Can we predict which patients will response to a JAK inhibitor?

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Dr. Kuykendall: I'm Andrew Kuykendall from Moffitt Cancer Center in Tampa, Florida. The question here is, “Are we able to predict which patients will respond to a JAK inhibitor?” I think this is a nuanced question. I think that it depends on how you frame this. Certainly, we have this RR6 model, which addresses worse overall survival in patients treated with a JAK inhibitor, and with this, we focus on patients that receive suboptimal doses of ruxolitinib, patients that do not achieve a spleen response. Patients that had developed transfusion dependency during the course of therapy, or at baseline.

Those are the patients that when treated with a JAK inhibitor are expected to do worse overall. That's slightly different than looking at who's predicted for a response to a JAK inhibitor. We can look at that as well, and I think prior studies have retrospectively looked at the COMFORT study, and looked at things that predict for that. Some studies have suggested larger spleen size, maybe less likely to respond. Other studies have not shown that. I think dose is a consistent factor that plays into this. Patients that are not able to get to say 15 or 20 milligrams twice a day are less likely to get a spleen response, and those that are on 10 or even lower doses, really 5 milligrams twice a day is just not a very effective dose really in terms of spleen or symptoms. We know at least 10 milligrams twice a day is important there.

The other thing I would say is, people that have a lot of mutations, so not just a JAK2 or CALR MPL mutation, but additional mutations, what we call molecular complexity, I think those patients are also less likely to respond or have durable responses to JAK inhibitors. I think that a lot of factors play in. I think we think about dose, you're also thinking about what impacts dose. Thrombocytopenia, patients that have thrombocytopenia are less likely to respond to say ruxolitinib, but that doesn't mean they're less likely to respond to other JAK inhibitors.

We've shown the data for fedratinib, obviously pacritinib and even momelotinib, these lower platelet counts seem to be able to achieve responses despite having thrombocytopenia, even though we see that as a risk factor or lack of response with ruxolitinib. It really just appears that the dose is what matters there.

Prithi, any thoughts there as well?

Dr. Bose: Certainly, Andrew, like you said, initially there were very few factors that predicted response to ruxolitinib. It seemed to work for all patients. When the initial studies were done, there were really no biomarkers. It works irrespective of driver mutation, for example, et cetera, but then, we've slowly found out that, yes, if there are a lot of other mutations, like you said, then the responses are lower. Perhaps even lower JAK2 allele burdens don't respond as well to ruxolitinib.

We've learned those things along the way, then also as you alluded to work from Francesca Palandri about large spleens and a long disease duration before you start the drug can also be negative predictors of response. Yes, we know those things, and there's certainly something to be said for starting ruxolitinb early. Again, we know that it's a reality that there will be issues with cytopenias transfusion requirements and this RR6 model that you and others have put together is a useful framework to objectify for clinicians. I believe there is an online calculator* for this that can help in terms of pointing out which patients are less likely to do well because the dose they're getting is not enough. Their spleen response is not that great, and they're requiring blood transfusions. I think those things are useful, but ultimately, of course, a lot of it is still a little imprecise and requires clinical judgment.

* DIPSS Plus Score for Prognosis in Myelofibrosis Online Calculator
https://qxmd.com/calculate/calculator_315/dipss-plus-score-for-prognosis-in-myelofibrosis

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