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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Optimizing Treatment of Metastatic G/GEJ Cancers: Balancing Efficacy and Adverse Effects With Combination Regimens

Announcer:
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Dr. Klempner:
Hi. My name is Sam Klempner. I'm a GI Medical Oncologist at Mass General in Boston, and I'm joined here by my colleague, Dr. Yelena Janjigian from Memorial Sloan Kettering, and we're going to be talking about balancing toxicity and efficacy in frontline management for gastroesophageal cancers.

So Dr. Janjigian, I'm going to kind of run through the sort of high-level tools we have, and then I'm going to ask you to sort of talk a little bit about class-specific effects in particular, and how you think through balancing toxicity and efficacy now that we're getting more and more tools.

So in HER2-positive patients, we have trastuzumab plus or minus checkpoint inhibitors. In MSI high patients, we have PD-1 plus or minus chemo. And then presumably in the near future, in claudin-positive patients, we'll have zolbetuximab plus chemo. So maybe go from immunotherapy to trastuzumab to zolbetuximab in terms of key toxicities people need to know and how you sort of monitor and manage.

Dr. Janjigian:
Absolutely. What we know about these agents is that the efficacy of targeted agents alone in our disease is not as robust as in combination with chemotherapy. So what we need to get used to as clinicians is managing adverse events related to the combination of these agents, and being able to tease out which one of these is causing the most of the problems, so that you know whether or not you are able to rechallenge or continue with the treatment.

So 5-FU platinum is our mainstay treatment, right, usually FOLFOX type of regimen. And with these regimens, in combination with HER2-directed agents, we've had relatively good track record for efficacy and tolerability, and now that with KEYNOTE-811, we're adding to a combination of trastuzumab plus immune checkpoint blockade and chemotherapy. You know, the tolerance suggests that combination of those agents can be given very safely.

The only crux of it is long-term use. Obviously, for HER2-directed agents, you have to monitor echocardiograms, and that's been important. Although there is a very low risk of immune-related adverse events, they're also possible.

Where things get complicated a bit is when you get into claudin inhibitor therapies. You know, obviously it's a class effect of claudin inhibitor, because it's a cell adhesion molecule, you can get nausea. So are you having nausea from the chemotherapy? Or are you having nausea with claudin inhibitors? There is, you know, as you're getting increasingly comfortable using these agents in the clinic, we do see the difference between quality and the type of nausea patients get with claudin inhibitors and how best to treat it. Sometimes you get, you know, these manifestations of on-target effect during the actual infusion, where people get really uncomfortable, dry

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heaving, and vomiting, and abdominal pain. So I think when in doubt, use nausea medicines. It helps with both. Use of olanzapine has really been accepted by ASCO as monitoring and treatment of chemotherapy, and now even potentially claudin inhibitor-induced nausea.

So and then lastly, with immune checkpoint blockade, that's particularly tricky for clinicians, because anything could be related to immune checkpoint blockade. Usually, you know, mild transaminitis or other immune-related adverse events, so you have to monitor them carefully. And when in doubt, the way that I approach it, since it's palliative care, I hold both chemotherapy and immunotherapy. And if things are getting dramatically better within a day or two without any steroids, you know, they're not immune related, they're probably chemotherapy related.

Dr. Klempner:
Yeah, I agree. I think maybe in the last minute, I'm going to ask you a couple nuances about the claudin. You know, it's like when you get something new, it's a learning curve. You get a new pet, you get a new phone, you've got to learn all this new stuff.

So for the listeners, you know, maybe tell us a little bit about some of the nuances of claudin management, like it, or nausea management in claudin, like timing and presence or absence of stomach, you know, relationships.

Dr. Janjigian:
Yeah, thank you for that. Thanks. That's a great point. So it takes time to kind of tachyphylax to the claudin effect. So over time, when you can reassure the patients, it looks like over 3 months or so, the nausea will improve, it's not going to stay as to the same degree. Second is if you have your stomach out, if you had a gastrectomy and then the cancer occurred, it's unlikely you're going to have any nausea. So actually, you can try and de-escalate nausea medicines pretty quickly.

And then lastly, slowing down the infusion or splitting it over two days actually has been dramatic improvement in nausea. And all of those tricks we're starting to get used to in the clinic to manage nausea related to claudin inhibitors. Of course, they're cumbersome to our chemotherapy units and take a lot of time and planning, but it's doable to get these drugs in.

Dr. Klempner:
Yeah, agreed. Thanks for joining, and always good to see you.

Announcer:
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