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EXPERT perspectives

New Treatments and a New Approach to Soft Tissue Sarcoma

Overview

Soft tissue sarcomas (STS) are a diverse group of malignant tumors that occur throughout the soft tissues. Although rare, these sarcomas account for more than 12,000 new cases annually in the United States. The possibility of a sarcoma must be considered in the differential diagnosis of any suspicious mass.

This CME activity provides guidance through the initial diagnostic workup and reviews the latest data of new and emerging therapeutic options for advanced, metastatic STS. For best results, community-based oncologists are encouraged to partner with an academic center specializing in the management of sarcoma. These multidisciplinary teams, together with the community oncologist, can optimize treatment outcomes for their patients with STS.

Content Areas

- Defining soft tissue sarcoma (STS)
- Diagnosis and initial workup
- Advanced STS therapy
- Combination treatments
- Second-line treatment
- Future direction

Section

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Target Audience

This activity was developed for medical and surgical oncologists, gynecologic oncologists, radiation oncologists, pathologists, PCPs, obstetricians, gynecologists, and other physicians interested in the management of soft tissue sarcoma (STS).

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Describe the benefits of early referral of soft tissue sarcoma (STS) patients in consultation to an academic sarcoma center
- Describe the benefits of comanagement of STS patients by community oncologists and academic sarcoma centers with multidisciplinary care teams
- Describe the safety and efficacy of new and emerging treatment options for advanced STS

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New Treatments and a New Approach to Soft Tissue Sarcoma

Defining Soft Tissue Sarcoma

Soft tissue sarcoma (STS) is a term used for a diverse group of malignant tumors that occur throughout the soft tissues, ie, fat, muscle, nerves, fibrous tissues, and blood vessels.[1,2] These sarcomas are rare, accounting for 1% of all cancers, with more than 12,000 new cases occurring annually in the United States, with equal distribution in males and females.[3-6] The prognosis of advanced, metastatic STS is poor, with life expectancy ranging from 12 to 16 months.[3,4,7] The location of the primary tumor, and its morphology, vary, resulting in more than 50 histological subtypes that present distinct molecular, histological, and clinical characteristics.[4] An analysis from Surveillance, Epidemiology, and End Results (SEER) noted that less than half (47.9%) of all STS cases arose from connective tissue. Soft tissue sarcomas can originate from different organ systems and other anatomical sites, such as the skin, uterus, retroperitoneum, stomach, or small intestine.[1,8] The recent WHO Classification of Bone and Soft Tissue Tumors provides cytogenetic analysis and molecular data, subclassifying these further into more than 117 different soft tissue tumors.[9,10]

The most common histologic subtypes include undifferentiated pleomorphic sarcoma (UPS), liposarcoma (LPS), leiomyosarcoma (LMS), synovial sarcoma (SS), and malignant peripheral nerve sheath tumors (MPNSTs).[3,9] Leiomyosarcomas represent 10% to 20% of all newly diagnosed STSs.[11] Uterine leiomyosarcoma (uLMS) is the most common subtype of uterine sarcoma, which can rapidly spread hematogenously, leading to remote metastases, and yield a poor prognosis.[9]

The incidence of LMS increases with age, most often occurring in the sixth and seventh decades of life. In contrast, uLMS occur most often in the perimenopausal age group, mainly in the fifth decade of life.[11] There are no clear predisposing factors for the development of LMS. The National Comprehensive Cancer Network (NCCN) Soft Tissue Sarcoma Panel indicates patients with inherited TP53 mutations, such as Li-Fraumeni syndrome, and familial adenomatous polyposis (FAP) are at risk for developing STS.[11,12] Radiation exposure also increases the risk of developing sarcomas, including LMS. Uterine LMS has been found to be associated with tamoxifen exposure.[11] A total hysterectomy is recommended for patients whose disease is limited to the uterus. Even then, the risk of recurrence of uLMS is 50% to 70%.[11]

Diagnosis and Initial Workup

Because of its relatively low incidence and often atypical clinical presentation, making an early diagnosis can be challenging. Soft tissue sarcomas affect predominantly lower extremities, followed by the upper extremities and trunk.[9] Symptoms may include painless soft tissue swelling or tender lesions; therefore, a thorough patient history is mandatory. The histologic grade, tumor size, and

tumor depth are the major prognostic factors for STSs. Lumps increasing in size (in the absence of bruising) as well as a growing soft tissue mass should raise suspicion for sarcoma. A core biopsy is preferred to acquire a sufficient amount of tissue. Pathologic evaluation is typically performed after complete resection. An expert review by pathologists at a tertiary center may be necessary in select cases.[9]

Staging the tumor will help quantify the extent of the disease, and is based on the physical exam, imaging, endoscopy reports, and diagnostic biopsies.[13] The American Joint Committee on Cancer (AJCC) staging method is appropriate and follows 3 determining factors[13]:

- Extent or size of the tumor (T)
- Spread to nearby lymph nodes (N)
- Spread to distant sites: metastasis (M)

Numbers or letters following these letters provide even more detail about the stage of the disease, and will help determine the best course of treatment.

Primary, localized disease is treated with surgical resection of the tumor, in addition to a safety margin of healthy tissue, followed by radiation treatment where indicated.[9] Treatment may involve a combination of chemotherapy and radiation therapy. The ability to perform a complete surgical resection at the time of initial presentation is the most important prognostic factor, in terms of survival.[9]

Striving for Optimal Care

Although STS is an uncommon disease, most oncologists have several sarcoma patients in their practice. These are often the most difficult to treat patients. Therapy is carefully planned by an experienced multidisciplinary care team.[9,11] For the best possible results, community-based oncologists may want to partner with an academic center specializing in the management of sarcoma.[12]

At the sarcoma centers, the teams are made up of surgical oncologists, medical oncologists, radiation oncologists, orthopedic surgeons, thoracic surgeons, physiotherapists, pathologists, radiologists, midlevel practitioners, billing specialists, and social workers.[9] This care team meets frequently to review and discuss the latest cases, as well as the latest treatment options available. An estimated 1000 new patients are seen each year at these centers, from which approximately 14% have metastatic STS.[6] Dedicated sarcoma centers are also more likely to have access to clinical trials.[14]

Three aspects remain crucial when clinicians are evaluating or considering treatment for a patient with a suspicious, asymptomatic mass[15]:

- Enlarging masses should be biopsied;
- A core needle biopsy is acceptable, but if an open biopsy is needed, it should be referred

to a surgeon experienced in these procedures (ideally a surgical or orthopedic oncologist), because an incorrectly performed biopsy can make the ultimate surgery more difficult; and

- Community-based oncologists are encouraged to stay in communication with academic centers so that the latest treatment options and potential clinical trials are available for their patients.[16-19] Most patients will be comanaged by the academic sarcoma specialists together with the community oncologists, given geographic (and financial) restrictions that apply in most cases.

Therapy for Advanced STS

Treatment for primary localized STS is surgical resection with the advent of neoadjuvant or adjuvant therapy. Circa 10% to 20% of patients with STS have advanced disease.[9] As of 2018, the standard therapy in the first-line setting of high-grade, advanced metastatic STS, regardless of subtype, remains anthracycline-based treatment with doxorubicin.[4,5,9] Doxorubicin is administered once every 3 weeks for a maximum of 6 cycles. Alone, this agent has a response rate ranging from 5% to 27%; however, the duration of the benefit is usually short, with a median overall survival ranging from 8 to 14.3 months,[3] and median progression-free survival (PFS) between 3 and 7 months.[4,5,20] Most dose-intensive treatment schedules involve doxorubicin at 75 mg/m^2. Cardiotoxicity, mucositis, and hematological toxicity are dose-limiting factors.[20,21] Patients must be assessed individually to determine the appropriate course of systemic therapy. Clinicians need to take into consideration comorbidities, organ function, performance status, and extent of disease.[3]

Combination Treatments

Today, there are an increasing number of therapeutic options for high-grade, advanced STS. First-line treatment may include an anthracycline in combination with other newly available agents. For patients who cannot be cured with surgery or radiation, one of these new treatments is olaratumab, a fully human IgG1 monoclonal antibody that binds to platelet-derived growth factor receptor α (PDGFR-α), which targets the PDGF/PDGFR-α pathway.[3,4] Overexpression of PDGFR-α has been shown to have worse disease-related outcomes in osteosarcoma, ovarian, breast, and prostate cancers.[3] Olaratumab is thought to alter the tumor stromal cell environment and potentially increase the efficacy of subsequent treatments.[3] In combination with doxorubicin, in a phase 2 trial involving patients with anthracycline-naïve disease (ClinicalTrials.gov NCT01185964; n=129), olaratumab demonstrated an overall survival of 26.9 months, compared to 14.7 months for those receiving doxorubicin alone.[4,5,7] This trial

also showed an improvement in PFS (6.6 months vs 4.1 months with doxorubicin alone).[5,7] Doxorubicin is given as continuous infusion on day 1, with olaratumab as an intravenous (IV) infusion over 60 minutes on days 1 and 8, every 3 weeks for 8 cycles. This is followed by a continuation of olaratumab alone.[4,7] Consideration shall be given to adding olaratumab to the treatment of any patient being considered for doxorubicin as a first-line treatment.[3] Infusion reactions, neutropenia, and mucositis can be encountered with this combination treatment.[3]

A phase 3 (NCT02451943) study is ongoing for doxorubicin and olaratumab combination therapy, and has enrolled approximately 460 advanced STS patients in a randomized (1:1), placebo-controlled trial with the primary endpoint overall survival (OS). Release of results is anticipated in 2019.[3,22]

Other chemotherapy agents (eg, ifosfamide and dacarbazine) have been used in combination with doxorubicin in an attempt to improve outcomes for STS patients, but these dual-agent cytotoxic regimens can also result in increased toxicities.[3] The addition of bevacizumab to doxorubicin has resulted in a different toxicity profile, including decreased cardiac function.[23] The primary endpoint of these studies is overall survival, but control of the disease is also an acceptable endpoint, and may include "providing management of symptoms related to disease, such as shortness of breath or pain," according to Koliou et al.[5]

Specific sarcoma subtypes have a distinct sensitivity pattern to chemotherapy. Ifosfamide is particularly active for synovial sarcoma and myxoid LPS, and seems less active for LMS. Dacarbazine has a modest activity against LMS. Paclitaxel is active against angiomyosarcomas.

Second-Line Treatment

Treatment should be tailored to histology and the molecular subtype, as well as taking into consideration patient characteristics, such as gender, location of the primary tumor, location of metastases, and histologic subtype.

At least 4 different trials confirmed the activity of the dual-agent cytotoxic regimen of gemcitabine and docetaxel in LMS.[5] The objective response rate of 32% and a PFS of 6 months was demonstrated.[5]

Three novel agents (ie, trabectedin, pazopanib, and eribulin) have improved treatment for some histological subtypes and have been approved for the treatment of high-grade STS in the second-line setting, after progression on anthracyclines.

Trabectedin is currently used for treatment of patients who have progressed after anthracycline-based chemotherapy. Its efficacy is specific for what is known as the L-sarcomas: leiomyosarcoma (LMS) and liposarcoma (LPS). In a phase 3 trial (ClinicalTrials.gov NCT01343277; n=518), trabectedin was compared to dacarbazine in patients with LPS or LMS. There was a PFS benefit observed (4.2 vs 1.5 months), but no OS advantage

or objective response rate (ORR) was documented.[11,24] A phase 2 study (ClinicalTrials.gov, NCT02131480; n=109) of trabectedin with doxorubicin was conducted by Pautier et al, in patients with uterine LMS and LMS, with a PFS benefit observed (8.2 in uLMS and 12.9 months in LMS), and OS of 20.2 in uLMS and 34.5 in LMS.[25]

The multikinase inhibitor, pazopanib**, is** an oral VEGF-targeting agent with activity in LMS and uLMS, but is not approved for LPS. Results from the phase 3 PALETTE study in 2012 (n=372) showed that it improved PFS (4.6 months vs 1.6 months) compared with placebo in STS; however, there was no difference in OS, and ORR was observed in only 4% of patients. A retrospective analysis limited to uterine sarcoma cases from the PALETTE study demonstrated only a modest efficacy with the use of pazopanib in this subgroup (response rate, 11%; PFS, 3 months; OS, 17.5 months) when compared to other subgroups.[2,11,26]

Eribulin mesylate was approved in January 2016 for unresectable or metastatic LPS for patients who have progressed after an anthracycline. Eribulin is a synthetically produced antimitotic version of halichondrin B, a natural product isolated from the marine sponge Halichondria okadai.[28] It inhibits the growth phase of microtubule dynamics, which prevents cell division. It has been shown to improve overall survival in the post-anthracycline setting.[4,29] A phase 3 randomized trial (ClinicalTrials.gov NCT01327885; n=452) was conducted across 110 study sites, in 22 countries comparing eribulin and dacarbazine in pretreated advanced LMS and LPS patients. The study showed 2 months overall survival benefit (13.5 vs 11.5 months) for patients who received eribulin, but no significant benefit was found with respect to PFS (2.6 months in both arms).[27,28] Adverse events include fatigue, neutropenia, nausea, alopecia, constipation, peripheral neuropathy, abdominal pain, and pyrexia. Major adverse events include bone marrow suppression, as well as neutropenia, leukopenia, anemia, and fatigue or weakness, all of which are considered manageable. Eribulin should not be used in patients with severe hepatic impairment.[5] This agent was initially approved in 2010 for the treatment of metastatic breast cancer.

While trabectedin, pazopanib, and eribulin offer clinical benefits in patients with specific histologic STS subtypes, they did not show a significant response rate or a decrease in tumor size.[5] That said, these novel agents may join the armamentarium as first-line therapies, in addition to the dual-agent cytotoxic regimen of gemcitabine and docetaxel.[29]

Future Direction

Soft tissue sarcoma patients can respond to the current first-line therapies and combinations, but the benefit from treatment is usually short and the side effects significant. Ongoing research in genomics-based sarcoma will continue to

investigate newer targeted therapies—targeting pathways, such as mTOR, Notch, Wnt, Hedgehog, and MDM2—to provide individualized treatment for specific STS subtypes. Enrollment in immunotherapy clinical trials is an appealing option for sarcoma patients, for those with few standard treatment options.[30] These drugs can be used either as single agents or to augment targeted or multimodality therapy for sarcoma.[30]

Researchers are also looking at adoptive T-cell therapy. Combination immunotherapy may benefit patients with sarcoma. A recent phase 2 study (ClinicalTrials.gov NCT02500797; n=85) showed that combination nivolumab-ipilimumab is effective in certain sarcoma subtypes.[31] These include undifferentiated pleomorphic sarcoma, myxofibrosarcoma, leiomyosarcoma, and angiosarcoma. Tumor responses appeared to be similar to those seen with standard chemotherapy, with a manageable safety profile comparable to current available treatment options.[11,31] Use of these agents is not yet warranted outside of the clinical trial setting, and further studies are needed. There is also hope that biomarkers may be identified to help optimize treatment choices for patients with LMS.[11]

Conclusion

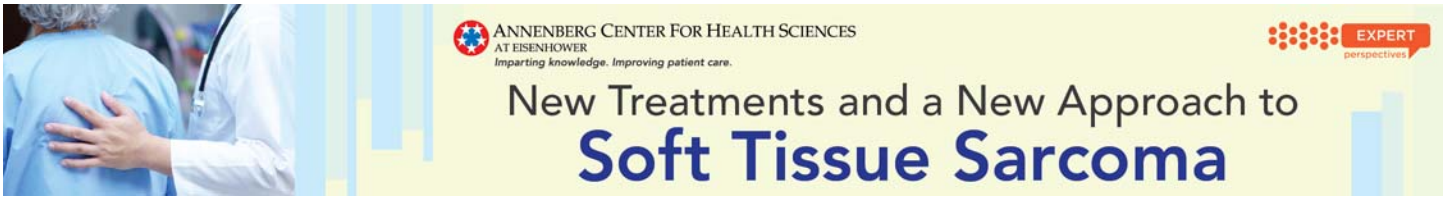
The possibility of sarcoma must be considered in the differential diagnosis of any suspicious mass. Early referrals for consultation at a specialized sarcoma center are encouraged to ensure the best possible outcome. Masses that cannot be core biopsied should be referred to an experienced surgical or orthopedic oncologist to avoid the possibility of contaminating healthy tissue, which would only make a complex disease more challenging. Treatment recommendations should take into consideration individual patient circumstances. Most patients can be successfully comanaged by the community oncologists together with academic sarcoma specialists. Knowledge of and access to available clinical trials is important so patients can take advantage of the forefront scientific advances based on specific tumor characteristics.

Clinical case scenario of a patient with advanced STS

A 90-year-old man presented with a right upper-neck mass and a new left-chest lesion. Oncologic history was significant for a locally advanced myxoid liposarcoma diagnosed in 2006, when he presented with a large mass in the left-inguinal region. The patient had radical resection of the mass at a specialized university center, followed by external beam radiation therapy. The tumor recurred locally in 2011 and was surgically excised. Other past

medical history was significant for hypertension, dyslipidemia, and chronic kidney disease. Review of systems was otherwise unremarkable. Conjunctival pallor was noted. In the right upper-neck area, he had an indurated mass measuring 4.0 x 3.0 cm. He also had a smaller lesion in the left-chest area measuring 2.2 x 1.2 cm. Nodal examination revealed a left-axillary adenopathy, measuring 2.0 x 2.0 cm, and a matted left-inguinal adenopathy, sized 4.0 x 3.0 cm. A fine-needle aspiration of the right-neck mass was consistent with a new diagnosis of malignant melanoma. Biopsy of the left-anterior chest mass showed metastatic myxoid liposarcoma. A positron emission tomography/computer tomography (PET/CT) scan showed distinct metastatic melanoma lesions in the right neck, bilateral lung parenchyma and right pleural cavity (high fluorodeoxyglucose [FDG] activity with standard uptake value [SUV] of 10-17.5) and myxoid liposarcoma metastases to the left inguinal area, left pelvis, chest wall, and left pleural cavity (lower FDG activity; SUV of 3-5.1). The patient was treated with 4 cycles of ipilimumab 3 mg/kg every 3 weeks. A restaging PET/CT scan showed a 32% decrease in size of melanoma lesions. Notably, a 25% decrease in size of myxoid liposarcoma lesions was also seen. The response was documented at nearly all metastatic sites, and there was a nearly 50% decrease in the FDG activity throughout. This response was maintained at 10 months after completion of ipilimumab therapy.

Enrollment in immunotherapy clinical trials is an appealing option for sarcoma patients either in conjunction with traditional treatment modalities or as single agents for those with few standard treatment options. Recent advances in sarcoma biology and cancer immunotherapy suggest that immune checkpoint inhibitors can be useful either as single agents or to augment targeted or multimodality therapy for sarcoma.[30]



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