Podcast Episode Title: Clinical Implications - updated Bone Sarcoma guidelines

Brought to you by:

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Transcript

Silvia Stacchiotti
Good day everyone and welcome to this podcast on updates and clinical learning points from the ESMO and NCCN Bone Cancer Guidelines. Today, together with Professor Robert Maki, we will discuss changes in the last version of the ESMO Clinical Practice guidelines and NCCN guidelines for Bone Cancer based on the latest clinical data and we will also try to make some comparison on the two different guidelines. I am Silvia Stacchiotti, medical oncologist. I work at the National Cancer Institute of Milan, Italy. I am fully dedicated to research and clinical management of adult patients affected by sarcoma of any sites. I collaborate with all the institutions, societies and patient advocates involved in the research and care of sarcomas with a special focus on ultra-rare sarcoma types. In particular, I am involved in all the ESMO activities regarding sarcomas, and I am the current subject editor for the ESMO Guidelines Committee for sarcoma and GIST, and I'm also the current president of the Italian Sarcoma Group. And you, Bob?

Robert Maki
I'm Bob Maki. I'm a medical oncologist working at Experimental Therapeutics and Sarcoma Medical Oncology at the University of Pennsylvania in Philadelphia. And it's just a pleasure to be able to talk with you, Silvia, about some of these issues that arise regarding treatment of this rare group of cancers. As we are both aware and deal with every day, sarcomas are very rare. They represent less than 1% of the cancers that happen in adults. But despite this rarity, people such as yourself, Sylvia and many of our colleagues have gotten together to assemble the guidelines both for ESMO and NCCN regarding diagnosis and management of these cancers. And I think it's really important to point out, which is highlighted, I think in both sets of guidelines, the role of the

multidisciplinary team in both diagnosing and treating sarcomas. Sylvia, can you make a few comments on some of the issues that you've had to address in Milan?

Silvia Stacchiotti
Let's start from a kind of general introduction on how the ESMO guidelines are considered. The ESMO guidelines are considered clinical practice guidelines, of course, in this case for treatment of bone sarcomas. They were published, the last version was published in 2021, and was the result of a discussion promoted by the ESMO in partnership with EURACAN, GENTURIS, and PaedCan, during a mutual consensus meeting that was held during the COVID pandemic in December 2020, and it was followed after by several rounds of email. The recommendations included in the guidelines, are the results of a consensus amongst the European multidisciplinary Sarcoma Community, I would say, of course, of experts in the field. And it is very clearly stated in the ESMO guidelines that sarcoma needs to be discussed within the multidisciplinary tumour board, of a centre or even a network with experience in sarcoma, to plan the optimal approach to each single patient. As it is being shown very well by our French colleagues over the last years, that being treated in a centre of expertise from disease onset, not only for the advanced phase, corresponds to a better outcome. So, the ESMO guideline discussion, to try to engage the largest representative of the European Sarcoma Community, involved the members of the ESMO Sarcoma faculty; but also experts appointed in the institution belonging to the sarcoma domain of the European Reference Network for Rare Adult Solid Cancers, which is called EURACAN; and a representative from the European Reference Network for Genetic Tumour Risk Syndrome, GENTURIS; and the European Reference Network for Paediatric Oncology, PaedCan. In addition, we discussed together with representatives from Japan and also from India. How the discussion happens to be within the NCCN guidelines?

Robert Maki
It's constructed a little bit differently. There's a group of about 30 experts who meets at this point, virtually and occasionally in person, at least in the original set up of the guidelines. The group is led by Margaret von Mehren, a sarcoma expert up at Fox Chase, also here in Philadelphia. And they oftentimes will add in new information more than once a year for a treatment pathway scheme for helping to manage this group of diagnoses, all the way from diagnosis through treatment of primary and metastatic disease. As new data become available from clinical trials, those data are incorporated into the guidelines. And I guess we can begin to dig into some of those specifics that's equally recognised in the NCCN guidelines, the importance of that multidisciplinary care between surgery, interventional radiology, medical oncology, radiation and pathology all contributing of course to the diagnosis and treatment of this group of patients. One key point, which I think is an evolving issue and not well brought out exactly when to do this sort of thing is when should we do genomic testing on sarcomas of soft tissue and bone? I guess we're mostly restricting things to bone today but has implications for diagnosis such as Ewing Sarcoma that can occur in both soft tissue and bone.

Silvia Stacchiotti
Oh, it's interesting, and do you also have paediatricians participating to the discussion?

Robert Maki
There are, they certainly do contribute simply because there's a lot of overlap, especially that adolescent and young adult age group who end up with that many of these diagnoses. Has the same thing happened with the ESMO? You did mention the paediatricians being involved there.

Silvia Stacchiotti
Yes and in fact, we have a representative from PaedCan, which makes especially for bone sarcoma, the discussion of course, much more interesting. So, the last version of the ESMO guidelines for Bone was completely reshaped compared to the prior ones, to align this to have the same structure that we have for soft tissue sarcoma and GIST. And in the guidelines in addition to pointing out the relevance of the multidisciplinary tumour board, we try to discuss how important it is to have a correct pathologic diagnosis and to assess the presence of molecular alteration at least every time this impacts the diagnosis. Of course, probably the ESMO guidelines compared to the NCCN –but you can correct me– are mostly focussing on what can be considered the standard approach, starting from diagnosis, and ending with the treatment. So, when a treatment is not formally approved, is not formally labelled for a given disease, this part is called investigational, and assessed within a clinical study, or optional, when a treatment can be discussed on a case-by-case basis, but there is not such strong evidence to consider it as a standard. So, in the new version of the guidelines, we are mentioning entities that were not even considered before, like *CIC-DUX* or *BCOR* tumour types. And compared to the past, we have now, a list of new compounds, such as, for example, regorafenib in osteosarcoma, for which there is some evidence of activity, even though they are not formally approved in the list. But I know that in the NCCN and it is a bit different, isn't it?

Robert Maki
Ywa that's exactly right Silvia, the committee meets relatively frequently to assess new data as they become available. I'll mention one of those points in just a moment, but as those data become available, they are added into the guidelines as potential options for care. What happens in the United States is that this document, the guidelines, are oftentimes used by insurance companies as to what's considered orthodox treatment for one or another diagnosis, that may be based on phase 2 data. But we may be lucky enough to have a randomised clinical trial. But in either case, if the experts believe that there's enough data to support the use of a medication or combination, it will be listed there. And I think it highlights also the differences that we have between the United States and Europe regarding access to some of these agents, which are not, as you mentioned, EMA approved necessarily. They have not gone through randomised clinical trials and gone through the full review process. I understand each country is quite different in Europe in terms of the ability to access what may have been active drug seen, let's say, in phase 2 trials. Is that an accurate statement?

Silvia Stacchiotti
It's absolutely correct. There are a lot of discrepancies across European countries as the system is completely different. And once, even after the approval by EMA a new compound, each single state and country has to confirm the approval and define if a compound can be available in the local place or not. While the proportion of patients who can cover the cost of an off-label drug by themselves thanks to the insurance, is, of course, very, very, very different. Yeah.

Robert Maki
While that may apply for some of the newer agents that are just being studied in phase 1 or phase 2, at least for some of the more standard agents that are available and used commonly, there's a fairly consistent use, it seems, of those agents. I think perhaps a very good example of that might be in Ewing Sarcoma, for example, where now we have randomised data looking at the VIDE versus VAC/IE, combinations in primary Ewing Sarcoma where it seems that the five-drug combination is superior. And I think that's been incorporated into both sets of guidelines for primary treatment of Ewing Sarcoma.

Silvia Stacchiotti
And for us is completely different, and as I said it varies a lot if you move from a country to the other one. So, there are places in which drugs are more often available while others, like Italy, it's very rarely the case. And so, you know, if there are drug with evidence of activity but not formally approved, it is very difficult for a patient to be treated or for us to change the conventional regimen.

Robert Maki
In other words, it may be that it's difficult to get off-label use of medications that might be thought to be useful and say, something like immunotherapy for particular subtypes of sarcoma, that are out there.

Silvia Stacchiotti
Yes absolutely, and it is interesting that this does not only apply to treatment, but also to diagnostic procedure, for example. If a molecular test that is not formally approved in a given setting, it can be completely not available. For example, in the guidelines now we talk about chondrosarcoma, we know that an *IDH* mutation that can be important for driving treatment within or outside clinical study. This kind of assessment is rarely done in our patients as it's not considered the standard diagnostic path or predictive analysis. So yeah, they are very different things.

Robert Maki
I was just thinking of some of these tumours of bone that we treat; Ewing Sarcoma, it's pretty much a standard of care to get at least FISH testing, although it's helpful perhaps to have more information like the fusion type between EWSR1 and FLI1. But for example, we don't get routine genomic testing on osteosarcoma, for example, even though it's now becoming clear that there are multiple genomic subtypes of that single diagnosis.

Silvia Stacchiotti
In Italy for example, FISH analysis to look at the most common translocation fusion genes, is available at least in regional centres for treatment of sarcomas, but of course we do not sequence on a regular basis osteosarcoma and also a less common fusion gene like *CIC-DUX* or *BCOR*- , are not searched on a regular basis; are only searched when there is a very strong diagnostic doubt and I'm sure that these impact the quality. Within the centres of expertise or networks of expertise, the policy is different, and for that reason it's so important to have all cases reviewed by expert pathologists.

Robert Maki
And that's a very good point. We don't routinely get every tumour sequenced here in the United States either with next generation sequencing, although it was again shown very well by our French colleagues that you change the diagnosis 15 or 20% of the time, even after you've made your initial diagnosis. The extra genetic information can really impact diagnosis. And if you don't get the diagnosis correct, well, then you're not going to treat the patient correctly either.

Silvia Stacchiotti
Then I think that's another important part that was added to the ESMO guidelines, this time was a small chapter with something more into supplementary data about the genetic predisposition. This was thanks to the participation of GENTURIS, as I said before this is the group of people working

on genetic predisposition and cancer. And we could include in the guidelines when, for example, the presence of p53 alteration has to be looked for. I think that would be very, very important to expand this area, maybe with a dedicated guidelines covering not only bone but all the sarcomas. Is there something on which are you also working?

Robert Maki
I work very closely with our clinical genetics team, and they have a large number of Li-Fraumeni patients with *TP53* mutations who they're following, as well as those with *BRCA1* or *2* or familial adenomatous polyposis families. And it's interesting to see that sarcoma patients can pop up in any of those syndromes, not just in Li-Fraumeni Syndrome, for example. I think there was really great work done by David Thomas and his colleagues in Australia, which showed that even when you didn't have a strong family history of sarcoma or other cancers, that as many as 12% of patients ultimately were shown to have a familial predisposition for cancer. So, I'm glad that there's been the recognition that, at least for the osteosarcoma patients, that we should be doing some screening for familial syndromes like Li-Fraumeni and some of these others. Since they're now able to analyse dozens, if not hundreds of genes that may either be rare or highly penetrant and highly penetrant, or maybe they have smaller impact but still affects the frequency of different cancers, including sarcomas, that it's critical that we keep that in mind as we treat sarcoma patients. So, I'm delighted to see those changes.

Silvia Stacchiotti
Yes, in particular with bone sarcoma, that is a kind of tumour, especially for Ewing again, and osteosarcoma, usually arising in children or younger adults. And in fact, we are planning to have a session fully dedicated to genetic predisposition and sarcoma during the ESMO conference in 2023. We hope so. So, with regards to osteosarcoma, what do you write about low grade osteosarcoma? Which kind of approach do you suggest to your patients.

Robert Maki
Well, those are very challenging tumours, those are a distinct minority of osteosarcomas to be sure. So perhaps the most common place for those to arise are in the mandible and sometimes in some of the long bones as well. We follow the guidelines, and we obtain a biopsy of such a patient, and it shows a low-grade tumour. Normally for high grade osteogenic sarcoma, we will give neoadjuvant chemotherapy as it’s a standard of care in both sets of guidelines. But for these low-grade osteosarcomas, surgery alone oftentimes is the best standard of care. And I think that's also highlighted in at least some of the guidelines. One of the, I think, complex issues regarding head-neck osteogenic sarcomas is again, kind of almost an additional layer of multidisciplinary care that needs to be undertaken for such patients, because you're not just dealing with medical oncologists and surgeons. These are head-and-neck surgeons, and you may also have to engage the orthopaedic surgeons or the plastic surgeons for reconstruction issues. And that makes it an exceedingly complex anatomic site for this, whatever it is, 10 or 15% of osteosarcomas that affect the head and neck area. I'm sure you've had equal challenges in trying to manage those sorts of patients.

Silvia Stacchiotti
In fact, this is the context in which it could happen that we suggest that radiation therapy even for a low-grade bone sarcoma, when the surgical resection has been an R1 marginal resection in head and neck low grade osteosarcoma, we discuss in the multidisciplinary board, also adding radiation. And I am happy today to say that in Europe where we have much more facility for proton beam and carbon ions radiation that were not here in the past. So, we could even specify in the

guidelines that this kind of treatment can be used when the anatomic location prevents the good amount of radiation with photons. So, this is niche again, but we used to treat such ultra-rare situations, as I said before. And with regard to, again, osteosarcoma, when we look at high grade osteosarcoma of course it's clear, which is the treatment below 40 years what about patients above 40, anything new that you added in the guidelines?

Robert Maki
I don't know there's anything new in the guidelines, other than I think it's well recognised that it's very difficult to treat patients above 40, at least with full doses of the chemotherapy that we give to what's typically adolescents. For example, the guidelines generally suggest the use of 12 grams per metre squared per dose of high dose methotrexate, one that's being incorporated into the methotrexate, doxorubicin, cisplatin combination that is part of both guidelines. Above age 40, though, it becomes difficult to give that high of a dose of methotrexate with and still have people's kidneys stay intact. So, in general, we'll see that people receive, in general, somewhere along the lines of 6 to 8 grams per metre squared per dose of methotrexate. We still think it's an active agent despite there being a couple of randomised trials that showed that it wasn't necessarily helpful, it still remains the standard of care. I think there's still some debate about its use, but as a practical issue, I generally start with the standard doxorubicin-cisplatin first before thinking about that methotrexate dosing for those patients over 40. I don't know if you've encountered similar issues?

Silvia Stacchiotti
We also do the same, even though with the lack of a direct comparison, if a patient above 40 is fit and has no comorbidities, we always try to – and is not of course over 70 years old – we always try to use also methotrexate because we cannot say that high dose ifosfamide is a surely super plausible. But yeah, of course above 40, is more challenging to treat the disease.

Robert Maki
Well, Sylvia, we've touched on Ewing Sarcoma, chondrosarcoma, osteogenic sarcoma, at least a little bit. Maybe we can talk a little bit just for a couple of minutes here at the end on chordoma, a sarcoma that you're well known for treating. And what is your approach for that particularly rare cancer which can affect either the sacrum or the clivus, two very difficult areas to operate on. And I think that's you do have some guidance in the guidelines for treatment for chordoma as well.

Silvia Stacchiotti
I mean chordoma is somehow always a frustrating disease because first of all, it usually arises in very challenging anatomic locations which prevent a complete surgical resection and are usually related to a very morbid procedure. Then due to the biology and also to the characteristics of the tissue, the proportion of patients relapsing, even after a complete surgical resection or high dose radiation therapy is high. I am not sure of which is the proportion of patients that can be cured, but it's not above 25%. So, the vast majority of patients at some point need to be treated with a systemic compound. And this is the perfect example of how patients with sarcoma can be discriminated as a we do not have a single potentially active compound approved in the disease. So, everything we use is formally off-label and in spite of studies – small studies of course, and not comparative – but showing some activity of anti-angiogenics or EGFR inhibitors, we are still missing a formally labelled drug. In any case, we do not give up and in collaboration with the Chordoma Foundation we are working hard and I'm very happy that we could have a chapter, a small chapter but fully dedicated to chordoma, also in the guidelines even though it is a very rare

disease. And what about you and chondrosarcoma. Many interesting new options are starting to be, at least within studies, available.

Robert Maki
We're certainly hopeful as you mentioned with those *IDH* mutations that will gather further data on the utility of IDH1 and 2 inhibitors and those 40 or 50% of tumours that have those mutations for the dedifferentiated version of chondrosarcoma, which oftentimes is treated like osteogenic sarcoma. And there are at least hints of the usefulness of immuno-oncology agents, PD-1 inhibitors and combinations of CTLA4 inhibitors. But those still remain investigational by-and-large. I think what you're pointing out is that this is one more reason to have patients seen in high volume centres that have studies, where even if it's difficult to access drugs, at least there is the possibility of a number of centres being able to offer something novel to a patient based on the biology of their very specific tumour.

Silvia Stacchiotti
I think that it’s great to see that at least in some areas there are new compounds under development.

Robert Maki
Well, time is short, so I think we'll stop things here for today. And Sylvia, thank you very much for the conversation together. I know we could break out any one of these topics into a much longer story or bring in some other friends for discussion on any one of these topics. And hopefully we'll be able to do that for a future session.

Silvia Stacchiotti
And we can maybe recall that there is another podcast in which our colleagues are presenting what was new during the ASCO 2022. In particular, in the plenary session, we had a study on Ewing Sarcoma which is not so very common to have for us, the rEECur study. And Dr Rebecca Dent, Dr Chiara Cremolini, Dr Lee, and Dr Jonathan Trent are discussing all about that in the podcast that can be seen on the website. I really want to thank the organisers for this event and to all of you for listening to the podcast.