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Clonal Hematopoiesis after Induction Chemotherapy for Acute Myeloid Leukemia

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Successful intensive induction chemotherapy for acute myeloid leukemia (AML) results in at least a 2 to 4 $\log_{10}$ reduction in the 1 trillion malignant cells that are present at diagnosis, often with recovery of normal platelet and neutrophil levels within a month after treatment initiation — an impressive result for a short course of treatment. More than half of patients with AML achieve remission after intensive induction therapy with an anthracycline and cytarabine, but relapse is common. Predicting the likelihood of relapse for an individual patient can be helpful in tailoring the intensity of postremission treatment.[1]

Even when a patient with leukemia is in complete remission according to conventional clinicopathological criteria, the burden of malignant cells that are still present is a strong predictor of relapse risk. Minimal residual disease is the term most commonly used to describe persistence of malignant cells below the level of detection on ordinary light microscopy supplemented by immunohistochemical analysis.[2]

In acute lymphoblastic leukemia, persistent minimal residual disease after induction and consolidation chemotherapy has been recognized for more than 20 years as a stronger risk factor for relapse than karyotype, patient age, and other measures. After initial therapy for acute lymphoblastic leukemia, assessment for minimal residual disease, typically with flow cytometry, is now standard clinical practice and guides subsequent therapy. In addition, in neoplasms that are characterized by an abnormal fusion transcript, such as chronic myeloid leukemia or acute promyelocytic leukemia, clinicians routinely monitor patients at regular intervals for persistence or reappearance of the aberrant transcript.

Previous studies indicate that assessment for minimal residual disease is also feasible in AML.[2,3] For example, measurement of minimal residual disease with quantitation of *NPM1* transcripts provided powerful independent prognostic information in the U.K. National Cancer Research Institute AML17 trial.[4] Next-generation sequencing is an especially attractive approach for monitoring the diverse somatic mutations that drive AML.

In this issue of the *Journal*, Jongen-Lavrencic et al.[5] present the results of targeted sequencing-based assessments for minimal residual disease in a cohort of patients with AML who were from a Dutch and Belgian study group and from a Swiss study group and received similar treatment with intensive therapy. Minimal residual disease was detected in 51% of the 430 patients after induction therapy, and its presence predicted relapse, even though 89% received some form of subsequent consolidation therapy, including allogeneic stem-cell transplantation in 44%. The exception to the association between persistent minimal residual disease and relapse risk was found among patients whose only detectable mutation after intensive chemotherapy was in one of three specific genes: *DNMT3A*, *TET2*, or *ASXL1*. Among those patients, relapse was rare, despite restoration to a state of monoclonal or oligoclonal hematopoiesis rather than to a healthy state of nonclonal hematopoiesis.

DNMT3A, *TET2*, and *ASXL1* mutations are commonly acquired in blood and bone marrow during aging.[6-9] When a mutation in one of these

or another leukemia-associated driver gene is present at a variant allele frequency of at least 2% but is not observed in the context of a diagnosable neoplasm, the state is called clonal hematopoiesis of indeterminate potential.[10] By age 70, more than 10% of the population has this condition, which is a risk factor for both the subsequent development of hematologic cancer (occurring in 0.5 to 1% of affected patients per year) and cardiovascular events (occurring in affected patients at a rate that is 4 times the rate among age-matched controls without clonal hematopoiesis).[11]

AML is caused by the sequential acquisition of somatic mutations. Clonal hematopoiesis of indeterminate potential represents initiating mutations that result in the clonal expansion of cells without overt malignancy. When additional mutations occur, antecedent clones persist. The bone marrow in a patient with AML is therefore genetically heterogeneous, including premalignant and malignant clones.[12] Chemotherapy may selectively target the most malignant cells, leaving premalignant cells behind. Mutations in *DNMT3A*, *TET2*, or *ASXL1* that persist in bone marrow during remission may be from the ancestral clone that gave rise to AML or may be from a separate clone that had also been present in the bone marrow of the patient.

In the study conducted by Jongen-Lavrencic et al., the median follow-up was 40 months, and it is possible that with longer follow-up, *DNMT3A*, *TET2*, and *ASXL1* mutations could confer a relapse risk. Such late relapses do occur in AML, although most relapses occur during the first few years after initial therapy. In the case of *DNMT3A*, *TET2*, and *ASXL1* mutations, recurrent disease may require the acquisition of new mutations, a process that may take more time.

In gaining a further understanding of the genetics of minimal residual disease in patients with AML, we are given the opportunity to refine postremission therapy. Allogeneic stem-cell transplantation, the most intensive therapy for AML, has not consistently improved outcomes among patients with minimal residual disease but could provide a benefit for those with particular genotypes.[13] Therapeutic targeting of specific mutations that are present during remission could delay or prevent relapse.

Although the concept of persistent minimal residual disease strikes fear in the hearts of oncologists because of its implications in acute lymphoblastic leukemia and other diseases, assessment for minimal residual disease in AML is more nuanced — one must take into account not only whether a mutation is present after initial therapy but what that mutation is. In some cases, as Dante pointed out, the devil is not so black as he is painted.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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