REVIEW ARTICLE

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Acute Myeloid Leukemia

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Acute myeloid leukemia (AML) is a form of cancer that is characterized by infiltration of the bone marrow, blood, and other tissues by proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated cells of the hematopoietic system. Although it was incurable 50 years ago, AML is now cured in 35 to 40% of adult patients who are 60 years of age or younger and in 5 to 15% of patients who are older than 60 years of age.[1] The outcome in older patients who are unable to receive intensive chemotherapy without unacceptable side effects remains dismal, with a median survival of only 5 to 10 months.

Although the cytogenetic heterogeneity of AML has been recognized for more than 30 years, the enormous molecular heterogeneity of the disease has become increasingly apparent over the past 15 years. The prognostic importance of this biologic heterogeneity is well accepted, but translation of this new information into improved therapy is just beginning. In this article, we describe recent advances in the disease classification, understanding of the genomic landscape, identification of prognostic factors, current treatment, and new therapies under investigation in types of adult AML other than acute promyelocytic leukemia.

Disease Classification

Morphologic assessment of bone marrow specimens and blood smears, analysis of the expression of cell-surface or cytoplasmic markers by means of flow cytometry, identification of chromosomal findings by means of conventional cytogenetic testing, and, more recently, screening for selected molecular genetic lesions are the diagnostic procedures used to classify AML. AML is classified according to the *World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues*,[2] which was last updated in 2008. The major categories of the current classification include AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related AML, and AML not otherwise specified.

A revision of the WHO classification is under way. Changes to the section on AML with recurrent genetic abnormalities are being discussed. First, the molecular basis of inv(3)(q21q26.2) or t(3;3)(q21;q26.2) has been revisited,[3] so that the revision shows rearrangement of a *GATA2* oncogenic enhancer element, rather than of the *RPN1* gene, in band 3q21 with the *MECOM* (*EVI*) gene in band 3q26.2. Second, the provisional entities "AML with *NPM1* mutation" and "AML with *CEBPA* mutation" will become entities; "AML with *CEBPA* mutation" will be restricted to patients with AML in whom there is a biallelic (and not a monoallelic) mutation, because only that form of AML defines a clinicopathologic entity that is associated with a favorable prognosis.[4] Finally, "AML with *RUNX1* mutation"[5,6] and "AML with *BCR-ABL1*" gene fusion[7] are being considered as provisional entities on the basis of their characteristic clinicopathologic features, and in the section on AML

with *BCR-ABL1* gene fusion, the need for including the use of tyrosine kinase inhibitor therapy is being discussed.

A section on familial myeloid neoplasms, which reflects the increasing recognition of familial syndromes, is also under development.[8] Inherited forms of myeloid neoplasms have been associated with germline mutations in at least 10 genes,[8-10] — *ANKRD26*, *CEBPA*, *DDX41*, *ETV6*, *GATA2*, *RUNX1*, *SRP72*, *TERC*, *TERT*, and *TP53*. For additional families carrying mutations associated with familial syndromes to be detected, it is important that physicians take detailed patient family histories, including data on cancer and bleeding problems. Awareness of inherited syndromes is clinically relevant, since these patients may require unique care, and family members should be screened, especially if allogeneic donor hematopoietic-cell transplantation is considered.

GENOMIC LANDSCAPE

Emerging data gleaned with the use of new genomic techniques — in particular, next-generation sequencing — are providing an unprecedented view of the spectrum and frequency of mutations, their distinct patterns of cooperativity and mutual exclusivity, their subclonal architecture, the clonal evolution during the disease course, and the epigenetic landscape of the disease.

The Cancer Genome Atlas Research Network analyzed the genomes of 200 patients with AML (50 with the use of whole-genome sequencing and 150 with the use of whole-exome sequencing, along with RNA and microRNA sequencing and DNA-methylation analysis).[11] Genes that were significantly mutated in AML were organized into several functional categories (Fig. 1). Data are lacking from studies involving larger patient cohorts to elucidate the complex interplay of these genetic lesions in individual patients with AML.

Studies have shown that most cases of AML are characterized by clonal heterogeneity at the time of diagnosis, with the presence of both a founding clone and at least one subclone.[11] Various patterns of dynamic clonal evolution that occur at relapse probably contribute to resistance to therapy.[12]

Other important findings revealed by next-generation sequencing studies relate to the pattern of mutation acquisition and the existence of preleukemic stem cells. Data from clonal evolution studies provide support for a model in which genes that are commonly involved in epigenetic regulation (i.e., *DNMT3A*, *ASXL1*, *IDH2*, and *TET2*) are present in preleukemic hematopoietic stem cells and occur early in the evolution of AML.[13-15] Such ancestral preleukemic stem cells are capable of multilineage differentiation, can survive chemotherapy, and can expand during remission, eventually leading to relapse. Recent studies show that clonal hematopoiesis with somatic mutations, commonly involving the same genes (*DNMT3A*, *TET2*, and *ASXL1*), increases as people age and is associated with an increased risk of hematologic cancer and death.[16-18] In absolute value, this risk is relatively low, and currently it has no clinical consequences.

The mutational pattern may be indicative of AML ontogeny (that is, whether the AML was newly diagnosed as primary disease or as a secondary disorder after an antecedent myeloid disorder such as a myelodysplastic syndrome). In a recent study, the presence of mutations in *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR*, or *STAG2* defined a distinct genetic subtype of AML that shares clinicopathologic features with clinically confirmed secondary AML.[19]

PROGNOSTIC CLASSIFICATION FACTORS

Prognostic factors can be subdivided into those that are related to the patient and those that are related to the disease. Patient-associated factors (e.g., increasing age, coexisting conditions, and poor performance status) commonly predict treatment-related early death, whereas disease-related factors (e.g., white-cell count, prior myelodysplastic syndrome or cytotoxic therapy for another disorder, and leukemic-cell genetic changes) predict resistance to current standard therapy. Because of marked improvements in supportive care in many older patients, the risk of treatment-related death is considerably lower than the risk that the disease will prove to be resistant to treatment. Indeed, treatment-related mortality appears to have decreased substantially in recent years.[20]

The evaluation of molecular genetic lesions as prognostic and predictive markers is an active research area (Table 1).[21,22] Currently, three molecular markers (*NPM1* and *CEBPA* mutations and *FLT3* internal tandem duplications) are used in

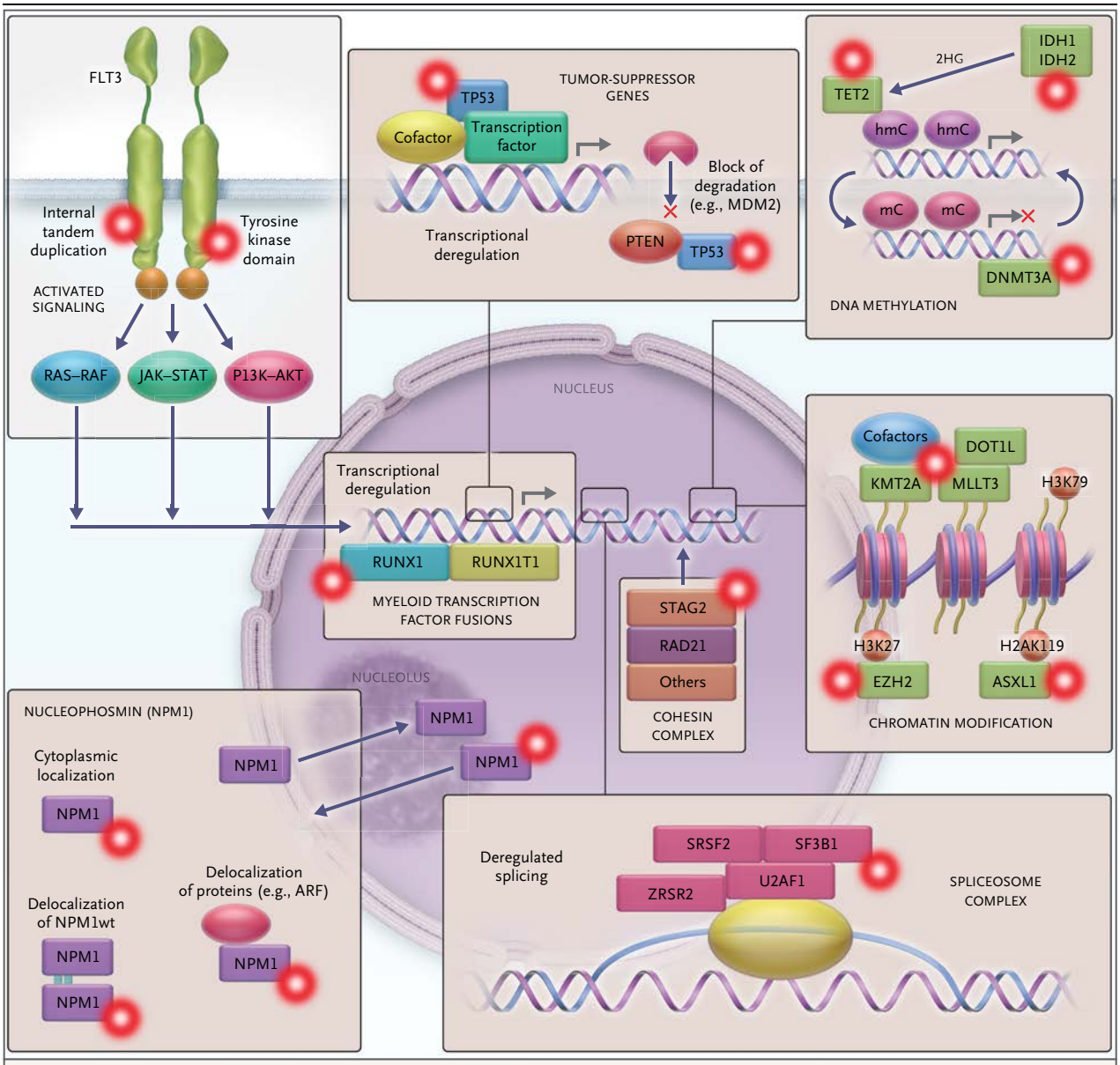

Figure 1. Eight Functional Categories of Genes That Are Commonly Mutated in Acute Myeloid Leukemia.

Mutations in signaling genes such as the class III tyrosine kinase receptor gene *FLT3* confer a proliferative advantage through the RAS–RAF, JAK–STAT, and PI3K–AKT signaling pathways (upper left box). Mutations in myeloid transcription factors such as *RUNX1* and transcription factor fusions by chromosomal rearrangements, such as t(8;21)(q22;q22);*RUNX1-RUNX1T1*, lead to transcriptional deregulation and impaired hematopoietic differentiation (center left box). In the nucleophosmin *(NPM1)* gene, encoding a multifunctional nucleocytoplasmic shuttling protein, mutations result in the aberrant cytoplasmic localization of NPM1 and NPM1-interacting proteins (lower left box). Mutations of spliceosome-complex genes such as *SRSF2*, *SF3B1*, *U2AF1*, and *ZRSR2* are involved in deregulated RNA processing (lower right box). Cohesin-complex gene mutations, such as *STAG2* and *RAD21*, might impair accurate chromosome segregation and transcriptional regulation (center middle box). Mutations of genes involved in the epigenetic homeostasis of cells, such as mutations of *ASXL1* and *EZH2*, lead to deregulation of chromatin modification (e.g., methylation of histones H3 and H2A on lysine residues K79, K27, and K119, respectively), as well as *KMT2A–MLLT3* gene fusion, which can impair other methyltransferases such as DOT1L (DOT1-like histone H3K79 methyltransferase) (center right box). *DNMT3A* and *TET2* mutations, as well as *IDH1* and *IDH2* mutations, acting through the 2-hydroxyglutarate (2HG) oncometabolite production, can lead to the deregulation of DNA methylation (hmC denotes 5-hydroxymethylcytosine, and mC 5-methylcytosine) (upper right box). In tumor-suppressor genes such as *TP53*, mutations can lead to transcriptional deregulation and impaired degradation through the mouse double minute 2 homologue (MDM2) and the phosphatase and tensin homologue (PTEN) (upper middle box). Data on functional categories are from the Cancer Genome Atlas Research Network.[11]

clinical practice, as reflected in the European LeukemiaNet (ELN) recommendations (Table 2).[1] It is expected that additional markers (e.g., *RUNX1*, *ASXL1*, and *TP53*) that have consistently been associated with an inferior outcome will soon be included in these recommendations. The prognostic importance of other mutated genes (e.g., *DNMT3A*, *IDH1*, *IDH2*) is less clear.

Despite the introduction of genetic testing at the initial diagnostic workup, the ability of clinicians to forecast resistance to treatment remains limited.[23] The monitoring of minimal residual disease by means of a quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay that detects leukemia-specific genetic targets or by means of multiparameter flow cytometry that identifies leukemia-associated aberrant phenotypes is another powerful tool to predict outcome.[24] The monitoring of minimal residual disease in core-binding factor AML and AML with the *NPM1* mutation is already integrated into clinical trials, and it allows for preemptive intervention when minimal residual disease is persistent or recurrent. Such monitoring probably will become the standard of care in many patients with AML.

CURRENT THERAPY

The general therapeutic strategy in patients with AML has not changed substantially in more than 30 years.[1] Initial assessment determines whether a patient is eligible for intensive induction chemotherapy. If complete remission is achieved after intensive therapy, appropriate postremission therapy is essential.

INDUCTION THERAPY

Continuous-infusion cytarabine with an anthracycline remains the mainstay of induction therapy (Table 3). Higher doses of daunorubicin than the doses that are currently used are being studied. In the United Kingdom National Cancer Research Institute (NCRI) AML17 trial, 1206 adults, most of whom were younger than 60 years of age, were randomly assigned to first induction therapy with daunorubicin at a dose of either 60 mg per square meter of body-surface area or 90 mg per square meter; no significant difference was shown with respect to the rate of complete response or the rate of overall survival.[25] Confirmatory studies may be needed, since the effect of the dose of daunorubicin may be related to the amount of additional anthracycline therapy used.

A complete response is achieved in 60 to 85% of adults who are 60 years of age or younger. In patients who are older than 60 years of age, complete response rates are inferior (40 to 60%). Older age per se should not be a reason to withhold intensive therapy; however, weighing disease-related and patient-related prognostic factors against treatment intensity is crucial. For example, older patients more often have adverse cytogenetic abnormalities, clinically significant coexisting conditions, or both. Such patients are less likely to benefit from standard induction therapy and are candidates for investigational therapy.

No other induction regimen has been shown convincingly to be superior, with one possible exception: the addition of gemtuzumab ozogamicin, a humanized anti-CD33 monoclonal antibody conjugated with the cytotoxic agent calicheamicin. A recent meta-analysis of five randomized trials showed that although adding gemtuzumab ozogamicin to induction therapy did not increase response rates, it reduced the risk of relapse and improved survival among younger and older adults with favorable-risk and intermediate-risk (but not adverse-risk) cytogenetic findings.[26]

CONSOLIDATION THERAPY

Standard postremission strategies include conventional chemotherapy as well as hematopoietic-cell transplantation. Whether allogeneic transplantation is recommended depends mainly on the leukemic genetic-risk profile, scores on established scales that predict the risk of treatment-related death, and specific transplantation-associated factors in the patient.[1,27-29]

Consolidation with Intensive Chemotherapy

In adults who are 60 years of age or younger, an increasingly preferred regimen is 2 to 4 cycles of intermediate-dose cytarabine (Table 3). The most appropriate dose and number of cycles remain open issues; however, compelling data indicate that doses of 2000 to 3000 mg per square meter are above the plateau of the maximal therapeutic effect.[30] Consolidation therapy with intermediate-dose cytarabine is generally administered in patients with leukemic cells that have a more favorable ELN genetic risk profile, and cure rates

Table 1. Frequency and Clinical Significance of Recurrent Gene Mutations in Adults with AML.*

Mutated Gene	Frequency	Clinical Significance
	% of patients	
NPM1	25–35	AML with an *NPM1* mutation is a clinicopathologic entity Most frequent in cytogenetically normal AML (45–60% of cases); frequently associated with other mutations (e.g., *FLT3*-ITD and mutations in *DNMT3A*, *IDH1*, *IDH2*, and *TET2*) In younger patients, cytogenetically normal AML with mutated *NPM1* without *FLT3*-ITD is associated with a favorable outcome; in general, there is no benefit from allogeneic hematopoietic-cell transplantation in first complete remission Older patients (>60 yr) with *NPM1*-mutated AML benefit from conventional intensive chemotherapy Genetic marker for assessment of minimal residual disease
CEBPA	6–10	Only AML with biallelic *CEBPA* mutations defines the clinicopathologic entity Incidence decreases with older age; associated with cytogenetically normal AML Associated with favorable outcome Associated with familial AML
RUNX1	5–15	Incidence increases with older age; associated with other mutations (e.g., in *ASXL1*, *SRSF2*, *IDH2*, and *KMT2A*) Associated with secondary AML evolving from a myelodysplastic syndrome *RUNX1* mutations predictive of resistance to induction therapy and of inferior outcome Associated with the autosomal dominant familial platelet disorder conferring a predisposition to AML
FLT3-ITD	Approx. 20	Most frequent in cytogenetically normal AML (28–34% of cases) Associated with unfavorable outcome, particularly in patients with a high mutant-to-wild-type ITD ratio, ITD insertion in the β1-sheet of the tyrosine kinase 1 domain, or both Patients with *FLT3*-ITD–positive AML may benefit from allogeneic hematopoietic-cell transplantation in first complete remission; this beneficial effect may be restricted to patients with a high mutant-to-wild-type ITD ratio Tyrosine kinase inhibitors with activity against FLT3 are in clinical development
KIT	<5	Mostly detected in core-binding factor AML (25–30% of cases) Confers unfavorable prognosis in AML with t(8;21); unfavorable effect in AML with inv(16)/t(16;16) less firmly established Tyrosine kinase inhibitors with activity against KIT are in clinical development
NRAS	Approx. 15	Most frequent in cytogenetically normal AML, AML with inv(16)/t(16;16), and AML with inv(3)/t(3;3) Mutant *RAS* may be predictive of sensitivity to cytarabine
DNMT3A	18–22	Early event in leukemogenesis Incidence increases with older age Most frequent in cytogenetically normal AML (30–37% of cases); associated with *NPM1* and *FLT3*-ITD mutations Moderate adverse effect on outcome; possibly limited to the unfavorable ELN molecular subgroup of cytogenetically normal AML Associated with clonal hematopoiesis in healthy elderly persons
ASXL1	5–17	Early event in leukemogenesis Incidence increases with older age Associated with secondary AML evolving from a myelodysplastic syndrome Frequent concurrent mutations (e.g., in *RUNX1*, *SRSF2*, and *IDH2*) *ASXL1* mutations predictive of inferior outcome Associated with clonal hematopoiesis in healthy elderly persons
IDH1 and *IDH2*	*IDH1*, 7–14; *IDH2*, 8–19	Incidence of the $IDH2^{R140}$ mutation increases with older age *IDH1* and *IDH2* mutations most frequent in cytogenetically normal AML (25–30% of cases); association with *NPM1* mutations (except for $IDH2^{R172}$) Prognostic significance dependent on mutational context (*NPM1* and *FLT3*-ITD status) and on type of mutation ($IDH1^{R132}$ and $IDH2^{R172}$ with possible adverse effect, $IDH2^{R140}$ with possible favorable effect) IDH1 and IDH2 inhibitors are in clinical development *IDH1* and *IDH2* mutations may identify patients who are likely to have a response to pharmacologic BCL2 inhibition
TET2	7–25	Early event in leukemogenesis Incidence increases with older age Mutually exclusive of *IDH1* and *IDH2* mutations Prognostic significance is not finally established; in some studies, *TET2* mutations are associated with inferior survival among patients with cytogenetically normal AML or in the favorable ELN subgroup of cytogenetically normal AML Associated with clonal hematopoiesis in healthy elderly persons
KMT2A-PTD	5	Associated with cytogenetically normal AML (5–11% of cases) and trisomy 11 (up to 90% of cases) Possible moderate adverse effect on outcome, but not an independent prognostic factor

Table 1. (Continued.)

Mutated Gene	Frequency	Clinical Significance
	% of patients	
TP53	Approx. 8	Incidence increases with older age *TP53* alterations predominantly detected in AML with complex aberrant karyotype (deletions, mutation, or both in 56–78% of cases) Mutations associated with –5 or del(5q), –7 or del(7q), monosomal karyotype, and genomic complexity, among other factors *TP53* mutations confer very poor outcome

* Approx. denotes approximately, BCL2 B-cell CLL–lymphoma 2 protein, ELN European LeukemiaNet, ITD internal tandem duplication, KIT v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homologue, and PTD partial tandem duplication.

among these patients is 60 to 70%. In clinical trials, monitoring of minimal residual disease with the use of a quantitative RT-PCR assay can guide postremission therapy in these patients, and preemptive salvage therapy, including allogeneic hematopoietic-cell transplantation, may be performed when there is molecular detection of persistent or relapsed AML.

Prospective randomized trials comparing single-agent higher doses of cytarabine with multiagent postremission therapy in adult patients who are 60 years of age or younger generally have not shown a significant difference in survival.[31] There is sparse evidence that combination therapy may be superior in patients with adverse-risk cytogenetic findings.[32] Autologous hematopoietic-cell transplantation generally does not improve the outcome, but it may still be considered as alternative consolidation therapy in selected patients.[33]

The outcomes in patients who are older than 60 years of age remain highly unsatisfactory. Randomized trials have compared more intensive consolidation chemotherapy with less intensive consolidation chemotherapy, but the results have been inconclusive.[31] Currently, it is generally recommended that patients with a favorable-risk ELN genetic profile and good performance status should receive repetitive cycles of an intermediate-dose cytarabine-based regimen (Table 3). Patients with an unfavorable genetic risk, clinically significant coexisting conditions, or both are unlikely to benefit from such therapy. Although patients with intermediate-risk genetic factors may fare better, the outcome also remains poor, with cure rates of only 10 to 15%. Given such dismal results, these patients should be offered investigational treatment that may include new maintenance therapies.

Allogeneic Hematopoietic-Cell Transplantation

Postremission therapy with allogeneic hematopoietic-cell transplantation provides the strongest antineoplastic therapy because of pretransplantation cytoreductive conditioning and the immunologic antileukemic graft-versus-leukemia effect.[29] Allogeneic hematopoietic-cell transplantation is reserved for patients who are unlikely to have extended complete remission with conventional approaches other than transplantation (Table 3).[27,28,34-38]

Addressing selection bias in trials of various treatments requires adjustment for comparative eligibility and time-to-treatment effects. Such adjustments have been used in multicenter network trials in which therapies that include hematopoietic-cell transplantation are compared with those that do not include hematopoietic-cell transplantation. Examples of such trials are the U.S. Blood and Marrow Transplant Clinical Trials Network (BMT CTN) and the U.K. NCRI trials.

Transplantation Techniques

Chemoradiotherapy conditioning is chosen because of its antileukemia potency plus sufficient immunosuppression to permit engraftment. Nonmyeloablative or reduced-intensity conditioning must be sufficiently immunosuppressive to prevent rejection of the donor graft. Agents that do not cause adverse effects beyond any limiting myelosuppression are best-suited for hematopoietic-cell transplantation, since bone marrow toxicity is no longer dose-limiting. Fludarabine plus cyclophosphamide or other alkylating agents (such as busulfan and melphalan) and total-body irradiation are often used. Older patients and those with coexisting conditions often receive reduced-intensity conditioning; however, too little conditioning can increase the risk of relapse.

Table 2. Current Stratification of Molecular Genetic and Cytogenetic Alterations, According to ELN Recommendations.*

Risk Profile	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD (normal karyotype) Biallelic mutated *CEBPA* (normal karyotype)
Intermediate-I†	Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse‡
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *GATA2–MECOM (EVI1)* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *KMT2A* rearranged –5 or del(5q); –7; abnl(17p); complex karyotype§

* Three changes were made to the original recommendations reported by Döhner et al.[1] First, cases of AML with mutated *CEBPA* are now restricted to cases with biallelic *CEBPA* mutations.[4] Second, the molecular designation of inv(3)(q21q26.2) or t(3;3)(q21;q26.2) has been changed to *GATA2–MECOM (EVI1)*.[3] Finally, for *MLL*, the official gene symbol *KMT2A* (lysine [K]-specific methyltransferase 2A) has been adopted.

† This category includes all cases of AML with a normal karyotype except for those included in the favorable subgroup; most of these cases are associated with a poor prognosis, but they should be reported separately because of the potential different response to treatment.

‡ Adequate numbers of most abnormalities have not been studied to draw firm conclusions regarding their prognostic significance.

§ A complex karyotype is defined as three or more chromosomal abnormalities in the absence of one of the World Health Organization–designated recurring translocations or inversions — t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), and inv(3)/t(3;3). About two thirds of patients with AML with a complex karyotype have a mutation of *TP53*, a deletion of *TP53*, or both. *TP53* alterations in AML rarely occur outside a complex karyotype.

One prospective comparison (though underpowered) between fully myeloablative and reduced-intensity conditioning hematopoietic-cell transplantation has been reported,[39] and another prospective trial, BMT CTN 0901 (ClinicalTrials.gov number, NCT01339910), has completed enrollment.

Donor Graft and Cell Source Options

An HLA-matched graft is generally preferred. Grafts from HLA-matched siblings are most often used, but since the late 1980s, grafts from HLA-matched volunteer adult unrelated donors have yielded nearly equivalent outcomes. However, these donors are not identified as often for patients with minority racial or ethnic backgrounds.[40] HLA heterogeneity, particularly in black or mixed-race populations, limits the identification of allele-matched unrelated donors, even in large worldwide networks (which include >20 million potential donors). Closely matched units of umbilical-cord blood and grafts from partially matched family donors provide graft alternatives.[41-45]

Hematopoietic-cell transplant grafts are large-volume marrow aspirates (harvests). For adults, but not children, filgrastim-mobilized peripheral-blood stem cells have largely replaced marrow. Numerous randomized trials have shown no overall survival advantage associated with the use of peripheral-blood stem cells, and one large trial involving unrelated donors showed similar rates of survival but higher rates of chronic graft-versus-host disease (GVHD) with grafts of mobilized peripheral-blood stem-cells.[46]

Complications of Allotransplantation

Early in the period after hematopoietic-cell transplantation, the risks of mucositis, veno-occlusive disease, interstitial pneumonitis, and infection predominate.[47] Acute and later chronic GVHD are major hazards that are not related to relapse. Excessive immunosuppression to limit GVHD can magnify the risks of opportunistic infection (e.g., reactivation of Epstein–Barr virus infection and lymphoproliferative disease) and recurrence of leukemia.[48] Acute or chronic GVHD may augment graft-versus-leukemia protection against relapse of leukemia, but more severe GVHD does not enhance antitumor effects.

A relapse of AML is the major complication (Table 4). Factors dictating the risk of relapse are the biologic characteristics of the AML and the degree of detectable residual leukemia. High-risk cytogenetic and molecular subgroups, therapy-related AML, AML after a myelodysplastic syndrome or myeloproliferative neoplasms, or hematopoietic-cell transplantation after the first complete remission all increase the risk of relapse. Pretransplantation consolidation therapy may not reduce the risk of relapse, but minimal residual disease that is detectable before transplantation may increase the risk.[49]

Relapse after Transplantation

The relapse of leukemia, particularly early after transplantation, is challenging to manage.[50] Some patients receive reinduction, either alone or supplemented with additional donor lymphocytes that were not immunologically tolerant to the recipient, in order to augment graft-versus-leukemia effects. Reinduction can yield durable remissions in a selected 20 to 30% of patients.

The rate of survival after relapse is poor, except among patients with a relapse 1 or more years after transplantation. For a minority of patients, a second allotransplantation during remission can extend leukemia-free survival.

New Approaches to Improving Outcomes of Transplantation

Limiting the risk of relapse and reducing the effects of GVHD in the peritransplantation period are both essential. New investigational antileukemic approaches include post-transplantation maintenance therapy (e.g., azacitidine)[51] and specific mutation inhibitors (e.g., the FLT3-tyrosine kinase inhibitor). Targeted therapy with immunotoxins (such as gemtuzumab ozogamicin), targeted radioantibody therapy, and total marrow irradiation[52] to augment pretransplantation myeloablation have been explored. Cytomegalovirus reactivation can induce sustained antileukemic activity, but its mechanism and the method for inducing it are uncertain.[53] Similarly, in spite of retrospective observations, data are lacking to better define the mechanism by which the donor killer-cell immunoglobulin-like receptor (KIR) genotype can limit post-transplantation relapse of AML.[54] Supplementation of post-transplantation treatment with antileukemia antibodies, synthetic bispecific T-cell engagers, or vaccines targeting leukemia-associated WT1 or PR1 antigens are under study.[55]

TREATMENT FOR PATIENTS WHO ARE INELIGIBLE FOR INTENSIVE THERAPY

The treatment of older or frail patients with AML includes best supportive care (including hydroxyurea), low-dose cytarabine, and, more recently, the hypomethylating agents decitabine and azacitidine (Table 3). Currently, no widely accepted algorithm provides treatment guidelines for older patients who cannot receive intensive chemotherapy. In clinical practice, the patient's age, general health, and specific coexisting conditions, as well as the disease features, the patient's wishes (and those of the patient's relatives), and the physician's attitude and interest all influence decision making.

Low-dose cytarabine induces responses in 15 to 20% of patients, but median survival is only 5 to 6 months. Systematic attempts to improve on this outcome (e.g., with the "pick a winner" program[56] of the Medical Research Council–NCRI AML Group, which involves serial testing of investigational compounds with low-dose cytarabine) have so far failed.

The hypomethylating agents may have promise. Both decitabine and azacitidine have been studied in phase 3 trials.[57,58] In an unplanned survival analysis, the use of decitabine, as compared with treatment chosen by the patient and physician (usually low-dose cytarabine), was associated with a survival advantage (median, 7.7 months vs. 5.0 months).[57] On the basis of this increase in survival, the European Medicines Agency, but not the U.S. Food and Drug Administration, granted approval for the use of decitabine for the treatment of older patients with AML. The AZA-AML-001 trial compared azacitidine with three conventional care regimens (i.e., low-dose cytarabine, intensive chemotherapy, or supportive care only).[58] The median survival was longer with azacitidine than with the conventional care regimens (10.4 months vs. 6.5 months), but the between-group difference was not significant.

TREATMENT OF RELAPSED AND PRIMARY REFRACTORY AML

Disease recurrence occurs in most patients with AML within 3 years after diagnosis. A short duration of remission (i.e., <6 months), adverse genetic factors, prior allogeneic transplantation, older age, and poor general health status are major determinants of outcome after relapse. At relapse, the major question is whether a patient is physically able or unable to receive intensive salvage therapy. The decision-making process should always be in keeping with the patient's goals.

Data are scarce with respect to controlled trials involving patients with relapsed or primary refractory AML.[59] Commonly used intensive salvage regimens aim at achieving a complete remission so that the patient can subsequently undergo allogeneic hematopoietic-cell transplantation (Table 3). Usually, the only treatment options for patients who are physically unable to receive intensive salvage therapy are low-intensity therapy or best supportive care. Given the poor outcome after these conventional care regimens, patients who are physically unable, as well as those who are physically able, to receive intensive salvage therapy should have the option of declining treatment or, if they wish, receiving new investigational therapies.

Table 3. Current Conventional Care of Patients with AML, Including Indications for Allogeneic Hematopoietic-Cell Transplantation.

Form of Therapy	Regimen	Comments
Induction therapy*		
Patients 16–60 yr	3 Days of an intravenous anthracycline (daunorubicin 60 mg/m^2; idarubicin 10–12 mg/m^2; mitoxantrone 10–12 mg/m^2) and 7 days of continuous-infusion cytarabine (100–200 mg/m^2) ("3+7" induction)	A second induction cycle is commonly used in patients with partial remission only
Patients >60 yr	For patients with favorable-risk and intermediate-risk cytogenetic findings and no coexisting conditions, induction therapy is the same as that in younger patients, and dose reduction may be considered for individual patients	Patients with adverse cytogenetic risk, coexisting conditions, or both are less likely to have a response to induction therapy (see also below under "patients who are ineligible to receive intensive therapy")
Consolidation therapy*		
Patients 16–60 yr	Patients with favorable genetic risk (according to ELN) should receive 2–4 cycles of intermediate-dose cytarabine† (1000–1500 mg/m^2 intravenously, usually administered every 12 hr over 3 days, or 1000–1500 mg/m^2 intravenously on days 1–6); for patients with intermediate-I, intermediate-II, or adverse risk, allogeneic hematopoietic-cell transplantation should be strongly considered; if not possible, consolidation therapy should be administered as above; combination chemotherapy (e.g., mitoxantrone–cytarabine) may be superior in patients with adverse-risk AML	Autologous hematopoietic-cell transplantation may be considered in lieu of consolidation chemotherapy for selected patients who do not have disease with high-risk features
Patients >60 yr	Patients with favorable ELN genetic risk (less common) and no coexisting conditions should receive 2–3 cycles of intermediate-dose cytarabine (500–1000 mg/m^2 intravenously, every 12 hr on days 1–3, or 500–1000 mg/m^2 intravenously, on days 1–6)	For patients with unfavorable genetic risk, coexisting conditions, or both, no value of intensive consolidation therapy has been established; investigational therapy should be considered
Allogeneic hematopoietic-cell transplantation (see Table 4)*		
Therapy for patients who are ineligible to receive intensive therapy	Only for patients with favorable-risk or intermediate-risk, not with adverse-risk cytogenetic subgroup: low-dose cytarabine (20 mg every 12 hr, subcutaneously, on days 1–10, every 4 wk; until progression)	Determination of eligibility is based on assessments of prior medical coexisting conditions, recent complications, performance status, and patient choice
	Hypomethylating agents: decitabine‡ 20 mg/m^2, intravenously, on days 1–5, every 4 wk, until progression; azacitidine§ 75 mg/m^2, subcutaneously, on days 1–7, every 4 wk, until progression	
	Consider investigational therapy in all patients	
	Best supportive care only in patients who cannot safely receive any antileukemic therapy	
Therapy for patients with relapsed AML or primary induction failure		Older age, poor general health status, primary refractoriness, or short duration of remission (<6 mo), adverse genetic factors, and prior hematopoietic-cell transplantation are major risk factors

Patients for whom intensive salvage therapy is considered to be suitable	Conventional intensive salvage regimens: cytarabine† (1000–1500 mg/m^2, intravenously every 12 hr, on days 1–3 [500–1000 mg/m^2 in patients >60 yr]; or 1000–1500 mg/m^2, intravenously, on days 1–6 [500–1000 mg/m^2 in patients >60 yr]); with or without daunorubicin 45–60 mg/m^2, intravenously, on days 1–3; or mitoxantrone 8–10 mg/m^2, intravenously, on days 1–3	
	MEC: Mitoxantrone 8 mg/m^2, on days 1–5; etoposide 100 mg/m^2, on days 1–5; cytarabine 1000 mg/m^2, on days 1–5	
	FLAG-IDA: Fludarabine 30 mg/m^2, intravenously, on days 1–5 (20 mg/m^2 in patients >60 yr); cytarabine 1500 mg/m^2 (500–1000 mg/m^2 in patients >60 yr) intravenously, 4 hr after fludarabine infusion, on days 1–5; idarubicin 8 mg/m^2, intravenously, on days 3–5; granulocyte colony-stimulating factor 5 μg/kg, subcutaneously, from day 6 to white-cell count >1 g/liter	
	Consider dose reductions in individual patients, in particular, in older patients (>60 yr) and in patients with relapse after allogeneic hematopoietic-cell transplantation	
	Allogeneic hematopoietic-cell transplantation for patients in complete remission; investigational hematopoietic-cell transplantation approaches for those with major cytoreduction, but no complete remission; consider reinduction (dose-reduced) and reduced-intensity conditioning allogeneic hematopoietic-cell transplantation in selected patients	
Patients for whom intensive salvage therapy is considered to be unsuitable	Low-intensity regimens, such as low-dose cytarabine, hypomethylating agents, or best supportive care only (including hydroxyurea); preserve quality of life	

* This therapy is for patients who are physically able to undergo the therapy and who do not have major coexisting conditions.
† Some regimens use higher doses of cytarabine (2000–3000 mg per square meter per single dose); however, data from pharmacologic studies and clinical trials suggest that such doses are above the plateau of the maximal therapeutic effect.
‡ This agent is approved by the European Medicines Agency (EMA), but not by the U.S. Food and Drug Administration (FDA), for patients who are 65 years of age or older, who have newly diagnosed primary or secondary AML, and who are not candidates for standard induction chemotherapy.
§ This agent is approved by the FDA and EMA for patients who have newly diagnosed AML with 20 to 30% bone marrow blasts and multilineage dysplasia and who are not candidates for allogeneic hematopoietic-cell transplantation.

Table 4. Indications for Allogeneic Hematopoietic-Cell Transplantation and Factors Influencing the Outcome.*

Indications for Allogeneic Hematopoietic-Cell Transplantation
Patients 16 to 60–65 yr
First complete remission (in general excluding ELN favorable-risk AML)
Other high-risk clinical features (e.g., therapy-related AML; secondary AML following a preceding myelodysplastic syndrome or myeloproliferative neoplasm)
Persisting minimal residual disease detectable by means of a quantitative real-time PCR assay or multicolor flow cytometry
Primary induction failure: alternative or investigational regimens to achieve complete remission followed by allografting
Second or higher complete remission; first relapse; satisfactory outcome with delay of hematopoietic-cell transplantation requires prompt attainment of second complete remission without major infectious or other condition that compromises later hematopoietic-cell transplantation
Patients >60–65 yr
Patients younger than 75 yr of age who are physically able to undergo transplantation, with careful consideration of coexisting conditions and patient goals; clinical and biologic indications similar to those for younger patients
Factors Influencing the Outcome of Allogeneic Hematopoietic-Cell Transplantation
Disease status
First complete remission best, with more relapses seen after hematopoietic-cell transplantation in patients with advanced complete remission, primary induction failure, or relapse
Increased risk of relapse if longer time to first complete remission or first relapse within 12 mo
Persisting minimal residual disease
Increased risk of relapse with minimal residual disease before hematopoietic-cell transplantation; uncertain whether added therapy to reduce minimal residual disease improves survival, since minimal residual disease may indicate resistant AML
High-risk genetic factors
Increased risk of relapse with high-risk cytogenetic or molecular phenotype
Risk of relapse may be overcome with allogeneic hematopoietic-cell transplantation in some groups, yet high-risk features still lead to higher rates of relapse after allografting
Age and performance status
Modest effect of age on treatment-related mortality among selected patients
Performance status or Hematopoietic Cell Transplantation Comorbidity Index predictive of treatment-related death
Lower risk of relapse with allogeneic hematopoietic-cell transplantation, yet published results of studies involving older patients with AML are limited and selected
Geriatric or frailty indexes may help to identify candidates for hematopoietic-cell transplantation
Despite clear indications, too few older patients with AML undergo hematopoietic-cell transplantation
Reduced-intensity conditioning regimen
Suitable for older or sicker patients who have major coexisting conditions
Lower rate of early treatment-related death with reduced-intensity conditioning, but similar rate of later treatment-related death due to acute or chronic GVHD
Increased risk of relapse with reduced-intensity conditioning
Similar survival with myeloablative hematopoietic-cell transplantation and hematopoietic-cell transplantation with reduced-intensity conditioning among older patients and those with coexisting conditions
Graft source and graft-versus-leukemia effect
Increased risk of GVHD (particularly chronic) with use of filgrastim-mobilized PBSCs
Similar potency of graft-versus-leukemia effect with sibling or unrelated-donor hematopoietic-cell transplantation
Higher treatment-related mortality, but potent graft-versus-leukemia effect with hematopoietic-cell transplantation with umbilical-cord blood
GVHD (acute, chronic, or both) associated with lower risk of relapse
Added antileukemic therapies (under study)
Cytomegalovirus reactivation–associated immune antileukemic activity
Post-transplantation maintenance therapy
Donor lymphocyte infusions: preemptive, or therapeutic for persisting minimal residual disease or relapse
Antigen-directed T cells, antibodies, or antileukemic vaccines

* Allogeneic hematopoietic-cell transplantation can be performed in patients who are physically able to undergo the therapy and who have no major coexisting conditions. GVHD denotes graft-versus-host disease, PBSCs peripheral-blood stem cells, and PCR polymerase chain reaction.

NEW THERAPIES

New compounds in the treatment of AML target a variety of cellular processes such as signaling through tyrosine kinases or other pathways, epigenetic regulation of DNA and chromatin, nuclear export of proteins, and antigens that are expressed on hematopoietic cells or, more specifically, on leukemic stem cells by antibody-based therapy (Table 5).[68-72]

The frequent occurrence of mutations in receptor tyrosine kinase genes (*FLT3* and *KIT*) has generated interest in the development of tyrosine kinase inhibitors. Results with first-generation FLT3 inhibitors so far have been disappointing.[69] When used as single agents, these inhibitors lead to only transient reductions in blast counts. Other drawbacks include toxicity due to their nonselectivity for FLT3 and the development of *FLT3* resistance mutations. The results of a recent randomized trial of sorafenib that involved 267 younger adult patients irrespective of their *FLT3* mutational status suggested a beneficial effect of the kinase inhibitor on event-free survival but no significant effect on overall survival.[63] A trial evaluating the use of standard chemotherapy with or without midostaurin as front-line therapy in 717 patients with *FLT3* mutations is under way (NCT00651261). Initial data from studies of second-generation FLT3 inhibitors suggest higher potency, but phase 3 trials have only started.

The presence of frequent mutations in genes involved in DNA methylation and chromatin modification, as well as the identification of new epigenetic targets by global proteomic approaches and functional screens, have informed another exciting and rapidly expanding therapeutic area — the development of new epigenetic therapies.[70,71] One promising new targeted approach is the inhibition of the mutant metabolic enzymes IDH1 and IDH2, which are frequently mutated in AML.[73] AG-120 and AG-221 are oral inhibitors of IDH1 and IDH2, respectively. In phase 1 trials, they have shown encouraging activity by triggering terminal differentiation of leukemic blasts in AML with *IDH* mutations.[61]

Besides addressing mutant proteins directly, investigators have shown increasing interest in targeting mutation-specific dependencies. For example, by using a functional-genomics screen, Chan et al.[74] showed that survival of *IDH1*-mutated and *IDH2*-mutated cells was highly dependent on antiapoptotic B-cell CLL–lymphoma 2 protein (BCL2) expression. Consistent with this finding, *IDH1*-mutated and *IDH2*-mutated AML cells were more sensitive to the BCL2 inhibitor venetoclax (also called ABT-199 or GDC-0199); this provided the basis for combinatorial therapy. Another example is the identification of BRD4, a member of the bromodomain and extraterminal (BET) family of bromodomain epigenetic readers, as a potential therapeutic target in AML[70]; BET bromodomain inhibitors such as OTX015 are in clinical development.[62]

SGI-110, a second-generation hypomethylating agent, is a dinucleotide of decitabine and deoxyguanosine that increases the in vivo exposure of decitabine by protecting it from inactivation by cytidine deaminase.[60] A phase 3 trial of this compound in older patients who are not candidates for intensive therapy is under way.

Inhibition of chromosome region maintenance 1 (CRM1), the major nuclear export receptor, is another promising approach. High expression of CRM1 is associated with short survival in AML.[75] A pivotal study in which selinexor, a new CRM1 inhibitor,[64] is being compared with specified investigator choices in older patients with relapsed or refractory AML is ongoing (NCT02088541).

New formulations of classic cytotoxic agents are also being developed. Vosaroxin, a new anticancer quinolone derivative, inhibits topoisomerase II. A pivotal study evaluated intermediate-dose cytarabine with or without vosaroxin in 711 patients with relapsed or refractory AML. Although the primary end point was not reached in the trial, in a prespecified subgroup analysis, a significant survival benefit was seen among patients 60 years of age or older who received cytarabine with vosaroxin (7.1 months vs. 5.0 months).[66] CPX-351 is a liposomal formulation of cytarabine and daunorubicin packaged at a 5:1 molar ratio within liposomes that are 100 nm in diameter. Results from a phase 2 study[67] suggest a clinical benefit, especially among patients with secondary AML; a pivotal phase 3 trial is under way.

Finally, antibody therapy for AML is undergoing a renaissance.[72] Current activities focus on the development of new monoclonal antibodies targeting CD33, either with the use of antibody–drug conjugates or bispecific antibodies (anti-CD33 and CD3). Another strategy aims at targeting antigens such as CD123, the transmembrane

Table 5. Selected Newer Agents in Clinical Development for the Treatment of AML.*

Drug Class and Action	Agent	Trial-Registration Number†	Reference
Epigenetic modifiers			
Hypomethylating agents	Decitabine (Dacogen)‡		Kantarjian et al.[57]
	Azacitidine (Vidaza)§		Dombret et al.[58]
	Oral azacitidine (CC-486)¶	NCT01757535	
	Guadecitabine (SGI-110)¶	NCT02348489	Issa et al.[60]
IDH1 inhibitor	AG-120	NCT02074839	
IDH2 inhibitor	AG-221	NCT01915498	Stein et al.[61]
DOT1L inhibitor	EPZ-5676	NCT01684150	
Bromodomain inhibitors	OTX015	NCT01713582	Dombret et al.[62]
	GSK525762	NCT01943851	
LSD1 (also called KDM1A inhibitor)	GSK2879552	NCT02177812	
Histone deacetylase inhibitors	Vorinostat¶	NCT01802333	
	Panobinostat	NCT01242774	
	Pracinostat	NCT01912274	
	Valproic acid¶	NCT00151255	
Tyrosine kinase inhibitors			
FLT3 inhibitors			
First-generation	Midostaurin¶	NCT00651261; NCT01477606	
	Sunitinib	NCT00783653	
	Sorafenib¶	NCT00373373, NCT00893373	Röllig et al.[63]
Second-generation	Quizartinib¶	NCT02039726	
	Crenolanib¶	NCT01657682; NCT02298166	
	ASP2215	NCT02014558	
KIT inhibitors	Dasatinib¶	NCT02013648; NCT01238211	
	Midostaurin	NCT01830361	
Cell-cycle and signaling inhibitors			
MDM2 inhibitor	Idasanutlin (RG-7388)	NCT01773408	
PLK inhibitor	Volasertib¶	NCT01721876	
Aurora kinase inhibitors	Barasertib¶	NCT00952588	
	Alisertib	NCT01779843	
Cyclin-dependent kinase inhibitors	Alvocidib¶	NCT01413880	
	Palbociclib	NCT02310243	
Phosphatidylinositol 3-kinase inhibitor	Rigosertib	NCT01926587	
PIM kinase inhibitor	LGH447	NCT02078609	
Hedgehog-pathway inhibitors	Vismodegib	NCT01880437	
	PF-04449913	NCT01546038	
mTor inhibitors	Everolimus	NCT01154439	
	Temsirolimus	NCT01611116	
Nuclear export inhibitor			
XPO1 (also called CRM1) inhibitor	Selinexor¶ (KPT-330)	NCT02088541	Etchin et al.[64]

Table 5. (Continued.)

Drug Class and Action	Agent	Trial-Registration Number†	Reference
Antibody-based therapies			
Antibody–drug conjugates	Gemtuzumab ozogamicin (anti-CD33 and calicheamicin)‖	NCT00893399	
	SGN-CD33A (anti-CD33 and pyrrolobenzo-diazepine dimer)	NCT01902329	
Bispecific antibodies	AMG 330 (anti-CD33 and CD3; bispecific T-cell engager)	NCT02520427	
	MGD006 (anti-CD123 and CD3; dual-affinity retargeting molecule)	NCT02152956	
Stem-cell targeting	Anti-CD123 antibody (CSL362)	NCT01632852	
	SL-401 (diphtheria toxin interleukin-3 fusion protein against CD123)	NCT02270463	
CXCR4 targeting	BMS-936564	NCT02305563	
Immune checkpoint blockade	Ipilimumab	NCT01757639; NCT01822509	
Chimeric antigen receptor T cells	CART-123 (anti-CD123 chimeric antigen receptor T cells)	NCT02159495	
Cytotoxic agents			
Quinolone derivative	Vosaroxin¶	NCT01191801	Ravandi et al.[66]
New drug formulation	CPX-351¶	NCT01696084	Lancet et al.[67]
Nucleoside analogues	Sapacitabine¶	NCT01303796	
	Clofarabine¶	ISRCTN 11036523	
	Cladribine¶	NCT02044796; NCT02115295	
Other agents			
B-cell CLL–lymphoma 2 protein inhibitor	Venetoclax (ABT-199/GDC-0199)	NCT01994837	
Immunomodulatory drug	Lenalidomide¶	NTR4376	
Aminopeptidase inhibitor	Tosedostat	NCT00780598; NTR2477	
Retinoic acid	All-*trans* retinoic acid¶	NCT00151242; ISRCTN88373119	
CXCR4 antagonist	Plerixafor	NCT00906945	
E-selectin antagonist	GMI-1271	NCT02306291	
Homoharringtonine derivative	Omacetaxine¶	ChiCTR-TRC-06000054	

* CRM1 denotes chromosome region maintenance 1, CXCR4 chemokine (C-X-C motif) receptor 4, KDM1A lysine (K)-specific demethylase 1A, LSD1 lysine-specific demethylase 1, E3 ubiquitin protein ligase, mTOR mechanistic target of rapamycin, PI3K phosphatidylinositol 3-kinase, PIM1 oncogene PIM1, PLK polo-like kinase, and XPO1 exportin 1.

† Chinese Clinical Trial Registry numbers begin with ChiCTR-TRC, ClinicalTrials.gov numbers begin with NCT, Current Controlled Trial numbers begin with ISRCTN, and Netherlands Trial Register numbers begin with NTR.

‡ This agent is approved by the EMA, but not by the FDA, for patients 65 years of age or older who have newly diagnosed de novo or secondary AML and who are not candidates for standard induction chemotherapy.

§ This agent is approved by the FDA and EMA for patients who have newly diagnosed AML with 20 to 30% bone marrow blasts and multilineage dysplasia and who are not candidates for allogeneic hematopoietic-cell transplantation.

¶ This agent is under investigation in randomized, phase 2 or phase 3 clinical trials.

‖ In 2000, this drug was granted accelerated approval by the FDA for the use of this treatment as a single agent in patients older than 60 years of age who had AML in first relapse and who did not meet criteria for intensive treatment. In 2010, it was withdrawn from the U.S. market because of a negative postapproval study (Southwest Oncology Group trial S0106).[65]

alpha chain of the interleukin-3 receptor, that are preferentially expressed on leukemic stem cells. CD123 is currently also under investigation as a target for chimeric antigen receptor T-cell–engineered cellular therapy.[76] Another interesting target for chimeric antigen receptor T cells is the expression of folate receptor β.[77]

Exciting developments in our understanding of the molecular pathogenesis of AML have not yet been translated into clinical practice. New compounds hold promise to improve treatment outcomes; however, it is unlikely that any of these compounds, when used as single agents, will cure the disease. A major challenge will be to identify predictors for a response to specific agents, which will allow for the rational design of combinatorial therapies.

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