High-dose vitamin C proves safe and well-tolerated in brain and lung cancer trials

Study identifies flaws in cancer cell metabolism that make high-dose vitamin C toxic to tumor cells

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Evidence is growing that adding high-dose, intravenous vitamin C in combination with standard chemotherapy and radiation treatment is a safe, relatively inexpensive approach that may improve outcomes for patients with a wide range of cancers.

In a new study published online March 30 in the journal *Cancer Cell*, researchers with Holden Comprehensive Cancer Center at the University of Iowa report promising results from a phase 1 clinical trial testing high-dose vitamin C therapy in patients with the brain cancer glioblastoma multiforme (GBM) and preliminary findings from a phase 2 trial in stage 4 non-small cell lung cancer (NSCLC).

“These two diseases really haven’t had a significant improvement in outcomes for two or three decades,” says Bryan Allen, UI assistant professor of radiation oncology and an author on the study. “This is a well-tolerated, very cost-effective treatment, and it may significantly improve patient outcomes. This could potentially change the landscape of how these diseases are treated, especially across the world, where finances can be limited for these types of cancer treatments.”

The revival of vitamin C as a cancer treatment has been pioneered over the last four decades by UI physicians and scientists and is based on laboratory studies showing that, at very high concentrations, vitamin C kills cancer cells but is harmless to healthy cells. It is not possible to achieve these high levels by simply consuming vitamin C because the body’s metabolism

strictly limits the amount of the vitamin that enters the bloodstream. Delivering vitamin C intravenously bypasses this metabolic checkpoint and leads to vitamin C levels in patients' blood that are comparable to the cancer cell–killing levels in the lab experiments. In the clinical trials, each infusion aims to raise the concentration of vitamin C in a patient's blood to 20,000 micromolar. The normal blood level for vitamin C in a healthy adult is about 70 micromolar.

The new study also reveals how flaws in cancer cell metabolism make high-dose vitamin C toxic to cancer cells.

Using animal and cell-based experiments in collaboration with Allen, Douglas Spitz and Garry Buettner, professors of radiation oncology and members of the Free Radical and Radiation Biology Program at the UI, led the team's efforts to investigate the underlying mechanisms of vitamin C's cancer cell–killing effects. The findings indicate that a glitch in cancer cell metabolism disrupts iron levels in the tumor cells. The excess free iron further reacts with the high levels of vitamin C, generating hydrogen peroxide and other free radicals (reactive oxygen molecules) that can damage DNA, causing cell death directly or making the tumor cells more sensitive to damage from radiation and chemotherapy. This toxic effect is not seen in healthy cells where normal metabolism keeps the levels of hydrogen peroxide and free iron under control.

"As we learn how ascorbate (vitamin C) might work (to sensitize cancer cells), we can choose to test it in cancers where we might make a difference in survival, but also choose cancers with standard treatment regimens that will synergize with the vitamin C biochemistry," Buettner says.

Spitz notes that the team's translational research constantly reveals surprising and exciting new facets of vitamin C's potential. In the case of the GBM trial, for example, the addition of vitamin C to standard treatment seemed particularly effective in a subgroup of patients with a genetic biomarker who typically benefit less from standard treatment than patients without the biomarker.

The results from the UI team's phase 1 GBM trial and phase 2 NSCLC trial show it is possible to safely achieve very high blood levels of vitamin C in patients. There were no serious side effects for patients. The ones that did occur were modest and included increased urination, dry mouth, and, occasionally, a temporary increase in blood pressure that subsided after infusion.

The patients in the phase 1 GBM trial received three infusions of vitamin C each week for approximately two months while receiving standard of care radiation and chemotherapy, followed by two infusions per week for approximately seven months while receiving chemotherapy.

Although this small, early stage trial was not designed to prove effectiveness, the data analyzed from 11 patients showed an increase in overall survival of 4 to 6 months (18–22 months) versus the 14–16 months survival typically seen with the standard treatment.

The results were promising enough that phase 2 clinical trials are planned, which will specifically test if adding high-dose intravenous vitamin C to standard cancer therapy improves overall survival and quality of life for patients with GBM and patients with locally advanced lung cancer.

If the therapy proves successful, it has the added advantage of being relatively inexpensive. The infusions of vitamin C used through the nine months of treatment of the GBM trial would add approximately $8,000 to the cost of the treatment. This cost is less than a single dose of some chemotherapy drugs or some of the newest immunotherapy treatments.

In addition to Allen, Spitz, and Buettner, the core research team included Joseph Cullen, UI professor of surgery, as well as John Buatti, UI professor and head of radiation oncology, and first author Joshua Schoenfeld, an MD/PhD student in the UI Carver College of Medicine working jointly in both Allen's and Spitz's labs. The research team also included 29 other UI faculty and staff collaborators involved in the execution of various aspects of the basic and clinical studies. Co-author Dennis Riley is the Chief Scientific Officer of Galera Therapeutics, Inc., which supplied some materials for use in the basic science studies.

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