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The Use of IV Vitamin C as an Adjunct to Chemotherapy and Radiation Therapy

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Vitamin C, also known as ascorbic acid, is a water-soluble vitamin. Unlike most animals, humans cannot produce their own vitamin C and must obtain it from their diet. Within the body, vitamin C functions as a cofactor in numerous vital enzymatic reactions. Vitamin C is required for the synthesis of collagen, carnitine, and catecholamines to name but a few. It also functions as an important antioxidant, protecting cells from oxidative stress. Clinically, vitamin C can be administered both orally and intravenously.

Ewan Cameron and Linus Pauling were the first to report that high doses of vitamin C given both intravenously and orally were effective in the treatment of cancer.[1] Follow-up randomized double-blind placebo-controlled clinical trials sponsored by the U.S. National Cancer Institute showed no survival advantage when similar doses of vitamin C were given orally. This led the mainstream medical community to largely dismiss the use of vitamin C as a potential cancer treatment in the 1980s. However, we now know that the route of administration greatly affects the bioavailability of vitamin C. Tissue and plasma concentrations are tightly controlled in response to oral intake, but this can be bypassed by intravenous administration resulting in significantly higher concentrations.[2] As a result researchers have continued to investigate the role of intravenous vitamin C (IVC) in cancer treatment and it is a commonly used therapy among complementary medicine providers for the treatment of numerous conditions including cancer.[3]

Despite its widespread use, clinical research investigating the effects of IVC in patients with cancer is lacking. This is especially apparent regarding its use in combination with other standard cancer therapies. This article will review the existing research examining the safety and efficacy of IVC administered in conjunction with chemotherapy and radiation therapy.

Mechanisms of Action

While several mechanisms have been proposed, the exact mode of action explaining vitamin C's antineoplastic effects remains uncertain. Cameron and Pauling had originally hypothesized that the formation of new collagen resists the malignant infiltration of cancer cells.[4] Later Chen et al. demonstrated both *in vitro* and *in vivo* (mice) that high concentrations of vitamin C have direct cytotoxic effects on cancer cells, but not normal cells.[5-7] However, they did not find a similar effect with low concentrations. High concentrations of vitamin C appear to be selectively cytotoxic to cancer cell lines through the generation of extracellular hydrogen peroxide. However, neither the selective toxicity nor the mechanism of peroxide-mediated cytotoxicity is fully understood. Most recently Ma et al. revealed that high concentrations of vitamin C caused oxidative DNA damage and adenosine triphosphate (ATP) depletion within ovarian cancer cells. This triggered the activation of the ataxia telangiectasia mutated (ATM)/adenosine monophosphate-activated protein kinase pathway (AMPK) and the inhibition of mammalian target of rapamycin (mTOR), leading to cell death.[8]

In addition to extracellular hydrogen peroxide formation, intracellular mechanisms have also been proposed to explain vitamin C's activity. High intracellular vitamin C concentrations may inhibit hypoxia-inducible factor 1-alpha (HIF1-a) activation.[9] The overexpression of HIF1-a has been shown to promote tumor progression through a number of mechanisms, including the development of resistance to chemotherapy and radiation therapy. This may provide some theoretical basis specifically for the combined use of IVC with standard cancer therapies.

IVC combined with chemotherapy

Although human data is limited, the safety of IVC, including in those with advanced disease, has been confirmed in clinical trials.[10, 11] Additionally, when it is combined with chemotherapy, IVC also appears to be well tolerated.

Several phase I/II clinical trials have specifically studied the use of IVC administered concurrently with arsenic trioxide-based chemotherapy in patients with refractory multiple myeloma to improve the tolerability of this therapy, as detailed in the review by Fritz et al.[12] Although these studies all used a lower dose of vitamin C (1 g) and a clear benefit has been difficult to assess due to the lack of control groups, the addition of vitamin C to the chemotherapeutic regimens was well tolerated and did not appear to cause any increase in adverse effects.

Two more recent observational studies looked at the concurrent use of IVC and chemotherapy and reported improvements in quality of life and the mitigation of chemotherapy-induced adverse effects.

Vollbracht et al. retrospectively studied a group of 125 women with early stage breast cancer undergoing standard therapy.[13] Fifty-three of these women were given 7.5 g of IVC once a week in addition to their standard therapy. These included various combinations of epirubicin, cyclophosphamide, methotrexate, fluorouracil and/or radiation therapy. It should be noted, however, that IVC was not administered on the same day as any chemotherapy or radiation therapy in this study. No side effects directly attributed to the IVC were reported. Moreover, patients in the IVC group reported significantly less nausea, loss of appetite, fatigue, depression, sleep disturbance, dizziness, and bleeding disorders and to have higher performance status scores during and after their standard therapy.

Takahashi et al. prospectively followed 60 patients diagnosed with advanced cancers who received high-dose IVC.[14] The dose was gradually escalated to achieve serum vitamin C concentrations between 350 and 400 mg/dL. Thirty-four of these patients were also undergoing standard treatment with chemotherapy. Similarly to the Vollbract et al. study, significant improvements were seen in fatigue, insomnia, pain, and constipation, as well as in overall quality of life scores as compared to baseline. However, in this study several adverse effects possibly attributable to the IVC were reported, including: headache (n=5), nausea (n=5), irritation at the site of injection (n=2), painful urination (n=1), dry mouth (n=1), and pain (n=1) at the tumor site. Nevertheless these were all considered mild (grade 1) events.

Whenever adverse effects of treatment are mitigated one must ask the question whether the desired effects of the treatment may also be inhibited. While vitamin C does not appear to affect cytochrome p450 drug metabolism,[15] most chemotherapeutics and radiation therapy exert their antineoplastic effects primarily through oxidative mechanisms. Thus concern has been raised with the concurrent use of any antioxidant with these agents.[16] However, the vast majority of preclinical evidence has shown that there is no decrease in efficacy when chemotherapeutic agents are administered in combination with vitamin C. In fact, *in vitro* and *in vivo* studies have repeatedly demonstrated that vitamin C has additive therapeutic effects with various chemotherapeutic agents including: bleomycin, cisplatin, cyclophosphamide, doxorubicin, etoposide, fluorouracil, gemcitabine, paclitaxel, and vincristine as outlined in the review by Wilson et al.[17] Nonetheless, there is also *in vitro* evidence that high concentrations of vitamin C may interfere with the cytotoxic effects of cisplatin, doxorubicin, methotrexate, vincristine, and DTIC,[18, 19] as well as the targeted agents imatinib and bortezomib.[20, 21] However, the results of one of these studies[19] have been called into question[22] as it used dehydroascorbic acid, an oxidized form of vitamin C, instead of ascorbic acid, the form of vitamin C that is used clinically. As mentioned above, while we know vitamin C is an important antioxidant in the body, it appears to also act as a pro-oxidant when present in higher concentrations, such as those attained with high-dose IVC therapy. This ability of high concentrations of vitamin C to specifically cause oxidative stress within cancer cells may help explain its ability to decrease the toxicity of chemotherapy while also increasing the effectiveness of these agents.

Regardless, there is also a growing amount of research to suggest that many antioxidants do not in fact interfere with the cytotoxicity of chemotherapy. Of note, a randomized clinical trial demonstrated that high doses of oral vitamin C, E and beta-carotene (all well-known antioxidants) did not reduce the therapeutic effects of paclitaxel and carboplatin chemotherapy.[23] In this study 136 patients with advanced non-small cell lung cancer were randomized to receive either chemotherapy alone or chemotherapy in combination with daily high oral doses of these antioxidants. There were no statistical differences in chemotherapy response rates or median or overall survival times between groups and in fact there was a trend towards improved response rates and survival times in the antioxidant arm. Toxicity profiles were also similar in both groups.

Data from clinical trials examining the effects of IVC on chemotherapy outcomes is scarce; only three small pilot studies to date have specifically looked at the effects of concurrent IVC with standard cancer care on the progression of disease. Interest in this area is increasing and all three of these studies were conducted in the last three years. Two of them examined the effect of IVC in combination with gemcitabine in patients with advanced pancreatic cancer. Monti et al. administered IVC to nine participants with newly diagnosed metastatic pancreatic cancer along with gemcitabine chemotherapy and the tyrosine kinase inhibitor erlotinib.[24] The IVC was administered in a dose-escalation design from 50 to 100 g three times per week for eight weeks. IVC was well tolerated by all participants and all serious adverse effects during the trial were attributed to progression of disease or treatment with gemcitabine or erlotinib therapy. Although progression-free survival and overall survival times were comparable to those previously reported for gemcitabine with erlotinib therapy alone, the authors suggest several reasons why their findings may have underestimated the full effect of the IVC and they recommend a larger randomized phase II follow-up study.

In a similar phase I trial Welsh et al. treated nine participants with metastatic pancreatic cancer using a combination of IVC and gemcitabine chemotherapy.[25] The dose of IVC was increased until a serum vitamin C concentration of 350 mg/dL was achieved (50 to 125 g per infusion). This dose was administered twice a week for at least four weeks until progression of disease was seen. Again, IVC was deemed a safe addition as the toxicities reported were actually less severe compared to other published trials of gemcitabine chemotherapy. Transient, mild symptoms possibly attributable to IVC included nausea (n=6), diarrhea (n=4), and dry mouth (n=4). While the authors are careful to point out that their small study was not powered to determine therapeutic efficacy, their results are striking when compared to previously published data with gemcitabine therapy alone. They reported a progression-free survival of 26 weeks and an overall survival of 12 months with the combination of gemcitabine and IVC. This is quite remarkable when compared to a progression-free survival of nine weeks and an overall survival of six months previously reported with gemcitabine therapy alone.

Most recently another clinical trial demonstrated that IVC in combination with paclitaxel and carboplatin may improve time to relapse and survival in patients with advanced ovarian cancer.[8]

Ma et al. randomized 25 participants with newly diagnosed stage III or IV ovarian cancer into two groups, to receive either standard chemotherapy with paclitaxel and carboplatin alone (n=12) or in combination with IVC (n=13). The dose was adjusted to achieve serum vitamin C concentrations between 350 and 400 mg/dL and was administered twice a week for 12 months. Participants were followed for five years. The authors reported no increase in grade 3 or 4 toxicities with the addition of IVC and furthermore grade 1 and 2 toxicities were decreased in the IVC arm. Although it did not reach statistical significance due to the small number of participants, the overall survival trended toward improvement with the addition of the IVC as did the median time to progression/relapse which was 8.75 months longer than in the standard chemotherapy group.

IVC combined with radiation therapy

Relatively few studies have focused on the effects of vitamin C on cancer cells alongside radiation therapy. The preclinical data reported, as with chemotherapy, has been conflicting though mostly positive. Koch and Biaglow demonstrated *in vivo* that a greater inhibition in growth of Erlich ascites tumor cells could be achieved using only half the dose of radiation when it was administered in the presence of vitamin C.[26] Similar findings were reported in brain cancer cell lines treated with radiation and the radiosensitizing agent fluorouracil when vitamin C was added.[27] However, a reduction in cell death from radiation has also been observed in myeloid leukemia cells treated with vitamin C.[28]

Clinical studies in this area are lacking. The only human research looking at the combination of radiation therapy and IVC is the observational study by Vollbracht et al. described above.[13]

Conclusion

Large randomized clinical trials examining the use of IVC in conjunction with standard cancer therapies are lacking, especially with radiation therapy, making it difficult to definitively assess the safety and the efficacy of this combination of therapies. However, based on the preliminary information available, IVC appears to be safe with certain chemotherapeutic agents and is unlikely to increase the toxicity, and may even decrease some of the adverse effects associated with these therapies. In addition to the potential for IVC to have synergistic effects with various chemotherapeutics, it may also contribute to improved outcomes by allowing patients to tolerate higher, and potentially more effective, doses of chemotherapy. Unfortunately clinical trials to date have been too small to provide statistically meaningful data on the efficacy of IVC in improving outcomes of standard chemotherapy regimens and larger studies are needed to confirm this plausible hypothesis.

In the meantime IVC continues to be a popular therapy provided by complementary medicine practitioners in the treatment of cancer. It has been suggested that administering natural health products five half-lives away from chemotherapy would help minimize the risk of direct interactions since this is the time required for a substance to be eliminated from the body.[29] The half-life of vitamin C itself is quite short; approximately two hours in patients with advanced cancer.[11] However, many chemotherapeutics have much longer half-lives and depending on the frequency of dosing may restrict the concurrent use of IVC. While this dosing schedule would help to avoid potential adverse interactions it would also prevent the benefit of potential chemosensitizing effects of IVC. Nevertheless, until we have more information this appears to be the safest strategy for patients. Because of the lack of clinical trials looking at the effects of IVC and radiation, and the fact that radiation therapy is generally administered five days per week, IVC would be difficult to schedule in such a way to prevent interactions and should therefore be delayed until after radiation therapy is complete.

Perhaps most importantly, this review should highlight the need for continued research into this emerging therapy. The first three clinical studies looking at the concurrent use of high-dose IVC and chemotherapy have only been published in the last three years and all have called for follow-up studies. There are five clinical trials using a combination of IVC and chemotherapy currently recruiting participants listed on the ClinicalTrials.gov website.[30] Naturopathic doctors who treat patients with cancer will need to stay abreast of the newly developing research into IVC as it evolves over the coming years.

About the Author

As a fellow of the American Board of Naturopathic Oncology (FABNO), **Daniel Lander** is one of only a handful of naturopathic doctors in Canada who are board certified in naturopathic oncology. His clinical training included a residency at the Cancer Treatment Centers of America. He is currently an associate professor at the Canadian College of Naturopathic Medicine teaching oncology and clinical nutrition, as well as supervising fourth-year interns in the Adjunctive Cancer Care Shift at the Robert Schad Naturopathic Clinic. He also maintains a small private practice in Toronto where he focuses in integrative oncology, supporting patients with cancer during and after their conventional care.

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