Longer survival of cancer patients given methylnaltrexone suggests role for mu opiate receptor in cancer progression

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A study of advanced cancer patients published in the journal *Annals of Oncology* and presented at this year's World Congress of Anaesthesiologists in Hong Kong suggests that opioid painkillers and their receptor in cells - the mu opiate receptor - could be involved in cancer progression, and could thus be a target for treatments. The study is by Dr Filip Janku, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, Dr Jonathan Moss, University of Chicago, IL, USA and colleagues.

Methylnaltrexone (MNTX) is approved in the USA and more than 50 other countries for treatment of opioid induced constipation (OIC). MNTX works by binding to the mu opioid receptor (MOR) in periphery, thereby blocking opioid drugs from binding to that same receptor. It does not cross into the brain, preserving centrally mediated pain relief while reversing the constipation caused by peripheral MORs in the gut. By acting in this way, MNTX is termed a 'peripherally acting mu opioid receptor antagonist'.

In this study, the authors pooled data from two placebo controlled randomised clinical trials of MNTX given by subcutaneous injection. In these trials, 229 patients with advanced cancer, treated with opioids for pain relief, and suffering OIC despite laxative treatment were randomised to MNTX or placebo. These patients were analyzed for overall survival (OS) in an unplanned post-trial analysis called a 'post-hoc' analysis. MNTX or placebo were given subcutaneously during the double blind phase of these studies, which was followed by an open label phase in which around half of patients originally on placebo switched to MNTX treatment.

Treatment with MNTX resulted in median OS of 76 days compared to 56 days in those given placebo (statistically significant); when looking specifically at responders to MNTX treatment (those able to defecate after treatment), these survived a median of 118 days compared to 55 days for non-responders (also statistically significant).

The authors say that the direct effect of MNTX on cancer progression is the most likely reason for increased survival, because neither treatment nor response to MNTX led to longer survival in 134 seriously ill non-cancer patients enrolled in the same trials. If the drug showed an overall survival benefit largely due to its effects on the gastrointestinal system, then then all patients would expected to benefit, not just the cancer patients.

They add: "Our results show that treatment with MNTX, and even more so response to MNTX are associated with increased overall survival in advanced cancer patients, which supports our earlier preclinical hypothesis that the mu receptor can play a role in cancer progression. Targeting this receptor with MNTX warrants further investigation in cancer therapy." This human study is consistent with more than a decade of molecular, cellular and animal studies by Dr Moss' team at the University of Chicago and other teams elsewhere.

The authors say: "To our knowledge this is the first human demonstration of improved OS for cancer patients following treatment with peripheral opioid antagonists...our data suggest that MNTX treatment in advanced cancer patients can prolong survival, plausibly through reduction of opioid induced mu receptor signaling."

However they conclude: "Our findings should be interpreted as preliminary, hypothesis generating, and not enough at this stage to suggest changes to clinical practice, where pain control remains an important issue. Prospective studies to confirm the

role of MNTX in advanced cancer patients are warranted to confirm clinical relevance of our findings."

In a linked comment published with the article, Professor Stein Kassa, Professor Per Sjørgen and Professor Stein Kassa, Norwegian University of Science and Technology, Trondheim, and Cancer Clinic, Trondheim University Hospital, Norway, say: "There is a pronounced need for investigating mu receptor mediated opioid effects on tumour biology and disease stages as well as effects of opioid type, dose and exposure in different settings."

More information: F. Janku et al. Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer, *Annals of Oncology* (2016). DOI: 10.1093/annonc/mdw317

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