Evolving Treatment of Soft Tissue Sarcoma

Presented by Suzanne George, MD

Abstract

Soft tissue sarcomas comprise multiple histologic subtypes, occur at a number of anatomic sites, and require individualized treatment. Over the past 5 years, 4 new drugs were approved for sarcoma, most of which are driven by histology or the anticipated response to treatment. Surgical resection remains the primary treatment for resectable tumors. For unresectable or metastatic disease, doxorubicin remains the backbone of chemotherapy, but other agents have improved on its single-agent efficacy. Chief among them is olaratumab, which, in combination with doxorubicin, is preferred over doxorubicin alone in the updated NCCN Clinical Practice Guidelines in Oncology for Soft Tissue Sarcoma.

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Soft tissue sarcomas (STSs) comprise multiple subtypes, varying by primary site and histology and responding differently to various treatment modalities. At the NCCN 22nd Annual Conference, Suzanne George, MD, Co-Clinical Director, Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, and Associate Professor of Medicine, Harvard Medical School, described current concepts in managing this malignancy.

This uncommon group of tumors is responsible for approximately 1% of cancers in adults and 15% in children. STSs occur in many different primary sites and comprise as many as 50 different histologic subtypes. The most common site is the lower extremity, followed by the upper extremity, retroperitoneal and intraperitoneal areas, trunk, and head and neck.

“The multiple primary sites and histologic subtypes makes precise pathologic diagnosis critical,” Dr. George emphasized. Because histopathologic reporting is often discordant, she said, “From my perspective, when one thinks about multidisciplinary management of sarcoma, a major contributor is the expert pathologist, because

fundamentally all downstream treatment decisions hinge on this initial diagnosis and subclassification of type.”

“The current question facing all of us,” she offered, “is not what’s the best treatment for STS in a general way, but what’s the best treatment for a particular patient with a particular subtype in a particular anatomic location.” In her presentation, Dr. George offered guidance on this topic with regard to retroperitoneal/intra-abdominal, extremity/superficial trunk, and head and neck sarcomas. She did not discuss gastrointestinal stromal tumors (GISTs).

Retroperitoneal Sarcoma

Retroperitoneal sarcoma accounts for 15% of all STSs. They are frequently asymptomatic until they grow large enough to impact adjacent structures or develop pain. After surgical resection, more than half recur locoregionally; for some subtypes, locoregional recurrences, rather than distant metastases, are fatal.

Liposarcoma and leiomyosarcoma are the most common subtypes. Outcomes vary based on histologic subtype, as shown in a recent study¹ involving 1,007 patients in which overall survival (OS) was best for well-differentiated liposarcomas (>80% at 8 years) and worst for high-grade dedifferentiated liposarcomas (<40%). Outcomes fell between these extremes for leiomyosarcomas, solitary fibrous tumors, and intermediate-grade dedifferentiated liposarcomas.

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George

Local recurrence risk is higher for dedifferentiated liposarcoma, whereas distant metastatic risk is higher with leiomyosarcoma, she added, noting, “Having a solid sense of this spectrum and the aggressiveness of various subtypes helps with prognosis and treatment strategies.”

These differences also have implications for screening. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for STS suggest imaging of the chest, abdomen, and pelvis for surveillance of retroperitoneal sarcoma; however, more specifically, for well-differentiated liposarcoma, an evaluation of the abdomen and pelvis only is reasonable, whereas for leiomyosarcoma and higher-grade dedifferentiated tumors, the chest (an important site of recurrence) should be added.

Surgical Management, With and Without Radiotherapy

Primary treatment of STS is with surgery, but the use of radiotherapy (RT) differs according to anatomic site. For extremity/superficial trunk and head and neck sarcomas (which are grouped together in the guidelines) that are localized, surgery is the gold standard if an acceptable functional outcome is likely. Preoperative or postoperative RT can also be administered and is a category 1 recommendation in the NCCN Guidelines. For non-GIST nondesmoid retroperitoneal or intra-abdominal sarcomas, surgery is the primary modality and RT is a category 2B recommendation, based on the lack of data for favorable outcomes and the risk of radiation toxicity to normal organs in this anatomic location.

Further guidance on the use of RT should come from results of the phase III STRASS trial, which is comparing surgery alone versus surgery plus preoperative RT in primary retroperitoneal sarcomas of any histology.

Patients for whom surgery is not an option present with unresectable or metastatic disease upfront. For these patients, the primary modality is cytotoxic chemotherapy, with attempts to downstage the tumor for resection or RT. In patients with metastatic disease or those in whom a good surgical outcome is unlikely, chemotherapy can be considered palliative and should be individualized, Dr. George said.

Doxorubicin: The Standard Backbone

Doxorubicin has remained the conventional backbone for chemotherapy regimens in advanced STS. The randomized phase III GeDDiS trial, however, questioned whether gemcitabine/docetaxel, which has been increasingly used, might be better.² OS was not significantly different at 24 weeks (86.8% with doxorubicin, 82.6% with gemcitabine/docetaxel; $P=.38$), and subgroup differences were at best slight. The greater number of withdrawals in the gemcitabine/docetaxel arm “highlights the challenge” of administering this regimen, according to Dr. George.

With similar outcomes, GeDDiS failed to define the optimal regimen. “From my perspective, and what’s in the NCCN Guidelines, they are both very solid options,” she maintained. “There is not a clearly superior first-line approach, at least based on these data.”

Other Single Agents Versus Combinations

As the conventional backbone agent, doxorubicin has been combined with a variety of other agents. An EORTC study compared single-agent doxorubicin versus doxorubicin plus ifosfamide and found no significant difference in OS, 1-year survival, or progression-free survival (PFS). However, response rates were higher with the combination (26.5% vs 13.6%).³ Due to improved responses, the combination can be valuable in certain clinical situations, such as for symptomatic or imminent life-threatening disease. The NCCN Guidelines recommend that multiagent regimens be considered on an individual basis.

Recently Approved and Preferred: Olaratumab

The newest agent in the arsenal, olaratumab, was approved in 2016 for use in combination with doxorubicin. “The introduction of olaratumab has raised questions about a number of different treatment standards and paradigms in this disease,” Dr. George indicated.

Approval was based on a randomized phase II study of patients with histologies deemed sensitive to anthracyclines, such as leiomyosarcoma and synovial sarcoma.⁴ Patients were randomized to receive

Soft Tissue Sarcoma

Figure 1. Kaplan-Meier curves for investigator assessment of (A) progression-free survival and (B) overall survival for olaratumab plus doxorubicin versus doxorubicin groups.

From Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomized phase 2 trial. *Lancet* 2016;388:488–497. Reprinted with permission from Elsevier. ©2016.

doxorubicin alone (75 mg/m²) or to the same plus olaratumab, with maintenance olaratumab if desired. Although only a favorable trend was shown for PFS, the difference in OS with the combination was impressive: 25.0 versus 14.7 months (hazard ratio [HR], 0.44; *P*=.0004; Figure 1).

“The results set a new standard of care,” Dr. George said. “Because of the OS advantage, this combination is being integrated into many practices.”

Olaratumab is now approved for doxorubicin-sensitive STSs that are not curable. In the updated NCCN Guidelines, olaratumab/doxorubicin is preferred over doxorubicin alone. Other studies

are evaluating olaratumab with other drugs used in this disease.

Beyond Anthracyclines

Three additional drugs were approved in the past few years for different subtypes: pazopanib (non-liposarcoma), trabectedin (leiomyosarcoma, liposarcoma), and eribulin (liposarcoma).

An approximately 3-month improvement in PFS was seen with both pazopanib, in the global phase III PALETTE trial,⁵ and trabectedin, in the phase III ET743-SAR-3007 study in liposarcoma.⁶ OS was similar to controls in both studies. Eribulin

George

was approved based on a modest OS (although not PFS) benefit in a phase III study of liposarcoma and leiomyosarcoma, as late-line treatment.⁷ “These new compounds—olaratumab, pazopanib, eribulin, and trabectedin—were somewhat nonspecific drugs but were matched with histologies and tumor types that made sense for their disease,” Dr. George noted.

“The field is moving forward, but there are challenges with regard to targeted therapy for STSs,” Dr. George said in conclusion. The lack of reliable pre-clinical models for some subtypes and the genomic complexity are challenges. Immunotherapies are also being investigated in this disease, but to date, activity seems limited at this time, although emerging data will help to define future directions and applications of this exciting field.

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