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Drug for digestive problem can extend survival for many advanced cancer patients

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Patients with advanced cancers who took a drug designed to relieve constipation caused by pain killers lived longer and had fewer reports of tumor progression than cancer patients who did not receive the drug, according to results presented Oct. 27 at the 2015 meeting of the American Society of Anesthesiologists in San Diego. This is the first study in humans to associate opioid blockade with improved survival.

The finding suggests that the drug—methylnaltrexone, approved for use by the United States Food and Drug Administration in 2008 to treat opioid-induced constipation—could play a role in cancer therapy.

"Early on, we began to suspect that methylnaltrexone might inhibit cancer growth" said Jonathan Moss, MD, PhD, lead author of the study and professor of anesthesia and critical care at the University of Chicago. "After more than a decade in the lab trying to assess how methylnaltrexone affects cancer, we have the first evidence that it can decrease tumor growth and extend survival in patients who respond to the drug."

The study, a retrospective survival analysis, included 229 patients who participated in two randomized, controlled clinical trials focused on relief of constipation for patients receiving palliative care for various types of late-stage cancer and other terminal diseases. None of the patients enrolled responded to conventional laxatives.

In these two trials, 117 cancer patients received methylnaltrexone

(marketed as Relistor) for opioid-induced constipation, while 112 were given a placebo. Fifty-seven percent of the patients who received methylnaltrexone experienced relief from constipation; 43 percent did not.

Those who received and responded to methylnaltrexone lived, on average, twice as long (118 days versus 58 days) as those who did not respond or were given the placebo. Patients who responded to methylnaltrexone also had significantly fewer reports of tumor progression (7.6 percent) compared to those who did not respond (22 percent) or who took the placebo (25.4 percent), based on physician reports of adverse events.

The researchers also analyzed the effects of methylnaltrexone on another 135 patients from the same trials who had advanced illnesses other than cancer, such as congestive heart failure, advanced chronic obstructive pulmonary disease or neurologic diseases. Methylnaltrexone relieved constipation for more than half of the patients, but brought no additional survival, even for those who responded to the drug's digestive effects.

"This makes it far less likely that improved bowel function is the only explanation for our finding of improved survival in cancer patients," said study co-author Filip Janku, MD, PhD, assistant professor of investigational cancer therapeutics at the University of Texas MD Anderson Cancer Center in Houston.

"We are not precisely sure why methylnaltrexone was associated with fewer reports of tumor progression and longer survival in our patients," Janku said. "Proving what causes this response is very difficult. But it could be that methylnaltrexone influences several side effects of opioids unrelated to pain relief. The findings are consistent with what we saw in the lab."

Methylnaltrexone was invented in 1979 by the late University of Chicago pharmacologist Leon Goldberg. Struck by the suffering of a friend with cancer who complained more about his morphine-induced constipation than his cancer-related pain, Goldberg tested derivatives of naltrexone, an established morphine-blocking drug.

He developed a version of naltrexone that could not cross the protective barrier that surrounds and protects the brain. So it blocked morphine's effects on the bowels, where it caused painful constipation, but it did not interfere with morphine's beneficial effect on pain, centered in the brain. Nearly three decades later it won FDA approval. Since then more than 800,000 patients have received the drug.

Meanwhile, suspicion emerged that opioids such as morphine could encourage cancer growth. In 2002, Moss and colleagues began to notice that some cancer patients in early studies of methylnaltrexone lived longer than expected.

"These were patients with advanced cancer and a life expectancy of one to two months yet several lived for another five or six months," Moss said. "It made us wonder: could there possibly be a direct effect on the tumors?"

Moss and colleague Patrick Singleton, PhD, assistant professor of medicine at the University of Chicago, subsequently found that cells from various human cancers have far more opioid receptors than non-cancerous cells. In the laboratory they showed how morphine can increase proliferation, migration and invasion of tumor cells.

"We also found that methylnaltrexone reduced tumor growth and spread in several cancer models," Singleton said. "Some of our findings with methylnaltrexone occurred without opioids, suggesting that the opioid receptor and its pathway may be a therapeutic target for cancer

treatment."

"Animal models, however, do not always translate to humans," he added. "It is exciting to see new human clinical data that is consistent with what we saw in the laboratory."

"Whether our findings in advanced cancers can be extended to the treatment of earlier cancers, or whether the medication can help physician anesthesiologists improve care during cancer surgery (where opioids are often given) will need to be tested directly," Moss said.

"This study raises novel questions about the role of the opiate receptor in cancer progression," said Ralph Weichselbaum, MD, chairman of radiation oncology and co-director of the Ludwig Center for Metastasis Research at the University of Chicago. "Could the opiate receptor become a therapeutic target? What are the significant side effects of opiates in cancer care? This is an important, hypothesis-generating result."

Provided by University of Chicago Medical Center