

CLINICAL UPDATE

Translating Scientific Advances into Clinical Practice

Disease State Awareness in Sarcoma

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H&O What is a sarcoma?

GD A sarcoma is a cancer of a connective tissue cell, such as those in the muscles, bones, fat, nerves, blood and lymph vessels, cartilage, and other body parts. It is important to emphasize that saying a patient has a “sarcoma” is no more descriptive than saying that a patient has “cancer.” Pathologists and clinicians need to ask for more specific details about a diagnosis of sarcoma, and clinicians, pathologists, molecular pathologists, and cytogeneticists must be aware of the many different kinds of sarcomas there are, so that we can pull the latest technology into the diagnostic realm and give that information to the physicians who are caring for these patients.

H&O Could you provide some background on sarcomas and discuss the current state of this disease?

GD Sarcomas are extremely varied in their presentation, and yet they are relatively unusual, with an annual incidence in the United States similar to the incidence of Hodgkin disease or testicular cancer. The enthusiasm to understand each of the individual subtypes—which are often very different from each other—has not been present simply because of the rarity of the disease. There is now an increasing understanding that it is pivotally important to patient management that the clinician understand the differences among sarcoma subtypes because the treatment choices and outcomes can vary dramatically.

H&O What are some of the challenges in diagnosing sarcoma?

GD One of the biggest challenges is that in the last 10–20 years, there has been a push to make the diagnosis in the

least invasive way possible, an approach that has often led to minuscule amounts of tissue being obtained—occasionally even just a few cells. If there is not enough tissue, making an accurate diagnosis can be not only challenging, it can be impossible. Although minimally invasive diagnostics are well-intended, I have seen cases in which this approach has resulted in delays in diagnoses, and possibly even wrong diagnoses. Therefore, if a sarcoma is suspected, it is probably a good idea to have an experienced team consider the optimal diagnostic possibilities to maximize accuracy with function-sparing approaches.

A major issue is that due to the rarity of the disease, many physicians may even not consider the possibility of sarcoma. I have great respect for the challenges of community-based physicians, who are most likely to see the most common diagnoses but who must also consider uncommon conditions. We ask community physicians to keep sarcoma in mind, and in cases in which a sarcoma diagnosis is a possibility, to consider referring the patient to an expert sarcoma center, or at least to avoid diagnostic or therapeutic interventions that could harm the patient, for example, by potentially compromising tissue planes.

H&O Are there certain diagnostic features or signs that can indicate the presence of a sarcoma?

GD There is no one simple answer to that question. With hundreds of different sarcoma subtypes, the physician has to be on the lookout for anything. Sarcomas can happen anywhere in the body. Recently, we saw a couple of testicular leiomyosarcomas that had been thought to be cysts. The difficulty for any primary care physician, of course, is that a scrotal mass is usually not a sarcoma, but sometimes it is. The challenge is to educate every subspecialty—every type of doctor—about sarcomas.

H&O What tools do pathologists at sarcoma centers use to diagnose sarcoma?

GD The biggest tool is experience. Most sarcoma centers have a highly experienced pathologist with a great interest in what distinguishes one type of sarcoma from another. Expert reference pathologists provide the first line of attack. Molecular diagnostics are the second line of attack, using such tests as fluorescent in situ hybridization, which

can be used, for example, to distinguish a Ewing sarcoma from a synovial sarcoma from some other poorly differentiated cancer, which might not even be a sarcoma.

In the future, as tumor genomic testing becomes less expensive and more disseminated, sarcomas will increasingly be characterized, as we are doing now in reference centers, by certain mutations. For example, we are genotyping gastrointestinal stromal tumors (GISTs) to determine exactly the genetic form of the mutation in the cancer-causing gene. In some sarcomas, like inflammatory myofibroblastic tumors (IMTs), approximately half of the patients have a rearrangement of the anaplastic lymphoma kinase (*ALK*) gene. That distinction will be critically important because there is a new *ALK* inhibitor (PF02341066, Pfizer) that has already shown promising data in IMTs clinically harboring the *ALK* translocation.

H&O Which patients should be treated at a sarcoma center and which patients can be treated in the community setting?

GD Most guidelines worldwide recommend that all patients should be under the care, in some way, of a multidisciplinary team with all the relevant disciplines, including an expert pathologist, an expert surgeon, and expert medical and radiation oncologists who are experienced in the care of sarcoma patients. Does that mean that all patients must receive their care at a sarcoma center? Not necessarily. Much routine chemotherapy can easily be managed in the community setting. But the plan of attack is best developed in conjunction with the physicians at a sarcoma center, where the following questions will be considered: Are there any new options that are very promising and should be offered to the patient? If chemotherapy should be used, what kind should it be? Should radiotherapy be used, and if so, how complex is the planning and implementation of that modality? What is the optimal function-sparing approach to surgery that would yield the best chance for long-term disease control or cure? At our sarcoma center, we strive for collaborative interaction with referring physicians that integrates the local care team, as well as patient preferences, deeply into the decision-making process.

As an example, we have a patient whose treatment approach will consist of surgery, radiation, and chemotherapy. The chemotherapy can probably be administered in his home state because we have great confidence in the capability of the patient's referring physician, and the chemotherapy regimen is straightforward. There are some technical considerations, however, about how the radiation and the surgery might interact, and how they are timed, and so there may be a reason for the patient

to have those procedures performed at our sarcoma center. That may not always be the case, and everything is always individualized based on patient-specific details; our surgeons are very good about saying, "This surgery is pretty straightforward. You can easily undergo this procedure in your home state if it is more convenient for you." Or the surgeons may say, "This surgery is more complicated. I would recommend you have it here." I view our sarcoma center as a resource for the people in the community to access.

H&O What are the current treatment options?

GD The treatment options are as varied as the disciplines in medicine. We use all the tools available for the different kinds of sarcomas. They range from surgery alone all the way up to high-intensity, multimodality therapies that use all available options: surgery, radiation, chemotherapy, molecularly-targeted new drugs and, potentially in the future, immunotherapies and vaccines. Sarcoma centers are references for community doctors and for patients all over the world, so that they can access all the right tools in the aim of matching the right treatment, no matter what it is, to the right patient, with the right disease, at the right time in their illness. Depending on the disease stage, patients may require very different approaches, very different goals of therapy, and, potentially, very different management tools.

H&O What are some emerging treatment approaches?

GD The theme of emerging treatment is matching the patient and the molecular subset of sarcoma to the right therapy. Physicians should identify the biologic reasons that a therapy will (or will not) work. The archetype of this approach is imatinib (Gleevec, Novartis) or sunitinib (Sutent, Pfizer) for GIST. Imatinib is also approved for dermatofibrosarcoma protuberans (DFSP). Perivascular epithelioid cell-omas (PEComas) are treatable with a class of targeted drugs, mammalian target of rapamycin (mTOR) inhibitors. Pigmented villonodular synovitis (PVNS) has been reported to respond to imatinib, and new targeted therapies are in active clinical trials targeting this disease—as well as many other subtypes of sarcomas. It is incredibly important to get the diagnosis right first, and then to match it with the right therapy. The type of sarcoma—among the hundreds of different subtypes—will increasingly determine the treatment as clinical and translational science evolves. Even within 1 subtype of sarcoma—GIST—the optimal dose of imatinib to be considered may vary according to the molecular subtype of the disease. The idea of personalized medicine is being

realized for sarcoma faster than for most other more common forms of cancer, and this approach is teaching us about how best to treat patients.

H&O What is new in the field of sarcoma research?

GD Physicians in the sarcoma community are increasingly using Internet-based collaboration and research tools. For example, there is an interesting research study for GIST patients called Project FLAG (www.projectFLAG.org). It is funded by the National Cancer Institute. My colleagues here at Dana-Farber/Harvard, Drs. Judy Garber and Suzanne George, are leading the study along with investigators at the Memorial Sloan-Kettering Cancer Center, Fox Chase Cancer Center, and M.D. Anderson Cancer Center. *FLAG* stands for “Families Learning About GIST.” We are trying to assess whether there are other tumor types that can be tracked within families of GIST patients. Anyone who has ever had a GIST can visit www.projectflag.org and arrange for a very simple phone interview with a medical geneticist, who will run through the patient’s family history.

The patient may then choose to participate in the study, without ever leaving his or her home.

The field is moving in this direction, in which we are trying to bring the latest research to sarcoma patients, no matter what part of the country they are in. This approach is facilitating our study of this limited population of patients. The new generation of sarcoma investigators are also developing into highly collaborative individuals. An incipient World Sarcoma Network is bringing together various sarcoma-specific study groups of investigators across the world, and this collaborative should help advance this field faster than ever before.

Sarcomas have a disproportionate prevalence in pediatric oncology and place a burden on our youngest patients and their families. In adults, sarcomas make up less than 1% of cancers, but in children, they comprise approximately 15% of cancers. There is a great desire to have an impact in sarcomas because children have their whole lives to look forward to. We are all working as rapidly as we can to find the best therapies for the kids who need us now as well as to lay the foundation for future advances that will improve the outcomes of all sarcoma patients.