Review Article

Acute Myeloid Leukemia: Historical Perspective and Progress in Research and Therapy Over 5 Decades

Hagop M. Kantarjian,[1] Nicholas J. Short,[1] Amir T. Fathi,[2] Guido Marcucci,[3] Farhad Ravandi,[1] Martin Tallman,[4] Eunice S. Wang,[5] Andrew H. Wei[6]

Abstract

With the Food and Drug Administration approval of 9 agents for different acute myeloid leukemia (AML) indications, the prognosis and management of AML is evolving rapidly. Herein, we review the important milestones in the history of AML research and therapy, discuss insights regarding prognostic assessment and prediction of treatment outcome, detail practical supportive care measures, and summarize the current treatment landscape and areas of evolving research.

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Introduction

Understanding the pathophysiology of acute myeloid leukemia (AML) has translated into rapid clinical applications that are transforming its treatment and outcome.[1-3] Recent translational successes include the novel targeted therapies directed at BCL2 (venetoclax), FMS-like tyrosine kinase 3 (FLT3), and isocitrate dehydrogenase (IDH). Such developments, and the highly effective novel combinations arising from them, raise the question of whether traditional intensive chemotherapy approaches, like the "3 + 7 regimen" (3 days of daunorubicin plus 7 days of cytarabine), should remain as the optimal standard of care in the current era. In the early cooperative group trials of 3 + 7 in highly selected younger patients (usually 55 years or younger), the 5-year survival rates were 40% to 50%.[4] Later trials included patients up to 60 to 65 years of age and reported lower long-term survival rates of 30% to 40%.[5] Patients older than 60 to 65 years receiving 3 + 7 experienced a higher risk of early mortality (4- to 8-week mortality rates greater than 10%-30%) and poor long-term survival rates of less than 10% to 15%.[6]

[1]Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA
[2]Leukemia Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[3]Gehr Family Center for Leukemia Research City of Hope, Duarte, CA, USA
[4]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA
[5]Leukemia Service, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA
[6]Department of Clinical Hematology, The Alfred Hospital and Monash University, Melbourne, Australia

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Address for correspondence: Hagop M. Kantarjian, MD, MD Anderson Cancer Center, 1400 Holcombe Blvd, Unit 428, Houston, TX, 77030 USA.
E-mail contact: hkantarjian@mdanderson.org

In community practice settings, patients treated with 3 + 7 are more likely to be older and less selected, with multiple clinically impactful comorbidities (cardiac, pulmonary, hepatic, renal, diabetes, or hypertension), or with adverse-risk AML more frequently evolved as a result of prior genotoxic therapy or AML evolving from treated myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or myeloproliferative neoplasm (MPN). All these factors contribute to worse outcomes with 3 + 7 or comparably intensive regimens, manifesting with higher rates of early mortality and lower rates of cure.[7-15] In the early publications from Swedish investigators, favorable results were reported with intensive chemotherapy in older patients,[10,11] but the subsequent updates indicated that only 60% of patients received intensive chemotherapy and that the early mortality rates were 6% to 9% in younger patients and 16% to 34% in older patients.[12] The 5-year survival rates were 10% to 20% in patients 50 to 75 years old, and the 2-year survival rate was 5% in patients older than 75 years.[12] The Mayo Clinic detailed its experience in 1123 adults with AML, among whom 766 (68%) were treated with intensive chemotherapy, leading to a complete response (CR) rate of 44%. An additional 33% of patients achieved CR with incomplete recovery of either neutrophils above 1×10^9/L or platelets above 100×10^9/L (CRi), resulting in an overall response rate of 77%. The 5-year survival rate was only 30% with intensive chemotherapy and less than 5% with lower intensity therapy or supportive care.[13] Similarly, poor results have been reported by others in younger cohorts of patients receiving intensive chemotherapy: 5-year survival rates of 20% in intermediate risk and only 10% in adverse risk.[15] Such findings have for some time highlighted the need to improve on the traditional cytarabine/anthracyclines regimens in younger or functionally fit

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patients (younger/fit) and to develop novel lower-intensity targeted therapy combinations that would be efficacious in older or less fit patients (older/unfit). Figure 1 shows the outcomes in AML in younger and older patients from 1970 to 2020 in a single institution referral center.

AML comprises several disease subsets that require different therapeutic approaches and carry very different prognoses. These include acute promyelocytic leukemia (APL) (now near universally curable with therapies incorporating all-*trans* retinoic acid (ATRA) and arsenic trioxide)[16-19] and core binding factor (CBF) AML (remission rates approaching 90% with traditional intensive chemotherapy plus gemtuzumab ozogamicin [GO] and high rates of survival).[20-24] The remaining non-APL, non-CBF AMLs can be prognostically and functionally divided according to their cytogenetic-molecular profiles, as well as according to fitness for intensive chemotherapy, into AML in younger/fit patients and older/unfit patients. The latter are underrepresented in historical studies of intensive chemotherapy but comprise most AML cases managed in community practice (60%-70%). Finally, the prognosis of de novo AML is superior to AML that has evolved from MDS, CMML, or MPN, particularly after prior exposure to hypomethylating agents (HMAs) and to therapy-related AML after exposure to chemotherapy (eg, alkylating agents or topoisomerase-II inhibitors) or irradiation as prior treatment of other malignancies.[7,13]

Herein we review important achievements in the history of AML research and therapy, discuss insights regarding prognostic assessment and prediction of treatment outcome, detail practical supportive care measures, and summarize the current treatment landscape and areas of evolving research.

Acceptance and Evolution of Newly Introduced Therapies in AML

The journey to the regulatory approval of various drugs and regimens for AML therapy in the United States, Europe, and elsewhere has historically followed at times convoluted paths.

Many drugs approved by the Food and Drug Administration (FDA) for a particular indication have subsequently been used for a different purpose. This is logical because much of the research and progress in cancer and medicine often occurs after the regulatory drug approval. This has been true for the first 2 modalities approved for the treatment of AML, cytosine arabinoside (cytarabine or ara-C) and daunorubicin. Five decades after their introduction into AML therapy, researchers continue to explore different dose schedules of cytarabine and daunorubicin during induction and consolidation therapy.

The research post–FDA approval is particulary vigorous for agents that have secure longer patent expiry terms, as this encourages greater pharmaceutical company investment to maximize commercial returns. For example, the FDA approved gilteritinib (FLT3 inhibitor) as monotherapy for refractory-relapsed *FLT3*-mutated AML and enasidenib (IDH2 inhibitor) as monotherapy for refractory-relapsed *IDH2*-mutated AML. However, it is likely that in a few years these targeted therapies will be used in combination with standard chemotherapy or in targeted therapy cocktails, both in salvage and frontline therapy, based on post–FDA approval research.

Several agents were never approved for AML therapy but are now the most commonly used drugs in some AML subsets and are even accepted by the FDA as a control arm in investigational phase 3 trials. For example, neither of the 2 HMAs, decitabine and azacitidine, was approved for the treatment of older/unfit AML (European Medicines Agency [EMA] approval of decitabine in 2012 and of azacitidine [AML with ≥ 30% blasts] in 2015). Yet, both HMAs are now the most commonly used drugs in older/unfit AML, and the combination of HMAs plus venetoclax was recently FDA approved (October 2020) for the treatment of newly diagnosed older/unfit AML. The combination of ATRA and arsenic trioxide for APL was approved by the EMA in 2016 and by the FDA only in 2018. Despite the lack of regulatory approvals, adenosine nucleoside analogues (fludarabine, cladribine, clofarabine) and etoposide (topoisomerase 2 inhibitor) are commonly used in AML combination regimens around the world. Some drugs are limited to particular geographies: amsacrine in Europe (not produced anymore); homoharringtonine in China.[25-30]

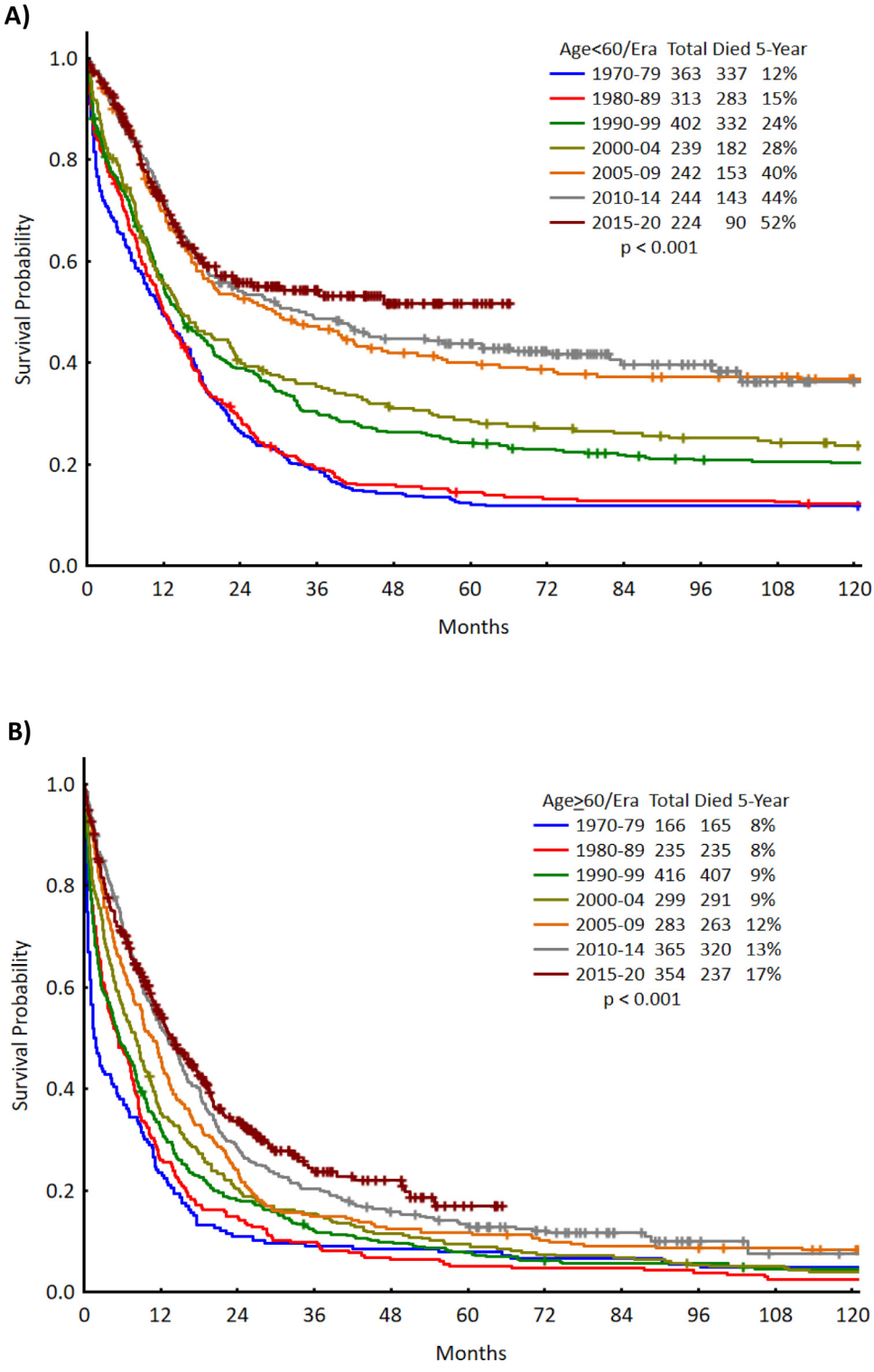
Finally, multiple agents have stumbled in their regulatory approval journey and, although potentially of value in AML therapy, may not be explored further. This is particularly true for "me-too" chemotherapy agents, in which interest waned in favor of rationally designed targeted therapies. Examples include topotecan, cloretazine, clofarabine, and vosaroxin.[31–34] But this also applies to targeted therapies such as sorafenib (first-generation FLT3 inhibitor), vadastuximab talirine (SGN-CD33A; CD33-conjugated monoclonal antibody), and others.

We are witnessing an ongoing "slow-motion" revolution in AML reseach and therapy, with the approval of 9 agents for different AML indications since 2017: GO; the 2 FLT3 inhibitors midostaurin and gilteritinib; the IDH1 inhibitor ivosidenib and IDH2 inhibitor enasidenib; the BCL2 inhibitor venetoclax; the oral HMA azacitidine; the liposomal formulation CPX351; and the hedgehog inhibitor glasdegib. Oral decitabine/cedazuridine was FDA approved for MDS and CMML and will likely be used as an alternative oral HMA in AML. An important challenge is how to promptly incorporate these drugs/modalities into effective and safe frontline and salvage combinations in AML.

Determinants of Outcome in AML

The outcomes in AML are very heterogeneous. With current therapies, some AML subsets are highly curable (eg, APL and CBF AML; cure rates, ≥ 75%), whereas others are highly adverse, with estimated 5-year survival rates of 10% or less: *TP53*-mutated AML; MECOM (MDS1 and EVI1 complex locus)–rearranged AML [inversion of chromosome 3 or t(3;3)(q21q26)]; AML with complex karyotype; secondary AML after MDS or CMML treated with HMAs or after MPN; and therapy-related AML. The determinants of AML outcome include variables related to the patient, the leukemia, and the response to therapy (achievement of CR, CRi, or other responses; measurable residual disease [MRD] in remission). The therapeutic environment and choice of therapy (intensive vs. low intensity) are also important determinants of AML outcome.

Figure 1 Survival of Patients < 60 Years of Age (A) and ≥ 60 Years of Age (B) With De Novo AML Treated at MD Anderson Over 5 Decades
Abbreviations: AML = acute myeloid leukemia.



Patient-Associated Factors

Age is a consistent determinant of AML prognosis because older age is tightly linked to poor performance, increased comorbidities, and poorer tolerance of and responsiveness to intensive chemotherapy. Older age is also associated with a higher frequency of AML-associated adverse factors such as non–de novo AML, complex karyotype, and unfavorable mutations (like *TP53*).

Multivariate analyses account for some of these interactions. In discussing the choice of "intensive" versus "low-intensity" chemotherapy, some AML experts discourage such treatment labels as too dichotomous, suggesting that there is a fine line between the 2 approaches. They and the FDA advocate for a therapeutic choice based on the patient's "biologic age" and comorbidities/organ dysfunctions, using tools such as the "Ferrara criteria" or the "Charlson morbidity index."[35,36] However, older age is always selected as independently adverse in prognostic models of AML, even after meticulous accounting for all other adverse factors.[37-41] Moreover, despite achieving good CR rates of 40% to 50% with intensive chemotherapy in older AML, outcome is invariably poor, and the early mortality rates often nullify any therapeutic benefit.[6,10-14,37,38] In the Surveillance, Epidemiology, and End Results (SEER) data from the United States, the early mortality in older AML is ≥ 25% in patients 60 years and older and ≥ 40% in patients 70 to 75 years or older.[7] The emerging data with low-intensity chemotherapy in combination with venetoclax show high CR-CRi rates (almost equivalent to intensive chemotherapy) and low early mortality rates. Thus, it is perhaps time to consider low-intensity therapy in all older AML (aged 60-65 years or older) regardless of the "fitness" factors, if the aim of AML therapy is to achieve a marrow CR safely, to bridge to a curative option of allogeneic stem cell transplant (SCT) in first CR. It is also perhaps time to consider low-intensity therapy combinations even in younger patients, particularly if they have comorbidities or when intensive chemotherapy is known to have poor results. Regardless, the SEER data show that only about 40% of older patients with AML receive any form of induction chemotherapy, highlighting the urgent need for a change in our AML standard practice.[42-44]

Leukemia-Associated Factors: Cytogenetic and Molecular Abnormalities

The National Comprehensive Cancer Network (NCCN) cytogenetic-molecular classification categorizes AML into "favorable," "intermediate," and "poor/adverse" risk groups.[45] The NCCN classification has most relevance for younger and de novo patients with AML but has less discriminatory value for older AML, AML evolving from MDS/MPN, or therapy-related AML. Similar observations apply to the European LeukemiaNet classification.[46] The current NCCN classification is not dynamic and does not incorporate the modifying effect of novel therapies on AML outcome (eg, with FLT3 inhibitors plus intensive chemotherapy for *FLT3*-mutant AML, and venetoclax-azacitidine for *IDH* mutant disease). It would be more relevant to categorize AML subsets based on estimated 3- to 5-year survival rates: favorable if rates are > 60%, intermediate if rates are 30%-60%, and unfavorable if rates are < 20% to 30%. For example, if we used absolute survival rates to guide risk stratification, nearly all older/unfit AMLs would be categorized as unfavorable, as would secondary and therapy-related AML. Such a dynamic risk stratification based on absolute (rather than relative) survival expectations would better reflect long-term clinical outcomes and comparisons across clinical trials.[47]

Based on current practice, we consider a simpler classification of the AML karyoptypes as follows: (1) favorable, APL and CBF karyotypes; (2) intermediate, diploid karotype; (3) unfavorable, 3 or more chromosomal abnormalities, monosomy 5/5q−, monosomy 7/7q−, translocation t(6;9), translocation t(9;22), all translocations involving 11q23, and translocations involving chromosome 3q26.2 (*EVI1*, location of the MECOM gene);[47] and (4) all others. Some studies consider certain cytogenetic abnormalities [eg, single trisomy 8, or single translocation t(9;11)] as intermediate risk.[45,46] The intermediate risk classification of a single translocation t(9;11)(p22;q23)/*KMT2A-MLLT3* has been debated.[48-51] Although the NCCN classification puts it under intermediate risk, this may be true for only the small subset of younger patients with de novo AML.[15]

Molecular studies have identified recurrent somatic mutations in more than 90% of patients with AML, the most frequent being *FLT3, NPM1, DNMT3A, NRAS, TET2, IDH2, CEBPA, RUNX1, PTPN11, IDH1, TP53*, and *SRSF2*.[52,53]

Mutations may be prognostic and targetable. Their prognostic-predictive effect may depend on several factors: (1) the particular mutation; (2) the mutation burden or variant allelic frequency (ratio of mutated gene/total); (3) the cytogenetic risk group it associates with (favorable, normal, unfavorable, other); (4) the presence of other mutations; (5) the patient's age; (6) whether the AML is de novo or evolving from MDS/MPN or therapy related; and (7) the treatment given.

In normal karyotype AML, a biallelic *CEBPA* mutation (2% or less of AML) or a mutation of nucleophosmin-1 (*NPM1;* 50% of AML with normal karyotype) are associated with better prognoses, provided no other adverse concurrent mutations are present.[45,46] A *FLT3* internal tandem duplication *(FLT3*-ITD) was traditionally associated with a poor prognosis; this is now changing with the use of newer and better FLT3 inhibitors with chemotherapy and as post-SCT maintenance. Prognosis was adverse particularly with a high allelic ratio (AR) (ratio of *FLT3*-ITD/FLT3 wild type using a semiquantitative DNA fragment analysis)[46] and in the absence of *NPM1* mutation. In normal karyotype AML, the prognosis with concurrent *NPM1* and *FLT3*-ITD mutations depends on the *FLT3*-ITD AR.[54-56] Other adverse mutations include *RUNX1, ASXL1*, and *TP53*; when present, they categorize the AML as adverse risk.[57-62] In general, a greater number of adverse mutations in a patient with AML indicates worse prognosis.

The prognostic effect of mutations is more relevant in diploid/intermediate karyotype AML.[54] Their impact in favorable and unfavorable karyotypes is lessened and context dependent. Among the favorable karyotype AML, *KIT* mutations have been reported to be adverse in some studies using 3 + 7[63,64] but not in trials using fludarabine-high dose cytarabine and GO (FLAG-GO; FLAG-IDA +/− GO).[20,21] In unfavorable karyotype AML, a *TP53* mutation worsens prognosis further in an already poor prognosis disease.[57,58]

The significance of mutations had been defined primarily in younger patients with AML. The prognostic value of mutations is generally worse among older patients. The same is true for therapy-related AML and AML evolving from MDS or MPN.

Because many of the molecular abnormalities are potentially targetable, the predictive value may change with the incorporation of effective targeted therapies into the standard chemotherapy regimens, simultaneously or sequentially. For example, the incorporation of FLT3 inhibitors into AML chemotherapy and as post-SCT maintenance is already changing the previously poor outcome of *FLT3*-mutated AML into a reasonably favorable one.[65-69] The *IDH1/2*-mutated AML (20% of AML) can be effectively treated with combinations of chemotherapy and IDH inhibitors. The *IDH* mutations also generate BCL-2 dependence for survival, making *IDH*-mutated AML sensitive to venetoclax-based therapy and suggesting the potential for improved outcome with a triple-agent regimen (HMAs + venetoclax + IDH inhibitor, simultaneously or sequentially).[70] The *TP53*-mutated AML responds poorly to intensive chemotherapy but may benefit from lower-intensity chemotherapy with HMAs and venetoclax and/or the addition of novel *TP53*-directed strategies like magrolimab.[71-74] The cytogenetic-molecular subset of "mixed-lineage leukemia" (translocations involving 11q23; *MLL1; KMT2A* rearrangement) may benefit from novel menin inhibitors (SNDX-5613, KO-539, others).[75-77] The *KIT*-mutated CBF AML, associated with unfavorable outcome in 3 + 7 trials, may benefit from the addition of GO or potent c-KIT inhibitors (avapritinib, dasatinib).[78,79] Predicting the outcome in patients with AML, especially the impact of gene-gene interactions, is made easier with artificial intelligence modeling ("knowledge bank") based on annotated large cohorts of patients.[80,81]

Treatment Response-Associated Factors: Achievement of CR Versus Less-Than-CR Response; Measurable Residual Disease in Remission

For decades, the achievement of CR with full hematologic recovery after intensive cytotoxic chemotherapy has been considered the only morphologic response associated with a significant survival benefit.[82] This is now challenged by multiple studies with intensive chemotherapy as well as with low-intensity therapy and targeted agents (FLT3 inhibitors, IDH inhibitors, venetoclax, GO).[13,83] More recently the term "CRh" has been used in a number of regulatory trials. The CRh requires the criteria for CR but with an absolute neutrophil count 0.5 to 1 $\times$ 10^9/L *and* platelets 50 to 100 $\times$ 10^9/L. Recent studies suggest prognosis for CRh is intermediate between CR and CRi/CRp. It is likely that patients with marrow CR and MRD negative status (regardless of whether therapy is intensive or low intensity) will have an outcome close to a traditional morphologic CR.

Measuring residual disease in AML in morphologic CR is now part of the standard of care in AML.[84-88] The detection of MRD at the time of morphologic CR or CRi is associated with a higher relapse rate and with worse survival. The MRD has been commonly investigated using 2 methodologies: multicolor flow-cytometric measurements , and molecular quantification of residual disease. Polymerase chain reaction (PCR) is used to monitor quantitatively unique AML-specific translocations and mutations (eg, in APL, CBF AML, and *NPM1*-mutated AML) and is expanding to other molecular subsets (*IDH1/2* and *FLT3* mutations). In APL and CBF AML, detection of MRD by quantitative PCR predicts for relapse.[89–91] Among patients with non-CBF/non-APL AML, monitoring MRD by next-generation sequencing of mutations is informative, for example in patients with *NPM1* mutations.[92,93] Combining multicolor flow cytometry and next-generation sequencing to detect molecular mutations in remission may further improve the capability of MRD studies to predict for relapse.[84] The persistence of some mutations like *DNMT3A, TET2*, and *ASXL1* (DTA mutations) does not predict for relapse and may be rather a feature of clonal hematopoiesis in some older patients.[84]

The MRD status of patients with AML in CR may lead to consideration of therapeutic interventions.[89,94] Interventions that may eradicate MRD in CR now include allogeneic SCT, more intensified chemotherapy regimens, HMAs plus venetoclax, targeted therapy combinations when indicated for particular molecular abnormalities (FLT3 or IDH inhibitors), antibody therapies (eg, CD123 or CD33 antibody drug conjugates or bispecific T-cell engagers), or immune therapies (eg, checkpoint inhibitors).

The Effect of the Environment Under Which the AML Is Treated, and the Impact of Supportive Care Measures

Historically, in the United States it was assumed that the outcomes of AML are equivalent across National Cancer Institute (NCI)–designated cancer centers, other academic centers, and in community practice. This is not likely the case. In a National Cancer Database of 60,738 patients with AML, the 1-month mortality was 16% in academic centers and 29% in nonacademic centers ($P < .001$). The estimated 5-year survival rates were 25% versus 15% ($P < .001$). The center effect was identified by multivariate analysis to be independently prognostic, with a hazard risk of 1.52 in nonacademic centers ($P < .0001$).[8] In another study from California, among 7007 patients with AML (1999-2014), the early 4-week mortality was 12% in NCI-designated cancer centers versus 24% in non–NCI-designated cancer centers. At MD Anderson, the early 4-week mortality is 5% or less with intensive chemotherapy in younger/fit AML and 2% to 3% in older/unfit AML (discussed and referenced later).

The routine use of antibiotics (levofloxacin, cefpodoxime, others) and antifungal prophylaxis (posaconazole, voriconazole) in all newly diagnosed acute leukemias has reduced the incidences of infections and associated morbidities but importantly also early mortality rates (5%-10%).[95-98]

AML is a rare cancer requiring cumulative expertise, constant vigilance, and prompt, readily available intensive supportive care (transfusion products, early recognition of sepsis, immediate implementation of needed care in an emergency center and in intensive care units). Even perceived "insignificant delays" in implementing intravenous antibiotics in sepsis can result in increased mortality, particularly among older patients (most patients with AML) who have poorer organ reserve capacities during sepsis and may deteriorate rapidly with multiorgan failure (pulmonary, cardiac, hepatic, renal) and have high complication and mortality rates.

Translating the Biologic Information Into Therapy and Clinical Research

The AML subsets are very heterogeneous and consequently benefit from selective therapies. Next, we discuss the treatment of different AML subsets using commercially available FDA approved agents, as well as approaches with investigational agents.

APL

APL (5%-10% of AML) is characterized by the cytogenetic translocation between chromosomes 15 and 17 [t(15;17)(q22;q21)], which results in the *PML-RAR alpha* fusion oncogene and its encoded oncoprotein. The latter acts as a dominant negative inhibitor of wild-type RAR *alpha*, causing a maturation block and the clinical-pathologic picture of APL.

In the 1970s, single-agent anthracyclines (daunorubicin) were first shown to produce cure rates of 30% to 40% in APL.[99] Single-agent cytarabine does not cure APL.[100] The addition of cytarabine to anthracyclines does not increase the APL cure rate substantially, nor does the addition of maintenance therapy with 6-mercaptopurine-methotrexate combinations.[101,102] A "differentiation syndrome" was also reported for the first time with chemotherapy in APL.[103] The early mortality from the complex coagulopathy, which includes disseminated intravascular coagulation and bleeding, was significant (20%-30%).

In the late 1980s and early 1990s, ATRA and arsenic trioxide were discovered to have major anti-APL activities. The curative effect of both agents is through induction of degradation of the PML-RAR *alpha* oncoprotein, thus reversing the maturation block and promoting differentiation of APL cells. Studies from China, India, and Iran of ATRA or arsenic trioxide as frontline APL monotherapy showed high CR rates and, with arsenic trioxide, 5-year disease-free survival (DFS) rates exceeding 50% to 60%.[104-106] Gemtuzumab ozogamicin was also highly active.[107] Both ATRA and arsenic trioxide, when added to chemotherapy during induction and/or consolidation in comparative trials, improved outcome in APL.[108-111] The combination of idarubicin and ATRA (AIDA regimen) became the standard of care in APL for a while.[112]

In the early 2000s, a nonchemotherapy regimen of ATRA plus arsenic trioxide was explored cautiously in APL salvage (2001), then as frontline APL therapy (2002). GO was added for high-risk APL. Following the demonstration of the high efficacy of this approach,[16,17,113] randomized studies confirmed the superiority of ATRA plus arsenic trioxide over AIDA in low- and intermediate-risk APL.[18,19,114,115] With ATRA plus arsenic trioxide, the CR rate is ≥ 95%, and the cure rate is ≥ 90%. Induction mortality from coagulopathy is low (about 5%), and resistant disease is rare, except in molecular variant APL (translocations between chromosome 11 and 17 [*PLZF-RAR alpha*] or between chromosome 5 and 17). Patients with high-risk APL benefit from the addition of GO (or anthracylines). The details of the regimen have been previously published.[16-19] The Medical Research Council (MRC) comparative trial investigated a lower and less frequent dose schedule of arsenic trioxide.[114] Oral formulations of arsenic trioxide would make the treatment of APL more convenient, particularly in maintenance (80 doses).[116,117]

Figure 2 shows single-institution results in APL among younger and older patients and significant improvement in outcome in the era of ATRA and arsenic trioxide. Some important (not well-known) considerations in APL management are detailed in the published literature.[118-120]

CBF AML

The CBF AML includes the cytogenetic-molecular subsets of inversion 16 [inv16(p13;q22)] or t(16;16)(p13;q22)], and t(8;21)(q22;q22). Historically, CBF AML was treated with cytarabine plus anthracycline induction chemotherapy followed by 1 to 4 high-dose cytarabine consolidations. The cure rate was 30% to 40% with 1 consolidation versus ≥ 50% with 3 to 4 consolidations.[121,122]Optimizing the combinations of established chemotherapy drugs (fludarabine plus high-dose cytarabine for 5-6 courses of induction consolidation; addition of GO to chemotherapy; monitoring and treatment of persistent MRD in CR) improved the cure rate in CBF AML to ≥ 75%.[20-24]A meta-analysis of 5 randomized trials showed that the addition of GO to chemotherapy improved the estimated 5-year survival from 50% to 75% in CBF AML.[24] GO is now a standard component of CBF AML therapy.

With fludarabine, high-dose cytarabine, and GO (FLAG-GO) during induction and consolidations (total, up to 6 courses), and modification of therapy (eg, allogeneic SCT, azacitidineazacitidine/venetoclax/GO) for persistent MRD in CR, the estimated 5-year survival rates were ≥ 75% in both inversion 16 and t(8;21) AML (Figure 3).[20,21] The results were better in younger patients. Patients who cannot tolerate FLAG-GO/IDA or who have persistent molecular disease may be offered HMA therapy (decitabine, azacitidine) in combination with venetoclax and GO, with the treatment duration adjusted according to the MRD results or for ≥ 12 months.

Frequent mutations noted in CBF AML are *FLT3* (15%-20%), *KIT* (25%-30%), *N/KRAS* (30%-50%) and others. Although some studies have reported worse outcomes with *KIT* or multiple mutations,[63,64] others have not, such as the experience with FLAG-GO/idarubicin. The improved efficacy of the regimen may have nullified the adverse effects of these mutations. Targeted therapies may also be considered (avapritinib or dasatinib for *KIT* mutations; FLT3 inhibitors for *FLT3* mutations).[78,79,123]

Choice of Intensive Chemotherapy in Younger/Fit AML Versus Low-Intensity Therapy in Older/Unfit AML

The median age in AML is 68 to 70 years.[7] Still, most of the clinical research with 3 + 7 based regimens has been conducted in younger patients and proposed for older patients if considered fit enough for intensive chemotherapy. This is despite the poor outcome with 3 + 7 in older AML.[7]

In a study of 813 selected patients 60 years and older (median age, 67 years) treated with 3 + 7 (randomization to higher vs. lower dose of daunorubicin), the early mortality rate was 11% to 12%, the median survival was 7 to 8 months, and the estimated 3-year survival rate was 20%/[6]This and other experiences from carefully controlled studies in selected patients with good performance, normal organ functions, and few comorbidities translated poorly into community practice. Examination of 29,000 patients with

Figure 2 Survival in Patients < 60 Years of Age (A) and ≥ 60 Years of Age (B) With Newly Diagnosed APL Treated at MD Anderson Over 5 Decades
Abbreviations: APL = acute promyelocytic leukemia.

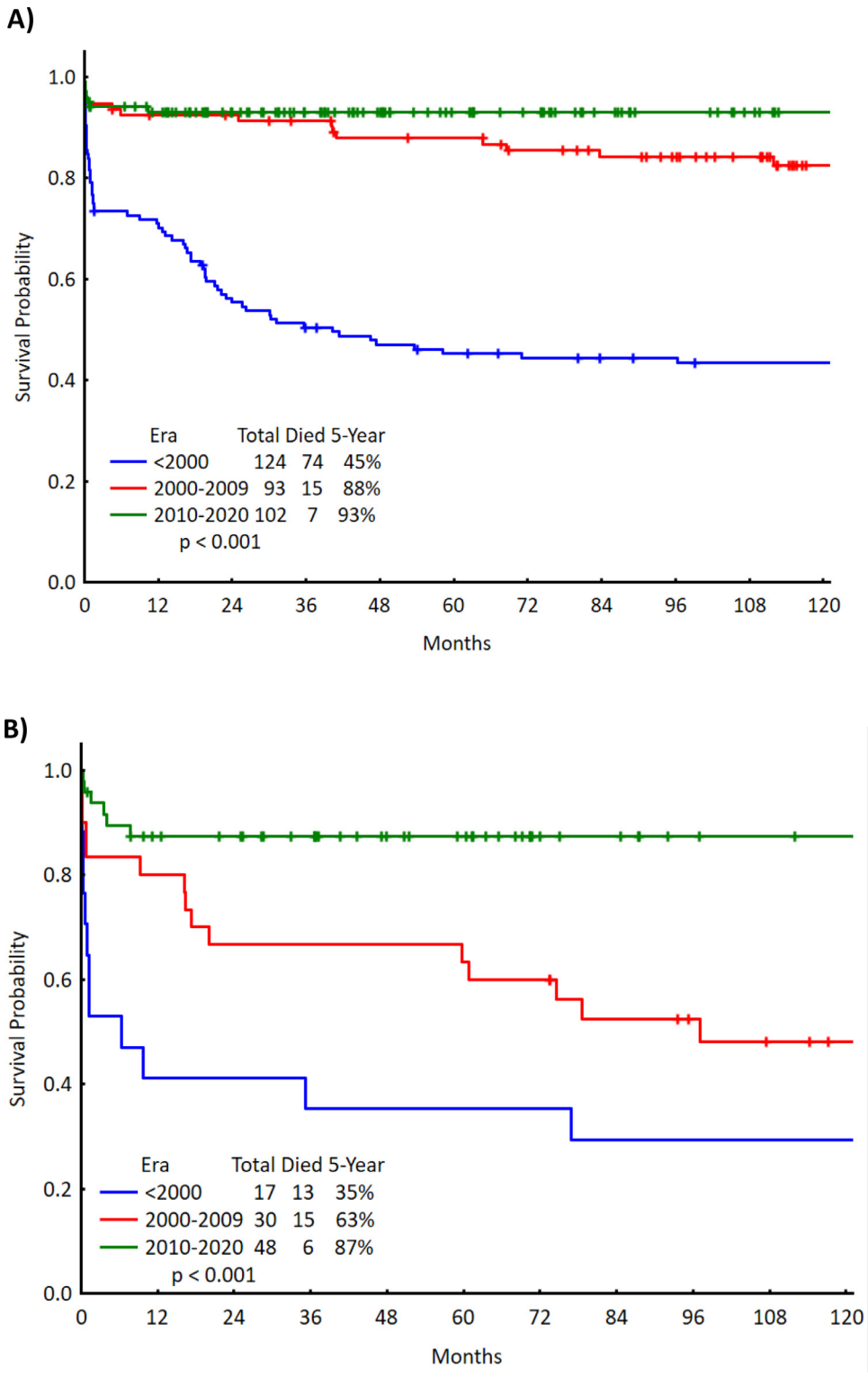
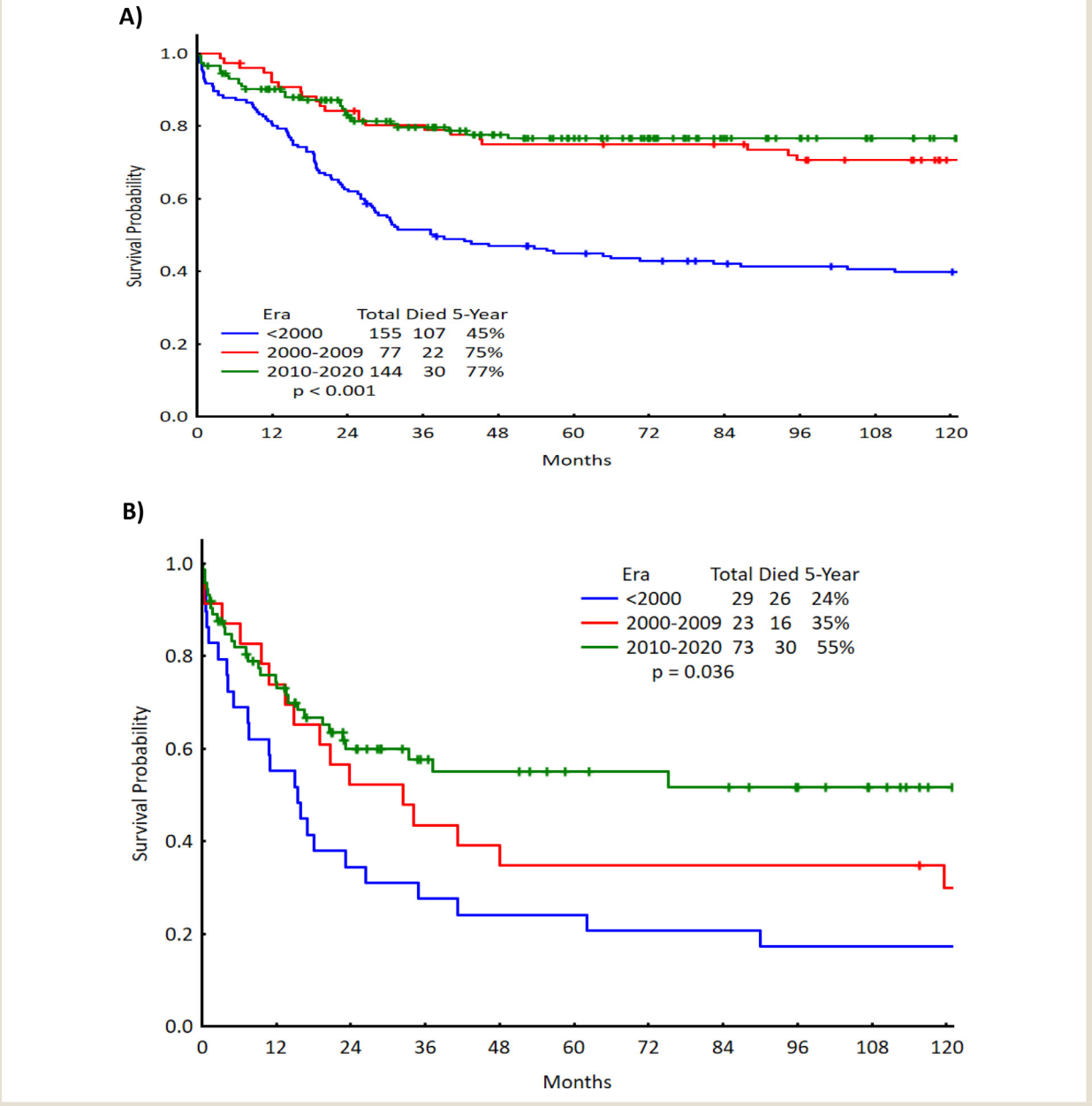


Figure 3 Survival in Patients < 60 years of Age (A) and ≥ 60 Years of Age (B) With Newly Diagnosed CBF AML Treated at MD Anderson Over 5 Decades
Abbreviations: CBF AML = core binding factor acute myeloid leukemia.



AML in the SEER database (which better reflects general oncology practice outcomes) showed significantly worse results, even in modern times (2000-2017). Among patients 40 to 59 years old with de novo AML (excluding APL and CBF AML), the early (4-week) mortality rate was 27%, and the 5-year survival rate was 40%. Among patients ≥ 70 years old, the 4-week mortality rate was 45% to 50% and the 5-year survival rate less than 5%.[7]

Historical studies with intensive chemotherapy in older AML (aged 60-65 years or older) produced CR rates of 40% to 50%, 4- to 8-week mortality rates of 26% to 36%, median survivals of 4 to 6 months, and 1-year survival rates of less than 30%.[37,38] By multivariate analysis, independent adverse factors predictive of early mortality with intensive chemotherapy were as follows: age 75 years and older; adverse karyotype with 3 or more chromosomal abnormalities; presence of an antecedent hematologic disorder; poor performance status (Eastern Cooperative Oncology Group Performance Status Scale, 2-4); creatinine level of 1.3 mg/dl or higher; and treatment outside a protected environment. The expected 8-week mortality

was 10% to 19% with the presence of 0 to 1 adverse factors and 36% to 65% with the presence of 2 to 5 adverse factors.[37]

An important question is, regardless of age and fitness, when should we consider alternatives to intensive chemotherapy for paticular AML subsets? We propose that if a patient has a combination of an expected low CR rate (< 40%), high early 4-week mortality (≥ 15% to 20%), and poor survival (median survival, 6 months or less; 3-year survival rate < 20%), then alternative strategies should be investigated (including low-intensity therapy [eg, decitabine 10 days with venetoclax], low-intensity triple nucleoside [cladribine/cytarabine/HMA] regimen with venetoclax, and specific targeted therapies when available). Perhaps this should not only apply to older/unfit AML but also to several poor risk AML subsets discussed earlier. Patients with AML and pneumonia at diagnosis have a significantly higher risk of early mortality (15%-20%) with intensive chemotherapy[124] (and unpublished from MD Anderson). Future studies may need to incorporate routine baseline chest CT findings into predictive models of early mortality in AML.

In single-arm trials, low-intensity regimens have produced marrow CR rates of 80% (comparable or better than intensive chemotherapy), low early mortality rates of 2% to 3% and encouraging 2-year survival rates of 40%[83] (and detailed later).

The Choice on Induction and Consolidation-Maintenance Therapy

The decision to use intensive versus low-intensity therapy, discussed earlier, depends on the patient's age; performance status and associated comorbidities and infections; cytogenetic and molecular abnormalities; and expected early mortality, CR rate, and long-term outcome with the proposed therapies. In general, intensive chemotherapy is a better choice if it is anticipated to be associated with a CR rate of 60% to ≥ 70%, an early mortality rate of 10% or less, and a 3- to 5-year survival rate of 40% to ≥ 50%. If the expected CR rate is < 40%, the early mortality rate is > 15% to 20%, and 3-year survival rate is < 20%, then alternative investigational or low-intensity therapies may be considered.

Once in CR, the decision to consider SCT depends on the patient's condition in CR, availability of donors, risk of allogeneic SCT, risk of leukemia relapse (depends on the cytogenetic and molecular abnormalities), and MRD status in CR. In general, patients with favorable NCCN/European LeukemiaNet risk may consider continuation of chemotherapy. Those with poor adverse risk benefit from allogeneic SCT. On average, patients younger than 70 to 75 years with a higher risk of relapse with standard chemotherapy should be offered the consideration of allogeneic SCT. Algorithms for patient selection and management have been detailed in previous reviews.[3]

Next, we discuss the role of intensive chemotherapy in younger/fit AML, and of low-intensity chemotherapy in older/unfit AML.

Intensive Chemotherapy in Younger/Fit Acute Myeloid Leukemia

A series of randomized trials in the 1970s established the 3 + 7 regimen as a standard of care for the next 5 decades: daunorubicin 50 to 60 mg/m² IV daily × 3 or idarubicin 12 mg/m² IV daily × 3; cytarabine 100 to 200 mg/m² continuous IV infusion daily × 7. High-dose cytarabine studies indicated that 6 to 12 doses of 3 g/m²was effective. This led to the Cancer and Acute Leukemia Group B (CALGB) randomized trial, which reported a superior survival with high-dose cytarabine consolidation therapy (3 g/m² IV over 2-3 hours every 12 hours on days 1, 3, and 5) for 4 courses, and established it as a new standard of care.[4] However, research over the next 2 to 3 decades has not yet clarified the optimal dose and number of high-dose cytarabine courses.[125-130] A series of MRC trials showed the following: (1) high-dose cytarabine 1.5 g/m² was equivalent to 3 g/m²; (2) 5 courses of high-dose cytarabine consolidation was not better than 4 courses; (3) daunorubicin 60 mg/m² had equivalent efficacy and lower toxicity than 90 mg/m² (confirmed by others); (4) patients who were able to tolerate 2 courses of FLAG-IDA followed by 2 courses of high-dose cytarabine had a 5-year survival rate of 66% versus 47% for those receiving 3 + 7 induction and 3 high-dose cytarabine consolidations.[22,125] A study from the Republic of Korea indicated that a cytarabine dose of 1.5 g/m² or more in consolidation was better than 1 g/m².[126] A German study used high-dose cytarabine with a higher dose schedule, 3 g/m² twice daily × 6 (total dose, 36 g/m² total/course; higher that what was used in the original CALGB study, which used a total 18 g/m²) and compared it with cytarabine 1 g/m² twice daily × 6 (total, 12 g/m²), showing no difference in survival.[127] A randomized study from Japan indicated that 3 courses of high-dose cytarabine consolidation were as effective as 4 courses.[128] The benefit of high-dose cytarabine may not fully apply when patients are referred for allogeneic (superior to chemotherapy on average) or autologous SCT (equivalent to intensive chemotherapy consolidations). In an editorial, Lowenberg suggested that a "single cycle of 1000 mg/m² cytarabine given twice daily in the treatment of AML might be sufficient" (presumably for 6 days, 12 g/m²; mostly in the setting of moving directly to allogeneic SCT).[130] At MD Anderson, high-dose cytarabine is used at a dose of 1.5 to 2 g/m² daily × 5 (total, 7.5-10 g/m² per course) during induction (decreased to 3 days during consolidations).

Several comparative trials evaluating the optimal choice and dose schedule of anthracyclines indicated the following: (1) daunorubicin 90 mg/m² daily × 3 was superior to 45 mg/m² daily × 3,[5,6] but daunorubicin 60 mg/m² daily × 3 was equivalent and less toxic than 90 mg/m² daily × 3;[131,132] and (2) Idarubicin 12 mg/m² daily × 3 (with cytarabine; 3 + 7 regimens) was equivalent or superior to daunorubicin.[133-136] With FLAG-IDA and with cladribine/idarubicin/high-dose cytarabine (CLIA), we reduce idarubicin to 8 to 10 mg/m² daily × 3 to avoid excessive myelosuppression.

Several studies have now reported on AML regimens that produced better results than those historically reported with the 3 + 7 regimens. The chemotherapy combinations in these studies have included the following components: (1) high-dose cytarabine combination during induction; (2) choice of the anthracycline and adjustment of the dose schedule (idarubicin; daunorubicin 60 mg/m² daily × 3 vs. 45 mg/m² or 90 mg/m² daily × 3); (3) addition of adenosine nucleoside analogues (fludarabine, clofarabine, cladribine) to cytarabine/anthracyclines; and (4) addition of the CD33-targeted monoclonal antibody GO in

favorable to intermediate-risk AML. Recent regimens have also incorporated targeted therapies like FLT3 inhibitors in *FLT3*-mutated AML (now standard practice), and venetoclax and/or IDH inhibitors as indicated (still investigational). With the recent FDA approval of oral azacitidine for maintenance in AML in first CR (CR duration, 4 months or less; patients unable to complete the curative intensive chemotherapy), such an approach may expand.

High dose cytarabine (1-3 g/m^2 twice daily on days 1, 3, and 5 or daily × 5, or twice daily × 6) consolidation is an established standard of care for AML consolidation.[4,125-130] But does it also add benefit if incorporated into AML induction? A meta-analysis of 3 randomized trials and other randomized trials suggested it does. Other randomized trials also confirmed this benefit.[137-141] Two randomized trials reported no benefit with high-dose cytarabine induction, but their design did not actually address well the value of high-dose cytarabine during induction. The first still delivered high-dose cytarabine during 1 of the 2 induction courses on both arms of the study.[129] The second implemented a significantly higher dose of cytarabine during consolidation in the control arm than in the investigational high-dose cytarabine induction arm.[142] The details of the high-dose cytarabine induction trials were detailed in other reviews.[3,120]

Because of the potential anti-AML benefits of adenosine nucleoside analogues (fludarabine, clofarabine, cladribine), studies incorporated them into AML frontline regimens referred to as fludarabine with high-dose cytarabine and idarubicin (+/− G-CSF) (FLAG-IDA or FAI); CIA (clofarabine replaces fludarabine); and CLIA (cladribine replaces fludarabine).[26,33,143] In a randomized trial (MRC AML 15), FLAG-IDA (induction with cytarabine 2 g/m^2 daily × 5, fludarabine 30 mg/m^2 daily × 5, and idarubicin 8-10 mg/m^2 daily × 3) was compared with 3 + 7 plus etoposide. It was reported that FLAG-IDA was more myelosuppressive and toxic; however, in patients who completed 4 courses on the FLAG-IDA arm (2 FLAG-IDA + 2 high-dose cytarabine), the 8-year survival rate was 66% versus 47% in the standard arm.[22,125] Other studies have also reported promising results with FLAG-IDA.[144-146] The Polish investigators reported that adding cladribine to 3 + 7 improved outcome,[147-149] including in those with *FLT3*-mutated AML.[149]

GO was originally approved by the FDA for the treatment of AML in 2000 but was withdrawn in 2010 after negative data from a randomized trial conducted by the SWOG investigators.[23] Following a meta-analysis of 5 randomized trials, it was reapproved in 2017 at a lower dose schedule in combination with chemotherapy (3 mg/m^2× 1 during induction and consolidation; 3 mg/m^2 on days 1, 4, and 7 during induction).[24] The meta-analysis involved 3325 patients and showed that the addition of GO reduced the risk of relapse (P = .0001) and improved survival (P = .01), mostly among patients with favorable (CBF AML; 5-year survival rate, 75% vs. 50%; P = .0006) and intermediate cytogenetics (P = .005). GO 3 mg/m^2 was as effective as 6 mg/m^2 and was associated with fewer early deaths.[24] Some studies have indicated that GO may also benefit older AML, and AML with *FLT3, RAS*, and possibly *NPM1* mutations.[150,151]

Role of Allogeneic SCT

Patients with AML in remission are frequently offered allogeneic SCT when indicated, with the following considerations: availability of donors; suitability for SCT based on patient age, comorbidities, and donor matching; pretreatment AML characteristics like cytogenetics and mutations; and MRD status in CR/CRi. If not eligible for SCT or if the patient declines the procedure, completion of 4 to 6 courses of consolidation is recommended, and the patient should be offered maintenance therapy with azacitidine +/− venetoclax, or targeted therapies as appropriate: FLT3 inhibitors for *FLT3*-mutated AML; IDH inhibitors for *IDH*-mutated AML. With this approach, the CR rate in younger patients with AML is ≥ 80%, and the long-term survival rate is 40% to 50%, better since 2015 (Figure 1).

Older/Unfit Patients With Acute Myeloid Leukemia: Low-Intensity Therapy

Hypomethylating Agents

Before 2000, most older patients (aged 60-70 or older) with AML were offered supportive palliative or hospice care in community practice and in many academic centers.[42-44] Because median survival was 3 months or less, and because intensive chemotherapy results were poor, investigators studied lower-intensity regimens in older/unfit AML. The MRC trial randomized older patients with AML to low-dose cytarabine 20 mg subcutaneously twice daily × 10 versus supportive care/hydroxyurea and showed the benefit of low-dose cytarabine: CR rate 18% versus 1% (P = .00006) and longer survival (odds ratio, 0.6; P = .0009).[152] This study was one of the first to encourage the notion that older/unfit patients with AML can benefit from active and tolerable treatments that improve survival and quality of life over supportive/hospice care.

In the meantime, the concept of epigenetic therapy and the use of HMAs was being explored in MDS and led to the FDA approvals of azacitidine in 2004 and of decitabine in 2006 for the treatment of higher-risk MDS and CMML.[153-155]

Decitabine was originally developed in Europe in the 1970s to 1980s as a classical cytotoxic agent at doses of 1000 to 2500 mg/m^2 per course.[156-158] Its development was abandoned because of severe and unpredictable prolonged myelosuppression, and neurotoxicity. Investigations of its possible differentiation/hypomethylation properties resulted in studies, starting in 1992, to explore different doses and schedules of decitabine, tied translationally to its hypomethylating effect. Decitabine was studied as an HMA at 1/20th of the cytotoxic doses, 10 to 20 mg/m^2 daily × 5 to 10 days.[157-162] The phase 3 trial of decitabine versus low-dose cytarabine in MDS used the 3-day continuous infusion schedule of decitabine 15 mg/m^2 over 4 hours every 8 hours × 3 days (total, 135 mg/m^2) based on the original studies of this dose schedule from Europe. The European study in MDS failed to meet its designed primary endpoint, possibly because of the suboptimal schedule of decitabine (3-day exposure monthly every 6-8 weeks × 8 courses).[156] Parallel studies with azacitidine in MDS (7-day exposure every 4 weeks until progression) resulted in its approval by the FDA (2004) and the EMA (2008) for the treatment of higher-risk MDS.[154,155] Today, decitabine and azacitidine are the most commonly used agents for the treatment of older/unfit AML.

The dose schedule of decitabine was optimized to 20 mg/m^2 daily × 5 every month and showed better results in MDS and AML.[159,161] This was confirmed by the ADOPT trial[163] and led to the phase 3 trial of decitabine 5-day schedule versus patient choice (with physician advice) in older AML. This study did not result in an FDA approval, although it showed a significant survival benefit with the mature data and supported the EMA approval of decitabine for the treatment of older AML.[153,164] A similar phase 3 study of azacitidine versus conventional care in older AML led to an EMA approval in 2015.[165] Longer durations of decitabine schedules (20 mg/m^2 daily × 10) have also been studied.[159,161,166]

In 2020, the FDA approved a 100% absorbable oral formulation of decitabine plus oral cedazuridine (cytosine deaminase inhibitor) for the treatment of MDS and CMML.[167,168] This provides an opportunity to investigate and develop an effective and easily deliverable oral therapy regimen for older/unfit AML (oral decitabine/cedazuridine plus venetoclax); this would simplify treatment delivery and improve quality of life as outpatient therapy in patients in CR after induction. Comparisons of intensive chemotherapy versus HMA therapy in older AML showed equivalent or better results with HMA therapy.[25,169,170]

Combination of Low-Intensity Drug Regimens

The benefit of HMAs in older/unfit AML has been limited, with median survivals of less than 12 months and 2- to 3-year survival rates of less than 20%. Because the adenosine nucleoside analog (clofarabine, cladribine) and cytarabine are also active in AML, the sequential low-intensity therapy combining an adenosine nucleoside analogue (clofarabine and later cladribine) with low-dose cytarabine, alternating the couplet drugs with decitabine over a period of 18 months, was evaluated. Among 248 patients (median age, 69; range, 48-85 years) treated, the CR rate was 59%, the 4-week mortality rate was 2%, and the median survival was 12.5 months. Among patients with normal karyotype, the median survival was 19.9 months, and the estimated 2-year survival rate was 45%.[171,172] This low-intensity triple-drug therapy appears to improve results over HMAs alone and represents a novel well-tolerated backbone that could be combined with venetoclax and other targeted therapies.

Incorporation of FDA-Approved Agents in AML Into Novel Optimized Regimens

Although we have been fortunate to have had FDA approval of several agents for various indications in AML, these drugs are very expensive (averaging over $20,000/month in retail prices) in relation to the treatment value they deliver in the context of the limited FDA approval indications. How can the treatment value of these drugs be enhanced, specifically in combinations with standard chemotherapy, in both the salvage and frontline settings? We will discuss such strategies next.

Venetoclax

Venetoclax and HMAs/Low-Dose Cytarabine: A New Standard of Care in Older/Unfit AML. Based on the promising preclinical studies, venetoclax was evaluated as a single agent in AML with modest activity, and later combined with low intensity chemotherapy (HMAs, low dose cytarabine). Single arm trials of these combinations yielded impressive results.[173,174] This led to 2 phase 3 randomized trials comparing azacitidine plus venetoclax versus azacitidine (VIALE-A), and low-dose cytarabine plus venetoclax versus low dose cytarabine (VIALE-C) in older/unfit AML.[175,176]

The VIALE-A phase 3 trial randomized 431 patients (2:1 randomization) with newly diagnosed AML who were ≥ 75 years or considered unfit for intensive chemotherapy to azacitidine +/− venetoclax. The addition of venetoclax improved survival (median survival, 14.7 vs. 9.6 months; $P < .001$) as well as overall response (66.4% vs. 28.3%; $P < .001$) and CR rates (29.7% vs. 17.9%; $P < .001$).[175] The VIALE-C phase 3 trial randomized 211 older/unfit patients (2:1 randomization) to low-dose cytarabine +/− venetoclax and showed similar findings with the maturing data: median survival, 8.4 versus 4.1 months ($P = 0.11$ at primary analysis; $P = .04$ on post hoc analysis); overall response rate, 48% versus 13% ($P < .001$); CR rate, 27% versus 7% ($P < .001$).[176] These studies established HMAs and low-dose cytarabine combinations with venetoclax as the new standard of care in older/unfit AML.

A study evaluated a longer schedule of decitabine (20 mg/m2 daily × 10-day induction, 5-day maintenance monthly) and venetoclax (21- to 28-day induction depending on day 21 marrow results; maintenance for 7-21 days depending on the degree of myelosuppression) in newly diagnosed older (median age 72 years) de novo AML. This regimen resulted in an overall response rate (CR + CRi) of 84%, a CR rate of 67%, a 4-week mortality rate of 0%, and a median survival of 18.1 months.[83]

Which subsets of patients with AML benefit most from HMA plus venetoclax therapy, and which need additional/different strategies? Patients with *IDH* mutations had a significant response and survival advantage with azacitidine plus venetoclax compared with azacitidine alone: CR rate, 44% versus 4%; CR + CRi rate, 79% versus 11%; median survival, 24.5 versus 6.2 months.[177] Similar results were observed in patients with a diploid karyotype, with or without an *NPM1* mutation.[83,175] In the subset of *FLT3*-mutated AML, the combination of azacitidine + venetoclax improved the response rate (CR, 40% vs.14%), but the *FLT3*-ITD subset had a median survival of only 11.5 months with azacitidine plus venetoclax versus 8.5 months with azacitidine.[178] Combining an HMA with a FLT3 inhibitor +/− venetoclax (triplet regimen) may improve outcomes but could also increase the risk of myelosuppression. Unfortunately, the benefit of an HMA plus venetoclax was limited in the subset of *TP53*-mutated AML: CR rate, 35%; CR + CRi rate, 54%; median survival, only 5.2 months.[179] Combinations of an HMA with a CD47 antibody (magrolimab or others) +/− venetoclax may have future promise in *TP53*-mutated AML.

Investigations of Venetoclax in Combination With Low-Intensity Chemotherapy and Intensive Chemotherapy. The combination of cladribine/cytarabine/venetoclax alternating with azacitidine/venetoclax was investigated in older/unfit newly diagnosed AML.[180] Among the first 48 patients treated (median age 68 years; range, 57-84 years), the CR rate was 77%, the overall response rate was 94%, the 4-week mortality rate was 0%, and the estimated 1-year survival rate was 70%. These preliminary results compare

favorably with the historical data with HMAs +/− venetoclax and with the triple-drug low-intensity chemotherapy (cladribine, cytarabine, and HMA) without venetoclax.

Intensive chemotherapy plus venetoclax is being actively explored. Wei and colleagues reported on a phase 1 study of intensive chemotherapy (2 + 5) with venetoclax, confirming the safety and efficacy of such a combination.[181]

The combination of FLAG-IDA or CLIA with venetoclax (7-14 days during induction; 5-7 days in maintenance) was evaluated in younger/fit patients with newly diagnosed AML, with good preliminary results.[182,183] Among about 60 patients treated on both studies so far, the overall response rate was ≥ 90%, and the estimated 1-year survival was ≥ 78%. The rate of MRD negativity in CR was also high, above 80%. We hope these results, if confirmed in a larger number of patients treated, may open exciting research avenues in the treatment of AML.

FLT3 Inhibitors

Midostaurin (FDA approved with chemotherapy in frontline *FLT3*-mutated AML) and gilteritinib (FDA approved as monotherapy in *FLT3*-mutated refractory-relapsed AML) are the 1 type 1 tyrosine kinase inhibitors (active against both *FLT3*-ITD and *FLT3*-TKD mutations) available for AML therapy. Sorafenib (type 2 inhibitor; effective against *FLT3*-ITD mutations) is commercially available. Quizartinib, another type 2 inhibitor, is only approved in Japan. Other newer-generation FLT3 inhibitors (crenolanib, FF10101) are under investigation.[184]

The phase III RATIFY trial (CALGB 10,603), which resulted in FDA approval of midostaurin, randomized 717 patients < 60 years with newly diagnosed *FLT3*-ITD (77%) and *FLT3*-TKD (23%)–mutated AML (median age, 48 years; range, 18-60 years) to 3 + 7 with or without midostaurin.[66] The addition of midostaurin improved survival (median survival, 74.7 vs. 25.6 months; $P = .009$; estimated 5-year survival rate, 50% vs. 42%). The benefit was noted in all subgroups, including *FLT3*-ITD low AR (AR ≤ 0.70), *FLT3*-ITD high AR (AR > 0.70) and *FLT3*-TKD AML.

Following the encouraging results with single-arm studies of gilteritinib in *FLT3*-mutated AML,[185] a phase 3 trial (ADMIRAL) randomized 371 patients with relapsed *FLT3*-mutated AML (2:1 randomization) to gilteritinib 120 mg daily (n = 247) or investigator-choice low- or high-intensity salvage chemotherapy (n = 124).[186] Gilteritinib therapy improved survival (median survival, 9.3 vs. 5.6 months; hazard ratio [HR], 0.637; $P = .0007$), and rates of CR (21% vs. 11%; $P = .013$) and CR/CRh (34% vs. 15%). The FDA approved single-agent gilteritinib as salvage therapy for *FLT3*-mutated AML. Ongoing studies are combining gilteritinib with HMA therapy (+/− venetoclax) and with intensive chemotherapy.[187] Pratz and colleagues investigated the combination of 3 + 7 with gilteritinib (120 mg daily × 14) in newly diagnosed AML (56% *FLT3* mutated). They reported a marrow CR rate of 86%, a 4-week induction mortality of 0%, and an estimated 2-year survival rate of 70%.[67]

Combination therapy of FLT3 inhibitors with agents that induce apoptosis may enhance cytotoxicity against *FLT3*-mutated and wild-type clones and potentially delay or prevent drug resistance to FLT3 inhibitor–based therapies. Preclinical data indicated a strong synergy between venetoclax and FLT3 inhibitors. Ongoing studies are evaluating such combinations (gilteritinib plus venetoclax, and triplet, HMAs/gilteritinib/venetoclax).

As mentioned earlier, sorafenib maintenance therapy after allogeneic SCT in *FLT3*-mutated AML improved outcomes in European and Chinese studies.[68,69]

Several nontargeted chemotherapy strategies have shown benefits in *FLT3*-mutated AML, including induction regimens containing high-dose cytarabine, cladribine, high-dose daunorubicin, and GO.[140,146,149,151,188] Future combinations with FLT3 inhibitors may be warranted.

IDH Inhibitors

Two orally bioavailable IDH inhibitors, enasidenib (IDH2 inhibitor) and ivosidenib (IDH1 inhibitor), are now FDA approved for the treatment of *IDH*-mutated AML

In the phase 1 to 2 study of enasidenib, 109 patients with refractory-relapsed, *IDH2*-mutated AML were treated with enasidenib 100 mg daily. The overall response rate was 40.3%, the CR rate was 19.3%, the median response duration was 5.8 months, and the median survival was 9.3 months.[189] This resulted in the FDA approval of enasidenib 100 mg daily as single-agent therapy in *IDH2*-mutated, refractory-relapsed AML. Side effects included grade 3 to 4 elevation of indirect bilirubin (12%) and a differentiation syndrome (11.8%, responsive to steroid therapy)

In the phase 1 to 2 study of ivosidenib, 125 patients with *IDH1*-mutated refractory-relapsed AML received ivosidenib 500 mg daily in the phase 2 efficacy portion. The overall response rate was 41.6%, the CR rate was 21.6%, the median overall response duration was 8.2 months, and the median survival was 8.8 months. Grade 3 to 4 side effects included prolongation of QT interval (7.8%) and a differentiation syndrome (3.9%).[190] These data led to the FDA approval of ivosidenib for the treatment of *IDH1*-mutated, refractory-relapsed AML and, shortly after, for frontline therapy of *IDH1*-mutated AML unfit for intensive chemotherapy.

Combinations of IDH inhibitors with chemotherapy appear promising. A total of 101 older patients with newly diagnosed *IDH2*-mutated AML (median age, 74 years; range, 62-85 years) were randomized to azacitidine + enasidenib (n = 68) or azacitidine (n = 33). The addition of enasidenib improved the CR rate (50% vs.12%; $P = .0002$), overall response rate (68% vs. 42%; $P = .015$), and EFS (median, 17.2 vs. 10.8 months; HR, 0.59; $P = .13$). The median overall survival was long but similar on both arms (median survival, 22 months vs. 22.3 months), likely because of the availability of effective salvage (venetoclax combinations, enasidenib combinations) in patients receiving azacitidine alone.[191]

Stein and colleagues treated 151 younger/fit patients with newly diagnosed *IDH*-mutated AML (*IDH1* mutation in 60; *IDH2* mutation in 91) with 3 + 7 and the appropriate IDH inhibitor. The overall response rate was 74% to 77%, and the estimated 1-year survival rate was 76% to 78%.[192]

Oral Azacitidine and Maintenance Therapy in AML

The benefit of maintenance therapy in AML was not established until recently. The oral azacitidine (CC-486) formulation is poorly

absorbed (10% absorption; AUC 30%-42% of intravenous azacitidine). The QUAZAR AML-001 phase 3 trial randomized 472 older patients (≥ 55 years old; median age, 68 years) with AML in first CR < 4 months who were ineligible for SCT to monthly oral azacitidine 300 mg daily × 14 (n = 238) or placebo (n = 234). Oral azacitidine prolonged survival (median, 24.7 vs. 14.8 months; HR, 0.69, $P = .0009$).[193]

A European study (HOVON97) randomized 116 older patients (≥ 60 years) with AML in CR (after 2 courses of intensive chemotherapy) to subcutaneous azacitidine 50 mg/m^2 daily × 5 every month × 12 courses (n = 56) or observation (n = 60). Azacitidine therapy improved DFS: 12-month DFS rate 64% versus 42% ($P = .04$) but not overall survival.[194]

The 2 currently FDA approved oral HMAs, oral decitabine/cedazuridine and oral azacitidine, are very different and approved for different indications. Oral decitabine/cedazuridine is 100% absorbable and approved as 35 mg daily × 5 every month for the treatment of MDS and CMML. Oral azacitidine is poorly absorbed, and FDA approved as 300 mg daily × 14 every month as maintenance therapy for AML in CR as described earlier. A 100% absorbable formulation or oral azacitidine/cedazuridine is under development as an alternative to subcutaneous/intravenous azacitidine. Current studies are investigating combinations of these oral HMAs with venetoclax and other targeted therapies.

Maintenance therapy may be beneficial post-SCT, as shown in studies with sorafenib.[68,69] In the pivotal ADMIRAL study detailed earlier, 51 patients with *FLT3*-mutated relapsed AML who achieved a response with gilteritinib and underwent allogeneic SCT either resumed gilteritinib after SCT (n = 35) or did not (n = 16). Gilteritinib resumption improved survival (median, 16.2 vs. 8.4 months; HR, 0.387; $P = .024$).[186]

Other FDA-Approved Agents for AML

CPX-351

This agent is a nanoscale liposome containing a fixed 5:1 molar ratio of cytarabine and daunorubicin. In a phase 3 trial, 309 patients with newly diagnosed secondary AML were randomized to CPX-351 or 3 + 7. CPX-351 was associated with longer survival (HR, 0.69; $P = .005$) and with higher response rates (CR rate, 38% vs. 26%; $P = .035$; CR + CRi rate, 48% vs. 33%, $P = .016$).[195] In a subgroup analysis, patients with secondary AML and prior HMA exposure did not benefit from CPX-351, highlighting the unmet need of effective therapies for this poor-risk AML subgroup. Ongoing studies are combining CPX-351 with venetoclax, GO, and other targeted therapies.

Glasdegib

This drug is a selective oral inhibitor of smoothened, a component of the hedgehog signaling pathway, which plays critical roles in embryogenesis and stem cell maintenance. Dysregulation of smoothened can favor the development, expansion, and maintenance of AML stem cells.[196] A phase 2 study investigated low-dose cytarabine plus glasdegib 100 mg daily versus low-dose cytarabine alone in older/unfit AML and high-risk MDS. The addition of glasdegib improved survival (median survival, 8.8 vs. 4.9 months; 12-month survival rate, 59.8% vs. 38.2%).[197] Glasdegib has not been widely adopted in clinical practice because of the poor comparator arm in this study and the inferior survival relative to venetoclax-based combinations. Glasdegib combinations with azacitidine and with intensive chemotherapy are warranted.

Ongoing Investigational Strategies in AML

Magrolimab and Other CD47 Antibodies. CD47 functions as a macrophage checkpoint, providing a potent "do not eat me" signal, which allows tumor cells to evade detection and immune destruction by macrophages. CD47 is upregulated in AML; its upregulation is associated with poor prognosis.[198,199] Magrolimab (Hu5F9-G4) is a humanized monoclonal antibody that binds CD47 and blocks its interaction with SIRPα (ligand on phagocytic cells). This results in phagocytic elimination of cancer cells.

Azacitidine plus magrolimab was evaluated in older/unfit newly diagnosed AML and intermediate/higher-risk MDS. Among patients with AML, the response rate was 63% (42% CR). The median survival in *TP53* wild-type AML was 18.9 months. Among patients with *TP53*-mutated AML, the response rate was 69% (CR rate, 45%), and the estimated median survival was 12.9 months. This compares favorably to expectations of HMA plus venetoclax in *TP53*-mutated AML.[72] Ongoing studies are evaluating the role of magrolimab combinations and other CD47 targeted therapies in AML.

Other Targeted Agents of Interest

These include (1) FLT3 inhibitors like quizartinib (potent type 2 FLT3 inhibitor) and third-generation FLT3 inhibitors (FF10101, crenolanib) to potentially overcome the gatekeeper mutations resistant to all current FLT3 inhibitors (eg, *FLT3*-ITD F691L mutation);[200] (2) IDH inhibitors like olutasidenib (FT-2102; IDH1 inhibitor)[201]; (3) agents targeting CD (cluster of differentiation) antigens (CD33, CD123, CD70, CD45, CD47, and others);[202,203] and (4) menin inhibitors in *MLL*-rearranged AML and other menin-dependent leukemia subsets, including *NPM1*-mutated AML.[75-77] These are detailed elsewhere.[3,120]

Summary and Conclusions

Over the last 50 years, our concept of AML has evolved from a morphologically described entity to one categorized by cytogenetic risk and, more recently, by increasing use of molecular gene mutation panels. Monitoring response to therapy in AML has also evolved from the limitations of light microscopy to highly sensitive MRD approaches, including flow cytometry and PCR-based molecular techniques to quantitatively track submicroscopic traces of disease for prognostic determination and, in the future, for possible intervention strategies prior to clinical relapse. Perhaps the most exciting development has been the surge of new treatment options that have become available in the last 5 years. These include targeted therapies directed at aberrant FLT3, IDH, and BCL2; novel formulations of existing drugs; antibody-linked cytotoxic warheads; and orally formulated epigenetic drugs permitting extended duration of administration. The future will focus on maximizing the potential of these new drug approvals, likely through the development of new combination approaches. One challenge for the future will be

the timely validation and regulatory approval for a disease that has become segmented into increasingly smaller subgroups, each with access to a multiplicity of potential treatment options.

Disclosure

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