Risk Stratification and Emerging Treatment Strategies in Acute Myeloid Leukemia

Presented by Margaret R. O'Donnell, MD

Abstract

Two major prognostic factors for outcomes with acute myeloid leukemia (AML) therapy center on cytogenetic/molecular markers and patient age. With the paucity of novel agents available for the treatment of AML, clinicians are forced to fine-tune existing treatment strategies based on risk status to achieve the best results. Dr. Margaret R. O'Donnell of the City of Hope Cancer Center explored the prognostic implications of molecular mutations and other risk factors in the treatment of AML and presented an update of the current treatment strategies, sharing relevant clinical trial data on which recommendations are based. She also provided a glimpse of a novel non-chemotherapy approach to acute promyelocytic leukemia, which has had a major impact on treatment guidelines for this hematologic malignancy. (*JNCCN* 2013;11:667–669)

"In the majority of our patients, the major risk factor for whether they will do well or poorly is related to their cytogenetic and/or molecular markers," stated Margaret R. O'Donnell, MD, Associate Clinical Director, Division of Hematology and Bone Marrow Transplantation, City of Hope Comprehensive Cancer Center, Duarte, California, and Chair of the Acute Myeloid Leukemia (AML) Panel of NCCN. Thus, the changes in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for AML reflect the prominent role of cytogenetic and molecular testing in deciding on consolidation or salvage therapy for newly diagnosed AML. In older patients, knowing cytogenetics before starting treatment may be paramount in deciding on standard therapy or a more conservative approach.

Presented by Margaret R. O'Donnell, MD, Associate Clinical Director, Division of Hematology and Bone Marrow Transplantation at the City of Hope Comprehensive Cancer Center, Duarte, California.

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Correspondence: Margaret R. O'Donnell, MD, City of Hope Comprehensive Cancer Center 1500 E. Duarte Road, Division of Hematology/BMT, Duarte, CA 91010-3000. E-mail: MO'donnell@coh.org

Prognostic Factors at Play in AML

Various prognostic factors play a role in the outcomes of AML therapy. These include cytogenetic and molecular markers (Figure 1), patient age, prior myelodysplastic syndrome or secondary AML (related to prior chemotherapy for breast cancer or lymphoma), and response to the initial induction therapy (ie, remission vs residual disease).

The NCCN Guidelines specify that risk status should be based on validated cytogenetics and molecular abnormalities. Better-risk markers include inv(16), t(8;21), t(16;16), t(15;17), and mutations of NPM1 or double mutations of CEBPA in the absence of the FLT3-ITD mutation. However even among those with favorable cytogenetics such as inv(16,)/t(16;16), Paschka et al[1] showed that secondary chromosomal or molecular mutations (such as c-KIT and FLT-3) had an adverse impact on outcomes. "Those with c-KIT did worse, and those with trisomy 22 did substantially better," said Dr. O'Donnell. "The only ones you might consider transplant up front for would be those with c-KIT." Furthermore, Cairoli et al[2] reached the same conclusion about c-KIT mutations and their adverse impact on outcomes.

Other mutations under study are the TET2 and IDH2 mutations, said Dr. O'Donnell. Metzeler et al[3] reviewed for TET2 mutations in 427 patients with cytogenetically normal AML. They found that TET2 mutations were associated with a decrease in both disease-free and overall survival and that IDH2 mutations (primarily in older patients) were linked with a decrease in complete remission rates and overall survival.[3]

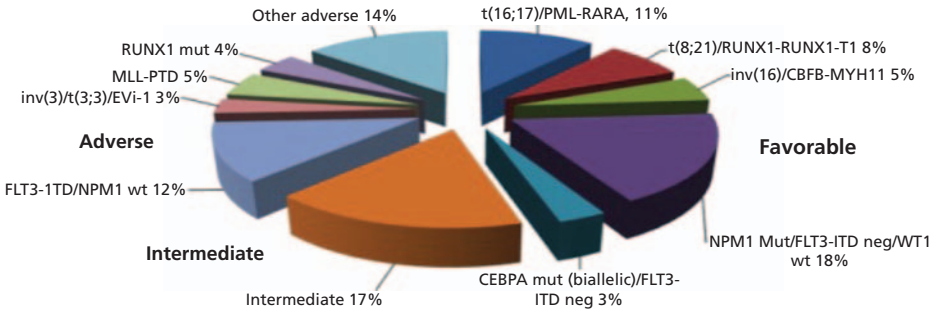

Figure 1 Cytogenetic and molecular markers in acute myeloid leukemia.

Poor-risk markers include monosomal karyotypes, −5, 5q, and FLT3-ITD mutations. "Patients with monosomal karyotypes do particularly abysmally, with survival rates in the range of 5% to 10% at best," noted Dr. O'Donnell. Studies have shown that overall survival outcomes differ based on cytogenetic status. According to the United Kingdom's Medical Research Council trials, at 10 years, 76% of those with good cytogenetics were alive, compared with only 11% of those with poor cytogenetics. Increasingly, molecular markers allow clinicians to differentiate those who were previously viewed as intermediate risk and sort them into tighter prognostic categories that better predict which patients will have outcomes poor enough to warrant the potential morbidity and mortality associated with allogeneic transplant or for whom a clinical trial might offer a better option than standard consolidation.

Current Treatment Strategies for Younger and Older Patients

Unfortunately, no new drugs for AML have been approved by the US FDA over the past 20 years, Dr. O'Donnell said. She added that we have been basically tinkering with the available drugs" by increasing the doses of cytarabine (Ara-C) or changing the dose of anthracycline to modulate outcomes.

Several groups of investigators have studied intensifying the treatment dose of cytarabine. Löwenberg et al[4] compared 2 dose schedules of cytarabine in double induction treatment in 860 patients with newly diagnosed AML. At a median follow-up of 5 years, no significant differences were seen between the groups with respect to complete remission rates, probability of relapse, event-free survival, and overall survival. The higher-dose cytarabine schedule resulted in excessive toxic effects with no clear advantage in any prognostic subgroup.

"Right now, there is no good rationale for high-dose cytarabine as initial induction therapy for patients with AML outside the context of a clinical trial," declared Dr. O'Donnell. In addition, problems with drug availability of both cytarabine and daunorubicin have occurred over the past 5 or 6 years. Thus, in case of drug shortages, she added, clinicians have some data that will support using lesser doses of cytarabine for consolidation than had previously been recommended, particularly for patients with intermediate or unfavorable cytogenetics.

The NCCN Guidelines recommend standard-dose cytarabine and high-dose daunorubicin (90 mg/m^2) or idarubicin for induction therapy in patients with AML younger than age 65 based on phase III data from Fernandez et al.[5] In their study, 657 patients (between ages 17 and 60) received daunorubicin at either the standard or a high dose along with cytarabine. They found that the higher dose of daunorubicin improved the rate of complete remission (71% vs 57%) and the duration of survival (23.7 vs 15.7 months) over standard-dose therapy.

For younger patients with AML who have better-risk cytogenetics or molecular abnormalities, postremission therapy consists of a clinical trial, high-dose cytarabine (category 1 recommendation), or high-dose cytarabine-based consolidation followed by autologous hematopoietic stem cell transplant (HSCT; category 2B recommendation). For younger patients with AML who have treatment-related disease or poor-risk cytogenetics or molecular abnormalities, postremission therapy consists of a clinical trial or matched-sibling or alternative donor HSCT. The HOVON trial also showed a benefit of higher dose daunorubicin (90 mg/m^2) for older age patients up to age 65 but no benefit to anthracycline intensification in patients above that age.

Older patients with AML generally have less chance of experiencing remission (especially those older than 75), stated Dr. O'Donnell. The key challenge is to decide which older patients would benefit from intensive first-line therapy. According to Dr. O'Donnell, those likely to do well with intensive

therapy (standard-dose cytarabine) tend to have favorable cytogenetic or molecular profiles and few comorbidities. For those with unfavorable cytogenetics, low-intensity therapy or a clinical trial would be recommended.

Two phase II studies evaluated 2 different first-line treatment options for older patients with AML viewed as not fit for standard induction chemotherapy.[6,7] Cashen et al[6] tested decitabine in 55 patients with a median age of 74 years, almost half of whom had poor-risk cytogenetics. The median event-free survival associated with this outpatient therapy was 25 weeks, and the 30-day mortality rate was 7%. Kantarjian et al[7] assessed the role of clofarabine in 112 older patients with a median age of 71 years.[7] This is a less-intensive therapy but requires inpatient hospitalization. Fifty-five percent of these patients had poor-risk cytogenetics. In this study, median event-free survival was 37 weeks, and the 30-day mortality was 10%.

The NCCN Guidelines for patients older than age 60 stratify patients for postremission therapy based on response to induction. For those with a complete remission, options include a clinical trial, reduced-intensity HSCT, standard-dose cytarabine, or low-intensity regimens. For those with induction failure, options include a clinical trial, reduced-intensity HSCT only in the context of a clinical trial, or best supportive care.

A Non-chemotherapy Option for Acute Promyelocytic Leukemia

For the first time, the NCCN Guidelines for acute promyelocytic leukemia (APL) were changed as a result of an abstract from the 2012 American Society of Hematology meeting.[8] Investigators in Italy compared the gold standard for newly diagnosed non–high-risk APL—simultaneous all-trans-retinoic acid (ATRA) and chemotherapy (idarubicin)—with the chemotherapy-free combination of ATRA and arsenic trioxide (ATO). ATO has been the treatment of choice for patients with relapse. A total of 154 patients, ranging in age from 18 to 70, participated in the study.

"The complete remission rates were fabulous in both arms," said Dr. O'Donnell, at 97%. All 75 patients treated with ATRA and ATO experienced complete remission whereas 3 patients in the chemotherapy arm died early in induction from bleeding or differentiation syndrome. The 2-year event-free survival rate was better in the non-chemotherapy arm than in the standard-treatment arm (97% vs 87%). "As expected, the hematologic toxicities were a lot less without chemotherapy," noted Dr. O'Donnell. However, more cases of hepatic toxicity and leukocytosis occurred in the ATRA plus ATO combination arm, and patients should be started on steroids before beginning this regimen, she said.

Thus, for the first time, the NCCN Guidelines have removed chemotherapy from the first-line treatment for APL. For treatment induction of patients with low or intermediate-risk APL, ATRA in 2 divided doses plus ATO is recommended until bone marrow remission.

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