Diagnosis and management of AML in adults: ٢٠١٧ ELN recommendations from an international expert panel

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Abstract

The first edition of the European LeukemiaNet (ELN) recommendations for diagnosis and management of acute myeloid leukemia (AML) in adults, published in ٢٠١٠, has found broad acceptance by physicians and investigators caring for patients with AML. Recent advances, for example, in the discovery of the genomic landscape of the disease, in the development of assays for genetic testing and for detecting minimal residual disease (MRD), as well as in the development of novel antileukemic agents, prompted an international panel to provide updated evidence- and expert opinion-based recommendations. The recommendations include a revised version of the ELN genetic categories, a proposal for a response category based on MRD status, and criteria for progressive disease.

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Introduction

In ٢٠١٠, an international expert panel, on behalf of the European LeukemiaNet (ELN), published recommendations for diagnosis and management of acute myeloid leukemia (AML).[١] These recommendations have been widely adopted in general practice, within clinical trials, and by regulatory agencies. During recent years, considerable progress has been made in understanding disease pathogenesis, and in development of diagnostic assays and novel therapies.[٢] This article provides updated recommendations that parallel the current update to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia.[٣,٤] For diagnosis and management of acute promyelocytic leukemia, readers are referred to the respective recommendations.[٥]

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Methods

The panel included ٢٢ international members with recognized clinical and research expertise in AML. The panel met ٣ times. Literature searches, categorization of evidence, and arrival at consensus were done as previously.[1] Relevant abstracts presented at the ٢٠١٣ to ٢٠١٥ meetings of the American Society of Hematology, and the ٢٠١٣ to ٢٠١٦ meetings of the American Association for Cancer Research, the European Hematology Association, and the American Society of Clinical Oncology were reviewed.

WHO classification

The current update of the WHO classification provides few changes to the existing disease categories (Table ١). Most importantly, a new category "myeloid neoplasms with germ line predisposition" was added (Table ٢).[6]

Table ١.
Myeloid neoplasms with germ line predisposition, AML and related precursor neoplasms, and acute leukemias of ambiguous lineage (WHO ٢٠١٦)

Table ٢.
WHO classification of myeloid neoplasms with germ line predisposition and guide for molecular genetic diagnostics

AML with recurrent genetic abnormalities

The molecular basis of AML with inv(٣)(q٢١.٣q٢٦.٢) or t(٣;٣)(q٢١.٣;q٢٦.٢) was revisited showing that repositioning of a *GATA* ٢ enhancer element leads to overexpression of the *MECOM* (*EVI ١*) gene and to haploinsufficiency of GATA٢.[7,8] A new provisional entity "AML with *BCR-ABL ١*" was introduced to recognize that patients with this abnormality should receive therapy with a tyrosine kinase inhibitor. Distinction from blast phase of chronic myeloid leukemia may be difficult; preliminary data suggest that deletion of antigen receptor genes (immunoglobulin heavy chain and T-cell receptor), *IKZF ١*, and/or *CDKN ٢A* may support a

diagnosis of AML rather than chronic myeloid leukemia blast phase.[9] AML with mutated *NPM1* and AML with biallelic mutations of *CEBPA* have become full entities; the latter category was restricted to cases with biallelic mutations because recent studies have shown that only those cases define the entity and portend a favorable outcome.[10-16] Both entities now subsume cases with multilineage dysplasia because presence of dysplasia lacks prognostic significance.[17-19] Finally, a new provisional entity "AML with mutated *RUNX1*" (excluding cases with myelodysplasia-related changes) was added; it has been associated with distinct clinicopathologic features and inferior outcome.[20-24]

AML with myelodysplasia-related changes

Presence of multilineage dysplasia, preexisting myeloid disorder, and/or myelodysplasia-related cytogenetic changes remain diagnostic criteria for this disease category. Deletion 9q was removed from the list of myelodysplasia-related cytogenetic changes because, in addition to its association with t(8;21), it also frequently occurs in AML with *NPM1* and biallelic *CEBPA* mutations.[16,25]

AML, not otherwise specified

The former subgroup acute erythroid leukemia, erythroid/myeloid type (≥50% bone marrow erythroid precursors and ≥20% myeloblasts among nonerythroid cells) was removed; myeloblasts are now always counted as percentage of total marrow cells. The remaining subcategory AML, not otherwise specified (NOS), pure erythroid leukemia requires >80% immature erythroid precursors with ≥30% proerythroblasts. French-American-British (FAB) subclassification does not seem to provide prognostic information for "AML, NOS" cases if data on *NPM1* and *CEBPA* mutations are available.[26]

Myeloid neoplasms with germ line predisposition (synonyms: familial myeloid neoplasms; familial myelodysplastic syndromes/acute leukemias)

Inclusion of this new category reflects the increasing recognition that some cases of myeloid neoplasms, including myelodysplastic syndrome (MDS) and AML, arise in association with inherited or de novo germ line mutations (Table 2).[6,27-30] Recognition of familial cases requires that physicians take a thorough patient and family history, including information on malignancies and previous bleeding episodes. Awareness of these cases is of clinical relevance because patients may need special clinical care.[27] Affected patients, including their families, should be offered genetic counseling with a counselor familiar with these disorders.

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Molecular landscape

The advent of high-throughput sequencing techniques has allowed new insights into the molecular basis of myeloid neoplasms.[31-37] Similar to most sporadic human malignancies, AML

is a complex, dynamic disease, characterized by multiple somatically acquired driver mutations, coexisting competing clones, and disease evolution over time.

The Cancer Genome Atlas AML substudy profiled ٢٠٠ clinically annotated cases of de novo AML by whole-genome (n = ٥٠) or whole-exome (n = ١٥٠) sequencing, along with RNA and microRNA sequencing and DNA-methylation analysis.[٣١] Twenty-three genes were found to be commonly mutated, and another ٢٣٧ were mutated in ٢ or more cases, in nonrandom patterns of co-occurrence and mutual exclusivity. Mutated genes were classified into ١ of ٩ functional categories: transcription factor fusions, the *NPM١* gene, tumor suppressor genes, DNA methylation-related genes, signaling genes, chromatin-modifying genes, myeloid transcription factor genes, cohesin complex genes, and spliceosome complex genes.

The use of genetic data to inform disease classification and clinical practice is an active field of research. Recently, ١٥٤٠ patients, intensively treated in prospective trials, were analyzed using targeted resequencing of ١١١ myeloid cancer genes, along with cytogenetic profiles.[٣٧] Patterns of comutations segregated AML cases into ١١ nonoverlapping classes, each with a distinct clinical phenotype and outcome. Beyond known disease classes, ٣ additional, heterogeneous classes emerged: AML with mutations in chromatin and RNA-splicing regulators; AML with *TP٥٣* mutations and/or chromosomal aneuploidies; and, provisionally, AML with *IDH٢*^{R١٧٢} mutations.

Mutant allele fractions can be used to infer the phylogenetic tree leading to development of overt leukemia. Clonal evolution studies in patients and patient-derived xenograft models indicate that mutations in genes involved in regulation of DNA modification and of chromatin state, most commonly *DNMT٣A*, *TET٢*, and *ASXL١*, are often present in preleukemic stem or progenitor cells and occur early in leukemogenesis.[٣٨-٤١] Such mutations are present in ancestral cells capable of multilineage engraftment, may persist after therapy, lead to clonal expansion during remission, and cause recurrent disease.

Recent studies in large, population-based cohorts have identified recurrent mutations in epigenetic regulators (*DNMT٣A*, *ASXL١*, *TET٢*), and less frequently in splicing factor genes (*SF٣B١*, *SRSF٢*), to be associated with clonal hematopoietic expansion in elderly seemingly healthy subjects.[٤٢-٤٦] The term "clonal hematopoiesis of indeterminate potential"[٤٧] has been proposed to describe this phenomenon which seems associated with increased risks of hematologic neoplasms. Preliminary data indicate that the rate of progression of clonal hematopoiesis of indeterminate potential to hematologic disease may be similar to the rate of progression of other premalignant states, such as monoclonal gammopathy of undetermined significance to multiple myeloma.

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Diagnostic procedures

Morphology

At least ٢٠٠ leukocytes on blood smears and ٥٠٠ nucleated cells on spiculated marrow smears should be counted. A marrow or blood blast count of ≥٢٠% is required, except for AML with

t(١٥;١٧), t(٨;٢١), inv(١٦), or t(١٦;١٦). Myeloblasts, monoblasts, and megakaryoblasts are included in the blast count. In AML with monocytic or myelomonocytic differentiation, monoblasts and promonocytes, but not abnormal monocytes, are counted as blast equivalents.

Immunophenotyping

Table ٣ provides a list of markers helpful for establishing the diagnosis of AML,[٤٨] as well as specific lineage markers useful for defining mixed-phenotype acute leukemia.[٣,٤]

Table ٣.
Expression of cell-surface and cytoplasmic markers for the diagnosis of AML and MPAL

Cytogenetics and molecular cytogenetics

Conventional cytogenetic analysis remains mandatory in the evaluation of suspected AML. Eight balanced translocations and inversions, and their variants, are included in the WHO category "AML with recurrent genetic abnormalities".[٣,٤] Nine balanced rearrangements and multiple unbalanced abnormalities are sufficient to establish the WHO diagnosis of "AML with myelodysplasia-related changes" when ≥٢٠% blood or marrow blasts are present (Table ١).

Other rare balanced rearrangements are recognized.[٤٩,٥٠] Although considered disease-initiating events, they do not formally define disease categories. They involve genes, for example, encoding epigenetic regulators (eg, *KMT٢A* [*MLL*], *CREBBP*, *NSD١*) or components of the nuclear pore complex (*NUP٩٨*, *NUP٢١٤*) (Figure ١). Some rearrangements are cytogenetically cryptic, such as t(٥;١١)(q٣٥.٢;p١٥.٤); *NUP٩٨-NSD١*, which occurs in ∼١% of AML in younger adults and predicts a poor prognosis.[٥١-٥٣] Recent studies have highlighted the potential of novel sequencing technologies to discover additional AML-associated fusion genes.[٥٤-٥٦]

Figure ١.
Molecular classes of AML and concurrent gene mutations in adult patients up to the age of ∼٦٥ years. Class definition is based on the study by Papaemmanuil et al.[٣٧] For each AML class denoted in the pie chart, frequent co-occurring mutations are **...**

If cytogenetic analysis fails, fluorescence in situ hybridization is an option to detect gene rearrangements, such as *RUNX1-RUNX1T1*, *CBFB-MYH11*, *KMT2A* (*MLL*), and *MECOM* (*EVI1*) gene fusions, or loss of chromosome 5q, 7q, or 17p material.

Molecular genetic testing

Diagnostic workup should include screening for (a) mutations in *NPM1*, *CEBPA*, and *RUNX1* genes because they define disease categories (provisionally for *RUNX1*); (b) mutations in *FLT3* (both for internal tandem duplications [ITDs] together with data on the mutant–to–wild-type allelic ratio,[57-60] and tyrosine kinase domain mutations at codons D835 and I836); activating mutations of *FLT3* are not only prognostic, but may beneficially be affected by tyrosine kinase inhibition[61]; and (c) mutations in *TP53* and *ASXL1* because they consistently have been associated with poor prognosis (Table 4).[62-70]

Table 4.
Tests/procedures for a patient with AML

Molecular testing by reverse transcriptase–polymerase chain reaction (RT-PCR) for recurring rearrangements can be useful (Table 4).

Although only a few of the recently identified molecular markers inform current clinical practice, the list (from the previous paragraph) will likely be expanded with testing for single genes replaced by gene panel diagnostics, or diagnostic platforms that simultaneously test for gene mutations and gene rearrangements.[55,56]

If AML with germ line predisposition is suspected, molecular testing should be performed in a specialized laboratory using a dedicated gene panel that includes the currently known predisposing alleles (Table 2).[71]

Biobanking

If possible, pretreatment leukemic marrow and blood should be stored within a biobank. Informed consent preferably should allow a broad array of correlative laboratory studies including analysis of germ line DNA. Pretreatment samples should include nucleic acid (DNA and RNA, stored at $-80°C$) and viable cells (stored at $-196°C$). Optimally, a plasma sample, a methanol/acetic acid-fixed cell pellet (from cytogenetic analysis), and frozen cell pellets from various time points during and after treatment (eg, at time of complete remission [CR], relapse, and for minimal residual disease [MRD] monitoring at defined time points during remission) should be obtained and stored under appropriate conditions.

Buccal swabs and sputum have been previously recommended for the analysis of germ line DNA; samples should preferably be obtained during remission to reduce the risk of contaminating DNA from leukemic cells. Skin fibroblasts may be the preferred tissue source. A skin biopsy can be performed using a punch biopsy or by taking a small biopsy at the site of skin incision during bone marrow aspiration or biopsy. When obtained at diagnosis, skin cells should be grown from the biopsy to avoid contamination of the specimen with leukemic cells; alternatively, the biopsy can be taken during remission without growing of fibroblasts. Other sources include finger nails and hair follicles, although the amount of DNA that can be extracted may be limited. Finally, bone marrow fibroblasts can be grown from viably frozen mononuclear cells.[٧٢]

Other diagnostic tests

Tests and procedures for a patient with AML are described in Table ٤.

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Prognostic factors

Pretreatment factors

Recent studies have explored the relative contribution of genetic and clinical variables to prediction of event-free survival (EFS) and overall survival (OS).[٣٦,٣٧,٧٣,٧٤] Genomic lesions account for about two-thirds of explained variation, with the other third contributed by demographic, clinical, and treatment variables. However, models incorporating all of these factors and aimed at predicting whether a patient with a given set of covariates will have a longer remission or life expectancy than another patient with a different set of covariates are correct in only ٧٥% to ٨٠% of cases. This emphasizes the need not only to identify other pretreatment prognostic factors but also to focus on posttreatment events, in particular the presence of MRD (see "Factors after diagnosis").

Patient-related factors.

Increasing age is independently associated with poorer outcomes. Performance status, general health, and specific comorbidities modulate the effect of age on tolerance of chemotherapy (see also "Current therapy" and "Older patients not considered candidates for intensive chemotherapy"), whereas specific age-related AML-associated genetic abnormalities increase the likelihood of resistance, as do previous MDS, chronic myelomonocytic leukemia, myeloproliferative neoplasm (MPN), or prior exposure to cytotoxic therapy for other disorders. Hence, age should not be the sole determinant of treatment decisions.

AML-related genetic factors.

Genetic abnormalities are powerful prognostic factors.[٣٦,٣٧,٥٠,٧٣,٧٥,٧٦] Results from conventional cytogenetics and from *NPM ١*, *FLT ٣*, and *CEBPA* mutational screening are currently being used in routine practice following ٢٠١٠ ELN recommendations.[١]

Recent data have led to several changes in these recommendations (see "٢٠١٧ ELN genetic risk stratification" and [Table ٥]). *RUNX ١* mutations although occurring with unfavorable features, such as older age, antecedent myeloid disorder, and concurrent gene mutations (eg, *SRSF ٢*, *ASXL ١*), identify patients with poor prognosis.[٢٠-٢٣,٣٧,٧٠,٧٣] Likewise, *ASXL ١* mutations are more common in older patients and associated with inferior survival.[٣٦,٣٧,٦٢-٦٥,٦٩,٧٠] *TP ٥٣* mutations are associated with complex karyotype, monosomal karyotype, and specific chromosomal aneuploidies (eg, −٥/٥q−, −٧/٧q−), and predict for very poor outcome.[٣٧,٦٦-٧٠,٧٣] *TP ٥٣* mutation and complex karyotype provide independent prognostic information, with the combination of both having the worst outcome.[٣٧]

[Table ٥.]
٢٠١٧ ELN risk stratification by genetics

The prognostic impact of many markers is context-dependent with the effect of a given abnormality dependent on the presence/absence of another.[٣٧] Simple examples of such gene-gene interactions are that a *NPM ١* mutation conveys a "favorable" prognosis only in the absence of a *FLT ٣*-ITD (or *FLT ٣*-ITD with a low allelic ratio),[٥٧-٥٩,٧٧] whereas mutations in both *ASXL ١* and *RUNX ١* confer a particularly poor prognosis.[٣٧,٦٥] Furthermore, tightly correlated clusters of mutated genes, that is, mutations in RNA splicing (*SRSF ٢*, *SF ٣B ١*, *U ٢AF ١*, *ZRSR ٢*), chromatin (*ASXL ١*, *STAG ٢*, *BCOR*, *KMT ٢A*^PTD, *EZH ٢*), or transcription (*RUNX ١*) regulators are found in high-risk MDS, high-risk MPN as well as secondary AML, indicating gene signatures identify high-risk myeloid disorders that cross-conventional diagnostic boundaries.[٣٧,٧٨-٨٢]

In core-binding factor (CBF) AML, in particular in AML with t(٨;٢١), the presence of *KIT* mutations, especially if higher mutant *KIT* levels are present, appear to be associated with poorer prognosis.[٨٣-٨٧] Nevertheless, presence of a *KIT* mutation should not assign a patient to a different genetic risk category; rather, patients should be monitored for MRD, whose absence abrogates the effect of *KIT*.[٨٥] Although both types of CBF-AML are associated with mutations in signaling genes (*NRAS*, *KIT*, *NF ١*, *FLT ٣*, *KRAS*), recent comprehensive mutation profiling studies have revealed a different spectrum of cooperating mutations ([Figure ١]).[٨٧,٨٨] AML with *RUNX ١*-*RUNX ١T ١* is significantly enriched for mutations in chromatin-modifying genes (٤٢%-٤٤%), including *ASXL ٢*, and for mutations in cohesin complex genes (١٨%-٢٠%), whereas they are nearly absent in AML with *CBFB-MYH ١١*.[٨٧-٨٩]

Although a genetic marker may currently not be prognostic, its presence may provide a target for new therapies as with IDH١, IDH٢, and KMT٢A (MLL).[٢] Likewise, a recent study in primary human samples identified co-occurrence of biallelic *CEBPA* mutations and mutations in the granulocyte colony-stimulating factor receptor gene *CSF ٣R* (signaling through the JAK-STAT pathway) as uniformly responsive to JAK inhibitors.[٩٠]

Factors after diagnosis

Monitoring of MRD.

Two approaches can be used to detect MRD, that is, multiparameter flow cytometry (MFC) and molecular techniques, including real-time quantitative PCR (RT-qPCR), digital PCR, and next-generation sequencing–based technologies. Standardized RT-qPCR assays are now available to detect AML-associated genetic lesions (Table ٤). Each methodology differs in the proportion of patients to whom it can be applied and in its sensitivity to detect MRD.[٩١,٩٢] It is expected that integrated evaluation of baseline factors and assessment of MRD will improve risk assessment and inform postremission therapy.[٩١-٩٣]

MRD can be assessed (١) at early time points, for example, following induction and consolidation courses to assess remission status and determine kinetics of disease response, and (٢) sequentially beyond consolidation to detect impending morphologic relapse. Remission status as assessed by MFC (which is informative in $\sim٩٠\%$ of AML patients) provides a more reliable predictor of outcome than conventional morphology-based CR assessment.[٩٢-٩٩] MFC can be used to assess "CR without MRD" (CR_{MRD-}) (see "Response criteria and outcome measures" and Table ٦). The depth of response assessed by MFC has been consistently shown to provide independent prognostic information and thus may inform risk stratification. Currently, analyses should be performed in experienced laboratories, until MFC techniques have been further standardized.

Table ٦.
Response criteria in AML

In $\sim٦٠\%$ of younger adults, the leukemia cells are informative for a molecular marker that can be tracked by RNA-based RT-qPCR assays. Assay sensitivity depends upon the relative expression of the target in leukemic blasts compared with standard housekeeping genes (eg, *ABL ١*) and varies according to the target, as well as between patients with the same target.[٩١] Assays for *MLLT٣-KMT٢A* are typically associated with the lowest sensitivity (~١ in $١٠^{٣}$) due to relatively low-level fusion gene expression,[١٠٠] whereas assays for *NPM ١* mutations achieve sensitivities of up to ١ in $١٠^{٦-٧}$ due to the high-level mutant allele expression.[١٠١-١٠٦] Many studies have shown that kinetics of MRD response to frontline therapy differs by molecular marker analyzed.[٨٥,١٠١-١٠٩] For example, reduction in *RUNX ١-RUNX١T ١* is slower than in *NPM ١* transcript levels. Importantly, MRD status has been found to be a better predictor of relapse risk than presence of cooperating mutations involving *KIT* and *FLT٣*-ITD in CBF-AML,[٨٥] or *FLT٣*-ITD, *DNMT٣A*, and *WT ١* in *NPM ١*-mutated AML.[١٠٦] These data support inclusion of molecular MRD assessment into routine care to help inform transplant decisions in first remission.

Sequential MRD-monitoring studies have shown that persistent high-level PCR positivity, or a rising level of leukemic transcripts after an initial molecular response, invariably predict relapse.[91] Whether the opportunity thus provided for early intervention to prevent overt relapse will be useful is under investigation. Preemptive therapy may be particularly relevant with allogeneic hematopoietic cell transplantation (HCT) where MRD status may inform conditioning strategy, or post-HCT measures aiming to avoid frank relapse.

Molecular markers can now be identified in virtually all cases. This has opened the way to detection of MRD using next-generation sequencing or digital PCR.[91] Although currently investigational, studies have already shown that mutational assessment at early time points can distinguish patients at differing probability of relapse.[110,111] Studies are needed to define which mutations are reliable indicators of leukemic clones associated with clinical relapse from mutations that are associated with preleukemic clones (eg, *DNMT3A*, *IDH1/2*) poorly predictive of relapse, although persistent at high levels after chemotherapy and during remission.[106,112,113]

٢٠١٧ ELN genetic risk stratification

The original intention of the ELN genetic categories was to standardize reporting of genetic abnormalities particularly for correlations with clinical characteristics and outcome. The distinction between the intermediate I and intermediate II categories was based on genetic characteristics, rather than on prognostic stratification. Although a subsequent study demonstrated longer OS in the intermediate I group than the intermediate II group, the ٢ groups were prognostically indistinguishable in older patients, who constitute the majority of cases of AML.[114]

Given these findings, the panel decided to simplify the ELN system by using a ٣-group classification (favorable, intermediate, adverse) rather than the previous ٤-group system (Table ٥). A few other changes have been made. Recent studies have shown that in AML with *NPM1* or biallelic *CEBPA* mutations, the presence of coexisting chromosomal abnormalities does not appear to modify the prognostic effect of the mutations[16,25,115]; prognosis may be more influenced by concurrent gene mutations.[37] Accordingly, and as in CBF-AML, the categorization of these cases is now based on the primary leukemia-defining genetic subsets irrespective of the karyotype. The higher relapse rate and poorer OS associated with *FLT3*-ITD largely depends on the ITD allelic ratio. Most recent studies suggest that patients with *NPM1* mutation and *FLT3*-ITD with a low (<0.5) allelic ratio (*FLT3*-ITD^{low}) have a similar (favorable) outcome as patients with a *NPM1* mutation but no *FLT3*-ITD; thus, both groups are now considered favorable.[57-60] In contrast, AML with wild-type *NPM1* and *FLT3*-ITD with a high (≥ 0.5) allelic ratio (*FLT3*-ITD^{high}) has a poor prognosis and is placed in the adverse-risk group,[57] although the panel acknowledges that the natural course of AML with *FLT3* mutation may change by use of FLT3 inhibitors.

RUNX1, *ASXL1*, and *TP53* mutations (see "Pretreatment factors"), and monosomal karyotype[116-120] have also been added to the adverse-risk group in recognition of their independent association with adverse risk. Although numerous studies have dealt with mutations in other genes, for example, *DNMT3A*, *IDH1*, *IDH2*, or genes in the chromatin/spliceosome group other than

*ASXL*١ and *RUNX*١, the panel did not feel enough evidence has as yet accumulated to warrant their assignment to an ELN prognostic group.

Response criteria and outcome measures

The panel proposes a few new response categories. Although recognizing these are arbitrarily defined, they reflect recent data and aim at harmonizing definitions used in different trials (Tables ٦ and and٧٧).

Table ٧.

Outcome measures for clinical trials in AML

CR$_{MRD-}$

The category CR$_{MRD-}$ is proposed because relapse is more likely in patients in CR or CR with incomplete hematologic recovery (CRi) with detectable residual disease.[91,92] The best time to test for MRD in patients in CR by conventional criteria is not settled. Assessment of MRD after cycle ٢ or even cycle ١ of induction allows earlier identification of poor responders.[91,92,97,106] However, MRD can disappear after consolidation therapy. The frequency with which this occurs may differ in different molecular subsets and future assessment of these frequencies will likely inform therapeutic decisions.

Primary refractory AML

The panel proposes criteria for "primary refractory disease" (also commonly termed "induction failure") because the definition of refractory disease currently differs in clinical practice and clinical trials. Failure to attain CR following exposure to at least ٢ courses of intensive induction therapy defines patients to be "primary refractory." Although possibly influenced by selection bias, CR rates from a second course of ٧+٣ can be ٤٠% to ٤٥%, which is often higher than the rate targeted by newer therapies.[121] Regimens containing higher doses of cytarabine are generally considered as the best option for patients not responding to a first cycle of ٧+٣. The likelihood of CR with a second course of a higher dose cytarabine-based regimen after failure of a first of the ٢ cycles may be relatively lower than is the case with a second ٧+٣ after failure of a first.[122,123]

Progressive disease

This proposed new category primarily applies to patients given less intense or single-agent targeted therapies. A uniformly accepted definition of progressive disease (PD) should facilitate a standardized interpretation of new drug trials. Because criteria for PD are arbitrary, it is unknown whether PD augurs a poorer prognosis than stable disease and warrants investigation. In the interim, observation of PD does not necessarily imply a patient should be removed from a given therapy.

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MDS-AML overlap/secondary AML

Genetic basis

The related and partially overlapping clinical phenotypes of MDS and AML are reflected in the genetic bases of the 2 diseases.[31,37,78-80,124] A subset of mutations are highly specific for de novo AML, whereas another set of mutations is specific for secondary AML and are found commonly in MDS. Genetic analyses of a panel of genes mutated in myeloid malignancies, and perhaps the addition of gene expression and DNA-methylation profiling, have the potential to inform the distinction between MDS and AML, and to determine which cases of AML arose from an antecedent MDS.[37,80,81] The prognoses of patients with clinically diagnosed de novo AML whose gene mutation profile resembles those of patients with clinically diagnosed secondary AML is more like secondary than de novo AML.[81]

Mutations associated with secondary AML occur in genes encoding SRSF2, SF3B1, U2AF1, and ZRSR2 (splicing factors); ASXL1, EZH2, and BCOR (epigenetic regulators); and STAG2 (a member of the cohesin complex).[81] In such cases, these mutations likely occur during an MDS phase, remain in the clone that progresses to acute leukemia, and often persist in clonal remission following chemotherapy. Similarly, mutations in *ASXL 1*, *EZH 2*, and *SRSF 2* genes have been shown to identify patients with primary myelofibrosis who are at risk for leukemic transformation and who have particularly poor outcomes.[82,125] In contrast, *NPM 1* mutations, and CBF and *KMT 2A* rearrangements are highly specific for de novo AML.[81]

Genetic features in MDS that are associated with prognosis and progression to AML include mutations in *TP 53*, *RUNX 1*, *ETV 6*, *EZH 2*, and *ASXL 1*.[78-80,124,126] *TP 53* mutations are associated with a particularly poor survival, including following allogeneic HCT.[127]

Blast count

Given the biologic overlap between secondary AML and MDS any minimum blast percentage used to distinguish AML from MDS with higher blast counts (ie, MDS with excess blasts-2 [MDS-EB2]) must be arbitrary. Thus, this minimum has decreased from 30% in the FAB system to 20% in the WHO system with many AML clinical trial groups allowing entry of patients with >10% blasts. Bone marrow failure is the usual cause of death in both AML and MDS-EB2, and most of the latter die without "progression to AML," with data suggesting the natural history of MDS-EB2 is more similar to AML than to lower risk MDS.[128,129]

These observations suggest that it is best to determine eligibility for an "AML" or "MDS" study based on disease- and patient-specific factors rather than on a fixed blast percentage. Integration of data from molecular genetics into future classification systems will be useful to refine current diagnostic algorithms and support a more biologically precise disease classification.

Current therapy

The general approach to current therapy has not changed substantially in recent years. Initial assessment evaluates whether a patient is considered a candidate for intensive induction chemotherapy. Although assessment of risk of treatment-related mortality (TRM) after intensive therapy is usually most relevant in older patients (commonly above the age of ٦٥ years), age is merely one, and not the most important, predictor of TRM.[١٣٠-١٣٥] Furthermore, TRM rates are declining due to improved supportive care and to better health status in older patients.[١٣٦,١٣٧]

Therefore, age alone should not be the decisive determinant to guide therapy. Although few randomized trials have addressed the question and these trials have been small, there are suggestions that older, medically fit patients may benefit more from "intensive" than "nonintensive" induction therapy, subject to the constraints of selection bias.[١٣٧] Hence, although recognizing that firm criteria to consider older patients (or any patients) unfit for intensive induction therapy cannot be provided, the panel feels these should include only factors such as poor performance status and significant comorbidities and, in the case of conventional regimens such as ٧+٣, adverse ELN cytogenetics/molecular genetics ([Table ٥](#)) because in these instances the benefit may not outweigh the risk. Results from cytogenetics should be obtained preferably within ٥ to ٧ days. Results from *NPM١* and *FLT٣* mutational screening should be available within ٤٨ to ٧٢ hours (at least in patients eligible for intensive chemotherapy), and results from additional molecular genetics within the first treatment cycle. Abnormal renal or liver function should not be considered solely but in the context of other comorbidities and, although dose reduction may be called for, should not per se exclude patients from administration of intensive therapy. Several systems to quantify comorbidities and/or risk of TRM after intensive induction therapy have been proposed (see "Older patients not considered candidates for intensive chemotherapy").

Intensive induction therapy

With ٣ days of an anthracycline and ٧ days of cytarabine (commonly referred to as "٧+٣" regimens), CR is achieved in ٦٠% to ٨٠% of younger adults and in ٤٠% to ٦٠% of older adults (٦٠ years or above) ([Table ٨](#)).[١,٢,١٣٨]

[Table ٨.](#)
Selected conventional care regimens for patients with AML

Anthracycline dose level.

Randomized studies have indicated that daunorubicin at ٤٥ mg/m² daily ×٣ is associated with a lower CR rate and a higher relapse rate than ٩٠ mg/m² daily ×٣ when daunorubicin is used in a single induction cycle.[١٣٩-١٤١] This clear dose-effect relation seems much less prominent in patients >٦٥ years of age. However, another comparison found that ٩٠ mg/m² daunorubicin daily ×٣ in a first induction cycle was not superior to daunorubicin at ٦٠ mg/m² daily ×٣.[١٤٢] In this study, both groups received additional daunorubicin at ٥٠ mg/m² for ٣ days once in CR which added significant toxicities to the high-dose schedule and may have obscured or counteracted the benefit of the ٩٠ mg/m² during the first cycle. A recent exploratory analysis from this study suggests the potential for improved outcomes among patients with *FLT٣*-ITD with anthracycline intensification, although this finding requires further validation.[١٤٣] Current evidence suggests that the dose of daunorubicin should not be <٦٠ mg/m².

In patients ٥٠ to ٧٠ years of age, daunorubicin (٨٠ mg/m² for ٣ days) or idarubicin (١٢ mg/m² for ٤ days) were compared with the usual idarubicin schedule (١٢ mg/m² for ٣ days). Although the CR rate was slightly higher with ٤ days of idarubicin, there were no differences between the ٣ arms in rates of relapse, EFS, or OS.[١٤٤]

Cytarabine dose.

Recent studies[١٢٣,١٤٥] confirm earlier ones demonstrating increased toxicity without improvement in efficacy with higher dose cytarabine (٢٠٠٠-٣٠٠٠ mg/m²). A randomized trial found that fludarabine + high-dose cytarabine + granulocyte colony-stimulating factor (G-CSF; FLAG) + idarubicin (FLAG-IDA) not only produced a lower relapse rate than daunorubicin-cytarabine with or without etoposide, but was also associated with more deaths in remission resulting in similar OS.[١٢٣] Only ١ randomized study has shown prolonged OS (٥٢% vs ٤٣% at ٦ years) with cytarabine at ٣٠٠٠ mg/m² (every ١٢ hours, days ١, ٣, ٥, ٧) compared with ١٠٠ mg/m² (daily ×٧) in cycle I, but only in patients <٤٦ and not ٤٦ to ٦٠ years of age.[١٤٦] The bulk of evidence indicates that cytarabine at doses >١٠٠٠ mg/m² should not be included in induction regimens.[١٤٧] Furthermore, neither this study nor any others have shown that particular cytogenetic subsets benefit from such high cytarabine doses (see also "Conventional postremission therapy").

Role of other drugs.

FLT٣ inhibitors.

The RATIFY trial evaluated intensive induction and consolidation chemotherapy plus midostaurin or placebo followed by a 1-year midostaurin/placebo maintenance phase in 717 patients aged 18 to 60 years with *FLT3*-mutated AML.[11] Use of midostaurin increased the CR rate when all CRs reported within 30 days of ending protocol therapy were considered (68% vs 59%; $P = .04$). The trial met its primary end point in improving OS (hazard ratio 0.78; $P = .009$), regardless of whether patients received allogeneic HCT. Thus, patients with *FLT3*-mutated AML may be considered to receive intensive chemotherapy in combination with midostaurin.

Gemtuzumab ozogamicin.

The role of gemtuzumab ozogamicin (GO), an antibody-toxin (calicheamicin) conjugate that targets $CD33^+$ AML, is complicated. Two randomized studies using a single GO dose during chemotherapy in patients primarily age <60 years failed to show a survival advantage,[148,149] although the first used a suboptimal daunorubicin dose (45 mg/m^2) in the GO arm vs 60 mg/m^2 in the control arm.[148] Both studies suggested the addition of GO was associated with longer relapse-free survival (RFS) in the favorable-risk subset of CBF-AML. The second study[149] extended this finding to survival in some patients with intermediate-risk cytogenetics. Two studies in older patients (median age, 61 and 67 years), 1 using a single 3 mg/m^2 GO dose and the other using 3 mg/m^2 GO on days 1, 4, and 7 of induction found survival benefit with GO, largely attributable to fewer relapses in patients with favorable- or intermediate-risk cytogenetics.[150,151] An individual patient data meta-analysis of these 4 studies and a fifth published in abstract form reinforced these conclusions.[152] In contrast, 1 large study in patients age 61 to 75 years found shorter survival ($P = .071$) in the GO arm largely reflecting higher early mortality in patients age 70 to 75 years.[153] The dose and schedule of GO may be critical for the benefit-toxicity ratio. GO is currently only available in clinical trials and through a compassionate use program sponsored by the US Food and Drug Administration (FDA).

CPX-351.

CPX-351 is an encapsulation in nanoscale liposomes of cytarabine and daunorubicin at a synergistic 5:1 molar ratio.[154-157] Phase 2 studies suggested a beneficial effect of the agent in first-line treatment of secondary and therapy-related AML,[155] and in the poor-risk stratum (by the European Prognostic Index [EPI])[158] of relapsed AML.[156] A subsequent phase 3 trial randomized 309 patients age 60 to 75 years with high-risk AML, defined as AML with myelodysplasia-related changes or therapy-related AML, to CPX-351 or "7+3".[157] CPX-351 produced a higher response rate (CR/CRi, 47.7% vs 33.3%; $P = .016$), and longer OS (hazard ratio, 0.69; $P = .005$ with medians of 9.6 vs 6 months and 2-year survival rates of 31% and 12%). Results were similar after accounting for allogeneic HCT. Thus, CPX-351 may improve therapy of older patients with high-risk features.

Purine analogs.

In 1 study, cladribine (at 5 mg/m^2 days 1-5) added to "7+3" in adults up to age 60 years produced a higher CR rate and better OS than 7+3, particularly in patients age 50 to 60 years and in those with adverse-risk cytogenetics.[159] However, the relatively low CR rate (56%) and median OS (14 months) in the control arm have raised questions, and we await independent confirmation. In the intensive arm of their AML16 trial in older patients (median age, 67 years),

the National Cancer Research Institute (NCRI) Cooperative Group randomized ٨٠٦ patients between daunorubicin (٥٠ mg/m^٢ days ١-٣) and either cytarabine (١٠٠ mg/m^٢ days ١-١٠) or clofarabine (٢٠ mg/m^٢ days ١-٥). Rates of CR (٦٦%-٧١%), relapse (٦٨%-٧٤% at ٣ years) and OS (٢٢%-٢٣% at ٣ years) were essentially identical.[160]

Intensive postremission therapy

Conventional postremission therapy.

Postremission strategies comprise intensive chemotherapy and high-dose therapy followed by autologous or allogeneic HCT (Table ٨). Assessment of residual disease by RT-qPCR or MFC is critical in monitoring patients in morphological remission to inform further therapy (see "Factors after diagnosis").

Conventional intensive consolidation.

Consolidation regimens include single-agent cytarabine at high doses and multiagent chemotherapy which lead to similar outcomes. Administration of up to ٤ cycles of high-dose cytarabine (٢٠٠٠-٣٠٠٠ mg/m^٢, commonly ٦ doses per cycle) has been widely used. Recent trials have questioned the need for such high doses. One study randomized ٩٣٣ patients, ١٥ to ٦٠ years of age, between consolidation with mitoxantrone and cytarabine at ٣٠٠٠ mg/m^٢ (every ١٢ hours for ٦ days) vs a similar chemotherapy program, but with intermediate-dose cytarabine (IDAC) at ١٠٠٠ mg/m^٢ for consolidation with no differences in outcome.[161] Similarly, in a study with multiple randomizations in induction, the postremission comparison between cytarabine ٣٠٠٠ mg/m^٢ and ١٥٠٠ mg/m^٢ (n = ٦٥٧) showed no difference in survival.[123] A third study in ٧٨١ complete responders (١٥-٦٤ years of age) failed to show a benefit for ٣ cycles of cytarabine at ٢٠٠٠ mg/m^٢ (every ١٢ hours for ٥ days) compared with ٤ cycles of a multiagent chemotherapy consolidation that contained ٢٠٠ mg/m^٢ cytarabine by ٢٤-hour continuous infusion for ٥ days.[162] None of these studies have identified a benefit of the high-dose cytarabine regimens in cytogenetically favorable-risk AML. In a smaller study in patients ١٥ to ٥٠ years of age, no difference in survival was noted between ٤ cycles of cytarabine at ٣٠٠٠ mg/m^٢ and a combination of multiple cytotoxic agents.[163]

Altogether, there is no convincing evidence that cytarabine regimens at ٣٠٠٠ mg/m^٢ are more effective than regimens at intermediate-dose levels at ١٠٠٠ to ١٥٠٠ mg/m^٢, with or without the addition of an anthracycline.[147] Open questions remain regarding the optimal number of cycles of consolidation therapy. In most studies, ٢ to ٤ cycles have been given after attainment of CR. In ١ randomized study, ٢ cycles of postremission treatment following ٢ induction cycles was not inferior to ٣ postremission cycles.[123] Intensified postremission chemotherapy in high-risk patients, especially older patients is without clear benefit.[164]

Intensive chemotherapy followed by autologous HCT.

One cycle of intensive chemotherapy followed by autologous HCT using peripheral blood CD٣٤$^+$ cells offers condensed treatment. In ١ randomized study, autologous HCT provided better RFS and similar OS as conventional consolidation chemotherapy.[165] Recent data addressing the value of autologous HCT come from retrospective analyses accounting for the "lead time bias"

consequent to the need for transplanted patients to live a minimum amount of time in order to receive a transplant. In these studies, autologous HCT leads to better EFS and RFS than chemotherapy.[١٦,١٦٦,١٦٧] This effect is mainly apparent in favorable- and intermediate-risk disease (mainly by ٢٠١٠ ELN criteria) where outcome after autologous HCT approaches results after allogeneic HCT if OS is the end point. Limiting autologous HCT to patients who are MRD⁻ might improve results.

Maintenance therapy.

At the present time, maintenance chemotherapy is not part of standard AML treatment given a lack of convincing evidence of benefit.[١٦٨,١٦٩]

Allogeneic HCT.

AML is the most frequent indication for allogeneic HCT with a ١٠% annual increase in transplants performed worldwide.[١٧٠-١٧٢] Expanded use of mismatched and unrelated donors as well as cord blood means a donor can be found for most patients. Furthermore, nonmyeloablative or reduced-intensity conditioning (RIC) regimens allow allogeneic HCT in patients aged up to ٧٥ years. Nonetheless, in reality, only a minority of AML patients undergo transplantation because of older age, comorbidities, toxicity of prior therapy, inability to achieve a remission, and early relapse or refractory leukemia.[١٧٣]

Indications.

The decision to perform allogeneic HCT depends on the assessment of the risk-benefit ratio (ie, nonrelapse mortality [NRM]/morbidity vs reduction of relapse risk) based on cytogenetic and molecular genetic features as well as patient, donor, and transplant factors.[١٧٤-١٧٧] AML with favorable-risk genetics are not a priori assigned to allogeneic HCT in first CR.[٥٧-٥٩,٧٧,١٧٤,١٧٧] Allogeneic HCT is generally recommended when the relapse incidence without the procedure is expected to be >٣٥% to ٤٠%. The higher the expected relapse risk, the more risk of NRM may be accepted. Especially in the adverse genetic group, it is generally assumed, although not unambiguously demonstrated, that the transplant should be performed as soon as CR has been achieved. Allogeneic HCT is the only curative option for patients with primary refractory disease.

Sequential MRD monitoring by RT-qPCR or MFC provides a reliable guide to management. Patients with persistent MRD or with early MRD reoccurrence can receive salvage therapy and proceed to transplant before hematologic relapse, or may proceed directly to transplant depending on the likelihood of success with salvage therapy. Although allogeneic HCT often produces superior outcomes to chemotherapy it does not abrogate the negative effect of unfavorable genetics or pretransplant MRD.[٩٩,١١٩] Patients without MRD or adverse genetics but with high risk of NRM could receive chemotherapy only or autologous transplantation in CR١.[١٦٧,١٧٨]

Myeloablative conditioning vs RIC.

RIC potentially extends the curative graft-versus-leukemia effect to patients of older age or to young patients with significant comorbidities.[١٧٩-١٨٢] Conditioning intensity varies. For instance, busulfan/fludarabine is more dose-intense than fludarabine/low-dose total-body irradiation.[١٨٣] Currently, >٣٠% of allogeneic transplants are performed using RIC and have yielded encouraging results.[١٨٤] Although RIC and ablative conditioning have produced similar survival in patients aged ٤٠ to ٦٠ years in first CR,[١٦٧] a trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN ٠٩٠١) randomizing ٢١٨ patients (+٥٤ with MDS) aged ١٨ to ٦٥ years and with HCT comorbidity index (HCT-CI) scores associated with <٢٠% to ٣٠% NRM between RIC (typically fludarabine/busulfan) and more ablative (typically busulfan/cyclophosphamide) regimens suggests an advantage for more ablative regimens.[١٨٥] This emphasizes the importance of randomized trials in transplantion with broad eligibility criteria to avoid selection bias. Currently, myeloablative regimens are generally recommended for healthy younger patients and RIC in elderly patients or in younger patients with severe comorbidities. Outcomes after myeloablative conditioning using busulfan/cyclophosphamide appear to be equivalent, if not superior, to outcomes after cyclophosphamide/total-body irradiation.[١٨٦-١٨٨]

Comorbidities and risk scores.

Several transplant-related models have been developed to optimize decision-making about suitable candidates for allogeneic HCT.[١٨٩] The HCT-CI is a validated tool that sums a patient's comorbidities into a single score that predicts the likelihood of NRM given a myeloablative or RIC regimen.[١٩٠] A Disease Risk Index based on disease stage and cytogenetics has been developed that predicts the likelihood of disease recurrence following myeloablative or RIC regimens, independent of age, conditioning intensity, graft source, and donor type.[١٩١] The modified European Society for Blood and Marrow Transplantation (EBMT) risk score was designed to predict OS rather than just NRM or relapse, and includes age, disease stage, donor source, gender mismatch, and time from diagnosis.[١٩٢] Recent reports suggest that a combination of the HCT-CI and the EBMT score may provide improved prediction of NRM and OS.[١٩٣,١٩٤]

New modalities.

Partial or complete T-cell depletion and posttransplant cyclophosphamide may reduce the risks of acute and chronic graft-versus-host disease (GVHD).[١٩٥-١٩٨] The biggest challenge remains prevention of posttransplant relapse.[١٩٩] Preparative regimens including novel agents or radiolabeled monoclonal antibodies,[٢٠٠] or therapy during the early posttransplant period with tyrosine kinase inhibitors or hypomethylating agents (HMAs) are being tested.[٢٠١-٢٠٣] Furthermore, cell-based therapies are being developed to enhance the graft-versus-leukemia effect, such as natural killer cell enrichment or adoptive transfer, and the use of genetically engineered antigen-specific T cells that target AML-specific antigens.[٢٠٤-٢٠٩]

Older patients not considered candidates for intensive chemotherapy

Some AML patients will not tolerate intensive chemotherapy. Several risk scoring systems are available that use patient-specific and disease-specific factors to make the choice of intensive or alternative treatment.[٧٤,١٣٢,١٣٣,٢١٠] The relevance of systems[١٩٣,١٩٤] originally designed to forecast NRM after allogeneic HCT is under investigation.[٢١١]

Treatment alternatives for unfit patients are limited to best supportive care, low-intensity treatment, or clinical trials with investigational drugs. Low-intensity options are either low-dose cytarabine (LDAC) or therapy with HMA (Table ٨). LDAC is generally well-tolerated and produces CR rates in the order of ١٥% to ٢٥%; however, OS (median, ٥-٦ months) is unsatisfactory.[٢١٢]

Therapy with HMA has been evaluated in randomized trials. An increase in median OS with decitabine vs mostly LDAC (٧.٧ vs ٥.٠ months) was observed.[٢١٣] The AZA-AML-٠٠١ trial compared azacitidine with ٣ conventional care regimens in patients aged ≥٦٥ years with >٣٠% blasts: LDAC (١٥٨ patients), ٧+٣ (٤٤ patients), or best supportive care only (٤٥ patients)[٢١٤]; azacitidine increased the median survival (١٠.٤ vs ٦.٥ months). Azacitidine may be particularly advantageous in AML with adverse cytogenetics.[٢١٥] Superiority of azacitidine over conventional care regimens was previously shown in AML with ٢٠% to ٣٠% blasts.[٢١٦] Up to ٦ courses may be needed to observe maximal response with azacitidine or decitabine, although patients without response after ٣ courses are unlikely to respond with further therapy.[٢١٧] HMA seem to alter the natural course of AML in some patients who do not achieve CR. Thus, hematologic improvement can also yield clinical benefit, that is, a reduction in transfusions and improved quality of life (QoL).

Treatment of unfit and most older patients with AML is currently unsatisfactory. We strongly recommend enrolling these patients in clinical trials.

Go to:

Relapsed disease and primary refractory disease

Treatment of patients with relapsed or primary refractory disease requires a balanced assessment of the likely benefit of further therapy vs the potential complications associated with salvage chemotherapy.[٢١٨]

Prognostic markers

Factors influencing survival were incorporated in the EPI score applicable to adults between ١٥ and ٦٠ years of age.[١٥٨] Poor outcome is associated with shorter CR١ duration, increasing age at the time of relapse, nonfavorable karyotype at initial diagnosis, or history of prior allogeneic HCT.

Salvage treatment

No specific salvage regimen has emerged as the standard for treating primary refractory or relapsed AML.[١٢٣,٢١٩-٢٢٦] Enrollment in a clinical trial should therefore be the priority for such patients whenever possible. Table ٨ provides recommendations for salvage regimens in patients considered fit for intensive therapy.

In younger adults (١٦-٤٩ years), a second CR can be achieved with intensive salvage therapy in about ٥٥% in the absence of prior allogeneic HCT.[٢٢٧] Two-thirds are able to proceed to

allogeneic HCT in CR٢, resulting in a ٤٠% ٥-year OS. Response rates are lower (∼٢٠%-٣٠%) in more unselected adult patients with relapsed/refractory disease.[٢٢٧] Benefit may also be derived from allogeneic HCT in the presence of active disease, with CR٢ achieved in ٤٢% and long-term survival observed in ٩% to ٢٢%.[٢٢٨-٢٣١]

Another approach for patients with refractory or active disease is to use a short course of chemotherapy such as fludarabine, cytarabine, and amsacrine immediately prior to RIC and allogeneic HCT. With this approach, CR rates after allogeneic HCT of ٧٠% to ٩٠% are achieved, with expected ٤-year survival ranging between ٣٢% and ٤٥%.[٢٣١,٢٣٢] The possible constraint of selection bias should again be noted; nonetheless, at least ٢٠% of patients with primary refractory disease can still be cured with allogeneic HCT.[٢٣٣]

Outcome for patients relapsing after allogeneic HCT during first or second CR is particularly poor.[٢٣٤,٢٣٥] The Center for International Blood and Marrow Transplant Research (CIBMTR) recently found[٢٣٤] ٣-year OS was ٤%, ١٢%, ٢٦%, and ٣٨% for relapses within ١ to ٦ months, ٦ months to ٢ years, ٢ to ٣ years, and ≥٣ years after allogeneic HCT, respectively. Lower mortality was independently associated with longer time from HCT to relapse and a first HCT using RIC; and inferior outcome associated with age >٤٠ years, active GVHD, adverse cytogenetics, mismatched unrelated donor, and use of cord blood for first HCT.[٢٣٤] Outcomes may be better if patients receive chemotherapy to reduce disease burden followed by donor lymphocyte infusion, rather than chemotherapy alone.[٢٣٦,٢٣٧] Use of HMA has modest efficacy in AML relapsing post-HCT, producing CR rates of ∼١٥%[٢٣٨]; responses may be higher when combining donor lymphocyte infusion and azacitidine.[٢٣٩] Responses have been observed in relapses after HCT, including extramedullary manifestations, using CTLA-٤ blockade with ipilimumab.[٢٤٠] The value of using a different donor for the second transplant remains unproven.[٢٣٥]

In patients not fit for intensive salvage chemotherapy, effective treatment options are lacking. Azacitidine and decitabine induce CR rates of ١٦% to ٢١% and median survival times of ٦ to ٩ months in older patients with relapsed/refractory AML[٢٢٣-٢٢٥]; median postrelapse survival after therapy with LDAC is ٥ to ٦ months.[٢٢٦] For patients in second or third relapse, various therapeutic options are associated with CR rates of ∼٢٠% and median OS outcomes of ∼٣ months,[٢٢١] stressing the need for enrollment into clinical trials.

Go to:

Therapy-related AML

Biology of t-AML

Therapy-related myeloid neoplasms (t-MNs) are a distinct category within the WHO classification including cases of t-MDS and t-AML. t-AML is a well recognized clinical syndrome occurring as a late complication following cytotoxic therapy for a primary neoplasm or a nonneoplastic disorder.[٢٤١,٢٤٢] Currently comprising ∼٧% of all newly diagnosed AML, the incidence of t-AML is rising due to increasing numbers of cancer survivors at risk and changes in treatment.[١٢٥,٢٤٣,٢٤٤]

These neoplasms have been thought to be the direct consequence of mutational events induced by cytotoxic therapy. Association between type of prior exposure and phenotype of t-AML support a direct role of prior cytotoxic therapy. The more common subtype, seen in ~75% of patients, typically occurs 5 to 7 years after first exposure to alkylating agents or radiation, is often preceded by MDS, and is frequently accompanied by chromosomes 5 and/or 7 abnormalities, complex karyotype, and *TP53* mutation. In general, t-AML is associated with more adverse genetic lesions.[245-248] In a study analyzing mutation hotspots of 53 genes in 70 t-MNs (28 t-MDS, 42 t-AML), *TP53* was the most commonly mutated gene in t-MDS (35.7%) and t-AML (33.3%).[248] Some individuals develop t-AML after treatment with topoisomerase II inhibitors; their latency period is often only 1 to 3 years, antecedent MDS is rare, and balanced rearrangements involving *KMT2A* (*MLL*) at 11q23, *RUNX1* at 21q22, or *PML/RARA* are common. The distinction between these 2 subtypes has become less evident due to the use of multiagent chemotherapy, often in combination with radiotherapy.

An alternative mechanism is suggested by cases with a preexisting myeloid clone that is resistant to chemotherapy.[249] Cases of t-AML were identified in which the exact *TP53* mutation found at diagnosis was already present at low frequency in blood or bone marrow many years before t-AML development.[249] Similarly, somatic mutations in *PPM1D*, a serine/threonine phosphatase that negatively regulates p53,[250] have been found in blood of patients with breast, ovarian, and lung cancer.[251-254] In ovarian cancer, the frequency of *PPM1D* mutations in blood was significantly associated with prior chemotherapy, and the variant allele frequency increased during chemotherapy.[251] These data suggest a model in which hematopoietic progenitor cells carrying mutations in the TP53 pathway undergo selective pressure by cytotoxic therapy, ultimately leading to t-AML.

Some cases of t-MNs have been shown to be associated with germ line mutations in cancer susceptibility genes.[255,256] In a recent study of survivors of breast cancer developing t-AML, many patients had personal or family histories suggestive of inherited cancer susceptibility; 10 of 41 patients studied (21%) carried germ line mutations in *BRCA1*, *BRCA2*, *TP53*, or *CHEK2* genes.[256] The identification of such preexisting conditions will facilitate screening and counseling of patients prior to treatment of their primary disease.

Treatment of t-AML

The survival of patients with t-MNs has remained poor mainly due to sequelae of prior therapy, and to adverse disease-related features.[257-261] Therapy may be compromised by a higher treatment-related morbidity and mortality.[259] There is still little prospective treatment data because these patients have often been excluded from frontline clinical trials. Clinical trials should allow enrollment of patients with t-MN. Allogeneic HCT should be considered, due to the poor results with conventional chemotherapy.

Go to:

Clinical trials

Necessity for biobanking

We strongly recommend storage of biosamples (see "Biobanking") be done in all clinical trials. Such biobanking can be performed as part of an interventional trial, or within a noninterventional biobanking or registry study.

Trial design

Trials of new therapies have traditionally been disease-specific, proceeding through phase ١ (determination of maximum tolerated dose [MTD]), phase ٢ (determination of efficacy), and phase ٣ (randomized comparison of new and standard therapies). Recent challenges to this paradigm have arisen.

Early drug development.

"Basket trials."

Basket trials test therapies that target a specific genetic mutation or a deregulated pathway found in a tumor regardless of its origin. Enrollment might include patients with AML and other tumor types provided their cells contain the aberration.[٢٦٢,٢٦٣]

MTD vs "optimal biologic dose."

When a drug's ability to modulate its target appears fundamental to its clinical activity, phase ١ studies might seek to identify the optimal biologic dose (OBD) rather than the MTD. Randomization between OBD and MTD might be considered in phase ٢ to shed light on which approach is preferable.[٢٦٢]

Combined phase ١-٢ designs.

To accelerate drug development, many phase ١ protocols now include an expansion phase which focuses on efficacy.[٢٦٤] On the assumption of a relation between efficacy and toxicity, multiple outcome designs simultaneously base dose finding on toxicity and efficacy, with a dose declared admissible for further study if associated with relatively low probabilities of toxicity and high probabilities of efficacy.[٢٦٥]

"Pick-a-winner designs" to accelerate drug development.

The conventional distinction between the single-arm phase ٢ trial and the larger (randomized) phase ٣ study has been questioned. The frequent failure of therapies found "promising" in single-arm phase ٢ trials to translate into truly successful treatments because of various biases in phase ٢ is well known.[٢٦٦] Because these biases can only be addressed by randomization, there has been increasing interest in randomized phase ٢ designs, also known as "selection" or "pick-a-winner" designs.[٢٦٧,٢٦٨] Here, randomization between a standard and a new treatment begins sooner than currently. A first stage enrolls a relatively small number of patients, thus allowing more agents to be investigated in a given time. Treatments that meet a particular efficacy criterion are carried forward against the standard into a larger second stage, analogous to standard phase ٣ studies, whereas treatments not meeting these criteria drop out. One limitation of the design is that small

sample sizes may preclude the identification of patients with biologically defined subsets of the disease that may benefit from a particular new agent.

Adaptive designs.

Adaptive designs use incoming information from the early stages of a trial to affect conduct of later stages.[٢٦٩,٢٧٠] Although designs such as the ٣+٣ and the Simon ٢-stage are technically "adaptive," newer designs make more frequent use of incoming information. An example is "adaptive randomization" in which patients are initially randomized ١:١ after which randomization probabilities change at various intervals, to reflect incoming results.[٢٦٩] An advantage is that fewer patients may receive an ultimately unsatisfactory therapy, whereas a disadvantage is a loss of power. Another example is the continuous reassessment method, which in phase ١ trials permits more account to be made of covariates other than dose than does the standard ٣+٣ design.[٢٧١]

End points

OS and EFS.

Table ٧ lists outcome measures, and Table ٩ recommended reporting criteria for phase ٣ clinical trials. OS is the end point most commonly used for approval of new therapies. However, OS may be an imperfect indicator of a new drug's efficacy because advances in rescue therapies and supportive care have made it possible to keep patients alive after AML has relapsed or failed to enter CR.[٢٦٢,٢٧٢] In contrast, EFS includes relapse and failure to enter CR as well as death and thus may better reflect a single treatment's efficacy.[٢٧٢-٢٧٥] Furthermore, less time is required to assess EFS, and use of EFS facilitates crossover designs, that is, patients are randomly assigned to a sequence of treatments.

Table ٩.
Recommended minimum reporting criteria for phase ٣ clinical trials

Incorporation of MRD.

The utility of CR as a surrogate for OS has been questioned.[٢٧٦,٢٧٧] Likewise, if CRs are short-lived, a higher CR rate may not result in meaningful improvements in EFS. Considerable evidence indicates that patients in CR by conventional criteria who have MRD as assessed by RT-qPCR or MFC are at higher risk of relapse and death than patients without MRD (see "Monitoring of minimal residual disease"). This suggests the potential utility of CR_{MRD-} as a

rapidly assessable end point that may serve as a surrogate for EFS or long-term survival provided these relationships can be confirmed and means to measure MRD can be harmonized.[٩١,٩٢]

QoL.

Regulatory drug approval agencies accept improvement in QoL as well as in quantity of life as a criterion for new drug approval. Although QoL has received little attention, clinical observation suggests that patients who achieve CR may have improved QoL, for example, due to receipt of fewer transfusions and spending less time in medical facilities than patients who do not achieve CR, even if survival is not improved; the same may apply with CRi.[٢٧٨]

Novel therapies

AML is an important field for new drug investigation.[٢,٢٦٢,٢٧٩] Novel therapies are usually first evaluated in patients with relapsed/refractory disease or in older patients not considered candidates for standard intensive chemotherapy. Novel therapies in preclinical or clinical development may be categorized as protein kinase inhibitors, epigenetic modulators, new cytotoxic agents, mitochondrial inhibitors including apoptosis therapies, therapies targeting specific oncogenic proteins, therapeutic and immune checkpoint antibodies and cellular immunotherapies, and therapies targeting the AML microenvironment (Table ١٠).

Table ١٠.

Table ١٠.
Novel therapies in clinical development in AML

Efforts to develop protein kinase inhibitors, inhibiting mutated forms of the FLT٣ receptor have led to successive generations of FLT٣ inhibitors.[٢٨٠] The first generation comprised tandutinib, sunitinib, lestaurtinib, sorafenib, and midostaurin, and the next generation quizartinib, crenolanib, and gilteritinib. These compounds differ not only in their ability to inhibit FLT٣-ITD or tyrosine kinase domain or even the wild-type receptor, but also in their selectivity for FLT٣ as well as their toxicity profiles. As discussed in "Intensive induction therapy," the phase ٣ trial evaluating midostaurin in younger adult patients with *FLT٣* mutations reached its primary end point, improvement of OS.[٦١] Randomized trials evaluating intensive chemotherapy with other FLT٣ inhibitors, such as lestaurtinib and sorafenib, failed to show an improvement in response rate and in OS.[٢٨١-٢٨٤] The trial with sorafenib in younger patients (not restricted to AML with *FLT٣* mutations) showed an improvement in EFS, mainly reflecting results in patients without

FLT٣-ITD, that did not translate into a significant OS benefit.[٢٨٤] Randomized trials evaluating next-generation FLT٣ inhibitors are ongoing.

Another rapidly expanding area is development of novel epigenetic therapies.[٢٨٥,٢٨٦] Guadecitabine (SGI-١١٠) is a second-generation HMA currently in phase ٣ development.[٢٨٧] Guadecitabine is a dinucleotide of decitabine and deoxyguanosine that increases the in vivo exposure of decitabine by protecting it from inactivation by cytidine deaminase. One novel targeted approach is the inhibition of the metabolic enzymes IDH١ and IDH٢ that are frequently mutated in AML.[٢٨٨] Early trial results with these inhibitors show durable responses and appear promising.[٢٨٩,٢٩٠] Other examples are targeting of BRD٤, a member of the BET family of bromodomain epigenetic readers,[٢٩١] or of *KMT٢A* (*MLL*)–rearranged leukemias.[٢٩٢,٢٩٣]

In a randomized trial conducted in patients with relapsed and refractory AML, the topoisomerase II inhibitor vosaroxin in combination with IDAC demonstrated a small survival benefit in patients older than ٦٠ years (٧.١ vs ٥.٠ months); a benefit was not shown in younger patients, potentially due to the higher transplant rate (٤٥.٨% <٦٠ years vs ٢٠.٢% ≥٦٠ years).[٢٢٢]

Finally, targeted immunotherapy is an important novel approach.[٢٩٤] A variety of therapeutic antibodies directed against AML antigenic targets (eg, CD٣٣, CD١٢٣, CLEC١٢A), bispecific T-cell engagers, or dual-affinity retargeting molecules as well as engineered chimeric antigen receptor T cells targeting the CD٣٣ and CD١٢٣ antigens are currently in early clinical trial.

Management of special situations

Hyperleukocytosis

A recent systematic review assessed early mortality in patients with an initial white blood cell count ≥١٠٠ × ١٠⁹/L and found neither leukapheresis nor hydroxyurea/low-dose chemotherapy influenced the early death rate.[٢٩٥] Hyperleukocytosis reflects a medical emergency. After immediate diagnostic testing, patients should begin cytoreductive treatment without delay preferably with the planned induction regimen.

Others

There have been no new developments in management of central nervous system (CNS) AML, myeloid sarcoma, or pregnancy in AML since the ٢٠١٠ ELN publication and readers are referred there for information.[١]

Supportive care

Prophylactic anti-infectious treatment

For prophylaxis and treatment of infections, prevailing institutional infectious organisms and their drug-resistance pattern should primarily be considered. As noted in the ٢٠١٠ ELN recommendations, prophylaxis with a quinolone should be given.[١]

A systematic survey of randomized trials in AML found "high-level evidence" supporting use of posaconazole to prevent invasive fungal infections during remission induction therapy and in patients with GVHD after allogeneic HCT. Micafungin can be used when azoles are strictly prohibited, although fluconazole is generally acceptable because it has a very low interaction with CYP٣A٤. There was insufficient evidence to guide antifungal prophylaxis in patients undergoing allogeneic HCT without GVHD or other high-risk factors.[٢٩٦]

Other issues

There have been few new developments regarding use of myeloid growth factors or transfusion support since the ٢٠١٠ ELN recommendations to which the reader is referred.[٢] Neither growth factors nor granulocyte transfusions can be recommended outside of the individual patient setting. In ٢ randomized trials comparing prophylactic (at a count $<١٠ \times ١٠^٩$/L) vs therapeutic (only if bleeding) platelet transfusion, more grade ٢-٤ bleeding occurred in the therapeutic arms together with a slight excess in fatal (CNS) hemorrhage.[٢٩٧,٢٩٨] Thus, prophylactic platelet transfusion at a count $<١٠ \times ١٠^٩$/L remains the standard for patients with AML.

Go to:

Acknowledgments