Sarcoma: Targeting Treatment by Activating Pathways

CME Learning Objectives

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

• Discuss the limitations of current treatment options for advanced or metastatic sarcoma.
• Describe the known pathways that can be used as potential targets in the treatment of sarcoma.
• Evaluate the clinical efficacy and toxicity of investigational agents that target signaling pathways to treat sarcoma.
Introduction

Although it is not one of the more commonly occurring cancers, metastatic sarcoma is a devastating disease with limited treatment options and poor overall survival. The treatment advances that have been made in certain subtypes of sarcoma, such as Ewing sarcoma and osteosarcoma, during the last 20 to 30 years have not been made in the treatment of metastatic sarcoma. There is an ongoing need to develop more agents that can delay progression and control disease with less toxicity. Recently, the results of the SUCCCEED trial have shed light on the utility of a new treatment approach for patients with metastatic or advanced sarcoma. The trial examined the efficacy of a mammalian target of rapamycin (mTOR) inhibitor as a maintenance therapy in patients with advanced sarcoma who had stable disease after standard treatment.

To provide a platform for sharing valuable information about this study, Vindico Medical Education, in conjunction with HEMONC TODAY, gathered Drs. Sant P. Chawla, the lead author of the SUCCCEED trial, as well as Drs. Scott H. Okuno, Monica Mita, and Andrew J. Wagner, who all served as contributors to the trial, to share their observations. These clinicians discussed the disease and how novel treatments are targeting molecular pathways. This monograph is based on their discussion and includes an extended review of current treatment options for sarcoma, the problems of balancing drug toxicity with patient quality of life, the role of surgery, molecular markers for prognosis, and the effect of new medications that target the mTOR pathway.

I thank the panelists for their insights and for their participation in the preparation of this monograph, which includes salient aspects of their discussion. We hope that it provides practitioners with relevant information that will improve their treatment of patients with sarcoma.

Scott H. Okuno, MD
Course Chair
Sarcoma: Targeting Treatment by Activating Pathways

Sarcomas are a heterogeneous group of malignant tumors that affect soft tissue and bone. Soft-tissue sarcomas comprise 1% of adult cancers and 7% of childhood cancers and can develop in a number of tissues, including muscle, fat, nerves, blood vessels, joints, and skin. There are estimates that in 2010, approximately 10,520 Americans will be diagnosed with soft tissue sarcomas and 2,650 Americans will be diagnosed with bone sarcomas. Approaches to treat these diseases.

Sarcomas are tumors of mesenchymal origin. They can occur in any location. Common types of soft tissue sarcoma are liposarcoma arising from fat, leiomyosarcoma arising from muscle, and malignant peripheral nerve sheath tumors (MPNST) arising from the peripheral nerves. For many soft tissue sarcomas, the etiology is unknown and their names are misnomers, such as synovial sarcoma which does not arise from the synovium, or malignant fibrous histiocytoma, which does not arise from histiocytes. There are some sarcomas where the cause of the tumor is known, such as Kaposi sarcoma, which affects the skin and digestive tract, is associated with infection by the human immunodeficiency virus (HIV), and is caused by human herpesvirus-8 (HHV-8). Most sarcomas are not caused by viruses.

As with most cancers, appropriate treatment for sarcoma is dependent on the patient’s age and the type, size, histologic grade, and stage of the tumor. Low-grade and localized tumors are usually treated with surgery, whereas for higher-grade and advanced disease, the role of chemotherapy should be considered, either alone or in combination with surgery and/or radiation.

Metastatic sarcoma has a poor prognosis and currently approved treatments have a high burden of toxicity. Even patients who can tolerate treatment and have stable or responding tumors ultimately have disease progression usually after 6 or 7 cycles of therapy. However, in the age of molecular targeted therapy, new strategies for treating sarcoma are emerging that may provide patients with prolonged progression-free survival and improved quality of life (QOL).

Treatments for Metastatic Sarcoma Chemotherapy

For advanced or metastatic sarcoma, chemotherapy is normally implemented either alone or in combination

Appropriate treatment for sarcoma is dependent on the patient’s age and the type, size, histologic grade, and stage of the tumor.
with surgery or radiation.\textsuperscript{5} Chemotherapy agents approved in the United States for sarcoma are doxorubicin and ifosfamide. In clinical trials for sarcoma, doxorubicin has been studied as a single agent\textsuperscript{6} or in combination with dacarbazine\textsuperscript{7} or ifosfamide/mesna.\textsuperscript{8,10}

Doxorubicin is an anthracycline antibiotic, first developed in the 1950s from \textit{Streptomyces peucetius}, a bacterium found in soil samples.\textsuperscript{11} The first compound derived from the bacterium, daunorubicin, entered clinical trials in the 1960s for the treatment of hematologic cancers. However, the drug produced fatal cardiotoxicity.\textsuperscript{12} Doxorubicin, a molecular derivative of daunorubicin, was developed in the 1970s. The anthracycline showed more therapeutic potential than daunorubicin, but still retained cardiotoxicity.\textsuperscript{13}

Ifosfamide is an oxazaphosphorine alkylating agent, similar to cyclophosphamide. After activation in the liver, ifosfamide interferes with DNA by creating phosphotriesters and DNA crosslinks, thus inhibiting protein synthesis and DNA synthesis.\textsuperscript{14}

Gemcitabine and docetaxel are approved in the United States for the treatment of other solid tumors, and are currently under investigation for sarcoma. Gemcitabine is approved for the treatment of cancers of the ovary, breast, pancreas, and non-small cell lung cancer (NSCLC).\textsuperscript{15} Docetaxel is approved for use in breast and prostate cancer, NSCLC, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck.\textsuperscript{16} The National Comprehensive Cancer Network (NCCN) lists this combination under regimens with activity in soft-tissue sarcoma.\textsuperscript{17} However, a number of questions about schedule, sequence, and kinetics remain and there are ongoing trials addressing these issues.\textsuperscript{18} Trabectedin is a marine-derived anti-tumoral agent approved in Europe for the treatment of sarcoma, but is available in the United States on an expanded access study.\textsuperscript{19}

For palliation of patients with unresectable disease, the National Cancer Institute (NCI) recommends chemotherapy with the following agents:

- Doxorubicin
- Doxorubicin + dacarbazine
- Doxorubicin + ifosfamide
- Doxorubicin + dacarbazine + ifosfamide/mesna
- High-dose ifosfamide regimens

\textbf{Surgery}

Surgical resection (with adjuvant radiotherapy when needed) is often curative for localized and low-grade sarcoma.\textsuperscript{20,21} In addition, surgery designed to be curative is sometimes used for patients with sarcoma and pulmonary metastases if the underlying disease is not aggressive (ie, small number of metastases, long disease-free survival, slow tumor growth) and if complete resection of the primary tumor is achieved.\textsuperscript{6} In other words, surgery is recommended only for patients with limited metastatic disease and even then, it is advisable to shrink tumors with chemotherapy prior to surgery.

\textbf{Radiotherapy}

Within a multidisciplinary approach, radiotherapy is an essential component of sarcoma treatment. Radiotherapy can be used either as neoadjuvant, adjuvant, or primary local therapy. Factors to consider when deciding on radiotherapy are the site and type of the tumor, the availability and acceptability of the surgical option, and the efficacy of the chemotherapy.\textsuperscript{22} According to a review published in 2005, radiotherapy should be considered for high-grade tumors of the limbs (in the absence of very wide margins) and for intermediate-grade tumors of the limbs with close or positive histologic margins. There is little role for radiotherapy in primary low-grade soft-tissue sarcoma, although it is appropriate for a recurrence.\textsuperscript{20}

\textbf{Treatment Selection Strategies for Metastatic Sarcoma}

Treatment strategies for advanced or metastatic sarcoma depend on several factors, such as the stage, grade, and size of the primary tumor, the location of the metastases, tumor histology, and whether treatment is intended to be curative or palliative. A multifactorial, patient-specific approach is essential for achieving optimal results with the least toxicity. Chemotherapy, radiotherapy, and surgery — alone or in combination — are all useful for advanced sarcoma depending on the circumstances and should be integrated within a multidisciplinary approach to treatment.\textsuperscript{5}

According to the NCI, local control of the primary tumor in metastatic (stage IV) sarcomas is optimally obtained by resection with negative margins, lymphadenectomy when appropriate, and postoperative external beam radiation therapy.\textsuperscript{3} For patients with nodal disease (ie, metastatic involvement of the regional lymph nodes), the NCI lists 3 standard treatment options:

- Surgical resection and lymphadenectomy for patients with clinically positive lymph nodes with or without postoperative radiation to the primary site;
- Radiation therapy prior to and following surgical extirpation; and
- Adjuvant chemotherapy for patients eligible for clinical trials.

For patients with distant metastases, surgical resection of the primary tumor with radiation therapy is an
option as long as all distant metastases are able to be surgically removed.

Resection of pulmonary lesions may be performed following definitive therapy of the primary tumor. Factors to consider include the following:

- Surgical excision with negative tissue margins may be used.
- If the tumor is resectable but wide margins cannot be obtained, radiation therapy may be added.
- If the tumor is unresectable, high-dose radiation therapy may be used, often with chemotherapy.
- For tumors of the retroperitoneum, trunk, and head and neck, surgical resection with preoperative and/or postoperative radiation therapy, and sometimes chemotherapy, may be used.

When selecting a chemotherapy regimen, particular attention should be given to toxicity. Aggressive combination chemotherapy regimens can be quite toxic and reduce a patient’s QOL.

The combination of doxorubicin and ifosfamide has improved response rates, but toxicities have increased with no measurable benefit in overall survival. Also, response rates with these agents are short-lived — between 6 months to 9 months with variability determined by histology. Docetaxel and gemcitabine are less toxic and appropriate for sarcoma subtypes that respond to these agents, such as leiomyosarcoma, but they too are commonly discontinued due to cumulative side effects. Taxanes are associated with worsening neuropathy and anthracyclines carry a significant risk for cardiac dysfunction. Docetaxel and gemcitabine are more often discontinued due to disease progression, which often occurs after 6 to 8 cycles.

Strategies for reducing toxicity while maintaining therapeutic efficacy include the use of lower doses of chemotherapy, single-agent therapy, or oral medications.

For example, the tyrosine kinase inhibitor (TKI) imatinib, which targets the RTK called KIT, was recently shown to significantly increase recurrence-free survival.

Histology studies have shown that some subtypes of sarcoma respond better to certain agents whereas some subtypes, such as gastrointestinal stromal tumor (GIST), alveolar soft part sarcoma, and clear cell sarcoma, are resistant to all forms of chemotherapy. For example, doxorubicin plus ifosfamide has been shown to be effective against small round cell sarcoma; leiomyosarcoma responds well to docetaxel and gemcitabine; and synovial sarcoma shows a good response to high-dose ifosfamide.

**Mammalian Target of Rapamycin (mTOR) Inhibitors**

Knowledge of the role of the mTOR pathway in tumorigenesis emerged in the mid-1990s when rapamycin, an antifungal immunosuppressive agent with a broad spectrum of anticancer activity, was discovered to target and inhibit mTOR. The mTOR pathway is dysregulated in many cancers, including sarcoma, and controls cell growth, metabolism, and angiogenesis. The pharmacokinetic properties of rapamycin were unfavorable for clinical use. However, later analogs with more favorable pharmacokinetic profiles that also targeted this pathway were developed, including temsirolimus and everolimus for kidney cancer and ridaforolimus for sarcomas.

The mTOR molecule lies at the interface of 2 important signaling pathways (Figure 1, page 6): one activated by phosphoinositide 3-kinase (PI3K) and one through serine threonine kinase 11 (LKB1). Mitogens binding to membrane receptor tyrosine kinases (RTKs) activate PI3K and Akt which in turn activates mTOR, leading to a phosphorylation cascade that stimulates angiogenesis, cell proliferation, and cell survival through mRNA translation. LKB1 phosphorylates and activates AMP-activated protein kinase (AMPK), which in turn inhibits mTOR activity. LKB1-mediated inhibition of mTOR also involves the tuberous sclerosis protein (TSC)1/2 complex. Disruption of LKB1 in mice has been shown to cause hepatic and gastrointestinal polyps.

Increased activation of the RTK/PI3K/Akt/mTOR pathway has been detected in many sarcoma subtypes and interruption of this pathway is being intensively studied, with significant clinical success in some sarcomas. For example, the tyrosine kinase inhibitor (TKI) imatinib, which targets the RTK called KIT, was recently shown to significantly increase recurrence-free survival.

(continued on page 7)
The mTOR signaling pathway is complex and can be regulated therapeutically at multiple steps.

and overall survival in gastrointestinal stromal tumors at high risk for recurrence. Imatinib has also been shown to induce regression in patients with unresectable, metastatic, or recurrent dermatofibrosarcoma protuberans. Studies have shown partial and complete responses in patients with metastatic disease.

Other sarcomas demonstrating activation of this pathway include rhabdomyosarcoma, Kaposi sarcoma, leiomyosarcoma, synovial sarcoma, Ewing sarcoma, and osteosarcoma.

**Ridaforolimus**

Ridaforolimus (AP23573, deforolimus) is a rapamycin analog that is not only active in a variety of tumor types, but may provide patients with sarcoma prolonged progression-free survival without having a dramatic effect on QOL.

In a phase 1 study of 32 treatment-refractory patients with solid tumors (7 with sarcoma) the maximum tolerated dose of ridaforolimus was found to be 18.75 mg/day (5 days every 2 weeks). Adverse events were generally mild-to-moderate and were dose-related. The most common adverse event was mouth sores. Other adverse events included erythematous maculopapular rash, hyperlipidemia, hyperglycemia, anemia, stomatitis.

<table>
<thead>
<tr>
<th>Route of Ridaforolimus</th>
<th>Number and Diagnosis</th>
<th>Clinical Benefit Rate</th>
<th>Rate of PFS at 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1/2 oral</td>
<td>147 (all tumors) 85 sarcomas</td>
<td>27%</td>
<td>23%</td>
</tr>
<tr>
<td>Phase 2 intravenous</td>
<td>212 sarcomas</td>
<td>29%</td>
<td>23%</td>
</tr>
<tr>
<td>EORTC historical review of sarcoma database for “active” agents</td>
<td></td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>

Clinical benefit rate: CR+PR+SD > 4 months


**Figure 2. SUCCEED Trial Design**

In the SUCCEED trial, patients with metastatic sarcoma were randomly assigned to receive placebo or ridaforolimus.

Key: IRC — Independent Radiology Committee; SOC — Standard of Care

Source: Chawla S. Presented at: 2011 ASCO Annual Meeting; June 6, 2011; Chicago, IL.
All 7 patients with sarcoma enrolled in this study experienced clinical benefit from ridaforolimus, including 2 partial responses. In a second phase 1 study, which used ridaforolimus with a weekly administration schedule, the most common side effects were fatigue, anorexia, and mucositis (the dose-limiting toxicity).

One phase 2 trial enrolled 216 patients (212 treated) with advanced sarcoma and grouped them into 4 cohorts according to sarcoma histology: bone sarcoma (n = 54), leiomyosarcoma (n = 57), liposarcoma (n = 44), and other soft-tissue sarcomas (n = 57). Patients were administered 12.5 mg of ridaforolimus daily for 5 days every 2 weeks. There were no restrictions on prior therapy. Patients had a clinical benefit rate (complete response, partial response, or stable disease for 4 months or more) of 29%, including 5 partial responses (Table 1, page 7). Most responses consisted of stable disease at 16 weeks. Median overall survival was 40.1 weeks. There was no significant difference in outcomes between the 4 subgroups.

An oral formulation of ridaforolimus has also been developed and tested in a large phase 1 study. The study enrolled 147 patients with advanced/metastatic solid tumors refractory to therapy; 85 patients had sarcoma. Seven different dosing regimens were investigated. The dose-limiting toxicity for all regimens was reversible stomatitis. The maximum tolerated dose and higher cumulative pharmacokinetic exposure (pre-dose trough on day 8; mean AUC, days 1-28) was increased using a weekly dose holiday interval, while maintaining convenience and tolerability. The clinical benefit rate was 25% overall and 27% for patients with sarcoma. In addition, progression-free survival at 6 months was 23%, which exceeds historical control reported in European Organisation for Research and Treatment of Cancer (EORTC) studies for active agents in sarcoma.

A pharmacodynamic analysis showed potent inhibition of mTOR with ridaforolimus. The study concluded that oral ridaforolimus has a safety and antitumor activity profile consistent with the IV formulation. The dose regimen of 40 mg once daily for 5 days each week was identified as an active, well-tolerated regimen.

**The SUCCEED Trial**

Results from the phase 1/2 trials of ridaforolimus prompted the initiation of a phase 3 placebo-controlled trial of maintenance therapy: the Sarcoma mUlti-Center Clinical Evaluation of the Efficacy of rIdaforolimus (SUCCEED) study. Patients with metastatic soft-tissue or bone sarcomas who had an ongoing favorable response to chemotherapy were enrolled and treated with an oral formulation of ridaforolimus (Figure 2, page 7).
Eligible patients included those with metastatic sarcoma who had achieved a complete response, partial response, or stable disease with first-line, second-line, or third-line chemotherapy, per standard of care. Patients may have had surgery or limited doses of radiation and they must have received a minimum of 4 cycles of chemotherapy to qualify. Some patients had received up to 12 cycles of chemotherapy. Patients were randomized 1:1 to receive either oral ridaforolimus (40 mg once daily for 5 out of 7 days per week) or placebo. All patients were monitored by radiologic studies every 8 weeks and results were reviewed centrally. Patients with progressive disease were not eligible for the study and if progressive disease developed during the trial, they were taken off the study.

The primary endpoint of the study was progression-free survival by central review. Secondary endpoints were overall survival, objective response defined by best target lesion response, cancer-related symptoms, and safety and tolerability. A total of 711 patients were enrolled into the study in less than 2.5 years: 347 in the ridaforolimus group and 364 in the placebo group. Sixty percent of these patients were from the United States; 40% were from other countries. Patient characteristics were balanced with regard to age, sex, Eastern Cooperative Oncology Group (ECOG) status (0/1), histology (soft tissue/bone), prior chemotherapy, sarcoma grade (high/low), and metastatic sites (lung/liver). The majority of patients had metastatic disease with most metastases in the lung.

**Progression-free survival**

The study met its primary endpoint of progression-free survival based on a central review (hazard ratio (HR), 0.72; *P* = .0001; Figure 3, page 8). Progression-free survival at 3 months was 70% in the ridaforolimus arm and 54% in the placebo arm, a 30% improvement. Progression-free survival at 6 months was 34% in the ridaforolimus arm and 23% in the placebo arm, a 51% improvement. The median progression-free survival was 17.7 weeks in the ridaforolimus arm vs. 14.7 weeks in the placebo arm. The results were consistently in favor of ridaforolimus across multiple subgroup analyses.

Although not statistically significant, a positive trend for overall survival was observed in the ridaforolimus group.

Source: Chawla S. Presented at: 2011 ASCO Annual Meeting; June 6, 2011; Chicago, IL.

![Figure 4. SUCCEED: Trend in Overall Survival (OS)](image-url)

**Figure 4. SUCCEED: Trend in Overall Survival (OS)**

- **Median OS**
  - Ridaforolimus: 21.4 months
  - Placebo: 19.2 months

- **HR = 0.88, P = 0.2256**
- **386 death events based on data cut-off date 4-30-2011**
- **(6 months after PFS data cut-off date)**

An investigator assessment also yielded a significant difference in favor of ridaforolimus (HR, 0.69; *P* = .0001), a 31% reduction in the risk for death or disease progression in the ridaforolimus arm. The 3-month and 6-month progression-free survival rates were similar to those of the central review and showed an improvement of 30% in progression-free survival at 3 months and 60% at 6 months in the ridaforolimus arm. The median progression-free survival was 22.4 weeks in the ridaforolimus arm vs. 14.7 weeks in the placebo arm. The results were consistently in favor of ridaforolimus across multiple subgroup analyses.
**Overall survival**

When examining the secondary endpoint of overall survival, researchers found that the median overall survival was 21.4 months for the ridaforolimus arm vs. 19.2 months for the placebo arm, a difference of 2.2 months (HR, 0.88; \(P = .2256\); Figure 4, page 9). Although this was a positive trend for improving survival in the ridaforolimus arm, it was not statistically significant. The clinical benefit rate was 40.6% for ridaforolimus and 28.6% for placebo (\(P = .0009\)).

**Pediatric patients**

There was a small subset of pediatric patients in the SUCCEED trial. Improvements with ridaforolimus were observed compared with placebo (Table 2). No major issues have been observed in this population. Some patients are still part of the study for the long term.

**Target lesion response**

The best target lesion response was assessed by mean tumor size in the whole group. Mean target lesion measurement showed a tumor shrinkage of 1.3% in the ridaforolimus group, whereas the placebo group had a mean tumor increase of 10.3% (\(P < .0001\)). Based on this finding, ridaforolimus controlled tumor growth more effectively than placebo. Survival following disease progression was similar in both the ridaforolimus arm and placebo arm (HR, 0.94; 95% CI, 0.76-1.18; \(P = .6152\)), indicating that ridaforolimus has no detrimental effect on subsequent survival following progression.

**Safety analysis**

The safety analysis showed that all patients in the ridaforolimus arm had at least 1 adverse event and 64% had an adverse events of grade 3 or worse (Table 3). However, 94% of patients in the placebo group also had adverse events (26%, grade \(\geq 3\)), suggesting that the study population had baseline toxicities due to their sarcoma. The most common adverse event was stomatitis (61% for all grades, 9% for grade \(\geq 3\)). This was the most common side effect leading to dose reduction or temporary discontinuation. The placebo group also had 18% of patients with stomatitis at all grades (<1% with grade \(\geq 3\)). Other important adverse events included infection, fatigue, thrombocytopenia, diarrhea, cough, and skin rash. Adverse events known to be associated with other mTOR inhibitors and seen in the SUCCEED trial included anemia, hyperlipidemia, hyperglycemia, and non-infectious pneumonitis. There were 6 deaths secondary to pulmonary disorders, including pleural effusion, pulmonary embolism, respiratory distress, and drug-related pneumonitis. The SUCCEED trial is ongoing but has discontinued recruitment.45

The investigators also conducted an exploratory analysis of survival cancer-related symptoms, which was inconclusive due to a lack of completed data. No information about cancer-related symptoms was gathered in those patients whose disease progressed. In summary, the SUCCEED trial met its primary endpoint of progression-free survival improvement with a trend towards overall survival benefit. Compared with placebo, there was improved control of tumor growth, no adverse effect on survival following disease progression, and no major unexpected adverse events and toxicities. These results are similar to that of other mTOR inhibitors.

**Conclusion**

Advanced and metastatic sarcoma remains incurable for most patients. However, mTOR inhibitors and other agents targeting the RTK/PI3K/Akt/mTOR pathway offer a viable alternative to toxic chemotherapy regimens, which lengthen life at the expense of lower QOL. In addition to ridaforolimus, targeted agents in phase 3 clinical trials for sarcoma (not including GIST) include trabectedin, pazopanib, and bevacizumab. As data from these trials become available, clinicians and patients with advanced sarcoma can expect increased antitumor efficacy with improved QOL.

**References**


### Table 2. Efficacy Results of Pediatric Population

<table>
<thead>
<tr>
<th>Ridaforolimus Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 patients enrolled</td>
<td>5 patients enrolled</td>
</tr>
<tr>
<td>64% tumor size reduction in 1 osteosarcoma patient</td>
<td>No responder</td>
</tr>
<tr>
<td>1 PR, 4 SD, 2 PD</td>
<td>1 SD, 4 PD</td>
</tr>
<tr>
<td>CBR: 5/7 = 71%</td>
<td>CBR: 1/5 = 20%</td>
</tr>
<tr>
<td>PFS durations: 59, 48, 23, 20, 19, 16, and 8 weeks</td>
<td>PFS durations: 20, 8, 4, and 4 weeks</td>
</tr>
</tbody>
</table>

Source: Chawla S. Presented at: 2011 ASCO Annual Meeting; June 6, 2011; Chicago, IL.
Table 3. Adverse Events Noted During SUCCEED Trial

<table>
<thead>
<tr>
<th>MedDRA System Organ Class Preferred Term</th>
<th>Placebo (n=359)</th>
<th>Ridaforolimus (n=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade ≥ 3 (%)</td>
</tr>
<tr>
<td>Percent of Patients with ≥ 1 Adverse Event</td>
<td>94</td>
<td>26</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infections (all sites included)</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Rash</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: Chawla S. Presented at: 2011 ASCO Annual Meeting; June 6, 2011; Chicago, IL.

16. Taxotere Prescribing Information. sanofi-aventis (last revision: June 3, 2010).


DISCUSSION

Can you describe the intent of therapy for patients with a metastatic sarcoma? What treatment strategies are appropriate for patients with metastatic sarcoma?

Monica Mita, MD: Based on the severity of the disease, practitioners can choose from chemotherapy, radiation, surgery, or a combination of these. In some cases, one might use neoadjuvant chemotherapy to shrink the tumor and possibly get the disease to the point of being resectable. Or, they can use radiation therapy or palliative chemotherapy with single agents or a combination of agents. Patients with limited metastatic disease can also be considered for surgery, depending on the location of the disease. Despite all of these treatments available to us, the prognosis is still quite dismal in patients with metastatic disease; only about 10% are alive at 5 years.

Andrew J. Wagner, MD, PhD: In the metastatic setting, except in rare circumstances, our treatments are devised at controlling disease or shrinking disease, and are not meant to be curative. The goals of treatment should focus on maintaining excellent disease control and quality of life. Those factors heavily influence my decisions when recommending different treatment options to patients. If a patient has bulky disease or is symptomatic, then I tend to use combination chemotherapy in an effort to shrink the disease and improve their symptoms. However, if a patient has less bulky disease, my goals of treatment are usually to control or sometimes even shrink the tumors if possible, but I also focus on limiting toxicities so we can maintain the patient's excellent quality of life.

Do you have any thoughts on when to decide to incorporate radiation in the palliative treatment of sarcoma?

Sant P. Chawla, MD: Radiation has been mainly used for primary sarcoma, either preoperatively, during surgery, or postoperatively. In the metastatic setting, the role of radiation is very limited except to the bones when pain has been occurring or to reduce the risk of pathologic fracture. Lately, we have used radiation as CyberKnife or radiosurgery where the disease cannot be resected, if it is growing rapidly, or if it is in the lung where a major resection is required.

Can you describe the role of cytotoxic therapy, in general, for the patient with metastatic disease?

Chawla: For patients with metastatic disease, we determine the histology, the extent of the disease, and the overall condition of the patient. In general, the standard for all soft tissue sarcoma is doxorubicin. If the patient is older we may use analogs of doxorubicin, which are less toxic, such as epirubicin. We use ifosfamide for patients who have limited disease or synovial sarcoma, or for young patients who can tolerate the toxicity of ifosfamide. I usually give front-line docetaxel and gemcitabine for patients with leiomyosarcoma, and as second-line treatment for patients who fail to respond to other agents. Experimental drugs such as trabectedin, which we get on a compassionate basis in the United States, are mainly limited to either second-line or third-line use or specific diagnosis such as myxoid liposarcoma, which shows a high chance of responding to these drugs.

What is the role of dacarbazine and temozolomide in the management of advanced metastatic disease?

Wagner: Dacarbazine was commonly used in combination with doxorubicin, ifosfamide, and mesna in what is referred to as the MAID regimen, but studies have shown that the combination added toxicity with little benefit in terms of overall survival. Instead, practitioners more commonly implement single-agent dacarbazine. In patients with more advanced disease, practitioners often use dacarbazine or temozolomide. At our center, we have been using temozolomide more often because it is an oral agent and patients can take it at home. Also, we see some significant benefits for some sarcoma subtypes, such as leiomyosarcoma. Temozolomide is often a well-tolerated medicine. Dacarbazine can also be well-tolerated, but it is an infusional agent and thus there are more demands on the patient’s time in terms of treatment.

Please describe the signaling pathways that researchers are exploring as other potential targets for novel therapies in sarcoma.

Wagner: As we have noted, there are many different histological subtypes of sarcoma that entail many different oncogenic pathways. We have been learning more about these pathways in the last decade through 2 different approaches. One is by performing a detailed analysis of the tumor subtypes, examining the different pathways and identifying mutations. The second is by using targeted therapies, observing responses, and trying to understand the mechanism of those responses. In individual tumor subtypes, we are seeing signs that these pathways are being activated. Some activation occurs at the level of the cell surface and RTKs — the classic example is GIST with activating mutations in KIT or platelet-derived growth factor receptor (PDGFR) alpha. In dermatofibrosarcoma protuberos and other tumor types, we see activation of PDGFR through overexpression of platelet-derived growth factor. Mutations in the PI3K pathway have been identified in approximately 20% of myxoid liposarcomas. They have mutations in the catalytic subunit of PI3K and there can be loss of the inhibitory protein phosphatase and...
DISCUSSION

tensin homolog (PTEN) in a large number of tumors as well. We see this predominantly in leiomyosarcoma, which may also have some activation in the PI3K pathway. We have also been interested in a tumor called perivascular epithelioid cell tumor (PEComa) and have found loss of an inhibitory protein called tuberous sclerosis complex (TSC) 1 or TSC2 which leads to hyperactivation of mTOR in those cells.

How are the findings of the SUCCEED trial likely to affect clinical practice when dealing with patients with advanced metastatic sarcoma?

Wagner: The conduct of the study is remarkable in that the investigators were able to integrate many different sites across the world and rapidly accrue patients with a unique trial design, which included maintaining disease control after conventional chemotherapy. Even more remarkable is the heterogeneous nature of the sarcomas that were enrolled, which theoretically could have rendered results difficult to achieve. Instead, the results highlight the significance of inhibiting the mTOR pathway across the spectrum of disease. There were patients whose disease was under greater control for a much longer period and unfortunately others in whom the drug did not help. I think this is another bullet to put in our armamentarium for treating sarcomas. One of the challenges will be identifying tumor subsets that are more susceptible to ridaforolimus, but it is remarkable that we have been able to achieve results given the pooled nature of the tumor types.

What is the key message for your patients after the SUCCEED trial?

Mita: We have now come to a point in sarcoma treatment that other tumor types have achieved and that is maintenance therapy. I personally am very happy that we are at this point. The main lesson from the SUCCEED trial is that we can use a targeted agent as maintenance therapy to help our patients and this is something that I would like my patients to understand. I can tell my patients that we now have maintenance therapy with a targeted drug that does not have the same side effects as chemotherapy and can help to improve progression-free survival, achieve stable disease, and perhaps improve survival.

How much is known about molecular markers in sarcoma? What prognostic markers for disease progression and response to treatment have been identified?

Wagner: The best surrogate to a molecular marker in sarcoma is the subtype of the tumor. Some forms of sarcoma are more likely to respond to treatment than others. Unfortunately, there is currently no other method to characterize prognosis.

Chawla: Given the lack of prognostic markers, practitioners make decisions about treatment based on tumor types. Although some treatment decisions are based on other patient characteristics, specifically age, performance status guides treatment as with other cancers. With regard to imaging, the standard practice is to administer chemotherapy and perform imaging after every 2 to 3 cycles of chemotherapy, which is about 2 to 3 months.

How does performance status affect your choice of treatments?

Wagner: For me, a choice of agents is certainly reflective of a patient’s performance status. If someone has an ECOG performance status of 1 (symptomatic but completely ambulatory), I might be more aggressive with using combination chemotherapy. But if someone is ECOG performance status of 2 (ambulatory but unable to work), I would probably implement single-agent therapy or find another treatment that is likely to be nontoxic.

When assessing response, one sometimes observes an increase in tumor size without the appearance of new tumors. In the clinical trial setting, how do you determine that you are observing tumor growth rather than just tumor necrosis with swelling and injury?

Chawla: If the increase in tumor size is approximately 20%, it is progressive disease; if it is less than 20%, it is stable disease, provided there are no new lesions. Occasionally, there are patients whose primary tumor may be increasing in size but they are still responding to treatment. We observe this in less than 10% of patients. Discovering major tumor necrosis following surgery on localized disease indicates that the patient was responding.

In sarcoma oncology, some people advocate the Choi criteria to assess response, which is recommended by the University of Texas MD Anderson Cancer Center. The Choi criteria are based on changes in tumor attenuation on computed tomography (CT), which reflect changes in tumor density. CT scans may show that the tumor is larger, but the standardized uptake value determines the response. Overall, for investigational purposes and for the majority of patients, tumor size is still used to assess response. If the tumor is stable with less...
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than 20% increase and no major toxicity, we will continue with chemotherapy.

Wagner: Certainly in clinical practice outside of a research setting, we are less obligated to precise Response Evaluation Criteria in Solid Tumors (RECIST) measurements. Clinical judgment plays more of a role. For example, if a patient has multiple lesions, most of which are responding to treatment, but with 1 lesion progressing or 1 new lesion detected, we are more likely to continue with the current treatment. In a clinical trial, that would be viewed as disease progression.

Clinical judgment also plays more of a role over strict research criteria when tumors are particularly small. For example, a few millimeters of growth would account for a 20% progression in a research study, but in a clinical scenario it may not be significant. I think that the Choi criteria are well-validated for first-line treatment of GIST, but I think that their role in sarcoma is less clear. There are cases where we observe some swelling of the tumor with significant necrosis and change in tumor density. There are other cases where the tumor density might change, but we would not necessarily classify it as a response.

Again, the clinical setting is different from the research setting because we are trying to consider what treatments we have available for the patient. If we have a limited number of conventional therapies available and if the patient is not interested or is not a good candidate for clinical trials, then we try to maximize the use of those agents before we move on to the next therapy.

With agents that target specific pathways, are there concerns that there may be unintended downstream consequences unrelated to cancer treatment? Discuss the steps taken to try to identify the overall effect of an agent on a patient’s health.

Chawla: Unfortunately, the duration of response with these agents does not last long enough for chronic side effects such as hyperthyroidism to be a concern. With regard to acute side effects, we always notice immediately and take action. Monitoring patients with metastatic disease who are taking agents such as ridaforolimus in the long term will be necessary. We are monitoring side effects such as hypertriglyceridemia, but we should also monitor other side effects. The situation is similar to when we started using adjuvant interferon after patients had a resection and chemotherapy. We failed to discover their hyperthyroidism until 6 months or a year had passed.

Wagner: Fortunately, most of our patients do not experience long-term toxicities with targeted agents. We still monitor them and administer treatment for side effects if they occur. We prescribe thyroid replacement therapy for patients who are on tyrosine kinase inhibitors that can affect the thyroid, such as sunitinib or sorafenib. Certainly, blood pressure control is important. Also, we must be alert for side effects such as hand-foot syndrome or ulcerations and encourage patients to report them to us so that we can help manage them before they become too serious.

For patients who are on long-term treatment with mTOR inhibitors, such as sirolimus, we often administer trimethoprim/sulfamethoxazole as prophylaxis against pneumocystis, although the risk is low. Additionally, there is a risk of pneumonitis with mTOR inhibitors, which renders it difficult to determine whether a patient has pneumocystis or pneumonitis if they are not on prophylaxis. The risk for pneumonitis with mTOR inhibitors can be as high as 29%. Thus if patients develop pulmonary symptoms such as cough or shortness of breath, then their chest should be re-imaged to look for pneumonitis and treat accordingly.

The SUCCEED trial was conducted in patients with advanced disease. Are there any indications for ridaforolimus and other mTOR inhibitors in early disease progression?

Chawla: The SUCCEED trial showed significant improvement in disease-free survival, but only for a few months or weeks. Ridaforolimus may yield different results when used as adjuvant therapy, but that would require another trial.

Wagner: The data from the phase 2 study suggests that time-to-progression may be prolonged, although in a non-randomized setting, it is difficult to determine whether that was due to selection of patients with indolent disease or whether it was a true drug effect. I do not think we are ready to use ridaforolimus as adjuvant therapy without a clinical trial, as Dr. Chawla stated. Also, I am not sure whether mTOR inhibitors should be used in advanced disease prior to chemotherapy except for patients who cannot tolerate chemotherapy.

Chawla: I agree. In the phase 2 trial, the response rate was low — less than 2%. The clinical benefit was 25%. Thus the first choice should still be chemotherapy unless we discover molecular markers.

Would you consider using an mTOR inhibitor on a patient who has progressed on chemotherapy with the aim of achieving disease stabilization, or would you use them only for responding patients? Where in the sequence of treatments do you place mTOR inhibitors?

Wagner: The phase 2 study enrolled patients who had progressed on prior chemotherapy and were treated with a single-agent mTOR inhibitor. So at our clinic we sometimes treat these patients...
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with an mTOR inhibitor. The response rate with these drugs may be low but it may help delay progression of disease.

Chawla: When treating sarcoma, we give a regimen containing doxorubicin and ifosfamide as first-line treatment and gemcitabine or docetaxel as second-line treatment. If there is a clinical trial available, we use trabectedin as third-line treatment and pazopanib as fourth-line treatment, depending on the patient’s status. If the patient is doing well and they have no other options and there is no clinical trial available, I will use off-label ridaforolimus or a similar mTOR inhibitor.

Do you think that mTOR inhibitors are more difficult to tolerate than other targeted agents? What is their potential for use with radiation or chemotherapy?

Wagner: My experience is that they are well-tolerated for the majority of patients. There are some patients who have a tough time with them, but often with dose modification the symptoms can improve and treatment can be continued. I do not have experience using mTOR inhibitors with conventional chemotherapy. However, there is no a priori reason for not using them in combination, other than the potential for toxicity that needs to be explored in safety studies. Reports on the safety of these combinations would make me more comfortable using them.

We sometimes combine mTOR inhibitors with other targeted agents, such as imatinib, sunitinib, and sorafenib. We have to be careful of drug/drug interactions because they can be metabolized by the same pathway, and there can be some additional toxicities or worsening toxicities such as diarrhea or mucositis. There have also been studies examining the combination of insulin-like growth factor-1 receptor (IGFR) antagonists with mTOR inhibitors. Those agents have been shown to be well-tolerated in combination, although they cannot currently be used outside of a clinical study.

Chawla: There are many targeted agents that could be synergistic in combination, such as mTOR inhibitors and IGFR inhibitors. The combination of mTOR inhibitors and AKT inhibitors is also attractive because both of these drugs affect the AKT pathway.

Combining chemotherapy with mTOR inhibitors has been difficult. In a phase 2 study of combination doxorubicin and ridaforolimus, we observed substantial mucositis and substantial myelosuppression, even with a low dose of doxorubicin (<50 mg/m²), so it seems that doxorubicin cannot be combined with an mTOR inhibitor. Drugs that do not cause mucositis or are less myelosuppressive may be useful.

In most studies, radiation is not given concomitantly with an mTOR inhibitor, so we have no experience in that regard. Overall, radiation plays little role in sarcoma treatment. In conclusion, further combination studies could be conducted using chemotherapy drugs that are not myelosuppressive and do not cause mucositis.

Based on the results observed in the pediatric population of the SUCCEED trial, would you be comfortable using ridaforolimus in children?

Chawla: For the regulatory agencies and for approval purposes, they will need another trial of ridaforolimus in pediatric patients, but not necessarily a large trial. If the drug gets approved, I would have no hesitation using it on a pediatric patient.

Wagner: As Dr. Chawla mentioned, there were some early responses in patients with osteosarcoma in the phase 2 trial. I think it would be of interest to offer this type of drug to patients with osteosarcoma. Patients with leiomyosarcoma can have good responses, and there are some preclinical data to suggest that PI3K is activated or PTEN is lost in some of those tumors. In malignant PEComas, we have found a loss of 1 of 2 proteins that suppress mTOR activity: TSC1 or TSC2. The loss of either of those proteins causes hyperactivation of mTOR and renders the tumors susceptible to mTOR inhibition. They are rare tumors, but it shows that in the right genetic context, you can potentially select the most appropriate targeted agent.

Many institutions in the country are now comprehensively studying tumors as they enter the clinic and are investigating potential targets for particular tumor types. This is still in the research stage and not yet ready for clinical application, but we are generating data that we can test in clinical trials and hopefully identify patients who would more reliably respond to this medication.

What comments are you hearing about the results of the SUCCEED trial and how it will impact clinical practice?

Chawla: Many clinicians comment that they are optimistic about the data and want to know when the company will be filing for approval.

Wagner: The data give a very different message than what many people are getting from the study. The message is that the improvement in progression was quite brief. However, Dr. Chawla made it clear that when you look beyond the median time to progression and examine metrics at different points along the progression time points, there is a consistent benefit with ridaforolimus. I think that the benefit is real, but we are dealing with a range of
tumor types and need to identify which patients will respond and derive benefit from treatment.

If you had a patient with metastatic leiomyosarcoma who asked you, “Is there anything else I can take to maintain my stable disease or responding disease,” would you offer them the mTOR inhibitor?

Chawla: Depending on the response and the patient’s condition, I would like to maximize benefit from standard treatment, after which I would enroll them in the SUCCEED trial or give them ridaforolimus when it is available. Also, if the patient is on second-line or third-line chemotherapy and is showing symptoms of toxicity, then I would implement the drug.

Wagner: Similar to Dr. Chawla, I would prefer to use conventional chemotherapy on patients who tolerate it. If there are issues about their ability to tolerate chemotherapy, I certainly would consider an mTOR inhibitor. If I had a patient with completely resected metastatic disease, I would wait and keep a close eye on them with serial scanning and treat when there is evidence of disease, perhaps with an mTOR inhibitor. I want to be able to measure the drug’s activity against the tumor.

Chawla: If a patient has metastatic disease with 1 or 2 lesions, I will resect them and would probably not administer ridaforolimus. On the other hand, 90% to 95% of patients with multiple lesions are going to relapse so I would consider using this drug in those patients. In the SUCCEED trial, we did not define the maximum duration of treatment. The majority of patients relapsed within 1 year, some within 2 years. So I would not implement ridaforolimus longer than 2 years.

The SUCCEED trial had stable disease and progression-free survival as endpoints rather than response. Shrinkage of the tumor was not a primary endpoint. Do you think there are any other translational opportunities to be used for disease-free progression as a benchmark in future trials?

Wagner: We need to examine the individuals who respond to treatment and try to understand why their tumors responded. Also, if you look at the median time to progression in the placebo arm of the SUCCEED study (approximately 15 weeks) and compare it with the median progression-free survival in the pazopanib vs. placebo study that was presented at the American Society of Clinical Oncology Annual Meeting (approximately 5 weeks) the difference in those 2 groups is patients who were progressing at the time of entry on the pazopanib study vs. patients who had disease control at the time of entry on the SUCCEED study. I find those numbers interesting, because they provide a benchmark regarding when to expect disease progression in different clinical contexts when other therapies are stopped. Another interesting finding from the SUCCEED study is that patients can do well for a few months after stopping conventional chemotherapy if they were under good control at the time. When tumors can be expected to progress should be considered when future studies are planned.

Patients often wonder what would happen if they stopped chemotherapy after achieving stable disease.

Wagner: We now have robust data in that regard. When we enrolled patients into the SUCCEED trial, we gave them 2 options after standard treatment: to take a break from chemotherapy or enroll in the study and potentially receive the study drug. Patients are typically nervous about stopping treatment, but we can now tell them that, statistically, it would be approximately 3 months before their disease would significantly progress again.

References
1. For the palliative treatment of patients with unresectable sarcoma, which of the following agents is NOT included in the chemotherapy regimens recommended by the National Cancer Institute (NCI)?
   A. Doxorubicin
   B. Ifosfamide
   C. Gemcitabine
   D. Dacarbazine

2. What is the reason that docetaxel and gemcitabine are often discontinued when treating patients with metastatic sarcoma?
   A. Toxicity
   B. Disease progression
   C. Availability of targeted agents
   D. High cost

3. Synovial sarcoma has been found to respond well to which chemotherapy agent(s)?
   A. Doxorubicin + dacarbazine
   B. Trabectedin
   C. Ridaforolimus
   D. High-dose ifosfamide

4. mTOR lies at the interface of which 2 signaling pathways?
   A. The retinoblastoma (RB) and p53 pathways
   B. The RAS and PI3K pathways
   C. The PI3K and LKB1 pathways
   D. The ErbB and Jak-STAT pathways

5. What is the active, well-tolerated dose of oral ridaforolimus, as determined in the phase 1 study by Mita et al?
   A. 18.75 mg/day
   B. 40 mg/day
   C. 75 mg/day
   D. 100 mg/day

6. Which type of sarcoma patients were enrolled into the SUCCEED trial?
   A. Patients with metastatic disease who had responded to chemotherapy
   B. Patients with limited metastatic disease and showing signs of progression
   C. Patients who had failed prior chemotherapy and showed progressive disease
   D. Patients who were intolerant of cytotoxic chemotherapy

7. What was the primary endpoint of the SUCCEED trial?
   A. Response rate
   B. Progression-free survival
   C. Overall survival
   D. Clinical benefit rate (complete response, partial response, or stable disease for 4 months or more)

8. According to the central review, what was the 3-month progression-free survival rate for ridaforolimus vs. placebo?
   A. 70% vs. 54%
   B. 34% vs. 23%
   C. 70% vs. 32%
   D. 54% vs. 32%

9. What was the most common adverse event attributed to ridaforolimus?
   A. Infections
   B. Fatigue
   C. Stomatitis
   D. Thrombocytopenia

10. Which drug may not be compatible with ridaforolimus?
    A. Imatinib
    B. Sunitinib
    C. Sorafenib
    D. Doxorubicin
Sarcoma: Targeting Treatment by Activating Pathways

POSTTEST

1 2 3 4 5 6 7 8 9 10

*Time spent on this activity: Hours ☐ Minutes ☐
(reading articles and completing the learning assessment and evaluation)

This information MUST be completed in order for the quiz to be scored.


PRINT OR TYPE

Last Name First Name Degree

Mailing Address

City State Zip Code

Date of Birth (used for tracking credits ONLY)

Phone Number Fax Number E-mail

Degree (please select one): ☐ MD ☐ PA ☐ DO ☐ NP ☐ Other _ Specialty (please select one):
☐ Primary Care ☐ Hematology ☐ Oncology

EVALUATION (must be completed for your CME Quiz to be scored)

Using the scale below, circle the number that corresponds with your opinion for each item.

1 = Poor 2 = Fair 3 = Good 4 = Very Good 5 = Excellent 6 = Does Not Apply

1. Rate the clinical usefulness of the publication to your daily practice. 
2. Rate the effectiveness of the teaching/learning methods.

Using the scale below, circle the number that corresponds with your opinion for each item.

1 = Strongly Agree 2 = Agree 3 = No Opinion 4 = Disagree 5 = Strongly Disagree 6 = Does Not Apply 7 = Already Do In Practice

3. The activity was presented objectively and was free of commercial bias. [Please use the "additional comments" field below to provide further information.]

Additional comments regarding bias:

4. Based on the information I learned during this activity, I feel more confident in treating patients within my practice.

5. Knowledge acquired from this activity will be utilized to improve outcomes in my patients.

6. Future activities concerning this subject matter are necessary.

CME ACTIVITY REQUEST

☐ Yes, I would like the opportunity to earn CME credits through activities sponsored by Vindico Medical Education.

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