New cancer drug sabotages tumour's escape route

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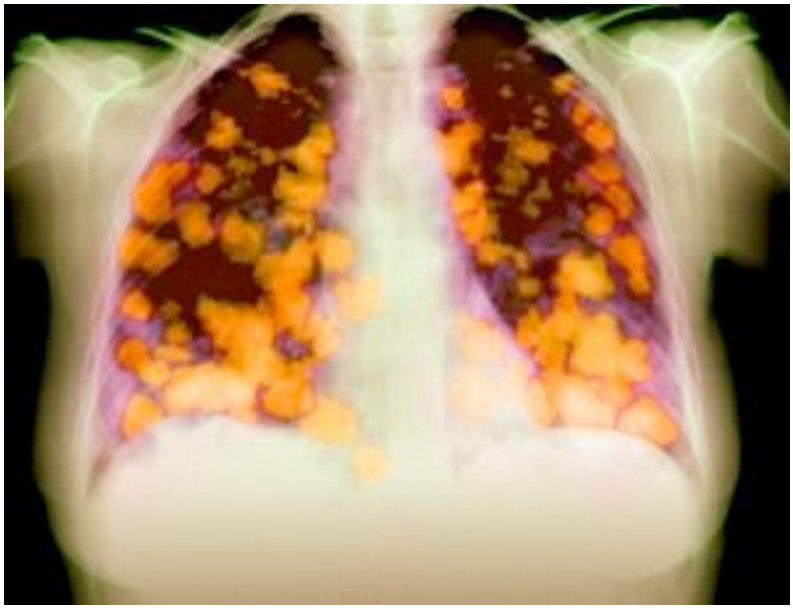

Some untreatable cancers could soon be held in check by an experimental drug that targets not only the tumour itself, but also how it evolves to spread through the body.

The new drug, Cabozantinib, or cabo for short, simultaneously neutralises two mechanisms cancers need to survive. First, it chokes each tumour's blood supply by blocking a molecule on the surface of its blood vessels, called vascular endothelial growth factor receptor (VEGFR). There is evidence in animals that cancers can respond to this kind of attack by invading new tissues, where they may be able to generate secondary tumours. Importantly, cabo foils this strategy by blocking a second receptor called c-MET that would otherwise help cancer cells spread to new tissue.

Tumours confined

To test whether the drug works in practice, Donald McDonald of the University of California at San Francisco and colleagues bred mice to develop tumours, or inoculated them with human cancers. After 14 weeks, the mice were given daily doses of cabo. All the treated mice survived to the age of 20 weeks, when the experiment ended. None of the mice that received a placebo survived that long.

"The absence of metastasis, confinement of the tumour to a smooth and compact cell mass and survival beyond 20 weeks has to my knowledge never been observed before in this mouse model of cancer," says Holger Gerhardt, who studies tumour blood vessel growth at Cancer Research UK in London.

The broader implication of McDonald's research is that existing drugs which cut the blood

supply to tumours could be improved by giving patients a second drug that blocks the c-MET receptor as well.

It may be that choking off the cancer's blood supply makes them more aggressive and more likely to spread. If so, giving a c-MET blocker as well might make treatment more successful.

Philippe Bishop at Genentech in San Francisco says that Avastin – one of the current drugs that blocks blood supply – is already being tested in combination with onartuzumab, an antibody that blocks signalling by c-MET.

"An Avastin and onartuzumab combination is being studied in trials for advanced triple-negative breast cancer, metastatic colorectal cancer and advanced non-squamous non-small cell lung cancer," he says.

Pain relief

Whether combining existing drugs with c-MET blockers works or not, cabo seems to be steaming ahead. Some 108 men with prostate cancer that had spread to their bones recently completed a three month course of cabo treatment. In 82 of them the cancerous lumps on their bone either shrank or vanished completely. The tumours grew in just three of them. "It was a stunning effect," says Dana Aftab of Exelixis, the company in South San Francisco that is developing Cabo.

Two-thirds of the men who received the drug also said that their pain receded. Some of them stopped taking morphine. Three-quarters of the men also saw their primary cancers shrink.

Howard Scher at the Memorial Sloan Kettering Cancer Center in New York says that two larger trials are now under way. The aim of one trial involving 246 patients will be to reduce pain; the other, with 960 patients, will attempt to prolong survival.

Cabo has also performed well against a type of kidney cancer, and a variant of thyroid cancer for which there are few treatment options.

Patrick Schoffski at the Catholic University of Leuven (KUL) in Belgium, who has been involved in some of the cabo trials, says that the results have been unexpectedly promising. Normally, new drugs do not work when tried against different tumour types. "Nine out of 10 tumour types typically get ruled out within a year," says Schoffski. The opposite happened with cabo, which generated promising responses in 12 out of 13 cancers tested.

As a result trial protocols had to be amended for cabo because it wasn't ethical to withhold the drug from people who had benefited. "I'm not aware of this happening before in oncology," says Schoffski.

Cautious future

Despite the progress, the company is keen to play down its potential. "We've always been very careful not to over-promise on anything," says Aftab. Likewise, Exelixis's chief medical officer, Gisela Schwab, warns that cabo only slows the cancer. "They are not cured, but their disease is being controlled," she says.

There is also the possibility that cancers will evolve yet another way to overcome cabo's double

punch. For now, its benefits are causing quite a stir in the cancer community. "The details unravelled [so far] are truly impressive," says Gerhardt.

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