MRD as a Predictor of Relapse in AML

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Recognizing the Drivers of Relapse in AML

Acute myeloid leukemia (AML) is the most common form of acute leukemia among adults; approximately 20,000 patients will be diagnosed with AML in the United States this year. More than 10,000 Americans will die of this disease annually, attesting to a significant unmet medical need. The median age of diagnosis is approximately 68 years, with slightly more than half of patients diagnosed at 65 years or older, and approximately a third diagnosed at 75 years or older.[1-3]

AML remains the principal cause of death in most patients with the disease. In a retrospective study of 4601 patients with newly diagnosed AML, 79% achieved complete remission (CR). Of these, 29% had a relapse-free survival (RFS) of ≤3 months, 40% had an RFS of ≤6 months, and 57% failed to achieve CR or had an RFS of ≤12 months. Thus, relapse and death from AML are generally not the exception, but the rule.[4,5]

At our clinic, based on the patient's performance status, age, mutations, cytogenetics, and other variables, the 5-year overall survival (cure rate, tantamount to cure) is no higher than 40%. Outcomes in elderly patients are quite poor, with a 5-year overall survival rate of 5% to 15%. The elderly unable to receive extensive chemotherapy have a median survival of only 5 to 10 months. The biologic diversity of the disease is also an important factor in outcomes.[4,6-9]

> "CR status is an important postdiagnosis prognostic factor in AML"

As noted, treatment outcomes in AML are highly variable and difficult to predict on an individual basis but age, performance status, genetics, and karyotype are useful prognostic factors. The initial goal of therapy for AML is to achieve a CR; CR is requisite, although not sufficient, for cure. As many as 85% of younger patients with AML and as few as 40% of intensively treated older patients achieve CR. Most patients with AML achieve CR but many will relapse. The rate of relapse after achieving CR increases with patient age and, of note, approximately one-third of patients with AML are diagnosed at 75 years of age or older.[3-9]

> "Most patients with AML achieve CR but many will relapse[5]"

The duration of first CR is a primary prognostic factor[10]

Investigators have long known that the duration of the first CR is a major predictor of outcome in AML. The duration of the first CR strongly affects the chance to achieve a second CR and the long-term outcome of patients with AML after relapse. Duration of the first CR of <12 months has been associated with worse outcomes, whereas those with longer CR duration have a reasonable chance of responding to repeat of the original induction therapy. Some investigators even suggest that the prognostic power of the first CR should not be reduced to a binary variable (eg, >6 months or <12 months), but is continuous (eg, a first CR of 6 months is associated with a better outcome than a first CR of 5 months, which in turn is associated with a better outcome than a first CR of 4 months, etc). In addition to duration of the first CR, the biology of the disease, age at relapse, and the frontline therapy received all appear to drive prognosis in AML after relapse.[10-14]

"Not all CRs are the same[7]"

Patients with AML in CR have a diverse clinical status, ranging from patients who have "deep" remissions and are likely to be cured to those whose leukemia burden is just below morphologic detectability to those with a residual leukemic burden just below clinically obvious relapse. As early as 1969, Hart et al recognized that CR is an early, important, necessary, but insufficient step on the path to long-term disease control in AML. At diagnosis, a patient with AML may have up to 10^{12} leukemic cells, equivalent to several pounds of solid tumor. After induction therapy, that same patient may have achieved CR (<5% blasts) but still harbor as many as 10^{10} leukemic cells, equivalent to a 2-cubic-centimeter solid tumor mass, suggesting that CR defined as <5% blasts inadequately characterizes the vastly heterogeneous range of AML burden and outcomes. An increasing body of data has demonstrated that the traditional CR criterion of <5% blasts is not sufficiently stringent in AML.[7,9,15-18]

Attempts to define remissions

The list of types of remissions in AML is growing rapidly in an attempt to detect relevant tumor burdens left behind after therapy. These CR definitions are in increasing use: mCR (morphologic complete remission: <5% myeloblasts in the bone marrow, absence of circulating blasts, absence of extramedullary disease, transfusion independence, full recovery of peripheral blood counts ANC ≥1000/μL, platelets ≥100,000/μL); CRi (incomplete CR: CR with incomplete blood count recovery, either ANC <1000/μL or platelets <100,000/μL, and transfusion independence with persistence of cytopenia [usually thrombocytopenia]); CRp (CR with incomplete platelet recovery); MLFS (morphologic leukemia-free state: <5% blasts in the bone marrow, absence of blasts with Auer rods or extramedullary disease, and no hematologic recovery required).[1,8,9,18]

"MRD heralds poor outcomes in AML[7]"

Residual disease in AML

Patients with AML generally have some leukemic cells that are not completely eradicated by initial therapy. Conventional therapy can suppress or eradicate dominant leukemic clones leading to CR but at the same time facilitate the rise of resistant clones. Such clones may possess a different group and composition of mutations than the clones that were present at diagnosis. The initial therapy will select for clones that may be enriched for genetic alterations associated with epigenetic changes, especially those associated with clonal hematopoiesis in normal adults.[19]

Many studies have demonstrated that the persistence of measurable (formerly *minimal* residual disease [MRD]) at the submicroscopic level, despite a reduction of blasts to <5%, identifies patients at high risk of disease recurrence. Given the fact that after induction a patient in mCR may harbor 10^{10} leukemic cells, it is not surprising that relapse from morphologic CR remains common. Some investigators contend that even in complete remission, MRD is present in AML, though not morphologically evident. They assert that all patients have MRD after induction, though the size of the MRD reservoir varies, as does the response to additional therapy. We need to pursue initial therapies that lead to a low level of disease burden at the time of CR.[7,15,20,21]

"The definition of CR, at <5% blasts, has changed little in the past 60 years[17]"

The evolution of new standards for MRD

The clinical use of CR, at <5% blasts, has changed little in the past 60 years. The ability to measure MRD in AML was not available in 1956 when criteria for the evaluation of response to treatment were first proposed, and so thresholds were set based on the technology available at that time—the light microscope. The criterion for CR, <5% blasts with count recovery, was maintained by the IWG response definitions for AML published in 2003, subsequently incorporated into the NCCN Guidelines®, and persists as a criterion for CR in the ELN 2017 recommendations.[8,17,18,22,23]

It was not until 2018 that the Consensus Document from ELN MRD Working Party recommended using 0.1% blasts usually measured by multiparameter flow cytometry as the threshold to distinguish MRD-positive (MRD_{pos}) from MRD-negative (MRD_{neg}) patients. The Working Party cautioned, though, that MRD below 0.1% may still be consistent with residual leukemia. It may be that there is no threshold of blasts at which clinicians may be assured that they have cured AML, especially early in initial treatment.[21]

The importance of MRD

A better definition of disease burden than morphological CR is emerging. The possibility of defining MRD far below the level of <5% blast cells is changing the landscape of risk classification. MRD now denotes the presence of leukemic cells down to levels of 1:1,000 to 1:100,000 cells, depending on the assessment technique, compared with 1:20 (<5%) in morphologic assessments. Thus, morphologic assessments

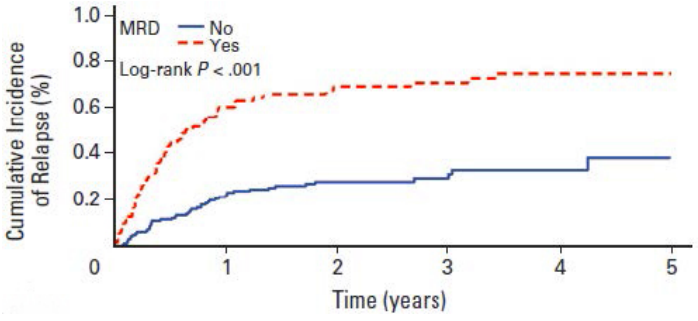
are not sensitive enough to detect clinically relevant tumor burdens left behind after therapy. Several studies have shown that the detection of MRD is a key prognostic variable in predicting relapse after induction chemotherapy in AML.[5,6,24]

MRD is associated with relapse in clinical trials

MRD persistence in AML can confer a negative prognosis for patients similar to the prognosis with ongoing active disease. Multiple studies have shown that detectable MRD is associated with high risk for relapse. For example, Chen et al (2015) determined MRD by 10-color multiparameter flow cytometry (MFC) in a retrospective analysis of 245 adults with AML who achieved CR, CRp, or CRi after induction therapy. MRD was lowest with CR. MRD tended to be associated with CRp or CRi regardless of treatment intensity or whether patients had newly diagnosed or relapsed or refractory AML. In a multivariate analysis, MRD positivity more than tripled the risk of relapse (HR 3.72).[25,26]

Ivey et al (2016), using a reverse-transcriptase quantitative polymerase-chain-reaction (RT-qPCR) assay, found that MRD increased the risk of relapse, nearly by a factor of 5 (HR 4.80), in 2569 samples obtained from 346 patients with *NPM1*-mutated AML. Jongen-Lavrencic used next-generation sequencing (NGS) to confirm the association of MRD with an increased risk of relapse in a cohort of 283 patients in CR after therapy for newly diagnosed AML. Thus, 3 major MRD detection techniques confirm MRD's marked negative effect on relapse rate in AML (Chen 2015, Ivey 2016, Jongen-Lavrencic 2018). In addition, studies indicate that decreased *NKD2* expression inactivated by promoter hypermethylation is a common event in AML and may contribute to adverse outcomes in cytogenetically normal disease.[26-29]

MRD increases relapse after induction therapy in patients with AML[26]



Adapted with permission from Chen et al. *J Clin Oncol.* 2015;33(11):1258-1264.

From "minimal" to "measurable." Now what?

The original term, minimal residual disease, downplayed the importance of the lingering leukemic cells, which, in most cases, would mutate or multiply, resulting in the death of the patient from AML. Thus, the term measurable residual disease is now generally employed. Currently, the 2 most widely applied methods for assessing MRD are RT-qPCR and multiparameter flow cytometry (MFC), each with its own advantages and disadvantages. MFC is more widely applicable (>90% of patients with AML), is rapid, specific, and can distinguish viable cells from bone marrow debris and dead cells. RT-qPCR is accurate, has fewer false negatives, is highly reproducible between laboratories, is rapid, and substantially reduces the risk of contamination. NGS is an emerging molecular technique which enables comprehensive, simultaneous detection of somatic mutations that are often patient-specific. Because NGS is scalable, NGS makes it possible to track multiple mutations simultaneously, with increasing read depth, which may provide further improvements in sensitivity.[9,28,30,31]

> "What to do about MRD after induction is still under investigation[7]"

Although the ELN guidelines now suggest MRD monitoring, the best course of action when MRD is detected remains controversial. It is useful to measure MRD because ultimately this knowledge may yield important prognostic information. Patients who go into transplant with MRD have a poor prognosis with a high likelihood of relapse. In our practice, we would strongly consider transplant in any patient with significant cytogenetic and genetically identifiable risks at diagnosis, even if MRD negativity was achieved. I would probably transplant an MRD-positive patient with good-risk cytogenetic and genetic features, but that's my personal view.[7,18]

Challenges of MRD

One challenge is that techniques of MRD assessment are not standardized in the United States and not easily measured for reasons that include lack of a central reference lab and lack of agreement on what technology should be used or employed. Another challenge is the lack of agreement on cutoffs. The monitoring schedule is also arbitrary; thus immunophenotyping and MRD monitoring by NGS or PCR have not been routinely incorporated into postremission strategies in patients with AML in the United States. There is an urgent need to find a means to improve the natural history of AML. This is a tall order, but assessment of MRD is a promising first step.[15]

The future of MRD

The 2017 revision of the ELN recommendations demonstrate global efforts to try to standardize MRD monitoring. Many prospective studies are underway, that investigate aspects of MRD assessment and its implications. It seems certain that the use of MRD assessment in AML will continue to expand and move from the realm of investigation into clinical practice. Technological advances have also facilitated understanding of aberrant DNA methylation and histone methylation/acetylation epigenetic changes that are key elements in the development of AML. Currently, clinical approaches to MRD in AML vary widely. Applications of the advances in MRD will strive to prolong CRs and prevent relapse in AML. Much remains to be learned before this collective knowledge may be exploited. The next decade will see unprecedented activity in preclinical and clinical investigation. We will continue to learn, clinicians and investigators, hand-in-hand, until our understanding can help bring new life to our patients with AML.[7,18,32,33]

In summary[5-8,30]:

- CR is requisite, although not sufficient, to achieve a cure in AML
- Most patients achieve an initial CR; many will relapse and succumb to progressive disease
- MRD provides independent prognostic information, conferring a negative prognosis consistent with persistent leukemia
- Patients with AML could relapse for a variety of reasons, but the depth of remission, reflected by MRD, could be the primary factor
- The possibility of detecting MRD below the level of 5% blast cells is changing the landscape of risk classification

"Measure what is measurable, and make measurable what is not so."
-Galileo Galilei

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