Solitary Fibrous Tumors: Research Advances, Treatment Strategies, and Hope for Sarcoma Patients Transcript

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Introduction and guest background

This is the Doctors Making a Difference podcast, living with metastatic cancer, highlighting patients, doctors, and researchers who are fighting to win against cancer.

Today, I am pleased to welcome Dr. Javier Martin Broto. Dr. Martin Broto is MD, PhD, and he works at Fundación Jiménez Díaz University Hospital in Madrid.

He's been active in the medical oncology research and patient care, has done a lot in this world, and has made a tremendous difference in the research and availability of information regarding various types of tumors, including solitary fibrous tumors.

And those who listen to this podcast a lot will know that I also have that type of cancer myself. And I'm delighted to welcome Dr. Martin Brotov. He gave me permission to call him Javier.

So Javier, would you mind introducing yourself more thoroughly to our audience? Yeah, absolutely, Peter. It's my big pleasure to be here with you. And yeah, this is Javier Martin Broto, a medical oncologist devoted to sarcoma care and research for more than 30 years.

And I finished my oncology residency 31 years ago. So my pleasure to be here and replying all the questions or topics you want to talk about that. Yeah.

Just briefly, how did you end up getting into oncology? You know, a young man studying in college, how did you end up in this research field? Because again, many people listening are physicians or maybe they're residents in training or medical students and are considering a career.

How did you end up choosing this as your career path? I finished my oncology residency in 1994. The residency as medical oncologist, time flies. Oh my God.

I was involved in sarcoma care maybe since January 1994. And yeah, during this time I tried to be transformative. I triggered the activation of the Spanish sarcoma group in this year.

in 1994. And honestly, the way we ended in the medical oncologist election is hard to say because there are many, many factors that can influence in this election, in this choice.

Maybe one of them is to avoid to give up to hold the knowledge about the medicine because medical oncologist is a specialty that renounced to the overall knowledge about the medicine.

You need to have the knowledge of internal medicine, for instance, but internal medicine is very competitive and maybe medical oncology is more innovative in some way that requires research.

And I don't know the kind of. details can influence in the election. And yeah, intensive care as well is the same concept of not renouncing to all the knowledge of the medicine, but it's more technical specialty.

So medical oncologist maybe was more fit with me, with my scope.

Choosing oncology and sarcoma research

And maybe this was the reason, but yeah, in the end, there are few little details because in the medical school, you

are not aware about how every single specialty is or is about.

So in the end, there are few details that maybe take importance in the election. But I will select medical oncologist again for me. Yeah. Well, you've done great work in this field.

Like you say, you've done for over 30 years and obviously you've stayed in it and you've been able to advance. You've done many publications. And as it pertains to solitary fibrous tumor, you know, that means a lot to me and to others who are suffering with this disease to have someone who's so committed and dedicated to learning about that disease and trying to develop better treatments.

And so. Thank you for what you're doing. I appreciate you sticking with it and making a difference for all these years. That's a tremendous accomplishment.

Thank you. This is a part of our task because we understand the medical oncology as not only caring patients, but also to research and also to teach. But research means that you will be transformative in some way.

And research, not only in focusing on clinical research, that means that new trials are activating in your side, but also in the preclinical setting where you can discover new relevant biological processes within one specific disease and maybe you can check the efficacy of different treatments.

This whole research is very, very convenient in the context of medical oncology. So this is a part of our specialty. This is the question. Maybe I began working in clinical research back in 1996 and moved into proclinical research in 2008. Since then, been leading Preclinical team focus on sarcoma research and right now we have around 40 projects going on in the preclinical setting with molecular biologists and technicians and pre-docs as well.

So I can imagine definitely medical oncologists without research and that research has to cover everything translational, proclinical, clinical, the whole perspective.

And our work obviously is always dively to help patients. And we have designed more than 30 clinical trials in sarcoma and always pushing to make a real difference in clinical practice.

This means that new treatments or new strategies are putting on the table in these clinical trials. SFT was one of the rare diseases within the sarcoma field.

There are more than 100 entities. But SFT for sure was an unmet need because we required new treatments. I think the first ever conducted clinical trial in SFT was designed by our team in two different cohorts.

So exploring the efficacy of antiangiogenesis, antiangiogenic pathopany. So first line of antiangiogenics. In two different cohorts, the formerly typical SFT and the formerly called malignant SFT.

In these two cohorts, when the patients had metastatic spread, we tested the efficacy of pathopany. And we essentially, we have learned two main messages.

The first was that. At the time of the diagnosis, the prognostic subset of SFT determines the behavior at the time of metastatic spread. I mean, for instance, one patient diagnosed with low risk SFT, if five years or 10 years later developed metastasis, this metastasis behaves more indolent than those diagnosed at the localized disease time as a malignant, as a high-risk SFT.

So this was important because the median progression free survival of the cohort typical was more than 10 months. And for the so-called cohort malignant, which is bad nomenclature, fortunately improved recently by WHO definitions, had a medium progressive resurveival in this high-risk operation of five months.

Another important message was that anti-angiogenic seems to be more important than chemotherapy agents and because the figures we achieved in terms of median of progressive free survival and even median overall survival.

were, by indirect comparison, better than what we can achieve with chemotherapy. And another message was that for those patients achieving at least a stable disease with toponyl, we can make some rotation at the time of progression with other antigenic agents.

and this was beneficial for the patients. So these were the three messages we learned. I just want to make sure I summarize, because I think those are all really interesting.

First, you found that Paisopanib and other antiogenics were more effective overall than traditional chemotherapy. And then I think you found, again, it used to be categorized into malignant versus non-malignant, but you found that the behavior of the disease depending on what it was at the time of diagnosis, modified a little bit later on.

In other words, it was something that was a high-grade, high-risk tumor was more likely to spread or become malignant rather than a low-grade tumor at the time of diagnosis.

Is that correct? It's absolutely correct. And the change was very convenient because there is no considered benign tumors in the context of SFT. So the most correct definition is low risk or high risk, but even low risk can develop metastasis spread.

And this is why we needed to know the behavior in the advances for those initially diagnosed low risk SFT. Yeah. Well, and that's an interesting characterization too because older literature that I've read on solitary fibrous tumor describes it as largely a benign process.

And now the more recent studies say high risk or low risk based on mitotic rate, amount of necrosis within the lesion, the size of the original tumor.

And those factors kind of influence the likelihood of malignancy. And I think you said, as it goes on, if somebody starts off with a high-risk tumor with a high mitotic rate, high necrotic rate, all the World Health Organization classifications, if they're high, they're more likely to have metastatic disease.

When you design treatment, you know, design studies around it, have you found that the anti-angiogenics, like Paisopanib, do they have an equal rate of effectiveness on those tumors, or does it vary quite a bit based on the original type of tumor and their grading?

Yeah, we took the advantage of explore several details in this prospective trial. And one of the important message was the detection of efficacy of these compounds.

One important consideration is that with these responses with antiangiogenics in this context are very uncommon. But on the contrary, choice responses are frequent within the context of antiangiogenics.

Choice responses means that the density of the tumor changes because of the effect of the antiangiogenic treatment. And this can be measured by radiologists with a kind of unit called Hansville units.

So this can be measured. And this was important as well, because we could quantify the impact of the antigenic agents in the tumor. So this was important.

Some correlation can be obtained between the response and the PFS, but it's true that maybe this correlation requires a higher number of patients to be more robust.

But yes, we detected this kind of response in both contexts, in high mitotic SFT or low mitotic SFT. It's true that in the specific subset of the differentiated SFT, anti-angiogenic agents are not working, so this required chemotherapy instead of anti-angiogenesis.

So de-differentiated ones didn't respond as well, but the majority of others did respond better to anti-angiogenic

agents than anything else. And like you said, I didn't realize that you, at least in clinical studies, could judge the effectiveness of the anti-angiogenic like Pesopanib by the Hounsfield units or by, in other words, by the density of the tumor rather than just the absence or presence of tumors.

Do you see that happen? Do you ever see that the tumors will regress or do they just become less dense with the anti-angiogenics? Yeah, less than the change that we can observe outside.

I mean, because it's darker in the CAT scan, the lesion comes darker after the treatment. And this can be measured obviously. Yeah. And some shrinkage you can also detect, but it's more frequently with density changes.

Yeah. With this specific treatment. It's not the best treatment, obviously, but it's more than double than the chemotherapy can demonstrate in the context of advanced SFT.

And I think it's a benchmark. We have now a benchmark of activity in terms of median of progression free survival for each cohort. and also for overall survival with this strategy of rotating anti-oxygenic agents.

But obviously we continue with the research and maybe new biological processes are important in the safety control or treatment. So yeah, we are investigating in different areas now.

Well, another one I think I had read is Bevacizumab versus Paisopanib and other angiogenics. I think a lot of your work had worked on Paisopanib, but a lot of patients also take Bevacizumab.

You mentioned you have to rotate them. Do you find a difference between the effectiveness, or does it seem to matter which of the angiogenics are used initially?

Yeah. Initially we thought that maybe Sunitinib, which is probably more potent anti-angiogenic agent than pathopony, could be more effective, at least in some ultra rare tumors where anti-angiogenesis is important.

For instance, in Velasov-Parsalcoma, the first ever conducted randomized clinical trial in this ultra rare tumor was conducted with fevirinib, which is an anti-angiogenic agent.

And in this context, sonitinib demonstrated higher activity compared to other anti-angiogenic agents. But it's difficult to say, and maybe bevacitumab with demosolamide is comparable in terms of efficacy with or sunitinib.

So I think the most important question of focus here is that we have seen that patients that progressing after treatment, that in those patients that at least you achieved an stable disease, After the rotation with another different antiangiogenic, you can also observe a choice response.

So this is important because the rotation is the key question. It seems that for some reason, antiangiogenesis is an important treatment way in SFT. So we have patients we treated with Thopanib and then maybe partial response was achieved and then maybe in eight months some leashes progress and then we rotate it to sunitiny furnaces and we use some efficacy or some signal of activity.

For instance, another CHOI response, and maybe six or 10 months later, we should change to another antiangiogenesis, antiangiogenic agent, for instance, bevathetomab or another, axitin for instance.

And this is interesting because it seems that it was not cross resistance between antiangiogenic agents. So this was important. That's an interesting finding because you would think it would develop resistance to the class of drugs, but what you're finding is as you rotate patients between anti-angiogenics, depending on what their density of their tumors are, you're still seeing a response.

And one of the challenges I think about as a patient with solitary fibrous tumor and on the physician side of it is how do we find agents that not only are palliative or slow down the progression of the disease, but start to reverse it?

Tumor grading, response patterns, and treatment rotation

And I noticed you had studied, you published something called predictive gene signature study earlier this year. It said predictive gene signature for the efficacy of Paisopanib.

And I thought that was interesting, a predictive model that you could use to try to predict which type of tumors would respond. I wondered if you could tell us more about that research.

Yeah, we are engaged with prediction as well. We are very happy with the seven gene signature of prediction for immunomodulation using anti-PD-1 compounds in a wide series of sarcoma treated with anti-angiogenic plus anti-PD-1.

And this was initially obtained by dynamic changes over time comparing the week six versus baseline. So those genes that were modulated in this time were important for us because this means that these genes were impacted by the treatment.

And then after we tested this seven gene signature, which is very, very nice validated in another series at the baseline. And we observed that is predictive.

I mean, there are two different populations. This signatory is able to distinguish two different populations and is validated with the SARC series. The SARC series is imposed by patients enrolled in pembrythoma in several sarcoma subtypes.

And so we are very happy with this signatory because it's validated. So for other signatures, we require more validation and maybe we cannot make a robust statement around that because sometimes validation is hard to find a similar series with transcriptomic and with the same genes explored in our signature.

But yeah, in the end, it is very important to have predictions about the efficacy of one specific drug. And for that, the best way is to obtain dynamic changes over time.

This required more effort by the patient because this means biopsy at baseline and biopsy in this case at week six. But in the end, this change over time is critical because you are ruling out those genes that are more important in prognosis, inherent of the biology of the tumor, and you are focusing on those genes that are modulated by the treatment.

And then after this dynamic signature, you can check if a baseline is enough to be predicted. And this was the case for this signature of immunomodulation.

So we are very happy with this signature. And for other signatures, we still required validation with independent series to observe that. So in this sense, for sure in SFT, we must continue investigation because the immunomodulation in the monosar 1 seems to offer some activity in SFT, but in monosar 2, which means six different cohorts based on the signal of activity we have detected in the previous study, plus two new cohorts of chemoimmunotherapy.

But one of these cohorts with antiangiogenic tests, antiPD-1, was a solitary fibers tumor. And unfortunately, after the interim analysis was not enough, the median progression free survival we obtained with immunomodulation to continue up to the second part.

But we are very convinced that maybe we have to modulate firstly macrophages. in the context of SFT. SFT contains maybe the greatest proportion of micro-figures in the MyCompignment compared to others in common.

And most of them are M2 micro-figures. This is a research line of our team as well. We have investigators devoted to microphages polarization and modulation with CSFR1 inhibitors.

So I think we require this kind of modulation before any other immunomodulation with anti-PD-1, for instance. So this is an interesting fact that we are considering.

And yeah, in some sarcoma, the microenvironment is called in the majority of sarcomas. And we required some in-plane activation with several strategies.

To get the more macrophages active. Yeah, because, you know, in sarcoma in general, the half of the mass of the tumor is constituted by macrophages. But specifically in SFT, this amount of macrophages is huge.

So this is important to take into consideration. And obviously these tumor associated macrophages are M2, which means that are polarized towards tumor growth.

And then these M2 macrophages facilitate the cold microenvironment or prevent the immunomodulation attack to the tumor. So it's important to modulate firstly, these M2 polarized microphages before any immunomodulation treatment in the SFT context.

This is one of our learning messages after this investigation. But there are other lines of research which are very, very promising and very appealing in SFT.

Predictive gene signatures and macrophage modulation

I just want to summarize for a second. That's quite interesting. You've done a lot of work on antiangiogenic agents, and it sounds like the microenvironment around the solitary fibrous tumor does have a lot of macrophages.

It requires an inflammatory response to recruit more macrophages. You want to create an environment that can be destructive to the tumors rather than promoting of the tumors.

So there's work being done around that microenvironment with macrophages. I noticed, published an article or a study, the ImmunosarC2 trial update, and I think you said you had multiple cohorts and solitary fibrous tumor was not included in that most recent publication.

Is that correct? Yeah, it's included in the investigation, but as I mentioned, in the Immunosac-2 trial, the specific cohort of SFD unfortunately had to be stopped in the interim analysis because we didn't achieve the minimum of progression-free survival to continue to the second part.

In some cases, we detect a signal of activity with Sunitinib and Ivoluma. It's true, but then we refocus our investigation and probably the fact of immunomodulation detected with these compounds is because this amount of microfetches in the context, in the microenvironment of SFT.

So this is one of the important research lines. We have to obtain some promising findings in the upcoming months because I think this could be positive.

Right now we have drugs that are able to modify the polarization of macrophages in some way. Some drugs called R1 inhibitors. Benzeltinib, bimicotinib, mactutumab are examples of this family of tumors and that are being registered for TGCT, which is a kind of benign tumor in the joints.

Tumor, yeah, this is the nocinovial gene cell tumors are very sensitive to this kind of modulation of CSF, CSF-R1 inhibition. This is the modulation of microfusions.

And this is important because we can modulate that. This research line definitely will be important because we continually to think that important immune modulation in SFT because we have published the peripheral inflammatory signature is prognostic, very prognostic in advanced SFT.

I mean, this kind of peripheral signature is… by the ratio between platelets and lymph cells or between neutrophils and lymph cells. And this means that cytokines has influence in SFT.

So definitely this is important, but we have to maybe find the key signaling pathways and that will allow the efficacy of anti-PD-1 compounds, for instance.

Yeah, it's interesting. So far it's not possible, but there are more promising research lines in SFT. And if you want, I can share some of them. Well, it's interesting, like you said, there's a lot of work around antiangiogenesis and a lot of work on the microenvironment around solitary fibrous tumor.

And I guess that was my next question. Where do you see the field of research going in the future? Are there other promising modalities that might provide help for people with solitary fibrous tumor or other sarcomas?

We have the privilege and the big pleasure to work with Dallas research team. And through them, we have tested the relevance of bed inhibition in the context of SFT.

And in the proclinical models, vet inhibition is working in SFT. So this is something that is promising in this disease. And unfortunately, so far we were unable to find a pharma company prone to investigate in SFT with these compounds.

But again, we are fine-tuned the results of these kinds of compounds. And for me, this is something that is very promising, obviously. And not all the bed inhibition is useful for SFT treatment, but those compounds that are able to inhibit the pan bed receptors, which is hard to explain now, but not all the bed inhibition is okay, but some of them is very convenient in the SFT context.

And another research line, I think this will bring hope and bring new activity in the context of SFT is the inhibition of alternative splicing, which is very, very disruptive and very innovative in oncology and in solid tumors at least.

And we are conducting now a clinical trial with Irtubivint, which is an inhibitor of some splicing factors. And for many reasons, we think that some specific translocation related sarcomas are sensitive to this kind of inhibition.

Future research directions and clinical trial updates

So in proclinical setting, we have seen very important, I will say the most important activity I have detected in proclinical setting in SFT is with alternative splicing inhibition.

which is very important. And in some patients included in the clinical trial we have activated this summer, we have detected a shrinkage of the tumors, which is very, very, very convenient.

So it's too early to withdraw conclusions, but hopefully in ESMO meeting we will be able to communicate the results of this phase two trial. This phase two trial is enriched by SFT patients.

Maybe we have included in these four or five months, 15 or 16 patients with SFT. And yeah, our experience so far is very good. And so we need more time to have the whole perspective of the activity.

But this is definitely one For me, one of the most helpful research line in the context of SFT. It's exciting to think that there's other things. Most of the stuff I read about sarcomas and then solitary fibrous tumor in general is more palliative to slow the disease, but not to eradicate the disease.

And so when you see trials going on where you can start to see tumor shrinkage, where it reduces in size, that's very promising. And I also think it's wonderful that you're already at the clinical trial stage.

There's a lot of pre-clinical work that goes, but if you're already able to give these trials to patients and publish that data, I think that moves the field along tremendously.

Yeah, initially we expected that for us committing, maybe we could be able to share this data, but the deadline for this is January 28th. And this will be very too early for communicating this activity and safety as well of steer tubing.

So we should wait for a small, but definitely this is something that we can check. And proclinically as well, we can make some tests in a specific patient, for instance, through the disaggregates.

So disaggregates of the tumor is important because you can check, you can test several drugs for this patient. And the interesting thing of these disaggregates is that you have the microenvironment there.

It's not about tumor cell culture, it's about the disaggregate which contains all the tumor cells plus the microenvironment. So the translational research to the patient maybe is more, I don't know if this word exists in English, we say extrapolable in Spanish, but it's more robust, the conclusion you can find.

And then this is something that we can do as well in a patient with progressing sarcoma, we can check what kind of drugs can be more active in this context.

And we can check this kind of new drugs we are testing and we are considering promising in this disease. So I think, yeah, there's arguments for hope.

And sometimes we have some strategies that can work, especially for those consider bulky tumors where surgery is not possible because the size. In some cases, we have treated these patients with trapectin glass radiation therapy.

We have a substantial experience with this strategy and we have seen responses in the context of SFT. So today is one strategy that can work. And we have even patients with brain SFT treated with trabectin plus radiation therapy with a shrinkage of maybe 80% of the tumor.

So this could be also achieved with this combination. So it's true that in general, the dissemination of SFT in the advances is through different metastasis and then it's more difficult to apply that.

Patient advice and closing remarks

But sometimes the problem is big mass. that should be reduced in size in order to obtain a good disease control and then we can offer this trabectidine class radiation therapy as well.

Well, I want to thank you for what you're doing. I know as we wrap up our time here, those who have listened to this will find that there is hope. There's a lot of research being done on solitary fibrous tumor, other sarcomas, and I appreciate you're one of the people who's done a lot of that work.

Do you have any final thoughts of things, of a message you would want to leave to patients who might be listening to this? Because again, most of the podcast listeners are doctors, but there are people who have this, and what other message would you want them to know?

Yeah, maybe the first message is you are not working alone. There are a lot of community around you, doctors, but also advocacy patients, patient groups.

So this is important. To share your situation is important as well in order to be encouraged by the experience of others and doctors. And so this is important.

And maybe the second message is obviously to be sure that the doctors that are in charge of your care are expert in sarcoma. So I think this is important as well because sarcoma patients should be treated by MDT, by multidisciplinary teams expert in sarcoma.

not only medical oncologists, but also radiation oncologists, pathologists, radiologists, surgeons, etc. This is important as well. These are the two main messages.

And then to be sure that you can also have access for innovative procedures, innovative treatments. So this is something that is also important to consider.

I think these are the message. I want to thank you again for taking the time to do this. Thank you for the research you're doing. Look forward to seeing the publications on the clinical trials you're doing.

And I'm really interested to see where the field goes. And again, thank you for you and for your research team for what you're doing. And I hope you'll keep in touch.

Thank you so much. Yeah. Thank you, Peter. It has been my pleasure. Bye-bye. Thanks for tuning in to the Doctors Making a Difference podcast. And thank you for what you do to help your patients and your community.

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