Acute Myeloid Leukemia: Past, Present, and Prospects for the Future

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Abstract

Dose intensification of chemotherapy and the combination of a third cytotoxic agent with standard cytarabine and anthracycline-based induction chemotherapy have led to improved outcomes in select groups of patients with acute myeloid leukemia (AML). However, despite some progress in this area, it appears that we might be reaching the limit of cytotoxic chemotherapy for the treatment of AML, especially in older patients and in those with poor-risk features whose disease tends to be relatively chemoresistant. Recent advances in the molecular classification of AML have identified pathogenic pathways that can be exploited with targeted agents and rational drug combinations. Novel nontransplant immunotherapies also show promise in the treatment of AML, especially when a targetable molecular aberration cannot be identified. Sensitive methods for detecting minimal residual disease in AML have not only improved prognostication of these patients but also provide the framework for risk-adapted strategies in this heterogeneous disease.

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Introduction

The combination of cytarabine and an anthracycline has been the standard acute myeloid leukemia (AML) induction regimen for >30 years.[1] Although there has been gradual improvement in the outcomes of patients with AML over the past several decades with modifications to this standard induction regimen, these gains have been largely restricted to specific subgroups of patients, particular younger patients with favorable-risk features.[2] Intensified chemotherapy regimens for patients with core binding factor (CBF) AML, molecular characterization and refined risk stratification of patients with normal karyotype AML and the use of targeted agents in acute promyelocytic leukemia (APL) have led to significant improvements in these specific disease groups. However, the prognosis remains relatively dismal for older patients and those with adverse disease-related features. Dose intensification of chemotherapy and combination of other cytotoxic agents with standard induction chemotherapy have generally failed to improve outcomes in these historically poor-risk groups. Future advances in AML will therefore require further molecular classification and identification of pathogenic pathways of this heterogeneous disease. Targeted therapies directed at molecular mutations and novel immune-based strategies hold promise in improving outcomes in AML, especially for those patients with particularly biologically complex disease that is relatively resistant to cytotoxic chemotherapy. The detection of post-treatment minimal residual disease (MRD) and innovative therapeutic approaches to eradicate MRD might also improve outcomes, although the optimal method of MRD quantification and the best way to incorporate this information into risk-adapted strategies remains an area of intense investigation.

Intensification of Chemotherapy

Higher doses of anthracycline administered as part of induction chemotherapy have been associated with improved outcomes in some trials. A large randomized study that compared induction with high-dose (90 mg/m^2) versus standard-dose (45 mg/m^2) daunorubicin resulted in a higher complete remission (CR) rate of 70.6% versus 57.3% and prolonged median overall survival (OS) of 23.7 versus 15.7 months with higher daunorubicin doses.[3] However, subgroup analyses suggested that these benefits were restricted to patients younger than 50 years of age with favorable or intermediate-risk cytogenetics and *FLT3* wild type disease. A similar study that compared these same doses of daunorubicin in patients age 60 years and older also showed a higher CR rate with higher doses of daunorubicin, although a survival benefit was only seen in patients aged 60-65 years, likely because of increased toxicity and

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more biologically aggressive disease in the older patients.[4] Notably, a more recent large randomized study of 1206 patients with previously untreated AML that compared induction with cytarabine combined with 90 mg/m^2 or 60 mg/m^2 of daunorubicin failed to show a difference in remission rates or survival outcomes with the higher-dose regimen among any prespecified subgroup, suggesting a limit to the benefit of anthracycline dose intensification.[5]

Dose intensification of cytarabine in patients with AML has also been explored. A large randomized study that compared induction with an anthracycline combined with either high-dose cytarabine (3 g/m^2 every 12 hours on days 1, 3, 5, and 7) or standard-dose cytarabine (100 mg/m^2 by continuous infusion over 10 days) showed higher CR rates with the high-dose cytarabine regimen (78.7% vs. 72.0%, respectively). Improved 6-year OS was also observed in patients aged 15-45 years who received high-dose cytarabine (51.9% vs. 43.3% with standard-dose cytarabine), although no difference was seen in older patients.[6] Similarly, the AML15 trial, which evaluated an intensive regimen of FLAG-Ida (fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor, and idarubicin) compared with standard induction chemotherapy in younger patients with AML showed that FLAG-Ida was associated with a significantly lower risk of relapse although no OS benefit was seen, likely because of the toxicity of the regimen.[7] However, among those patients who were able to receive all scheduled induction and consolidation cycles, FLAG-Ida was associated with superior OS. This translated to an impressive 8-year OS of 95% in patients with favorable-risk and 63% in patients with intermediate-risk AML.

The combination of a third cytotoxic agent with the induction chemotherapy backbone has been met with mixed results. For example, an early report suggested that the combination of etoposide with standard AML induction prolonged the duration of CR,[8] but this has not been shown to confer a survival benefit.[7,8] Nucleoside analogues used in combination with cytarabine have been shown to increase intracellular levels of cytarabine triphosphate, the active antileukemic metabolite of cytarabine, providing a rationale for the combination of these drugs.[9] A number of studies have therefore evaluated the combination of nucleoside analogues to cytarabine and anthracycline-based induction. A randomized trial showed that the addition of cladribine, but not fludarabine, improved survival in patients who underwent induction for AML.[10] Our group has reported that the combination of clofarabine, idarubicin, and cytarabine for induction in younger patients with newly diagnosed AML is associated with improved survival compared with a historical cohort of patients treated with idarubicin and cytarabine alone.[11] Notably, this improvement in outcomes with the clofarabine-containing regimen was most pronounced in patients aged 40 years and younger.

Gemtuzumab ozogamicin (GO) is an anti-CD33 antibody-drug conjugate that has been extensively studied in combination with standard induction chemotherapy. A recent meta-analysis showed that GO results in lower relapse rates and prolonged survival when combined with standard chemotherapy in patients with favorable or intermediate cytogenetic-risk AML, but not in patients with adverse cytogenetics.[12] The benefit of GO has been especially pronounced in patients with CBF leukemia,[12-14] and in a report of 896 patients with CBF leukemia treated between 1988 and 2012 only the combination of GO with induction chemotherapy was associated with prolonged survival in multivariate analysis.[14]

Improvements of outcomes in patients with AML through dose intensification strategies and the combination of a third cytotoxic agent with the induction backbone have largely been restricted to younger patients with more favorable-risk disease. Thus, we propose that we can simplistically divide patients with AML into patients with chemosensitive or chemoresistant disease, on the basis of patient age, cytogenetic, and molecular abnormalities and the presence or absence of an antecedent hematologic malignancy (Table 1). This distinction provides a useful conceptual framework for the development of novel therapeutic strategies for AML. Those patients with chemosensitive disease—younger patients and those without antecedent hematologic malignancy, adverse cytogenetics, or deleterious mutations—are more likely to derive a survival benefit from higher doses of cytotoxic chemotherapy during induction and consolidation, despite the potential added toxicity of these more intense regimens. Thus, for this population, further refinement of the induction regimen through modification of the induction backbone and the combination of alternate chemotherapeutic agents and dosing strategies is reasonable. Conversely, for those patients with more biologically complex and resistant disease, we have likely reached the limit of cytotoxic chemotherapy; in this subset of patients with chemoresistant disease, novel treatment strategies are needed.

Novel Molecular and Immune-Based Therapies

Targeted Agents

For many decades, risk stratification of AML was largely on the basis of cytogenetic analysis.[15,16] However, recent advances have identified new molecular aberrations that have refined our prognostication of AML[17-19] and have identified common pathological pathways.[20] The discovery of recurrent molecular abnormalities in AML has led to a surge in the development of novel agents targeting these mutations. Many of these new drugs have shown significant clinical activity in patients with relapsed/refractory disease and some have been combined upfront with chemotherapy in younger, fit patients or with hypomethylating agents in those who are not good candidates for intensive therapy.

FLT3 inhibitors are perhaps the most studied of the novel targeted therapies for AML. *FLT3* mutations occur in approximately 30% of

Table 1 A Simplified Classification of AML on the Basis of Sensitivity to Chemotherapy

Type of AML	Characteristics	Treatment Approach
Chemosensitive	• CBF leukemia (without *KIT* mutation) • Diploid AML with *NPM1* or *CEBPα* (without *FLT3* mutation) • Others (younger patients without t-AML or AHD)	Dose intensification of chemotherapy might be helpful
Chemoresistant	• Adverse cytogenetics • *FLT3*-ITD mutation • Others (older patients or younger patients with t-AML or AHD)	New agents are needed (eg, molecular targeted or immune-based therapy)

Abbreviations: AHD = antecedent hematologic disorder; AML = acute myeloid leukemia; CBF = core binding factor; ITD = internal tandem duplication; t-AML = therapy-related AML.