ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Are We Ready for Precision Medicine in Acute Myeloid Leukemia?

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H&O In what way do genetic mutations lead to the development of acute myeloid leukemia (AML)?

GR Many mutations have been identified in patients with AML. Two of the burning questions we have in AML biology are, how are these mutations acquired and how do they lead to the development of the disease? We do not know the answers to these questions. Most cases of AML are not inherited, but there are some examples of inherited genetic mutations that are associated with AML. Most of the time, the mutations are acquired, or somatic. We do not know exactly why this happens.

Certain mutations associated with AML have prognostic importance. For example, patients with a double mutation in a gene called CCAAT/enhancer binding protein alpha (*CEBPA*) often have an excellent prognosis, whereas patients with a mutation in fms-related tyrosine kinase 3 with internal tandem duplication (*FLT3*-ITD) are likely to require aggressive treatment with chemotherapy and stem cell transplant to be cured.

In some cases, a targeted treatment may be available against a specific mutation. For example, FLT3 inhibitors are being tested for patients with *FLT3* mutations. However, just because a targeted agent may be available does not mean that the disease is more easily cured.

To make matters more complicated, an individual patient may have one or several mutations associated with his or her particular disease at the time of diagnosis, but these mutations may change over time. Mutations sometimes disappear at the time of remission, and different ones may appear at the time of disease relapse. We do not yet know how frequently to monitor mutations and how exactly to track and interpret their comings and goings during treatment. Following the rate and extent of clearance of mutations in AML after treatment is an area of intensive investigation. There are also worldwide efforts to test molecularly targeted agents and figure out how to best use them, either alone or in combination with chemotherapy.

H&O What type of diagnostic testing should be done in patients with suspected AML?

GR The baseline evaluation of a patient with suspected AML must include flow cytometry for immunophenotyping and cytogenetics (see Table). Many centers also perform a fluorescence in situ hybridization (FISH) panel to test for abnormalities that are associated with myelodysplastic syndrome and AML. For example, a FISH panel can detect the presence of core binding factor inv(16) or t(8;21), both of which are associated with a better prognosis. Molecular genetic testing also is increasingly becoming standard practice, although different commercial laboratories have significantly different panels of genetic tests. The National Comprehensive Cancer Network guidelines consider testing for nucleophosmin (*NPM1*), *FLT3,* and *CEBPA* mutations to be part of the standard of care. Commercial laboratories typically offer testing for these mutations as part of a larger panel of genetic tests, so oncologists and patients may be faced with a long list of abnormalities, some of which have no known impact on a patient's treatment. It can be confusing for patients and their doctors to wade through mutation

Table. Important Diagnostic Tools Used in Acute Myeloid Leukemia

- Morphology
- Flow cytometry
- Cytogenetics
- Fluorescence in situ hybridization (FISH)
- Polymerase chain reaction (PCR)
- Molecular genetics

profiles and try to figure out which ones may be relevant to treatment planning. For now, only information about *NPM1, FLT3,* and *CEBPA* mutations drives routine clinical care, whereas information about other mutated genes has the potential to be relevant for a clinical trial or possibly off-label use of a particular agent.

H&O How does information about mutations affect prognosis and treatment?

GR Approximately 30% of patients with AML have *FLT3* mutations. Most of these *FLT3* mutations are ITD mutations or point mutations of the tyrosine kinase domain (TKD). As I mentioned earlier, the *FLT3*-ITD mutations are associated with highly proliferative disease and usually carry an inferior prognosis. These patients are unlikely to be cured with chemotherapy alone, and should be considered for allogeneic stem cell transplant in first remission, for a trial of a novel agent, or for both.

Some patients with a mutation in *FLT3* may benefit from sorafenib (Nexavar, Bayer). Insurance does not always cover sorafenib for patients with AML because it is not approved by the US Food and Drug Administration (FDA) for this indication, so a clinical trial may be the best option for patients with a *FLT3* mutation.

Interpretation of molecular data in AML is challenging because factors such as allele burden, other concomitant mutations, and the clinical scenario are also relevant. For example, not all patients with a *FLT3* mutation have a poor prognosis. Data suggest that *FLT3* alone does not predict poor prognosis among patients in their 70s, 80s, and beyond, so we should not use the presence of this mutation to withhold treatment from older patients. Also, the overall prognosis is better when a *FLT3*-ITD mutation is present concomitantly with an *NPM1* mutation, and a *FLT3*-TKD mutation is slightly more favorable than a *FLT*-ITD mutation.

Also, the effect of *FLT3* mutations on the prognosis of patients with core binding factor mutations, such as inv(16), is less clear. Some data suggest that the presence of this mutation may worsen the prognosis in comparison to inv(16) alone, but other series have failed to corroborate this. It has not been standard to offer an allogeneic transplant in first remission to patients with a core binding factor mutation plus a *FLT3* mutation, but this is an area of controversy.

My point is that the presence of a *FLT3* mutation does not always mean a poor prognosis. These are some of the reasons why physicians in more general oncology practices who do not see many patients with leukemia should seek additional information or advice. The situation is not as simple as *A* mutation leading to *B* result; there are many exceptions to the rule.

Patients with normal cytogenetics and an isolated mutation in *NPM1* have a relatively favorable prognosis and generally are not referred for allogeneic stem cell transplant in first remission. New data suggest that quantitative monitoring of *NPM1* transcript levels, or minimal residual disease, is important to assess response to treatment and for predicting relapse. Hopefully, it will be possible to design treatments that can eradicate minimal residual disease that remains after intensive chemotherapy. Patients with biallelic mutations in *CEBPA* also generally have favorable outcomes after standard chemotherapy and are not typically referred for allogeneic stem cell transplant in first remission. Routine monitoring of minimal residual disease for these patients is not yet part of the standard of care.

H&O What other mutations play a role in AML?

GR Mutations in isocitrate dehydrogenase 1 (*IDH1*) and isocitrate dehydrogenase 2 (*IDH2*) are of great interest because of their central role in cellular respiration and basic biological processes and, of course, ongoing clinical trials of IDH1 and IDH2 inhibitors. Inhibitors of IDH1 and IDH2 have produced some exciting preliminary results in clinical trials when used as single agents in patients with AML who have *IDH1* and *IDH2* mutations.

Still, we are not yet routinely able to identify a treatment plan for a particular patient based solely on mutational profile. First of all, most patients have several mutations. We do not know how the targeted therapies will fare if their target is just one of a collection of mutations. Secondly, using a targeted agent to apply selective pressure to 1 clone may permit other leukemic clones without the mutation to rise up. In AML, we are not yet in a position to forgo multiagent therapy in favor of monotherapy, which may only work in the short-term. Another important ongoing area of research is in

identifying which mutations or mutation profiles may be part of familial hematologic malignancy syndromes. This type of information has significant implications for families of patients with leukemia and other hematologic malignancies, as well as for the selection of related donors for stem cell transplant. Despite the advances in precision medicine, I would caution that we still are not close to curing AML.

H&O What should the role of clinical trials be in AML?

GR Patients with AML should at least consider enrolling in a clinical trial if possible because outcomes with standard treatment are generally unfavorable for both older and younger patients. Now, in the age of molecular genetics, it is more important than ever to study patients in clinical trials. AML is rare, so being able to study mutations that are present only in subgroups of patients requires capturing every possible patient in clinical trials. We do not want to have to wait 10 years to enroll enough patients for the results to be statistically significant.

H&O How should acute promyelocytic leukemia be diagnosed and treated?

GR Cytogenetics and FISH should be used to diagnose the acute promyelocytic leukemia subtype of AML, which is characterized by t(15;17). We should use all-trans retinoic acid (ATRA) to treat patients with suspected acute promyelocytic leukemia, even prior to the diagnosis being confirmed. This is a rare example in oncology in which early treatment is essential, because the disease can lead to death in just a few days. Treatment with ATRA is so benign that there is no reason not to implement it immediately if the clinician has even the smallest suspicion of acute promyelocytic leukemia.

H&O Will future agents for AML depend on molecular testing?

GR I believe that we will become better and better at using molecular diagnostics for prognostication, treatment planning, and following the results of treatment. For example, use of an IDH1 inhibitor would depend on the demonstration of an *IDH1* mutation, at least in theory. What is not clear is whether a specific companion diagnostic would be required in order to use the agent, or whether testing from a commercial laboratory would be acceptable.

A phase 3 study recently showed a survival benefit from the investigational FLT3 inhibitor midostaurin in combination with chemotherapy, so we will likely see approval of this agent by the FDA in the near future. Still, the exact application of this agent for AML patients with a *FLT3* mutation is not completely clear. For example, although it is clear that midostaurin should it be used in combination with induction chemotherapy, its roles alone or in combination with chemotherapy during consolidation and/or after allogeneic stem cell transplant need to be clarified. We hope that clinical trials will continue even after midostaurin is approved, so that doctors and patients can learn more about its optimal use.

Disclosures

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Suggested Readings

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