Evolving Management Options for Soft-Tissue Sarcomas

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Overview
This activity is designed to inform physicians about the latest treatment advances in soft-tissue sarcomas (STS), including approved and investigational management strategies.

Target Audience
This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat patients with STS. Surgical oncologists, radiation oncologists, pathologists, fellows, physician assistants, and other healthcare providers interested in the management of STS are also invited to participate.

Learning Objectives
After participating in this CME activity, learners should be better prepared to:
- Describe the shared-care model and its application to treatment of patients with STS
- Explain the significance of recent and upcoming studies in STS management
- Discuss the appropriate uses of combination therapy for STS
- Describe the primary principle regarding sequencing therapy for STS

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With an approximate annual estimate of 12,000 newly diagnosed soft-tissue sarcomas (STS) in the United States,[1] STS is a relatively rare form of cancer. Thus, it is not seen often by community-based physicians. Despite the low incidence of STS, this group of cancers is complex and is a topic of major research interest. At the 2015 meeting of the American Society of Clinical Oncology (ASCO), more than 70 abstracts reporting on studies in STS were presented.[2]

Confounding the approach to treatment is the fact that STS comprises a multitude of subtypes, each of which has specific biologic characteristics and may respond to different therapeutic approaches. Recently, the World Health Organization expanded its estimate of the number of STS subtypes from approximately 50 to more than 100. The characteristics of the tumor, along with patient factors such as age and comorbidities, determine the choice of treatment.[3] As a result of the heterogeneity of STS subtypes and the historical paucity of large, controlled clinical trials, there is no single standard of treatment for patients with advanced STS,[4] and the overall relative 5-year survival rate for patients with STS is only about 50%.[1]

Until recently, nonsurgical treatment of STS was limited to use of standard cytotoxic drugs such as doxorubicin and ifosfamide, administered as single agents, in combination, or sequentially. Cumulative doxorubicin treatment, however, is associated with cardiomyopathy, and ifosfamide is associated with several potentially serious adverse events, such as neutropenia and renal toxicity. Gemcitabine, docetaxel, and dacarbazine are also used in STS, as monotherapy or in various combinations.[5] Results, however, have not always been encouraging. For example, the addition of bevacizumab to the combination of gemcitabine/docetaxel did not improve survival in first-line treatment of uterine leiomyosarcoma.[6] Similarly, the GeDDiS trial failed to show superiority of gemcitabine/docetaxel over doxorubicin in first-line treatment of advanced STS.[7]

Efforts to discover newer, more effective, less toxic agents and combinations are ongoing. Currently, 389 clinical trials in STS are listed at ClinicalTrials.gov that are either recruiting or about to start recruiting.[8] The efficacy of imatinib in treating gastrointestinal stromal tumors (GIST) has led to further exploration of targeted therapies for other STS subtypes.[9] In addition, interest in immunotherapies in STS continues to be strong.[10]

Novel agents that are showing great promise include the marine-derived drugs trabectedin and eribulin. In phase III, randomized, multicenter studies, treatment with each of these drugs yielded significantly longer survival times than did treatment with dacarbazine, with no unexpected toxicities.[11,12] Also under investigation are novel formulations of existing drugs. For example, in a phase 2b open-label study, aldoxorubicin, a prodrug of doxorubicin, demonstrated superiority over doxorubicin in prolonging progression-free survival. In addition, there was no evidence of acute cardiotoxicity.[13] Finally, evofosfamide (formerly known as TH-302) is a prodrug that is activated in hypoxic environments, as are seen in sarcoma tumors; thus, such an agent may have a tumor-specific therapeutic effect. The results of phase I and II trials have led to the initiation of phase III trials of evofosfamide.[3]

Data on current and emerging treatment options for STS were presented at the 2015 ASCO Annual Meeting. George D. Demetri, MD, of the Dana-Farber Cancer Institute in Boston, shares his insights on the significance of recent discoveries and the optimal application of emerging data to the planning and implementing of multidisciplinary treatment for patients with STS.

Moderator: What are some of the most pressing unmet clinical needs in the management of STS?

Dr. Demetri: Number 1 is to recognize that 85% if not more of cancer patients in the United States are cared for in the community, not at specialty academic centers. Also, STS is not one disease; it's a class of probably more than 500 or 600 different diseases. So the first thing is to be sure that patients with STS are subcategorized and managed appropriately. I can't stress that enough, because the more we learn about STS, the more we realize that there are actionable differences between the subtypes, important differences, and if you're in a busy community practice, you don't see a lot of these patients. There are just not enough of them for most community doctors to see more than 1 or 2 a year, and many doctors may not be aware of just how important it is to parse the diagnoses more finely than ever before. Going forward, it's going to be more important that the diagnosis is right, that the right tests have been done, and that management is really bespoke, personalized, for each patient based on all the data. I think we have to get the word out that it's not an academic exercise; it really can mean a dramatic difference in patient outcomes.

Moderator: Given that community physicians don't see that many patients with STS, what would be the best way for them to know what to look for?

Dr. Demetri: I think this is going to be a shared-care model in which community physicians who have patients with STS think, whom do I call who sees a lot of these patients? It is going to be a situation in which we in the academic centers support our colleagues in the community. We're not here to take all the patient care away, we're here to help plan a course of action much of which can and should be delivered in the community, after certain decision points are passed. Initial diagnosis review, initial planning, and then if the disease were to come back or progress – those are decision points. I think experts are very rationally involved in those decisions with people in the community. Again, sarcomas are rare – maybe 20,000 new cases a year in the United States. There are a number of experts scattered throughout the country. Certainly the big 3 that people think of are Dana-Farber/Harvard, Memorial Sloan Kettering, and MD Anderson. There are others, as well.

Here are 2 examples of the shared-care model: The first was GIST.

GIST has a driver mutation; even the different subtypes of GIST are clinically important. This sarcoma is a totally different type. I think that community pathologists educated themselves quickly. We don't see misdiagnoses of GIST anymore, but even with GIST, there are still subtle differences where expert input can be useful.

The other example is that melanoma is the great imitator. We see about 1000 new sarcoma referrals a year, and about 5 out of those are melanomas where our pathologists can see why the outside pathologist thought it was a sarcoma, but it is not a sarcoma, it is a melanoma. In this new age of immunotherapy and BRAF inhibitors and all the appropriate melanoma-targeting therapies that make such a difference for patients, it is hugely important to know whether the diagnosis is truly a sarcoma and not a melanoma.

So those are simple examples that should resonate with every physician. There are only a few places in the country that have pathologists with the experience to say definitively, "yes," "no," or "I can't tell." When the great pathologists say "I can't tell," they usually send it to some other great pathologist and ultimately get a consensus opinion, and that winds up being our gold standard. I'm just a medical oncologist; I can only treat what the pathologist tells me the patient has, so we are dependent on the expertise of the pathologist. And in "sarcomaland," it's not like breast cancer, which is far easier to diagnose. Sarcomas can be tricky. About twice a year, people come in with a sarcoma diagnosis and we are able to tell them, "Our expert pathologist says you have a benign mimic of a sarcoma. This is not something that has metastatic potential; this is a benign inflammatory condition. We see why your doctor thought it could be a sarcoma, but the good news is that it's not."

So the biggest unmet need is that education piece. We and the patient advocate groups are saying it really does make a difference to have a shared-care model where community doctors can reach out to the academic centers and we work together for the good of our patients.

Moderator: What do you think of some of the recent data coming out of clinical trials with novel agents, formulations, and combinations?

Dr. Demetri: We know that about half the patients with sarcomas are curable with even current technology – multidisciplinary care for localized disease. That's a wonderful number, but you can also look at that and say, that means half the people won't be cured. That's where we need better therapies, and that is where some of the recent data have been very exciting. We are finally getting high-quality data from our field, not limited to 1 or 2 centers but collaborative data that can be extrapolated to most practice settings.

These studies have given us a sense of objectivity, because the numbers are bigger. We can really use the data to say to our patients, "Here's what is likely to happen if we choose this therapy, here's what might happen if we choose that therapy, here are the risks, here are the potential benefits."

Ultimately, from the better knowledge comes the question of how to identify the most risky sarcomas and be able to prognosticate accurately. And then from the deeper biological understanding of the disease comes the question of how we can develop better drugs that actually work, that have meaningful clinical benefit and a real impact on how patients feel, function, and survive – the classic trio that the FDA looks for.

Before 2012, except for the dramatic push of targeted therapies for the GISTs, we really hadn't done much for our patients with STS despite years of trial, years of arguing, many years of wishful thinking about developing effective drugs. We were still very reliant on drugs from the 1970s, such as doxorubicin, dacarbazine, ifosfamide – older drugs. The 1980s and 1990s brought us the ability to mix and match these drugs in different doses and schedules, and at the end of the day there were marginal changes. The late '90s brought us gemcitabine, and it took a while to recognize that that drug, which was first approved for pancreatic cancer, also works in lung cancer and breast cancer, and a decade later we found it works in sarcomas.

So, it's been an evolution of developing newer drugs for sarcomas, and now we've finally got some new drugs, some promising data. There have been some new FDA approvals, and there are a number of large studies heading towards registration endpoints.

Moderator: Is there a particular class of drugs that looks most promising?

Dr. Demetri: I think the WHO classification of STS is a vast oversimplification; for example, there are at least 15 clinically meaningful different types of GIST alone. One interesting thing about this diversity of human cancers that we call sarcomas is that we're going to be able to pull from kinase inhibitors, antibody therapy, standard cytotoxics, both natural and engineered, antibody drug conjugates. Part of our challenge as a community of investigators is to do that match.com, or eHarmony of experiments to say, what's the good match here? What's the right kind of sarcoma to match up with the right type of drug?

Moderator: And not to be formulaic about it?

Dr. Demetri: I don't think we can be. We're learning new things almost on a monthly basis about issues that we thought we understood. Right now the epigenetic space happens to be particularly exciting. Some of the ways of targeting epigenetic aberrations in different sarcomas are very scientifically promising, with some clinical data already showing, for example, that an EZH2 [catalytic subunit of the polycomb repressive complex 2, a histone methyltransferase] inhibitor has extraordinary activity in certain molecularly defined subtypes of very rare sarcomas.

If we can identify an STS subtype whose mechanism we understand and then find a drug that targets that mechanism, if it hits that mechanism in a human as opposed to just in a mouse model, then we're on the road to either proving that our knowledge of that cancer was right or to saying, why didn't it work? Was there some other compensatory mechanism that blocked the intended effect? Or if we do see the effect, we can all pat the patient on the back and say, here's a good drug for you, go live a nice life and prosper. There's no feeling

as good as doing that for a patient.

Developing drugs becomes an addiction, because you start seeing that we can help the next generation. We are helping this patient right now, but we are also helping the next generation of patients with this kind of disease. It is an extraordinary time for our field. It comes from such a wasteland too. It comes from 15 years during which nothing was working; in the early '90s you could see the seeds planted by some extraordinary molecular biology advances where, for example, people were first discovering the unique chromosome translocations that defined Ewing sarcoma. There has also been a tight correlation between basic science advances, clinical pathology, and diagnostic advances, and then moving from that to a rational therapeutic approach.

A lot of things haven't worked where we had hoped they would work; mTOR [mammalian target of rapamycin] inhibitors are a good example. I ran a big randomized trial with an mTOR inhibitor that was statistically positive. The drug had an impact, but the impact was so small that the academic community and the FDA agreed, "this is not clinically meaningful enough to use an mTOR inhibitor by itself in all STS." Subsequently, though, investigators identified a specific kind of sarcoma, known as a PEComa [perivascular epithelial cell sarcoma], that has TSC1/TSC2 mutations. In that kind of sarcoma, the mTOR inhibitors have impressive activity.

Before, we were treating all sarcomas as if they were the same, with very specific targeted therapies. Now, there are other less-specific therapies also. There's a whole new way of looking at STS where we can paint with either a very fine brush or a broader brush. To me sarcomas are a microcosm of what's happening in oncology in general. There are advances with standard broad-brush chemotherapy, but then also very exciting advances in the most targeted therapies you can imagine for the most precise molecular mechanisms.

Moderator: Are there differences in terms of toxicity between standard chemotherapy and these new targeted and more specific drugs?
Dr. Demetri: There are, and it varies to some extent by patient. For all of us who trained in the 1980s and 1990s, it's a different world now. We are really trying to develop better, smarter drugs. Like the car ad, it's not your grandfather's chemotherapy. There are a lot of differences, both in the drugs themselves and in their formulations. For example, one of the first known HIV diseases was Kaposi sarcoma. In the early days it was treated with doxorubicin, a standard drug for sarcomas, and HIV patients couldn't tolerate doxorubicin because their immune systems were already so compromised. So one of the first interesting formulation differences was to put the drug in a fat bubble called a liposome, which changed the toxicity profile, and now liposomal doxorubicin is approved for sarcoma as well as for ovarian cancer. It was that type of discovery that got me interested in formulation research as something that could make a significant difference.

There currently are some exciting studies with completely new drugs. Even though they may not have been genetically engineered by scientists, they were genetically engineered over the millennia by sea creatures. Sea creatures have some of the best, most advanced chemistry sets on the planet, because they're sitting in a dark, dank environment. How do they protect themselves from predators? They synthesize really impressive chemical warfare weapons.

Two new drugs have shown activity in sarcomas. One, trabectedin, is from a sea squirt; the other, eribulin, is from a sea sponge. Both of them have had positive phase III clinical trials. Trabectedin was approved by the FDA in October 2015. It was approved just about everywhere else in the world in 2007. It took a new trial to finally reach FDA registration. Both of these molecules have beautiful chemical complexity. They are extraordinary anticancer drugs. We have to figure out how to use them better. We have to figure out what the biomarkers of sensitivity are, because some patients, especially with trabectedin, can get a tremendous amount of benefit, even if most patients only have a few months of benefit. A few patients can stay on the drug for several years and control their metastatic disease. If we could figure out who those extraordinary responders are, we could probably target therapy even better.

Trabectedin also is a pretty good quality of life drug for many patients. Even though it's given intravenously, a lot of patients find that they're still able to live a pretty normal quality of life. For a few days they might be tired, but it does not cause hair loss. It is a very interesting drug on multiple levels.

Eribulin has been FDA approved for breast cancer for several years, so most doctors know how to use it, and it's got some activity. We understand the side-effect profile, and it's pretty well-tolerated chemotherapy in general for most patients. It's all about appropriate combinations. There's an old adage that says drug development starts when a drug gets FDA approved for an indication, and I think that's true for these two drugs. Putting them into combinations, figuring out how to use them is now the primary responsibility of our whole research community.

We've also seen a great deal of interest in older drugs such as gemcitabine. It took a long time for our field to recognize that gemcitabine, with or without docetaxel, has activity against many types of STS, most notably leiomyosarcomas, but also other forms of STS. Then the question comes up, is that something that should displace other therapies? What's the right first-line therapy? Is there a best first-line therapy? The GeDDiS trial, comparing gemcitabine/docetaxel with doxorubicin alone, showed that you can customize the choice for your patient. There's no right or wrong answer. The side-effect profile and other logistical elements may help a doctor have a rational conversation with a patient, use that patient's preferences for risk and convenience, other comorbid clinical findings, to choose a way to start.

Moderator: What about sequencing therapy?
Dr. Demetri: The nice thing is that if you choose one, if it doesn't work, you can switch to the other one and vice versa. What's interesting about sarcomas is that most people will get most drugs. If you

start with drug X, or combination X, you'll then get drug Y as number two. If you start with drug Y, you'll get drug X. Sarcoma patients and their doctors, especially at the academic centers, are very nimble about switching quickly so that they can give patients the benefit of sequential therapies, if need be. Or, they can keep somebody on a drug for a reasonably long time if that drug is working to control the disease.

Moderator: Is the switching happening primarily because you find out a drug wasn't working optimally, or because they lose efficacy as time goes on?
Dr. Demetri: The switching is either because there's primary resistance; in other words, you give the drug and the tumor grows without having stopped. Or there's secondary resistance, which means you give the drug, the tumor is controlled for a while, but it starts to grow later. Sometimes patients can be switched because of tolerance issues, but that's usually not the reason; sarcoma patients tend to be younger and healthier than many other kinds of carcinoma patients, so people wind up switching easily for lack of effectiveness rather than for any kind of side-effect profile problem.

The other important thing is that our field has recognized that a tumor can be controlled without shrinking. For example, with imatinib, you can stop a GIST cold in its tracks even if the tumor does not shrink. That is true in other kinds of sarcomas treated with the newer chemotherapies. We used to see that with doxorubicin all the time, and now we're seeing it with drugs like trabectedin and eribulin. That was the basis for FDA approval of the other targeted drug, the multikinase inhibitor pazopanib.

The sequence issue is a huge challenge for our field because most patients are well enough to receive multiple lines of therapy, and it's up to the doctor not to give up too early, not to be unrealistic. For example, there have been patients who have had doxorubicin, ifosfamide, gemcitabine, docetaxel, pazopanib, and for some of them, nothing ever worked. They start trabectedin and it controls their disease for a long time. Had the doctor said, "nothing else has worked, I'm not even going to try this," those patients never may have gotten to that point. Trabectedin is a good example of a situation in which patients can go from one drug to the next, to the next and get sequential benefit from each one.

We're pretty good about predicting where a kinase inhibitor is going to work, but with chemotherapies – ifosfamide, doxorubicin, gemcitabine – we're still not so good at predictions. Decisions whether and when to switch from one drug to another are very difficult decisions based on specific patient factors, and this is where that shared-care model often comes in. Oncologists at sarcoma centers have enough experience to be able to tell patients, "I've seen 30 patients like you and here's what happened to 20 of them, here's what happened to 10. Let's make a decision about what's best for you; then we can talk to your community physician, who can continue to care for you."

Moderator: What is the role of combination therapy?
Dr. Demetri: There are very few cancers that could be cured with a single drug. Even the easiest-to-treat solid tumors such as testicular cancer are not curable with platinum alone. You need a combination. In "sarcomaland," we expect that part of having new drugs will be the ability to build new combinations, new regimens, that might offer better benefit to patients from the start. That's part of the value of clinical trials. If there aren't clinical trials, it's our job as investigators to write those protocols if there are good ideas to be tested.

I find this a particularly exciting time, because we have these new drugs, and we have many others I haven't talked about here. For example, we know that even though cancer is thought of as a genetic disease, which it generally is, there are many cancers that are driven by the epigenome, by the readers of the DNA. This is a whole other level of biology, and we're just starting to see that we can target that as well. It's so exciting to be able to take these pathways, turn them into drugs, and then figure out where they're going to work, where they're not going to work, and offer those things to patients.

Moderator: In the meantime, what would you offer to patients?
Dr. Demetri: What we offer currently is a menu. We can choose one from column A, one from column B, one from Column C, go sequentially and in any order you want. We can even start with C, move to B, go to A, whatever.

Moderator: So sequencing doesn't mean just continuing on a set path. You set the path as you go.
Dr. Demetri: And you vary. It is so individual for patients, based on where they live, what is important to them in terms of quality of life, activity level, etc. Those differences help us customize a plan for a patient. And this is what community doctors do very well. They know their patients, and they match the goals set up by the patient with the evidence, with the available medicines. This is not a one-size-fits-all disease by any means. STS is a large field to deal with but it's very rewarding right now, because we're really making advances that are meaningful.

Moderator: What about old gold standard drugs like doxorubicin? Do they still have a place?
Dr. Demetri: Absolutely. I think doxorubicin is undergoing a renaissance right now, because it is being formulated differently and also combined with newer agents. People have yet to show that anything is superior to doxorubicin in the first-line setting. Some new data are coming out saying that the combination of doxorubicin with olaratumab, a monoclonal antibody targeting the PDGF receptor, is effective. In a small, underpowered study, there was a very dramatic overall survival difference without quite as dramatic a difference in control of disease. This is the basis of a very large international effort that's currently under way to test the hypothesis that the addition of olaratumab improves outcomes versus those with doxorubicin alone. If the hypothesis is supported, this would be a very big benefit to patients.

Formulating doxorubicin differently is also interesting. As an analogy, if you take paclitaxel and put it in a nanoparticle, you've got nab-paclitaxel, which has very different clinical properties from those of the parent taxane. This idea of nanoparticle formulation is the basis of one of the newer drugs, aldoxorubicin, which has a linker molecule to doxorubicin, so that the minute it hits the bloodstream, it forms a conjoiner, a moiety, with albumin, and that makes it essentially a nanoparticle.

What it seems to have done is change the side-effect profile of doxorubicin so as to get rid of one of the most feared side effects of cumulative doxorubicin, which is cardiotoxicity. It's been known for years that if you get enough doxorubicin, you damage the heart irreversibly. So far many patients have gotten really huge cumulative doses of aldoxorubicin without evidence of cardiac damage. There's a very large phase III trial still accruing, and then it will take a while for the data to mature, but if that shows benefit, that will be a very nice addition to the armamentarium.

Finally, there is a new drug that used to be known as TH-302, now known as evofosfamide, which takes the active part of ifosfamide and puts a warhead on it so it seeks out areas of tumors that are hypoxic, and then that activates the drug. The booster rocket falls off as it were, and the active drug is there in the hypoxic environment and goes after the tumor cell targets. That phase III trial has completed accrual, and we are all waiting for the data to come out – hopefully it will be at ASCO 2016 – to see whether a properly powered and expertly executed clinical trial will show benefit for that drug. So our field has all these very nice, very clever chemically sophisticated ideas just about to be told.

Moderator: Is there anything else you think is important to mention?
Dr. Demetri: I'd like to say a word about how great the FDA has been. They have given us two approvals in the last 3 years, trabectedin and pazopanib for STS. I think it's a good example of how the FDA is fulfilling their mission, paying attention to safety and efficacy but also recognizing that we're not going to have big 10,000-patient clinical trials in the world of sarcoma. They're respecting the limitations of the rarer disease populations, and I think that's important, and we've been able to make progress because of that. It's been a great working relationship.

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