

PI3K/mTOR inhibitors may be effective against some uterine sarcomas

February 23 2017

The protein P-S6S240 may serve as an indicator of poor prognosis for patients with a hard-to-treat type of uterine sarcoma called leiomyosarcoma, and preclinical data suggest that patients whose tumors have this protein may respond to PI3K/mTOR inhibitors.

The study is published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research, by Frédéric Amant, MD, PhD, a professor at the Leuven Cancer Institute in Belgium and at the Netherlands Cancer Institute in Amsterdam.

Uterine sarcomas comprise about 2 to 5 percent of all uterine malignancies, and leiomyosarcomas account for 30 percent of all uterine sarcomas, according to the National Cancer Institute. Patients with localized disease have a 5-year survival rate of around 50 percent, which declines to 10 to 30 percent for those with metastatic disease, Amant said.

"We wanted to generate a clear view on the presence of targetable proteins in all subtypes of uterine sarcomas, with the aim of improving treatment options for these patients," Amant said.

His team also investigated whether any of the targetable proteins might be potential biomarkers for predicting clinical outcomes.

"Identifying biomarkers is crucial because novel treatments are expensive, underscoring the importance of patient selection," Amant

said.

Amant; Tine Cuppens, a doctoral student in Amant's laboratory; and colleagues studied five proteins of interest in 288 uterine sarcoma samples, which included 157 leiomyosarcomas, 52 benign uterine stromal tumors, and 41 normal uterine tissues; the rest were endometrial sarcomas, adenosarcomas, and other undifferentiated types of uterine sarcoma.

The researchers found that one of the proteins studied, the activated S6 ribosomal protein P-S6S240, was present more frequently in high-grade tumors (32 percent) than in low-grade tumors (9 percent). The presence of this protein was also associated with shorter progression-free survival and disease-specific survival in patients with leiomyosarcoma.

P-S6S240 plays a role in the PI3K/mTOR cell-signaling pathway, a cellular process that stimulates cancer growth, Amant explained.

The team implanted fresh human tumor fragments in mice and generated five leiomyosarcoma patient-derived xenograft (PDX) models. They then treated them with an investigational dual PI3K/mTOR inhibitor and observed tumor shrinkage in two models, a stable tumor in the third model and a decrease in tumor growth in the fourth. The PDX model that did not respond was negative for the activated S6 protein, while all responding models were positive for this protein, suggesting that the activated S6 protein can be a marker for response.

"This, along with our findings that uterine leiomyosarcoma patients with activated S6 [protein](#) relapse faster, suggests that P-S6S240 may serve as a prognostic marker," Amant said.

Earlier versions of mTOR inhibitors that targeted only one of the two active mTOR complexes only achieved mild responses but had

substantial toxicity in patients with uterine sarcomas, because of which they did not receive FDA approval for the treatment of sarcoma, Amant explained. "We used a new-generation dual PI3K/mTOR inhibitor [BEZ235; dactolisib] in our preclinical study and were mostly surprised by the efficacy. Such a strong treatment response is rarely seen in leiomyosarcomas," he added. Development of this class of drugs with an acceptable toxicity profile is important, he noted.

"Uterine sarcomas have generally been underexplored due to their rareness; nevertheless, they behave aggressively and are difficult to treat, resulting in a high clinical need," said Amant. "Leiomyosarcoma is a neglected field and we now have solid data offering a rationale for testing PI3K/mTOR inhibitors against this disease in clinical trials. Patient participation in such studies is also strongly hoped for," he noted.

A limitation of the study is that the xenografted mice lack an immune system, therefore, immune-related treatment responses or toxicities cannot be detected using such models, Amant said.

Provided by American Association for Cancer Research

Citation: PI3K/mTOR inhibitors may be effective against some uterine sarcomas (2017, February 23) retrieved 19 April 2024 from <https://medicalxpress.com/news/2017-02-pi3kmtor-inhibitors-effective-uterine-sarcomas.html>

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