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### Tenosynovial Giant Cell Tumor (TGCT): New Perspectives on Advances in Treatment

Announcer:

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Dr. Tap:

Tenosynovial giant cell tumor, or TGCT for short, are rare, non-malignant tumors that can involve the joint synovia, bursae, or even the tendon sheath, leading to significant morbidity and compromise quality of life. While many patients can be treated with surgery, surgery is not necessarily a cure. And what happens when surgery is not an option?

This is CME on ReachMD, and I'm Dr. William Tap. Joining me to discuss the surgical and medical management of TGCT are Drs. Sylvia Stacchiotti, Andrew Wagner, and Michiel Van de Sande.

Welcome to you all.

Dr. Tap:

TGCT is certainly a rare condition that frequently goes undiagnosed for quite some time. Dr. Wagner, can you tell us a little bit about TGCT? And can you please walk us through some of the important things we should know about this disease?

Dr. Wagner:

Sure. Tenosynovial giant cell tumor, or TGCT, sometimes called pigmented villonodular synovitis is a rare condition. It typically presents in the joints; most typically in the knee or hip or ankle, but it also can occur as a similar condition in the fingers or the flexor compartments of the limbs. It can affect people of any age, although it is something that commonly affects younger people; young adults in their 20s, 30s, and 40s. Because these are usually very active people, it often shows up as a swollen joint that can be painful and is thought to be traumatic. And the patient will often present to an orthopedic surgeon or sports medicine specialist. Sometimes it can take awhile to reach a diagnosis because of the possibilities of other diagnoses. It often will be clearer on imaging, if imaging is performed, such as an MRI scan with a characteristic appearance. And this can be confirmed by biopsy. What's become really interesting about this tumor is the discovery several years ago of the characteristic translocation in the cells in the tumor. A small proportion of the cells are actually the neoplastic cells. These cells contain a characteristic translocation involving a collagen gene and the gene-encoding protein called CSF1. This leads to constitutive overproduction of CSF1, and these cells then draw in other normal cells, normal inflammatory histiocytic cells, to form this tumor mass. The mass is very inflammatory and can cause pain, can cause joint destruction, and can cause swelling, can cause bleeding within the joints. And this is what leads to the clinical presentation of patients.

For some patients with tenosynovial giant cell tumor, surgery alone can cure them of their disease, but unfortunately for many others, the disease recurs. And if the disease remains in the joint space, it can cause really significant morbidity. This can lead to destruction of cartilage and accelerated arthritis, leading to early joint replacement. It also can cause pain, functional limitations in terms of range of motion, and joint instability. So our patients that we see with advanced disease in the joints can really be suffering. They often are on

narcotic pain medications, and in some cases antidepressants. Some are unable to work because of their symptoms. These are patients who often no longer have an acceptable surgical outcome. And for these, we really need to find an effective medical therapy.

Dr. Tap:

So, when we are presented with a patient with TGCT, Dr. Van de Sande and Dr. Stacchiotti, how do you determine if this patient is a good candidate for surgical management? Or may possibly be suited for medical management?

Dr. van de Sande:

Thank you for that very interesting question. It's I think very important to differentiate patients that are primary patients that have never had any treatment before to patients that have had many treatments before already. And if there are patients with a long history of surgeries or systemic treatment, even radiotherapy, it becomes more and more difficult to successfully remove the tumor tissue from the joints and keep functional joints and a happy patient after the surgery. And other factors, of course, that make us decide if surgery is still possible are both patient-specific factors such as location in the body, but also in and around the joints because when it's outside of the joint, it's less easy to take out the tumor without morbidity to either the joint or the extremity. So location and former treatment both are important factors for us to decide if surgery is possible. Finally, I think describing a single patient that is not suitable for surgery is very difficult. And the optimal way to assessing who should benefit – who could benefit from surgery and who could benefit from systemic treatment is a decision that needs to be made together with the oncologist, the patient, and the surgeon. So all sides of the treatment, both response rates or surgical success rates versus complications and side effects need to be addressed, and then the patient together with their whole team of physicians can make a decision for either surgical or either nonsurgical treatment.

In patients with a localized disease, often the resection is simple, and therefore not very difficult. It makes postoperative rehabilitation short and pain easily managed with light pain medication. But if it's disease diffuse in the joints, even outside the joints, it becomes a larger resection, and I would specify for the knee, as most patients in about 65% have the location of the TGCT in the knee, tumor in the front of the knee intraarticular is painful to resect, and when you resect it, the postoperative time in hospital is often five days. They are under general anesthetic and use epidurals to have sufficient pain relief and be able to directly start with rehabilitation and flex the knee. The surgical resection of the extraarticular location mostly in the back of the knee in the posterior side of the knee is less painful, but still provides patients with an incision and a scar in the front and in the back of the knee. And this needs to be balanced with the risk of having a local recurrence for diffuse disease, which is, according to our publication in The Lancet, around 50% within five years. So if patients would accept a high risk for local recurrence within five years, but a long rehabilitation period after the surgery, the surgery is still a good option.

Dr. Tap:

For those just tuning in, you're listening to CME on ReachMD. I'm William Tap, and today I'm speaking with Drs. Stacchiotti, Wagner, and Van de Sande regarding the management of tenosynovial giant cell tumors or TGCT.

Dr. Stacchiotti, in a scenario where surgery is not the most optimal approach, what options do we have at our recourse as medical oncologists for the treatment of TGCT?

Dr. Stacchiotti:

So based from what we know from clinical studies and clinical experience, a medical treatment for TGCT patient is advisable, if available, in adult patients suffering of local regional advanced relapse of TGCT, not amenable of surgical resection, suffering of the symptoms, and with radiologic evidence of disease progression, or even symptoms are not there, the radiologic evidence of progression can be enough when the disease is located at a critical site. Patients should be, of course, very clearly informed of the benefit expected with the treatment and also of the risk of side effects, which is related to the treatment, the medical treatment they are going to receive. Available treatment currently varies a lot across countries.

Dr. Tap

So, thank you, Dr. Stacchiotti. I think it's critical, as you said, to truly understand what are the needs of our patients, and potentially what are the goals of treatments that we're trying to offer them. And this is something that often comes out with long discussions with our patients. I think the other important thing to realize is sometimes when patients come to tertiary care centers that really have expertise in this disease, there can be tremendous improvements in symptoms just by bringing in supportive care services; physical therapy, better pain control, and actually beginning to discuss with patients what we may actually be able to do from a medical standpoint to improve their conditions. Then, we really can start to think about medications and when is the appropriate time to use those medications. I often find that even with just supportive care measures, we can even begin to delay the use of medical treatments for our patients. And then when we do decide to use them, we have to think about the risk profile of the different medications that we have available in the United States. We are fortunate here that we can often use drugs such as imatinib and nilotinib off label. These are weaker inhibitors of CSF1 receptor, and so they can allow for improvement in conditions, but we tend not to see the dramatic shrinkages

in the size of the tumor mass that we can often see with some of the stronger CSF1R inhibitors such as pexidartinib. However, the side effect profile of these drugs are well known. We often use these drugs in many of our patients with certain malignancies. So we can really set the expectations for our patients. I think our patients do understand that with these drugs we can often allow for stability, potentially some slight shrinkage of their disease, but really help with symptoms. Alternative to this is the stronger CSF1R inhibitors such as pexidartinib, which has been approved by the FDA, or even newer drugs coming out in clinical trials. With these drugs, we tend to see dramatic improvements in the tumor mass, inflammation, as well as quick improvement in symptoms that are related to TGCT. Oftentimes, as has been discussed before, patients may have other issues with their joint because of the long-standing disease, the joint destruction that it caused, or even the various surgeries they may have. These types of symptoms need to be mitigated with other supportive services, as I mentioned before. But regardless, with the use of drugs such as pexidartinib, we have to have strong considers of some of the rare toxicities that we're seeing with this drug, such as we mentioned before, such as the cholestatic hepatotoxicity. This is a very rare and unpredictable side effect of the drug, and we really have to educate our patients about determining if the drug is right for them. And I think this is critical in the informed discussions that we can have with our patients.

Dr. Tap:

So, as Dr. Stacchiotti mentioned, we do now have one approved therapy, pexidartinib, in the United States for patients with TGCT. Dr. Wagner, can you provide some information on how this agent works? And maybe walk us through some of the results of the Phase 3 ENLIVEN study that supported its approval?

Dr. Wagner:

Sure. This is the first prospective placebo-controlled study of a drug in patients with tenosynovial giant cell tumor. It enrolled 120 patients who were randomly assigned to receive either pexidartinib or placebo in a blinded fashion. They received the study drug for up to 24 weeks, at which time their assignment could be unblinded and patients were then permitted to cross over the pexidartinib if they were found to have received placebo in the first 24 weeks. The results were pretty impressive. There was 39% response rate by RECIST in patients receiving pexidartinib in those first 24 weeks, and 0% response rate in patients receiving placebo. Now one of the real challenges of tenosynovial giant cell tumor is in how we measure the disease. It is not a spherical lesion that has very defined dimensions. It is very typically multilobulated, extending in different dimensions, and there is no simple way to measure the volume, and there's no simple way to measure the extent of disease. RECIST is not a perfect tool for this, so another metric called the Tumor Volume Score was developed that determines the size of the tumor in proportion to the maximally distended volume of the synovial cavity. Using this metric, the response rate was even higher; now 56% in patients in the first phase, the first 24 weeks of the study. With further follow-up, both by RECIST and the Tumor Volume Score, the response rates increased further, suggesting that patients did not necessarily all reach their maximal benefit in those first 24 weeks. In addition to measuring changes in the size of the tumor, the study also measured changes in patient-reported outcomes, including the PROMIS physical function scale, range of motion, patient-reported stiffness and pain, and shows statistically significant improvements in these with the exception of pain where there was a trend to improvement that did not meet statistical significance. So altogether from an efficacy perspective, pexidartinib resulted in a greater reduction in the size of the tumor and improvement in patient symptoms compared to placebo.

Dr. Tap:

So, Dr. Wagner, I think that was really well said. I chose the complexity of this disease, the complexity of the outcome measures within this study, but also how this drug really helped patients with TGCT. Importantly, what you also highlighted was again this rare cholestatic hepatotoxicity, which is unpredictable and can be serious for some patients. This really calls into mind, now that we have a drug approved, what is the best way to use this drug? Are there ways that we can mitigate and watch for the potential of any cholestatic hepatotoxicity with the drug? And what may be the right patient population to use this drug? And what are we looking for in responses?

Dr. Stacchiotti:

Following what Dr. Wagner was saying, my general comment is that this study was a great opportunity for us as a community of experts in the disease to better know this tumor. And my general comment is that is really crucial to select the right patient in which there is a perfect balance between the benefit and risk. This can be done only within the center of expertise because it is the only setting in which it is possible to really identify the good patient for medical treatment. This has to do with disease that is said to be a benign tumor, and in fact the risk of metastases in these tumors is almost 0, but in which especially along the natural history of the disease, the tumor can be very aggressive and can impact quality of life very much.

Dr. Tap:

So, this has been a fascinating discussion, but our program is unfortunately is coming to a close. So, let's offer our learners some parting thoughts. Dr. Van de Sande, let's begin with you. What is one key takeaway for our audience?

Dr. van de Sande:

Thank you very much, Dr. Tap. I think it remains of crucial interest that we discuss our possibilities and limits with the patient in a team where there is sufficient experience in both the surgical, but also the systemic treatment of this very rare disease that most of the time – I think the key take-away from a surgical point of view is that we need to communicate our options and our successes, but also our complications in honesty, and preferably together with the oncologists in order to create an honest shared decision-making to patients with a really rare disease.

Dr. Wagner:

I completely agree with the comments of Dr. Van De Sande and Dr. Stacchiotti. This was a remarkable experience where we could unite the international community in conducting a randomized study in a rare tumor. A drug that showed clear signs of efficacy, but also with a caution that there is close monitoring that is required, and it's also very important and remains very important for this to be a multidisciplinary team that is evaluating the patient and deciding on the best treatment. For some patients, surgery is still the most appropriate therapy, and that needs to be carefully considered. But for others, medical therapy may be warranted, and hopefully can continue to provide good benefit for patients with minimal toxicity.

Dr. Stacchiotti:

Following what was said by Dr. Wagner, the activity of pexidartinib and other potentially active drugs in this disease, is a major achievement for our patients. I think that what is difficult to understand is that TGCT is said to be a benign disease, and this is related to the risk of metastasis is really very low, almost 0. So we are dealing with a disease which has a locally aggressiveness, but not a metastatic risk. This means that there is no impact in the survival of our patients, but still there can be really a major impact in the quality of life. That is something we are seeing almost every day in our clinic where we have a patient in need of something to improve their quality of life. This is very difficult to understand, and this is part of the discussion we had and we are still having with regulators to try to let them understand that there are really patients in the need for medical treatment. What is absolutely crucial is to identify the right patients. So to have a very good selection of the patients to avoid unnecessary toxicity for those patients who do not need medical therapy, and to offer what is needed for those patients who are in the need of medical therapy. This can be done only within the center of expertise, where you can join together surgeon, orthopedic surgeon, and medical oncologist; able to really identify which is the right patient for the treatment and to talk with the patient, sharing with him which is the balance between the expected benefit and toxicity.

Dr. Tap:

So this has been a wonderful discussion. For me, what's important is actually forming this multidisciplinary team around our patients with TGCT. The patient must be very much included within these discussions and informed about the options we have; both surgical and medical, and the pros and cons of each. Important with this multidisciplinary team now inclusive of the patient is trying to figure out what is the right way to develop therapies and actually appropriately apply some of the new medical treatments that we have for that. This is going to be critical in the upcoming years for our patients in the academic community to partner with so we can best serve them with some of the new medical treatments that are being developed.

So, as we wrap up our discussion, I'd like to thank my guests, Sylvia Stacchiotti, Andrew Wagner, and Michiel Van de Sande, for helping us better understand new options for the management of TGCT. It was really great speaking with all of you.

Announcer:

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