Profiles in Leukemia
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For years, scientists have postulated the evolution of a cancer as a series of acquired mutations and epigenetic alterations that accumulate in a progressive way, beginning with a single transformed cell. Within this process, subclones of cells develop that acquire new properties, giving cells advantages, such as the ability to resist chemotherapy or to metastasize. Two articles¹,² now provide experimental evidence for this model of cancer and a glimpse of how we may evaluate patients with cancer in the near future.

In one article, Walter et al.¹ used high-throughput sequencing, DNA copy-number analysis, and microarray-based gene-expression studies to define the acquisition of gene mutations that accompanied tumor progression from a precursor myelodysplastic syndrome to acute myeloid leukemia (AML) in seven patients. They found that the myelodysplastic-syndrome clones contained hundreds of acquired mutations and that the leukemias that arose subsequently were derived from at least one subclone that had gained new mutations or genomic rearrangements, providing experimental proof for the model of the sequential development of cancer. From this large group of mutated genes, Walter et al. were able to identify 11 genes that mutated recurrently, 4 of which had not been implicated previously in myeloid diseases: UMODL1, CDH23, SMC3, and ZSWIM4. This work suggests that the genetic definition of tumor cells will provide new insights into the biologic characteristics of cancer. In addition, it will help to guide diagnostic, prognostic, and therapeutic decisions, as shown by Patel et al.²

Patel and colleagues have moved to this next phase of molecular medicine by defining the mutational profiles of 18 genes in the stored samples obtained from 502 patients with AML who had participated in the Eastern Cooperative Oncology Group E1900 clinical trial (ClinicalTrials.gov number, NCT00049517), in which two doses of induction chemotherapy were tested. With very economical use of patient material, the investigators were able to ask a new question using data already collected. What is the complement of mutations present in primary AML, and do they have prognostic value? They found that 97% of the patients with AML had mutations in the genes selected for analysis, a finding consistent with the results of a study involving patients with myelodysplastic syndrome that showed that a majority of patients had detectable point mutations.³ Poor survival was seen in patients with tandem duplication mutations of FLT3 or MLL and in those with point mutations of ASXL1 or PHF6. Favorable outcomes were seen for patients with CEBPA or IDH2 mutations and for those with NPM1 mutations with concurrent IDH1 or IDH2 mutations. Importantly, the group was able to show that patients with mutations of DNMT3A or NPM1 and those with MLL rearrangements had improved survival if they had been in the trial group that received high-dose daunorubicin.

If we think about extending the findings of Patel and colleagues to clinical practice, we would need to know the genetic profile of patients with AML within the first few days of presentation, in order to tailor an induction regimen to the patient. In at least one published case, the genetic profiling of AML has provided critical diagnostic categorization, which was unachievable with standard approaches,⁴ arguing for increased reliance on these techniques. Rapid clinical assessment is under way within the Cancer and Leukemia Group B, which is identifying patients with core-binding-factor leukemias by means of molecular testing within 48 hours after presentation, allowing those patients to participate in a clinical trial (NCT01238211) testing the effectiveness of adding dasatinib to induction and consolidation therapy.

So, how does the field of leukemia diagno-
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The current standard evaluation of acute myeloid leukemia samples includes morphologic evaluation, flow cytometric determination of cell lineage, cytogenetic and fluorescence in situ hybridization (FISH) studies to delineate recurrent chromosomal rearrangements, and molecular testing for expression of chromosomal fusion transcripts and the presence of mutations in FLT3, NPM1, and CEBPA (shown at the left of the figure). Testing in the future may be dominated by genomics-based molecular profiling, which may include real-time polymerase-chain-reaction (PCR) assays, microarray analysis, and next-generation sequencing; together, these tests have the capacity to define the gene-expression signature of the leukemia and thereby determine the cell lineage of the disease, as well as to identify common chromosomal rearrangements and gene mutations (shown to the right of the figure). In the future, prognostication in myeloid cancers may rely on the analysis of many genes with clinical relevance. We may also have the capacity to study a patient’s germline simultaneously with the disease, enabling an assessment of inherited predispositions. Several challenges exist to widespread implementation of molecular profiling to generate diagnostic and prognostic information, but these challenges may be overcome soon, and molecular profiling may herald a new approach to testing in leukemia and, by extension, other cancers.

**Figure 1. Current Clinical Evaluation of Acute Myeloid Leukemia and Potential Future Testing.**

The current clinical evaluation of acute myeloid leukemia includes morphologic evaluation, flow cytometric determination of cell lineage, cytogenetic and fluorescence in situ hybridization (FISH) studies to delineate recurrent chromosomal rearrangements, and molecular testing for expression of chromosomal fusion transcripts and the presence of mutations in FLT3, NPM1, and CEBPA (shown at the left of the figure). Testing in the future may be dominated by genomics-based molecular profiling, which may include real-time polymerase-chain-reaction (PCR) assays, microarray analysis, and next-generation sequencing; together, these tests have the capacity to define the gene-expression signature of the leukemia and thereby determine the cell lineage of the disease, as well as to identify common chromosomal rearrangements and gene mutations (shown to the right of the figure). In the future, prognostication in myeloid cancers may rely on the analysis of many genes with clinical relevance. We may also have the capacity to study a patient’s germline simultaneously with the disease, enabling an assessment of inherited predispositions. Several challenges exist to widespread implementation of molecular profiling to generate diagnostic and prognostic information, but these challenges may be overcome soon, and molecular profiling may herald a new approach to testing in leukemia and, by extension, other cancers.

**Current Evaluation**
- Morphologic features
- Flow cytometric analysis
- Cytogenetic–FISH analysis
- Molecular studies

**Future Evaluation**
- Molecular profiling
- Real-time PCR
- Microarray analysis
- Next-generation sequencing

**Challenges**
- Testing will need to be rapid if results will affect choice of induction regimen
- Clinicians will need to decide whether to do panel testing or whole genome or exome sequencing
- The role of standard morphologic, flow cytometric, and cytogenetic-FISH testing will need to be evaluated
- Cost will need to be assessed

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