What is the approach to the management of differentiation syndrome arising after therapy with IDH inhibitors?

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Welcome to *Managing AML*. My name is Dr. Amir Fathi, and I'm going to go through some questions that are frequently asked regarding the management of AML. One question is: What is the approach to the management of differentiation syndrome arising after therapy with IDH inhibitors? One of the manifestations of therapy with IDH inhibitors that I've seen in my practice and has been actually published on relatively recently is the development of differentiation syndrome.

IDH inhibitors work by suppressing the production of the oncometabolite 2HG. 2HG is a key suppressor of TET enzymes that are involved in the process of myeloid differentiation and maturation. When TET is suppressed from heightened 2HG, there is aberrant hypermethylation of genes that usually help differentiate the myeloid cells, and they are no longer differentiated, so when you suppress 2HG, allow TET to do its job. Release the block on myeloid differentiation, cells differentiate, and that process of differentiation, that therapeutic process of differentiation can have an inflammatory aspect to it.

Differentiation syndrome is a pleomorphic diverse manifestation of that inflammatory process and can manifest in a very diverse way. Patients can come in with unexplained fevers, pulmonary infiltrates, hypoxia, cough, pleural effusions, rash, renal failure, adenopathy. The challenge is that these manifestations are also a feature of infections, common in AML, cardiopulmonary compromise, common in AML, and even AML progression itself, so how do you tease these out? Sometimes it's impossible because they mimic each other.

What I say is if there is a concern for differentiation syndrome after starting therapy, generally arising about two weeks to six months after therapy, a long window, I realize, but if the symptomatic manifestations are suggestive of differentiation syndrome, I would not ignore it. If you're also worried about infection, you can treat the infection. If you're worried about cardiopulmonary issues, treat that as well, treat the leukemia. Also, if it's consistent with differentiation syndrome, if there is worry for differentiation syndrome, that should be treated. The treatment is dexamethasone, generally 10 milligrams twice daily and continued until the patient gets better. If it is differentiation syndrome, they should get better relatively quickly and you can taper down the dexamethasone after that.

Differentiation syndrome can also be accompanied by hyperleukocytosis, a rapid rise in white blood cell count, in which case hydroxyurea may be needed. It can be accompanied by a tumor lysis syndrome or disseminated intravascular coagulation, and those have to be managed. It's a very challenging syndrome and should be looked for vigilantly and managed. I will say that just stopping the drug will not lead to a prompt stoppage of differentiation syndrome because of the long half-life of these drugs. The treatment is really steroids. You can stop the drug but that should not be the first step.