Pancreatic cancer: Researchers find drug that reverses resistance to chemotherapy

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For the first time researchers have shown that by inhibiting the action of an enzyme called TAK-1, it is possible to make pancreatic cancer cells sensitive to chemotherapy, opening the way for the development of a new drug to treat the disease.

Dr Davide Melisi told Europe's largest cancer congress, ECCO 15 - ESMO 34, in Berlin today (Thursday 24 September) that resistance to chemotherapy was the greatest challenge to treating pancreatic cancer.

"Pancreatic cancer is an incurable malignancy, resistant to every anti-cancer treatment. Targeting TAK-1 could be a strategy to revert this resistance, increasing the efficacy of chemotherapy," said Dr Melisi, who until the start of September was a Fellow at the M.D. Anderson Center in Houston (Texas, USA); he has now moved to a staff position at the National Cancer Institute in Naples (Italy). "During the past few years we have been studying the role played by a cytokine or regulatory protein called Transforming Growth Factor beta (TGFbeta) in the development of pancreatic cancer. Recently we focused our attention on a unique enzyme activated by TGFbeta, TAK-1, as a mediator for this extreme drug resistance."

Dr Melisi and his colleagues investigated the expression of TAK-1 (TGFbeta-Activated Kinase-1) in pancreatic cell lines and developed a drug that was capable of inhibiting TAK-1. They tested the activity of the TAK-1 inhibitor on its own and in combination with the anti-cancer drugs gemcitabine, oxaliplatin and SN-38 (a metabolite of the anti-cancer drug irinotecan) in cell lines, and the activity of the TAK-1 inhibitor combined with gemcitabine against pancreatic cancer in mice.

"The use of this TAK-1 inhibitor increased the sensitivity of pancreatic cells to all three chemotherapeutic drugs. By combining it with classic anti-cancer drugs, we were able to use doses of drugs up to 70 times lower in comparison with the control to kill the same number of cancer cells. In mice, we were able to reduce significantly the tumour volume, to prolong the mice survival, and to reduce the toxicity by combining the TAK-1 inhibitor with very low doses of a classic chemotherapeutic drug, gemcitabine, that would have been ineffective otherwise," said Dr Melisi.

The use of gemcitabine on its own against the cancer in mice was ineffective because of the drug resistant nature of the disease. However, once it was combined with the TAK-1 inhibitor, Dr Melisi and his colleagues saw a 78% reduction in tumour volumes. "The median average survival for the control, TAK-1 inhibitor, gemcitabine on its own, or TAK-1 inhibitor combined with gemcitabine was 68, 87, 82 and 122 days respectively," he said.

"This is the first time that TAK-1 has been indicated as a relevant target for the treatment of a solid tumour and that it is a valid approach to reverting the intrinsic drug resistance of pancreatic cancer. The TAK-1 inhibitor used in this study is an exciting drug that warrants further development for the treatment of pancreatic cancer. In the near future, we will study whether it is also able to make other chemotherapeutic agents, such as oxaliplatin, 5-FU or irinotecan, work against pancreatic cancer in mice.

"Our main goal is to translate this combination approach from the bench to the bedside, conducting a clinical trial that could demonstrate the safety of this TAK-1 inhibitor in combination with gemcitabine, and its efficacy, in pancreatic cancer patients."

Source: ECCO-the European CanCer Organisation