Emerging Treatments in Acute Myeloid Leukemia: Current Standards and Unmet Challenges

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Abstract: Acute myeloid leukemia (AML) is rare and difficult to treat. Although remission is achieved in most patients with newly diagnosed disease, relapse occurs in most cases. For more than 40 years, the standard up-front induction treatment has been a combination of continuous-infusion cytarabine and an anthracycline. Risk stratification by molecular and cytogenetic characteristics and measurable residual disease (MRD) status informs decisions regarding referral to consolidative allogeneic hematopoietic cell transplant. In 2017, for the first time in years, 4 drugs are under consideration for approval by the US Food and Drug Administration. One of these agents, the multikinase inhibitor midostaurin, has already been approved for the treatment of patients with *FLT3*-mutated AML. The heterogeneity of AML suggests that single-target agents are unlikely to succeed at curing large numbers of patients, and that combinations of novel agents and traditional chemotherapy will be required to achieve this goal. Additionally, the 2017 European LeukemiaNet criteria suggest that treating physicians should strive for the new, stringent remission category (ie, complete remission without MRD). How the new drug approvals in 2017 will change practice is not clear, and further work remains to be done in treating and curing patients with AML.

Background

Despite clinical advances, acute myeloid leukemia (AML) is a fatal disease with a current 5-year survival rate of only 26.6% for all subtypes combined, according to the cancer registry of the Surveillance, Epidemiology, and End Results (SEER) Program.[1] Although younger patients also are affected, the incidence of AML increases sharply with age, and the median age at diagnosis is 67 years.[1] AML is defined by the World Health Organization as the presence of at least 20% myeloblasts or equivalents in the blood or bone marrow, or the localized accumulation of myeloid blasts in tissues (so-called myeloid sarcoma).[2] The finding of certain characteristic cytogenetic abnormalities—including t(8;21), inv(16), and t(15;17)—is sufficient to establish the diagnosis of AML without the blast threshold of 20% having been reached.

Without active treatment other than supportive care, patients typically have a life expectancy on the order of months, and considerably less if they present with a high white blood cell count. If active treatment is used, the first goal is to produce a complete remission (CR), defined as a marrow with fewer than 5% blasts on morphologic assessment, an absolute neutrophil count higher than 1000/µL, and a platelet count higher than 100,000/µL. More than 50 years ago, Freireich and colleagues showed that people who attained CR lived longer than those who did not, with the difference based almost entirely on time in CR.[3] However, without further therapy, AML recurs in most people who achieve CR, and cure generally requires therapy after remission.[4] Therapy is chosen after prognostic information about cytogenetics and molecular changes has been obtained and the patient's response to initial therapy has been determined. This decision involves whether to proceed with chemotherapy alone or to refer the patient for allogeneic hematopoietic cell transplant (HCT). The role of measurable (or "minimal") residual disease (MRD) is still being elucidated. MRD is defined as disease detectable by flow cytometry or molecular testing that is undetectable by morphology. The presence of MRD can have a sensitivity of 80% for predicting eventual morphologic relapse, and probably an even higher specificity. Accordingly, the 2017 European LeukemiaNet (ELN) guidelines have established CR without MRD as a distinct response category. Any increase in MRD will undoubtedly change the approach to a patient's AML therapy in terms of treatment intensity, need for novel agents, and referral for allogeneic HCT.[4]

This review highlights the current standards for the treatment of AML, emerging treatments (including several drugs that have already been approved or are likely to be approved in 2017), and unmet challenges—areas in which improvements are still needed. The pace of treatment change in AML has been slow, but it may accelerate as new drugs and drug combinations become more rationally based. The National Comprehensive Cancer Network guidelines for AML highlight that participation in a clinical trial, if available, should be the first treatment choice for all patients. The possible exception to this dictum is any patient for whom current standard therapy is felt to be reasonably satisfactory—for example, a younger, fit patient with the cytogenetic abnormalities inv(16) or t(8;21) (the 2 subtypes collectively referred to as core-binding factor [CBF] leukemias) or with a mutation in the *NPM1* gene but not the *FLT3* gene.[5]

Current Standard Therapy

Remission Induction

The standard treatment for AML for more than 4 decades has been a combination of infusional cytarabine for 7 days plus an anthracycline for 3 days (so-called 7+3 therapy).[6] Cytarabine is usually administered at a dose of 100 to 200 mg/m^2 per day, and the anthracyclines most commonly used are daunorubicin and idarubicin. The optimal dose of daunorubicin has been examined in multiple trials, with large randomized studies suggesting that a dose of 90 mg/m^2 improves outcomes compared with a dose of 45 or 60 mg/m^2, although the benefit may be greatest in younger patients and toxicity may be increased with the higher dose.[7-10] A more recent randomized trial from the United Kingdom showed no difference for daunorubicin at 90 or 60 mg/m^2 (the dose currently considered standard in 7+3), except for a likely benefit in patients with *FLT3*-internal tandem duplication (ITD)–mutated AML.[11] This combination of 7+3 leads to expected pancytopenia for several weeks, during which time patients are dependent on transfusions of platelets and red blood cells; profound neutropenia means that infectious complications are common as well. Advances in supportive care have led to significant decreases in early or treatment-related mortality in patients receiving induction therapy.[12-14] Comparisons of daunorubicin and idarubicin are complicated by the need to conduct the comparisons at doses producing equivalent levels of toxicity.

At the time of count recovery after induction chemotherapy, generally between days 21 and 35, the bone marrow is evaluated to assess the response to treatment. If the percentage of bone marrow blasts is greater than 5% and the patient's functional status is acceptable, the treating physician will administer another cycle of induction chemotherapy (either 7+3 again or a distinct salvage regimen). The question of whether the chemotherapy should remain the same or be changed for patients whose disease is refractory to the first cycle recently has been examined in a retrospective fashion. An analysis of 1505 patients following Southwest Oncology Group (SWOG) protocols who received 7+3 chemotherapy showed that the CR rate was 48% with the first cycle (early death rate, 9%).[15] However, of 638 patients with refractory disease that did not respond to the first cycle of 7+3, only 333 (52%) went on to receive a second cycle; of those, 43% achieved CR (early death rate, 10%).[15] These data, combined with the European practice of administering a double induction to all patients with newly diagnosed AML, suggest that the disease of patients receiving 7+3 induction should not be considered refractory to therapy until they have received at least 2 cycles of 7+3.

Another option for the up-front treatment of AML is a regimen of high-dose cytarabine (doses >1 g/m^2). A randomized trial showed that the IA regimen developed at the University of Texas MD Anderson Cancer Center, which combined idarubicin at a dose of 12 mg/m^2 daily

for 3 days with cytarabine at 1.5 g/m^2 per day for 4 days by continuous infusion, was not superior to 7+3 in any group and was more toxic.[16] However, a randomized trial involving 1268 patients conducted by the National Cancer Research Institute in the United Kingdom showed that another regimen from MD Anderson—FLAG-IDA (fludarabine at 30 mg/m^2 for 5 days, cytarabine at 2 g/m^2 for 5 days, granulocyte colony–stimulating factor [G-CSF] administered for 7 days, and idarubicin at 10 mg/m^2 for 3 days)—decreased the cumulative incidence of relapse compared with 10+3, although an increased rate of nonrelapse mortality resulted in similar survival rates; however, the survival rate was 95% at 8 years in patients with CBF AML.[17] The Australasian Leukaemia & Lymphoma Group routinely uses ICE therapy (idarubicin at 9 mg/m^2 for 3 days; cytarabine at 3 g/m^2 twice daily on days 1, 3, 5, and 7; and etoposide at 75 mg/m^2 for 7 days), which results in high CR rates.[18] A German study randomly assigned 1770 patients to receive induction with tioguanine, cytarabine, and daunorubicin (TAD, with cytarabine given at 100 mg/m^2 daily for 7 days by continuous infusion) followed by high-dose cytarabine and mitoxantrone (HAM) or induction with 2 courses of HAM (ie, TAD-HAM vs HAM-HAM); in each case the second course was begun 21 days after the start of the first ("double induction").[19] No significant differences were found between the 2 arms, although it is difficult to extrapolate the results of this and other European studies because double induction is not used routinely in the United States.

Postremission Therapy

If CR is observed, the patient will typically receive postremission (also known as consolidation) chemotherapy. If chemotherapy alone is to be used, in the event of favorable-risk AML (eg, CBF AML or *NPM1*-mutated/*FLT3*-unmutated AML) or logistical difficulties with HCT, the most common consolidation regimen in the United States is high-dose cytarabine administered for 3 to 4 cycles.[20-22] Although cytarabine doses often consist of 3 g/m^2 twice a day on days 1, 3, and 5, randomized trials indicate that doses of 1 g/m^2 twice daily for 5 days are equivalent, regardless of whether a patient proceeds to HCT.[20,21]

Some patients may be directly referred to allogeneic HCT, depending on genetic risk stratification (ie, those with intermediate-risk or adverse-risk disease based on the 2017 ELN guidelines, who are unlikely to be cured with chemotherapy alone) and MRD status. Methods for identifying MRD with flow cytometry and molecular detection are highly sensitive,[23,24] and the prognostic significance of MRD is well established in AML as a whole[25-27] and in subsequent allogeneic HCT.[28-31] However, a major limitation to promulgating the use of MRD is that standardized methodology for the detection of MRD is often unavailable outside large academic medical centers. Donor identification for allogeneic HCT can take several months (particularly the identification of matched unrelated donors), and HLA typing often is performed soon after the time of AML diagnosis; acceptable sources include matched sibling donors, matched unrelated donors, cord blood units, and haploidentical donors. Cord blood units and haploidentical donors often can be mobilized more quickly than matched unrelated donors, but it is unclear if any one source is more effective than any other. An ongoing study from the Bone Marrow Transplant Clinical Trials Network (BMT CTN 1101) will help to answer this question (NCT01597778), although it appears that institutional preference may be the primary driver of donor source allocation. Determination of the pretransplant conditioning regimen depends on patient age and donor source. Although both myeloablative and nonmyeloablative regimens allow a beneficial graft-vs-leukemia effect, a large BMT CTN trial showed that relapse was less likely to occur in patients between the ages of 18 and 65 years with HCT comorbidity indices of 4 or lower who were randomly assigned to a myeloablative arm rather than a reduced-intensity arm, and the trial was closed early.[32] Criticisms of this study include that the primary reduced-intensity conditioning regimen used (fludarabine and busulfan) may be less efficacious than fludarabine and melphalan, although randomized comparisons are lacking.[33] Additionally, the increased relapse rate in the reduced-intensity arm that led to trial closure was anticipated in the trial design, and it is still unclear whether or not the decreased treatment-related mortality would offset the higher relapse rate.

Older/Less Fit Patients

For most patients, regardless of age, up-front intensive therapy is the appropriate choice. In fact, the 2017 ELN guidelines indicate that even older patients should have another patient-related factor (eg, significant comorbidity not related to AML) or disease-related factor (eg, adverse cytogenetic features) before less-intensive therapies are considered.[4] Retrospective data from the Swedish Acute Leukemia Registry suggest the benefit of intensive therapy in older patients.[34] This benefit has been supported in a large retrospective analysis of 1295 patients given induction therapy between 2008 and 2012, although the patients with high composite scores in the prognostic model developed as part of this study had poor outcomes regardless of the treatment administered.[35] Age is a major contributor to treatment-related mortality, but it is not as important as performance score and probably comorbidities.[36] Similarly, cytogenetic features rather than age

are the major determinant of resistance to chemotherapy (although adverse-risk cytogenetic features are more common in older patients with AML).[37,38] Regardless of the reason underlying treatment choice, most older patients in the community receive palliative or supportive care alone as reported in a large SEER-linked analysis of Medicare claims data.[39]

Many older patients considered eligible for treatment receive low-intensity treatment with hypomethylating agents, most commonly azacitidine.[40-44] There is a hint that 10-day decitabine may improve outcomes,[45] especially in certain subsets, such as patients with complex cytogenetic features or *TP53* mutations.[46] Such lower-intensity treatment may provide a bridge to transplant with less toxicity than that of standard induction chemotherapy. However, many investigators believe that the likelihood of cure with less-intensive treatment alone remains low. An ongoing European Organisation for Research and Treatment of Cancer (EORTC) trial ("InDACtion" vs "3+7" Induction in AML; NCT02172872) is randomly assigning patients to 10 days of decitabine (so-called inDACtion) or 7+3 chemotherapy. This trial will attempt to determine definitively whether there is a difference in overall survival (OS) between patients receiving less-intensive and those receiving more-intensive chemotherapy.

Allogeneic HCT with reduced-intensity regimens is an important consolidative treatment to consider for older patients in CR. An analysis of 1080 patients reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) indicated that older age alone should not be a contraindication to allogeneic HCT.[47] Certainly, new treatments that balance intensity, toxicity, and efficacy are needed for older patients, particularly if such treatments are able to bridge them to allogeneic HCT.

Areas in Which New Treatments Are Needed

Despite improvements over time, the 5-year survival rate for AML has remained remarkably low—approximately 25%[1]—although mediating factors such as age and cytogenetic/molecular risk status can help subclassify patients and determine the treatment algorithm at the time of diagnosis. Increasing evidence indicates that prognostic information can be refined according to response to chemotherapy, with data on remission status and presence of MRD useful for determining the likelihood of benefit from further chemotherapy and/or allogeneic HCT. Many recently completed or ongoing studies are attempting to fill the known gaps in the therapeutic armamentarium for AML, and the remainder of this review will focus on emerging treatments that may gain approval from the US Food and Drug Administration (FDA).

Small Molecule Inhibitors

FLT3 Inhibitors

Outside traditional cytotoxic chemotherapy, the drug class that has received the most attention in AML is that of the tyrosine kinase inhibitors (TKIs). Approximately 25% of patients with AML carry a mutation in the FMS-like tyrosine kinase 3 (*FLT3*) gene.[48] The FLT3 protein is involved in the maintenance of cell division and differentiation, and mutations typically lead to a proliferative state, particularly in patients with a high allelic ratio of mutated to normal protein. The most common *FLT3* mutation is an ITD that is clearly associated with a deleterious clinical phenotype. As such, *FLT3*-ITD–mutated AML is an adverse genomic risk factor in the 2017 ELN classification.[4] Tyrosine kinase domain mutations are seen less frequently, and their clinical implications are less clear. Additionally, in most AML cells, even those without detectable *FLT3* mutations, FLT3 signaling is dysregulated. The poor clinical outcome of patients with *FLT3* mutations, combined with the ability to target the FLT3 receptor with specific inhibitors, has made the development of FLT3 inhibitors an attractive goal for more than a decade.

It is unclear whether more benefit will occur with TKIs that appear to largely affect only FLT3 (eg, crenolanib and quizartinib) than with TKIs that have broader kinase inhibitory effects in the cell (eg, sorafenib [Nexavar, Bayer], midostaurin [Rydapt, Novartis], and lestaurtinib).[49] The off-target benefits of a multikinase inhibitor may be considerable, but the toxicities can counterbalance such positive effects. For example, lestaurtinib had unacceptable toxicity in a large randomized trial of patients with *FLT3*-mutated AML in first relapse.[50] However, in April 2017, the multikinase inhibitor midostaurin (also known as PKC412) was approved by the FDA for the treatment of AML on the basis of results from the international phase 3 randomized, placebo-controlled RATIFY trial (Daunorubicin, Cytarabine, and Midostaurin in Treating Patients With Newly Diagnosed Acute Myeloid Leukemia), which were originally presented at the American Society of Hematology (ASH) annual meeting in 2015 (Table 1). The study enrolled 717 patients aged 60 years or younger with newly diagnosed *FLT3*-mutated disease who received 7+3 induction chemotherapy with or without midostaurin during induction, postremission, and maintenance therapy. A clear OS benefit was observed in the midostaurin arm.[51] After a median follow-up of 57 months for surviving patients, the 5-year event rate was 50.8% (95% CI, 45.4-55.9) in the midostaurin arm and 43.1% (95% CI, 37.6-48.4) in the placebo arm; median OS was 74.7 months in the midostaurin arm and 26.0

Table 1. Emerging Treatments for Acute Myeloid Leukemia

Drug	Mechanism	Phase of Testing in AML	Notes on Activity/Approval
Midostaurin	Multikinase inhibitor with activity against FLT3	3 (completed)	Positive results in randomized trial (vs placebo in combination with 7+3 for patients with newly diagnosed *FLT3*-mutated AML); FDA-approved in April 2017
Sorafenib	Multikinase inhibitor with activity against FLT3	3 (completed)	FDA-approved for solid tumors, but available only off label for AML
Quizartinib (AC220)	Second-generation FLT3 inhibitor	3 (ongoing)	Two randomized trials ongoing (vs placebo in combination with 7+3 for patients with newly diagnosed *FLT3*-mutated AML and as a single agent vs chemotherapy in patients with R/R *FLT3*-mutated AML)
Crenolanib	Second-generation FLT3 inhibitor	3 (ongoing)	Randomized trial (vs placebo in combination with mitoxantrone/cytarabine for patients with R/R *FLT3*-mutated AML)
Gilteritinib (ASP2215)	Dual FLT3 and AXL inhibitor	3 (ongoing)	Randomized trial (vs salvage chemotherapy for patients with R/R *FLT3*-mutated AML)
AG-120	IDH1 inhibitor	2 (ongoing)	Phase 1 combination with induction therapy ongoing; phase 1b/2 combination with azacitidine ongoing
Enasidenib (AG-221)	IDH2 inhibitor	3 (ongoing)	Randomized trial ongoing (vs conventional care); seeking FDA approval in 2017
Venetoclax	BCL2 inhibitor	3 (opening soon)	Approved for relapsed CLL; combination studies with low-intensity therapy in AML ongoing
Dasatinib	KIT inhibitor	2 (completed)	Approved for CML; results not yet available for combination with chemotherapy in CBF AML
CPX-351	Liposomal formulation of cytarabine and daunorubicin in a fixed 5:1 molar ratio	3 (completed)	Positive results in randomized trial vs 7+3 in older adults; likely to be FDA approved in 2017
Gemtuzumab ozogamicin	Antibody-drug conjugate targeting CD33	3 (completed)	Seeking FDA reapproval in 2017
Vadastuximab talirine (SGN-CD33A)	Antibody-drug conjugate targeting CD33	3 (ongoing)	Randomized trial (vs placebo in combination with azacitidine/decitabine in older patients with newly diagnosed AML)
AMG 330	Bispecific T cell–engaging antibody targeting CD33	1 (ongoing)	Single-agent first-in-human continuous IV infusion
MGD006	Dual-affinity retargeting antibody against CD123	1 (ongoing)	Single-agent first-in-human administration

AML, acute myeloid leukemia; CBF, core-binding factor; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; FDA, US Food and Drug Administration; FLT3, FMS-like tyrosine kinase 3; IDH, isocitrate dehydrogenase; IV, intravenous; R/R, relapsed/refractory; 7+3, cytarabine for 7 days plus an anthracycline for 3 days.

months in the placebo arm, even though CR rates were similar in the 2 arms (59% vs 54%; P=.018).[51] The rates of grade 3 or higher adverse events were similar in the 2 arms, and the benefit of midostaurin was seen across all *FLT3* subgroups when patients were stratified by allelic ratio at diagnosis and regardless of whether they received HCT.[51] Updated survival data are expected to be available soon. The combination of midostaurin and azacitidine in older patients with newly diagnosed disease is being investigated as part of an ongoing multiple-arm randomized phase 2/3 SWOG trial (Azacitidine With or Without Nivolumab or Midostaurin, or Decitabine and Cytarabine Alone in Treating Older Patients With Previously Untreated Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome; NCT03092674), and the benefit of midostaurin as post-HCT maintenance in patients with *FLT3*-ITD–mutated AML is being studied in another trial (RADIUS: A Phase 2 Randomized

Trial of Standard of Care With or Without Midostaurin to Prevent Relapse Following Allogeneic Stem Cell Transplant in Patients With *FLT3*-ITD–Mutated Acute Myeloid Leukemia; NCT01883362).

Sorafenib is the other major multikinase inhibitor currently used for the treatment of AML. Unlike midostaurin, sorafenib has been studied primarily in unselected patients with AML. A phase 1/2 study of sorafenib in combination with intensive induction chemotherapy showed promising activity, but with high rates of toxicity.[52] A double-blind, placebo-controlled trial in Germany randomly assigned 276 younger patients (<60 years) with untreated AML to receive 7+3 induction followed by high-dose cytarabine consolidation with or without sorafenib.[53] Increased toxicity was noted in the sorafenib arm, including higher rates of fever, diarrhea, bleeding, cardiac events, and hand-foot rash. The median event-free survival (EFS) was 9 months in the placebo group vs 21 months in the sorafenib group; OS was not reached in either group after 3 years of follow-up. Although an exploratory subgroup analysis of the 46 patients with *FLT3*-ITD mutations showed a trend toward improved EFS and OS with sorafenib, most of the benefit reflected outcome in patients who were negative for *FLT3* mutations.[53] However, a similar randomized German trial performed in 211 patients older than 60 years with newly diagnosed AML showed no difference in EFS and OS in the sorafenib group. A high early death rate in the sorafenib group was noted (17% vs 7% in the placebo arm; P=.052), suggesting that any potential antileukemic effect was counterbalanced by increased toxicity; as a result, patients in the sorafenib group were much more likely to receive less chemotherapy and to stop maintenance early.[54] A subgroup analysis of patients with *FLT3*-ITD–mutated AML also showed no survival benefit with sorafenib.[54] Sorafenib has also been investigated as a maintenance therapy for patients with *FLT3*-ITD–mutated disease following allogeneic HCT, and in a retrospective analysis the 2-year OS was 81% in the sorafenib arm (26 patients) vs 62% in the control arm (55 patients).[55] Despite its relatively common use in patients with AML, it should be noted that sorafenib is not approved by the FDA for the treatment of AML. Sorafenib is approved only for the treatment of solid tumors, including kidney, liver, and thyroid tumors.

More potent and specific second-generation FLT3 inhibitors are under development, including quizartinib (AC220), crenolanib, and gilteritinib (ASP2215). In vitro, these drugs have a potent inhibitory effect on the FLT3 kinase without the off-target effects that characterize midostaurin and sorafenib. The rate of response to quizartinib as a single agent in relapsed/refractory (R/R) *FLT3*-ITD–mutated AML is high (53% response rate in the phase 1 dose escalation study in adults).[56] The phase 2 studies have yet to be reported outside abstract form, but quizartinib has been combined with azacitidine and low-dose cytarabine (overall response rate, 67%)[57] as well as with 7+3 chemotherapy.[58] Most of the responses seen in these studies are incomplete, and because of the association of these incomplete responses with MRD, and of MRD with relapse, the clinical significance of the responses is unknown. Based on these early-phase data, two randomized phase 3 studies are ongoing. The first, known as QuANTUM-First (Quizartinib With Standard of Care Chemotherapy and as Maintenance Therapy in Patients With Newly Diagnosed FLT3-ITD [+] AML; NCT02668653), examines quizartinib vs placebo in combination with standard induction (7+3), consolidation, and maintenance in patients aged 18 to 75 years with newly diagnosed *FLT3*-ITD–mutated AML. The second, called QuANTUM-R (An Open-label Study of Quizartinib Monotherapy vs. Salvage Chemotherapy in Acute Myeloid Leukemia Subjects Who Are FLT3-ITD Positive; NCT02039726), is an open-label phase 3 study of quizartinib monotherapy vs salvage chemotherapy (both intensive and nonintensive options) in patients with R/R AML.

The FLT3 inhibitor crenolanib is at a similar phase in testing. Crenolanib may be better tolerated than quizartinib, with decreased myelosuppression and the ability to overcome resistance mutations.[59] Smaller trials are ongoing, but a phase 3 randomized, placebo-controlled study recently opened in which crenolanib is administered in combination with mitoxantrone and cytarabine to patients with R/R AML. The plan is to enroll 276 patients (Study of Crenolanib in Combination With Chemotherapy in Patients With Relapsed or Refractory Acute Myeloid Leukemia and Activating FLT3 Mutations; NCT02298166).

The newest member of the class is gilteritinib, which is a combination FLT3 and AXL inhibitor. The outcomes for 252 patients enrolled in the phase 1/2 open-label study of gilteritinib were reported at the ASH annual meeting in 2016. The majority of patients (194) had an *FLT3* mutation, and the overall response rate was 52% among the 169 patients with *FLT3*-mutated AML who received a dose of 80 mg or higher.[60] Based on these data, a phase 3 open-label study (A Study of ASP2215 Versus Salvage Chemotherapy in Patients With Relapsed or Refractory Acute Myeloid Leukemia With FMS-like Tyrosine Kinase Mutation; NCT02421939) has been initiated that is randomly assigning patients with R/R AML to receive gilteritinib vs salvage chemotherapy (low-dose cytarabine; azacitidine; mitoxantrone, etoposide, and cytarabine; or FLAG-IDA).

It remains to be seen how FLT3 inhibitors will be incorporated into standard practice now that midostaurin

has been approved. We anticipate that midostaurin and sorafenib will be used in the up-front setting and that the second-generation drugs will be used, at least initially, in the R/R setting. The phase 3 studies ongoing for quizartinib, crenolanib, and gilteritinib are targeted primarily at patients with R/R AML, and because many of the early-phase studies for these drugs have included large numbers of patients with previous FLT3 inhibitor exposure, the drugs may be effective in R/R *FLT3*-mutated AML.

Isocitrate Dehydrogenase Inhibitors

About 15% to 20% of patients with AML have mutations in the isocitrate dehydrogenase 1 or 2 gene (*IDH1* or *IDH2*), with a prevalence that increases with age. Because these mutations are associated with a poor prognosis, they have become a target for drug development.[61,62] Although a pan-IDH inhibitor is in clinical development, the inhibitors that are closest to potential FDA approval are IDH-selective. The small molecule AG-221 (now known as enasidenib) is an IDH2-specific inhibitor. This drug is under consideration by the FDA, with a decision expected later in 2017 based on a single-agent phase 1/2 trial demonstrating an overall response rate of 41% in patients who have R/R AML with *IDH2* mutations.[63] Recent updates to the data are not available. An ongoing phase 3 trial (An Efficacy and Safety Study of AG-221 Versus Conventional Care Regimens in Older Subjects With Late Stage Acute Myeloid Leukemia Harboring an Isocitrate Dehydrogenase 2 Mutation [IDHENTIFY]; NCT02577406) has been initiated in patients with *IDH2*-mutated AML, randomly assigning them to single-agent enasidenib vs conventional care regimens. Similarly, the IDH1 inhibitor AG-120 has been studied in a phase 1 trial limited to patients with *IDH1*-mutated disease, with an overall response rate of 36%.[64] The inhibitors seem to be well tolerated, with side effects of indirect hyperbilirubinemia and nausea reported most frequently.[63]

There are several notable caveats to the IDH inhibitor experience. It takes several cycles to achieve the best response. A relatively large percentage of patients have stable disease, with normalization of peripheral blood neutrophils and transfusion independence associated with a differentiation of blasts to neutrophils (and a differentiation syndrome similar to that seen in acute promyelocytic leukemia)[65] but persistence of circulating and marrow blasts. This has led to a still-unsubstantiated hypothesis that such responses, which are less than CRs, will improve survival by converting AML to a chronic disease. However, a higher CR rate was seen when people with R/R AML and *IDH* mutations received FLAG.[66] Without a randomized comparison vs conventional salvage chemotherapy, it is not clear whether there is a benefit to single-agent IDH inhibitors in the R/R setting.[66] Results of combination studies, similar to the placebo-controlled RATIFY trial combining midostaurin with 7+3, are needed for the IDH inhibitors. Ongoing combination trials include a phase 1b/2 study in which AG-120 or AG-221 is combined with azacitidine (A Safety and Efficacy Study of Oral AG-120 Plus Subcutaneous Azacitidine and Oral AG-221 Plus Subcutaneous Azacitidine in Subjects With Newly Diagnosed Acute Myeloid Leukemia; NCT02677922) and a phase 1 study of each drug in combination with standard induction chemotherapy (Safety Study of AG-120 or AG-221 in Combination With Induction or Consolidation Therapy in Patients With Newly Diagnosed Acute Myeloid Leukemia With an IDH1 and/or IDH2 Mutation; NCT02632708). In both of these studies, enrollment is limited to patients with the appropriate *IDH1* or *IDH2* mutations.

BCL2 Inhibitors

Because AML cells frequently overexpress BCL-2, BCL2 inhibitors have been studied in R/R AML. The prime example is venetoclax (Venclexta, AbbVie/Genentech), which was first found to be effective in relapsed chronic lymphocytic leukemia.[67] A phase 1b open-label dose escalation study of venetoclax in combination with decitabine or azacitidine in older, treatment-naive patients with AML showed a response rate of approximately 70% (Phase 1b Acute Myelogenous Acute Leukemia Study With ABT-199 + Decitabine or Azacitidine [Chemo Combo]; NCT02203773),[68] leading to a randomized, double-blind, placebo-controlled, phase 3 study comparing venetoclax vs placebo in combination with azacitidine (A Study of Venetoclax in Combination With Azacitidine Versus Azacitidine in Treatment Naïve Subjects With Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy; NCT02993523). Another ongoing trial combines venetoclax with low-dose cytarabine in patients with newly diagnosed disease (A Study Evaluating Venetoclax in Combination With Low-Dose Cytarabine in Treatment-Naïve Subjects With Acute Myelogenous Leukemia; NCT02287233).

Dasatinib

The tyrosine kinase inhibitor dasatinib (Sprycel, Bristol-Myers Squibb) is approved for the treatment of chronic myelogenous leukemia. In addition to its ability to inhibit the BCR-ABL fusion protein, dasatinib is a potent inhibitor of KIT. On the basis of the poor outcomes of patients with CBF leukemia who have *KIT* mutations or KIT overexpression, a phase 2 trial (A Phase II Study of Induction [Daunorubicin/Cytarabine] and Consolidation [High-Dose Cytarabine] Chemotherapy Plus Dasatinib and Continuation Therapy With Dasatinib Alone in Newly Diagnosed Patients With Core Binding Factor

Acute Myeloid Leukemia; CALGB 10801) enrolled 61 adult patients with CBF leukemia, who received dasatinib together with 7+3. The combination was well tolerated, but survival data are not yet available.[69] A similar German study, also using dasatinib plus chemotherapy in patients with newly diagnosed CBF leukemia, should also release results soon (Dasatinib [Sprycel™] in Patients With Newly Diagnosed Core Binding Factor Acute Myeloid Leukemia; NCT00850382).

Novel Formulations

CPX-351 combines cytarabine and daunorubicin in a fixed, optimally synergistic 5:1 molar ratio within a liposomal carrier. The drug has been administered primarily to older patients. The phase 3 study (Phase III Study of CPX-351 Versus 7+3 in Patients 60-75 Years Old With Untreated High Risk [Secondary] Acute Myeloid Leukemia; NCT01696084), reported in abstract form, described 309 patients aged 60 to 75 years with newly diagnosed AML and unfavorable characteristics, such as therapy-related AML, antecedent hematologic disorder, or AML with myelodysplastic syndrome (MDS)–related cytogenetic abnormalities. Patients were randomly assigned 1:1 to CPX-351 vs 7+3 in the same dosing pattern used in the phase 2 study.[70] Response rate, EFS, and OS were all superior in the CPX-351 arm (median OS, 9.56 vs 5.95 months; hazard ratio, 0.69; P=.005).[70] The rates of grade 3 to 5 adverse events were high in both arms (92% vs 91%); the most common toxicity was febrile neutropenia (68% in the CPX-351 arm vs 71% in the 7+3 arm), and count recovery appeared to be slightly slower in the CPX-351 arm.[70] An exploratory analysis from the study indicated that there were more patients in the CPX-351 arm who underwent allogeneic HCT (34%), and that 100-day mortality was lower (9.6% vs 20.5% in the 7+3 arm).[71] A similar benefit was seen in the CPX arm regardless of whether patients received HCT, suggesting that a higher proportion of CPX-produced CRs were unaccompanied by MRD. CPX-351 was granted breakthrough designation by the FDA, and approval is anticipated in the summer of 2017. FDA approval of CPX-351 likely will be limited to use in older patients but will open the door for studies in other therapeutic applications, such as patients in CR who have MRD.

Immunotherapy

Gemtuzumab Ozogamicin

CD33 is commonly expressed on the surface of AML cells, and the antibody-drug conjugate gemtuzumab ozogamicin (GO) was the first drug designed to target CD33-expressing leukemia cells. GO initially received accelerated US marketing approval in 2000 for adults older than 60 years with relapsed CD33-positive AML who were not candidates for cytotoxic chemotherapy, on the basis of data from 3 phase 2 trials showing an overall response rate of approximately 30%.[72] GO was voluntarily withdrawn in most countries in 2010 after the FDA-mandated confirmatory postmarketing trial failed to confirm clinical benefit in unselected adults with AML and raised concern over increased early mortality. Subsequently, criticisms have been leveled at the study design (including the study population and choice of the anthracycline dose in the experimental arm).[73,74]

More recently, several studies have investigated GO in addition to intensive chemotherapy in adults with newly diagnosed AML.[74] Although these studies used GO in different schedules, a meta-analysis of all 3325 patients in these trials showed that GO significantly reduced relapse risk and improved survival; benefits were seen primarily in patients with favorable cytogenetic features and also, to a lesser extent, in those with intermediate but not adverse cytogenetic features.[74] These findings are complemented by a randomized trial in which GO provided a very modest benefit over best supportive care and hydroxyurea in untreated older adults considered unfit for intensive chemotherapy.[75] Regulatory paperwork has been submitted to the FDA in 2017 for reconsideration of approval for GO.

SGN-CD33A

Issues with GO, including nonuniform drug conjugation, extrusion of the toxic moiety via drug transporters, and its current unavailability, have made room for the introduction of SGN-CD33A, now also known as vadastuximab talirine, an antibody-drug conjugate targeting CD33.[76] No direct comparisons of GO and SGN-CD33A have been conducted in patients. SGN-CD33A is under investigation as a single agent and in combination with azacitidine and decitabine; in these combinations, a composite response rate of 76% in a phase 1 study among 53 patients with a median age of 75 years (range, 60-87 years) has been observed.[77] Based on these data, a pivotal phase 3 randomized trial opened for accrual, randomly assigning older patients with newly diagnosed AML to SGN-CD33A vs placebo in combination with azacitidine or decitabine (Vadastuximab Talirine Combined With Azacitidine or Decitabine in Older Patients With Newly Diagnosed Acute Myeloid Leukemia [CASCADE]; NCT02785900). SGN-CD33A is also being studied in combination with standard chemotherapy, including 7+3 during induction and high-dose cytarabine during consolidation, for patients with newly diagnosed disease (A Safety Study of SGN-CD33A in Combination With Standard-of-care in Patients With AML; NCT02326584).

Table 2. Areas in Which New AML Therapies Are Needed

Areas Under Investigation	Why New Treatments Are Needed
Up-front induction treatment	Overall survival rate for AML is only 25%.
Treatment of MRD	Presence of MRD is an important negative prognostic factor for patients with or without subsequent allogeneic HCT; the 2017 ELN criteria include a new, stringent response category of CR without MRD.
Less-intensive induction therapies	Less-fit patients may not be able to tolerate induction chemotherapy, but hypomethylating agents are unlikely to lead to cure.
Treatment of R/R AML	Prognosis of patients with R/R AML is poor, so new drugs are needed to help patients achieve remission and to bridge to allogeneic HCT.
Maintenance (after completion of consolidation and/or after HCT)	Relapses of AML are most likely within the first 2 to 3 years after completion of planned treatment.

AML, acute myeloid leukemia; CR, complete remission; ELN, European LeukemiaNet; HCT, hematopoietic cell transplant; MRD, measurable residual disease; R/R, relapsed/refractory.

Bispecific Antibodies

Bispecific antibodies have garnered considerable interest following the approval in late 2014 of the CD19-directed bispecific T-cell engager (BiTE) blinatumomab (Blincyto, Amgen) for the treatment of R/R B-cell acute lymphoblastic leukemia. CD33 is the target of the BiTE antibody AMG 330, which entered phase 1 testing in 2016 in response to promising preclinical data (A Phase 1 Study of AMG 330 in Subjects With Relapsed/Refractory Acute Myeloid Leukemia; NCT02520427).[78] An alternative structure of a bispecific antibody, the so-called dual-affinity retargeting (DART) antibody, forms the basis for MGD006, which targets CD123 and CD3 and has also entered phase 1 testing (Safety Study of MGD006 in Relapsed/Refractory Acute Myeloid Leukemia or Intermediate-2/High Risk MDS; NCT02152956).[79] No clinical data are yet available for either compound.

Unmet Challenges

Because of the heterogeneity of AML, a complex therapeutic algorithm with treatments of varying intensity is required. For the first time in many years, decisions regarding the approval of 4 drugs for the treatment of AML have been made or are expected from the FDA in 2017: midostaurin (approved in April 2017), CPX-351, the IDH2 inhibitor enasidenib, and GO. Many other classes of drugs are also in development. These include the histone deacetylase inhibitor pracinostat, the topoisomerase II inhibitor vosaroxin, and the hedgehog signaling pathway inhibitor glasdegib. How the introduction of targeted inhibitors such as midostaurin will change the current management of AML is still unknown. Further, the adoption of midostaurin (and the other drugs under FDA consideration) will depend on the willingness of insurance companies to pay for undoubtedly expensive medication.

However, despite the rapid pace of change in AML clinical trials and the FDA approvals expected in 2017, significant gaps remain in our therapeutic options for AML. There are 5 major areas in which new approaches are needed for the treatment of AML: (1) up-front induction treatment, particularly for patients with complex cytogenetic abnormalities and refractory primary AML; (2) treatment of patients with suboptimal remission (ie, patients with MRD); (3) less-intensive options for adults unable or unwilling to tolerate induction; (4) treatment of relapsed disease; and (5) maintenance following completion of chemotherapy or transplant (Table 2). Perhaps most concerning is the fact that relapse occurs in most patients who initially achieve remission. Ongoing trials may help to define the optimal therapeutic options for the subsets of patients with AML, but new targets and new agents are certainly needed.

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