Spindle cell sarcomas are part of a rare, heterogeneous family of connective tissue tumors. These tumors are primarily treated with surgery and have a high risk of recurrence and distant metastasis with elevated mortality rates. Other than the evidence for first-line therapy with doxorubicin in advanced soft tissue sarcoma, little evidence exists to point to an optimal second-line therapy. This is due to the diversity of soft tissue sarcomas, which encompass approximately 70 different histologic subtypes that can each respond differently to treatment. As such, newer strategies, including immunotherapy and targeted molecular drugs, are being developed.

Quiescent in most adult tissues, the Hedgehog signaling pathway, when inappropriately activated, has been implicated in the development of multiple types of cancers, including basal cell, breast, prostate, hepatocellular, pancreatic, and brain cancer. The Hedgehog signaling pathway is an important regulator of cell growth and differentiation in early development, but when inappropriately activated can lead to cell proliferation and increased angiogenic factors, decreased apoptosis, and breakdown of tight junctions promoting cancer growth and metastasis. Recent data reveal that the Hedgehog pathway plays a specific role in activation of satellite cells, proliferation of myoblasts, and differentiation of skeletal muscle. Activation of this embryonic pathway has been implicated in embryonal rhabdomyosarcoma, osteosarcoma, and chondrosarcoma.

This pathway has recently been recognized as a therapeutic target, with the development of vismodegib, a targeted Hedgehog pathway inhibitor. This novel agent is in active use for treatment of advanced basal cell carcinoma and is currently undergoing trials for various other malignancies. Recently, a phase 2a basket study, called MyPathway, evaluated the use of targeted therapies in 35 different advanced refractory solid tumors harboring specific molecular alterations. Out of 21 patients with mutations in the Hedgehog pathway, 3 had a partial response to vismodegib—one had an unknown primary tumor, another a squamous skin cancer, and the third a salivary gland cancer. Vismodegib (GDC-0449) was also evaluated in a phase 2 multicenter clinical trial in patients with progressive advanced chondrosarcoma. Although the study did not meet its primary endpoint, the proportion of patients with non-progressive disease was 25.6% at 6 months. Investigators observed that the benefit occurred in the subset of patients with overexpression of the Hedgehog ligand. Genomic studies for mutations in SMO and PTCH genes were available for only 28 and 26 patients, respectively, of the 45 patients enrolled on the trial. While there were no mutations identified, expression data revealed that overexpression of the Hedgehog ligand was present in 65% of cases tested (13 out of 20 patients). In patients with stable disease at 6 months, all had overexpression of the Hedgehog ligand. These studies point to the potential use of vismodegib in both bone and soft tissue sarcomas, and more specifical-
ly, to the importance of genomic testing in these cases.

**CASE PRESENTATION AND SUMMARY**

This report describes the novel use of vismodegib, an oral Hedgehog signaling pathway inhibitor, in the treatment of a patient with metastatic soft tissue sarcoma.

An 18-year-old female with no particular previous illnesses was initially diagnosed with superficial soft tissue sarcoma overlying the right hip in 2013. Due to the complexity of pathology, a second opinion was requested and revealed atypical cellular spindle and epithelioid cells, morphologically and immunohistochemically suggestive of spindle cell sarcoma, not otherwise specified. She underwent negative-margin resection in January 2014. Her course was complicated by two recurrences in the right inguinal lymph nodes in July 2014 and July 2015. She was treated with lymph node dissection in 2014, followed by numerous right lymph node dissections and adjuvant radiation in 2015.

A routine computerized tomography (CT) scan of the thorax-abdomen and pelvis in August 2016 revealed recurrence of disease, with multiple lung nodules as well as metastases in the retroperitoneum. She received 6 cycles of gemcitabine and docetaxel with stability of disease. The patient was then started on a PI3K inhibitor as part of a clinical trial, as genotypic analysis of the tumor revealed an activating mutation of the PI3K gene. The patient's course was complicated by acute obstructive renal failure requiring a double J stent for right-sided hydronephrosis. Repeat imaging revealed disease progression, and the patient was then switched to liposomal doxorubicin alone for 4 months and then in combination with olaratumab. She received the combined treatment for a total of 3 months, which was then stopped when she was found to have new peritoneal implants and worsening ascites. At this time, tissue was sent for FoundationOne® next generation sequencing (NGS)-based genomic testing, and the patient received one dose of nivolumab.

In January 2018, 2 days after receiving her first dose of nivolumab, the patient required admission for worsening abdominal pain secondary to progression of her disease (FIGURE 1). She was found to have acute kidney injury on top of chronic kidney disease due to hydropneumosis requiring a left-sided double J stent. She also had transaminitis resulting from a common bile duct stricture treated with a biliary stent and worsening ascites requiring regular paracentesis. This was all in the context of new or growing metastatic implants.

At this time, the result of the FoundationOne genomic testing revealed PTCH1 loss of exons 1-24 and CDKN2A/B loss. Mutation of tumor suppressor gene PTCH1 leads to Hedgehog pathway activation and therefore the patient was started on vismodegib on January 22, 2018. She was discharged from the hospital in stable condition a day later, on January 23.

The patient's clinical status subsequently improved, with significant reduction in her chronic abdominal pain and very minimal side effects. Clinically, the patient's acute kidney injury resolved (from a creatinine of 272 µmol/L at discharge to 85 µmol/L after a week of treatment) and her liver enzymes normalized (from an alkaline phosphatase of 301 U/L to 83 U/L, and alanine transaminase of 111 U/L to 38 U/L). CT scan of her chest...
and abdomen, which was performed 1 month post treatment, revealed stability of disease with absence of ascites (Figure 2). The patient continued to have a good response to treatment for 6 months, with no recurrence of pain or ascites.

Six months later, in July 2018, the patient developed increasing pain and a CT scan revealed worsening of abdominopelvic carcinomatosis. In this context, vismodegib was discontinued on July 17. In the next 5 months, she went on to receive carboplatin and paclitaxel, gemcitabine, and nivolumab consecutively with no response. She was admitted to hospital on December 30 for a pain crisis. She passed away on January 9, 2019, from fecal peritonitis.

**DISCUSSION**

To the best of our knowledge, this is the first patient with metastatic sarcoma to receive vismodegib, a Hedgehog signaling pathway inhibitor. She achieved an excellent clinical response with progression-free disease for approximately 6 months after starting treatment.

There is no current standard second-line treatment for metastatic soft tissue sarcoma. The choice of systemic therapy is histology-driven and therefore treatment is individualized for each patient. The future of oncology is heading towards an even more personalized approach with molecular profiling. Our case report highlights the relevance of genomic testing and targeted therapies, especially in cases of diverse clinical and biological disease behavior.

Molecular targeting is even more necessary in patients with advanced cancer who have failed multiple lines of treatment. As in our study, these patients can obtain a significant response with meaningful improvement in their quality of life. Future research is currently focusing on identifying new molecular targets in patients with advanced refractory cancers. Further studies will need to be done to determine whether these molecular targeting agents, such as vismodegib, lead to significant outcome changes in these patients.

**REFERENCES**