New Directions in Acute Myeloid Leukemia

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Presenters' disclosures of conflicts of interest are found at the end of this article.

https://doi.org/10.6004/jadpro.2019.10.3.18

Acute myeloid leukemia (AML) is diagnosed in about 20,000 people a year and remains a very challenging malignancy to treat. Advanced practitioners at JADPRO Live 2018 were updated on risk classification, response criteria, and encouraging new therapies by Kelda Gardner, PA-C, MHS, teaching associate at the University of Washington, Seattle, and Melinda Tran, PharmD, BCOP, clinical instructor at the University of Washington and clinical pharmacist with YouScript, Inc.

AML BASICS

Ms. Gardner provided background for the AML discussion, noting that the median age at diagnosis is 68 and the median 5-year survival rate is only 27% (National Cancer Institute, 2018). While this is a discouraging outcome, it is an improvement over the 6% rate observed in 1975, largely owing to better treatments and supportive care. In 5% to 10% of individuals with AML, a genetic predisposition is found, most commonly mutations in *GATA2, RUNX1, CEBPA,* and *TERC/TERT*, and Fanconi anemia. "In our center, we test for inherited conditions in patients younger than 45 and in those with a strong family history of AML or myelodysplastic syndrome (MDS)," she indicated. Prior treatment with chemotherapy or radiation are risk factors for treatment-related AML, as is an antecedent hematologic disorder. For these patients with so-called secondary AML, survival is "strikingly" worse than for those with de novo or primary AML (Granfeldt Østgård et al., 2015).

Acute myeloid leukemia is diagnosed by the presence of ≥ 20% myeloid blasts in the bone marrow or peripheral blood, although 20% is not required for diagnosis in the presence of t(8;21), inv(16), t(16:16), or t(15;17) abnormalities (Arber et al., 2016; Döhner et al., 2017). "With the diagnosis of AML comes the pretreatment knowledge that outcomes range from death within a few days of starting therapy to a potential cure," she said. Therefore, the University of Washington mandates testing on blood or marrow at diagnosis to reveal morphology, cytogenetics, molecular profile, and immunophenotype (by flow cytometry). "The importance of the full-panel workup at diagnosis is this: not only does it give a prognostic indication, it reveals the potential need for transplant or novel therapies, and it

J Adv Pract Oncol 2019;10(3):299–303

suggests what markers we should monitor for response to therapy," she offered.

Older age alone should not be a reason to withhold intensive therapy for AML, she continued. "Multiple retrospective analyses indicate that older patients benefit from higher-intensity therapy," she noted. The 2017 revision of the European LeukemiaNet (ELN) guidelines state that nonintensive therapy is only warranted for patients with older age in addition to another factor, such as poor performance status or comorbidities (Döhner et al., 2017).

IMPORTANCE OF IDENTIFYING CYTOGENETIC ABNORMALITIES

As Ms. Gardner described, most patients with AML have a normal karyotype, but with advancing age, mutations emerge in hematopoietic cells, as they do in the noncancer population. The molecular landscape is heterogeneous, with frequent colocalization of mutations. The ELN's revised 2017 risk classification system incorporated cytogenetics in three ways: (1) intermediate-1 and intermediate-2 risk levels were combined, (2) *TP53* mutation (the single worst adverse factor) was added, and (3) patients with *FLT3* mutations were separated according to allelic ratios (Döhner et al., 2017). (Response criteria was also revised, as described in the following sections.) In the Japan Adult Leukemia Study Group (JALSG) AML201 study, survival probabilities varied greatly between favorable and highest risk groups in this classification (Harada et al., 2018).

HEMATOLOGIC EMERGENCIES

Patients with myeloid leukemias are at risk for several hematologic emergencies, including hyperleukocytosis, tumor lysis syndrome, and thrombohemorrhagic syndrome. Hyperleukocytosis is defined as a white cell count > 100,000/μL and most commonly affects the central nervous system and lungs. Treatment includes cytoreduction with hydroxyurea and leukapheresis (with or without high-dose dexamethasone for pulmonary symptoms) and one or two doses of cytarabine. "When deciding to intervene, the main things to look for are stroke-like symptoms, which may tell you more than the total white cell count," Ms. Gardner added.

Tumor lysis syndrome is more common in acute lymphoblastic leukemia and lymphoma but can be seen with myeloid malignancies as well. It can be spontaneous or induced by chemotherapy, the result being hyperkalemia, hyperphosphatemia, and hypocalcemia. Sufficient but judicious hydration is a mainstay of treatment. Hemorrhagic syndrome is a common concern in acute promyelocytic leukemia and can be fatal. Supportive care is critical, including transfusions of platelets, fresh frozen plasma, and cryoprecipitates.

NEW ASSESSMENT APPROACHES

The treatment-related mortality calculator, a scoring system developed by Drs. Walter and Estey at Fred Hutchinson Cancer Center (2018) for use in newly diagnosed AML, can roughly assess the risk of death within 28 days of induction chemotherapy. The calculator considers age and type of AML (primary or secondary), white blood cell count, percentage of peripheral blasts, and levels of albumin, creatinine, and platelets.

The ELN also updated its AML response criteria: (1) a new category of complete remission (CR) without minimal residual disease (MRD) was added, (2) MRD status—positive, negative, or unknown—was added to the CR category, and (3) the category of complete remission with incomplete hematologic recovery (CRi) now encompasses all CR criteria except absolute neutrophil count (ANC) < 1000/μL and/or platelets < 100,000/μL (Döhner et al., 2017). "Whether or not a patient has recovered his/her neutrophils or platelets, he/she can be put into the CRi category," Ms. Gardner explained.

Depth of response after induction therapy and MRD status, as determined by polymerase chain reaction (PCR) or flow cytometry, have become important indicators for outcomes. In a retrospective analysis of 245 patients, achievement of CR was critically important for relapse-free and overall survival out to 5 years (Chen et al., 2015). "The study showed that having less than 5% blasts in the peripheral blood was not sufficient. Complete remission with incomplete platelet recovery (CRp) and CRi responses were inferior as compared to full CRs," she noted.

The study also accentuated the importance of MRD status, as patients who were MRD-negative

had significantly greater relapse-free and event-free survival. A recent study in *The New England Journal of Medicine* evaluated the risk of relapse according to MRD by multiparameter flow cytometry and next-generation sequencing (Jongen-Lavrencic et al., 2018). Patients who were MRD negative according to both assays had a relapse risk of only 25% at 5 years, compared to 75% for patients who were positive according to both assays (Figure 1). "The question remains as to what to do about MRD. Outcomes are clearly worse," Ms. Gardner revealed.

"At our center we call MRD 'measurable residual disease,' because in the eyes of the patient any leftover leukemia cells are not 'minimal,' " she commented. She added that many clinical trials require the magnitude of MRD to be at least 5% before further treatment is initiated, but her team becomes "highly suspicious," she said, if there is any indication of remaining disease. "If a patient is still *FLT3* mutation–positive after induction, for example, we may consider pushing toward a transplant or additional high-dose therapy," she explained. "I wish we could make more therapy available for 'anything that's present,' but we are not there yet."

Clearly, a role is emerging for MRD status in modifying postremission therapy. The Beat AML Master Trial, conducted by the Leukemia & Lymphoma Society, is assigning personalized treatment based on genomic status, and single centers are testing multiple drugs against remaining cancer cells in an effort to predict efficacy ahead of treatment. Reimbursement for these approaches, however, remains a challenge, the speakers said.

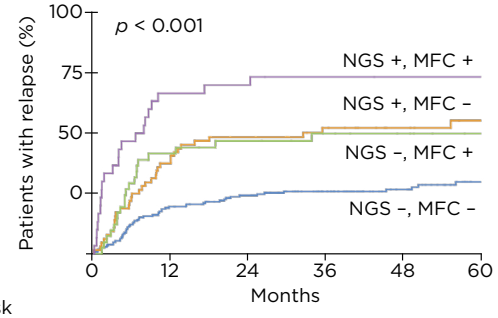
Dr. Tran cautioned that although MRD status is being applied "as a kind of standard of care" in AML, it has not been formally accepted by guideline committees, at least in AML.

ALTERNATIVES TO INTENSIVE INDUCTION

A number of regimens serve as standard induction therapy for newly diagnosed AML patients (Table 1). Alternatives to these intensive approaches currently include azacitidine, decitabine, clofarabine, and lenalidomide, but encouraging new drugs are now available or in development, as discussed by Dr. Tran.

Liposomal daunorubicin and cytarabine (CPX-351; Vyxeos) incorporates a liposomal 5:1 molar ratio of cytarabine to daunorubicin. The drug utilizes nanoscale delivery technology to enhance uptake by leukemic cells and increase efficacy while decreasing toxicity. "In many older patients, 7 + 3 is almost as toxic as it is beneficial. By 'repackaging' it in this liposomal formulation, we are hopefully decreasing the tissue distribution and toxicity and providing the same therapeutic benefit," Dr. Tran explained.

This drug was approved in August 2017 based on data from a phase III trial of 309 previously untreated high-risk older AML patients in which CPX-351 was superior to 7 + 3 for all endpoints. (Lancet et al., 2016). It was also associated with lower 60-day mortality and had a comparable safety profile, with the exception of more prolonged neutrophil and platelet recovering times and a higher rate of hematologic and infectious adverse effects, which did not translate to an increased risk of death or early death. Importantly, CPX-351 treatment allowed more patients to undergo successful allogeneic transplant, and for this group, median overall survival was not reached, but was 10.25 months for patients on 7 + 3 (haz-



No. at risk						
NGS +, MFC +	30	8	7	5	4	4
NGS –, MFC +	41	22	18	14	11	7
NGS +, MFC –	64	39	30	22	15	11
NGS –, MFC –	205	153	130	101	69	42

Figure 1. Rate of relapse according to results of next-generation sequencing and multiparameter flow cytometry. Shown is the cumulative incidence of relapse, according to the presence of positive (+) or negative (–) results for the detection of persistent non-*DTA* mutations during complete remission on next-generation sequencing and on multiparameter flow cytometry. Adapted from Jongen-Lavrencic et al. (2018).

Table 1. Fundamental Principles of Induction

- Most common therapy for 40+ years: 7 + 3 × 1–2 cycles
  - » Anthracycline × 3 days
    - Daunorubicin 60–90 mg/m²/day
    - Idarubicin 10–12 mg/m²/day
    - Mitoxantrone 12–15 mg/m²/day
  - » Cytarabine 100–200 mg/m²/day continuous infusion × 7 days
- Other options include HiDAC-containing regimens, such as IA, FLAG-idarubicin, or G-CLAM
- Moreover, per ELN 2017, age alone should not preclude intensive therapy
- NCCN Guidelines: "The best management of any cancer patient is in a clinical trial."

Note. HiDAC = high-dose cytarabine; IA = idarubicin and cytarabine; FLAG-idarubicin = fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; G-CLAM = granulocyte colony-stimulating factor, cladribine, cytarabine, and mitoxantrone; ELN = European LeukemiaNet; NCCN = National Comprehensive Cancer Network. Information from Yates, Wallace, Ellison, & Holland (1973).

ard ratio [HR], 0.46; p = .0046). This drug may be a viable option for transplant-ineligible patients with high-risk AML, even those of advanced age and poor performance status (the types of patients included in the study).

Gemtuzumab ozogamicin (Mylotarg), which targets the CD33 antigen on leukemia cells, became the first-approved antibody-drug conjugate (ADC). Upon underwhelming results and increased mortality observed in the confirmatory SWOG S0106 trial (Petersdorf et al., 2009), however, gemtuzumab was voluntarily removed from the market in 2010, only to make a comeback in 2017 when a meta-analysis (Hills et al., 2014) as well as the ALFA-0701 trial (Castaigne et al., 2014) demonstrated benefits, especially in favorable-risk patients. A better understanding of optimal dosing and clinical experience using gemtuzumab also helped it gain favor. Its notable adverse effects include prolonged cytopenia and veno-occlusive disease, Dr. Tran said.

IDH1/2 inhibitors target mutations of isocitrate dehydrogenase (IDH), which are found in up to 15% to 20% of newly diagnosed patients and are associated with worse prognosis. The oral IDH2 inhibitor enasidenib (Idhifa) was approved in 2017, followed in 2018 by the IDH1 inhibitor ivosidenib (Tibsovo). "Both drugs are able to produce clinically meaningful responses that are also quite durable, averaging 8.2 months for each (DiNardo et al., 2018b; Stein et al., 2017)," she said. While IDH1/2 inhibitors are relatively well tolerated, differentiation syndrome has been observed. Symptoms include acute respiratory distress, lymphedema, peripheral edema, pleural effusion, pericardial effusions, weight gain, and leukocytosis, "and the condition is very dangerous," she noted. Steroids are required until symptoms resolve; when severe, the drug may need to be discontinued. Drug interactions are also possible, Dr. Tran cautioned.

Venetoclax (Venclexta) is a BCL2 inhibitor that targets a key protein "gatekeeper" to apoptosis. As Dr. Tran explained, the BLC2 family contains both pro-apoptotic and anti-apoptotic proteins and the presence of one or the other shifts the balance between cell survival and cell death. BCL2 inhibitors such as venetoclax can displace the pro-apoptotic protein from the BCL protein, thus allowing it to fulfill its mission and initiate apoptosis. In a study of venetoclax plus a hypomethylating agent in older patients not eligible for intensive chemotherapy, the response rate was 67% and median overall survival was 17.5 months (DiNardo et al., 2018a). In a similar population, venetoclax plus low-dose cytarabine led to a response rate of 75%, with median survival not reached for responders (Lin et al., 2016).

Midostaurin (Rydapt), an oral FLT3 inhibitor, targets the receptor kinase FLT3, which plays a key role in tumor cell growth, proliferation, and differentiation. When mutated, as occurs in about 23% of AML cases, FLT3 is always "on," which results in poor prognosis for patients. The FLT3 internal tandem duplication mutation (*FLT3-ITD*) can be a particularly adverse risk factor, and its impact depends on the allelic ratio. Midostaurin, which targets *ITD*- and *TKD*-mutant *FLT3,* was approved based on the RATIFY trial, in which patients treated with midostaurin plus standard 7 + 3 had a median overall survival of 74.7 months, compared to 25.6 months with standard therapy (p = .009; Stone et al., 2017).

TP53 is a tumor suppressor gene that is yet to be therapeutically targeted. "*TP53*-mutated patients tend to be older and have very complex karyotypes, and conventional chemotherapy only provides them with 4 to 6 months of overall survival time," Dr. Tran indicated. The optimal treatment of patients with *TP53* mutations is still not clear.

Future directions include chimeric antigen receptor (CAR) T-cell therapy and bispecific T-cell engager (BiTE) antibodies, but these approaches are in their infancy in AML, she added.

Disclosure

Ms. Gardner and Dr. Tran have no conflicts of interest to disclose.

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