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REVIEW ARTICLE

Acute myeloid leukemia management and research in 2025

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Abstract

The first 5 decades of research in acute myeloid leukemia (AML) were dominated by the cytarabine plus anthracyclines backbone, with advances in strategies including allogeneic hematopoietic stem cell transplantation, high-dose cytarabine, supportive care measures, and targeted therapies for the subset of patients with acute promyelocytic leukemia. Since 2017, a turning point in AML research, 12 agents have received regulatory approval for AML in the United States: venetoclax (BCL2 inhibitor); gemtuzumab ozogamicin (CD33 antibody–drug conjugate); midostaurin, gilteritinib, and quizartinib (fms-like tyrosine kinase 3 inhibitors); ivosidenib, olutasidenib, and enasidenib (isocitrate dehydrogenase 1 and 2 inhibitors); oral azacitidine (a partially absorbable formulation); CPX351 (liposomal encapsulation of cytarabine:daunorubicin at a molar ratio of 5:1); glasdegib (hedgehog inhibitor); and recently revumenib (menin inhibitor; approved November 2024). Oral decitabine-cedazuridine, which is approved as a bioequivalent alternative to parenteral hypomethylating agents in myelodysplastic syndrome, can be used for the same purpose in AML. Menin inhibitors, CD123 antibody–drug conjugates, and other antibodies targeting CD123, CD33, and other surface markers are showing promising results. Herein, the authors review the frontline and later line therapies in AML and discuss important research directions.

KEYWORDS
acute myeloid leukemia, acute promyelocytic leukemia, antibody–drug conjugate, measurable residual disease

INTRODUCTION

The past 5 decades in acute myeloid leukemia (AML) therapy were dominated by one modestly effective and poorly tolerated standard of care: the combination of cytarabine and anthracyclines. Often referred to as the *7 + 3* regimen (or *3 + 7* or *3 + 10*), it consists of 7–10 days of cytarabine and 3 days of daunorubicin. Research then led to the development of high-dose cytarabine; exploring other anthracyclines (doxorubicin, mitoxantrone, idarubicin, others); advances in allogeneic hematopoietic stem cell transplantation (HSCT), including different preparative regimens, different donors (related, unrelated matched, haploidentical, cord), and different strategies to enhance the antileukemic effect but still mitigate the graft-versus-host effect; and improvements in supportive care measures (antibacterials, antifungals,

antiemetics, growth factors, and transfusion quality and indications). These are taken for granted today, but not in the early 1980s (when some of the authors began their careers), when the choice of antibacterials was limited, the only approved antifungal drug was the toxic (and less effective) original amphotericin B (no azoles, echinocandins, or liposomal amphotericin preparations), and no antiviral therapies were available. Research was progressing; however, compared with contemporary times, it occurred at a snail's pace. This included the discovery of all-*trans* retinoic acid (ATRA) and arsenic trioxide in China in the 1990s as highly effective against acute promyelocytic leukemia (APL), and the approval of gemtuzumab ozogamicin (GO; a CD33 antibody–drug conjugate bound to calicheamicin) in 2002.[1–3] Thus, some progress happened, but it was slow and limited.

The gradual unraveling of AML pathophysiology, and the sequencing of the whole genome of cytogenetically normal AML in 2008[4,5] dramatically accelerated progress in translational-clinical research aimed at targeting the leukemogenic molecular events[4–11] and, with it, the dilemma of how to translate targeted therapeutics rapidly into the modern treatment paradigms. The traditional approach of large, randomized trials that compare 7 + 3 with or without a novel targeted agent cannot accommodate the plethora of novel options that require testing in a reasonable timeline for rare molecular AML subsets. It would commit hundreds of patients to studies that may take 5–10 years to arrive at a conclusion—a timeline that could render any results obsolete by the time the data would be presented. The cure rates with 7 + 3 are ≤40% among patients younger than 60 years who are fit and eligible to receive intensive chemotherapy (*younger/fit*) on trials (strict exclusion criteria for many comorbidities).[12] These registrational trials also excluded prior therapies: for example, hypomethylating agents (HMAs) for myelodysplastic syndrome (MDS), which defines a particularly adverse AML subset referred to as *treated secondary AML* (15%–20% of AML; poor prognosis). Patients older than 60 years who are eligible to receive intensive chemotherapy fare even more poorly and have a median overall survival (OS) of 9 months and a 5-year OS rate of 10%.[13]

Before research with HMA-based epigenetic therapy, patients aged 70–75 years and older and those judged unfit for intensive chemotherapy (*older/unfit AML*) often received supportive or hospice care; their median OS was usually from <3 to 6 months. This subset constitutes about 30%–40% of all patients with AML (considering that the median age in AML is 68 years and that many patients have significant comorbidities). Today, the improved lower intensity combinations offer effective and tolerable therapy to more than two thirds of these patients, prolonging survival and improving quality of life.

NOVEL THERAPIES FOR AML

Coupled with a rapidly advancing understanding of the pathophysiologic–molecular abnormalities in AML, targeted therapies have made their way into the clinic. To date, 11 novel agents have been approved for different AML indications by the US Food and Drug Administration (FDA) since 2017 (Table 1): venetoclax (BCL2 inhibitor); three fms-like tyrosine kinase 3 (FLT3) inhibitors (gilteritinib, quizartinib, midostaurin), two isocitrate dehydrogenase 1 (IDH1) inhibitors (ivosidenib, olutasidenib), one IDH2 inhibitor (enasidenib); GO (CD33 antibody–drug conjugate approved in 2002, withdrawn in 2010, re-approved in 2017),[14] oral azacitidine,[15] CPX-351 (liposomal formulation with a 5:1 cytarabine:daunorubicin molar ratio), and glasdegib (hedgehog inhibitor).[16] Oral decitabine-cedazuridine (highly absorbable bioequivalent HMA) received approval as an alternative to parenteral HMAs in MDS and chronic myelomonocytic leukemia, and is used in AML (with a European Medicines Agency approval but no FDA approval to date).[17] This *total oral therapy* could reduce hospitalizations and clinic visits, improve patients quality of life, and reduce the cost of care. Additional promising agents include the menin inhibitors in *KMT2A*-rearranged acute leukemia, in nucleophosmin-1 (*NPM1*)-mutated AML, and in AML with the HOX-A9/MEIS signature (potentially 50% of patients)[18,19] and the CD123-targeted antibody–drug conjugates (ADCs). Revumenib, a menin inhibitor, was approved by the FDA for the treatment of refractory-relapsed acute leukemia with *KMT2A* translocation in November 2024.

Herein, we briefly review pertinent patient and disease features that affect AML treatment and focus on novel treatments that might become standards of care in a few years.

CYTOGENETIC AND MOLECULAR ABNORMALITIES

The cytogenetic–molecular abnormalities, collectively called *genomic abnormalities*, in AML are listed in Tables 2-4. Of note, the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) categories are derived from data in younger patients (younger than 60 years) treated with 7 + 3 intensive chemotherapy. They may not apply to younger/fit patients treated with more intensive regimens, such as 7 + 3 combined with targeted therapies (trials in progress), or to older patients (whether fit or unfit) treated with 7 + 3 or with lower intensity regimens with or without targeted therapies. Although gender is well represented, almost all trials include largely patients of White/European descent. Minorities and other groups are underrepresented, and issues related to background genetics/genomics and drug sensitivities are less clear.

The four cytogenetic categories are: (1) favorable—translocation (15;17)(q22,q21) in APL, inversion 16 (p13; q22) or translocation (16;16) (p13;q22) and translocation (8;21)(q22;q22) in core binding factor (CBF) AML, (2) intermediate—essentially a normal karyotype (40%–50% of AML), (3) unfavorable—complex karyotype (three or more abnormalities) and translocation/inversion 3q26 (*MECOM*; *MDS1/EV1* complex locus), and (4) others.[20]

Next-generation sequencing (NGS) identifies recurrent molecular abnormalities in 90% of individuals with AML.[21–29] The most frequent mutations are *FLT3*, *NPM1*, *DNMT3A*, *IDH1*, *IDH2*, *TET2*, *RUNX1*, *TP53*, *NRAS*, *CEBPA*, and *WT1*, which can be observed as single mutations or, more often, concurrently with other mutations. Their frequencies

TABLE 1 Drug approvals in acute myeloid leukemia since 2017.

Drug (approval date)	Target inhibition/mechanism	Indication
Venetoclax (November 2018)	BCL2	Newly diagnosed AML; aged 75 years and older or with comorbidities that preclude the use of intensive chemotherapy—use with azacitidine/decitabine or low-dose cytarabine
Midostaurin (April 2017)	FLT3	Newly diagnosed, *FLT3*-mutated AML—use with standard 7 + 3 induction and high-dose cytarabine consolidation
Gilteritinib (November 2018)	FLT3	Relapsed-refractory, *FLT3*-mutated AML
Quizartinib (July 2023)	FLT3	Newly diagnosed *FLT3*-ITD AML—use with standard cytarabine and anthracycline induction and cytarabine consolidation; and maintenance monotherapy after consolidation
Enasidenib (August 2017)	IDH2 inhibitor	Relapsed-refractory, *IDH2*-mutated AML
Ivosidenib (1. July 2018; 2. May 2019)	IDH1	1. Relapsed-refractory, *IDH1*-mutated AML 2. Newly diagnosed, *IDH1*-mutated AML; aged 75 years and older or ineligible to receive intensive chemotherapy
Olutasidenib (December 2022)	IDH1	Relapsed-refractory, *IDH1*-mutated AML
Gemtuzumab ozogamicin (September 2017)	CD33 (antibody drug conjugate)	Adult, newly diagnosed, CD33-positive AML; relapsed-refractory, CD33-positive AML (aged 2 years and older)
CPX-351 (August 2017)	Liposomal cytarabine:daunorubicin (fixed 5:1 molar ratio)	Newly diagnosed therapy-related AML, secondary AML, AML with myelodysplasia-related changes
Glasdegib (November 2018)	Hedgehog pathway	Newly diagnosed AML aged 75 years and older, or with comorbidities that preclude intensive induction chemotherapy—use in combination with low-dose cytarabine
CC-486 (September 2020)	Oral azacitidine hypomethylating agent (15%–30% absorption)	Continued treatment of AML in CR/CRi post intensive induction chemotherapy, not able to complete intensive curative therapy
Oral decitabine-cedazuridine (July 2020)	Oral hypomethylating agent (full absorption)	Alternative to parenteral decitabine for adults with MDS (pretreated/untreated; de novo/secondary)
Revumenib (November 2024)	Menin inhibitor	Relapsed-refractory *KMT2A*-rearranged acute leukemia, aged 1 year and older

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; *FLT3*, fms-like tyrosine kinase 3; *IDH1*, isocitrate dehydrogenase 1; *IDH2*, isocitrate dehydrogenase 2; ITD, internal tandem duplication; MDS, myelodysplastic syndrome.

[Correction added on 19 December 2024, after first online publication: New row 'Revumenib' has been added to the Table 1 and for the 'Oral decitabine-cedazuridine' Drug, the 'Indication' part has been revised.]

TABLE 2 National Comprehensive Cancer Network cytogenetic–molecular classification of acute myeloid leukemia.

NCCN risk category	Karyotype	Molecular abnormalities
Better risk	Inversion (16), t(16;16) Translocation (8;21) Translocation (15;17)	Normal (diploid) karyotype: *NPM1* mutation without *FLT3*-ITD; bZIP in-frame *CEBPA* mutation
Intermediate risk	Normal (diploid) karyotype Trisomy 8 alone Translocation (9;11) Other nondefined	*NPM1*-mutated and *FLT3*-ITD *NPM1* wild type and *FLT3* wild type
Poor risk	Complex karyotype (three or more clonal cytogenetic abnormalities) Monosomal karyotype: - 5, 5q−, 7, 7q−11q23, non-t(9:11) - Inversion (3), t(3;3) - Translocation (6;9), or (9;22), or (8;16)	*TP53*-mutated Mutation of *RUNX1*, *ASXL1*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2* *NPM1* wild type and *FLT3*-ITD (high allelic ratio)

Note: NCCN and European LeukemiaNet risk definitions are applicable to younger patients with de novo acute myeloid leukemia (AML; aged <60 to 65 years) treated with 7 + 3 regimens and may not apply to older patients with AML, those with secondary/therapy-related AML (worse prognosis), and those receiving lower intensity therapy. The t(9;11) translocation may be intermediate risk only in younger patients with de novo AML; all other *KMT2A*-rearranged AML considered adverse at The University of Texas MD Anderson Cancer Center.

Abbreviations: ITD, internal tandem duplication; *MECOM*, *MDS1/EV1* complex locus; NCCN, National Comprehensive Cancer Network; *NPM1*, nucleophosmin-1; t, translocation.

Adapted from the European LeukemiaNet/NCCN.

TABLE 3 European LeukemiaNet cytogenetic–molecular classification of acute myeloid leukemia.

ELN risk category	Genetic lesion
Favorable	Translocation (8;21)(q22;q22); *RUNX1::RUNX1T1* Inversion (16)(p13.1q22); *CBFB::MYH11* Mutated *NPM1* without *FLT3*-ITD bZIP in-frame mutated *CEBPA*
Intermediate	*NPM1*-mutated with *FLT3*-ITD *NPM1* wild type with *FLT3*-ITD t(9;11)(p21.3;q23.3); *MLLT3::KMT2A* Cytogenetic abnormalities not favorable or adverse
Adverse	Translocation (6;9)(p23;q34.1); *DEK::NUP214* Translocation (v;11q23.3); *KMT2A*-rearranged Translocation (9;22)(q34.1;q11.2); *BCR::ABL1* Inversion (3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *MECOM(EVI1)* 5 or del(5q); −7; −17/abnormality (17p) Complex karyotype (three or more cytogenetic abnormalities), monosomal karyotype Mutation of *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSF2* *TP53*-mutated

Note: ELN and National Comprehensive Cancer Network risk definitions are applicable to younger patients with de novo acute myeloid leukemia (AML; aged <60 to 65 years) treated with 7 + 3 regimens and may not apply to older patients with AML, those with secondary/therapy-related AML (worse prognosis), and those receiving lower intensity therapy. The t(9;11) translocation may be intermediate risk only in younger patients with de novo AML; all other *KMT2A*-rearraged AML is considered adverse at The University of Texas MD Anderson Cancer Center.

Abbreviations: del, deletion; ELN, European LeukemiaNet; *FLT3*, fms-like tyrosine kinase 3; ITD, internal tandem duplication; *MECOM*, *MDS1/EV1* complex locus; *NPM1*, nucleophosmin-1; t, translocation.

Adapted from the ELN/National Comprehensive Cancer Network.

depend on the patient's age as well as their therapy-related AML status.[30] AML mutations can be prognostic and/or predictive. In some cases, they are actionable targets.

The prognostic value of mutations is most notable in patients with intermediate karyotypes.[22,31,32] The negative effect of unfavorable karyotypes (complex, *MECOM*) typically trumps that of mutations (however, the *TP53* mutation is frequently associated with a complex karyotype and worsens the outcome compared with a complex karyotype alone). Mutations associated with favorable-karyotype AML (e.g., *FLT3* in APL; *c-KIT*, *N-RAS*, and *FLT3* in CBF AML) may not be adverse when treated with novel regimens.[33–36]

The predictive value of mutations for the selection of treatment may evolve as additional, large-scale analyses are conducted in different patient groups, AML subsets, and therapies. For example, whereas patients with *FLT3*-mutated APL present with high white blood cell/blast counts, it has not been associated with an adverse prognosis when managed optimally with ATRA-arsenic trioxide with or without GO, nor has it required the addition of an FLT3 inhibitor.

The significance of a mutation depends on multiple factors/events, such as co-occurring mutations, the AML subtype (APL or CBF AML vs. others), the size of the mutated clone (variant allele frequency [VAF]), and the proposed therapy (intensive, low-intensity, addition of venetoclax).[23–26] All of these factors must be accounted for when determining appropriate treatment. In addition, once again, the predictive value of mutations for the selection of treatment may evolve as additional, large-scale analyses are conducted in different patient groups, AML subsets, and with changing therapies. A simple analogy is to consider mutations as different colors in a painting. The final painting depends on the colors used (mutations), how much they are used (VAF), which other colors are mixed in (co-mutations), and the brush and style (classical, impressionism, fauvism, abstract, cubist, etc.—equivalent to the therapy used). After all of the above are considered, the final painting value is additionally tied to the artist (Gauguin or Cezanne paintings are better than those of lesser artists). Similarly, the ultimate outcome of AML therapy depends on the leukemia expertise.

The above analogy is illustrated by the variable prognosis of an *NPM1* mutation when it co-occurs with other mutations and when the treatment changes. An *NPM1* mutation occurs in about 30% of AML (about 50% of normal-karyotype AML) and is favorable in younger patients who have a normal-karyotype AML treated with intensive chemotherapy. Such patients benefit from treatment with high-dose cytarabine,[37] the combination of HMA-venetoclax[23] plus GO, and potentially with menin inhibitor–based regimens.[19,38–45] *NPM1*-mutated AML has a worse outcome when associated with *FLT3* mutations (unless FLT3 inhibitors/allogeneic HSCT are incorporated). A triple mutation of *NPM1*, *FLT3*, and *DNMT3A* is associated with a poor outcome in patients treated without FLT3 inhibitors (3-year survival rate, 20%; 3-year cumulative relapse rate, 40%; no benefit from allogeneic HSCT).[43,46]

In the ELN 2022 classification, the pertinent mutations in younger patients treated with 7 + 3 intensive chemotherapy are: *NPM1* without *FLT3* (favorable); CEBPA in the bZIP domain (favorable); and *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*, *and TP53* (unfavorable). Of note, the ELN 2022 classification was not predictive for survival in older/unfit patients with AML treated with HMAs with or without venetoclax. A proposal of a

TABLE 4 Clinically relevant molecular abnormalities.

Mutation	Incidence, (with diploid karyotype), %	Comments
FLT3-ITD	20 (30–35)	Intermediate risk with regimens incorporating FLT3 inhibitors (quizartinib, gilteritinib, midostaurin) with frontline intensive chemotherapy in younger patients with AML, followed by allogeneic HSCT in first remission Adding FLT3 inhibitors (gilteritinib, quizartinib, sorafenib) post-transplantation maintenance recommended In older/unfit patients with AML, triplet regimens with hypomethylating agents, venetoclax, and FLT3 inhibitors (gilteritinib/quizartinib) show promising early results
FLT3-TKD	5–10	Prognostic significance uncertain; addition of type I FLT3 inhibitors (gilteritinib, midostaurin) to frontline therapy recommended *FLT3*-TKD with *NPM1*-mutated = favorable outcome; HSCT in first CR not mandatory; monitor longitudinally using *NPM1* high-sensitivity PCR
NPM1	30 (40–50)	*NPM1*-mutated, *FLT3* wild-type = favorable *NPM1*-mutated + *DNMT3A*-mutated = adverse *NPM1*-mutated + secondary type mutations = uncertain Sensitive to cytarabine, gemtuzumab ozogamicin, venetoclax, menin inhibitors. Older/unfit *NPM1*-mutated = sensitive to hypomethylating agents and venetoclax.
KMT2A-rearranged	10–12	Adverse prognosis; menin inhibitors in combinations showing positive results; revumenib FDA approved November 2024 High incidence of central nervous system and extramedullary disease; recommend intrathecal therapy prophylaxis (2–4 intrathecal injections)
CEBPA	<5	Biallelic mutations and bZIP type mutations = better prognosis (if without concomitant unfavorable mutations)
DNMT3A	20 (30–35)	Associated with *NPM1* and *FLT3*-ITD mutations Adverse prognosis, especially with concomitant *FLT3* mutations in the setting of frontline intensive chemotherapy
RUNX1	10	Adverse prognosis
ASXL1	10–15	Adverse prognosis
KIT	5	Higher incidence in CBF-AML; unfavorable outcome in CBF-AML with 7 + 3 but not with FLAG-GO
NRAS	10–15	40%–50% of inversion 16 AML; no definite prognostic association Mechanism of resistance to BCL2, IDH, and FLT3 inhibitors at relapse; RAS/MEK-inhibitors in clinical trials
IDH2	10–20 (20–30)	Benefit from enasidenib-based or venetoclax-based combinations; triplet regimens of enasidenib + hypomethylating agents + venetoclax show positive results
IDH1	7–10 (10–15)	Benefit from ivosidenib-based, olutasidenib-based, or venetoclax-based combinations; triplet regimens of ivosidenib + hypomethylating agents + venetoclax ongoing
TET2	10–15	Adverse prognosis
TP53	2–20	Frequent occurrence with complex karyotype; very adverse prognosis; no clear benefit of any treatment strategy yet

Abbreviations: AML, acute myeloid leukemia; CBF, core binding factor; CR, complete remission; FLAG, fludarabine and high-dose cytarabine; FLT3, fms-like tyrosine kinase 3; GO, gemtuzumab ozogamicin; IDH, isocitrate dehydrogenase; ITD, internal tandem duplication; HSCT, hematopoietic stem cell transplantation; *NPM1*, nucleophosmin-1; PCR, polymerase chain reaction analysis; TKD, tyrosine kinase domain.

molecular classification using four mutated genes (*NRAS*, *KRAS*, *FLT*-internal tandem duplication [*FLT*-ITD], and *TP53*) was predictive of outcome with HMA-venetoclax treatment and is now included in the ELN 2024 classification for lower intensity therapy.[47,48] However, this molecular signature was not predictive of outcome with the *triple-nucleoside-venetoclax* regimen (unpublished observations), highlighting that any prognostic score will depend on the treatment received.

TP53 mutations and/or deletions are detected in 2%–20% of patients with AML and occur more frequently in secondary or therapy-related disease and in older patients. They are often associated with a complex karyotype (90%) and with a very poor

prognosis (except in the less common situation of a *TP53* monoallelic mutation, VAF<20%, and diploid karyotype; 10%–15% of cases).[49–51]

NRAS mutations in newly diagnosed AML treated with high-dose cytarabine regimens are associated with favorable outcomes. But *RAS* pathway signaling mutations (*NRAS*, *KRAS*, *NF1*, *PTPN11*) in relapsed AML are associated with poor outcomes.[24–26] In refractory-relapsed AML, *RAS* pathway mutations may be clonally selected (clonal expansion, mutation acquisition) as a resistance mechanism.[27] Occasionally, *BCR::ABL1*-rearranged AML develops after FLT3-based frontline therapy; in relapsed patients, it should be tested for because it may respond to combination therapies, including BCR::ABL1 tyrosine kinase inhibitors).[28]

In analyses conducted at The University of Texas MD Anderson Cancer Center (MD Anderson),[52,53] the independent significant mutations selected by multivariate analysis in younger patients treated with intensive chemotherapy (after accounting for complex cytogenetics and patient-associated and leukemia-associated factors) were *NPM1* (favorable), and *TP53* and *PTPN11* (unfavorable).[52] *FLT3* mutations were no longer unfavorable with the addition of FLT3 inhibitors and the implementation of allogeneic HSCT in first complete remission (CR).[54–58] Among older patients receiving low-intensity regimens, *NPM1* and *IDH2* (both favorable), and *TP53* (unfavorable) were significant.[53]

The cytogenetic–molecular categories have become more fluid as newer therapies elevate subsets into more favorable categories. For example, Philadelphia chromosome-positive AML is associated with a 5-year survival rate of 50% in studies combining chemotherapy with BCR::ABL1 tyrosine kinase inhibitors and subsequent HSCT.[59] The addition of FLT3 inhibitors to chemotherapy combinations shifted younger patients with *FLT3*-ITD AML to the intermediate category.[60] The outcome of *KMT2A*-rearranged AML may improve now that menin inhibitors are being studied in combinations.

Unfortunately, some adverse factors have persisted over time and despite new therapies: elderly age (75 years and older), adverse performance status, abnormal organ functions, complex cytogenetics, mutations in *TP53* and *PTPN11*, and *MECOM* fusion.[61]

The significance of a mutation and whether it should be targeted may depend on the dominance of the mutated clone.[29] This is expressed as the VAF (the ratio of mutated clone/total cells). The exception is the *FLT3*-mutated clone, which is reported as the *FLT3* allelic ratio (area under the curve of *FLT3*-ITD/area under the curve of *FLT3* wild type).[62–64] This may cause some confusion; recent studies are now also reporting the size of the *FLT3*-mutated clone as the VAF.

Approximately 10% of patients with AML are suspected to have an inherited predisposition because of germline mutations (for instance, the Li-Fraumeni syndrome [germline *TP53* mutation; enriched in patients with therapy-related, *TP53*-mutated AML] and *DDX41* mutations). These can be recognized because of the mutation (for instance, a *DDX41* founder mutation at heterozygous frequency in a patient with AML) or when multiple cancers occur in one patient and/or family. They are also suspected when the mutation VAF is high (from >40% to 50%) and especially if the mutation remains present at heterozygous frequency in morphologic CR. Such mutations should be recognized and confirmed because they may have therapeutic consequences: tolerance to chemotherapy, choice of related donor for HSCT, therapy selection. For example, in *DDX41*-mutated disease, venetoclax added to chemotherapy may improve outcome.[65] Case studies also highlight the benefit of lenalidomide in *DDX41*-mutated AML.[66]

Translating the cytogenetic–molecular knowledge

There are now multiple therapies that target the molecular abnormalities: combined regimens that include venetoclax in people with AML deemed older/unfit or younger/fit; FLT3 inhibitors in *FLT3*-mutated AML; high-dose cytarabine, GO, HMA-venetoclax, or menin inhibitors in *NPM1*-mutated AML; IDH inhibitors in *IDH*-mutated AML; and menin inhibitors in *KMT2A*-rearranged AML. FLT3 inhibitor-containing regimens are being explored in *FLT3* wild-type AML with an *FLT3*-like signature,[67–69] as are menin inhibitors in AML with a *HOXA9/MEIS* signature (30%–40% of AML).[18,19]

FLT3 mutations describe *FLT3*-ITD and *FLT3*-tyrosine kinase domain point mutations (often D835). Before the era of FLT3 inhibitors, these mutations were historically unfavorable (particularly if there was a higher allelic burden in *FLT3*-ITD).[62–64] This is no longer the case now that FLT3 inhibitors are incorporated into frontline intensive chemotherapy regimens followed by allogeneic HSCT. Type I inhibitors (gilteritinib, midostaurin) target both *FLT3*-ITD and *FLT3*-tyrosine kinase domain mutations. Type II inhibitors (quizartinib, sorafenib) target only *FLT3*-ITD.

HMA combinations with enasidenib or venetoclax are effective in *IDH2*-mutated AML, which is particularly sensitive to the addition of enasidenib to venetoclax-based therapy.[70,71] In *IDH1*-mutated AML, HMAs plus ivosidenib may be better than HMAs plus venetoclax.[71–73]

The triplet regimens incorporating HMA-venetoclax with FLT3 inhibitors in *FLT3*-mutated AML and IDH1/IDH2 inhibitors in *IDH1*/IDH2-mutated AML are producing better results than the doublets.[74–76] However, they appear to be more myelosuppressive (especially FLT3 combinations) and may require refinement of dose schedules (based on the induction day-14 bone marrow results), shortening the duration of venetoclax, and adjusting the FLT3 inhibitor doses and schedules before their acceptance in clinical settings.

c-KIT mutations have predicted for inferior outcomes with the 7 + 3 regimens in CBF AML,[77,78] but this ceases to be the case when GO is added to high-dose cytarabine (e.g., with the fludarabine, high-dose cytarabine, GO [FLAG-GO] regimen).[35,36]

FLT3 mutations in APL and CBF AML are associated with leukocytosis but do not predict for worse outcomes with modern regimens. Hence, adding FLT3 inhibitors (not explored to date) may not add value in APL or CBF AML.

Outcomes in *KMT2A*-rearranged AML may improve with the incorporation of menin inhibitors into chemotherapy. Menin inhibitors include revumenib, ziftomenib, bleximenib, and enzomenib.[19,38–41] Revumenib was approved by the FDA in November 2024 to treat refractory-relapsed leukemia with *KMT2A*-rearrangement, based on the results of the AUGMENT-101 trial.

MEASURABLE RESIDUAL DISEASE

Measurable residual disease (MRD) status is gaining importance, with new technologies that detect disease at 10^{-6} rather than 10^{-4} sensitivity.[79–90] Positive multicolor flow-cytometry (MFC-MRD; detection sensitivity, 10^{-4}) status predicts for a high risk of relapse (60%–80%) unless a radical treatment change occurs, such as allogeneic HSCT. Although undetectable MFC-MRD does not fully protect against relapse (risk of relapse is still 30%–40%), it is used in decision making on the role of allogeneic HSCT for patients in first CR.

The reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) assay (sensitivity, 10^{-6}) is commonly used to monitor APL and CBF AML. RT-qPCR has also recently been used to monitor AML with *NPM1* and *FLT3* mutations. Polymerase chain reaction (PCR) monitoring of *PML::RARα* fusion in APL and of *CBFB::MYH11* fusion and *RUNX1::RUNX1T1* fusion in CBF AML can identify early molecular relapse. Early therapeutic interventions in such settings may result in high cure rates.[91–93] Those who have the t(8;21) translocation may have MRD positivity below 0.1% and still maintain CR.

Standard NGS panels to detect molecular MRD have a sensitivity of 1%–2%. Recently developed PCR–NGS assays can detect molecular MRD at a level of 10^{-5} quantitatively (qualitatively, 10^{-6}).

Monitoring of *NPM1* and *FLT3*-ITD mutations by the new, highly sensitive assays (RT-qPCR, PCR–NGS) is informative and predictive of clinical outcomes. Different studies have used assays of various sensitivities, and standardization is needed. *NPM1* MRD monitoring (RT-qPCR; sensitivity, 10^{-4}) is predictive for relapse and OS.[93,94] The persistence of *NPM1* or *FLT3*-ITD molecular disease pre-HSCT (targeted, error-coded NGS; sensitivity, 10^{-4}) predicted for a higher incidence of relapse and worse OS in patients with AML in first CR who proceeded to allogeneic HSCT.[95] *NPM1* MRD clearance (RT-qPCR; sensitivity, 10^{-5}) after two induction courses indicated lack of benefit from HSCT in first CR (3-year OS, 79% vs. 82%). This lack of benefit was also demonstrated when the analysis was restricted to AML with co-occurrence of *NPM1* and *FLT3*-ITD.[94] Gilteritinib maintenance post-allogeneic HSCT was not beneficial in patients who showed clearance of the *FLT3*-ITD (PCR–NGS; sensitivity, 10^{-6}) immediately before or after allogeneic HSCT.[96] Ultrasensitive, novel PCR–NGS assays (10^{-6}) for *NPM1* mutations are now commercially available in the United States.

It should be emphasized that the routine NGS molecular panels commonly used at diagnosis to detect AML mutations are not ideal to assess MRD in CR (sensitivity, 1%–2%) compared with the significantly more sensitive RT-qPCR and PCR–NGS assays.[97]

Interventions that may help eliminate MRD-positive AML include HSCT, intensified chemotherapy, HMAs + venetoclax, targeted therapy combinations for specific mutations or molecular targets (HMA + venetoclax + FLT3, IDH1/IDH2, or menin inhibitors), combinations including CD123/CD33 antibody therapies, and immune therapies (e.g., natural killer [NK] cellular therapy). The significance of persistent *DNMT3A*, *TET2*, or *ASXL1* mutations in remission was indicated in predicting for relapse, but this has been questioned, in part because of the issue of discriminating residual clonal hematopoiesis versus residual AML MRD.[43,79,98,99]

INCORPORATION OF NOVEL TARGETED STRATEGIES IN THE TREATMENT OF AML

Acute promyelocytic leukemia

APL (<10% of AML) is characterized by the pathognomonic cytogenetic translocation t(15;17) and the related *PML-RARα* molecular abnormality.

Discovering the high anti-APL efficacy of ATRA and arsenic trioxide and combining ATRA with chemotherapy led to adopting the AIDA regimen (ATRA plus idarubicin) as the standard of care, at least for a while.[100]

In 2001, the MD Anderson group investigated ATRA plus arsenic trioxide (with or without GO) in APL and reported that this chemotherapy-free regimen was highly effective (Table 5).[33,34,101] This was later confirmed to be superior to AIDA in several randomized trials in both lower and higher risk APL (white blood cells $>10 \times 10^9$/L).[102–106] ATRA plus arsenic trioxide was associated with 10-year OS rates ≥90% compared with 75% using the AIDA regimen. With cumulative experience, the induction mortality was reduced to <5%.[103]

Induction therapy in APL consists of ATRA 45 mg/m^2 daily given orally in two daily doses, and arsenic trioxide 0.15 mg/kg given intravenously once daily. GO (6–9 mg/m^2) is given in high-risk APL (presenting white blood cell count $>10 \times 10^9$/L or increasing above that during induction). After achieving CR (usually 3–4 weeks; may need to interrupt ATRA–arsenic for 7–10 days after CR to allow recovery of counts), consolidation therapy consists of 9 months of ATRA, given for 2 weeks every month, and arsenic trioxide (daily for 5 days, weekly for 4 weeks [20 doses per course], and every other month for 4 months [total consolidation, 80 doses]; total, 110 doses of arsenic trioxide with induction). GO is used in consolidation for persistent *PML-RARα* molecular MRD documented by PCR from 2 to ≥3 months into CR. This is rare and should be documented at least twice because of possible false-positive tests. Low-level PCR positivity may be present immediately after induction CR and is not of concern.

Because APL is rare and cumulative experience is limited, we highlight some maneuvers to optimize therapy: (1) Granulocyte-colony–stimulating factors should *never* be used (can worsen APL).[107] (2) ATRA and arsenic trioxide during induction may cause insidious fluid retention, leading to pulmonary and multiorgan failure (occasionally

TABLE 5 General approach to patients with acute myeloid leukemia at The University of Texas MD Anderson Cancer Center.[a]

Disease	Therapy and comments	5-year survival, %
APL	ATRA + arsenic trioxide High-risk APL (WBC count >10 × 10^9 pretreatment or during induction); persistent MRD molecular disease for ≥2 months in CR; GO, add 3-–6 mg/m^2 (round to a flat dose of 4.5–9.0 mg)	>90.0
CBF AML	FLAG-GO induction + four or five consolidations; three total doses of GO 3.0 mg/m^2, one during induction and two in two consolidation courses Aged 60 years and older: Adjusted-dose FLAG-GO Intolerance to FLAG-GO: Hypomethylating agent (HMA) + VEN + GO (according to molecular MRD)	>80.0
AML in younger patients	FLAG-IDA + VEN or CLIA + VEN induction + three or four consolidations *FLT3*-ITD AML: Add FLT3 inhibitor (quizartinib or gilteritinib) to replace VEN Refer all eligible, nonfavorable patients to allogeneic SCT Consider maintenance therapy post-consolidation or post-transplantation	≥50.0
AML (older than 60 years)	*Triple-nucleoside-venetoclax regimen* (cladribine, low-dose cytarabine, and VEN alternating with azacitidine/decitabine-VEN) *Triplet* combinations (mutation-specific) ongoing: - HMA + VEN + quizartinib/gilteritinib (*FLT3*-mutated) - HMA + VEN + IDH inhibitor (*IDH1*/*IDH2*-mutated) - HMA + VEN + menin inhibitors (*KMT2A*-rearranged, *NPM1*-mutated, *NUP98*-rearranged) - Azacitidine/decitabine + VEN + investigational agents (ADCs, phase 1; other investigational agents)	≥30.0
Allogeneic HSCT	In CR1, if poor cytogenetics, secondary/therapy-related AML, *FLT3*-ITD, adverse mutations (including secondary type mutations), MRD-positive, and low anticipated treatment-related mortality of HSCT procedure, we recommend SCT in CR1 In intermediate-risk AML (excluding the above-mentioned), with MRD-negative CR1 after intensive chemotherapy, consider proceeding to HSCT versus maintenance with oral decitabine with or without VEN or with or without targeted therapy In CR2 and beyond: All potential patients	
Salvage therapy	CR1 duration ≥12 months: High-dose, cytarabine-based regimens with addition of VEN (FLAG-Ida-venetoclax); or addition of FLT3 inhibitor, IDH1/IDH2 inhibitor, or menin inhibitor (if target identified); HMA-VEN–targeted therapy triplet if suitable target identified (FLT3, IDH1/IDH2, menin target genes) CR1 duration<12 months: Phase 1–2 trials OR azacytidine/decitabine-VEN–targeted therapy triplet if suitable target identified Always recheck for mutations (next-generation sequencing), particularly for *FLT3*, *IDH1/IDH2*, *KMT2A*, *NPM1*, *NUP98*, and other *MEIS1/HOXA*-activating, menin-sensitive mutations; if targetable mutations/molecular aberrations, then target-based therapy	
Supportive measures	Antibiotic/antifungal/antiviral prophylaxis for all patients Day-21 bone marrow on HMA-VEN, breaks for count recovery, growth factor use if delayed count recovery or infections once bone marrow remission confirmed; decrease VEN to 7–14 days or less in subsequent cycles after MRD-negative remission with 5-week to 6-week cycles, allowance for suitable count recovery between cycles Protected environment/reverse isolation if aged 50 years and older plus intensive chemotherapy OR if aged 60 years and older plus low-intensity therapy	

Abbreviations: ADCs, antibody–drug conjugates; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ATRA, all-*trans* retinoic acid; CBF, core binding factor; CLIA, cladribine, high-dose cytarabine, and idarubicin; CR1, first complete remission; CR2, second complete remission; ELN, European LeukemiaNet; FLAG-GO, fludarabine, high-dose cytarabine, plus gemtuzumab ozogamicin; FLAG-Ida, fludarabine, high-dose cytarabine, plus idarubicin; *FLT3*, fms-like tyrosine kinase 3; GO, gemtuzumab ozogamicin; HSCT, hematopoietic stem cell transplantation; *IDH1*, isocitrate dehydrogenase 1; *IDH2*, isocitrate dehydrogenase 2; ITD, internal tandem duplication; MRD, measurable residual disease; NCCN, National Comprehensive Cancer Network; SCT, stem cell transplantation; VEN, venetoclax; WBC, white blood cell.

[a]See Dohner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377. 10.1182/blood.202201686760.[60]) Adapted from NCCN, Version 3.2024 (https://www.nccn.org/; accessed June 28, 2024).

requiring intubation, dialysis). This picture is often confused with *differentiation syndrome* but is managed differently—holding treatment coupled with aggressive diuresis.[108] (3) The differentiation syndrome is preventable with steroids during induction (dexamethasone 10–20 mg daily for 1–2 weeks). (4) Cap the total daily dose of arsenic trioxide at 15 mg; higher doses can occasionally cause renal failure.[109] (5) Recognize that ATRA can cause severe headaches and, rarely, increased intracranial pressure (papilledema, high cerebrospinal fluid opening pressure). Reduction of the ATRA dose and addition of acetazolamide (125–250 mg two to four times daily) may help. If ATRA must be discontinued, GO can be used instead (3 mg/m^2 every 4–6 weeks for five or six doses). (6) Rarely, APL-associated disseminated intravascular coagulation is dominantly thrombotic, with or without bleeding. Idarubicin or GO are most effective against thrombotic disseminated intravascular coagulation (ATRA could worsen this thrombosis setting). These complications are reviewed in more detail elsewhere.[6,110]

Core binding factor AML

CBF AMLs include inversion 16 AML (or translocation [16;16]), and AML with translocation (8;21). They constitute 12%–15% of adult AML and 25%–30% of pediatric AML. Eosinophilia may be present in inversion 16 AML, and translocation (8;21) AML may express CD19.

The cure rate in CBF AML increased from 30%–40% to 50% with three to four high-dose cytarabine consolidation courses after 7 + 3.[111] It further increased to 75% with the addition of GO to high-dose cytarabine.[14,35,36,112] At MD Anderson, after a review of several studies conducted historically, the FLAG-GO regimen was used (fludarabine, high-dose cytarabine, and GO) for up to six courses (three courses incorporate GO 3 mg/m^2). The outcome was better with GO compared with idarubicin added to FLAG.[36] Older patients are treated with FLAG-GO using reduced-dose schedules. Patients intolerant to FLAG-GO and those with persistent MRD in CR may be treated with HMA-venetoclax and/or GO.[113] The data on adding c-KIT inhibitors if *c-KIT* is mutated, or FLT3 inhibitors if *FLT3* is mutated, are scant.[114]

Common mutations in CBF AML are *c-KIT* (30%), *NRAS* (15%–20%), *FLT3* (15%), *ASXL2* (15%), and *ASXL1* (10%). Some studies reported worse outcomes with *c-KIT* or multiple mutations when 7 + 3 regimens were used. In a study of 520 patients treated with 7 + 3 (only 13% received GO), the CR rate was 94%, and the 5-year OS rate was 63%. In multivariate analysis, high *c-KIT* VAF (≥25%), *FLT3*-ITD mutations, and *TET2* mutations were associated with worse OS.[115] This was not the case with the FLAG-GO regimen, in which we could not identify an association of mutations with worse survival.[35,36]

Approach to younger/fit patients with AML (and older patients fit for intensive chemotherapy)

Most of the literature reports on 7 + 3 regimens and other intensive combinations in AML included relatively younger patients (upper age limit, 60 or 65 years). The median age in AML is about 70 years. Thus the published results of these large-scale cooperative trials may not translate well into the real world.[116]

The 7 + 3 anthracycline-cytarabine regimens, high-dose cytarabine consolidations, additions of GO and adenosine nucleoside analogs, and choice of anthracycline

Today, the 7 + 3 regimen (cytarabine 100–200 mg/m^2 by continuous infusion daily for 7 days; daunorubicin, 60–90 mg/m^2 daily for 3 days or idarubicin 12 mg/m^2 daily for 3 days) is an accepted standard of care. But it is imperfect because it is associated with a long-term OS rate of 40% in younger patients and <10% in older patients who are fit for intensive chemotherapy.[12,13]

The value of high-dose cytarabine in both induction and consolidation is discussed elsewhere in detail.[6–11,117–125] It is also generally accepted today that allogeneic stem cell transplantation (SCT) in first CR improves outcomes in the nonfavorable AML subsets (intermediate-risk and high-risk AML) after 7 + 3 chemotherapy.

The FLAG plus idarubicin regimen (FLAG-IDA; developed at MD Anderson in the 1990s)[118,126–129] combines several important anti-AML elements (induction with high-dose cytarabine, addition of fludarabine, idarubicin instead of daunorubicin). It is more intensive and more difficult to manage than 7 + 3 because of myelosuppression-associated side effects but may increase long-term survival compared with 7 + 3. Hence, this regimen requires specialized administration, preferably at leukemia centers.

The optimal high-dose cytarabine dose schedule is still under discussion after more than 30 years.[118] The MD Anderson trials incorporate high-dose cytarabine 1.5–2.0 g/m^2 daily for 5 days during induction, and for 3 days in consolidations. Polish investigators added cladribine to 7 + 3 and reported better results than with 7 + 3 alone.[130,131] Daunorubicin 60 mg/m^2 daily for 3 days is as potent as 90 mg/m^2 daily for 3 days, and it is safer. Daunorubicin 45 mg/m^2 is inferior to 90 mg/m^2.[12,13] Idarubicin 12 mg/m^2 daily for 3 days is as effective as daunorubicin and superior in some studies.[132,133]

The use of GO benefits AML with favorable-risk/intermediate-risk cytogenetics. GO 3 mg/m^2 was safer than 6 mg/m^2 and equally effective.[14,112,134,135] The value of combining GO with intensive chemotherapy (FLAG-IDA; cladribine, high-dose cytarabine, and idarubicin [CLIA]) and other targeted therapies is an important research question but may increase the risk of myelosuppression-associated complications.

Combinations of intensive chemotherapy with venetoclax or other targeted agents (FLT3, IDH, and menin inhibitors)

In younger/fit patients with AML, the treatment options today include 7 + 3 or more intensive regimens (FLAG-IDA, CLIA) with or

without targeted therapies.[37,136–145] We may soon reach a time when most AML experts would consider that 7 + 3 should be used only with additional therapeutic maneuvers (GO, venetoclax; FLT3 or IDH inhibitors).

At MD Anderson, in younger/fit patients, FLAG-IDA or CLIA is combined with either venetoclax (7-day induction, 5-day consolidations) or an FLT3 inhibitor (gilteritinib, quizartinib) in *FLT3*-mutated AML.[146–148] We are cautiously exploring the possible addition of two targeted agents to intensive chemotherapy (e.g., venetoclax + GO; venetoclax + FLT3 or an IDH inhibitor).

The frontline trials of FLAG-IDA and CLIA with venetoclax have produced better results than the historical results from the same intensive regimens without venetoclax. The outcomes are still better when allogeneic HSCT is performed in first CR, particularly in patients with intermediate or unfavorable disease.[146–148] In an update of CLIA-venetoclax, among 95 patients treated (median age, 48 years), the CR plus CR with incomplete hematologic recovery (CR/CRi) rate was 95%, the rate of MFC-MRD negativity was 90%, and the 3-year OS rate was 73%. The 2-year OS rate was 82% with HSCT (performed in 66%) and 60% without HSCT. In an update of FLAG-IDA-venetoclax (68 patients), the CR/CRi rate was 96%, the MFC-MRD negativity rate was 89%, and the 2-year OS rate was 75%. The 2-year OS rate was 80% with HSCT (performed in 57%) and 44% without HSCT.[149] Studies of 7 + 3 or 5 + 2 with venetoclax are also showing encouraging early results.[150,151]

Some younger/fit AML subsets are highly resistant to intensive chemotherapy. These include *TP53*-mutated AML, *MECOM*-AML, and secondary treated AML. They constitute about 5%–10% of AMLs in community practice and 20%–30% of AMLs referred to tertiary centers. Such patients should ideally be referred immediately for investigational approaches and analyzed separately to dissect more precisely the benefit of novel strategies in such very high-risk AML (expected CR rates from <40% to 50%; historical 12-month survival rates, <20%) versus other AMLs.

Routine use of prophylactic antibiotics (levofloxacin/ciprofloxacin/cefpodoxime proxetil, azole antifungals, valacyclovir/acyclovir) necessitates dose adjustments of venetoclax (usually 400 mg daily). It should be reduced to 50 mg daily when given with posaconazole, to 100 mg daily when given with voriconazole, and to 200 mg daily when given with isavuconazole. It should be increased to 600 mg daily when given with ivosidenib (if no azoles are used).[152,153]

Once in CR, patients with nonfavorable-risk AML are offered allogeneic HSCT. This decision is based on donor availability, patient performance status and comorbidities, and MRD status (ideally determined by RT-qPCR or ultrasensitive PCR–NGS rather than MFC) in CR. Patients who are not candidates for allogeneic HSCT receive up to four high-dose cytarabine consolidation courses and are offered HMA-venetoclax maintenance or an individualized targeted approach (e.g., FLT3 inhibitors if *FLT3*-mutated).[154] Supportive care measures are listed in Table 5.[60]

The benefit of FLT3 inhibitors has been demonstrated in several randomized trials in frontline AML, post-HSCT, and in later line therapy. In frontline AML therapy, two randomized trials of 7 + 3 with or without midostaurin (*FLT3*-mutated AML) and of 7 + 3 with or without quizartinib (*FLT3*-ITD AML) demonstrated a significant benefit in OS and a reduction of the relapse rate with the addition of the FLT3 inhibitor. The phase 3 RATIFY trial (ClinicalTrials.gov identifier NCT00651261) randomized 717 patients younger than 60 years (median age, 48 years) with *FLT3*-mutated AML to receive 7 + 3 with or without midostaurin. Midostaurin improved CR (CR rate, 59% vs. 54%; $p = .045$) and OS (median OS, 74.7 vs. 25.6 months; $p = .009$; 5-year OS rate, 50% vs, 42%).[54] The phase 3 QUANTUM-First study (ClinicalTrials.gov identifier NCT02668653) randomized 539 patients with *FLT3*-ITD AML to receive 7 + 3 with or without quizartinib. Adding quizartinib did not improve the CR rate (55% in both arms) but improved OS significantly (median OS, 31.9 vs. 15.1 months; $p = .032$; 3-year OS rate, 50% vs. 42%).[55] The value of FLT3 inhibitors in *FLT3*-mutated AML was also demonstrated in real-world data.[57,155]

Sorafenib and gilteritinib maintenance post-HSCT reduced the relapse rate and improved OS in *FLT3*-mutated AML, particularly in patients with PCR–NGS MRD-positive status before or after HSCT.[156,157]

In a Spanish trial, 273 newly diagnosed, younger patients (aged 70 years and younger) with *FLT3*-ITD wild-type AML were randomized to 7 + 3 plus quizartinib ($n = 180$) or placebo ($n = 93$). Adding quizartinib improved survival (2-year OS rate, 63% vs. 47%; $p = .004$).[67] This benefit was restricted to patients with an FLT3-like genomic signature (50% of patients), with improvement in OS, recurrence-free survival, and event-free survival.[67] A *simplified*, reproducible FLT3-like signature and confirmation of the results in other studies may expand the benefit provided by quizartinib (and perhaps other FLT3 inhibitors) beyond *FLT3*-ITD AML (25%–30% of AML) to about 65% of patients with newly diagnosed AML (*FLT3*-ITD–mutated AML and AML with an FLT3-like signature).[69]

Several non-FLT3 agents have also been shown to improve outcomes in *FLT3*-mutated AML: GO, cladribine, and higher doses of cytarabine and daunorubicin.[45,158,159]

In total, 151 patients (median age, 62 years) with newly diagnosed *IDH1/IDH2*-mutated AML were treated with 7 + 3 and ivosidenib (*IDH1*-mutated, n = 60) or enasidenib (*IDH2*-mutated, $n = 91$). Adding ivosidenib to 7 + 3 resulted in a CR rate of 70%, an overall response rate (ORR) of 78%, and a 3-year OS rate of 67%. Adding enasidenib to 7 + 3 resulted in a CR rate of 57%, an ORR of 74%, and a 3-year OS rate of 61%.[160] A HOVON (Hemato-Oncology Foundation for Adults in the Netherlands) German phase 2 study comparing 7 + 3 with or without ivosidenib/enasidenib in younger patients with AML completed accrual.

The *KMT2A*-rearranged and *NPM1*-mutated AMLs are driven by overexpression of *HOX* genes, which depend on the menin-*KMT2A* interaction. Disrupting the binding of menin to *KMT2A* (with menin inhibitors) can reverse the process. Preclinical studies have demonstrated the activity of menin inhibitors in *KMT2A*-rearranged AML as well as in *NPM1*-mutated AML, *NUP98*-fusion AML, and possibly other subsets with *HOXA9/MEIS1*-signature AML. The phase 1 and 2 trials of single-agent menin inhibitors in refractory-relapsed AML reported promising activities, with ORRs of 40%–50% but brief durations of

remissions (3–12 months) unless followed by allogeneic HSCT. Several serious side effects were observed, including differentiation syndrome (multiorgan failure, occasional deaths) and QTc prolongation. These are managed with drug interruptions/dose reductions, cytoreduction with hydroxyurea/cytarabine, and steroids. Acquired somatic mutations in the *MEN1* gene (commonly M327 and G331) develop under menin-inhibitor therapy, which may impede the drug–W346 residue interaction (W346 residue is key to binding of the menin inhibitor to the menin site) and may cause AML resistance. Combinations of menin inhibitors with chemotherapy with or without venetoclax are ongoing with promising results in AML (*KMT2A*, *NPM1*, *NUP98*) and *KMT2A*-rearranged acute lymphocytic leukemia.[18,38–41,161] The mature results from these studies (response rates and durability, toxicities, resistance mechanisms, and novel menin inhibitors that may overcome *MEN1* mutation resistance) will guide definitive trials that may improve the outcomes of several hitherto difficult-to-cure AML and acute lymphocytic leukemia subsets.

Approach to older patients with AML (or younger patients who are unfit for intensive chemotherapy)

The 7 + 3 regimen yields poor results, even when tolerated, in older/fit patients with AML. Using 7 + 3, Lowenberg and colleagues compared high-dose daunorubicin 90 versus 45 mg/m^2 daily for 3 days in 813 newly diagnosed patients aged 60 years and older (median age, 67 years). The CR rate was 54%–64%, the 30-day mortality rate was 11%–12%, and the median OS was 7–8 months (3-year OS rate, 20%).[12] Intensive chemotherapy regimens in unselected older patients with AML (aged 60–65 years or older) resulted in CR rates of 40%–50%, 4-week to 8-week mortality rates of 26%–36%, and a median OS of 4–6 months.[162,163] The early mortality rate increased significantly in patients older that 70–75 years, particularly if the performance status was 2–4 and in the presence of complex karyotype, antecedent hematologic disorder, renal dysfunction (creatinine 1.3 mg/dl), or pneumonia/pulmonary pathology (by chest computerized tomography).[162] In the US Surveillance, Epidemiology, and End Results (SEER) 2010–2017 data, reflective of the real-world results, in patients aged 60 years and older, the 4-week mortality rate was 24%–44%, and the 5-year OS rate was 4%–18%.[116] Thus, the 7 + 3 standard of care is suboptimal, even in patients fit to receive intensive chemotherapy, let alone those who are borderline fit or aged 70 years or older. The prevailing alternative—supportive care/hospice (common practice in most patients with AML before 2000; associated with a median OS of 2–3 months)—is also unappealing.[164]

In the 1990s, lower intensity strategies were evaluated in older/unfit patients with AML, including low-dose cytarabine and HMAs.[165–167] Decitabine was re-developed as epigenetic therapy at MD Anderson beginning in 1992, and HMAs became the cornerstone of therapy in older/unfit AML around 2007. But the results were modest.[166–169] This changed with the addition of venetoclax, and, in 2020, HMAs-venetoclax emerged as a new standard of care in older/unfit patients.

Preclinical and phase 1–2 trials confirmed the efficacy of venetoclax,[170,171] and single-arm trials of HMAs-venetoclax showed promise.[172,173] The VIALE-A phase 3 trial (ClinicalTrials.gov identifier NCT02993523) randomized 431 patients aged 75 years or older or who were unfit for intensive chemotherapy (2:1 randomization) to receive either azacitidine-venetoclax (n = 286) or azacitidine (n = 145). Adding venetoclax significantly improved OS (median OS, 14.7 vs. 9.6 months; $p < .001$), the CR/CRi rate (66.4% vs. 28.3%; $p < 0.001$), and the CR rate (29.7% vs. 17.9%; $p < .001$).[174–176] A longer follow-up reported that the 3-year OS rate was only 25% with azacitidine-venetoclax.[175] The more mature results highlight that this new standard of care in older/unfit AML is an important advance and, at times, is less toxic than intensive chemotherapy, but further improvements are needed.[175,177–179]

Preceding the research with HMAs-venetoclax, and based on the anti-AML efficacy of low-dose cytarabine and adenosine nucleosides analogs, lower intensity regimens of clofarabine and, later, of cladribine plus low-dose cytarabine alternating with an HMA (*triple-nucleoside* therapy) were investigated.[180–182] Among 248 treated patients (median age, 69 years), the ORR was 66%, the 4-week mortality rate was 2%, and the median OS was 12.5 months (diploid karyotype: median OS, 19.9 months; 2-year OS, 45%).[180–182] The results of similar regimens were reported by others.[183,184]

Although the original HMAs-venetoclax trials used a 21-day to 28-day schedule of venetoclax, recent studies indicated that shorter durations of venetoclax (7–14 days per course) could potentially be as effective and less toxic.[185–188] This may allow the development of safer triplet regimens.

As the data matured with HMAs-venetoclax, and based on the efficacy of the triple-nucleoside regimen, the MD Anderson group explored the triple-nucleoside plus venetoclax regimen (cladribine-cytarabine-venetoclax alternating with azacitidine/decitabine-venetoclax).[189,190] Among 141 treated patients (median age, 68 years), the CR/CRi rate was 85%, and the MFC-MRD–negative rate was 78%. The 8-week induction mortality was 3%. The 4-year OS rate was 52% (79% with allogeneic HSCT in first CR vs. 42% without). Confirming the benefit of the triple-nucleoside plus venetoclax regimen and its efficacy compared with intensive chemotherapy in older AML (fit or unfit) could help establish it as a new standard of care.[191]

A fully absorbable oral formulation of decitabine was approved as HMA therapy for MDS/chronic myelomonocytic leukemia in July 2020.[17] It can now be used in AML to allow the delivery of a fully oral regimen (decitabine, venetoclax, plus other oral targeted drugs). The oral absorbable decitabine is different from the approved oral azacitidine (15% absorption; approved as maintenance therapy in AML in first CR and inability to complete full curative therapy).[15] A fully absorbable formulation of azacitidine may soon be available.

Positive results were reported when HMAs were combined with FLT3 or IDH inhibitors. Preclinical studies demonstrated synergism between FLT3 inhibitors and venetoclax, leading to trials with the triplet of HMAs, venetoclax, and FLT3 inhibitors.[74–76] In 30 older patients (median age, 71 years) with newly diagnosed, *FLT3*-mutated

AML, the triplet regimen of azacitidine (7 days), venetoclax (14 days), and gilteritinib (14 days at 80 mg) produced a CR rate of 90%, an MFC-MRD–negative rate of 93% (PCR–NGS MRD-negative rate, 65%) in responders, and a 1.5-year OS rate of 72%.[76] This triplet regimen is myelosuppressive, necessitating reducing venetoclax-gilteritinib to 14 days in induction. During consolidation courses, azacitidine is reduced to 5 days and venetoclax is reduced to 7 days; gilteritinib 80 mg daily is given continuously.

Triplets of HMAs, venetoclax, and IDH inhibitors are promising. Oral decitabine, venetoclax, and an indicated IDH1/IDH2 inhibitor given to 28 newly diagnosed patients with *IDH*-mutated AML produced a CR rate of 90%–100%, an MRD-negative rate of 80%–93%, and a 1.5-year OS rate of 75%. Because of the interaction of ivosidenib (a CYP3A4 inducer) and venetoclax (resulting in a reduction in the venetoclax area under the curve), venetoclax in this regimen is increased to 600 mg daily (without azole prophylaxis).[73,74]

Developing potentially more curative quadruplet regimens with HMAs-venetoclax plus two other targeted therapies will be challenging in view of the potentially additive myelosuppression but may be feasible if venetoclax is reduced to a 7-day schedule.

The experience with menin inhibitors is moving rapidly in both frontline and salvage studies from treatment as single agents to combinations in *KMT2A*-rearranged, *NPM1*-mutated, and *NUP98*-fusion AML. All nine patients with refractory AML (*KMT2A*-rearranged, *NPM1*-rearranged, or *NUP98*-rearranged; median, three prior therapies) treated with combined oral decitabine, venetoclax, and revumenib achieved a response.[192] The combination of revumenib (113–163 mg daily) with azacitidine (7 days per course) and venetoclax (daily) in 26 newly diagnosed patients (median age, 70 years) with *KMT2A*-rearranged (35%) or *NPM1*-mutated AML (65%) resulted in CR in 69%, composite CR in 88%, MRD-negative status in 85%, and a 1-year OS rate of 62% (three relapses, six deaths).[41]

CPX-351 is available as frontline therapy for secondary AML. The approval was based on a phase 3 trial that randomized 309 patients with secondary AML to receive either CPX-351 or 7 + 3 and demonstrated that CPX-351 improved OS (hazard ratio, 0.69; $p = .005$), the CR rate (38% vs. 26%; $p = .035$), and the CR/CRi rate (48% vs. 33%; $p = .016$). Patients in CR after receiving CPX-351 proceeded to allogeneic HSCT more often (20% vs. 12%) and had a longer OS post-HSCT.[16] In ongoing studies, CPX-351 is being investigated in older patients with treated secondary AML in combination with GO, venetoclax, and other targeted therapies.

Glasdegib was approved by the FDA for the treatment of patients with AML/high-risk MDS who are ineligible for intensive chemotherapy based on a phase 2 trial comparing low-dose cytarabine with or without glasdegib, which demonstrated that the addition of glasdegib improved the CR rate and OS,[193] A recent phase 3 randomized trial (BRIGHT AML 1019; ClinicalTrials.gov identifier NCT03416179) of 7 + 3 or azacitidine with gladegib versus placebo in newly diagnosed AML did not demonstrate a survival benefit with glasdegib, thus questioning its role in AML therapy.[194,195]

Maintenance therapy

Maintenance therapy was recently confirmed as effective in AML in first CR based on a phase 3 pivotal trial (QUAZAR AML-001; ClinicalTrials.gov identifier NCT01757535) that randomized 472 older patients (median age, 68 years) who were in first remission for <4 months and could not complete curative therapy, to receive either oral azacitidine 300 mg daily for 14 days per course ($n = 238$) or placebo ($n = 234$). Oral azacitidine maintenance was associated with a longer median OS (24.7 vs. 14.8 months; $p = .0009$).[15] Whether such maintenance would benefit younger patients (who complete intensive chemotherapy consolidation or post-HSCT) or specific AML subtypes is unknown.

The HOVON97 study randomized 116 older patients in CR after two courses of intensive chemotherapy to either azacitidine 50 mg/m^2 subcutaneously daily for 5 days every month for 12 months ($n = 56$) or observation ($n = 60$). The 12-month disease-free survival rate was 64% with azacitidine versus 42% with observation ($p = .04$).[196]

At MD Anderson, patients who are not candidates for allogeneic HSCT in first CR are offered HMA-venetoclax for 2 years. Other targeted therapies (currently FLT3, IDH1/IDH2, and menin inhibitors) are also considered according to the AML molecular profile (Table 1). Patients who undergo allogeneic HSCT are also considered for similar maintenance/targeted therapies post-transplantation.[154]

HOW WELL DO THE EXPERIENCES FROM THE PUBLISHED LITERATURE TRANSLATE INTO THE REAL WORLD?

An analysis of US SEER data, which are representative of AML results in oncology community practices, demonstrated that outcomes were worse than those reported in single-institution and cooperative group trials.[116] Multiple factors may explain the disparate results: selection of better patients on trials; exclusion of older patients, those with treated secondary AML, and those with poor performance and organ dysfunctions; the regimens offered (investigational vs. standard); supportive care measures/capacities; and leukemia cumulative experience. The SEER data indicate significant improvements in survival since 2000, particularly in the easier-to-treat AMLs, for example, APL (5-year survival, ≥60% with the incorporation of ATRA and arsenic trioxide), CBF AML (5-year OS rate, ≥50% with the incorporation of GO and high-dose cytarabine), and younger AML. However, even in the 2000–2017 period, the 4-week mortality rate in younger patients (aged 40–59 years) with de novo AML was still 27%, and the 5-year OS rate was 40%. In patients aged 70 years and older, the 4-week mortality rate was 45%–50%, and the 5-year OS rate was <5%. Similar results were reported in studies comparing induction mortality and overall outcomes of patients treated in academic centers versus those treated in community oncology centers

and National Cancer Institute-designated cancer centers versus other cancer centers, confirming the value of leukemia expertise and access to state-of-the-art supportive care.[197,198]

Allogeneic and autologous stem cell transplantation

A meta-analysis of randomized trials showed a significant survival advantage of allogeneic HSCT implemented in first CR.[199] An MRC study reported that OS with chemotherapy versus allogeneic HSCT in first CR was similar if the benefit of later HSCT was considered.[200] With the availability of venetoclax and FLT3 and IDH inhibitors, the value of allogeneic HSCT in first CR requires constant re-evaluation regarding its benefits versus risks. The advent of newer, more effective therapies for older patients with AML induced higher rates of deep remission with less toxicity, resulting in more referrals of older patients to HSCT—leading to a steady increase in OS in this population.[201]

Allogeneic HSCT should be an integral part of the continuum approach that considers chemotherapy, targeted therapies, and post-HSCT maintenance. Potential post-HSCT strategies to reduce the risk of relapse include HMAs-venetoclax; FLT3, IDH, and menin inhibitors; repeated sequential donor lymphocyte infusions, etc.

In the United States, autologous HSCT has been largely abandoned in AML (except in APL and CBF AML in second CR). It is still used in Europe in first CR as an alternative to intensive chemotherapy consolidation. A recent Spanish analysis of 1300 patients with AML in first CR who either underwent autologous SCT ($n = 658$) or continued chemotherapy ($n = 652$) suggested a benefit for autologous SCT in younger patients (younger than 65 years: median OS, 153 vs. 71 months; $p = .02$).[202] Recognizing that, historically, infused autologous cells were contaminated with residual AML disease, future research could explore the value of autologous HSCT using MRD-negative infusions. At MD Anderson, autologous HSCT is occasionally performed in patients with APL or CBF AML in second CR and with molecular MRD-negative collected stem cells.[203]

Postfrontline therapy

Multiple options are available in refractory-relapsed AML. Their benefits depend on the AML type, prior therapies, prior HSCT, duration of first CR, and definition of refractoriness.

Later line therapy for APL often includes longer durations of therapy with ATRA and arsenic trioxide and adding GO and chemotherapy. It often considers whether the patient has been adequately treated with APL frontline therapy (they often were not) and the frontline therapy used. Optimal APL later line therapy is potentially highly curative.[203] The cure rates are also significant with second-line therapy in CBF AML (FLAG-GO and autologous or allogeneic HSCT) and in relapsed AML after a durable first remission duration (1–3 years).

The results of later-line therapy in other AML subsets depend on the context. For instance, patients are often declared to be refractory to frontline 7 + 3 therapy because bone marrow analysis on days 14–21 reveals AML blasts; these may resolve on later bone marrow analyses (without additional therapy) or respond well to later line therapy followed by HSCT. Patients who relapse after a first remission of ≥2 years have potential cure rates of 30%–50% with effective therapy. In contrast, in patients who have true AML resistance after frontline FLAG-IDA-venetoclax or CLIA-venetoclax and in those who relapse after 7 + 3 with a first short remission duration <6 to 12 months, the cure rate is <20%.[149,204,205]

Often forgotten is that the best AML rescue therapy is allogeneic HSCT in situations of low disease burden (bone marrow blasts, <20%). Allogeneic HSCT then offers a potential cure rate of 10%–20%. Transplantation experts are reluctant to offer HSCT to these patients unless they can achieve CR and/or negative MRD status, which is often impossible because transplanting such patients may lower the success rates of the HSCT center (resulting in potential exclusion from some insurance networks).[205]

The more common situation seen involves patients with a truly resistant AML despite effective frontline therapy whose disease shows unfavorable features (complex karyotype, *TP53* or other adverse mutations, and no targetable mutations). These patients should be offered investigational therapies or else palliative care given the dire prognosis.

All patients who relapse should have mutational re-analysis to assess for persistent or emerging mutations that had not been targeted with prior therapies (mutations in *NPM1*, *FLT3*, and *IDH1/IDH2*; fusions with *KMT2A* and *NUP98*). Such patients are then treated with combinations that include the targeted therapy.

In younger patients who progress on 7 + 3 regimens, the first CR duration may determine therapy. If the CR duration is longer than 6–12 months, FLAG-IDA-venetoclax or CLIA-venetoclax induce high CR rates, bridge frequently to allogeneic HSCT, and result in a potential cure.[149] If the CR duration is less than 6–12 months, salvage therapies include HMA-venetoclax or triple-nucleoside–based combinations that may include adding an investigational drug. Patients in second or later relapse are offered phase 1 and 2 clinical trials.

All patients who achieve later remission or minimal disease (bone marrow blasts <20%) should be considered for immediate allogeneic HSCT (despite some reluctance of HSCT experts) and informed about the realistic low cure rates and risks of HSCT.

Other investigational therapies are under way in refractory-relapsed AML. AML surface antigens (CD33, CD123, CD70, CLL1/CLEC12a) may be targetable with unconjugated antibodies (ineffective to date), antibodies conjugated to toxins, or bispecific T-cell or NK-cell engagers. Antibodies conjugated to toxins have demonstrated efficacy: these include GO and tagraxofusp and pivekimab sunirine (target CD123) in blastic plasmacytoid dendritic cell neoplasm. Pivekimab and tagraxofusp are being combined with chemotherapy in AML.[206] Delivery of radioisotopes through antibodies that target AML surface antigens (CD45-targeted antibodies, e.g., Iomab-B [a radiotherapeutic comprised of anti-CD45 monoclonal antibody with an Iodine-131 payload] or ^{90}Y-BC8-DOTA [Yttrium-90–labeled anti-CD45

antibody]) have shown promise. A phase 3 trial evaluating Iomab-B versus physician's choice salvage did not meet the study primary endpoint.[207,208] Studies of bispecific T-cell–engaging antibodies designed to target AML cells (CD33, CD123, CD70) are ongoing. Modest efficacy (response rates of 20%–30%) and side effects (cytokine release syndrome) were reported. The experience with autologous and allogeneic chimeric antigen receptor T-cell therapy in AML is not encouraging to date.

Patient advocate's perspective and voice (A.L.)

Targeted agents have shifted the treatment paradigm in AML from chemotherapy-centered regimens to precision treatments. These novel treatments are tailored to the genetic leukemic profile (cytogenetic–molecular) and the patient clinical profile (age, performance, organ functions). Given the rapid research advances and the aggressive nature of the disease, the benefits and positive outcomes of the newly approved medications/strategies should rapidly translate to the real-world, including cancer community practices and medical centers, to improve quality of life and confer long-term survival/higher cure rates to many more patients than are currently treated in clinical trials. A greater research translational speed would positively affect the lives of many more patients with AML, rather than the few (5%–10%) on trials.

The new treatments come with their own side effects and toxicities (e.g., differentiation syndrome with FLT3, IDH, and menin inhibitors; organ dysfunctions; drug–drug interactions; among others). Rapid recognition and optimized management of these toxicities in real-world practice are needed.

Several standard tests (cytogenetic analysis; molecular testing; on-therapy MRD monitoring by the newer, more precise methods) are critical in informing optimal targeted treatment decisions and are not typically available in community practice in a timely fashion (3–5 days). Consequently, conventional induction chemotherapy may be initiated to avoid life-threatening complications before pivotal test results are available. Improving such infrastructures at cancer health care centers is critical to overcome operational barriers in choosing the most beneficial treatments.

The high cost of AML treatment imposes financial barriers to many patients who may remain untreated or undertreated because AML medications are unaffordable.[209–211] Cost-effective strategies must be devised to make these life-saving medications accessible to the entire population, including vulnerable patients (elderly, disadvantaged, and of low socioeconomic status) in the United States and other countries rather than being selectively accessible to the fortunate few.

Allogeneic HSCT is now considered in larger proportions of patients with higher risk AML in first remission because the procedure has become significantly safer than it was in the early 1980s. Today, even older, fit patients (up to age 75 years) can be potential candidates for allogeneic HSCT. A broader range of patients can receive stem cells from haplotype and unrelated donors and have access to better preparative regimens, supportive care, reduced-intensity conditioning regimens, and graft-versus-host prophylaxis and therapy. Still, HSCT is associated with high rates of disease recurrence and morbidity/mortality that may outweigh benefits. Given the range of breakthrough therapies developed in the last decade and new technologies to accurately determine MRD, the management of AML may gradually steer away from HSCT in patients at lower risk of relapse and gear toward the increasingly effective targeted treatment combinations.

Today's later line strategies offer minimal cure hopes, and frontline therapy has serious innovation gaps. All research efforts should rapidly coalesce to optimize frontline therapy; incorporate all novel targeted agents into frontline regimens as soon as they become available; assess MRD with more precise technologies; and optimize knowledge about the need, timing, and better HSCT procedures to decide on the risks and benefits of HSCT versus non-HSCT AML therapy.

A final point from a patient's perspective is psychosocial support. Many patients with AML travel long distances or even relocate for 6–12 months to a nearby center of leukemia expertise. Estrangement from their extended family and local network support may affect their view and decisions. Strengthening psychosocial support (psychiatric consultation, support from social workers and case managers to clarify insurance issues, medications, housing, etc.) can help patients retain their optimism and improve compliance on therapy.

SUMMARY

Several targeted therapies that were investigational just 5–10 years ago are part of today's routine standard of care in AML frontline and salvage therapy. These include venetoclax, FLT3 inhibitors (gilteritib, quizartinib, midostaurin), IDH inhibitors (ivosidenib, enasidenib, olutasidenib), GO, and oral HMAs. With the existing novel therapeutic modalities, we believe that there are better combinations of intensive chemotherapy with targeted therapies that offer potentially higher cure rates in younger/fit patients with AML than 7 + 3, and there are better lower intensity combinations with targeted therapies that improve outcomes in older/unfit patients with AML. Promising targeted therapies are now under investigation, including menin inhibitors, CD123 antibodies, NK cellular therapies, MDM2 degraders, RAS inhibitors, and others. As these novel investigations mature into potential new standards of care, they will again reshuffle the AML strategies in induction, consolidation, maintenance, and peri-HSCT/post-HSCT. Accelerating the pace of research may require innovative statistical designs that use single-arm trials with Bayesian inferences, comparisons with contemporary historical controls (propensity score matching, synthetic control groups, real-world data), and surrogate end points for long-term outcomes (achievement of MRD-negative status).[89]

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