Optimizing Use of Newly Approved Agents for Acute Myeloid Leukemia

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Abstract

Until recently, treatment advances in acute myeloid leukemia (AML) had been slow since the 1970s. However, in the past few years, as the understanding of the pathophysiology of AML has advanced, numerous treatments have been approved by the U.S. Food & Drug Administration. This article reviews the mechanisms of action, indications, and clinical trial details for eight novel agents, as well as the current discussions surrounding monitoring minimal residual disease.

Since the 1970s, the historical standard of care regimen for fit patients with acute myeloid leukemia (AML) was 7 continuous days of cytarabine and 3 days of an anthracycline (7+3 regimen; Winer & Stone, 2019). Numerous clinical trials were conducted in an attempt to improve outcomes by enhancing or changing the 7+3 regimen, with little success until 2017. The exception is azacitidine, which emerged during the early 2000s as an effective treatment for patients in whom a less intense therapy is preferred (Pleyer et al., 2017). As molecular techniques improved and the understanding of the pathophysiology of AML advanced, with the resulting new targets, new therapies were developed. As a result, eight novel agents were approved between 2017 and 2019 with 7 different mechanisms of action (Table 1; for more detailed information about the indi-

cations and clinical implications of these novel agents, see Appendix A; for dosing information, see Appendix B; and for adverse events and drug-drug interactions, see Appendix C).

The National Comprehensive Cancer Network (NCCN) Guideline has been updated to encompass these new agents (NCCN, 2019). Treatment recommendations are stratified by age, cytogenetic risk category, and molecular features for induction, postinduction, and consolidation. A review of these recommendations is beyond the scope of this supplement but is accessible through the NCCN website. Instead, this supplement will focus on the novel therapies for AML that were approved by the U.S. Food & Drug Administration (FDA) in 2017 and 2018.

NOVEL THERAPIES FOR AML

The novel agents approved for AML between 2017 and 2019 can be gen-

erally categorized according to their mechanisms of action. These currently include targeted agents that inhibit specific enzymes that harbor mutations; an antibody-drug conjugate (ADC) that targets CD33; and cytotoxic therapy with a new formulation to improve its safety profile.

Targeted Therapy

FLT3 Inhibitors

FMS-like tyrosine kinase 3 (FLT3) is a transmembrane protein that plays a role in the proliferation and apoptosis of hematopoietic stem cells (Winer & Stone, 2019). In approximately 30% of AML cases, there is an *FLT3* mutation in which there is either an internal tandem duplication (ITD; 23%) or an activating point mutation in the tyrosine kinase domain (TKD; 7%; Heuser, Mina, Stein, & Altman, 2019). These mutations result in constitutive downstream activation of signaling pathways that lead to proliferation and leukemogenesis. Second-generation FLT3 inhibitors that are FDA-approved for AML include midostaurin and gilteritinib.

Midostaurin

Midostaurin is a multitargeted kinase inhibitor that inhibits FLT3 harboring either the ITD or TKD mutations. It is FDA-approved for the treatment of first-line treatment of adults with *FLT3* mutation in combination with standard cytarabine and daunorubicin induction followed by cytarabine consolidation (FDA, 2017d). The *FLT3* mutation should be detected using the FDA-approved companion diagnostic, the LeukoStrat CDx *FLT3* Mutation Assay (FDA, 2017d).

The midostaurin approval was based on data from the phase III CALGB10603/RATIFY Alliance trial (Stone, Larson, & Döhner, 2017). This double-blind trial randomly assigned 717 adult patients (age 18 to 59) with newly diagnosed AML with an ITD or TKD *FLT3* mutation to receive standard chemotherapy induction and consolidation with either midostaurin or placebo. Patients were stratified by the type of mutation, including TKD (162 patients) or a high (214 patients) or low (341 patients) ratio of ITD. Patients who

Table 1. Summary of FDA-Approved Treatments for AML, 2017–2019

Agent	Approval year	MOA	Indication
Midostaurin	2017	FLT3 inhibitor	First-line treatment of adults with <i>FLT3</i> mutation in combination with cytarabine/daunorubicin induction and cytarabine consolidation
Enasidenib	2017	IDH2 inhibitor	Adults with relapsed/refractory disease with <i>IDH2</i> mutation
CPX-351	2017	Liposomal formulation of daunorubicin/cytarabine 5:1	First-line treatment of adults with therapy-related AML or AML with myelodysplastic changes (AML-MRC)
Gemtuzumab ozogamicin	2017	ADC targeted to CD33	First-line or relapsed/refractory treatment of adults or relapsed/refractory pediatric (age ≥ 2) with CD33-positive AML; may be used with daunorubicin/cytarabine in adults
Ivosidenib	2018, 2019	IDH1 inhibitor	Adults with relapsed/refractory disease with <i>IDH1</i> mutation or first-line treatment of adults age ≥ 75 or with comorbidities that preclude intensive induction chemotherapy
Glasdegib	2018	SMO inhibitor	First-line treatment of adults age ≥ 75 or with comorbidities that preclude intensive induction chemotherapy in combination with low-dose cytarabine
Venetoclax	2018	BCL2 inhibitor	First-line treatment of adults age ≥ 75 or with comorbidities that preclude intensive induction chemotherapy in combination with azacitidine, decitabine, or low-dose cytarabine
Gilteritinib	2018	FLT3 inhibitor	Adults with relapsed/refractory disease with an <i>FLT3</i> mutation

Note. For more detailed information about the indications and clinical implications of these novel agents, see Appendix A; for dosing information, see Appendix B; and for adverse events and drug-drug interactions, see Appendix C. MOA = mechanism of action; ADC = antibody-drug conjugate. Information from FDA (2019); Winer & Stone (2019).

achieved complete remission (CR) after consolidation entered the maintenance phase with either midostaurin or placebo. Allogeneic transplantation was allowed. The primary endpoint was overall survival (OS), and the secondary endpoint was event-free survival (EFS).

Midostaurin significantly prolonged median OS at 74.7 months compared with 25.6 months with placebo (hazard ratio [HR], 0.78; 95% confidence interval [CI] = 0.63–0.96; $p = .009$), which was similar among the *FLT3* mutation subgroups (Table 2; Stone et al., 2017). The 4-year OS rate was 51.4% with midostaurin and 44.3% with placebo. Event-free survival was also prolonged, with a median of 8.2 months with midostaurin compared with 3.0 months with placebo (HR, 0.78; 95% CI = 0.66–0.93; $p = .002$). A similar number of patients achieved complete remission (CR) between the groups, with 59% and 54% in the midostaurin and placebo arms, respectively. The median time to CR was 35 days (range, 20 to 60 days) for both groups.

The safety profile was consistent with that of typically intensive chemotherapy for AML, with no significant difference in the rate of serious adverse events (AEs) between groups (Stone et al., 2017). Patients in the midostaurin arm experienced significantly higher rates of grade 3, 4, or 5 anemia (92.7% vs. 87.8%, respectively; $p = .03$) or rash (14.1% vs. 7.6%, respectively; $p = .008$) compared with placebo. The rate of nausea was higher with placebo than midostaurin (9.6% vs. 5.6%, respectively; $p = .05$).

Gilteritinib

Gilteritinib is a selective *FLT3* and *AXL* inhibitor that is FDA-approved as monotherapy for the treatment of adults with relapsed/refractory AML that harbors an *FLT3* mutation (FDA, 2018a; Heuser et al., 2019). The *FLT3* mutation should be detected using the FDA-approved companion diagnostic, the LeukoStrat CDx *FLT3* Mutation Assay.

The approval of gilteritinib was based on the interim analysis of the phase III ADMIRAL trial, which was presented at the 2019 American Association for Cancer Research (AACR) annual meeting, but has not yet been published (Perl et al., 2019). The open-label trial randomly assigned 371 patients with relapsed/refractory AML with either the ITD or TKD *FLT3* mutation to receive gilteritinib or standard of care salvage chemo-

Table 2. Pivotal Phase III Efficacy Outcomes for Midostaurin

Endpoint	Midostaurin	Placebo
mOS	74.7 mo	25.6 mo
HR (95% CI)	0.78 (0.63–0.96); $p = .009$	
4-yr OS	51.4%	44.3%
mEFS	8.2 mo	3.0 mo
HR (95% CI)	0.78 (0.66–0.93); $p = .002$	
4-yr EFS	28.2%	20.6%
CR	59%	54%

Note. m = median; OS = overall survival; HR = hazard ratio; CI = confidence interval; EFS = event-free survival; CR = complete response. Information from Stone et al. (2017).

therapy. Chemotherapy regimens were selected prior to randomization and included low-dose cytarabine (LoDAC), azacitadine, mitoxantrone plus etoposide and cytarabine (MEC), or fludarabine plus cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA). Prior use of an *FLT3* inhibitor was excluded. The primary endpoints were OS or the combined metric of CR, CR plus partial hematologic recovery (CR/CRh). The key secondary endpoints were EFS and CR rate.

Single-agent gilteritinib significantly prolonged OS, with a median of 9.3 months compared with 5.6 months with chemotherapy (HR, 0.637; $p = .0007$; Table 3; Perl et al., 2018). The 1-year OS rate was 37.1% with gilteritinib and 16.7% with chemotherapy. The median EFS was also longer, at 2.8 months in the gilteritinib arm compared with 0.7 months in the chemotherapy arm (HR, 0.793; $p = .0830$). CR and CR/CRh were also significantly higher in the gilteritinib group. The rate of CR was 21.1% and 10.5% with gilteritinib compared with chemotherapy, respectively ($p = .0106$). The CR/CRh was 34.0% and 15.3%, respectively ($p = .0001$).

Grade 3 or higher AEs more common in the gilteritinib arm were anemia, febrile neutropenia, thrombocytopenia, and decreased platelet count (Perl et al., 2019). Other any-grade common AEs were similar between groups, including febrile neutropenia, anemia, and pyrexia.

IDH Inhibitors

Isocitrate dehydrogenase (IDH) enzymes convert isocitrate to α -ketoglutarate during oxidative

phosphorylation (Winer & Stone, 2019). IDH1 is located within the cytosol, whereas IDH2 is located within the mitochondria. *IDH1* and *IDH2* mutations are present in approximately 8% and 12% of patients with AML, respectively, and result in the formation of an alternate product—2-hydroxyglutarate instead of α -ketoglutarate. 2-hydroxyglutarate causes epigenetic changes that impair myeloid differentiation. IDH1 and IDH2 inhibitors substantially decrease 2-hydroxyglutarate levels and thus restore myeloid differentiation. There are currently two IDH inhibitors approved for the treatment of AML, enasidenib and ivosidenib.

Enasidenib

Enasidenib is a selective IDH2 inhibitor that was approved for the treatment of adults with relapsed/refractory AML with an *IDH2* mutation, as determined by the RealTime IDH2 Assay companion diagnostic (FDA, 2017c). The approval was based on results from a phase I/II trial; the phase III IDHENTIFY trial is ongoing (FDA, 2017c; Galkin & Jonas, 2019).

The first-in-human phase I/II trial determined the maximum tolerated dose (MTD), pharmacokinetics and pharmacodynamics, and efficacy of enasidenib among patients with relapsed/refractory AML harboring an *IDH2* mutation (Stein et al., 2017). The primary endpoint was safety and MTD and a key secondary endpoint was clinical

activity. The MTD was not reached, and 100 mg once daily was selected as the appropriate dose.

Among patients in the efficacy analysis (176 patients), the objective response rate (ORR) was 40.3% and the median time to first response was 1.9 months, with 87% of patients responding by cycle 5 (Stein et al., 2017). The ORR with enasidenib was higher for patients with the *IDH2* R127 mutation at 53.3% compared with 35.4% with the *IDH2* R140 mutation. Complete remission was achieved by 19.3% of patients, and of those, 21% were documented by cycle 3, 68% by cycle 5, and 82% by cycle 7. The median OS was 9.3 months and the 1-year OS was 39% after a median follow-up of 7.7 months. The median OS of patients who achieved CR was 19.7 months, and for patients who achieved a partial remission (PR), 14.4 months.

Treatment-emergent adverse events (TEAEs) occurred in 82% of patients in the safety analysis (238 patients; Stein et al., 2017). The most common grade 3 to 4 enasidenib-related TEAEs were indirect hyperbilirubinemia (12%) and IDH inhibitor-associated differentiation syndrome (IDHS; 6%). Enasidenib-related TEAEs led to discontinuation in 5% of patients.

Ivosidenib

Ivosidenib is an IDH1 inhibitor that was FDA-approved for the treatment of relapsed/refractory AML in 2018 and for the first-line treatment of adults aged 75 or older or who have comorbidities that preclude the use of intense chemotherapy induction (FDA, 2018c, 2019). Both indications are for AML with an *IDH1* mutation, as determined by the companion diagnostic Abbott RealTime IDH1 Assay. The initial approval was based on results from the phase I AG120-C-001 trial (DiNardo, 2018).

In the open-label phase I dose-escalation and -expansion study, 258 adult patients with AML with an *IDH1* mutation were treated with ivosidenib (DiNardo, 2018). The key primary endpoints were MTD and clinical activity, including (but not limited to) remission duration, time to remission, and OS. The MTD was not reached and 500 mg once daily was selected at the appropriate dose.

Among the primary efficacy population (125 patients), the median OS was 8.8 months after a

Table 3. Pivotal Phase III Efficacy Outcomes for Gilteritinib

Endpoint	Gilteritinib	Salvage chemotherapy ^a
mOS	9.3 mo	5.6 mo
HR	0.637; $p = .0007$	
1-yr OS	37.1%	16.7%
mEFS	2.8 mo	0.7 mo
HR	0.793; $p = .0830$	
CR	21.1%	10.5%
CR/CRh	34.0%	15.3%

Note. m = median; OS = overall survival; HR = hazard ratio; EFS = event-free survival; CR = complete response; CRh = complete response plus partial hematologic recovery. Information from Perl et al. (2019).

^aSalvage chemotherapy = LoDAC, azacitidine, MEC, or FLAG-IDA.

median follow-up of 14.8 months (DiNardo, 2018). Complete remission was achieved by 21.6% of patients and CR/CRh by 30.4%. This subgroup demonstrated a longer OS, which was not reached, compared with 9.3 months for patients whose response was not CR or CRh and 3.9 months for patients who did not respond. The rate of CR and CR/CRh was similar among patients who enrolled with relapsed/refractory or previously untreated AML, between 30% to 35%. The median time to first response was 1.9 months and the median time to CR was 2.8 months.

Among patients who received the 500-mg dose, 20.7% experienced a treatment-related adverse event (TRAE) of grade 3 or higher (DiNardo, 2018). Of these, the most common were QT prolongation (7.8%), IDH-DS (3.9%), and anemia (2.2%). There were no treatment discontinuations due to QT prolongation or IDH-DS.

BCL2 Inhibition

BCL2 inhibits apoptosis by regulating the mitochondrial apoptotic pathway, thereby promoting leukemic blast survival. Inhibition of BCL2 induces apoptosis (Winer & Stone, 2019). Currently, there is one BCL2 inhibitor approved for the treatment of AML—venetoclax.

Venetoclax

A selective BCL2 inhibitor, venetoclax is approved for use in combination with azacitidine, decitabine, or low-dose cytarabine for the treatment of adults with AML who are age 75 or older or who have comorbidities that preclude the use of intense induction with chemotherapy (FDA, 2018d). The approval was based on phase I and II trials that showed a CR and CR duration benefit. Historical CR plus CR with incomplete blood count recovery (CRi) with azacitidine, decitabine, or low-dose cytarabine monotherapy range from 11% to 26% with a median OS of less than 1 year (DiNardo et al., 2019; Wei et al., 2019).

Both studies were open-label trials of newly diagnosed patients with AML; Study M14-358 treated patients with venetoclax and azacitidine or decitabine, whereas Study M14-387 treated patients with venetoclax plus low-dose cytarabine (DiNardo et al., 2019; Wei et al., 2019). The efficacy endpoints of the studies included CR plus

CRi and PR, as well as OS. The approved dose of venetoclax with azacitidine or decitabine includes a dose-escalation period of 100 mg on day 1, 200 mg on day 2, and 400 mg on day 3, followed by 400 mg beginning on day 4 when combined with azacitidine or decitabine, or 600 mg beginning on day 4 when combined with low-dose cytarabine (AbbVie Inc., & Genentech USA, Inc., 2019)

In M14-358, the median age at baseline was 74 (range, 65 to 86), 49% had poor-risk cytogenetics, and 25% had secondary AML (DiNardo et al., 2019). The CR plus CRi rate among patients who received 400 mg of venetoclax (the approved dose) was 76% when combined with azacitidine and 71% when combined with decitabine, with a median duration of response not reached or 12.5 months, respectively. The CR plus CRi and PR rate was 76% and 71% for venetoclax combined with azacitidine or decitabine, respectively. The median OS was not yet reached for venetoclax plus azacitidine and was 14.2 months with venetoclax plus decitabine.

In M14-387, the median age was also 74 (range, 63 to 90), 32% had poor-risk cytogenetics, and 49% had secondary AML (Wei et al., 2019). The CR plus CRi rate among patients who received 600 mg of venetoclax was 54% and the median duration of response was 8.1 months. The median OS was 10.1 months.

In M14-387, the most common grade 3 or higher AEs that occurred during 400 mg of venetoclax treatment included febrile neutropenia, thrombocytopenia, white blood cell count decrease, anemia, neutropenia, hypophosphatemia, and hypokalemia (Wei et al., 2019). In M14-358, the most common grade 3 to 4 TEAEs that occurred with 400 mg of venetoclax included febrile neutropenia, decreased white blood cell counts, anemia, and hypokalemia (DiNardo et al., 2019).

Hedgehog Pathway Inhibition

The normal function of the Hedgehog signaling pathway is embryogenesis and fetal development; however, aberrant signaling as a result of mutated signaling components results in proliferation of leukemia stem cells and enhanced chemoresistance (Winer & Stone, 2019). The Hedgehog pathway is downregulated by the patched (PTCH) transmembrane protein and positively regulated by the smoothened (SMO) transmembrane protein.

The SMO inhibitor, glasdegib, is currently the only Hedgehog pathway inhibitor approved for the treatment of AML. Glasdegib is indicated for newly diagnosed AML for adults who are aged 75 or older or who have comorbidities that preclude the use of intense chemotherapy induction (FDA, 2018b).

Glasdegib

The FDA approval of glasdegib was based on the results of the phase II BRIGHT AML 1003 trial, which was an open-label trial that randomly assigned 132 patients with AML who were not candidates for intensive chemotherapy to receive glasdegib plus low-dose cytarabine (LDAC) or LDAC alone (Cortes et al., 2019). The median age at baseline was 76 (range, 58 to 92), and 42% had poor-risk cytogenetics. The primary endpoint was OS and secondary endpoints included clinical efficacy and safety and tolerability.

The addition of glasdegib to LDAC significantly prolonged OS, with a median of 8.8 months compared with 5.9 months with LDAC alone (HR, 0.513; 95% CI = 0.394–0.666; $p = .0004$; Table 4; Cortes et al., 2019). The OS rate was substantially higher with glasdegib. The 6- and 12-month OS rates were nearly 60% and 40%, respectively, with glasdegib and LDAC compared with 38% and 9.5% with LDAC alone. In the glasdegib arm, 17% of patients achieved CR, whereas only 2.3% achieved CR in the LDAC-only arm.

Treatment-related treatment discontinuation occurred in 10.7% and 7.3% of patients in the glasdegib and LDAC-only groups (Cortes et al., 2019). The rate of grade 3 to 4 TEAEs was 64.3% in the glasdegib/LDAC group and 56.1% in the LDAC-only group. The most common grade 3 to 4 TEAEs reported in the glasdegib group was anemia, febrile neutropenia, thrombocytopenia, and pneumonia.

Antibody-Drug Conjugates

Antibody-drug conjugates specifically bind to target cells, are internalized by the cell, and then release a highly potent, cytotoxic payload (Thomas, Teicher, & Hassan, 2016). This activity is achieved because of their unique structure, which links a humanized monoclonal antibody that acts as the homing “device,” with a potent cytotoxic agent.

Gemtuzumab ozogamicin

The humanized monoclonal antibody component of gemtuzumab ozogamicin (GO) is targeted to CD33, and its payload is calicheamicin, an antibiotic that causes double-strand DNA breaks and binds to the minor groove of DNA, resulting in rapid cell death (FDA, 2017b). GO was originally approved by the FDA for the treatment of relapsed/refractory AML in 2000; however, the manufacturer voluntarily withdrew GO from the market when a trial in 2010 raised safety concerns and demonstrated lack of clinical benefit.

The new approval of GO in 2017 was based on 2 trials—ALFA-0701 and AML19—that reduced the dose of GO (from 2 doses of 9 mg/m² 14 days apart to 3 mg/m² given on days 1, 4, and 7), which mitigated the safety concerns. GO is now indicated as monotherapy or in combination with daunorubicin and cytarabine for the treatment of adults with CD33-positive AML (FDA, 2017b). It is also approved for the treatment of children ages 2 and older with relapsed/refractory CD33-positive AML.

The phase III ALFA-0701 randomly assigned 271 adult patients (age 50 to 70) with newly-diagnosed, CD33-positive AML to receive daunorubicin and cytarabine with or without GO (Jen et al., 2018; Lambert et al., 2019). Patients who responded underwent consolidation therapy with two courses of daunorubicin and cytarabine with or without GO (single 3 mg/m² dose). Patients who did not respond could undergo a second induction with daunorubicin and cytarabine alone. The primary endpoint was EFS and the key sec-

Table 4. Phase II Efficacy Outcomes for Glasdegib

Endpoints	Glasdegib/LDAC	LDAC
mOS	8.8 mo	4.9 mo
HR (95% CI)	0.513 (0.394–0.666); $p = .0004$	
6-mo OS	59.8%	38.2%
12-mo OS	39.5%	9.5%
CR	17%	2.3%
Duration of response	9.9 mo	6.5 mo

Note. LDAC = low-dose cytarabine; m = median; OS = overall survival; HR = hazard ratio; CI = confidence interval; CR = complete response. Information from Cortes et al. (2019).

ondary endpoint was OS. The baseline median age was 61 (range, 50 to 70), and 21% of patients had poor cytogenetics.

The addition of GO to daunorubicin and cytarabine significantly improved EFS, with a median of 17.3 months compared with 9.5 months with daunorubicin and cytarabine alone (HR, 0.56; 95% CI = 0.42–0.76; $p < .001$; Jen et al., 2018). The median OS was similar between arms, with a median of 27.5 months and 21.8 months with or without GO, respectively, (HR, 0.81; 95% CI = 0.60–1.09). Complete remission was also achieved by a similar proportion of patients between arms (Lambert et al., 2019).

The open-label, phase II/III AML19 trial randomly assigned patients with newly-diagnosed CD33-positive AML to GO monotherapy or best supportive care (BSC; Amadori et al., 2016; Jen et al., 2018). Patients were older than 75 or were 61 to 75 years old with a World Health Organization (WHO) performance status greater than 2 or were unwilling to receive intensive chemotherapy. The GO dose was 6 mg/m² on the first day and 3 mg/m² on the eighth day; continuation of up to 8 courses of 2 mg/m² of GO on day 1 every 4 weeks was available for patients with no evidence of disease or substantial toxicity. The primary endpoint was OS. At enrollment, the median age was 77 (range, 62 to 88), and 27.5% had poor cytogenetics.

GO monotherapy significantly prolonged OS, with a median of 4.9 months compared with 3.6 months with BSC (HR, 0.69; 95% CI = 0.53–0.90;

$p = .005$; Table 5; Jen et al., 2018). These results were similar in a subgroup analysis, except there was no efficacy for patients with CD33 positivity below 20% and in patients with poor cytogenetics. The CR was lower with GO at 8.1% compared with 15.3% with BSC (Amadori et al., 2016).

The most common grade 3 or higher AEs that occurred with GO monotherapy were infection, febrile neutropenia, bleeding, fatigue, and cardiac dysfunction, which were somewhat similar in rates to BSC (Jen et al., 2018). The AEs of special interest are veno-occlusive disease (VOD), liver dysfunction (i.e., elevated aspartate aminotransferase or alanine aminotransferase), and hemorrhage. The lower GO dose decreased the risk of these AEs (and improved efficacy outcomes) compared with the original dose; however, these AEs did occur in the ALFA-0701 trial. Early mortality occurred in 4% and 2% of patients in groups with or without GO, respectively. In the GO arm, the treatment-related deaths were a result of VOD or hemorrhage, whereas the deaths were due to infection in the chemotherapy alone arm. Veno-occlusive disease occurred in six patients (5%) in the GO arm, which resulted in three deaths. An additional two patients developed VOD who were originally in the control arm, but then received GO for relapsed disease.

Novel Formulation of Chemotherapy

Anthracycline and cytarabine remain important pillars of AML treatment. However, a ratio-metric

Table 5. Efficacy Outcomes With GO Monotherapy or in Combination With Chemotherapy

Endpoints	AFLA-0701		AML19	
	GO/DA	DA	GO	BSC
mEFS	17.3 mo	9.5 mo	NR	NR
HR (95% CI)	0.56 (0.42–0.76); $p < .001$		NR	NR
2-yr EFS ^a	38.5%	NR	NR	NR
3-yr EFS ^a	36.5%	NR	NR	NR
mOS	27.5 mo	21.8 mo	4.9 mo	3.6 mo
HR (95% CI)	0.81 (0.60–1.09)		0.69 (0.53–0.90); $p = .005$	
CR	70.4%	69.9%	8.1%	15.3%

Note. GO = gemtuzumab ozogamicin; DA = daunorubicin plus cytarabine; BSC = best supportive care; m = median; EFS = event-free survival; NR = not reported; HR = hazard ratio; OS = overall survival; CR = complete response. Information from Amadori et al. (2016); Jen et al. (2018); Lambert et al. (2019).

^aBy blinded independent review.

dosing approach was developed based on the rationale that the dose ratio between 2 agents could maximize their synergistic efficacy (Chen, Fathi, & Brunner, 2018). The 5:1 ratio of cytarabine to daunorubicin was preclinically determined to yield the maximum synergistic effects of these agents, and led to higher response rates in animal models. In addition, the liposomal formulation extended the half-life, enabling greater leukemic accumulation of the drugs. The result of this drug development was a novel liposomal formulation of 5:1 cytarabine and daunorubicin, CPX-351, which was approved by the FDA in 2017 for the first-line treatment of adults with either therapy-induced AML or AML-MRC (AML with myelodysplasia-related changes; FDA, 2017a).

CPX-351

The FDA approval of CPX-351 was based on an open-label, phase III trial that randomly assigned 309 patients age 60 to 75 with newly diagnosed therapy-related AML or AML-MRC to receive CPX-351 or the conventional 7+3 regimen (Lancet et al., 2018). The primary endpoint was OS and secondary endpoints included CR, CR plus CRi, remission duration, and EFS. The mean age at enrollment was 68 and 54% had unfavorable cytogenetics.

CPX-351 significantly prolonged OS, with a median of 9.56 months compared with 5.95 months with 7+3 (HR, 0.69; 95% CI = 0.52–0.90; $p = .003$; Table 6; Lancet et al., 2018). The OS benefit was similar regardless of age, and among patients with *FLT3* wild-type disease, therapy-related AML, AML-MRC, and favorable or intermediate cytogenetics. The 1-year OS rates were 41.5% with CPX-351 and 27.6% with 7+3; the 2-year OS rates were 31.1% and 12.3%, respectively. The EFS was also significantly improved with CPX-351, with a median of 2.53 months compared with 1.31 months with the 7+3 regimen (HR, 0.74; 95% CI = 0.58–0.96; $p = .021$). The duration of EFS was similar between arms at 6.93 and 6.11 months, respectively. More patients achieved CR with CPX-351 at 37.3% compared with 25.6% with conventional 7+3. The CR plus CRi rates were 47.7% and 33.3% with CPX-351 and 7+3, respectively.

The safety profile of CPX-351 was similar to that of the conventional 7+3 regimen (Lancet et al., 2018). The most common grade 3 to 5 AEs

included neutropenia, pneumonia, and hypoxia. The early mortality rate was lower with CPX-351 at 5.9% compared with 10.6% with the 7+3 regimen through day 30.

MONITORING TREATMENT RESPONSE

Currently, the NCCN recommends assessment for response using morphologic and cytogenetics criteria to determine if the patient has experienced a complete response or PR (NCCN, 2019). Patients who respond to induction may continue to consolidation. For patients who show no response or experience disease progression, reinduction via clinical trial of targeted therapies, alternative systemic therapy, or best supportive care are recommended.

Minimal residual disease (MRD) as a prognostic biomarker for treatment decisions is not yet recommended by the NCCN; however, the European LeukemiaNet (ELN) published a consensus document in 2018 that states that MRD is important for treatment planning and provides recommendations, while acknowledging the need for future improvements for its assessment, reporting, and use in clinical trials (NCCN, 2019; Schuurhuis et al., 2018). The ELN does caution the use of MRD to guide treatment decisions because there are currently no prospective, randomized studies to support its use (Heuser et al., 2019). Retrospective studies suggest that pa-

Table 6. Phase III Efficacy Outcomes for CPX-351

Endpoint	CPX-351	Conventional 7+3
mOS	9.56 mo	5.95 mo
HR (95% CI)	0.69 (0.52–0.90); $p = .003$	
1-yr OS	41.5%	27.6%
2-yr OS	31.1%	12.3%
CR	37.3%	25.6%
CR + CRi	47.7%	33.3%
EFS	2.53 mo	1.31 mo
HR (95% CI)	0.74 (0.58–0.96); $p = .021$	
Duration of response	6.93 mo	6.11 mo

Note. m = median; OS = overall survival; HR = hazard ratio; CI = confidence interval; CR = complete response; CRi = CR with incomplete blood count recovery; EFS = event-free survival. Information from Lancet et al. (2018).

tients with MRD who are treated more aggressively—consolidation therapy with allogeneic hematopoietic cell transplant vs. chemotherapy alone—experienced improved outcomes (Heuser et al., 2019). In addition, patients who were MRD-negative and treated with chemotherapy alone experienced better outcomes as well.

The ELN recommends that MRD be evaluated after 2 cycles of chemotherapy during induction and then again after consolidation is completed (Heuser et al., 2019; Schuurhuis et al., 2018). For patients who undergo allogeneic hematopoietic cell transplant, MRD should be evaluated at a maximum of 4 weeks prior to transplant. During the follow-up phase, it is recommended that MRD be assessed from bone marrow and peripheral blood every 3 months for the first 2 years. After 2 years of follow-up, MRD assessment should be individualized. However, the use of MRD as a guide for treatment decisions for patients with AML is still being evaluated.

CONCLUSION

The eight novel agents provide advanced practitioners and their patients with much-needed options for treatment, including new first- and second-line treatment options, as well as agents targeted specifically to patients whose disease harbors a specific genetic aberration. In addition, a new chemotherapy formulation improved survival and the safety profile compared with the standard 7+3 regimen. Clinical trials of these agents are ongoing in an effort to continue to refine their optimal use and, in some cases, to shift their use to earlier in the disease course. These important future directions are highlighted in the next article of this supplement, *The Role of the Advanced Practitioner in Enhancing Outcomes*. ●

Disclosure

Dr. Nix has served on the speakers bureau for Cohrus BioSciences and advisory boards for Bristol-Myers Squibb, Genentech, Puma, Sandoz, and Teva. Ms. Price has served as a consultant for Agios and on an advisory board for Daiichi Sankyo.

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