Experimental cancer drug resurfaces

Small clinical trial yields promising results for controversial molecule.

Heidi Ledford

A compound shown to shrink tumours in rats by correcting metabolic oddities found in cancer cells has now been tested in five patients with brain cancer.

The results, published today in *Science Translational Medicine*\(^1\), provide clues as to how the drug, a small molecule called dichloroacetate (DCA), works. But it is too soon to say whether it will provide an effective treatment against cancer in humans, says lead author Evangelos Michelakis, a cardiologist at the University of Alberta in Edmonton.

DCA has had a stormy history. In 2007, Michelakis and his colleagues reported that feeding the chemical to rats slowed the growth of tumours without any apparent side effects. They suggested that it might work by stimulating glucose metabolism in energy-producing cellular structures called mitochondria\(^2\).

Many cancer cells produce energy differently from normal cells, shifting glucose metabolism from the mitochondria to the cytoplasm. This shift, Michelakis says, might also make the cancer cells resistant to programmed cell death signals that are controlled by the mitochondria. If so, reactivating glucose metabolism in the mitochondria could render the cells sensitive to those suicide cues, leading to cancer cell death and a reduction in tumour growth.

DCA was a particularly compelling drug candidate: known to inhibit the mitochondrial enzyme pyruvate dehydrogenase, it had been used for decades in the treatment of people with inherited mitochondrial disorders, and showed low toxicity. The compound, wrote the authors, could be "rapidly translated" into late stage clinical trials for cancer therapy\(^2\). Unfortunately, because DCA was already in the public domain it was not patentable, meaning that pharmaceutical companies were unlikely to invest the millions of dollars required to conduct large clinical
In search of a miracle

The story made headlines, and DCA was trumpeted as a possible cancer cure. The news resulted in some people with cancer buying DCA independently and designing their own courses of treatment (see Cancer patients opt for unapproved drug). But the US Food and Drug Administration eventually started to shut down Internet DCA suppliers.

"There was a huge frenzy," says Leonard Lichtenfeld, deputy chief medical officer for the American Cancer Society in Atlanta, Georgia. In a February 2007 blog post titled DCA: Cancer Breakthrough or Urban Legend?, the oncologist expressed concern about the impact of the hype on cancer patients. "For some of you out there to inappropriately make [patients] feel that DCA is the answer to their prayers based on this single early stage report in a medical research journal is, in my opinion, not acceptable at best and despicable at worst," Lichtenfeld wrote.

Since then, Lichtenfeld says, he has learned more about the link between altered metabolism and cancer cells, and says that the approach warrants further investigation. But, he says that the recent research on the drug may be blown out of proportion again. "I find this very intriguing, but the clinical information — I'm not sure what to make out of it," he says. "These are only five patients, treated in different ways at different stages of their disease."

Follow-up

To conduct the latest study1, Michelakis and his colleagues cobbled together funds from individual donations - he says they have collected hundreds of thousands of dollars - and philanthropies, as well as the Canadian Institutes of Health Research. Some local hospitals also provided services for free or at reduced cost to the researchers.

The team studied tumour samples from 49 patients with glioblastoma — a particularly aggressive and common form of brain cancer in humans — and found that all of them had altered mitochondrial function that could be reversed by DCA.

They then treated five glioblastoma patients with DCA for up to 15 months, and tumour tissue was compared before and after DCA treatment in three of the patients. In all three, there were signs that the tumour growth had slowed, and more cancer cells were undergoing programmed cell death after the treatment with DCA.

The results are preliminary, but may be enough to get the attention of pharmaceutical companies, says Lewis Cantley, a cancer researcher at the Harvard Medical School in Massachusetts. "It's very difficult with such a small number of patients to conclude what's going on, but it's certainly encouraging," he says.

Although the companies may not be interested in pursuing DCA itself, they could search for better, more-selective drugs that target the same pathway. Two years ago, Cantley co-founded Agios Pharmaceuticals, a Cambridge, Massachusetts-based company that focuses on cancer metabolism, and says that large pharmaceutical companies have also taken an interest in cancer metabolism, fuelled by recent discoveries that several cancer-promoting genes affect these basic
In the interim, Michelakis remains opposed to self-medication of cancer patients with DCA, given how little is known about the effects of the drug and how it may interact with other medications: "If there is even a little bit of hope, should we be providing it to people? No, because there is a chance you might hurt them and make them even worse."

- References


- Cheap, 'safe' drug kills most cancers

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  New Scientist has received an unprecedented amount of interest in this story from readers. If you would like up-to-date information on any plans for clinical trials of DCA in patients with cancer, or would like to donate towards a fund for such trials, please visit the site set up by the University of Alberta and the Alberta Cancer Board. We will also follow events closely and will report any progress as it happens.

  It sounds almost too good to be true: a cheap and simple drug that kills almost all cancers by switching off their "immortality". The drug, dichloroacetate (DCA), has already been used for years to treat rare metabolic disorders and so is known to be relatively safe.

  It also has no patent, meaning it could be manufactured for a fraction of the cost of newly developed drugs.

  Evangelos Michelakis of the University of Alberta in Edmonton, Canada, and his colleagues tested DCA on human cells cultured outside the body and found that it killed lung, breast and brain cancer cells, but not healthy cells. Tumours in rats deliberately infected with human cancer also shrank drastically when they were fed DCA-laced water for several weeks.

  DCA attacks a unique feature of cancer cells: the fact that they make their energy throughout the main body of the cell, rather than in distinct organelles called mitochondria. This process, called glycolysis, is inefficient and uses up vast amounts of sugar.

  Until now it had been assumed that cancer cells used glycolysis because their mitochondria were irreparably damaged. However, Michelakis's experiments prove this is not the case, because DCA reawakened the mitochondria in cancer cells. The cells then withered and died (Cancer Cell, DOI: 10.1016/j.ccr.2006.10.020).

  Michelakis suggests that the switch to glycolysis as an energy source occurs when cells in the middle of an abnormal but benign lump don't get enough oxygen for their mitochondria to work properly (see diagram). In order to survive, they switch off their mitochondria and start producing energy through glycolysis.

  Crucially, though, mitochondria do another job in cells: they activate apoptosis, the process by which abnormal cells self-destruct. When cells switch mitochondria off, they
become "immortal", outliving other cells in the tumour and so becoming dominant. Once reawakened by DCA, mitochondria reactivate apoptosis and order the abnormal cells to die.

- "The results are intriguing because they point to a critical role that mitochondria play:
  - they impart a unique trait to cancer cells that can be exploited for cancer therapy," says Dario Altieri, director of the University of Massachusetts Cancer Center in Worcester.
  - The phenomenon might also explain how secondary cancers form. Glycolysis generates lactic acid, which can break down the collagen matrix holding cells together. This means abnormal cells can be released and float to other parts of the body, where they seed new tumours.
  - DCA can cause pain, numbness and gait disturbances in some patients, but this may be a price worth paying if it turns out to be effective against all cancers. The next step is to run clinical trials of DCA in people with cancer. These may have to be funded by charities, universities and governments: pharmaceutical companies are unlikely to pay because they can't make money on unpatented medicines. The pay-off is that if DCA does work, it will be easy to manufacture and dirt cheap.
  - Paul Clarke, a cancer cell biologist at the University of Dundee in the UK, says the findings challenge the current assumption that mutations, not metabolism, spark off cancers. "The question is: which comes first?" he says.

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