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Improving Clinical Practices in the Management of Tenosynovial Giant Cell Tumor (TGCT)

Announcer:

Welcome to CME on ReachMD. This activity, entitled "Improving Clinical Practices in the Management of Tenosynovial Giant Cell Tumor (TGCT)" is provided by Prova Education and is supported by an independent educational grant from Daiichi Sankyo.

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Dr Tap:

Meet MB, a 38-year-old woman with significant pain and swelling in her right knee, reduced range of motion, and her quality of life and ability of work has been significantly impaired. She suffers from tenosynovial giant cell tumor, or TGCT for short. TGCT 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 for diffuse type TGCT is not necessarily a cure. And what happens when surgery is not an option?

This is CME on ReachMD. I'm Dr. William Tap.

Joining me to discuss the surgical and medical management of TGCT are Drs. Sylvia Stacchiotti, Andrew Wagner, Michiel Van de Sande.

Welcome to you all.

Dr. Tap:

As I was mentioning in the introduction, MB is a young woman, 38 years of age, and she has pretty extensive TGCT in the right knee. She is in constant pain managed with high-dose pain medication. She has significant swelling in the knee with reduced range of motion. Her quality of life is significantly reduced, as it is impacting her ability to work and to socialize with her friends. She has already had three prior surgeries to address her TGCT, and she is back with another recurrence. So this is not an unfamiliar story, unfortunately, for people with TGCT.

Dr. Tap

So knowing this, Dr. Van de Sande, is this patient a good candidate for surgery? Do you have concerns about surgery? And what type of discussion do you have with the patient about the possible pros and cons or expectations regarding surgery?

Dr. Van de Sande:

Well, when a patient that is about 38 years old and had three surgeries over the last five years, it will be very difficult to ever present her with a cure of the disease from a surgical point of view. From our knowledge and experience, and also from our papers that we published, we see that patients with recurrent disease have less than 20% chance of being tumor free within the next three years. So in the discussion with this patient, I would explain that a surgical approach to this problem can only be to improve complaints, but not to cure the disease. I think she will again have a long rehabilitation period, and I would be reluctant to go again into a surgical treatment

with a six-month rehabilitation period. In the end there is some room for a surgical approach, one could consider doing a synovectomy, either arthroscopically or open, to reduce the complaints, but discuss that this will not cure the disease.

Dr. Stacchiotti

So based on what was pointed out by Dr. Van De Sande, I don't think that this patient is a good candidate for an additional surgical resection since it looks like the expected morbidity is going to be superior than the expected improvement in symptoms. So, for that reason, this patient can be considered for medical therapy. According to what we know from clinical data right from clinical studies, the perfect candidate for medical treatment in case of an advanced and progressive TGCT is the case of patient with good general condition with the symptoms, with evidence by radiology of measurable disease, and without any comorbidities, which can increase the risk of side effects.

Dr. Tap

So this is a wonderful discussion, and I really appreciate the discourse between the medical oncologist and the orthopedic oncologist. I think this is so critical in the management of patients with diffuse type and extensive TGCT. It really allows for multidisciplinary approach that can help the patient and the treating physicians make some tough decisions regarding treatment. For this patient, we can see that she has extensive disease. The surgery would not be curative, and may actually have some degree of morbidity. So, for that reason, I think it's very reasonable to explore medical management. So with that, Dr. Stacchiotti, what options do you have for treating MB?

Dr. Stacchiotti

A medical option available for adult locally-advanced, non-resectable TGCT are different across countries. Formally, the only approved potentially active drug in the disease is pexidartinib, which has been recently approved by FDA in the U.S. While this drug is still under assessment by EMA in Europe. So as said, in Europe, for example, there are no active drugs formally approved for treatment of this group of patients. This corresponds to a huge amount of differences with regard to the accessibility to potentially active drug across countries. In the EU, pexidartinib can be used together with other drugs, which are not formally approved, but are available, like imatinib that has been investigated only retrospectively, not within a prospective clinical study. And it is available in Europe only as an off-label treatment in some particular settings. Then there is another drug that has been evaluated within prospective clinical trial that is erlotinib, but is a drug that has really limited activity. And finally, a new experimental treatment under investigation within prospective clinical trials open both in the U.S. and in Europe. For some patients, especially in Europe, this is the only opportunity to receive the potentially active drug for the disease is pexidartinib is not available over there. With the drug currently available, no matter if approved or off label, we unfortunately cannot think about curing any patient. What we can try to achieve is improvement in symptoms and tumor shrinkage, which can also translate into an improvement in function. This has been seen some with imatinib, but of course this has been seen much more with pexidartinib.

Dr. Tap:

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. William Tap, and today I'm speaking with Drs. Stacchiotti, Wagner, and Van de Sande as we address best ways to manage a patient with tenosynovial giant cell tumors or TGCT.

So, let's continue with the review of the systemic therapies that we have available to us. We have one approved drug and several off-label medications that we can use in this disease. Dr. Wagner, can you introduce the concept of some of the therapies we use; some of the initial data that we can actually apply towards our patients in this multidisciplinary discussion between the surgeon, patient, and medical oncologist?

Dr. Wagner

The key finding that led us to be able to use medical therapy for tenosynovial giant cell tumor was the discovery from Dr. Van De Sande that two different genes are inappropriately fused together in the neoplastic cells. And this brings gene-encoding CSF1 under the control of a collagen gene promoter, and it leads to overproduction of CSF1. This leads to proliferation of the neoplastic cells, but also a drawing into the tumor of inflammatory histiocytic cells that cause pain, swelling, bleeding into the joints, and joint destruction. So these patients can have really significant functional limitations from the size of the mass, from pain, from accelerated arthritis, and other physical challenges. So when we look at the medical treatment of patients with advanced TGCT, we really want to focus on two things; one is shrinking the tumor, and the other is improving their symptoms. The first medical treatment that's been described successfully was a case report by Dr. Blay, describing the use of imatinib in a patient with TGCT of her elbow, and demonstrating complete response. And this led many of us to start using imatinib as an off-label therapy for patients with unresectable TGCT. Now this has been summarized in a couple of publications. Most recently describing over 50 patients who have been treated with imatinib in a retrospective analysis and showing that about 29% of patients had shrinkage of their disease. There's been another prospective study of a drug called nilotinib, which also has some ability to inhibit the CSF-1 receptor. And in this prospective study of 58 patients, the primary endpoint was met, which was progression-free survival at 12 weeks, where over 92% of patients were free of progression, but there

were no responses to treatment in terms of tumor shrinkage. The drug pexidartinib was studied in tenosynovial giant cell tumor first as an expansion cohort in its Phase 1 study, and this actually showed dramatic improvement in the size of the tumors and led to the randomized Phase 3 study, placebo-blinded pexidartinib in what's called the ENLIVEN study. In this study, 120 patients were randomly assigned to receive either pexidartinib or placebo for 24 weeks, after which point they could be unblinded and patients on placebo could cross over to pexidartinib. At the 24-week assessment, 39% of patients who were assigned to pexidartinib had significant shrinkage of their disease as measured by RECIST, and it was over 50% as measured by another score that looks at the volume of the tumor, and this was in comparison to 0% response rate in patients on placebo. With continued treatment in the extension phase of the study, additional patients developed responses, showing that not all patients received or meet the criteria for response in those first 24 weeks and it can be ongoing tumor shrinkage with longer periods of treatment.

Dr. Tap

So, Dr. Wagner, I agree. I think that was a very nice assessment of the medications that we actually have available for us. What's important for the patient to realize is that we have several drugs that we can use; both now on label with pexidartinib and off label with drugs like imatinib and nilotinib. As you pointed out, each of these have slightly different efficacy assessments that were used in their clinical trials, but all of them can be helpful for our patients. I think a lot of it has to do with what are the goals of the therapy that we're trying to offer the patient. Are we looking for rapid decrease in tumor size and rapid potential improvement in symptoms? Or are we looking for an improvement in symptom stability of disease over time? And, as has been mentioned, this is a very diverse disease. Each patient presents with multiple symptoms different from the next patient. So we really have options to try to individualize approach for our patients. What's clear though, is that all of these drugs have different side effect profiles. Some of them can be very serious, although it seems to be very rare. This is compounded by the fact that many of the patients that have TGCT are younger; therefore, the pros and cons, the risk and benefits, the side effects of any medications have to be really considered when using a medication, especially such as pexidartinib, which had a very rare but serious type of liver toxicity, which was cholestatic hepatotoxicity. This really is being now considered as we appropriately use the drug. And I know many of our colleagues here, as we have been discussing and will discuss, have serious considerations as to what is the appropriate patient and how to actually allow for informed consent to come into those discussions with the patient, as well as the surgeons. But there are a lot of considerations about the appropriate use of the drug. What is the appropriate dosing and schedule? Do we need to start off at higher doses of 800 mg per day? Can we use lower doses that can potentially allow for responses, but maybe not as rapid, but generally over time? There's a lot of thought potentially about using strong CSF1 inhibitors in a neoadjuvant adjuvant fashion, a perioperative fashion. Could that help increase the likelihood of a cure or long-term outcomes for patients? I think there's also a lot of questions in patients with very chronic and diffuse disease is whether or not we need continued dosing. Can we actually treat the maximal response improvement of symptoms, and then actually give interruptions within the dosing? If we do that, what is the appropriate time to actually reintroduce drug if we begin to see growth of the disease or actually new symptoms? These are really important questions that the academic community and experts in TGCT, both our orthopedic oncology colleagues and our medical oncologies are really beginning to think about.

Dr. Stacchiotti

So then it is very important to discuss together in the presence of the radiologist, the surgeon, the orthopedic surgeon, and the medical oncologist if there is any possibility for surgical resection, which is the benefit for the patient, because in the past, it was very common to see repeated surgery with worsening instead of improvement of the symptomatic aspect related to the disease. And this is something that the patients had complained of a lot. Many patients who asked for medical therapy say that they do not want to undergo surgery anymore. And finally, since we know that medical treatments are not without toxicity or risk, we really need to select the perfect patient for medical treatment. Sharing after the discussion we have together with our colleagues, which is the expected balance between risk and benefit.

Dr. Tap:

So this has been a fascinating discussion, but unfortunately our program is coming to a close.

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

Announcer:

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