Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/living-rheum/diagnosing-and-treating-immune-checkpoint-inhibitor-colitis-effectively/32873/

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

Diagnosing and Treating Immune Checkpoint Inhibitor Colitis Effectively

Dr. Buch:
This is *GI Insights* on ReachMD. I'm Dr. Peter Buch, and today I'm joined by Dr. Yinghong Wang, who is a Professor in the Department of Gastroenterology, Hepatology, and Nutrition at MD Anderson Cancer Center in Houston, Texas. She has many other credentials, including Director of the Oncology-GI Toxicity Program, Director of Fecal Microbiota Transplantation, Deputy Division Head of Research, Division of Internal Medicine, and Chair - MD Anderson Cancer Center Immunotherapy Toxicity Working Group at the University of Texas MD Anderson Cancer Center. We'll be discussing immune checkpoint inhibitor colitis, also known as ICI colitis. Dr. Wang and her team have achieved multiple breakthroughs in the treatment of immunotherapy-induced colitis.

Dr. Wang, welcome to the program. I'm really looking forward to our discussion.

Dr. Wang:
Thank you for the nice introduction. It's my great pleasure to be here to share our experience and knowledge in the field of immunotherapy colitis.

Dr. Buch:
Dr. Wang, let's get started. What are the typical and atypical presentations of ICI colitis?

Dr. Wang:
Excellent question. Usually, the typical symptoms include diarrhea, rectal bleeding, mucus in the stool, abdominal pain, or fever. Atypical presentations may include some constipation complaints, anemia, fatigue, or rectal pain. So those are not the typical kind of symptoms that we hear from our patients that need to raise the flag whether we need to have those kind of evaluations as well.

Dr. Buch:
And moving ahead, what is the appropriate workup when considering ICI colitis?

Dr. Wang:
Yes. So the initial evaluation should include the stool studies to rule out infections, and then assessment for inflammatory markers. If the infection is excluded but the inflammatory markers are positive or elevated, then endoscopic evaluation is usually strongly recommended. In patients with significant abdominal pain or fever, then a CT scan of the abdomen should also be considered to rule out complications.

Dr. Buch:
And tell us, in your experience, do you ever find patients who have both ICI colitis and something else going on at the same time?

Dr. Wang:
There could be a coexisting infection, such as C. diff, and if the colitis is significant and causing perforations, then we do need to know, and the CT scan usually will help to clarify that condition. And you may see the perforation. You may see the intraabdominal abscesses.

Dr. Buch:
Thank you. And, Dr. Wang, after making the diagnosis of ICI colitis, when and how do you select appropriate therapies?

Dr. Wang:
Yes. The treatment selection depends on the clinical and endoscopic severity of colitis and should be initiated very promptly. For the mild cases, usually conservative symptomatic management is sufficient, and the ICI therapy can be continued. For the moderate-to-severe colitis, then immunosuppressive therapy is standard. Corticosteroids, such as prednisone, prednisolone, and budesonide are the

first line, followed by the biologic agents, such as infliximab, vedolizumab, ustekinumab, and tofacitinib. Response rates range from 60 to 85 percent, although there could be complications, especially with steroid treatments, such as infections, hyperglycemia, insomnia, anxiety, etc. And we understand too, novel prospective clinical trials of frontline and salvage fecal microbiota transplantation has also demonstrated about 80 percent efficacy without immunosuppression exposure or after failure of this treatment. For those refractory cases, they may require second- or third-line biologic agents, although the efficacy tends to decrease with subsequent trials. The fecal transplant shows this 80 percent success even in refractory setting. So in the moderate-to-severe cases, the ICI therapies are usually held but can be resumed once the colitis remission is achieved.

Dr. Buch:
Thank you. And I've got some follow-up questions with regard to that. How often do patients with mild ICI colitis progress to something more severe?

Dr. Wang:
That's an excellent question. We don't have the exact number based on our retrospective data, but we do see a small subgroup of patients that do progress, and this progression can happen within a month, maybe with or without continuation of ICI during this time. So if a patient has reported a progression of their symptoms or persistent symptoms despite being on the appropriate treatment, then we usually, always, intensify our evaluation strategies to make sure that we monitor them closely and appropriate treatment is going to be implemented.

Dr. Buch:
Thank you for that. And the next follow-up question for that—you had described the more advanced kind of therapies—how do we choose among the more advanced therapies that we would use for a patient, because there are so many choices right now? Is there a preferential medication for ICI colitis, or is that data still being evaluated?

Dr. Wang:
I think the decision can be made based on multiple factors that the physicians need to take into consideration when you look at a case. For example, if the patient only has GI toxicity without other organ site involvement, then usually vedolizumab is my top choice, because it's a GI-targeted immunosuppression, so I have less concerns about counteracting effects with immunotherapy and maybe potentially taking away the benefit of immunotherapy for their cancer benefit. But for the patient who has other organ toxicity together with GI, then infliximab or ustekinumab may be my top choice because they can cover multi-organ sites to provide the benefit. So this is not something that vedolizumab can achieve, so the decision can be affected by that.

The other main impacting factor is the insurance coverage. So we may be limited by what the insurance preference is, although we do submit appeal letters all the time if we think that one is definitely a better fit for the case than the others. But otherwise, I think the efficacy is very similar based on my observation. The infliximab, vedolizumab, and ustekinumab—so far that's the most experience that we have in the literature and from our group as well.

Dr. Buch:
Thank you for that. And the further follow-up question with regard to item number three that we just talked about is stool transplantation. Is that pretty much standard of care right now in refractory ICI colitis?

Dr. Wang:
It is not a standard care, but it is a standard care for prevention of recurrent Clostridioides difficile infection, which is a common GI infection related to immunosuppressive conditions and immunocompromised patients, as well as frequent antibiotic use. And the antibiotic efficacy is usually low, up to 50 percent, but a fecal transplant efficacy is up to 90 percent, so we use this idea of introducing this healthy microbiome for our immunotherapy colitis patient because of robust translational or preclinical data. And based on that, and also our experience of the prospective clinical trials on the protocol for the past six years or so, we have demonstrated that fecal transplant has shown a very high efficacy of 80 percent for this refractory immunotherapy colitis and with very favorable safety profile.

Dr. Buch:
Thank you very much for that response. But in follow-up to that, should fecal transplants be used in a community hospital setting outside of investigational protocols?

Dr. Wang:
That's the future direction that I'm aiming for because I think based on all the existing data on the safety of fecal transplant for recurrent C. diff, even among the cancer population, which is the higher risk and vulnerable population, we have already demonstrated a very good safety profile. And if the efficacy can be also validated, then I think that's the future direction, as fecal transplant is such a fast-acting phase and a highly efficacious, natural treatment option for our patients. So if we can minimize the immunosuppression treatment

for our patient, I think that's a huge benefit for them.

Dr. Buch:
And when we're talking about the fecal transplant, have you come to use some of the other commercial products—the capsules, the enemas—that are commercially available in the last year or two?

Dr. Wang:
Yes, that's a that's a great question. So those are commercial products available within the past two years, and, we do use them routinely for our patient for recurrent C. diff prevention, and there is definitely interest on our end then to further investigate these commercial products to be used for immunotherapy colitis as well in the future. But currently, our protocol is using our research collaborator stool bank from UT School Public Health. That's the FDA-approved stool bank that has been used for multiple clinical trials they are running and as well as the collaboration with many academic centers in the US.

Dr. Buch:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Yinghong Wang about immune checkpoint inhibitor colitis, or ICI colitis.

So moving ahead, Dr. Wang, if a patient has a previous episode of ICI colitis, what governs whether these medicines can be restarted?

Dr. Wang:
Practice has shifted significantly in the recent years regarding that, and historically, oncologists usually avoided resuming ICI therapy after initial colitis episodes due to high recurrence rates. Usually, on our multicenter study, we have demonstrated it's up to 35 percent for PD-1/PD-L1 monotherapy at the time of rechallenge or as high as 80 percent with a CTLA-4 agent. However, the concurrent use of biologic agents, such as the infliximab or vedolizumab, during the ICI rechallenge can reduce the recurrent rate from about 37 percent to 17 percent. So the optimal timing of resumption is still under investigation, but generally, the ICI can be restarted once both the clinical and endoscopic remissions are achieved, which may take up to two months. And fecal transplant has also shown a long-term benefit, even after the ICI rechallenge, and represents another promising strategy to maintain patients on cancer therapy.

Dr. Buch:
Thank you. And moving on, how safe is it for patients with pre-existing inflammatory bowel disease to receive immune checkpoint inhibitors?

Dr. Wang:
Usually, IBD patients are typically excluded from clinical trials of IO and high-quality prospective data are limited. Retrospective studies, however, suggested that cancer outcomes are comparable to non-IBD patients. However, the risk of colitis exacerbation and the need for aggressive treatment are higher. Even with PD-1/PD-L1 monotherapy, those are being labeled as low-risk checkpoint inhibitors. Therefore, these patients require close monitoring, proactive management, and a high level of multidisciplinary attention and care.

Dr. Buch:
Moving on, how do immune checkpoint inhibitors affect the microbiome?

Dr. Wang:
The microbiome can be influenced by multiple factors, including the antibiotic used, the cancer itself, the therapy such as ICI, chemo, radiation or surgery, and these infections can definitely negatively impact both cancer outcomes and treatment-related toxicities. Our group has shown that the use of anaerobic antibiotics is associated with more severe immunotherapy-mediated colitis and worse cancer survivals. Therefore, the antibiotics should be avoided as first-line therapy for immunotherapy colitis unless infection is confirmed. Distinctive microbiome signatures are seen in the cancer responders or no responders and in patients with and without colitis. The fecal transplant from healthy donors has been effective in resolving refractory colitis and in some cases, has restored cancer responsiveness to PD-1 therapy, so these findings continue to inspire the investigations in the future into therapeutic roles of microbiome in cancer care.

Dr. Buch:
Do you recommend at all, at this point, any probiotics for patients who are taking immune checkpoint inhibitors?

Dr. Wang:
Actually, no. Based on scientific data, the over-the-counter probiotic formularies are not demonstrated to be beneficial. Instead, it may potentially cause harm to the cancer outcome among patients who are taking immune checkpoint inhibitors. Therefore, we don't routinely recommend our patients take over-the-counter probiotics when they take their immune checkpoint inhibitor for their cancer.

Dr. Buch:
And in the last few moments of our conversation, Dr. Wang, do you have any final takeaways you'd like to share?

Dr. Wang:
Yeah. There are many knowledge gaps remain in the management of immune-related toxicity, and addressing these challenges will require high-quality research and collaboration across the community to push the boundaries of current practice and improve the patient outcome.

Dr. Buch
Why don't you just tell our audience the protocols that you're running and your research assistant to contact if any of the clinicians want to get patients into the protocols?

Dr. Wang:
Yes, we have two ongoing prospective clinical protocols for fecal transplant. One is for refractory immunotherapy colitis, and one is a frontline treatment of fecal transplant for immunotherapy colitis, and both of them are listed on clinicaltrials.gov. You can use the keyword and my name. You should be able to find those trials and enrollment status, as well as the contact information. And we are currently open for enrollment. And also, soon we will have another trial opened that will investigate the role of ustekinumab in treating immunotherapy colitis, which we'll keep updated on clinicaltrials.gov.

Dr. Buch:
I want to thank my guest, Dr. Yinghong Wang, for a comprehensive review of immune checkpoint inhibitor colitis. Dr. Wang, it was a pleasure speaking with you today.

Dr. Wang:
It's a pleasure.

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