Vitamin C and Cancer: Clarification of a Recent News Brief

Jorge R Miranda-Massari, PharmD[a,*]
Inés Alfaro, MD[b]

DOI 10.14200/jrm.2019.0115

INTRODUCTION

A news brief circulated by the EFE News Media Company in July 2019 claimed that scientists from Chile had found that vitamin C immortalizes cancer cells. This study was carried out by a group of highly qualified scientists[1] and published in a reputable scientific journal. The news agency, however, reported the study in a way that did not capture its main findings, and the story confused the general public and even medical professionals. It is important to clarify that this was an *in vitro* study, and the study did not actually find that cancer cells become immortal with vitamin C. In addition, this study did not contradict thousands of published studies that explain the many biological mechanisms and beneficial effects of vitamin C use in cancer. The purpose of the present article is to clarify the EFE news report and put into perspective the bigger picture of the findings in this study.

Cancer is one of the leading causes of death globally. The World Health Organization, in its press release 263 published in September 2018, cites findings of recent studies based on world cancer statistics of the International Agency for Research on Cancer. These findings indicate an increase in new cases of cancer to 18.1 million per year, with 9.6 million cancer deaths occurring in 2018. Current conventional medical treatments are harsh, expensive, and often have limited success. Precisely because of the high mortality and serious adverse effects of conventional oncological therapies, many patients resort to complementary and/or integrative therapies that are outside the medical guidelines. Integrative therapies include lifestyle changes, mainly in diet supplementation with vitamins, minerals, and botanical medicines; and exercise and mind–body medicine. Some of these therapies have been studied extensively, and there are a large number of publications that support them.

VITAMIN C RESEARCH

The usefulness of a treatment must be evaluated in the totality of all the knowledge and experience established in the medical literature. This knowledge ranges from pharmacological studies that reveal mechanisms of action at the cellular and molecular levels, to studies in animals aimed at improving understanding of toxicology, and finally to human clinical studies.

*Corresponding author: Jorge R Miranda-Massari, Professor, Faculty of Pharmacy, University of Puerto Rico, Medical Sciences Campus, Puerto Rico; E-mail: jorge.miranda2@upr.edu
[a]Faculty of Pharmacy, University of Puerto Rico, Medical Sciences Campus, Puerto Rico
[b]Metabolic Medicine Institute, Accredited by George Washington University,

The scientific literature on vitamin C published in peer-reviewed journals is extensive. A search in PubMed will identify tens of thousands of published studies about vitamin C, of which over 5000 are on the topic of vitamin C and cancer. Of these, 852 are *in vitro* studies, 545 were done in animals (*in vivo*), and over 1000 were done in in humans (clinical).

The recently published study by the Chilean scientists that was reported in the EFE news report is titled "Increased expression of mitochondrial sodium-coupled ascorbic acid transporter 2 (mitSVCT2) as a central feature in breast cancer." This study was carried out in test tubes using cell lines from normal breast tissue and four types of breast cancer tissue. The purpose was to determine how these tissues acquire vitamin C. It was found that human breast cancer tissues express a form of transporter (sodium-coupled ascorbic acid transporter 2 [SVCT2]) differently, which is increased in malignant cells and absent in normal cells. It was also observed that the malignant cells do not use that SVCT2 transporter; instead, they depend on the glucose transporter to acquire vitamin C. In addition, the SVCT2 transporter is completely absent from the plasma membrane but is overexpressed in the mitochondria of breast cancer cells, where it mediates transport of ascorbic acid. In the discussion of the article's findings, it is mentioned that the increased expression of mitochondrial SVCT2 seems to be a common property in all human cancers. The merit of this study is the description of the transporters in the cell membranes. The authors speculated (but did not observe) that the transporters described could have implications for the survival capacity of cancer cells against pro-oxidant environments.

Going beyond this study, the use of vitamin C in cancer has been studied extensively in test tubes, animals, and humans as summarized below:

- Vitamin C can protect against cisplatin (CP)-induced nephrotoxicity and damage without reducing CP's effectiveness in Lewis lung carcinoma mice.[2]
- It has already been demonstrated in *in vitro* studies that vitamin C at pharmacological concentrations is a pro-oxidant and is selectively toxic to cancer cells and not to normal cells.[3]
- The effect of vitamin C has been studied in conjunction with various chemotherapeutic agents, and it has been shown to augment the toxic effect of most chemotherapies against malignant cells.[4]
- Some studies have shown that vitamin C activates sensitivity to chemotherapeutic agents in malignant cells that were previously resistant.[5]
- At least a dozen biochemical, metabolic, and biological anticancer mechanisms of vitamin C have been documented.[6–10]

Vitamin C has been used for more than 40 years in patients with cancer, and although it has not been incorporated into medical guidelines, it has been documented in published studies to be very safe. A US survey of 172 practitioners who had used intravenous vitamin C with a total of 20,009 patients concluded that, other than the known precautions, high-dose intravenous vitamin C appears to be remarkably safe.[11]

It is worth mentioning that in 1999, a research group from Memorial Sloan Kettering Cancer Center, led by Dr. David Golde, published the original studies that described the way in which vitamin C enters the cancer cell.[12] Their studies demonstrated that the transport of dehydroascorbic acid by GLUT is a means by which tumor cells acquire vitamin C. In that publication, as part of the discussion, concern was expressed about using vitamin C in patients with cancer regarding whether it might neutralize the pro-oxidant effect of chemotherapy. This comment neglected the fact that the main mechanism of action of intravenous vitamin C in pharmacological doses is precisely its pro-oxidative effect by increasing peroxide formation in malignant cells.

Although the central finding in the study by Agus[12] in 1999 was the mechanism of entrance of vitamin C into the cancer cell, it was the unsubstantiated comment within the discussion that was quoted in the media. The speculation expressed, and not the findings of the study, was widely disseminated. This journalistic work became a significant obstacle to considering the use of vitamin C in patients with cancer at the beginning of the 21st century.

The preponderance of data supports the use of vitamin C in cancer. Very recent studies continue to show the great potential of vitamin C in this regard. For example, in a study recently published in the journal

Cancer Research, ascorbate in pharmacological doses was shown to improve the cytotoxicity of pancreatic tumor cell radiation as well as to have potential to offer protection against radiation damage in normal surrounding tissue. This makes vitamin C an optimal agent to improve the treatment of locally advanced pancreatic adenocarcinoma.[13] More recently, another group studied the effect of high-dose vitamin C in three different cancer cell lines (MCF7, SK-BR3, and MDA-MB-231). Vitamin C was studied alone and in combination with common anticancer drugs (eribulin mesylate, tamoxifen, fulvestrant, or trastuzumab). It was found that vitamin C had beneficial effects on its own and that it could also increase the effectiveness of all the drugs studied.[14]

In clinical trials, intravenous vitamin C has also been shown to reduce adverse effects of chemotherapy, improve response to conventional chemotherapy, and improve patient quality of life. A study of 125 patients with breast cancer concluded that intravenous vitamin C was well tolerated and that it reduced adverse effects of chemotherapy and radiotherapy by half compared with the control group.[15] A group at Thomas Jefferson University published their clinical experience in using intravenous vitamin C over a period of 7 years with a total of 86 patients with cancer. The doses ranged between 50 and 150 mg with minimal adverse effects. In addition, participants reported less fatigue and pain, as well as improvement in mood.[16] A case report of a woman with glioblastoma who received intravenous vitamin C as an adjuvant therapy found that she lived for more than 4 years from diagnosis. She also experienced good quality of life the majority of the time.[17]

CONCLUSION

The value of the *in vitro* study performed by Peña *et al.*[1] relates to vitamin C transport in cellular and intracellular membranes. It does not contradict the findings of thousands of other studies of vitamin C; the preponderance of evidence published over the decades based on *in vitro*, *in vivo*, and clinical studies indicates that intravenous vitamin C therapy has several mechanisms of action that are beneficial in the management of cancer. Vitamin C has been shown to be remarkably safe as well and to have a number of clinical benefits for thousands of patients throughout the world.

REFERENCES

1. Peña E, Roa FJ, Inostroza E, *et al*. Increased expression of mitochondrial sodium-coupled ascorbic acid transporter-2 (mitSVCT2) as a central feature in breast cancer. *Free Radic Biol Med*. 2019;135:283–92.
2. Chen MF, Yang CM, Su CM, Hu ML. Vitamin C protects against cisplatin-induced nephrotoxicity and damage without reducing its effectiveness in C57BL/6 mice xenografted with Lewis lung carcinoma. *Nutr Cancer*. 2014;66:1085–91.
3. Chen Q, Espey MG, Krishna MC, *et al*. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. *Proc Natl Acad Sci USA*. 2005;102:13604–9.
4. Ma Y, Chapman J, Levine M, *et al*. High-dose parenteral ascorbate enhanced chemosensitivity of ovarian cancer and reduced toxicity of chemotherapy. *Sci Transl Med*. 2014;6:222ra18.
5. Schoenfeld JD, Alexander MS, Waldron TJ, *et al*. Pharmacological ascorbate as a means of sensitizing cancer cells to radio-chemotherapy while protecting normal tissue. *Semin Radiat Oncol*. 2019;29:25–32.
6. Chen Q, Espey MG, Sun AY, *et al*. Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo. *Proc Natl Acad Sci USA*. 2007;104:8749–54.
7. Chen Q, Espey MG, Sun AY, *et al*. Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice. *Proc Natl Acad Sci USA*. 2008;105:11105–9.
8. Du J, Martin SM, Levine M, *et al*. Mechanisms of ascorbate-induced cytotoxicity in pancreatic cancer. *Clin Cancer Res*. 2010;16:509–20.
9. Polireddy K, Dong R, Reed G, *et al*. High dose parenteral ascorbate inhibited pancreatic cancer growth and metastasis: mechanisms and a phase I/IIa study. *Sci Rep*. 2017;7:17188.
10. Serrano OK, Parrow NL, Violet PC, *et al*. Antitumor effect of pharmacologic ascorbate in the B16 murine melanoma model. *Free Radic Biol Med*. 2015;87:193–203.

11. Padayatty SJ, Sun AY, Chen Q, *et al*. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. *PLoS One*. 2010;5:e11414.

12. Agus DB, Vera JC, Golde DW. Stromal cell oxidation: a mechanism by which tumors obtain vitamin C. *Cancer Res*. 1999;59:4555–8.

13. Alexander MS, Wilkes JG, Schroeder SR, *et al*. Pharmacologic ascorbate reduces radiation-induced normal tissue toxicity and enhances tumor radiosensitization in pancreatic cancer. *Cancer Res*. 2018;78:6838–51.

14. Lee SJ, Jeong JH, Lee IH, *et al*. Effect of High-dose vitamin C combined with anti-cancer treatment on breast cancer cells. *Anticancer Res*. 2019;39:751–8.

15. Vollbracht C, Schneider B, Leendert V, *et al*. Intravenous vitamin C administration improves quality of life in breast cancer patients during chemo-/radiotherapy and aftercare: results of a retrospective, multicentre, epidemiological cohort study in Germany. *In vivo*. 2011;25:983–90.

16. Bazzan AJ, Zabrecky G, Wintering N, *et al*. Retrospective evaluation of clinical experience with intravenous ascorbic acid in patients with cancer. *Integr Cancer Ther*. 2018;17:912–20.

17. Baillie N, Carr AC, Peng S. The use of intravenous vitamin C as a supportive therapy for a patient with glioblastoma multiforme. *Antioxidants (Basel)*. 2018;7:E115.