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

ICIs & Gastrointestinal Side Effects: What You Need to Know

Dr. Buch:
Immune checkpoint inhibitors, or ICIs for short, have revolutionized the treatment of cancer, but there are many important gastrointestinal side effects we need to take into consideration.

This is *GI Insights* on ReachMD. Joining us today is Dr. Rashid N. Lui, a specialist in gastroenterology and hepatology from the Chinese University of Hong Kong. Dr. Lui has published extensively and received numerous awards for his work in this field. Dr. Lui is also the lead author of a study, titled “Management of Gastrointestinal Side Effects of Immune Checkpoint Inhibitors” published in Clinical Gastroenterology and Hepatology in 2021.

Dr. Lui, welcome to the program.

Dr. Lui:
Hi, Dr. Buch, and thanks so much for inviting me to this.

Dr. Buch:
Dr. Lui, to start us off, can you tell us which of the ICIs is more likely to result in GI and liver side effects?

Dr. Lui:
That's a very good question. The cytotoxic T lymphocyte associated antigen for inhibitors are known to cause more problems of the GI tract and also liver toxicities, and we also know that combination immune checkpoint inhibitors, so when you give a CTLA-4 inhibitor together with other type of immune checkpoint inhibitors, which are known as cell protein—programmed, protein 1 or its ligand PD-L1, if they are given in combination, then we also know that the risks of having GI and liver complications are higher.

Dr. Buch:
And how do you evaluate and treat patients with suspected ICI diarrhea?

Dr. Lui:
So, it's actually quite similar to when we make a diagnosis of inflammatory bowel disease. There's actually no single good test that we can rely on. It's a clinical diagnosis, made largely by exclusion, so you have to take a detailed history, do an examination and also blood tests, the routine blood tests like inflammatory markers, the C-reactive protein, the ESR, etc. And similar to inflammatory bowel disease, some stool tests that are markers of inflammation, such as lactoferrin or calprotectin can also be used. And these have to be coupled with sometimes with cross-sectional imaging, with endoscopy, and also the histology to really, get the final diagnoses.

Of course, we also have to rule out enteric infections and other possibilities would be other like drug side effects, because a lot of time these patients might be on other treatments, such as chemotherapies, and chemotherapies can also cause side effects that might have a similar profile. And also the tumor itself, like it might have like tumor hyper-progression or some tumor-related side effects or symptoms, so that's usually a thought process when we're encountering these patients that were given immunotherapy and develop, these constellation of symptoms.

Dr. Buch:
So just honing down just a little bit further, can you just tell us the criteria for doing colonoscopies in these patients?

Dr. Lui:
That's a very good question. Actually, there are various guidelines available. We have the European Society for Medical Oncology, the ESMO guidelines. We have the American Society of Clinical Oncology guidelines, the ASCO guidelines. And recently, the American

Gastroenterological Association also published their critical practice update. And usually if the grade and/or the severity of diarrhea is mild, we usually just monitor, and it might not really require endoscopy for mild cases, but if the patient develops more profuse diarrhea, or if we're worried about competing diagnoses, then we have a very low threshold to subject these individuals for colonoscopy because the main points would be several-fold. The first would be to have an endoscopic and also obtain histology for a histological diagnosis, and the second would be we could also try our best to rule out other differentials, such as enteric infections or cytomegalovirus infections, especially in these cancer patients who are known to be immunosuppressed.

Dr. Buch:
That's great. I really appreciate that information. So, now we're going to ask a little bit more difficult kind of question. What are your thoughts on using ICIs in patients with inflammatory bowel disease?

Dr. Lui:
That's also a very common question that comes up in the clinics. There has been a retrospective study that showed that preexisting inflammatory bowel disease, patients they were find to have an increased risk of having severe gastrointestinal adverse events, when they are treated with immune checkpoint inhibitors. But firstly, this is a retrospective study, so with their inherent biases. We have to take this into the context because these patients, they might have stable inflammatory bowel disease for a long time and suddenly they have this really dreaded diagnosis of an advanced malignancy, and much of the time, when we're using immunotherapies, it might be, one of the later lines of treatment or the patient might have already not responded to prior, more conventional treatment arms. So, in that context, I think it's really important that we tell the patients that, 'Yes, you might have a theoretical increased risk of these complications,' but, I think in the broader sense of things, if it's to treat an advanced malignancy that's progressing really rapidly, which might have a immediate impact on health, I think we have to frame it in a way that we tell them, frankly, about the risk of complications, but then we should be giving them some reassurances that as gastroenterologists, we'll be there to help them manage the complications if they do arise, and taking care of them together with the oncologists.

Dr. Buch:
That's great. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Rashid Lui about the GI side effects of immune checkpoint inhibitors.

So, Dr. Lui, let's shift gears and focus on side effect prevention. Should we be considering prophylactic budesonide or other medications to prevent ICI colitis?

Dr. Lui:
That's a good question as well. I think up-to-date currently there's actually no good data that mesalazine or 5-ASAs are useful to prevent, these immune checkpoint inhibitor-related colitis. Actually, in a lot of these patients, diarrhea might occur like in around 40 to 50 percent of patients, especially if they are, like, taking combination immune checkpoints, but if we're talking about an effective diagnosis of colitis which we mean by endoscopic findings and also from biopsies, that actually is a bit lower. If you're just using single, agent immune checkpoints, we're talking about maybe in the range of around 10 to 20 percent, only. So, I think the risks of having these side effects definitely does not outweigh the benefits of using immune checkpoint inhibitors. And, if only like around 10 to 20 percent of patients will develop it, I think, an easier way to manage and not make them so anxious about using these drugs is just say that we'll be keeping a close eye on their symptoms, and if they do develop, we'll be there to check in on them as soon as possible.

Dr. Buch:
So let's move on to ICI hepatitis. How should we be managing that?

Dr. Lui:
Immune checkpoint inhibitor in hepatitis is actually slightly less common than that of colitis, and management, again, we have to stratify usually whether they are mild elevations of the liver transaminases or if it's moderate or more severe elevations. For mild elevations, usually we just monitor. We could keep the ICIs on board, with close monitoring. If the patients do develop a bit worse of liver functions or raised bilirubin, etc., then usually have to recode the immune checkpoint inhibitors and start systemic steroids. And, if the liver functions progressively get worse or there's no good response, then we might have to use second-line immunosuppressants, which usually include some conventional immunosuppressants, such as MMF, mycophenolate mofetil, or even tacrolimus.

Dr. Buch:
Before we conclude, are there any other insights you'd like to share with our audience today?

Dr. Lui:
I think it's worth mentioning for immune checkpoint-related colitis, so after initially, if it's less severe, then we just monitor. If it's worse, we would withhold the immune checkpoint inhibitors again and consider starting some systemic steroids. And if that doesn't work, then

the treatment algorithm is actually quite similar to that of severe fulminant ulcerative colitis where we have to consider an early usage of, anti-tumor necrosis factor, biological agents. And if that doesn't work, anecdotal reports that we resume MAB or even off-label use of fecal microbiota in transplant patient has also been discussed. And, in most centers, and including ours, we would also refer very fulminant cases for our surgeons to consider colectomy, as is in the case of severe, ulcerative colitis, but the usual reply would be that they're not fit for surgery because, we have to keep in mind that a lot of times these patients are having advanced malignancies and they might not be very good, or ideal candidates for major surgery.

Dr. Buch:
With these, extremely important insights in mind, I want to thank my guest, Dr. Rashid N. Lui, for an excellent discussion. Dr. Lui, it was a pleasure having you on the program today.

Dr. Lui:
Thank you, Dr. Buch, and ReachMD. It was indeed my pleasure to be sharing my insights on this. Thank you so much.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit reachmd.com/GI-Insights, where you can Be Part of the Knowledge. Thanks for listening, and see you next time.