[MUSIC PLAYING]

**KEITH KIRKWOOD:** I'm a periodontist. I see patients once a week down at Roswell. So I'm happy to share some of my experiences with you, not as a periodontist but more of a bone biologist in aspects of what I'm talking about today. So osteoradionecrosis necrosis and medication induced osteonecrosis of the jaws, I want to talk to you about today.

Disclosures are really related to federal grants and industry support for some of my science.

And today, I want to talk to you really about the differences between radiation-induced osteonecrosis and medication-induced osteonecrosis as well as understanding some of the mechanisms behind that because the mechanisms really allow us to deep probe into it's some of the therapies that we're now utilizing to treat and manage these cases. So understanding mechanisms, for those who know me, is sort of like what I like. Unlike Mehi who gets locked up in the basement somewhere with oral pathology. I get locked up in the ivory tower at the south campus of UB, so that I can focus on research primarily. And they let me out once a week just to be nice and play with others at Roswell.

So we're also going to talk about some of the newer therapeutics that are being utilized for managing both these conditions, both radiation-induced as well as medication-induced osteonecrosis and then really understanding preventive strategies similar to what Dr. Crowe had presented, really focusing on prevention, knowing that a majority of the audience here is in auxiliaries as well as hygiene. And so you guys play a significant role with this.

So the first slide really talks about bone biology. And we think about bone as sort of this static structure. But really, it's constantly going under renewal all of your lifetime. Every year, your skeleton is almost completely replaced three times that year.

And you have this bone resorption that occurs about three weeks. And about three months after that, you have deposition of new bone. So bone remodeling, OK, what occurs in adult skeleton, is dynamic and occurs constantly.

And so most of us think about this as something that is balanced. OK? And that balance allows the skeleton to maintain what we think about as homeostasis. OK? And then when it's imbalanced, OK, as a periodontist, I think about it with gum disease. But it could be in the context of any other inflammatory disease, rheumatoid arthritis, osteoarthritis, things like that, that can impact bone homeostasis. And so this impaction on bone really is how we think about the therapies that we can use to control this.

So osteoradionecrosis, Dr. Singh is the expert. I get to see some of the side effects of this downtown or, actually, across the street here. But head and neck cancer really has a large consequence with radiation-induced necrosis. So about 50% to 60% of patients who do have a cancer diagnosis will undergo radiation therapy following surgical therapies.

And about 5% to 15% of those will develop osteoradionecrosis of the jaw. So this is a significant side effect of radiation-induced necrosis. As Dr. Crowe mentioned, it occurs more in the mandible than the maxilla. It's also more prevalent in females versus males.

She covered some of the issues with trismus and pain, xerostomia, and prevention with this. Trauma from surgery seems to be the main issue. And this is induced by periodontists, for instance, or oral surgeons taking out teeth. Also just the trauma from healing.

So what Dr. Crowe was saying, extractions with alveoloplasty. And we have the residents at Roswell, and we talk to them about doing alveoloplasty with multiple extractions not only to facilitate wound closure, but a lot of these people need to have radiation done fairly quickly. And so you need to have primary closure before they can initiate this. And so that two to three week window of what we have to work with trying to get these teeth out before radiation is paramount for preventing this.

As a periodontist, I have to tell you that periodontal disease is a significant risk factor for this. Not only just severe disease, but any local factors that could be subgingival calculus and plaque, but also caries. Subgingivally, something adjacent to the bone margin is also going to help initiate this if it's untreated. So understanding that is really important not only for treating prior to radiation therapy, but management of these people afterwards, as well.

And I'll go through some other slides in a minute because radiation-induced osteoradionecrosis, if it's going to occur, primarily will occur within a three year window. But that's not absolute. You can have radiation induced necrosis years afterwards, sometimes up to 30 or 40 years after radiation-induced necrosis in some studies.

The thought processes about how this occurs really initiated with Robert Marx who is here for the greater Niagara meeting as a keynote speaker talking about these issues as well as medication-induced osteoradionecrosis. What he had promoted was the fact that hypoxia was one of the key things that contributed to this osteoradionecrosis. Since then, that paradigm has changed 'cause he came out with that in about 1983. In the last 10 years, there's been a shift in how this process occurs in the bone, and therefore how we address that therapeutically.

OK, so I want to go through some of those things. Because if you look at hyperbaric oxygen or increase oxygen to help treat and manage these, it's had marginal success. OK?

So some of the pathophysiology of what's occurring with osteoradionecrosis, there's three different phases. You don't need to memorize this, but basically this is an inflammatory response early on. And then instead of bone remodeling and-- I showed you on the initial slide with you have bone resorption option and then deposition of bone by osteoblasts, that's lost. It's all irregular kind of fibrosis.

So it's healing by essentially a scar within the bone cavity itself. It's very irregular and a lot of inflammation initially. And so that matrix that's laid down is disregulated, and you end up really with fibrosis within the jaw.

Schematically, this is illustrated here, where you have radiation-induced reactive oxygen species. And this actually has therapeutic implications because one of the agents that we like to use now, vitamin E, helps scavenge for these free radicals being produced. And this is part and parcel of how we think about the changes and how this is occurring with the therapies that we're using against this for trying to manage this. But a lot of this has to do with injury to the endothelium or the vasculature that prevents the nutrients coming in there, the vasculature coming in there to help renew the skeleton, at least in the jaw. So a lot of this is healing by fibrosis.

So therapeutically, the PENtoxifylline, TOcopherol, and CLOdronate-- which is actually a bisphosphonate and I'll cover that in a minute-- but these agents are actually very good at inhibiting some of the mechanisms that are involved with this fibrosis. So initially there was inflammation, toxifylline helps target some of the key inflammatory mediators, namely TNF alpha. It also can help with healing some of these radiation-induced injury, increasing the blood flow, increasing red blood cells' plasticity within this microenvironment to help heal it. OK? Vitamin E, as I mentioned, can act as a scavenger, and it also can help promote things like TGF beta, which is needed for wound healing and other mechanisms, as well.

CLOdronate-- and this is going to be very clear-- is not approved in the US for use, for the management of this. But there have been clinical trials both in Australia as well as in France or Belgium that have looked at this for healing after osteoradionecrosis. And what this does is it really helps reduce the numbers of macrophages that can become osteoclasts. So this decreases osteoclast number and activity really is by getting rid of the precursors that become osteoclasts that resorb the bone matrix itself. Also it increases osteoblast proliferation and formation, which is completely disregulated in this fibrotic event.

So in summary for this part, because I have two parts I have to talk about in 10 minutes, characterisation of this really occurs, as I mentioned, within the first three years. It has to be independent of a tumor, meaning this can't be a second primary tumor within the jaw. So it's independent of any cancer in the jaw itself. It's over 60 or 70 grays. Typically hygiene, periodontal disease, tobacco, alcohol use all contribute towards this. And what we do is conservative treatment initially if it's very small, but surgical management if it's larger.

So in the next five minutes or less, I will cover medication-induced osteonecrosis of the jaw. And this is a little bit different in terms of its mechanism, and therefore it's different in terms of how we're trying to address it, as well. OK? So this is really inhibiting osteoclast resorption. It also has implications for inhibiting angiogenesis and some of the mechanisms involved with this.

One of the main culprits-- and those who are dentists and treating in private practices, there's different forms of bisphosphonates. Some are taken orally for osteoporosis. Those aren't really the drugs that causes many problems, OK?

The incidence of osteonecrosis of the jaw following medications like low dose of bisphosphonates is really less than 0.1%. That's not a big problem. It jumps tenfold if you have higher doses, which are used to treat tumor metastasis, for instance lung, breast, prostate, going into bone, as well as hypercalcemia associated with malignancy. So these higher doses that are given intervenously are the ones that cause this side effect, OK?

These came out in the early 70s. In fact, Merck is out there today. Merck was one of the first to invest in these, and one of the oral biologists, actually, from University of Connecticut was the first to discover bisphosphonates. And then he became part of Merck, and that's Gideon Rodan. And so there's a lot of these approved, they're available worldwide.

And so they work by latching on to the bone matrix. You don't have to worry about the mechanism, what the take home message is here is not to prescribe anything like Dr. Singh was pointing out, but to understand that the half life of these drugs is really, really long. And what that means is they last typically over 10 years. So anything that requires us-- so prevention is paramount. If we can prevent this from happening, that's more impactful because afterwards these drugs last for a long time.

So discontinuing these drugs doesn't make it easier to treat them. In fact, it doesn't go away. The problem doesn't go away with drug holidays. And I know that Dr. Marx was here and he was one of the proponents of the drug holiday, but there's no data.

And Dr. Markowitz and others, who are oral surgeons in the audience, understand that their society, their association has put forward ideas that suggest that there's no rationale for drug holidays. So they last a long time. Every time you have a bone that's resorbed and replaced, they're being rereleased so they can reattach to the hydroxyapatite or the mineral component of bone.

The other drug that has more or less the same incidence, actually, is Denosumab. And so this inhibits one of the key cytokines, the key players involved with bone resorption that allows osteoclasts to be made. This is called RANK ligand, the receptor activator of NF-kappa B ligand. And without that, you get no osteoclasts. So basically if you block this molecule, you'll get no osteoclasts being made, and therefore you can block rather potently bone resorption. It's given biannually.

And you can see that there's changes that occur in the blood measuring this. So schematically this is an old slide from Amgen. Amgen is actually the company-- I have no disclosures relative to Amgen-- it's a very good company. However, they're the ones who actually first identified RANK ligand and its receptor RANK and also made therapeutics against this. And so this is basically showing you how bone resorption is blocked through inhibiting osteoclast function and survival with these agents. And so these also contribute towards this side effect of osteonecrosis of the jaw.

Some other medications have been put forward. Most of these involve shutting down blood flow, angiogenic inhibitors. And they have some mechanisms that are involved with this, but most of these actually synergize with the other bisphosphonates or the Denosumab, the anti RANK ligand blocking agents.

Risk factors for both of these are people who are older, pre-existing disease like diabetes, other local factors including dental infections. Previous dental treatment can also make a difference. Hygiene-- people who don't have a clean mouth have more osteonecrosis of the jaw. As a scientist, I also do a lot of preclinical models, and the best example that I can share with you is that if you give it a preclinical animal-- a rat or a mouse-- one of these drugs the bisphosphonates or Denosumab and take out the tooth, they don't get ONJ.

However, if you tie a ligature around that same tooth and take out that tooth, 100% percent of those animals will get osteonecrosis of the jaw. So plaque, bacteria either around the gum line that's causing infection, does cause osteonecrosis of the jaw. So it's paramount to reduce these local factors before. So I get off my soapbox about that.

So what should you remember? This is pretty prevalent. Most of this is a risk factor following surgery for medication-induced osteonecrosis after extractions. Not always so, but it seems to be one of the main traumas, and it does lead itself to having these osteonecrosis issues. The range is very big because of the studies that are being done, but importantly for bisphosphonates, the oral bisphosphonates used to manage and treat osteoporosis osteopenia don't seem to have the same issues as the systemic given bisphosphonates for cancer treatment.

Obviously, the pre-existing disease Dr. Crowe covered. I will just highlight these issues, rather periodontal disease or periapical disease, has to be dealt with before. And if you're dealing with this afterwards and you can't have the crystal ball, as she put it, and predict what's going to happen, then a lot of the management there is not really to take out the tooth but to treat it with endodonic therapy, non-surgical periodontal therapy, and trying to manage the situations that way.

So prevention is paramount. Implementing the right screening and appropriate dental measures has reduced a lot of the incidence of this. So most of the cancer facilities, cancer hospitals associated with having dental within their armamentarium within their hospitals have implemented these types of protocols to reduce this.

Decrease in the concept of a drug holiday to decrease this incidence really has not held true for the bisphosphonates. Although the Denosumab-- the anti RANK ligand inhibitors-- have a much shorter half life, it's a biannual delivery of this therapeutics. So the half life is roughly six months. Intuitively, then, if you discontinue this, you would think that you would reduce the incidence of this. However, there's a lack of prospective studies to actually confirm this.

So as mentioned earlier, non-restorable teeth, teeth with poor prognosis should be extracted. Trauma should be reduced with dentures and partials, and working as a team to understand how to manage this with the oncologist is really critical for us to work together as a example, really, of interdisciplinary and interprofessional relationships with Madison.

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