

A Mind Map for Managing Minimal Residual Disease in Acute Myeloid Leukemia

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Abstract: Advances in detecting traces of leukemia that were previously unidentifiable have increasingly led to the incorporation of information about residual disease into clinical decision making for patients with leukemia in both the postinduction and consolidation settings. This review discusses current concepts related to minimal residual disease (MRD), which is defined as submicroscopic disease detected during morphologic complete remission. The focus is on acute myeloid leukemia (AML). Basic methods for detecting MRD include flow cytometry, reverse transcription-polymerase chain reaction, and mutation analysis. Several studies using these assays have demonstrated prognostic implications based on MRD-positive vs MRD-negative status. As our understanding of the biological factors responsible for MRD in AML evolves, residual disease should be evaluated in the context of other prognostic markers. Current therapeutic options for managing MRD in AML are limited, and the clinical implications of a positive MRD test result can be significant. Regarding individual patients, an evidence-based approach must be applied while the institution- and assay-specific differences that currently exist are considered. Challenges associated with MRD assessment, such as the limited standardization of available assays and the paucity of effective agents to eradicate MRD, will need to be overcome before physicians who treat leukemia can use MRD as a tool for clinical management.

Introduction

Because of advances in detecting submicroscopic leukemia, detectable residual disease has become an important prognostic marker that is useful in clinical decision making. Residual disease may be detected in several ways, and for several types of leukemia. This review focuses on minimal residual disease (MRD) in acute myeloid leukemia (AML), with MRD defined as any detectable evidence of persistent disease during morphologic complete remission (CR) after treatment. This definition generally implies that leukemia is not detectable by microscopic examination; instead, it must be assayed with a more sensitive method that provides evidence of its presence. We review basic methods for detecting

Keywords

Acute myeloid leukemia, experimental leukemia, minimal residual disease

MRD, the prognostic implications of MRD-positive and MRD-negative disease in the context of other prognostic markers, and the therapeutic implications of MRD testing. An evidence-based approach should be applied in MRD assessment, and MRD should be considered in the context of previously defined baseline characteristics. Finally, forward-thinking research questions must be posed and addressed in the treatment of AML. MRD may be used as a guide, especially as newer and more sensitive MRD detection technologies become available.

Baseline characteristics, such as age, cytogenetic features, and mutation status, can be used to predict how successful a treatment for AML may be in a given patient.¹ Baseline characteristics do not, however, take into account additional interactions between patient and therapy that determine the response to therapy. In addition, although AML therapy historically has focused on anthracycline/cytarabine combinations, recent and future discoveries are likely to lead to several new therapeutic strategies. Certain characteristics are associated with better response rates and a lower probability of relapse. Significant heterogeneity exists among patients with AML, however, and variability in the responses to any particular therapy can be significant.² Subtle features, such as peripheral blast disappearance, may provide significant additional information about prognosis that is potentially useful in therapeutic decision making.³ Newer predictive models require updated information in real time as a patient undergoes therapy, and adaptive prognostication must take into account a more precise nature of disease response and disease resistance.

MRD would seem to represent either the remnant or resistant fraction of leukemia cells, and it is presumed to be responsible for relapse in many cases. Leukemia cells are destroyed with chemotherapy in an exponential decay fashion, and it is possible that a 2- to 3-log cell kill is simply not enough to complete the task in patients with large numbers of leukemia cells.⁴ What remain after therapy are residual cells that were not adequately exposed to chemotherapy. An alternate hypothesis is that residual disease consists of a selected population of leukemic cells that are inherently resistant to the therapeutic agents used.⁵ These 2 concepts are both worthy of consideration and are not mutually exclusive. MRD is the leukemia cell population that evades therapy, whether through pharmacokinetic/pharmacodynamic failure or through mechanisms of resistance. In either case, MRD is a prognostic factor associated with a higher likelihood of relapse, as documented in a number of prior studies.⁶⁻¹¹ Furthermore, cells that rely on hematopoietic stem and progenitor cell-like molecular pathways are potential candidates for MRD.^{12,13} Such cells are believed eventually to promote disease recurrence and ultimately lead to treatment failure.

The relevance of detectable MRD, and its value in clinical decision making, is highly dependent on the method of detection and the specific clinical scenario in which MRD is detected. To determine the predictive value of MRD, it is crucial to know details about the biology of the leukemia treated, the mechanisms of action of the drugs administered, the sensitivity and reproducibility of the assay used for MRD detection, and the quantity of MRD present.

Methods for Detecting MRD

The methods currently used to detect MRD can be broadly categorized as either flow cytometry or genetic testing. A snapshot of current MRD assessment, which includes details of some assays presently in clinical use, appears in the Figure. An assay may be selected based on the AML subtype, such as reverse transcription-polymerase chain reaction (RT-PCR) in core binding factor AML (CBF-AML) or *NPM1*-mutated AML. However, other assays, such as multiparametric flow cytometry (MFC), are used more universally. Flow cytometry and real-time quantitative PCR (RT-qPCR) are the most widely used and validated methods at the present time. Assays based on next-generation sequencing (NGS) also are of significant interest and are being evaluated in several settings.

Flow Cytometry

MFC has become a standard method of detecting MRD at several institutions.^{14,15} Trained hematopathologists rely on a panel of normal and abnormal markers to detect leukemic myeloblasts by using difference-from-normal (DFN) immunophenotypes or known leukemia-associated immunophenotypes (LAIPs).^{11,16} The level of detection is on the order of 1 abnormal cell in 10^4 , making these tests among the most sensitive methods available for detecting MRD. The LAIP at diagnosis frequently—but not always—serves as a guide for detecting MRD during remission.¹⁷ The immunophenotype of normal regenerating bone marrow must be well established. The detection of MRD by MFC is operator-dependent, although automated algorithms have been explored.¹⁸ An advantage of MFC is that most AML samples, regardless of molecular characteristics, have an immunophenotype that a well-trained pathologist can detect by flow cytometry with reasonable specificity.

Real-Time Quantitative Polymerase Chain Reaction

Among genetic studies, RT-qPCR is one of the most reliable and validated methods of MRD detection.¹⁹ It also has a level of detection that is at least as sensitive as that of MFC, and possibly an order of magnitude greater (detecting approximately 1 in 10^5 cells). In specific circumstances, when the genetic aberration is known

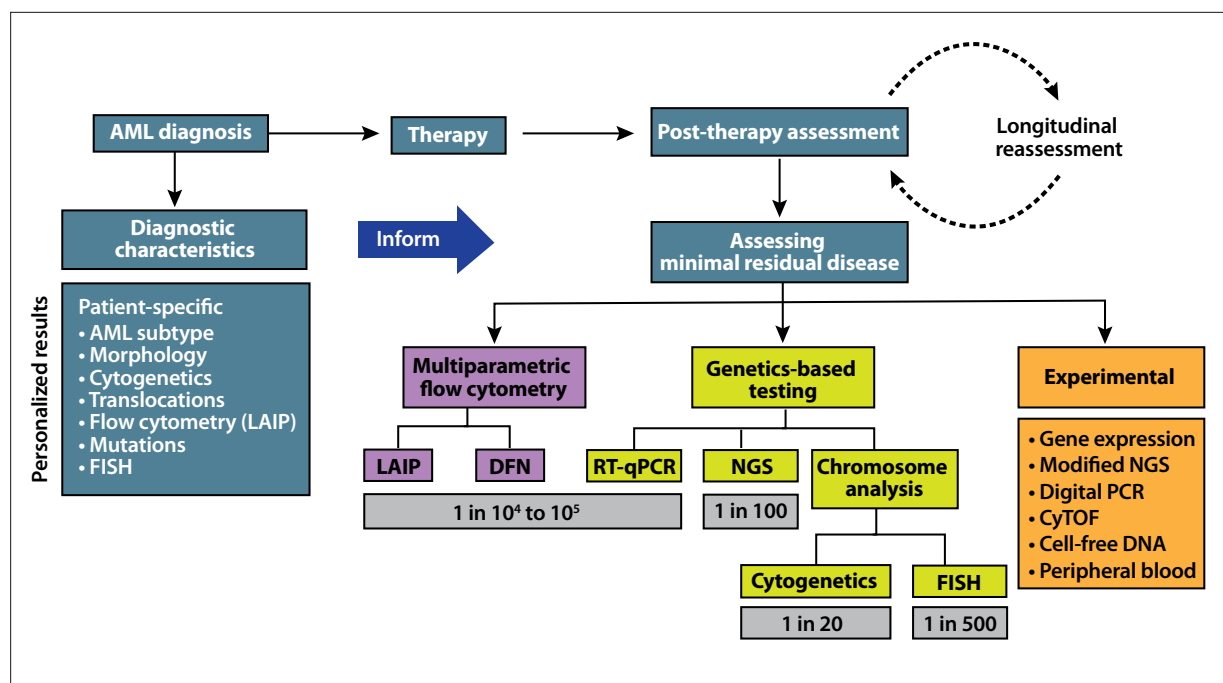


Figure. Snapshot of the current status of MRD assessment in AML. Left to right: At diagnosis, AML may be characterized to derive patient-specific data that inform later assessments. After therapy, marrow is assessed for MRD when the percentage of blasts is below 5% and the patient has achieved a morphologic CR. Most current MRD assessments can be categorized into 3 types: (1) multiparametric flow cytometry, (2) genetics-based testing, and (3) experimental testing, which typically encompasses newer and/or less-studied/less-validated approaches. The most standard types of MRD assessment are shown for each category. Estimations of sensitivity (as the number of cells that may be reliably detected) are shown in gray under widely used MRD assessments.

AML, acute myeloid leukemia; CR, complete remission; CyTOF, cytometry by time-of-flight; DFN, difference from normal; FISH, fluorescence in situ hybridization; LAIP, leukemia-associated immunophenotype; MRD, minimal residual disease; NGS, next-generation sequencing; RT-qPCR, real-time quantitative polymerase chain reaction.

and informative, it can assist in clinical management. RT-qPCR detects specific molecular abnormalities and quantifies abnormal leukemic gene transcripts in comparison with normal genes measured from the same sample. This technique requires the presence of well-described genetic abnormalities and is therefore primarily useful in AML with (1) a known translocation, such as CBF-AML, or (2) a specific mutation, such as an *NPM1* mutation. Frequently tested translocations include *PML-RARA*, *RUNX1-RUNX1T1*, *CBFB-MYH11*, and *MLL* translocations. Several recent studies have demonstrated the utility of detecting *NPM1*-mutated clones or clones with known translocations as markers for MRD monitoring.^{10,20}

Mutation Analysis

Several methods of mutation analysis have been increasingly studied in the context of MRD detection. NGS and PCR along with traditional Sanger sequencing are used to determine whether mutations detected at diagnosis remain after treatment. Point mutations in *TP53*, *DNMT3A*, *IDH1*, *IDH2*, *JAK2*, *RUNX1*, *RAS*, and *KIT*,

among others, may have utility in the future.²¹ The use of mutation analysis following treatment is currently undergoing investigation, and several questions remain incompletely answered. Although the level of detection may be estimated by the allelic frequency, confounders may lead to false-negative or false-positive results. The presence of a mutation in an emerging subclone may remain undetected in recovering marrow owing to its low variant allelic frequency, leading to a false-negative result. Conversely, a mutation in a preleukemic hematopoietic stem/progenitor cell (HSPC; a nonleukemic cell with potential for emergent disease) could theoretically be detected, falsely indicating the presence of AML MRD.²² Understanding the results of mutation analysis is a rapidly evolving area of research, along with the disappearance and emergence of detectable mutations and the use of novel methods for MRD gene mutation testing. For example, electrophoretic *NPM1* mutation detection is a well-described technique. It is estimated to have a level of detection of approximately 1:40, which is a sensitivity lower than that of RT-qPCR.²³ Other insertions, duplications, and mutations in genes

(such as occur with *FLT3*-ITD, *FLT3*-D835, *MLL*-PTD, and *CEBPA*) are candidates for similar electrophoretic tests to detect MRD.²⁴

Fluorescence In Situ Hybridization

In cases with an informative chromosomal abnormality at diagnosis, fluorescence in situ hybridization (FISH) may sometimes be useful in detecting residual leukemia cells during remission.²⁵ Between 200 and 500 cells frequently can be examined. The technique may be particularly useful to establish the presence of AML myeloblasts in a hypocellular marrow specimen, when too few cells are available for MFC and other assays but hundreds of cells may be prepared for assay on a FISH slide. In such cases, the early detection of leukemia cells may be possible. The way that information translates into clinical management has not been established, however, and would depend on the individual circumstances of the AML case.

Karyotyping

Cytogenetics may reveal the presence of residual AML, but 20 metaphases typically are reported.²⁶ If a chromosomal abnormality that was detected in the pretreatment AML sample is detected on karyotypic analysis after treatment, disease is often also detectable by microscopic histologic examination or may be easily confirmed by another method of MRD detection. Karyotypic analysis may be useful to detect cytogenetic evolution and the emergence of a new clone in partially treated AML. The presence of a single abnormal metaphase that is different from the diagnostic karyotype may be a challenge to interpret in isolation, however.

Gene Expression Analysis

Overexpression of individual AML-related genes may provide a basis for MRD detection. *WT1* overexpression has been evaluated as a potential marker for MRD in AML, but there are inconsistencies in its reported utility.¹⁹ Analyzing the expression levels of a panel of genes with gene expression assays may also have use in AML, but the confounding effects of gene expression in normal hematopoiesis must be considered and may make interpretation more challenging.²⁷ Gene expression assays based on *WT1* have also been used in the setting of patients who underwent transplant.^{28,29} Sensitive RNA-sequencing detection methods may provide useful information for the clinical management of AML MRD when combined with alternate methods of MRD detection, such as flow cytometry.

Challenges to the Detection of MRD and the Application of MRD Testing

Several challenges to detecting and using MRD measurements exist, and some measures to overcome them

have been investigated.²² Notably, multiple methods are available, largely reflecting the heterogeneity of AML. Different methods are used at different institutions, each of which often has specific expertise. Furthermore, different methods have been used in separate clinical studies, at times making correlations more of a challenge. For any AML MRD method to be universally useful, it must be practical, available, validated, and shown to be adequate in a prospective fashion at multiple centers. Given the variety and availability of MRD methods, individual institutions may be able to use data from their detection of residual disease in the context of other factors to assist in clinical decision making. However, the widespread use of standardized technologies is still uncommon.

Although methods of MRD detection have improved significantly over the past decade, residual disease continues to remain undetected. AML relapse in patients who are MRD-negative occurs all too frequently, indicating that the various assays are far from perfect. The reasons why leukemic cells may evade MRD detection are several and include persistence of the disease at a level below the sensitivity of the assay.⁴ MRD also may evade detection in specific ways with specific assays. For example, if residual disease does not possess a leukemic or DFN immunophenotype, it will not be detected in MFC. Additionally, MRD may be present in a microenvironmental niche that is not well sampled during the collection and testing of marrow aspirate that is composed largely of peripheral blood. Attempts have been made to detect MRD from peripheral blood, and studies are ongoing.^{30,31}

False-positive results and over-detection are also possible, especially as detection methods become more sensitive. MRD testing may detect a stable nonleukemic, preleukemic clone in which the tested molecular abnormality is present.²² Remnant preleukemic HSPCs may not possess the same potential for relapse as AML cells. Likewise, MFC may detect an abnormal immunophenotype that does not lead to relapse. The detected abnormal cells may represent preleukemic HSPCs or abnormal recovering bone marrow. Results that are inconsistent with the presence of true AML MRD will be further quantified as techniques are refined and widely tested in larger numbers of patients.

Prognostic Assessment and Therapeutic Management Based on MRD

As might be expected, the presence of MRD by most testing methods is generally associated with a greater risk for relapse and less favorable outcomes. The timing, method, and absolute level of MRD detection may be instrumental in determining the significance of the effect. Furthermore, baseline characteristics may influence the relative importance of MRD detection. For example,

the significance of a negative MRD test by RT-PCR in a patient with CBF-AML who achieved complete remission by day 28 and who at baseline had a high white blood cell count from leukemic blasts may differ from the significance of a negative MRD test by suboptimal specimen MFC on day 28 in a patient with *TP53*-mutated AML who at baseline had a low-normal white blood cell count and who continued to recover counts at the time of assay. The second patient has fewer cells to test and is known to be at high risk for relapse with a less favorable prognosis because of the *TP53* mutation. Conversely, if the first CBF-AML patient had a positive RT-PCR MRD test at 28 days, this might be interpreted as less significant than the MFC-positive MRD test at 28 days after induction in the patient with *TP53*-mutated AML. In the first patient, RT-qPCR negativity after 3 cycles of therapy still suggests a favorable outcome, whereas a positive MRD test in a patient with *TP53*-mutated disease likely suggests resistance and forebodes impending, early relapse.²⁰

Currently, there is no universally accepted standard for MRD in therapeutic decision making for AML that does not fall into the category of acute promyelocytic leukemia.³² Several studies have established the clear significance of MRD detection as a prognostic indicator, however. MRD currently must be viewed in the context of other clinical and prognostic variables. Clinicians may incorporate MRD findings into their assessment on the basis of best available data to recommend one course of action over another. Such risk-directed decisions involve the recommendation to undergo hematopoietic stem cell transplant (HSCT) or to participate in a clinical trial that targets MRD. Other decisions about dosage and number of cycles of chemotherapy, and the determination of response to a particular therapy, may be influenced—but not dictated—by the presence or absence of MRD. Selected larger studies evaluating the risk-directed management of patients with AML on the basis of MFC MRD assessment are shown in Table 1. At the current dawn of more precise, individualized, and patient-specific treatment decisions in AML, MRD information and other indices will likely be further established as important tools for decision making.³³

Opportunities in Research

MRD assessment in AML is rapidly evolving as more is discovered about the nature of MRD and as more precise technologies become available to improve its detection. Several opportunities are available for advancing the management of AML with MRD assessment. From a clinical standpoint, the standardization of assays will be welcome, allowing their more widespread use in the future. Additionally, the integration of MRD detection

methodologies (eg, MFC plus NGS) for comprehensive MRD assessment may be possible. Finally, clinical trials designed specifically to target MRD in AML are already under way (Table 2), underscoring recognition of the need to clear MRD to improve outcomes.

Additional methods of MRD detection may become critically important. Several promising methods are on the horizon. Assessing circulating cell-free DNA is a recent technique that may be applicable to MRD detection.³⁴ Assays of circulating tumor DNA, as used in solid tumors, are being conducted increasingly to detect leukemia cell DNA.³⁵ Improvements in immunohistochemical staining resulting from technological advances, such as the use of imaging mass cytometry, may lead to the better detection of residual AML cells from marrow biopsy sections.³⁶ This may be especially relevant for detecting residual AML cells adhering to a marrow niche. Finally, the rapidly emerging technology of digital droplet PCR, which has the capacity to carry out targeted sequencing on multiple, separate small quantities (droplets) of DNA simultaneously, has relevance in rare cell and MRD detection.³⁷ Resulting data give an indication of the number of leukemia cells that are present in a sample. Further, digital droplet PCR has the potential to reveal the subclonal architecture of a patient's AML, characterizing shared and unshared mutations in each thermocycling reaction—information relevant for mutation clearance, cooperation, and the detection of preleukemic mutations. PCR of a subfractionated sample, as is accomplished with digital PCR, may identify smaller quantities of MRD and additionally identify subclones not previously detected.^{38,39} The use of these technologies is currently in the research setting. Their use in clinical medicine may shortly follow, especially as additional information about AML heterogeneity is needed.⁴⁰

Other experimental methods of MRD detection that increase the sensitivity of testing in AML, particularly in specific subsets, are active areas of investigation. Examples of other novel PCR approaches include bar coding PCR and molecular tagging, which are meant to detect rare mutations with NGS more sensitively.^{41,42} In an effort to provide personalized MRD assessment for any AML patient, exome sequencing from diagnostic AML samples has been used to identify mutations that are tested by using deep sequencing of subsequent samples after treatment.⁴³ Novel flow cytometry technologies/instruments, such as the mass cytometer, also known as cytometry by time-of-flight (CyTOF), can simultaneously assay tens to hundreds of extracellular and intracellular markers.⁴⁴ The technology has demonstrated the potential to detect a wide range of cellular subtypes in AML and may better classify AML subtypes.⁴⁵ Because mass cytometry uses an increased number of markers with each run, it would also serve to reduce the number of marker panels that are

Table 1. Selected Multiparametric Flow Cytometry Studies of AML MRD That Included More Than 100 Patients and Investigated MRD in Adult, Nonacute Promyelocytic Leukemia AML

Study	MRD Description/ Definition	Timing of MRD Assay	Pts, No.	CR Status	Cutoff for Comparison	MRD Predicted Values*	P Value
San Miguel et al, ⁴⁷ 2001	Aberrant IP (1) Cross-lineage antigen expression, (2) asynchronous antigen expression, (3) antigen overexpression, and (4) abnormal light scatter pattern	First marrow in CR	126	CR	MRD cells, No. 1 in $<10^{-4}$ 1 in 10^{-4} to 10^{-3} 1 in 10^{-3} to 10^{-2} 1 in $>10^{-2}$	Relapse rate at 3 y 0% 14% 50% 84% RFS	.0001 .003
Kern et al, ⁴⁸ 2004	LAIP-positive cells (1) Asynchronous antigen expression, (2) cross-lineage expression of lymphoid antigens, (3) lack of antigen expression, and (4) antigen overexpression	Day 16 of induction	106	CR and non-CR	Median LD16 (log difference between day 1 and day 16 in LAIP-positive cells)	CR rate: 81% vs 51% EFS at 2 y: 53% vs <20% OS at 2 y: 58% vs 43% RFS at 2 y: 65% vs 30%	.002 <.0001 .01 .004
Buccisano et al, ⁴⁹ 2006	Fifteen patient-specific LAPs	Postinduction and postconsolidation	100	CR	$>3.5 \times 10^{-4}$ MRD cells	Relapse rate: 46% vs 72% postinduction; 25% vs 84% postconsolidation RFS at 5 y: 51% vs 22% postinduction; 71% vs 13% postconsolidation OS at 5 y: 48% vs 25% postinduction; 64% vs 16% postconsolidation	.01 <.001 .02 <.001 .003 <.001
Maurillo et al, ⁵⁰ 2008	Patient-specific LAPs	At mCR	142	CR	$>3.5 \times 10^{-4}$ MRD cells	RFS at 5 y: 60% vs 16% OS at 5 y: 62% vs 23%	<.001 .0001
Terwijn et al, ⁸ 2013	LAP-positive cells (1) Asynchronous antigen expression, defined as the simultaneous expression of early and late maturation markers on the same cell; (2) cross lineage antigen expression, defined as the expression of lymphoid markers on myeloid cells; (3) underexpression of antigens, which mostly includes the absence of expected myeloid antigens; (4) antigen overexpression; and (5) in the absence of a primitive marker, the above-mentioned aberrancies on more mature leukemic cells	Post-C1, C2 (post-C2 analyzed), and postconsolidation	183	CR	$>0.1\%$ of WBCs	Relapse rate: 42% vs 72% RFS at 4 y: 52% vs 23%	.001 by MVA for relapse incidence

(Table continued on next page)

Table 1. (Continued) Selected Multiparametric Flow Cytometry Studies of AML MRD That Included More Than 100 Patients and Investigated MRD in Adult, Nonacute Promyelocytic Leukemia AML

Study	MRD Description/ Definition	Timing of MRD Assay	Pts, No.	CR Status	Cutoff for Comparison	MRD Predicted Values ^a	P Value
Freeman et al, ⁹ 2013	LAIP-positive cells Cell populations that deviated from the normal antigen profiles with sufficient detection sensitivity and comprised >10% of leukemic blasts at diagnosis	Post-C1, C2	427	mCR and blasts <5% by FC	>0.1% of TNCs	CIR at 3 y Post-C1: 71% vs 83% Post-C2: 79% vs 91% OS at 3 y Post-C1: 42% vs 26% Post-C2: 38% vs 18%	<.001 .01 <.001 .04
Buccisano et al, ⁵¹ 2015	Patient-specific LAIP-positive cells	Postinduction and postconsolidation (postconsolidation analyzed)	210	CR	>3.5 × 10 ⁻⁴ MRD cells	CIR at 5 y^b: 27% vs 67% DFS at 5 y: 56% vs 25% OS at 5 y: 60% vs 26%	<.0001 ^c <.0001 <.0001
Araki et al, ⁵² 2016	Different from normal Deviation from normal antigen expression patterns seen in specific cell lineages at specific stages of maturation	Pre-HSCT	311	CR	>0	CIR at 3 y^b: 22% vs 67% PFS at 3 y: 67% vs 12% OS at 3 y: 73% vs 26%	<.0001 ^c <.0001 <.0001
Vidriales et al, ⁵³ 2016	Different from normal Leukemic phenotypes that are absent from or extremely infrequent in normal bone marrow	At mCR	306		MRD, % ≥0.1% 0.01%-0.1% <0.01%	OS at 5 y 38% 50% 71%	.002

AML, acute myeloid leukemia; C1, cycle 1; C2, cycle 2; CIR, cumulative incidence of relapse; CR, complete remission; DFS, disease-free survival; EFS, event-free survival; FC, flow cytometry; HSCT, hematopoietic stem cell transplant; IP, immunophenotype; LAIP, leukemia-associated immunophenotype; LAP, leukemia-associated phenotype; mCR, morphologic complete remission; MRD, minimal residual disease; MVA, multivariate analysis; OS, overall survival; PFS, progression-free survival; pts, patients; RFS, relapse-free survival; TNCs, total nucleated cells; WBCs, white blood cells; y, years.

^a For all MRD predicted values, column percentages are given for patients in the following order: MRD-negative vs MRD-positive.

^b Percentages for this study are best estimates for all patients (both young and elderly) based on best values provided.

^c P values calculated with chi-square test for association based on given values; this study included an additional 48 patients with active disease before HSCT.

needed for testing. The use of CyTOF in AML MRD detection would require the creation of a clinical assay, and its use in the context of residual disease is experimental.⁴⁶ These novel techniques may eventually prove to be invaluable guides for clinical management, especially as newer therapeutic approaches emerge.

Whatever MRD measurements eventually become universally available, it is optimal to incorporate MRD into correlative studies of treatment protocols currently, so that the knowledge base about MRD grows. The type of MRD testing that is a part of any study should include a method that will potentially be accessible to many hematologists and oncologists treating leukemia and is useful for a variety of AML cases. Examples include the

following: (1) MFC, especially if automated analysis is available and validated, and (2) NGS, especially given that the cost of analysis is expected to decrease exponentially over time according to Moore's Law. The association of MRD with other characteristics of response to therapy, such as peripheral blood AML cell behavior during treatment, may also allow management based on an early assessment of other factors, even outside the context of MRD in remission.³ Correlative research studies will reveal such information, and these data can be captured in a well-planned investigation. Most importantly, existing and new information will be used in prospective trials that assess the use of MRD for clinical decision making, an imperative next step for its use in recommended practice.

Table 2. Selected Clinical Trials Recruiting Patients With MRD-Positive AML in 2017

Identifier	Therapy	AML Patient Population
Hypomethylating agents		
NCT03021395	Decitabine	MRD after consolidation
NCT01462578	Azacitidine	Remission (<5% blasts) with MRD
NCT02684162	SGI-110 + donor lymphocyte infusion	MRD after allo-HSCT
Targeted antibody therapy		
NCT02789254	FLYSYN	<i>NPM1</i> mutation, FLT3 expression, with MRD
NCT02270463	SL-401	First CR, MRD allowed
Immunomodulatory therapy/immunotherapy		
NCT02370888	Lenalidomide (Revlimid, Celgene)	MRD after allo-HSCT
NCT02126553	Lenalidomide	High-risk AML in first or second CR or CRi, MRD allowed
NCT02275533	Nivolumab (Opdivo, Bristol-Myers Squibb)	First CR or CRi with MRD
NCT02532231	Nivolumab	High-risk AML in first CR, CRi, CRp, PR (<10% blasts) or second CR, MRD allowed

allo-HSCT, allogeneic hematopoietic stem cell transplant; CR, complete remission; CRi, complete remission with incomplete count recovery; CRp, complete remission with incomplete platelet recovery; FLYSYN, FLT3-targeted antibody; MRD, minimal residual disease; PR, partial remission; SGI-110, guadecitabine; SL-401, CD123-targeted therapy.

The study of AML MRD will help to answer questions about AML relapse and may assist in the development of new therapeutics meant to target resistant AML subpopulations. Theoretically, therapy targeting MRD may prevent relapse of disease. Therapeutic targets may be discovered by studying MRD and searching for vulnerable phenotypic characteristics that are distinct from those of the bulk of a patient's AML. Up-front, prophylactic, or maintenance treatment against known resistant and evasive MRD cell populations could signal a breakthrough that contributes to an increased number of AML cures. If recurrent, common characteristics are found among MRD cells from different patients, this information could be used to determine whether MRD subclones are present at diagnosis. Alternately, if MRD results from genetic evolution/drift, evidenced by subclonal emergence, personalized therapy based on specific MRD characteristics detected in real time can be envisioned. Prospects for the study of residual and resistant leukemia abound and will predictably contribute to improvements in the management of AML that are based on patient-specific findings related to MRD.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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