Recent advances in the treatment of acute myeloid leukemia
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Abstract
Acute myeloid leukemia (AML) is a disorder with significant molecular and clinical heterogeneity. Although there have been clear advances in the identification of somatic genetic and epigenetic alterations present in the malignant cells of patients with AML, translating this knowledge into an integrated view with an impact on the clinical treatment of AML has been slower to evolve. Recent clinical advances in the treatment of AML include studies demonstrating the benefit of dose-intense daunorubicin therapy in induction chemotherapy for patients of any age. We also review use of the DNA methyltransferase inhibitor azacitidine for treatment of AML in elderly patients as well as a study of global patterns of DNA methylation in patients with AML. Lastly, we review a recent assessment of the role of allogeneic hematopoietic stem cell transplantation in AML in first complete remission.

Introduction and context
Acute myeloid leukemia (AML) is the more common acute leukemia in adults. Genetic and functional studies have demonstrated that AML develops as a result of acquisition of genetic and epigenetic alterations that result in abnormal differentiation and unlimited self-renewal. Although patients with AML, with the exception of acute promyelocytic leukemia, are treated with similar therapies, it has long been recognized that there is significant biological, clinical, and genetic heterogeneity in AML. Recent genetic studies have continued to elucidate molecular alterations in AML with clinical and prognostic significance, and there is an ever-increasing list of somatic genetic abnormalities described in AML. In addition to mutations in MLL, FLT3, NPM1, CEBPA, K/N-Ras, KIT, and WT1, mutations in the putative epigenetic modifiers TET2 [1-4] and ASXL1 [2,5] as well as in the metabolic enzymes IDH1 and IDH2 [6,7] have been described in AML in the past year.

Although increasing knowledge of the genetic abnormalities present in AML has continued to improve our understanding of the biology of this disorder, an integrated view of the genetic and epigenetic abnormalities found in AML is greatly needed. Even more challenging will be translating such a comprehensive characterization into a clinically useful decision algorithm.

In this review, we summarize the findings from four recent clinical studies of treatment in AML. The first two studies focus on optimizing induction chemotherapy regimens in AML using anthracycline dose-intensification. The third study evaluates the role of the DNA methyltransferase inhibitor azacitidine in the treatment of elderly patients with AML and a low blast count. The final study is a discussion of a recent meta-analysis regarding the use of allogeneic hematopoietic stem cell transplantation (HSCT) in first remission of AML.

Recent advances
Optimizing induction chemotherapy in AML with anthracycline dose-intensification
The current standard of care for induction chemotherapy of AML is 3 days of an anthracycline and 7 days of...
cytarabine (100-200 mg/m² continuous intravenous) [8]. While attempts to increase response rate with the addition of agents such as thioguanine [9], etoposide [10], fludarabine [11], and topotecan [11] have failed, two studies published in the fall of 2009 demonstrated that intensification of the dose of daunorubicin improves outcome in de novo AML [12,13].

The first study by the Eastern Cooperative Oncology Group randomized previously untreated AML patients aged 17-60 years to standard dose (45 mg/m²) or high-dose (90 mg/m²) daunorubicin in combination with 7 days of cytarabine (100 mg/m² continuous infusion) [12]. Patients in complete remission (CR) were then offered allogeneic HSCT or high-dose cytarabine, with or without gemtuzumab ozogamicin, followed by allogeneic HSCT. Treatment with high-dose daunorubicin resulted in improved CR rate (70.6% versus 57.3%, \( P < 0.001 \)) and longer overall survival (OS; median, 23.7 versus 15.7 months).

As the results of this study were published, Löwenberg et al. [13] simultaneously reported the use of a similar daunorubicin dose-intensification induction regimen in elderly AML patients. In this study, newly diagnosed AML patients aged 60 years or older (median age 67) were randomly assigned to receive cytarabine (200 mg/m² continuous intravenous infusion) plus daunorubicin for 3 days at the conventional dose of 45 mg/m² or at the escalated dose of 90 mg/m². This treatment was then followed by a second cycle of cytarabine at a dose of 1000 mg/m² every 12 hours for 6 days. The elevated dose of daunorubicin led to an increased CR rate (64% versus 54%, \( P = 0.002 \)) but did not affect OS in the study in general. However, there was a significant improvement in OS in patients aged 60-65 years who received the higher-dose of daunorubicin compared with the conventional dose.

Importantly, in both studies, treatment with high-dose daunorubicin did not result in significant differences in hematologic toxicity or adverse events. Moreover, treatment with high-dose daunorubicin did not prolong time to receive consolidation therapy. These studies suggest that there is a dose-response relationship between anthacycline therapy and AML, and that anthacycline dose-intensification results in improved responses without marked increases in attendant toxicity. Whether dose-intensified daunorubicin is associated with improved long-term survival remains to be seen given the short duration of follow-up for these studies, and more importantly, whether specific molecularly defined subtypes of AML specifically benefit from dose-intensified induction regimens.

**Use of azacytidine as treatment in AML**

Given that most patients with AML are aged 60 years or older and that treatment with intensive chemotherapy (such as the dose-intense daunorubicin plus cytarabine induction described above) is limited to 30-60% of elderly AML patients [14], there has been great interest in developing alternative therapeutic strategies for elderly AML patients. However, clinical trials with low-dose cytarabine [15], the farnesyl transferase inhibitor tipifarnib [16], and gemtuzumab ozogamicin [17] have demonstrated little or no improvement in overall survival in elderly patients with AML. Importantly, a recent phase III randomized trial of the DNA methyltransferase inhibitor azacytidine demonstrated an improvement in survival as a single agent in older AML patients with 20-30% bone marrow blasts compared with ‘conventional care regimens’ [18]. In this study, conventional care regimens were defined as best supportive care, low-dose cytarabine, or intensive chemotherapy. Most patients (86%) were considered unfit for intensive chemotherapy and azacytidine resulted in an overall survival of 24.5 months compared with 16.0 months for patients receiving conventional care regimens (\( P < 0.001 \)). Moreover, azacytidine was associated with fewer days in hospital and higher two-year overall survival rates.

With further clinical study of epigenetic targeted therapies in AML, it will be important to correlate response to epigenetic therapies with genome-wide methylation data before and after treatment. The largest study of the genome-wide methylation status of AML genomes was recently published by Figueroa et al. [19]. In this study, genome-wide promoter DNA methylation profiling was performed using the HELP assay (HpaII tiny fragment enrichment by ligation-mediated PCR). In the first part of the study the authors found that the known cytogenetic subsets of AML (e.g., t(15;17), inv(16), t(11q23)) were associated with distinct global DNA methylation patterns. More interestingly, the authors then integrated DNA methylation array data with gene-expression profiling and identified unique subsets of AML. These specific subsets of AML did not align with kinase abnormalities described in AML (mutations in Flt3, N/K-Ras, CBL, KIT, JAK2), suggesting that methylation and gene-expression changes in AML may be influenced by alterations other than single activating kinase mutations. As the molecular characterization of the epigenetic machinery and landscape of AML improves, it will be interesting to correlate data from
Current state of allogeneic HSCT for AML in first remission

The goal of therapy in the treatment of younger patients with AML is to achieve a cure. While ≥70% of patients with AML aged <60 years will achieve first CR (CR1), a substantial number of patients relapse during or after consolidation therapy [20]. Thus, treatment with allogeneic HSCT in young patients with AML in CR1 has been frequently studied, but until recently the use of allogeneic HSCT was not well-defined for all risk groups of AML. Less than 1 year ago, Koreth et al. [21] performed a meta-analysis of all published data on the use of allogeneic HSCT versus non-allogeneic HSCT options (autologous HSCT, consolidation chemotherapy, or both) for patients with AML aged <60 years in CR1. They used an intention-to-treat analysis based on donor availability to capture information from all patients with AML evaluated for up-front allogeneic HSCT with a donor search as part of a prospective trial. They found that allogeneic HSCT significantly improved relapse-free survival and OS for intermediate- and poor-risk AML (based on cytogenetic risk) but not in good-risk AML. Five-year OS was estimated at 45% and 20% for intermediate- and poor-risk AML, respectively, with non-allogeneic HSCT options. This is compared with OS rates of 52% and 31% for patients with intermediate- and poor-risk AML, respectively, who underwent allogeneic HSCT.

Previous studies have shown that mutational status is an important predictor of outcome and treatment response in AML, including response to allogeneic HSCT. The landmark study by Schlenk et al. [22] demonstrated the importance of correlating mutational status of normal karyotype AML patients with likelihood of attaining complete remission after chemotherapy and chance of benefiting from an allogeneic HSCT. In this study, the mutational status of NPM1, Flt3, CEBPa, MLL, and N-Ras were assessed in 872 adults aged <60 years with cytogenetically normal AML. In addition to revealing the mutational frequency of each of these genes in normal karyotype AML, the study more importantly demonstrated that the factors associated with CR in normal karyotype AML include the genotype of mutant NPM1 without Flt3 internal tandem duplication (ITD), the mutant CEBPa genotype, and younger age. Moreover, because 150 individuals in this study underwent HSCT from an HLA-matched related donor, the authors were able to identify that the benefit of the transplant was limited to the subgroup of patients with Flt3 ITD or the genotype consisting of wild-type NPM1 and CEBPa without Flt3 ITD.

Implications for clinical practice

The recent clinical studies reviewed here demonstrate the benefit of high-dose daunorubicin in induction therapy of AML for patients of any age eligible to receive intensive chemotherapy [12,13]. Following successful achievement of complete remission, recent detailed meta-analyses suggest that allogeneic HSCT is beneficial for any patient in cytogenetically defined intermediate- or poor-risk categories [21]. For elderly AML patients with <30% bone marrow blasts who are not eligible to receive intensive chemotherapy, treatment with azacitidine appears to improve OS compared with alternative treatments [18]. Given that many molecular alterations in AML have been demonstrated to influence response to clinical therapies [8,12], further efforts to integrate genome-wide molecular alterations with treatment response and outcome are needed and will inform future analyses of the cohorts described in these clinical trials. Characterization of primary AML samples by the use of high-throughput genetic, epigenetic, and RNA/microRNA expression techniques continues to improve, and it will be important to incorporate molecular analyses into existing and future clinical trials to delineate genetic and epigenetic predictors of response and outcome to specific therapies. With the identification of new mutated genes in AML since the publication of the study by Schlenk et al. [22] as well as the ability to profile the epigenetic state of AML samples, it will be intriguing to repeat such correlative efforts. In particular, it will be especially useful to use this biological information to ascertain the benefit of response to allogeneic HSCT for those under the age of 60 and the likelihood of achieving CR for the elderly with AML.

Abbreviations

AML, acute myeloid leukemia; CR, complete remission; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; OS, overall survival; PCR, polymerase chain reaction.

Competing interests

The authors declare that they have no competing interests.

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