Podcast Episode Title: Clinical Implications - updated Bone Sarcoma guidelines

Brought to you by:

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Transcript

Robin Jones

Welcome everybody to our podcast covering clinical practice and patient management highlights from CTOS 2022. The meeting this year was held in Vancouver, Canada, from November 16th to 19th. My name is Robin Jones and I'm, a medical oncologist at The Royal Marsden Institute of Cancer Research in London, specializing in the treatment of sarcomas.

Jon Trent

Hi I'm Jon Trent I'm joining Robin today, as we discuss the important results from the Connective Tissue Oncology Society, annual meeting and I am a sarcoma medical oncologist at Sylvester, Comprehensive Cancer Center in Miami, Florida, USA. I'd like to begin by introducing CTOS so, Connective Tissue Oncology Society is an international group, comprised of physicians and scientists who have a primary interest in tumors of the mesenchymal and connective tissues. The overall goal of the society is to advance the care of patients with these types of tumors, and to increase knowledge of all aspects of the biology of these tumors, including clinical research, translational research, basic science and even population science, as well as patient, reported outcomes. This year we had nearly 600 attendees for 10 sessions, specific for sarcoma and over 300 posters.

Robin Jones

The tumor of the year was desmoid fibromatosis, and this is a rare locally aggressive tumor that does not metastasize. It can be challenging to treat and can cause profound symptoms of pain and also limited movement and limited function. There were a number of very interesting abstracts on desmoid tumors this year, and I'll hand over to Jon to describe the results of the DeFI trial.

Jon Trent

Yeah, that's a very great point, Robin. So, desmoid tumor is not a malignant tumor, it is really a considered a benign tumor, but it's locally aggressive, and can even be life threatening in select cases. Nirogacestat is an oral gamma secretase inhibitor that was developed to interfere with the pathway that's downstream from the activating driver mutations in beta-catenin or deletion of the gene APC. When these driver mutations occur, or there's deletion of APC, there's activation of a downstream pathway including gamma secretase. So this inhibitor was developed to interrupt that pathway, kill the desmoid tumor cells and shrink the tumor, improving patient outcomes. And so in this study, it was a phase 3 study, randomizing nirogacestat to a placebo. Patients who received nirogacestat seemed to have substantial benefit of those who received placebo in terms of objective response rates, median time to response as well as duration of response. Moreover, nirogacestat was very well tolerated with only really grade 1/2 toxicity, including diarrhoea, nausea, and fatigue. So nirogacestat was statistically superior to placebo in all of these aspects of efficacy as well as alleviating the tumor burden improving the function and quality of life of patients.

Robin Jones

Thanks, Jon, I agree the results at the DeFI trial of are very interesting. There were a number of other good abstracts in the desmoid tumor session. Of course, it's important to us to highlight that the majority of patients will be managed by active surveillance and pain control, and that only the patients with severe symptoms or progression require systemic therapy. There were other abstracts focusing on metronomic schedules of chemotherapy. A very important abstract from Tata Memorial Hospital in India, and of course the results of the DeFI trial will lead to a change in our practice, likely for desmoid tumors. The optimal duration of therapy is one thing that remains to be decided, and of course, further follow up with variant suppression is important, which was observed in the trial. And of course, it's important in this patient group, because it tends to affect younger women. So do you have any thoughts regarding the side effect profile, and also the other abstracts focusing on surveillance and the more sort of cost-effective schedules of metronomic chemotherapy?

Jon Trent

Yeah, I think those are all really great points, Robin. And so, I was impressed by the number of desmoid tumor abstracts the ones that you mentioned, as well as the cryoablation abstract, which is an effective therapy in select patients, that is not a systemic therapy. In fact, it's direct treatment of the tumor through interventional measures. And then certainly low cost is important as well as having a too like this new tool that was used in the DeFI trial to really understand the patient's symptom burden, and the patient's overall toxicity from the

medicine versus the toxicity, from the agent nirogacestat. So in our practice at Sylvester, we generally give the patients a period of observation, so at least a serial MRI is performed generally about 3 months apart, before we determine whether there is going to be spontaneous regression or not. There was a lot less spontaneous regression in the DeFI trial than there was, in the prior study of sorafenib in GIST which I thought was interesting. But we all see spontaneous regression, so I do think it's reasonable to give a period of observation, as this is not a metastatic tumor. And then, if the patient does have a progressive desmoid tumor we have to really think about all of these treatment options we have cryoablation, we have sorafenib and we have old-school standard cytotoxic chemotherapy, which is quite effective, and we have an increasing number of new agents that are being developed specifically for patients with desmoid tumor, which is a great problem for us to have as treating physicians. We just have to work together to figure out what treatment is best used and most effective and best tolerated by the patients and their specific scenarios. I wonder how the DefI trial is going to impact your practice at the Marsden, Robin?

Robin Jones

Yeah, thanks, Jon, we do have a compassionate access program open for the drugs. So, we have been treating symptomatic patients with this gamma secretase inhibitor. I think, as was discussed at the meeting, the drug will now go through the approval process in many countries including Europe and the UK, and we'll just have to see what the decision is in the UK regarding funding approval, but certainly a very effective and well tolerated agent for this challenging disease. One of the other challenging types of sarcoma that we treat is advanced, dedifferentiated or well differentiated liposarcoma. And again, there are a number of really promising abstracts, primarily from phase 1 trials of MDM2 inhibitors in recurrent retroperitoneal liposarcoma, and two abstracts in particular led to the initiation of randomized trials. So, the first BI907828, which has led to a randomized trial versus doxorubicin in the first line, and of course the other abstract was for milademetan, which has been evaluated in a randomized phase 3 trial compared to trabectedin. And again, it's really good to have promising data and hopefully more treatment available for this challenging subtype of sarcoma in particular. And I just wanted to do you have any thoughts on those results specifically presented at CTOS, Jon?

Jon Trent

I'm with you completely, dedifferentiated liposarcoma is a challenging type of sarcoma to treat. They're often retroperitoneal in the peritoneal metastases, and so they're very difficult to operate on for our surgeons and the recurrence rates are very high. And we do treat with chemotherapy, standard cytotoxic chemotherapy like doxorubicin ifosfamide, gemcitabine, docetaxel, trabectedin, and even eribulin. But you know they're just not that effective, for most patients. Responses are often transient and so we do need new therapies. And we've known for many years that dedifferentiated and well differentiated liposarcoma are driven by amplification of a certain region in the chromosome, including MDM2, among other genes. MDM2 has the unique capability of binding to wild type p53, and removing it from the cell function similar to a p53 deletion, which is highly tumorigenic in individuals and p53 is one of the most common genes that's impacted in tumorogenesis across all tumor types. So being able to develop a novel agent to target that pathway has been a goal for many years. Years ago early MDM2 inhibitors were developed that just had too much toxicity and not much efficacy. So we are all really delighted to see new agents developed by these small

pharmaceutical companies who are who are interested in developing active agents in oncology, and focusing really on MDM2 inhibitors that are able to bind to that amplified protein, release p53, and allow p53 to actively kill, resulting apoptosis of the tumor cells. And so, these two studies were presented at CTOS, and both of these studies showed promising results with reasonably good response rates and pretty good efficacy, and pretty good, fairly few limited adverse events. Now we do have to be cognizant that both of these agents can cause prolonged thrombocytopenia. But it seems like the schedule is being developed in such a way to minimize the risk of thrombocytopenia and still managing to show durable efficacy. And I agree with you, it's very exciting that these agents are already moving into phase 3 registration studies. So, it's quite possible in the next few years that if these studies are positive, we could have new targeted therapies for patients who are affected by dedifferentiated and possibly well differentiated liposarcoma.

Robin Jones

Agreed Jon, and there were many other interesting abstracts from early-stage clinical trials. I suppose following on with this theme of drug developments and the process from phase 1 leading to a registration randomized trial, Dr Van Tine presented the phase 1 data for the PTC596 or unesbulin, tubulin inhibitor in leiomyosarcoma, that has also led to the initiation of a randomized trial. And what are your thoughts on this particular drug and the abstract presented at CTOS?

Jon Trent

Why, I think that the, you know this new agent the PTC agent, is quite compelling in its activity, and we do need new agents for leiomyosarcoma. Leiomyosarcoma is a smooth muscle phenotype sarcoma and this type of sarcoma is one of the more common ones, and with the smooth muscle features it can arise from blood vessels in muscle, retroperitoneum, subcutaneously, and, as I was saying it's very common. And sure, we have old-school chemotherapy, trabectedin, pazopanib, but we don't really have a good targeted therapy for leiomyosarcoma, because there are many, many different types of mutations, not a solitary driver mutation. But one thing that's emerged over the years is that leiomyosarcoma may have some sensitivity to microtubules, given the responses that we see with eribulin and the responses that we see with the addition of docetaxel to gemcitabine, so I think it is very exciting to see an interest in developing a new microtubule inhibitor for leiomyosarcoma. And in this phase 1 study patients were treated with this new agent and they may have received dacarbazine in combination with unesbulin and clearly, you know, in the study they showed some efficacy for leiomyosarcoma patients. So, I think it's a very exciting time to see a new agent move into the space of the unesbulin. We've had recent approvals with trabectedin and pazopanib fairly recently, but really not the kind of efficacy that we need to be delivering to our patients. So, I'm very excited to be participating in this phase 3 study that arose from a phase 1 study, presented at CTOS from our from our sarcoma community.

Robin Jones

Great, and interestingly as well, Dr McCabe presented updated results of the rECCur trial. And in many ways, this is a completely different trial of evaluating drugs that have been used for a relatively long time in the treatment of recurring to advanced Ewing sarcoma. And again very informative and a very an important trial in terms of clinical practice reinforcing the

important role of ifosfamide in this disease. And again, what are your thoughts regarding the results and how will this impact your practice in Miami, Jon?

Jon Trent

Yeah, I think that's an amazing trial to be able to do a study that large in such a rare subset of a rare tumor and Ewing sarcoma is really commendable, and I was impressed by the data and also impressed by the study design, really methodically evaluating salvage therapies for patients with Ewing sarcoma. And this is pertinent to all of us. Sure, Ewing sarcoma is one of the more common pediatric sarcomas. But if you do the numbers, there's actually more adults with Ewing sarcoma than there are children. So understanding salvage therapy is critical in our practice. And so these salvage therapies we use most of them, but a lot of times patients don't make it through all of the salvage therapies. And so it's very important to understand which ones are the most active, so that you can have a higher probability of getting a response in patients that have limited treatment options. The use of high dose ifosfamide is a very common salvage therapy in our practice, particularly in individuals who are under 50 years of age. Older than that, I think it's a little challenging in terms of toxicity. But I feel personally validated, that it meshes very well with the practice that we have here at Sylvester. And so, I was very excited to see the data presented at CTOS this year.

Robin Jones

Indeed, and there were many more interesting abstracts. I'm conscious of the time. But Dr. Loong presented updated efficacy and safety data on entrectinib, in patients with NTRK fusion positive sarcomas, again reinforcing the tremendous activity of this class of drug in NTRK fusion positive sarcomas. And also a very interesting abstract by Dr Kleinerman and colleagues of a novel CD103 + cDC1 dendritic cell vaccine for osteosarcoma. So, there were many, many fascinating and interesting abstracts at the meeting this year, and unfortunately, we don't have time to present them all. But a very, very good meeting, in my opinion.

Jon Trent

Yeah, I had a I had a great meeting. Perhaps we could maybe just end mentioning briefly some of the abstracts on gastrointestinal stromal tumor, since it's one of the more common tumors that we see in patients with GIST, and I thought there were several good presentations. One of the presentations, by Steve Bialick and colleagues from our institution, looked at circulating tumor DNA in patients with GIST who were progressive on prior therapies. And really we're starting to tease out which patients benefit from which agents. And so it's been known from pre-clinical data that sunitinib is highly effective against exon 13 mutated GIST and also anecdotes that it's not very effective against exon 17 mutated resistant GIST and conversely, regorafenib is active at exon 17, but not so active at exon 13. And so it was really nice to see clinical validation of pre-clinical models suggesting that perhaps patients with exon 13 mutated GIST should be receiving sunitinib, no matter what line of therapy, if that's the driver mutation as compared to regorafenib. Did you see any other interesting GIST abstracts Robin?

Robin Jones

Yeah, I think all the abstracts in the GIST session were great, and I particularly like the abstract focusing on the analysis of micro GIST following through to larger tumors. Again,

giving a fascinating insight into the development of this disease. You know one of the things I really like to say, is that there were a number of other great sessions. I thought that the retroperitoneal sarcoma session was excellent. Particularly the discussion on operability, there was an abstract from the UK showing the challenges of actually deeming a retroperitoneal tumor as inoperable which, of course, has important implications in terms of the management of the patient, all the way through to eligibility in terms of clinical trials if the tumor is deemed inoperable. And as I say, I thought that the program committee had done a great job in organizing and selecting all of these abstracts. And suppose with that one of my well, my last question to you, Jon is what are your key takeaway message messages or the key highlights from the meeting this year?

Jon Trent

I agree with you. I'd like to commend the program committee for really selecting important biological studies, clinical studies, translational research that's helping us not only understand the disease, but really focus on developing new therapies. And so I think the key takeaway is that there's a lot of promise for new agents, for patients with advanced dedifferentiated liposarcoma, which we really need, there's promise for patients with leiomyosarcoma, which we really need new agents there as well. We found active salvage therapy in Ewing sarcoma and also it would be remiss not to mention the ENLIVEN study where confirmation, long-term presentation data from the study confirms that patients with TGCT do get relief of symptoms by taking an oral TKI. And you know I'd like to really say that I also like to say that I'm really looking forward to next year's meeting and all of the new advances that are going to be taking place over this year. And certainly, on this podcast I've enjoyed working with you, Robin, and hopefully we can report out on next year’s CTOS as well.

Robin Jones

Fantastic thank you Jon, and thank you everybody for listening, and I just like to say likewise allways a pleasure to work with you. Thanks so much.

Jon Trent

Thank you.