Clinical Challenges with New and Emerging IDH1/IDH2 Inhibitors

Jorge E. Cortes, MD
Deputy Chair and Professor of Medicine
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Welcome to *Managing AML.* My name is Jorge Cortes, and I would like to address an important issue in the management of patients with IDH1 or IDH2 mutations with some of these new drugs that are inhibitors of IDH. It's important because two of these drugs, one an IDH2 inhibitor (enasidenib) and one an IDH1 inhibitor (ivosidenib), are already approved and some others are on their way. Responses to these drugs may take some time to occur. It is important because patients need to be maintained on therapy. I'll describe two scenarios that may represent clinical challenges that are important to recognize to avoid unnecessary changes of therapy.

One is the possibility of a patient showing an increase in the white cell count, even the blast count, during the course of therapy. This frequently represents a differentiation syndrome and many times it's associated with fluid retention, peripheral edema, hypoxia, etc. This can be managed with hydroxyurea to control the white cell count, with diuretics, with corticosteroids, sometimes a brief treatment interruption of the drug, and then you can continue therapy.

The other scenario is patients that have only stable disease or perhaps just a minor improvement in the blast, but really have not achieved a complete remission after one cycle or two cycles. We need to keep in mind that part of the effect of these drugs is, as I mentioned, some differentiation, so response takes some time to occur. Patients that have stable disease may later on, and sometimes very late, evolve into a patient with a complete remission over time. As long as the patient is stable and tolerating the treatment well, the best approach is to continue the treatment. There has been an analysis with the IDH2 inhibitor, for example, on patients that have had a stable disease for 90 days (three months on therapy) and only had stable disease. What the analysis of the pivotal study showed is that among those patients, about 25% to 30% of patients eventually achieved a complete remission after day 90, or at least a CRp (complete remission with incomplete platelet recovery). Another 45% of patients maintained the stable disease and still were doing well with the continuation of therapy, and some of them eventually may have progressed to a complete remission, etc.; and only about a quarter of patients had progression of the disease after day 90.

This underscores that probably three-quarters of the patients may still have clinical benefit – including achievement of complete remission – even if they've only had a stable disease after 90 days. This is important to recognize and maintain the patients on the drug as long as they're tolerating it well and having a stable disease. Thank you for your attention.