCR are already integrated in all therapeutic AML studies established in Germany; the importance of immunophenotyping for MRD diagnosis still requires to be validated.

Nevertheless, many questions still remain unresolved. For example, the value of high-dose chemotherapy with autologous stem cell transplantation (which is used to improve hematopoietic regeneration) in AML has not yet been conclusively proven (16). There is also a continuing

BOX 3

Recurrent molecular mutations in AML

FLT3 length mutations/internal tandem duplication (FLT3-LM/ITD):

Insertion of several hundred base pairs in the FLT3 gene which codes for a tyrosine kinase. The mutation leads to constitutive activation of this tyrosine kinase resulting in increased cell proliferation.

NPM1 mutation:

Mutation in the nucleophosmin gene which codes for the NPM1 protein. The mutation leads to an aberrant localization of the protein in the cytoplasm of the cells. The normal function of the NPM1 protein, which consists in the blockade of uninhibited cell proliferation, is thus disturbed.

CEPBA mutation:

The CEPBA gene codes for a transcription factor. The mutation leads to a disturbance in the transcription process, thereby impeding the maturation of granulopoiesis.

MLL-PTD:

Partial tandem duplication and/or insertion in the MLL (mixed lineage leukemia) gene which has a control function in transcription processes.

need to clarify the prognostic significance of numerous mutations, for example in the NRAS proto-oncogene. Within distinct genetic subgroups, considerable variabilities in the clinical course are observed which may be partly attributable to interaction with other mutations. The usually prognostically favorable APL may be considered as an example: In about 30% of the affected patients, a coincidence is found between FLT3 length mutations and a worsening of the prognosis. Further examples are the coincidence of FLT3 length mutations with NPM1 mutations or PML-RARA (e27).

The indication for allogeneic transplantation is therefore far from being conclusively defined. The further development of therapeutic and transplantation strategies for AML will continue to require a vigorous interaction with leukemia-specific diagnostics and its further development. The developments ongoing in the conventional therapeutic modalities, including the use of new molecular targeting substances, as well as the improvements introduced in allogeneic transplantation procedures with broader applicability including in older or comorbid patients are already providing, through differentiated use, successful therapy in more AML patients. Future studies should continue to aim at optimizing the criteria for allogeneic stem cell transplantation.

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Conflict of interest statement

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REVIEW ARTICLE

Allogeneic Stem Cell Transplantation in Acute Myeloid Leukemia

Establishment of Indications on the Basis of Individual Risk Stratification

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