[MUSIC PLAYING]

ANURAG SINGH: When you see one of my patients, we're going to talk about head and neck radiation mucositis pain management. There's one thing you need to remember. Do not prescribe them anything. OK?

So the abstract is left blank, so that you can write down, do not prescribe them anything. All right? If you forget everything else about this talk, just remember don't prescribe them anything. All right?

I have no disclosures of note. However, that is not for lack of trying. So if anybody knows anybody, OK, I'm available. All right?

Today, we're basically just going to go over the incidence and etiology, supportive care, a couple of new directions, and then a recent study that we're on the verge of publishing. Mucositis refers to mucosal damage secondary to cancer therapy occurring in the mucosa of the ailimentary tract. So this can actually happen anywhere.

I know we're all a concerned with above the clavicles. OK? But it can happen anywhere in the GI tract. Typically, it's very painful, requires opioid analgesics, and impairs nutritional intake and quality of life. Mary Platek will talk to you this afternoon about the nutritional intake.

So the incidence of mucositis. So if you've got a patient who's undergoing conventional chemotherapy, one or two out of every five of those patients will experience mucositis. If patients are getting high dose chemotherapy prior to stem cell transplant, that's going to be almost 80%. OK? That's a population that you need to be aware of but that we're not really going to talk about too much more in this talk.

For head and neck chemoradiation, which is going to be the focus here, it's 90 plus percent. All right? In fact, in about 1,000 patients, I would be hard pressed to recall one or two who made it through seven weeks of treatment without mucositis. So if we look at the incidence and go by the total number of patients, you see that the numbers are large. OK? And these are summarized in a chapter that we did a while back.

So how does mucositis happen? Basically, the concurrent chemoradiation does bad things to DNA. That activates nuclear transcription factor, NF-kappaB, which interacts with an interleukin and tumor necrosis factor and does a variety of other gene related things that ends up with what you see on the bottom, where you have the DNA injury. Then you get generation of messengers. You get apoptosis tissue injury. Finally, you start seeing the ulceration and the pain.

This is very important because patients will complain of pain before you can see it. OK? That is the natural history of the mucositis. And then finally, you remove the offending agent, and you get healing with new tissue growth.

So WHO grading, grade one is you're sore. But you don't necessarily have erythema. OK, so it's with or without erythema. WHO grade two, there are erythema and ulcers present. But the patient can still swallow solid food.

Grade three, now you've got ulcers with extensive erythema. And now the patient can no longer swallow food. And grade four is you've got mucositis to the extent that alimentation is no longer possible. And basically, they need TPN. Grade four, hopefully, you're only going to get with bone marrow transplant. But there is the occasional odd patient who will have some neutropenic fever and get problems throughout the entire mucosa.

Now as Dr. Ballard pointed out in his morning talk, right, you can still get abscess ulcers. So these patients are not immune from abscess ulcers. Please don't always blame the radiation. OK?

I love it when I've got a lung cancer patient that I give the left lower lobe 30 gray times one. And somebody will call me back and say they've got mucositis in the head. I said, boy, that must have been a really bad day because I missed by a lot. OK?

So mucositis prevention, so how can we prevent this as radiation oncologists? One thing that we can do is try to avoid as much of the mucosa as possible, right? And so you've got a radiation dose map.

The pretty colors just mean what dose it is. The warmer colors indicate that you're giving a higher dose. And you can see that we're sparing, in this particular case, we're sparing everything but really low dose to most of the anterior oral cavity.

Another thing that you can do is you can use bite blocks, right? So if you're treating a floor of mouth tumor, you can use a bite block, lift the maxilla out of the field or lower the jaw. And you can spare some of the mucosa that way.

Smoking-- or another bite block that we have started using is apples. So sometimes patients will have metal fillings. You know that the radiation beam is obligated to go through that area. The metal will interact with the low dose scatter electrons and scatter coherently, right? So that is repeatedly over and over into the same spot into the mucosa.

So for instance, if it's in the posterior, if you're treating a base of tongue tumor, and they've got a lot of metal in the posterior teeth, you're going to get some very severe hot spots. Those low dose scatter electrons can be absorbed by anything that contains a lot of water. Apples, I've found, are easily accessible. Patients can put them in their own mouths.

By the end of treatment, if their mouths are sore or you're having problems with opening, they don't have to necessarily put them in. It has the effect of displacing the normal tissue and absorbing those low dose scatter electrons. In my way of thinking, they're also delicious and nutritious. So it's a win-win-win all the way around.

And then finally, don't smoke. Smoking makes all of this much, much worse. OK? So a patient that you can get through treatment with minimal toxicity, when they're smoking, that toxicity will be several fold higher and occur much earlier in the treatment. OK?

So the thing I love best, you got to stop smoking. It makes a significant impact to your overall outcome. Yeah, doc, I gotcha. I gotcha. OK, when I tell patients that and they tell me that they've stopped smoking, I know for a fact that 50% of them are lying. OK? I know that.

I don't go through the rigmarole of testing their urine and proving it. Because at that point, what are you going to do? But you will say, hey, it's week two, and you've got grade three mucositis. How is that happening? Could you possibly be smoking?

Meanwhile, they've got the pack of cigarettes right here. OK? And they'll tell you, no, not doing it. Really? That's amazing because let me guess. I think you're smoking Marlboros. How'd you know? No clue whatsoever that the packet is right there. OK?

So nutritional support, again, Mary's going to talk about this. PEG tube, to prophylax or not to prophylax. Some of the surgeons in the audience, at your particular institutions, I'm sure you have a very strong and completely not evidence-based opinion about this. But generally speaking, there is some data now that patients who get feeding tubes actually have worse outcomes. We've found that in our population as well. But that's for another talk.

And then high calorie supplements. You really want to minimize the amount of transit time for the nutrition through the mucosa or the area of mucositis. And so my patients, in week six or seven of radiation, that's not the time to start with the kale and the broccoli. OK? So a nice solid Buffalo diet of high fat, high calorie foods. All right?

Now the MASCC/ISOO clinical practice guidelines for oral mucositis in head and neck cancer, this is going to become a repeated theme. OK? Dr. Praveen Irani is here. Stand up, Praveen, so that everyone can throw tomatoes at you. He's part of the guideline committee, and they repeatedly say, there's no evidence for but do it anyway, patient education, sodium bicarbonate rinse.

Strong evidence for benzydamine mouthwash for low dose radiation therapy up to 50 gray without chemotherapy. Guess what? That's no relation to head and neck cancer patients. Maybe lymphoma of the tonsil, something like that. But for the vast majority of your patients, this does not apply. And what's the one thing you need to remember? Don't prescribe anything to my patients, right? OK.

There is weaker evidence for a low level laser therapy in head and neck patients with RT without chemotherapy. This is in distinction to the bone marrow transplant patients where there is stronger evidence for that. That's your plug, Praveen. You owe me $5. OK?

And then there's multi-agent mouthwash for patients undergoing chemo RT. Now we get to the chlorhexidine. Heidi, I'm sorry. The guidelines say there is weaker evidence against. Don't do it.

SPEAKER: I didn't talk about using it during treatment because we don't prescribe to your patients.

OK, all right. Great. OK, so there's strong evidence against a lot of these other things, sucralfate, other things. Who here has prescribed any one of the four things that there's strong evidence against here? Come on. Nobody? All right. Dr. Hicks took the bullet for all of you that are unwilling to speak up.

OK, so now, however, we do have evidence for DLA, which is or otherwise known as BMX, right? So it's diphenhydramine, some lidocaine like agent, and an antacid, and doxepin. OK? So this is a paper that just came out in *JAMA,* looked at 275 patients undergoing radiation or chemoradiation with a three-way randomization to doxepin, DLA, or placebo. OK?

And I just want you guys to look at this is the pain score on a scale of zero to 10. So patients roughly had-- they were required to have a pain score or greater than four. And they did. And you see this is the time on the axis here. And what that shows you is that, yes, there is a drop with both of these agents.

What's interesting about this, and completely undiscussed in the manuscript, is that look at the placebo group. And actually, if you look at five minutes, the placebo group has the greatest effect. OK? So what does that tell us?

Well, that tells us, one, that the lidocaine and the doxepin actually burn while you're using them, right? So the placebo, which was just sugar water, is better after five minutes, right? But look at this.

Four hours later, the placebo is still hanging in there, OK, doing really well. So give them something, right? But the data, when you do the fancy statistics, does support either one of the two agents.

And there was a continuation phase of this study. And again, when you looked at it over multiple days, maybe there was a little bit more benefit to the doxepin than the DLA. But again, the placebo was not an insignificant effect over time.

So unilateral versus bilateral, I said I can avoid the oral tongue, and maybe that will help. Well, what if I avoid half the body altogether? So these are both oropharynx patients, N2b, but one is a well lateralized tonsil. And I treated only half of that patient. And the other is a base of tongue where I was obligated to treat both sides of that patient.

And you would think that if you treat less, you should have fewer side effects. Who believes that? If I treat less, I should have fewer side effects. Who is asleep and has just given up? All right. I'm going to assume that it's most of you.

So unfortunately, we looked at the data and had really good quality of life evidence. And there's not a darn bit of difference between either group. OK? So it turns out that you can think of it like this. If I put two people in a room, and I go in and I kick one of them in the shins, right, in one shin, and I go and kick the other one in both shins, they're both going to write me up. OK? So it doesn't really matter how objectively bad the insult was. The quality of life decreases.

All right, and then this is the last one that we're going to talk about. This is a study where we randomized patients to different pain regimens. The first one had high dose gabapentin, up to 2,700 milligrams per day. The second one had low dose gabapentin followed by methadone. So arm one, high dose followed by Lortab. Arm two, low dose followed by methadone.

It is a little complicated trial design. But we have a limited number of patients. And we wanted to ask a lot of questions. So we had to use a parsimonious design here.

So we found, as has been reported before, that prophylactic gapapentin reduces total opioid dose and unplanned treatment breaks, delays feeding tube use, and leads to earlier removal, and reduces unintentional weight loss. And there was a dose effect. So the 2,700 did a better job of all these things than the 900 did.

We also found that methadone was superior. And this is consistent with previously published data showing that it's long-acting, lacks euphoric side effects. Means that no one's going to break into your house for it. It's superior to fentanyl for head and neck cancer patients with neuropathic pain. And it's non-inferior for patients undergoing chemoradiation therapy.

In fact, not only did we find that it was non-inferior-- this is a schema of our patients. Not only did we find that it was non-inferior, but we found that, on a variety of quality of life metrics, favored the methadone. So all our patients now get high dose gabapentin and methadone.

It's made a tremendous difference. We actually get some population of patients through without any opioid analgesics at all. And everybody finishes on time. OK?

And the morphine milligram equivalents, so the total amount of narcotic that was required, was also really substantially reduced, cut by 1/3. But the numbers were too small to get a significant p-value. So thank you very much. And if you've forgotten everything else, what's the one thing you need to remember?

ALL: Don't prescribe to your patients.

ANURAG SINGH: Got it. Thank you.