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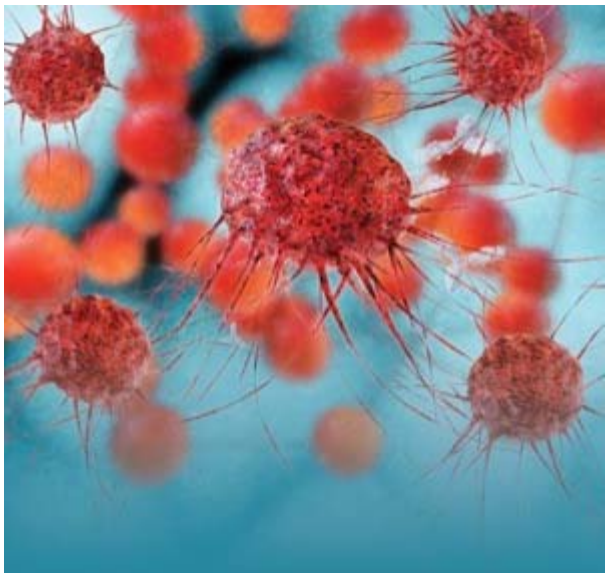
Methylnaltrexone for Opioid-Induced Constipation Might Also Improve Overall Survival in Advanced Cancer Patients



San Diego—Methylnaltrexone, a peripherally acting μ-opioid receptor (MOR) antagonist, may play a role in slowing tumor progression, new research has found. According to the study, methylnaltrexone influenced cancer progression and prolonged survival in patients with advanced cancer, suggesting that the MOR antagonist may be an important therapeutic target.

"Our data suggest that methylnaltrexone used in advanced cancer patients treated with opioids is associated with prolonged survival, particularly in those patients that respond with laxation," said Jonathan Moss, MD, PhD, professor of anesthesia and critical care at The University of Chicago Medicine. "While our findings are in patients with advanced malignancies, the hypothesis that μ-opioid antagonism may have a potential therapeutic value also extends to earlier tumors and to the perioperative period."

Interest in Methylnaltrexone Not New

As Dr. Moss reported at the 2015 annual meeting of the American Society of Anesthesiologists (abstract A4032), methylnaltrexone is FDA approved as palliative care for opioid-induced constipation (OIC) in patients with advanced illness who do not respond to conventional laxatives. Early on, however, researchers began to suspect that methylnaltrexone might also inhibit cancer growth.

"Based on laboratory studies we and others had done over the last decade, we hypothesized that peripheral antagonism of opioid-mediated side effects may attenuate disease progression in cancer patients," said Dr. Moss, who noted that methylnaltrexone does not affect centrally mediated analgesia.

For this study, Dr. Moss and his colleagues examined pooled data from two randomized, placebo-controlled registration trials of patients with advanced disease who were treated for OIC and analyzed those with cancer post hoc to identify whether methylnaltrexone, given at regular clinical doses, could affect survival during the trial period.

"Methylnaltrexone appears to provide relief for patients who have not been helped by conventional laxatives," said Dr. Moss, "and the drug is effective as a laxative in about two-thirds of these patients."

As Dr. Moss reported, patients treated with methylnaltrexone, administered subcutaneously (n=117), had a longer median overall survival (OS) than 112 patients treated with placebo (76 vs. 56 days; P=0.033). Patients who responded to methylnaltrexone (n=72) also had a longer median OS than patients (n=45) who did not respond (118 vs. 58 days; P=0.001).

In addition, survival in cancer patients adjusted for crossover from placebo to methylnaltrexone showed similar positive results. Patients treated with methylnaltrexone (n=117) had a longer median OS than patients treated with placebo (n=56) without subsequent crossover to methylnaltrexone (76 vs. 26 days; P<0.001). Patients who crossed over to methylnaltrexone (n=56) had a longer median OS than patients treated with placebo (n=56) who did not cross over (75 vs. 26 days; P<0.001).

In patients with advanced illness other than cancer, however, researchers found no difference in OS between

methylnaltrexone and placebo (n=134).

Although the mechanism of action remains #ff0000 in this post hoc analysis, Dr. Moss indicated that attenuation of opioid-mediated MOR signaling may be a plausible explanation. “These are the first human data and are consistent with our animal and cellular studies showing that the MOR pathway influences tumor growth and metastasis. We had thought the improved survival might in part be related to improved GI function, but the fact that patients with other forms of advanced illness did not show extended survival makes it much less likely as an explanation.

“A clinical trial that will randomize patients with selected advanced cancer to standard systemic therapy with or without methylnaltrexone is merited,” said Dr. Moss, who also noted that these findings should not change clinical practice.

“Our studies are limited to opioid antagonists. Patients should continue using opioids if they need them,” he concluded.

Focus on Pancreatic Cancer

The moderator of the session, Magdalena Anitescu, MD, PhD, associate professor of anesthesia and critical care at The University of Chicago Medicine, noted, “Gastrointestinal cancer, especially pancreatic cancer, has been associated with significant pain that debilitates patients and decreases their quality of life. Pain in severe and advanced pancreatic cancer is treated with high doses of opioids an d all are associated with significant side effects.

“Methylnaltrexone, initially thought to improve only constipation as a significant side effect of opioids, has been recently found to improve survival in patients with advanced pancreatic cancer,” she said. “This is a very important finding that might benefit a significant number of patients in this situation and might change the model of how pancreatic cancer is currently treated.”

—Chase Doyle

The original clinical trials were funded by Salix, now owned by Valeant Pharmaceuticals. Dr. Moss is a consultant for Valeant. Dr. Anitescu reported no relevant financial disclosures.