• LETTERS •

Vitamin C and Cancer: What can we Conclude - 1,609 Patients and 33 Years Later: comment on the article by Cabanillas

To the Editor:

It is a questionable assertion that we do not know how much vitamin C is effective against cancer (1). Indeed, we do know, and we are failing our duty to patients when we fail to recommend vitamin C as adjunctive cancer therapy. There are many controlled studies that demonstrate that vitamin C improves both length of life and quality of life. Positive studies have typically used between 10,000 and 100,000 mg intravenously. As Dr. Fernando Cabanillas correctly noted, success with 10,000 mg/day by IV was initially reported back in the 1970s by Cameron and Pauling. But Dr. Cabanillas has then omitted some key information. It is important to note that the negative, much-touted Moertel-Mayo studies were not true replications of Cameron and Pauling's work, as A) they used oral doses only, and B) vitamin C was discontinued at the first sign of disease progression. Would we administer injectable chemotherapy orally, and then discontinue chemotherapy if the patient worsened? No, we would administer it properly, and, if possible, stay with it.

Pauling and Cameron's work was promptly confirmed, first at Japan's Saga University by Murata et al. Dr. Murata employed over 30,000 mg per day and had even better results with terminally ill cancer patients (2). In the words of Dr. Louis Lasagna of the University of Rochester Medical School, "It seems indefensible not to at least try substantial doses of vitamin C in these patients" (3).

Many clinical reports from orthomolecular (nutritional) physicians including Dr. Hugh Riordan and colleagues do in fact indicate that IV vitamin C is effective. Says Dr. James A. Jackson, "Dr. Riordan's IV protocol (4) starts out at 15,000 mg intravenous ascorbate and slowly goes up. It is given twice a week. The IVs are continued until the post-IV vitamin C levels reach what our research established as the killing level of 350 to 400 mg/dL. This has been verified (5). Once this level is reached, the frequency of the IV may be reduced to once a week, or to one or two times a month."

Puerto Rican oncologist Victor Marcial, M.D., says:

"We studied patients with advanced cancer (stage 4). 40 patients received 40,000-75,000 mg intravenously several times a week. These are patients that have not responded to other treatments. The initial tumor response rate was achieved in 75% of patients, defined as a 50% reduction or more in tumor size. . . As a radiation oncologist, I also give radiation therapy. Vitamin C has two effects. It increases the beneficial effects of radiation and chemotherapy and decreases the adverse effects. But this is not a subtle effect, is not 15-20%. It's a dramatic effect. Once you start using IV vitamin C, the effect is so dramatic that it is difficult to go back to not using it" (6).

There is no absolutely reliable cure for cancer. Conventional chemotherapy contributes only 2.1% to five year cancer survival in the USA (7). But with vitamin C, we are on the right track. It has been reported since McCormick in the 1950s (8-10) that cancer patients invariably have abnormally low levels of the vitamin. Vitamin C is vital to a cancer patient. What is dangerous is vitamin deficiency. What is even more dangerous is warning people off the very therapy that may help them, and frequently has been shown to make a significant difference.

Precisely how significant remains to be seen. But there are intriguing indications. Linus Pauling took 18,000 mg/day of vitamin C. Pauling died from cancer in 1994. Dr. Charles Moertel of the Mayo Clinic, critic of vitamin C, died of cancer the same year. Moertel was 66. Pauling was 93. Did vitamin C fail to cure Pauling's cancer? If so, then not taking vitamin C failed to cure Moertel's. Pauling lived 27 years longer with ascorbate than Moertel lived without it.

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Disclosure: Andrew W. Saul is Editor of the peer-reviewed Orthomolecular Medicine News Service, a non-profit and non-commercial newsletter. http://orthomolecular.org/resources/omns/index.shtml All members of the OMNS editorial review board, and the editor, serve without pay.

Vitamin C and Cancer: What can we Conclude - 1,609 Patients and 33 Years Later: comment on the article by Cabanillas

To the Editor:

Our group (RECNAC 2) has been at the forefront of the Vitamin C and Cancer research for the past decade and many of our papers have been published in this journal including in-vitro, animal and clinical studies (1-7). In addition, we authored a review paper on Vitamin C and Cancer published in 2005 (8) which is currently the third most cited article in the peer reviewed journal Integrative Cancer Therapies. We would like to respond to the review on the topic by Dr. Cabanillas.

We would like to point out and discuss certain misleading statements written in this review. The first inaccurate statement is in the title, it is not only 1,609 cancer patients that have been treated with IV Vitamin C. The Center for the Improvement of Human Functioning (now Riordan Clinic) has treated at least 1,500 Cancer patients with IV Vitamin C (9). In addition, The Cancer Treatment Centers of America have treated Cancer patients with IV Vitamin C and many physicians in many countries have also used this therapy for years. In a recent publication (10) it was documented that thousands of cancer patients have been treated each year with intravenous vitamin C in USA (1379 in 2006 and 1509 in 2008).

In order to clarify the facts, in the 1976 Cameron-Pauling Study (on prolongation of survival times with supplemental Vitamin C) the actual protocol was 10g/day by intravenous infusion for 10 days and orally thereafter. The study was criticized because of the use of historic controls. Dr. Cabanillas claims that the experimental group (Vitamin C) was declared terminally ill much sooner than the control group to create a longer survival time. There is absolutely no credible data to support this claim. Dr. Cabanillas cites as a source for this claim, a non peered review publication (Your Patient and Cancer) in which the author "reasoned" that to obtain these results the experimental group must have been declared terminally ill sooner. The third double-blind study cited was not a published paper but an abstract presented in 1983. The discrepancy between the findings of these studies and the Cameron –Pauling studies, may be due mainly to the route of administration of ascorbate. The Cameron –Pauling group administered Vitamin C both orally and intravenously while the Mayo Clinic group gave it exclusively by the oral route.

The first Phase I study done with Vitamin C and terminally ill cancer patients is the Riordan study (6). As all Phase I studies, it was done to establish safety, pharmacokinetics and dose ranging; it was not designed to assess response to treatment. Nevertheless Dr. Cabanillas claims that nobody responded to ascorbate but it is documented that at least one patient had stable disease and continued treatment for 48 weeks.

There is published information on the plasma level of Vitamin C that can reduce tumor growth. Doses of 50-100 g given intravenously may result in plasma concentrations of about 14,000 micromol/L. At concentrations above 1000 micromol/L, vitamin C is toxic to cancer cells but not to normal cells in vitro. Infusions of 60 g of Vitamin C produced peak plasma concentrations exceeding 20 mM with an area under the curve (24 h) of 76 mM per hour. Thus, tumoricidal concentrations of Vitamin C may be achievable in vivo. However, it is important that when referring to the plasma concentrations necessary to achieve antineoplastic activity there are other numerous factors involved that will affect the specific response. Some of these include sensitivity of tumor, hypoxia inducible factor, intracellular RedOx signal transduction and gene expression, apoptosis, autoschizis, effect of collagen on tumor encapsulation and others.

Despite its remarkable safety profile, adverse effects can occur with intravenous vitamin C. But when compared to chemotherapy, these negative effects are extremely rare and occur basically in people with previous specific medical problems. In a recent publication (10) of a total 20,109 patients very few renal side effects were reported. In 11,233 patients in 2006, there were a total of two kidney stone reports and no renal failure was reported. In 2008 of a total of 8,876 patients, two kidney stones were reported (one oxalate and one urate) and one renal failure in a patient with previous renal problems that had a partial renal failure and was suffering of metastases to kidneys.

Moreover, in another published phase I trial of high dose intravenous vitamin C in advanced malignancy, adverse effects were minimal at all dose levels. In a study to assess the risk of oxalate crystallization in the urinary space, it was found that less than 0.5% of a very large intravenous dose of ascorbic acid is recovered as urinary oxalic acid in people with normal renal function.

Research in vitamin C and cancer has increased substantially in the past five years and the preponderance of the evidence demonstrates its effectiveness inhibiting and killing a wide variety of tumor cell lines. In addition, it has been shown to improve quality of life in Cancer patients. In light of the safety of high dose intravenous vitamin C, its antitumor activity and

its multiple physiological benefits, it seems a fair option in the treatment of cancer patients, especially when dealing with cases that do not respond to chemotherapy while producing serious toxic effects. In light of the evidence that the use of vitamin C and other nutrients can reduce the toxicity of chemotherapy and might even improved tumor response and survival, a more open and earnest discussion (and research) is warranted.

We agree with Dr. Cabanillas that vitamin C has not received a fair and adequate trial and that more studies are needed. There is no absolutely reliable cure for cancer. Conventional chemotherapy contributes only 2.1% to the five year cancer survival in the USA. For the past 50 years there has been practically no change in Cancer mortality rates. These are the main reasons we pursue a non-toxic protocol for Cancer Treatment. Based on the available published evidence i.v. Vitamin C is a step forward in achieving this goal.

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Reply

To the Editor:

Although not a Vitamin C expert, as an experienced investigator and board certified oncologist, I feel qualified to pass judgment and assess the value of cancer clinical trials with this agent.

Both Dr. Saul and González bring up the Cameron-Pauling study (1) which I criticized in my article because of its three major flaws:

1. The study was totally retrospective in nature.

2. They failed to provide any data to demonstrate that the patients in the control and Vitamin C groups were matched by tumor stage, performance status, and other important prognostic variables. We teach our fellows in hematology-oncology early on during their training the importance of obtaining a balanced distribution of prognostic factors in both the control and experimental groups. This is a fundamental and critical principle behind any legitimate research study. I am astonished that González et al are willing to accept Cameron's and Pauling's conclusions without proof that the Vitamin C and control groups were balanced in their distribution of prognostic features.

3. According to the authors, patients were started on Vitamin C when they were judged to be untreatable or terminal and their subsequent survival was compared to that of the control patients from the time they had also been labeled as terminal. Because survival was measured from the time the patients were declared terminally ill to the time when they died, if the Vitamin C group was labeled terminal sooner than the control group that would result in an artificially longer survival for those assigned to receive Vitamin C. González et al state that "There is absolutely no credible data to support this claim." Allow me to review the reasoning and the data behind my allegation which I credit to Dr. William DeWys, who was chief of the clinical investigations branch of the National Cancer Institute's cancer therapy program (2). Logic tells us that if the Vitamin C and control groups were truly comparable, the average time from the initial diagnosis to terminal status should be similar for both groups, yet according to Dr. DeWys' investigations, they were not. For that reason he deduced that many of the Vitamin C patients had been labeled as terminal earlier in the course of their disease and would therefore be expected to live longer. DeWys also pointed out that more than 20% of the patients in the control group had died within a few days of being declared terminal, while none of the Vitamin C patients died early on. It is highly unlikely that Vitamin C had such a quick positive impact on their survival. This observation also implies that the Vitamin C group had less advanced disease at the time they were labeled terminal. Perhaps González et al and Saul have a justification for these inconsistencies but they didn't offer an explanation for them in their letters.

Dr. Saul claims that Cameron's study was confirmed by Murata et al (3). I couldn't obtain that paper published in 1982 in

a journal that ceased to exist in 1989. Dr. Saul was kind enough to provide me with a copy of the article. I was equally disappointed to find out that Murata et al, instead of conducting a prospective study to confirm Cameron's hypothesis, performed the same type of retrospective comparison with the same structural problems as the Cameron-Pauling study. Furthermore, in the Murata study the treatment and control groups received various doses and at different times, which make their conclusions even more dubious.

Dr. Saul states that he knows how effective Vitamin C is against cancer. He sustains that "there are many controlled studies that demonstrate that Vitamin C improves both length and quality of life". Unfortunately he fails to submit those "controlled studies". Certainly the Cameron-Pauling and the Murata studies can't be considered as well controlled studies. Dr. Saul states that "what is dangerous is warning people off the very therapy that may help them". He quotes Dr. Victor Marcial who claims that he has treated 40 patients with advanced cancer and obtained a response rate of 75%. I have personally asked Dr. Marcial if he had an IRB approved protocol to conduct such research and surprisingly his reply was that he did not. To say the least, this is a dangerous, unethical conduct and a serious breach of professional behavior. Furthermore, basing conclusions on a clinical trial conducted without a protocol is unscientific, improper and deplorable. Finally, Dr. Marcial, as a well trained radiation oncologist, should very well know that cancer is an extremely heterogeneous group of disorders. For example, results of treatment for lung cancer are very different to lymphoma. For that reason, serious, self-respecting investigators don't report the results of a broad phase II trial in "advanced cancer" without specifying what type of cancers were treated and which responded. To say that Vitamin C has a 75% response rate in "advanced cancer" is absurd.

González et al fill up a lot of space in their letter reviewing pharmacology data. They also mention two phase I studies but fail to mention a single prospective phase II or III clinical trial using high dose intravenous Vitamin C. Unless González et al can provide information to the contrary, which they did not in their letter, I stand by my assertion "that we still do not know whether Vitamin C has any clinically significant antitumor activity" (4). I also stand by my statement that "a phase II study using 1.5 g/kg three times weekly would be in order so as to establish if there is any hint of antitumor activity." There are more than enough pharmacology studies on Vitamin C but when are the obligatory prospective phase II-III cancer clinical trials going to be performed with high dose I.V. Vitamin C?

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