

# CLINICAL UPDATE

Translating Scientific Advances into Clinical Practice

## New Therapies in Soft Tissue and Bone Sarcomas

Margaret von Mehren, MD  
 Director, Sarcoma Program  
 Fox Chase Cancer Center  
 Philadelphia, Pennsylvania

### H&O What is the current treatment landscape in soft tissue and bone sarcomas?

**MvM** Soft tissue sarcomas are a rare group of tumors of mesenchymal origin, and bone sarcomas are tumors of the bone. These are challenging tumors to treat because they can present in various sites of the body. There are anywhere from 50 to 70 histologic subtypes alone in soft tissue sarcomas. The biggest challenge for most practitioners is that these types of tumors are relatively uncommon. Because there are so many different types of soft tissue and bone sarcomas, it is difficult to make sure that the pathologic diagnosis is accurate, and, if there is a diagnosis, to know what to do with one of the uncommon tumor subtypes.

For oncologists who do not have much exposure to sarcoma patients, it can be a tricky diagnosis to make, because there are some subtleties with the various histologies that might change the way one would treat that patient.

### H&O What factors are considered when deciding whether or not to give chemotherapy?

**MvM** There are usually 2 types of patients that present with soft tissue and bone sarcomas. In the first type of patient, there is a presence of a primary tumor, and the goal is to cure the patient and obtain the best possible outcome. In these types of patients, it is important to involve a multidisciplinary team (the surgeon, the radiation oncologist, the medical oncologist, nurses, etc) in order to make decisions on whether the patient's lesion is appropriate for upfront resection, whether there is a role for preoperative therapy with radiation and/or chemotherapy, and whether this is a particular lesion in which

the oncologist might want to consider using adjuvant therapy (although the data on adjuvant chemotherapy has its limitations). In larger tumors, upfront therapy before surgery with radiation and/or chemotherapy may help a patient with an extremity lesion have the best surgical outcome, because by potentially limiting the extent of surgery, the patient can have a better functional outcome in a limb-sparing procedure.

The second type of patient is one who presents with metastatic disease; the goals with this type of patient are very different. In patients with metastatic disease, the objective is to determine the best way to help the patient achieve maximum quality of life for as long as possible. How aggressive the treatment approach should be depends on the patient's clinical situation and the extent of his or her disease.

### H&O What are some of the new treatment approaches?

**MvM** Regional hyperthermia plus chemotherapy is a treatment approach that has been suggested to have some benefits, although it is not performed extensively in the United States. It involves giving chemotherapy in the location of the tumor and providing warmth to the localized area. It has been tested mostly in Europe, although there was 1 US center that participated in a study of regional hyperthermia with chemotherapy. The findings did suggest better long-term disease-free and overall survival outcomes. Phase III data have shown that chemotherapy with regional hyperthermia prolongs disease-free survival compared to chemotherapy alone in the neoadjuvant setting. However, more side effects were seen in those patients who received regional hyperthermia and chemotherapy compared to chemotherapy alone.

Trabectedin (Yondelis, Zeltia/Johnson & Johnson) is another agent currently being investigated in soft tissue and bone sarcomas. Trabectedin is a compound that was extracted from a marine organism. Its mechanism of action is not fully understood, but it seems to have some activity in sarcoma, particularly in liposarcomas and specifically myxoid liposarcoma. Trabectedin appears to produce stable disease rather than tumor shrinkage. It is still an investigational agent, and further studies are warranted.

There have also been studies looking at more targeted therapies in soft tissue and bone sarcomas. Pazopanib (Votrient, GlaxoSmithKline) is a tyrosine kinase inhibitor that targets vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Phase II experiences have suggested some benefit in certain types of sarcomas but not in liposarcoma. There is a completed large phase III study looking at pazopanib compared to placebo in advanced metastatic sarcoma. It will be interesting to see the results of this study, which we hope to have some time in 2011.

In regard to VEGF inhibitors, there have been some phase II studies looking at sorafenib (Nexavar, Bayer) and sunitinib (Sutent, Pfizer). The data that are available for these 2 agents suggest some activity in several tumors. In particular, there seems to be consistent efficacy in angiosarcomas; there has been suggestion of activity in leiomyosarcomas as well. Interestingly, most of the findings suggest that liposarcomas do not benefit from this type of approach. Further, there are reports of efficacy in chondrosarcomas, and sunitinib has demonstrated some evidence of efficacy in alveolar soft part sarcoma, which is a relatively rare subtype of sarcoma. Certainly, there is the sense that in some specific tumor types, these agents may be of benefit, but there have not been large, prospective, phase III studies looking at these agents. The studies that have been completed with sorafenib and sunitinib were done in many tumor types, so it is difficult to determine whether there is a specific effect.

The question in sarcomas is always whether there will be larger studies, and it is commonly a balance of this relatively rare population with the level of evidence we need to obtain.

Another class of drugs that is being evaluated in sarcomas is mammalian target of rapamycin inhibitors. Ridaforalimus (Ariad/Merck), also known as AP23573 or diforalimus, was tested in over 200 patients with bone and soft tissue sarcomas. In a phase II study, many patients were heavily pretreated. There were rare objective responses, though interestingly some were seen in bone sarcomas. In addition, approximately 20–25% of the 4 sarcoma subtypes studied were without evidence of

progression at 6 months. Ridaforalimus has completed phase III testing comparing it to placebo as maintenance therapy in patients with sarcomas that have achieved stable disease or response with cytotoxic chemotherapy for metastatic disease in the first- to third-line setting. This trial will be reported shortly.

Eribulin (Halaven, Eisai) is a novel murine compound derived from a sponge that inhibits microtubular function. An initial phase II trial conducted by the European Organisation for Research and Treatment of Cancer demonstrated stable disease at 3 months in greater than 20% of patients previously treated for metastatic leiomyosarcomas, “fat” sarcomas, and synovial sarcoma; there was also evidence of responses. The agent is currently undergoing phase III testing in advanced sarcoma.

### **H&O** What combination therapies are being investigated?

**MvM** Doxorubicin is the standard of care, and, particularly in Europe, is considered the standard of care for advanced disease. In the United States, we oftentimes use doxorubicin in combination with ifosfamide. There is also a new drug being developed called palifosfamide (Ziopharm Oncology), which is a metabolite of ifosfamide, that may have some benefits in terms of ease of administration; palifosfamide is now in a phase III trial versus doxorubicin alone. The combination of gemcitabine and docetaxel has been studied extensively and has shown activity in sarcomas, particularly in leiomyosarcoma, in the second-line and first-line settings. Various studies have demonstrated the benefits of this combination in terms of overall response.

### **H&O** Are biomarkers being integrated into sarcoma diagnosis and treatment?

**MvM** There are some molecular markers that are being investigated that are less diagnostic and more indicative of understanding the disease process. For example, we know that in some forms of liposarcoma, on chromosome 12, there is an area that is amplified. The genes seen in that location, like the gene for cyclin dependent kinase, have been identified and drugs are being developed for this target. As such drugs are being developed, if they make it through the phase I hurdle, then there will be interest in evaluating them in patients with certain types of liposarcoma. With these markers we are trying to see if there is something we can identify about the genetic makeup of the specific tumor so that we can then utilize a drug to target that tumor biology.

**H&O** What are the limitations seen with the currently available agents, and how do we go forward in this rare cancer?

**MvM** I think there are 2 main limitations. One is that we refer to soft tissue sarcomas and bone sarcomas as one disease entity when, in fact, it is really not. One of the things we struggle with is how to better design clinical trials to answer such questions as “Is there a particular type of sarcoma that benefits from the particular agent we are studying?” Sometimes it is necessary to turn to preclinical data to look for information that suggests that the drug may have activity, and to try to move it forward in the clinical setting. Sometimes we do not have that data and it is difficult to know how to move forward. The other limitation, in terms of assessing the agents available now and how we have used them, is that it is challenging for patients to tolerate the drug combinations, and they can be difficult to administer because of their compound toxicities (eg, doxorubicin, ifosfamide). We are familiar with hematologic toxicities, but there are other toxicities that arise, such as renal or neurologic events, that make it more

challenging than some of the other standard chemotherapies that we are used to giving in other disease settings.

The median survival is about a year for patients with metastatic soft tissue and bone sarcomas, so it is exciting to see ongoing research looking at novel combinations and newer approaches with targeted therapies. This is complex, however, because the tumors are so rare and biologically different, and the groups of patients with these tumors represent only a small percentage of patients in clinical trials. It will take some time to sort out which tumor types will best be treated with individual targeted therapies.

**Suggested Reading**

Demetri GD, Antonia S, Benjamin RS, et al. Soft tissue sarcoma. *J Natl Compr Canc Netw*. 2010;8:630-674.

Penel N, Van Glabbeke M, Marreaud S, Ouali M, Blay JY, Hohenberger P. Testing new regimens in patients with advanced soft tissue sarcoma: analysis of publications from the last 10 years. *Ann Oncol*. 2010 Dec 23. [Epub ahead of print].

Verschraegen CF, Chawla SP, Mita MM, et al. A phase II, randomized, controlled trial of palifosfamide plus doxorubicin versus doxorubicin in patients with soft tissue sarcoma (PICASSO). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2010;28: Abstract 10004.