ManagingAML

Third-generation FLT3 inhibitors in clinical development

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Welcome to Managing AML, I am Dr. Alexander Perl. I am going to take a minute to discuss third-generation FLT3 inhibitors in clinical development. We know the first-generation inhibitors were relatively nonselective, multi-kinase inhibitors: these include midostaurin, sorafenib, and lestaurtinib (which is no longer in clinical development). These drugs all shared the ability to inhibit FLT3 along with a number of other kinases that unfortunately limited their single agent activity in the clinic, because as we would increase their doses we would find it would have a lot of off-target toxicity. The second generation of drugs, however, were much more potent against FLT3, much more selective against FLT3, and were able to be given at doses that would potently inhibit FLT3, and led to better clinical outcomes as single agents. Those drugs include quizartinib, gilteritinib, and crenolanib. One problem that we saw, however, as we became more selective for FLT3 inhibition is that we would see drugs that would select for resistant clones that would have a new mutation in FLT3 that would not be inhibited by the drug that was being used for therapy, and so in order to develop drugs that would be able to inhibit all the different potential for mutations in FLT3, one development has been the advantage of a drug that inhibits not the ATP-binding pocket, but covalently binds to FLT3. This is analogous to how ibrutinib inhibits BTK in the therapy of CLL. One other advantage of this drug is that we know that there can be resistance to FLT3 inhibitors that is mediated by binding of FLT3 ligand to leukemic blast. This can shut off the ability of the drugs to inhibit their target, and it would be expected that a covalently binding irreversible inhibitor might be able to guard against FLT3 ligands' ability to overdrive the FLT3 kinase. Currently being developed is a drug called FF10101-01 which is a drug that is an irreversible inhibitor of FLT3, and this is undergoing phase 1 testing. We still do not have any data available for this drug, but the idea is that it might be better in terms of both preventing primary resistance mediated by FLT3 ligand upregulation, and also secondary resistance that happens from mutations that occur in FLT3 during therapy. Thank you for listening.