

Acute myeloid leukemia - Section 3

Who should be transplanted in the molecular era?

Richard Schlenk

University of Ulm, Germany

Standard strategies for intensive postremission therapy in patients with acute myeloid leukemia (AML) comprise chemotherapy alone, allogeneic and, less frequently, autologous hematopoietic cell transplantation (HCT). The choice of postremission strategy is guided by the individual genetic profile of the disease and specific host factors, *e.g.*, age, comorbidities and graft availability. For more than 30 years, knowledge about the cytogenetic heterogeneity of AML has been accumulated. A new dimension of genetic complexity has been added in recent years by deciphering the enormous molecular diversity of the disease. The cytogenetic risk classification recognizes three AML risk groups (low, intermediate, high). The European LeukemiaNet recommendations have implemented the molecular markers FLT3 internal tandem duplication (FLT3-ITD), mutant NPM1 and mutant CEBPA, resulting in a refinement of the cytogenetically based risk classification; in consequence, the low-risk group has been enlarged, and the intermediate-risk group has been dissected into two separate groups. Allogeneic HCT is recommended for younger high-risk patients. However, the role of allogeneic and autologous HCT in intermediate- and low-risk patients is still a matter of debate. This is attributed to mixed effects on outcome seen in the genetic subgroups combined in one risk group, and to important molecular characteristics with prognostic impact within genetic subgroups (*e.g.*, FLT3-ITD allelic ratio). Beyond genetic profile and risk-group assignment at initial diagnosis, minimal residual disease (MRD) after induction and during consolidation therapy emerges as one of the most important prognostic factors. Whether MRD is also a predictive factor favoring allogeneic HCT as preferred consolidation strategy in MRD-positive patients is the subject of current investigations.

References

- *1. Ivey A, Hills RK, Simpson MA, Jovanovic JV, Gilkes A, Grech A, et al. Assessment of minimal residual disease in standard-risk AML. *N Engl J Med*. 2016;374:422-33.
Provides data supporting that MRD is the most important prognostic factor in NPM1-mutated AML.
- *2. Zhu HH, Zhang XH, Qin YZ, Liu DH, Jiang H, Xu LP, et al. MRD-directed risk stratification treatment may improve outcomes of t(8;21) AML in the first complete remission: results from the AML05 multicenter trial. *Blood*. 2013;121:4056-62.
In this study, allogeneic HCT performed in first complete remission was able to overcome the negative influence of MRD positivity in patients with t(8;21)-positive AML.
3. Schlenk RF, Kayser S, Bullinger L, Kobbe G, Casper J, Ringhoffer M, et al. Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation. *Blood*. 2014;124:3441-9.
- *4. Röllig C, Bornhäuser M, Kramer M, Thiede C, Ho AD, Krämer A, et al. Allogeneic stem-cell transplantation in patients with NPM1-mutated acute myeloid leukemia: results from a prospective donor versus non-donor analysis of patients after upfront HLA typing within the SAL-AML 2003 trial. *J Clin Oncol*. 2015;33:403-10.
Provides data supporting the use of allogeneic HCT in younger low-risk patients characterized by the genotype mutated NPM1 without FLT3-ITD.
5. Middeke JM, Fang M, Cornelissen JJ, Mohr B, Appelbaum FR, Stadler M, et al. Outcome of patients with abn(17p) acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation. *Blood*. 2014;123:2960-7.
- *6. Stone RM, Mandrekar S, Sanford BL, et al. The multi-kinase inhibitor midostaurin (M) prolongs survival compared with placebo (P) in combination with daunorubicin (D)/cytarabine (C) induction (ind), high-dose C consolidation (consol), and ss maintenance (maint) therapy in newly diagnosed acute myeloid leukemia (AML) patients (pts) age 18-60 with FLT3 mutations (mut): an international prospective randomized (rand) P-controlled double-blind trial (CALGB 10603/RATIFY Alliance) [abstract]. *Blood*. 2015;126:6.
Provides data supporting that the FLT3 inhibitor midostaurin given during induction therapy in FLT3-mutated AML improves survival overall and, in particular, after allogeneic HCT in first complete remission.
- *7. Middeke JM, Herold S, Rücker-Braun E, Berdel WE, Stelljes M, Kaufmann M, et al. TP53 mutation in patients with high-risk acute myeloid leukaemia treated with allogeneic haematopoietic stem cell transplantation. *Br J Haematol*. 2016;172:914-22.
This study supports the integration of TP53 mutational status in the standard AML and pre-transplant work-up.
- *8. Araki D, Wood BL, Othus M, Radich JP, Halpern AB, Zhou Y, et al. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia: time to move toward a minimal residual disease-based definition of complete remission? *J Clin Oncol*. 2016;34:329-36.
This study showed that MRD status assessed by flow cytometry before HCT is the most important prognostic factor for post-transplant outcome.
- *9. Ustun C, Courville EL, DeFor T, Dolan M, Randall N, Yohe S, et al. Myeloablative, but not reduced-intensity, conditioning overcomes the negative effect of flow-cytometric evidence of leukemia in acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2016;22:669-75.
This study shows that the choice of conditioning regimen before allogeneic HCT is important in MRD-positive patients.
- *10. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Heuser M, Thol F, Bolli N, Ganser A, Döhner K, Schlenk RF, Döhner H, Campbell PJ. Dissecting genetic and phenotypic heterogeneity to map molecular phylogenies and deliver personalized outcome and treatment predictions in AML [abstract]. *Blood*. 2015;126:803.
This study gives a comprehensive overview of the genetic alterations and their prognostic impact in AML.