

Adverse effects from cancer drug trials explained

July 24 2020, by Nancy Bazilchuk



Some drug combinations used to combat cancer can actually be harmful. New research has identified a type of drug that can be problematic in treating cancer if combined with other drugs. Credit: Colourbox

A team of researchers investigating how a certain type of drugs can kill

cells has discovered that these drugs can do more harm than good when used in combination with other cancer treatments.

The researchers wanted to know more about how the drugs, which are called pan-Bcl-2 or Bcl-xL-specific inhibitors, help encourage [cell death](#), specifically cells that have damaged RNA, DNA or proteins.

They had a hunch that chemical and physical factors that damage the DNA, RNA or proteins of otherwise healthy cells—such as [cancer](#) treatments like radiation—might also predispose formerly healthy cells to die if they were exposed to the pan-Bcl-2 or Bcl-xL-specific inhibitor drugs. A number of cancer treatments use combinations of drugs and other treatments to try to combat cancers that have become resistant to single [drug](#) treatments.

It turns out that their hunch was correct.

Explains clinical trial problems

"Our study explains why clinical trials with 31 drug combinations with Bcl-2 inhibitors have been terminated, withdrawn or suspended," said Denis E. Kainov, the senior author of the new study, which has been published in MDPI Cancers.

Kainov specifically identified trials with the pan-Bcl-2 drug navitoclax plus bendamustine and rituximab in patients with relapsed diffuse large B cell lymphoma, and navitoclax plus [abiraterone acetate](#) with or without hydroxychloroquine in patients with progressive metastatic castrate refractory prostate cancer (NCT02471391, NCT01423539).

"We think that clinicians and patients should be aware of adverse effects of certain drugs like navitoclax," said Aleksandr Ianevski, the first author of the study. "This information has the potential to save lives and

improve care of cancer patients."

Tested in roundworms, cells

The researchers tested their idea by exposing healthy small roundworms (*C. elegans*) to a DNA-damaging substance plus a Bcl-xL specific inhibitor.

The roundworms that were treated with the two substances died faster than those that had been given only one or no substances. They also found reproductive and developmental defects in the roundworms given the combination treatment.

They also tested the toxicity of the combined treatment on healthy, non-malignant human, monkey and dog cells, and found that the treatment killed all the cells. A similar test on [malignant cells](#) also showed that the combined treatment would kill these cells, too. But since the goal of a successful [cancer treatment](#) is to kill the cancer cells while leaving healthy cells alone, the combination doesn't meet that goal.

Viral infections could be a problem

When cells are infected by a virus, the virus inserts its own RNA or DNA into the cell and turns the cell into a virus-making factory.

The pan-Bcl-2 or Bcl-xL-specific inhibitors can cause these infected [cells](#) to die.

Kainov said that the pan-Bcl-2 or Bcl-xL-specific inhibitors could have adverse effects because cancer patients could be infected with different viruses (such as herpes, coronavirus or influenza).

More information: Aleksandr Ianevski et al. Chemical, Physical and Biological Triggers of Evolutionary Conserved Bcl-xL-Mediated Apoptosis, *Cancers* (2020). [DOI: 10.3390/cancers12061694](https://doi.org/10.3390/cancers12061694)

Provided by Norwegian University of Science and Technology

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