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ALLOGENEIC STEM CELL TRANSPLANTATION IN FIRST COMPLETE REMISSION

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Abstract

Purpose of review—The optimal post-remission therapy of acute myeloid leukemia (AML) in first complete remission (CR1) is uncertain. This review summarizes the recent developments in the clinical research and therapeutic applications defining the role of allogeneic hematopoietic stem cell transplantation (allo-HCT) in CR1.

Recent findings—Molecular markers in combinations with cytogenetics have improved the risk stratification and informed decision-making in patients with AML in CR1. In parallel, several important advances in the transplant field, such as better supportive care, improved transplant technology, increased availability of alternative donors, and reduced-intensity conditioning have improved the safety as well as access of allo-HCT for a larger number of patients.

Summary—The progress in risk stratification and transplant technology dictate that early donor identification search should be initiated for all eligible AML patients in CR1.

Keywords

acute myeloid leukemia; allogeneic stem cell transplantation; first complete remission

Introduction

Achieving cure in acute myeloid leukemia (AML) has been a challenge and depends on successful induction therapy to achieve a complete remission (CR) and subsequent post-remission therapy to prevent relapse. While more than 70% of adult AML patients will enter a first CR (CR1) after induction chemotherapy, most later experience disease relapse [1]. The overall survival (OS) of adults with AML is poor, even in the most favorable cytogenetic groups, such as those with core binding factor (CBF) translocations [2]. The options for post-remission treatment are broad and the choice of therapy is determined by

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the prognostic factors at diagnosis and beyond. Physician and patient biases also impact the choices of therapy offered and chosen. Among the alternatives, allogeneic hematopoietic stem cell transplantation (allo-HCT) after myeloablative conditioning (MAC) may be a preferred curative option for younger patients with AML in CR1. However, concerns regarding allo-HCT related toxicity and questions regarding its benefit, limit its use for patients in CR1. The current recommendations for allo-HCT for patients in CR1 are limited to those whose risk of relapse significantly exceeds the mortality from allo-HCT and is based on cytogenetic stratification into good-, intermediate-, and poor-risk AML. These are summarized in treatment guidelines of the National Comprehensive Cancer Network (V2.2011: available at http://www.nccn.org). However, with progress in understanding the disease biology of AML and identification of new molecular markers, current practice may of course, still evolve. Additionally, with advances in transplant field including better supportive care, the use of high-resolution allele-level human leukocyte antigen-(HLA) typing leading to better donor selection and the introduction of reduced intensity conditioning (RIC), the risk-benefit ratio of allo- HCT has improved.

Is there benefit with allo-HCT in AML CR1?

Multiple prospective trials investigated the role of allo-HCT for AML in CR1. Treatment assignment has been based on donor availability: patients with HLA-matched related donors (MRD), usually siblings, are recommended to undergo allo-HCT (donor group), and those without matched siblings are assigned to nonallogeneic HCT therapy (no-donor group). These donor: no donor comparisons may be confounded by limited application of the assigned therapy and the results have not always been consistent leaving the role of allo-HCT in AML patients in CR1 unclear [3–7]. A large meta-analysis analyzed 24 prospective studies including over 6000 patients with AML in CR1 compared the role of HCT to non-HCT treatments [8]. In the studies, 3,638 patients were analyzed by cytogenetic risk category, including 547 good-risk, 2,499 intermediate-risk, and 592 poor-risk patients. Compared with nonallogeneic therapy, the hazard ratio (HR) of relapse or death with an allo-HCT for patients in CR1 was 0.80 (95% CI 0.74 to 0.86). But when the analysis was broken down by risk category and outcome, there was a significant survival advantage for allo-HCT during CR1 in intermediate- and high-risk AML patients, but not in good-risk patients. Although these results were encouraging to define allo-HCT as a better treatment, most studies addressed patients younger than 60 leaving unclear whether older patients could benefit similarly. There are also concerns about various late effects such as graft-versus-host disease (GVHD) that might lower the quality of life (QOL) after cure of AML with allo-HCT. Recently, a Markov decision analysis compared survival outcomes after allo-HCT (related and unrelated donors) and chemotherapy using a QOL evaluation from a database of 2029 adult AML patients (up to age 70, median age 50) who achieved CR1 [9]. In this study, patients with favorable-risk AML in the chemotherapy group had a longer life expectancy (LE) than patients in the allo-HCT group. In contrast, patients with intermediate, unfavorable, and unknown-risk AML in the allo-HCT group had a longer median LE than patients in the chemotherapy group (intermediate risk, 73.6 vs 66.4 months; unfavorable, 61.6 vs 53.4 months). Although quality-adjusted life expectancy (QALE) was less favorable in the allo-HCT group, the median QALE remained longer in the allo-HCT group with

intermediate- and high-risk risk cytogenetics (intermediate, 59.4 vs 55.6 months; unfavorable, 47.6 vs 44.4 months). Both younger and older patients with intermediate- and high- risk disease had improvements in LE and QALE, but the older patients with a suitable related donor benefited the most from allo-HCT in CR1. This study was conducted with patients treated between 1999 and 2006. One might expect even better results after unrelated donor allo-HCT using allele level matching, a practice of recent years.

Identification of gene mutations, deregulated expression of genes and noncoding RNAs (ie, microRNAs) is unraveling the enormous molecular genetic heterogeneity within cytogenetically defined subsets of AML, in particular the large group with cytogenetically normal (CN) AML [10–14]. It has become clear that specific chromosome abnormalities and molecular genetic changes are among the most important prognostic markers and may therefore be used for stratification to apply risk-adapted therapeutic strategies. Recently European LeukemiaNet proposed a standardized reporting system for genetic abnormalities using data correlating genetic findings with clinical outcome (Table 1) [15].

Role of allo-HCT in CN-AML

Several authors have shown the prognostic significance for mutations in the *NPM1, CEBPA*, and *FLT3* genes, alone or in combination for both younger and older adults with CN-AML, which constitutes 40%–50% of all AML (Table 2)[16–18]. CN-AML patients harboring internal tandem duplication (ITD) of the *FLT3* gene have an inferior outcome compared with cases without *FLT3*-ITD [19–21]. There is also evidence that outcome may be more related to the level of the mutated allele [21, 22] and to the insertion site of the ITD [23, 24]. The prognostic significance of *FLT3*-TKD mutations remains controversial in view of conflicting data [25, 26]. *NPM1* mutation in CN-AML has been associated with higher CR rates and better relapse free survival (RFS) and event-free survival (EFS) [27, 28]. However, 40% of patients with *NPM1* mutations also carry *FLT3*-ITD. Multiple studies have shown that the genotype “mutated *NPM1* without *FLT3*-ITD” represents a favorable prognostic marker, with higher CR rates, and better RFS and OS; similar to patients with inv(16) or t(8;21) [19, 27, 28]. The favorable impact of mutated *NPM1* (without *FLT3*-ITD) on survival endpoints also seems to hold up among patients of older age [29]. CN-AML with mutations in *CEBPA* has also been associated with a favorable prognosis [30, 31]. Though the groups are small, the survival data are similar to those of AML patients with mutated *NPM1* without *FLT3*-ITD. Recently, it was shown that only cases with double CEBPA mutations, usually biallelic, have a favorable outcome [32].

In a study from Germany, researchers analyzed the role of mutational status of *NPM1, FLT3, CEBPA*, along with *MLL* and *NRAS* in guiding post-remission therapy for CN-AML in CR1 younger than age 60 [19]. For post-remission therapy, patients with an HLA- MRD were assigned to undergo allo-HCT in CR1; those without a donor were randomly assigned to receive high-dose cytarabine consolidation or autologous transplant. Importantly, the assigned allo-HCT was performed in 82% of patients. Autologous transplant or consolidation therapy resulted in similar outcomes. An intention-to-treat analysis on the basis of donor availability demonstrated significantly longer RFS in the donor group ($P = .009$). Data were further analyzed on the basis of mutation status, and patients were

subdivided into 2 groups: patients with "mutated (m)*NPM1* without *FLT3*-ITD," and patients with all other genotypes. Because of small numbers, patients with m*CEBPA* were excluded. RFS was similar either with or without a donor in the favorable genotype patients having m*NPM1* without *FLT3*-ITD ($P = .71$). Among the patients with CN-AML and other genotypes, superior RFS was observed in those with a donor. Therefore again, other than the most favorable genotype group, outcomes were better with a donor for allo-HCT.

There is a growing list of genetic abnormalities potentially influencing the outcome of AML. These include mutation analyses of the *WT1* [33], *RUNX1* [34], *TET2* [35] and *IDH1* genes [36] and the analyses of gene expression signatures [37, 38] or of deregulated expression of single genes, such as *EVI1*[39], *ERG* [40], *MN1* [41], and *BAALC* [42] genes.

Despite abundant information about the prognostic impact of single markers, little is known about their cumulative effect on disease outcomes. A recent study by HOVON/SAKK analyzed clinical and molecular markers to develop an integrative prognostic risk score (IPRS) in CN-AML patients younger than 60 to determine treatment strategies in CR1 [43]. In the dataset of 275 adult patients, 2 clinical (age, white blood cell count) and 7 molecular markers (mutation/polymorphism status of *FLT3/NPM1, CEBPA, WT1* SNP rs16754, expression levels of *MN1, BAALC, ERG*, and *WT1*) fulfilled the significance criteria and 3 risk groups were defined having different OS and RFS. These results were confirmed in 2 independent validation cohorts. The prognostic benefit of a MRD allo-HCT in CR1 in defined risk groups was outlined. In the low risk group, there was no difference in OS and RFS between donor and no-donor group. In the high risk group, donor availability was independently associated with improved OS and RFS. On the other hand, in the intermediate risk group, donor availability was an independent predictor for shorter OS and RFS. One particular finding of this study was the high prevalence of *NPM1*/*FLT3*-ITD high-risk mutation status in all IPRS groups (30%, 61%, and 92% in the low-, intermediate-, and high-risk IPRS groups, respectively). Although most patients in the IPRS high-risk group were identified by *NPM1*/*FLT3*-ITD mutation status, there was a significant proportion of patients appeared not to benefit from allo-HCT that could be identified by IPRS apart from the *NPM1*/*FLT3*-ITD mutation status.

Allo-HCT in Favorable Cytogenetic Risk AML

No advantage has been shown for allo-HSCT in CR1 for CBF AML [8, 44]; if intensive consolidation chemotherapy is administered. However, in one subgroup with worse prognosis; CBF AML with *KIT* mutations, allo-HCT may be considered. *KIT* mutations are found in 25% to 30% of cases of CBF-AML while rare in other AML subsets [45]. In most studies, *KIT* mutations have been associated with inferior outcome [37]. Although there is no clear data supporting the use of *KIT* mutational status to guide therapy, allo-HCT can be considered in CR1 for patients with KIT mutation as their 5-year relapse risk is similar to that reported with adverse cytogenetics.

Logistics of allo-HCT in CR1: The role of alternative donors and age

Meta-analysis of prospective biologic assignment studies comparing the role of HCT to non-HCT treatments have shown a strong survival advantage of allo-HCT using a MRD for intermediate- and high risk AML patients in CR1. Yet only 30% of patients have a suitable MRD. Thus, it is important to expand the acceptable donor pool for patients with AML. Registry data from the Center for International Blood and Marrow Transplant Research (CIBMTR) [46] and two prospective studies [7, 47] comparing MRD with unrelated donor (URD) with adverse risk AML patients in CR1 have shown comparable outcomes. These suggest that when a MRD is not available, an HLA-well matched URD is appropriate. There is lesser consensus whether such a strategy should be routinely adopted for patients with intermediate cytogenetics lacking a MRD due to insufficient prospective studies and inherent selection bias in patients chosen for such procedure. Unrelated umbilical cord blood (UCB) has emerged as an alternative source for allo-HCT and may be particularly valuable for patients who have a narrow time window of opportunity to proceed to transplantation. Recent studies have demonstrated similar leukemia free survival (LFS) after UCB and URD transplantation after MAC in patients with acute leukemia [48, 49]. Although various hematological malignancies at different disease stages were included in those studies, it can be suggested that those results would also apply to AML patients in CR1.

Haploidentical transplants (haplo-HCT) present another alternative for patients with a poor prognosis for whom no sibling donor is available. Although there are less cumulative data on using this procedure than on using URD transplants, a recent European Bone Marrow Transplant Registy (EBMTR) study indicated that the haplo-HCT results for high-risk AML in CR are similar to what has been reported for URD transplants [50]. Conventional chemotherapy options are not curative in a large majority of AML patients ≥ 60 years of age [51, 52]. Short leukemia free survival is due mainly to inability to maintain CR. There has been no consolidation chemotherapy that has been shown to improve LFS with acceptable toxicity although this has been the mostly applied post-remission therapy in older AML patients. The introduction of RIC has extended the availability of allo-HCT to this population. A recent CIBMTR analyses demonstrated that transplantation toxicity, relapse, and survival for older adults are similar to those for younger adults undergoing RIC allo-HCT in AML CR1 (2 year OS was ~ 30%) [53]. A recent study compared the outcome of 100 AML patients aged 60–70 years who received RIC allo-HCT in CR1 and were reported to the CIBMTR to that of 96 AML patients treated with only standard induction and post-remission chemotherapy on Cancer and Leukemia Group B protocols (47). In the chemotherapy-treated group, only patients who remained in CR1 for at least 4 months were included in order to reduce selection bias. Allo-HCT was associated with longer LFS compared to chemotherapy. The 3-year LFS from CR1 for HCT patients was 34% compared to 17% for chemotherapy-treated patients.

Despite these encouraging results, in a small prospective study, less than 15% older AML patients received allo-HCT in CR1 [54]. Reluctance to use allo-HCT may be due to concerns that selection bias leads to selection of only the "fittest” older patients for RIC HCT and that results of the procedure may not generalize to majority of older patients in CR1. Data from

prospective clinical trials are required to overcome skepticism for observational data that might overestimate the efficacy of allo-HCT.

Real World Data

The only population based study for AML patients undergoing allo-HCT was presented by Swedish Acute Leukemia Registry where all high risk AML patients were recommended for allo-HCT [55]. Intermediate risk patients were also transplanted if the balance between disease-related and transplant-related risk favored allo-HCT, but patients with favorable cytogenetics were not transplanted. Among 797 AML patients younger than 60 diagnosed between 1996 and 2007, 29% of patients underwent allo-HCT in CR1. Approximately half of the donors were unrelated. The median time to HCT from diagnosis was 136 and 176 days for MRD and URD, respectively. Superior 5-year survival from CR1 was observed in patients who were transplanted in CR1 compared with non-transplant approaches (61% vs. 48%, p=0.005). This study was unique since it included not only medically fit patients, but also those with poor performance status who might not be included in clinical trials.

Conclusion

Decision-making about allo-HCT in AML CR1 is complex requiring consideration of patient and disease characteristics, but also available donor type, conditioning regimen chosen and anticipated TRM. However, available data suggests the initiation of an early donor search for all AML patients and directed efforts to ensure that eligible patients receive transplants in a timely manner. Since survival of relapsed patients is poor, all suitable patients with other than the most favorable disease features should proceed with allo-HCT during CR1.

REFERENCES

1. Lowenberg B, Downing JR, Burnett A. Acute myeloid leukemia. N Engl J Med. 1999; 341(14): 1051–1062. [PubMed: 10502596]
2. Cassileth PA, et al. Varying intensity of postremission therapy in acute myeloid leukemia. Blood. 1992; 79(8):1924–1930. [PubMed: 1562720]
3. Cassileth PA, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. N Engl J Med. 1998; 339(23):1649–1656. [PubMed: 9834301]
4. Burnett AK, et al. The value of allogeneic bone marrow transplant in patients with acute myeloid leukaemia at differing risk of relapse: results of the UK MRC AML 10 trial. Br J Haematol. 2002; 118(2):385–400. [PubMed: 12139722]
5. Suciu S, et al. Allogeneic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of the EORTC/GIMEMAAML-10 trial. Blood. 2003; 102(4): 1232–1240. [PubMed: 12714526]
6. Cornelissen JJ, et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? Blood. 2007; 109(9):3658–3666. [PubMed: 17213292]
7. Basara N, et al. Early related or unrelated haematopoietic cell transplantation results in higher overall survival and leukaemia-free survival compared with conventional chemotherapy in high-risk acute myeloid leukaemia patients in first complete remission. Leukemia. 2009; 23(4):635–640. [PubMed: 19151786]

8. Koreth J, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. JAMA. 2009; 301(22): 2349–2361. [PubMed: 19509382]

9. Kurosawa S, et al. A Markov decision analysis of allogeneic hematopoietic cell transplantation versus chemotherapy in patients with acute myeloid leukemia in first remission. Blood. 2011; 117(7):2113–2120. [PubMed: 21106987] The authors compared allo-HCT and chemotherapy in 2029 adult AML patients who achieved CR1 using Markov decision model. QOL-adjusted life expectancies in most of the subgroups remained longer in the allo-HCT group than in the chemotherapy group.

10. Frohling S, Dohner H. Chromosomal abnormalities in cancer. N Engl J Med. 2008; 359(7):722–734. [PubMed: 18703475]

11. Mrozek K, et al. Clinical relevance of mutations and gene-expression changes in adult acute myeloid leukemia with normal cytogenetics: are we ready for a prognostically prioritized molecular classification? Blood. 2007; 109(2):431–448. [PubMed: 16960150]

12. Mardis ER, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med. 2009; 361(11):1058–1066. [PubMed: 19657110]

13. Schwind S, et al. BAALC and ERG expression levels are associated with outcome and distinct gene and microRNA expression profiles in older patients with de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. Blood. 2010; 116(25):5660–5669. [PubMed: 20841507]

14. Becker H, et al. Mutations of the Wilms tumor 1 gene (WT1) in older patients with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. Blood. 2010; 116(5):788–792. [PubMed: 20442368]

15. Dohner H, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010; 115(3):453–474. [PubMed: 19880497]

16. Marcucci G, Haferlach T, Dohner H. Molecular genetics of adult acute myeloid leukemia: prognostic and therapeutic implications. J Clin Oncol. 2011; 29(5):475–486. [PubMed: 21220609]

17. Haferlach T, et al. Insight into the molecular pathogenesis of myeloid malignancies. Curr Opin Hematol. 2007; 14(2):90–97. [PubMed: 17255785]

18. Bacher U, Schnittger S, Haferlach T. Molecular genetics in acute myeloid leukemia. Curr Opin Oncol. 2010; 22(6):646–655. [PubMed: 20805748]

19. Schlenk RF, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med. 2008; 358(18):1909–1918. [PubMed: 18450602]

20. Kottaridis PD, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood. 2001; 98(6):1752–1759. [PubMed: 11535508]

21. Thiede C, et al. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood. 2002; 99(12):4326–4335. [PubMed: 12036858]

22. Gale RE, et al. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. Blood. 2008; 111(5):2776–2784. [PubMed: 17957027]

23. Breitenbuecher F, et al. Identification of a novel type of ITD mutations located in nonjuxtamembrane domains of the FLT3 tyrosine kinase receptor. Blood. 2009; 113(17):4074–4077. [PubMed: 18483393]

24. Kayser S, et al. Insertion of FLT3 internal tandem duplication in the tyrosine kinase domain-1 is associated with resistance to chemotherapy and inferior outcome. Blood. 2009; 114(12):2386–2392. [PubMed: 19602710]

25. Whitman SP, et al. FLT3 D835/I836 mutations are associated with poor disease-free survival and a distinct gene-expression signature among younger adults with de novo cytogenetically normal

acute myeloid leukemia lacking FLT3 internal tandem duplications. Blood. 2008; 111(3):1552–1559. [PubMed: 17940205]

26. Mead AJ, et al. FLT3 tyrosine kinase domain mutations are biologically distinct from and have a significantly more favorable prognosis than FLT3 internal tandem duplications in patients with acute myeloid leukemia. Blood. 2007; 110(4):1262–1270. [PubMed: 17456725]
27. Dohner K, et al. Mutant nucleophosmin (NPM1) predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics: interaction with other gene mutations. Blood. 2005; 106(12):3740–3746. [PubMed: 16051734]
28. Verhaak RG, et al. Mutations in nucleophosmin (NPM1) in acute myeloid leukemia (AML): association with other gene abnormalities and previously established gene expression signatures and their favorable prognostic significance. Blood. 2005; 106(12):3747–3754. [PubMed: 16109776]
29. Becker H, et al. Favorable prognostic impact of NPM1 mutations in older patients with cytogenetically normal de novo acute myeloid leukemia and associated gene- and microRNA-expression signatures: a Cancer and Leukemia Group B study. J Clin Oncol. 2010; 28(4):596–604. [PubMed: 20026798]
30. Marcucci G, et al. Prognostic significance of, and gene and microRNA expression signatures associated with, CEBPA mutations in cytogenetically normal acute myeloid leukemia with high-risk molecular features: a Cancer and Leukemia Group B Study. J Clin Oncol. 2008; 26(31):5078–5087. [PubMed: 18809607]
31. Frohling S, et al. CEBPA mutations in younger adults with acute myeloid leukemia and normal cytogenetics: prognostic relevance and analysis of cooperating mutations. J Clin Oncol. 2004; 22(4):624–633. [PubMed: 14726504]
32. Wouters BJ, et al. Double CEBPA mutations, but not single CEBPA mutations, define a subgroup of acute myeloid leukemia with a distinctive gene expression profile that is uniquely associated with a favorable outcome. Blood. 2009; 113(13):3088–3091. [PubMed: 19171880]
33. Paschka P, et al. Wilms' tumor 1 gene mutations independently predict poor outcome in adults with cytogenetically normal acute myeloid leukemia: a cancer and leukemia group B study. J Clin Oncol. 2008; 26(28):4595–4602. [PubMed: 18559874]
34. Osato M, et al. Biallelic and heterozygous point mutations in the runt domain of the AML1/PEBP2alphaB gene associated with myeloblastic leukemias. Blood. 1999; 93(6):1817–1824. [PubMed: 10068652]
35. Delhommeau F, et al. Mutation in TET2 in myeloid cancers. N Engl J Med. 2009; 360(22):2289–2301. [PubMed: 19474426]
36. Marcucci G, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol. 2010; 28(14):2348–2355. [PubMed: 20368543]
37. Bullinger L, et al. Use of gene-expression profiling to identify prognostic subclasses in adult acute myeloid leukemia. N Engl J Med. 2004; 350(16):1605–1616. [PubMed: 15084693]
38. Valk PJ, et al. Prognostically useful gene-expression profiles in acute myeloid leukemia. N Engl J Med. 2004; 350(16):1617–1628. [PubMed: 15084694]
39. Lugthart S, et al. High EVI1 levels predict adverse outcome in acute myeloid leukemia: prevalence of EVI1 overexpression and chromosome 3q26 abnormalities underestimated. Blood. 2008; 111(8):4329–4337. [PubMed: 18272813]
40. Marcucci G, et al. High expression levels of the ETS-related gene, ERG, predict adverse outcome and improve molecular risk-based classification of cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B Study. J Clin Oncol. 2007; 25(22):3337–3343. [PubMed: 17577018]
41. Langer C, et al. Prognostic importance of MN1 transcript levels, and biologic insights from MN1-associated gene and microRNA expression signatures in cytogenetically normal acute myeloid leukemia: a cancer and leukemia group B study. J Clin Oncol. 2009; 27(19):3198–3204. [PubMed: 19451432]
42. Langer C, et al. High BAALC expression associates with other molecular prognostic markers, poor outcome, and a distinct gene-expression signature in cytogenetically normal patients younger than

60 years with acute myeloid leukemia: a Cancer and Leukemia Group B (CALGB) study. Blood. 2008; 111(11):5371–5379. [PubMed: 18378853]

43. Damm F, et al. Integrative prognostic risk score in acute myeloid leukemia with normal karyotype. Blood. 2011; 117(17):4561–4568. [PubMed: 21372155]
44. Schlenk RF, et al. Individual patient data-based meta-analysis of patients aged 16 to 60 years with core binding factor acute myeloid leukemia: a survey of the German Acute Myeloid Leukemia Intergroup. J Clin Oncol. 2004; 22(18):3741–3750. [PubMed: 15289486]
45. Paschka P. Core binding factor acute myeloid leukemia. Semin Oncol. 2008; 35(4):410–417. [PubMed: 18692691]
49. Gupta V, et al. Comparable survival after HLA-well-matched unrelated or matched sibling donor transplantation for acute myeloid leukemia in first remission with unfavorable cytogenetics at diagnosis. Blood. 2010; 116(11):1839–1848. [PubMed: 20538804] Using registry data, authors sowed that allo-HCT using HLA-well-matched URD and MRD resulted in similar LFS and OS in AML patients in CR1 with unfavorable cytogenetics. Outcomes of HCT from HLA-partially-matched URD were inferior.
47. Schlenk RF, et al. Prospective evaluation of allogeneic hematopoietic stem-cell transplantation from matched related and matched unrelated donors in younger adults with high-risk acute myeloid leukemia: German-Austrian trial AMLHD98A. J Clin Oncol. 2010; 28(30):4642–4648. [PubMed: 20805454]
48. Eapen M, et al. Effect of graft source on unrelated donor haemopoietic stemcell transplantation in adults with acute leukaemia: a retrospective analysis. Lancet Oncol. 2010; 11(7):653–660. [PubMed: 20558104]
49. Brunstein CG, et al. Allogeneic hematopoietic cell transplantation for hematologic malignancy: relative risks and benefits of double umbilical cord blood. Blood. 2010; 116(22):4693–4699. [PubMed: 20686119] Studying 536 patients at the Fred Hutchinson Cancer Research Center and University of Minnesota with malignant diseases, the authors showed that leukemia-free survival after dUCB transplantation was comparable with that observed after MRD and MUD transplantation. This study indicates that for patients without an available HLA matched donor, the use of 2 partially HLA-matched UCB units is a suitable alternative.
50. Ciceri F, et al. A survey of fully haploidentical hematopoietic stem cell transplantation in adults with high-risk acute leukemia: a risk factor analysis of outcomes for patients in remission at transplantation. Blood. 2008; 112(9):3574–3581. [PubMed: 18606875]
51. Rowe JM, et al. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. Blood. 2004; 103(2):479–485. [PubMed: 14512295]
52. Goldstone AH, et al. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. Blood. 2001; 98(5):1302–1311. [PubMed: 11520775]
53. McClune BL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol. 2010; 28(11):1878–1887. [PubMed: 20212255] Using registry data in 1080 patients older than age 40 years with AML in CR1 or MDS, the authors showed thatage did not have an impact on disease outcomes. This sduty indicated that age should not be a containdication to allo-HCT.
54. Estey E, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). Blood. 2007; 109(4):1395–1400. [PubMed: 17038533]
55. Juliusson G, et al. Hematopoietic stem cell transplantation rates and long-term survival in acute myeloid and lymphoblastic leukemia: Real-World Population-Based Data From the Swedish Acute Leukemia Registry 1997–2006. Cancer. 2011 This is a population based study showing that 42% of AML patients younger than age 60 received alloSCT, and long-term survival was better than in recently published large international studies, despite their lack of selection bias.

Key points

- Current recommendations for allo-HCT for patients in CR1 are limited to those whose risk of relapse significantly exceeds the mortality from allo-HCT and is based on cytogenetic stratification into good-, intermediate-, and poor-risk AML
- Recent studies have shown significant survival advantage for allo-HCT during CR1 in intermediate- and high-risk AML patients.
- Based on risk stratification and patient characteristics, allo-HCT should be considered and donor search be initiated early in the disease course.

Table 1

Standardized reporting for correlation of cytogenetic and molecular genetic data in AML by European LeukemiaNet [15]

Genetic Group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD (normal karyotype) Mutated *CEBPA* (normal karyotype)
Intermediate-I	Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *MLL* rearranged −5 or del(5q); −7; abnl(17p); complex karyotype‡

‡Three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions, that is, t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3).

Source: Reproduced with permission from: *Dohner, H., et al., Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood, 2010. 115(3): p. 453–74.*

Table 2

Genetic alterations in CN-AML

Mutation	Frequency in CN-AML (%)
NPM1	45–55
FLT3-ITD	35–45
IDH1[*]	8–9
MLL-PTD	5–10
CEBPA	~10
NRAS	5–10
WT1[*]	8
RUNX[*]	14–34
FLT3-TKD	5–8

[*] Requires confirmation by additional studies.

Abbreviation: CN, normal cytogenetic.

Source: Original