Use of gastric acid suppressants may negatively impact survival outcomes in sarcoma patients treated with pazopanib

February 14 2019

In patients with soft tissue sarcoma, the concomitant use of gastric acid suppressant (GAS) therapy and the anticancer therapeutic pazopanib (Votrient) was associated with significantly reduced progression-free survival and overall survival, according to results published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

"Our results indicate that gastric acid suppressants reduce the efficacy of pazopanib in patients with advanced soft tissue sarcoma," said Olivier Mir, MD, Ph.D., MPH, medical oncologist and clinical pharmacologist at the Gustave Roussy Cancer Institute, University of Paris-Sud. "Oncologists and pharmacists should pay close attention to patients' concurrent medications, as they may have a significant impact on cancer treatment outcomes."

The use of GAS therapy is relatively prevalent; it is estimated that up to 50 percent of those undergoing cancer treatment utilize this therapy. Common GAS drugs include proton pump inhibitors, such as omeprazole (Prilosec) and esomeprazole magnesium (Nexium), or histamine H2-receptor blockers, such as ranitidine (Zantac). In many Western countries, these medications are available over the counter (OTC).

The absorption of pazopanib, a multi-kinase inhibitor used in the

treatment of renal cell carcinoma and soft tissue sarcoma, is pH-dependent, noted Mir. "We know that pazopanib tablets taken orally need to go into an acidic environment, namely the stomach, in order to dissolve," he explained. "As the primary function of GAS therapy is to reduce the acidity in the stomach, these drugs can reduce the absorption of pazopanib," Mir continued.

Previous work has shown that GAS therapy reduced the absorption of pazopanib as measured in plasma in patients with solid tumors, noted Mir. "We wanted to determine if the use of GAS drugs had an effect on survival outcomes in sarcoma patients taking pazopanib," he said.

Mir and colleagues analyzed data combined from two completed clinical trials; one phase II trial evaluated the tolerability and antitumor activity of pazopanib in patients with advanced soft tissue sarcoma, and one phase III trial evaluated the efficacy of pazopanib, versus placebo, in patients with advanced soft tissue sarcoma who received prior therapy. A total of 333 patients treated with pazopanib were eligible for analysis; of these, 117 (35.1 percent) received GAS drugs at least once during pazopanib treatment, 59 (17.7 percent) utilized GAS therapy concomitantly for more than 80 percent of pazopanib treatment duration, and 19 (5.7 percent) were already utilizing GAS drugs at the time of trial registration.

Following multivariable analysis, compared to patients who did not use GAS therapy during pazopanib treatment, those who concomitantly utilized GAS for at least 80 percent of treatment duration had significantly reduced progression-free survival (median of 4.6 months compared to 2.8 months, respectively).

Concomitant use of GAS also significantly reduced overall survival; those who utilized GAS therapy for at least 80 percent of treatment duration had shorter median overall survival (8 months) compared to

those who did not use GAS therapy (12.6 months).

Among the 110 placebo-treated patients from the phase III trial who were eligible for analysis, there were no associations between concomitant GAS use and progression-free survival or overall survival. "This suggests that the drug-drug interaction between GAS and pazopanib directly affected the survival outcomes of sarcoma patients," Mir said.

Mir and colleagues also found that GAS therapy did not reduce the frequency of pazopanib-related toxicities.

"I think that our results are practice-changing, and I would discourage oncologists against prescribing gastric acid suppressants when patients are treated with pazopanib, unless it is the only option for the patient," Mir said.

"Patients often utilize GAS therapy for abdominal pain, which is not always related to stomach acidity," said Mir. "I would predict that the majority of patients taking GAS drugs could utilize a different therapy to aid in their abdominal discomfort. Moreover, it is important for patients to inform their oncologists of all the medications that they are taking during cancer treatment (including those available OTC) so that potential drug-drug interactions can be identified and avoided."

Limitations of the study include a relatively small sample size and a lack of pharmacokinetic data, which are not routinely collected in late-phase trials.

More information: Olivier Mir et al. Impact of Concomitant Administration of Gastric Acid–Suppressive Agents and Pazopanib on Outcomes in Soft-Tissue Sarcoma Patients Treated within the EORTC 62043/62072 Trials, *Clinical Cancer Research* (2019). DOI:

Medical Xpress

10.1158/1078-0432.CCR-18-2748

Provided by American Association for Cancer Research

Citation: Use of gastric acid suppressants may negatively impact survival outcomes in sarcoma patients treated with pazopanib (2019, February 14) retrieved 24 April 2024 from https://medicalxpress.com/news/2019-02-gastric-acid-suppressants-negatively-impact.html

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