Developments in Systemic Therapy for Soft Tissue and Bone Sarcomas

Presented by Suzanne George, MD

ABSTRACT

The past year has led to significant changes in systemic therapies used to treat soft tissue sarcomas, mainly dominated by the removal of the recently approved drug olaratumab as part of combination therapy with doxorubicin from the NCCN Guidelines for Soft Tissue Sarcoma, according to Dr. Suzanne George. Several histology-specific drugs have entered the space, including pazopanib and pembrolizumab, the latter of which was approved as a category 2B recommendation for alveolar soft part sarcoma, highlighting the rather limited role of immunotherapy in sarcomas. Dr. George also discussed updated data for sorafenib in the treatment of desmoid tumors, as well as the importance of larotrectinib in TRK fusion-positive tumors.

The past year has seen major changes in the treatment of soft tissue sarcomas (STSs), according to Suzanne George, MD, Associate Professor of Medicine, Harvard Medical School, and Co-Clinical Director, Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute. Negative preliminary phase III results led to the removal of olaratumab from the NCCN Guidelines, where it was given in combination with doxorubicin as systemic therapy, while other histology-specific drugs have entered the space and demonstrated promising efficacy.

“The importance of understanding specific histologies, as well as the impact of systemic therapy choices, continues to evolve and mature in the sarcoma world,” said Dr. George at the NCCN 2019 Annual Conference, where she discussed updates in the treatment of STS. “This space has been much more active with regard to drug development and new drug indications than the bone sarcomas space,” she noted. “But hopefully that will change soon.”

Overview of Sarcomas

Sarcomas are a rare group of diverse diseases, with approximately 16,000 new cases reported each year in the United States. They represent <1% of all adult cancers but are overrepresented in children, with approximately 15% of all pediatric malignancies being in the sarcoma field.

Approximately 50% of patients will either present with or ultimately develop metastatic disease, but misdiagnosis and misclassification are common with sarcomas and likely lead to underreporting. “It’s not at all uncommon for sarcoma of the kidney, for example, to be quoted as a kidney cancer in insurance databases and sometimes even in tumor registries,” she said. “It’s likely that the number of cases per year may actually be different; it’s just hard for us to know because of the way the things are captured.”

There are >70 different subtypes of sarcomas (eg, adipocytic, myogenic, vascular), but according to Dr. George, these are likely unique and biologically distinct entities. “Because they’re rare and uncommon, we lump them together for a variety of reasons. However, it’s important to start thinking about separating them so that we don’t lose potential opportunities for therapeutic intervention,” she said. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Soft Tissue Sarcoma outline recommendations for drugs in both a histology-specific and non-histology-driven approach.

Removal of Olaratumab From the Guidelines

According to Dr. George, a lot has transpired with olaratumab in the past couple of months. Olaratumab is a PDGFR-α antibody with a mechanism of action that is poorly understood. It is thought to possibly interact with the tumor stroma, leading to increased delivery of complementary drugs; therefore, in sarcoma, the drug has been developed in combination with other systemic therapies.

The first trial that impacted the care of STS was a phase II study comparing combination olaratumab + doxorubicin versus doxorubicin alone.1 A total of 133 patients with metastatic sarcoma were randomized 1:1
in an exploratory study. An unexpected result was the dramatic and statistically significant difference in overall survival (OS): median OS for the combination arm was >26 months compared with just more than 15 months for doxorubicin alone. Because of this study, olaratumab received accelerated approval by the FDA in October 2016, was subsequently added to the NCCN Guidelines, and had become part of standard treatment for STS.

But the randomized phase III trial tempered the excitement around this drug combination. The ANNOUNCE trial compared doxorubicin + placebo versus doxorubicin + olaratumab in advanced STS, with no crossover allowed (ClinicalTrials.gov identifier: NCT02451943). There was a preplanned subset analysis for leiomyosarcoma—one of the more common histologies—within this general STS cohort. The first results of the study were released in January 2019, announcing no OS advantage for olaratumab.

As a result, the FDA and European Medicines Agency sent out rapid communications that no new patients should be started on olaratumab. However, because the phase III trial did not demonstrate any new safety signals, patients already on the drug could potentially continue but should be assessed on a case-by-case basis. “I think as a community we were disappointed that the OS benefit was not confirmed, but it really emphasizes the importance of properly powered phase III trials when an unexpected result is seen initially,” said Dr. George.

The FDA is continuing to review the data and is working to determine the next appropriate steps. “Again, this has all [come] from press releases, and I think we’re all looking forward to seeing what the data look like in full when they are released, which I suspect will happen sometime later this year,” she said.

This led to significant changes in the NCCN Guidelines, with the removal of the recommendation for olaratumab in combination with doxorubicin. Doxorubicin remains as a recommended single agent while ongoing trials with olaratumab in STS continue.

Systemic Therapy Updates
Pazopanib as a multitargeted tyrosine kinase inhibitor (TKI) has been included in the NCCN Guidelines for several years. Its inclusion is based on the randomized phase III PALETTE trial comparing pazopanib versus placebo in patients with chemorefractory STS. Importantly, liposarcoma and gastrointestinal stromal tumors (GIST) were excluded because liposarcoma had no benefit from pazopanib in a previous trial and GIST was its own “biologic beast,” she noted. PALETTE demonstrated a statistically significant improvement in median progression-free survival of 4.6 versus 1.6 months for pazopanib versus placebo, respectively (P<.0001). This led to FDA approval of pazopanib for patients with advanced STS who have received prior chemotherapy, as well as integration of the drug into the NCCN Guidelines.

However, the PALETTE trial also raised curiosity about other broad-spectrum TKIs that have potent VEGF inhibition, and whether those may be similarly effective in this group of diseases. This led to evaluation of regorafenib, a broad-spectrum TKI, in non-GIST STS. A French study suggested benefit of regorafenib in various STS subtypes, including leiomyosarcoma, synovial sarcoma, and others. Based on these data, regorafenib is now included as a systemic therapy option in the NCCN Guidelines (not in the first line).

Histology-Specific Updates: Alveolar Soft Part Sarcoma
Alveolar soft part sarcoma (ASPS) is a rare subtype of sarcoma that often impacts young adults. Metastatic disease is common at initial presentation (typically lung and brain metastases), and ASPS tends to be refractory to cytotoxic chemotherapy. “It can have an indolent course, but there is no cure,” she noted. “This is a clear unmet need, particularly in this very vulnerable young adult population."

A global retrospective review from multiple centers sought to assess the potential activity of agents in ASPS, and examined cases using 2 different systemic therapies (trabectedin or pazopanib). “The sarcoma community really collaborated to put cases together from our own centers to try to develop a database to help us think about hypothesis-generation and signal-seeking for compounds in these ultrarare histologic subtypes,” said Dr. George. Group A patients (n=27) were treated with trabectedin and Group B patients (n=37) with pazopanib. Median progression-free survival for pazopanib was almost 14 months versus <4 months in the trabectedin group. Similarly, OS in the trabectedin cohort was approximately 9 months and for the pazopanib cohort was not yet reached.

Dr. George warned of the obvious limitations of this retrospective collaboration, including nonstandardized patient selection, nonstandardized assessment technique/timing, and nonstandardized dosing/compliance. But it is, nonetheless, a collection of real-world data from across the globe in a rare tumor type. As a result of these findings, pazopanib was added to the NCCN Guidelines as a histology-specific option for ASPS.
Role of Immunotherapy Remains Limited
Pembrolizumab was also added to the guidelines as a category 2B histology-specific treatment option (non-uniform NCCN consensus), based on extremely limited evidence of its efficacy in ASPS. However, ongoing trials of checkpoint inhibition in advanced ASPS should clarify whether it should remain as category 2B or move to a higher level of recommendation.

A few small checkpoint inhibitor studies in STS have produced somewhat “modest” results, said Dr. George. Beyond ASPS, immunotherapy remains with a limited—but emerging—role in the treatment of sarcomas.

Understanding Natural History of Desmoids
Desmoid tumors are a rare nonmalignant neoplasm. They do not spread or metastasize but can cause significant morbidity and mortality, depending on location. Desmoid tumors occur in 10% to 20% of patients with familial adenomatous polyposis, and also occur sporadically in approximately 1,000 patients per year in the United States. They can arise anywhere, but are most concerning when they occur intra-abdominally or near vital structures in the head and neck (Figure 1).

Sorafenib has demonstrated activity in several studies, establishing it in the guidelines as a treatment option for patients with desmoid tumors. A randomized, double-blind, phase III trial was halted after a median follow-up of 27 months based on a progression-free survival rate of 81% in patients on sorafenib versus 33% in the placebo group. “But in addition to confirming the benefit of sorafenib in desmoids, this study also provided a framework for the natural history of untreated desmoids, including prolonged stable disease and spontaneous tumor reduction,” said Dr. George. “This really highlights the importance of patient selection for any therapeutic intervention, whether it be drug, surgery, radiation, or other.”

Dr. George highlighted a footnote from the desmoid tumor guidelines stating that, “For tumors that are symptomatic, or impairing or threatening in function, patients should be offered therapy with the decision based on the location of the tumor and potential morbidity of the therapeutic option.”

“This is really about balancing the risks and benefits,” she noted. “I think observation is a very reasonable option for many patients with desmoids, and I think the data from the phase III study of sorafenib versus placebo support that; we do not need to jump to systemic therapy if a tumor is relatively small or if it’s asymptomatic.” She added that a tumor that is causing pain or a functional threat would be an exception.

“I would not wait with those patients to see if it happens to be one of the [tumors] that’s going to spontaneously regress,” she said.

More Questions in TRK Fusion–Positive Tumors
Based on dramatic responses in a study of larotrectinib in TRK fusion–positive cancers (not just sarcomas), it was added to the NCCN Guidelines for use in sarcomas with TRK fusions. Although sarcomas represented a significant proportion of cases enrolled in that trial, multiple histologies were represented in both pediatric and adult patients. According to Dr. George, this raises questions around the most efficient way to identify patients with TRK fusions.

“Will there eventually be a screening or immunohistochemistry test, or will we always rely on next-generation sequencing?” she asked. “How do we ensure that we’re not missing the patients who could have such a dramatic benefit?”

The study also raises questions about the true prevalence of TRK fusions in sarcomas and whether specific histologies are more or less likely to harbor this genomic feature. Dr. George emphasized that these questions remain to be answered.

New Agents in GIST
There have been no changes to the NCCN Guidelines for the treatment of GIST, but 2 new investigational compounds, avapritinib and ripretinib, have demonstrated “interesting efficacy,” said Dr. George.

In preclinical data, avapritinib has demonstrated activity in tumors with exon 11 mutations (the most common primary activating mutation in GIST) and in hybrid mutations, particularly exons 11 and 17. In a phase I trial, avapritinib showed tremendous potency in patients with GIST and a PDGFR-α D842V mutation, a previously “undruggable” target. The drug also showed activity in up to a quarter of patients with other commonly...
occurring KIT mutations. “This is a mutation that’s resistant to imatinib, sunitinib, and regorafenib,” she noted. “So, this is a small population, but with a big unmet need.” Avapritinib is currently being investigated in a randomized phase III trial with regorafenib in patients with metastatic GIST and who are regorafenib-naive.

Ripretinib has also shown encouraging efficacy in all lines of treatment for GIST, and will be tested against placebo in the fourth line and beyond, a complete unmet need in GIST. It will also be evaluated head-to-head with sunitinib in the second line, she reported.

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