Vitamin C and Cancer

Vitamin C deficiency is fairly common among cancer patients. In a study that compared serum and salivary vitamin C levels in 30 patients with oral cancer, 30 patients with potentially malignant oral disorders, and 30 healthy controls, the mean serum and salivary vitamin C levels were significantly decreased in oral cancer and potentially malignant disorders compared to healthy controls.[1] Additionally, plasma vitamin C deficiency (<11 micromol/L) was identified in 15 of 50 (30%) patients with various types of advanced cancer.[2] Low vitamin C levels were associated with low dietary intake, low albumin, high platelet count, high CRP level, and shorter survival time.

Multiple studies have attempted to demonstrate benefit from the oral administration of vitamin C in the treatment of various forms of cancer. Their attempts, however, have been unsuccessful. Randomized, controlled trials failed to demonstrate measurable benefit with the administration of high-dose oral vitamin C in both cancer patients who had previously undergone chemotherapy[3] and those who had not undergone chemotherapy.[4]

In a small, open-label pilot study that assessed the use of oral vitamin C as an opioid-sparing agent in the treatment of chronic cancer-related pain, researchers were unable to demonstrate clinically significant benefit from vitamin C in conjunction with opioids in cancer-related pain.[5]

Adverse effects associated with the oral administration of high-dose vitamin C included loose stools (diarrhea).

Oral vitamin C has different effects on the body compared to intravenous vitamin C. This is largely due to the fact that the body does not permit plasma vitamin C levels to rise beyond a certain point with oral consumption; it limits the amount of vitamin C absorbed at any given time. In one study, 17 healthy volunteers were hospitalized and administered various doses of oral and intravenous vitamin C.[6] Vitamin C plasma and urine concentrations were measured after administration of doses ranging from 0.015 to 1.25 grams. At a dose of 1.25 grams, oral vitamin C led to plasma concentrations of 134.8 +/- 20.6 micromol/L, while intravenous vitamin C at the same dose led to mean plasma concentrations of 885 +/- 201.2 micromol/L. Researchers concluded that because peak plasma and urine levels of vitamin C are tightly controlled when the

intestinal absorption system is involved, only intravenous administration of vitamin C leads to the high plasma and urine concentrations which may lead to antitumor effects.

Intravenous vitamin C is commonly used as an adjunct therapy in cancer treatment. Low doses and high doses of intravenous vitamin C affect the body differently. For example, low-dose intravenous vitamin C (1 gram or less) has been assessed for its ability to decrease toxicity of certain chemotherapeutic and other companion drugs[7-9] and to enhance immune function in individuals with cancer.[10] The results have been underwhelming. Research demonstrated that low-dose vitamin C was well-tolerated alongside arsenic trioxide-based chemotherapy regimens, which also included bortezomib, melphalan, dicitabine, and dexamethasone; however, because the studies were uncontrolled, they were unable to definitely conclude that intravenous vitamin C improved tolerability. Researchers were also unable to demonstrate enhancement of immune function with low-dose vitamin C.

High-dose intravenous vitamin C has been demonstrated to have antitumor and chemo-sensitizing properties.[11-13] The most common hypothesis regarding the anti-cancer effects of high-dose vitamin C pertains to its ability to generate significant quantities of hydrogen peroxide at high doses.[14] High dose vitamin C produces a high flux of hydrogen peroxide in tumors. The hydrogen peroxide generates oxidative stress that preferentially targets cancer cells. Cancer cells have lower levels of catalase, the enzyme that is responsible for removing hydrogen peroxide, and are therefore able to remove extracellular hydrogen peroxide on average only half as quickly as normal cells. Higher levels of hydrogen peroxide lead to DNA damage and depletion of ATP, both of which lead to higher rates of tumor cell death.

Another hypothesis concerning the mechanism of action by which high-dose vitamin C exerts its anti-tumor effects pertains to its ability to stimulate the 2-oxoglutarate-dependent dioxygenase family of enzymes (2-OGDDs), which includes the hydroxylases that regulate the hypoxic response, a major driver of tumor survival, angiogenesis, stem cell phenotype and metastasis, and the epigenetic histone and DNA demethylases.[15]

Research demonstrates beneficial effects of high-dose intravenous vitamin C in various forms of cancer. In vitro trials demonstrate that ascorbic acid induces necrotic cell death in laryngeal squamous cell carcinoma Hep2 cells through reactive oxygen species generation, protein kinase C activation, and cytosolic calcium signaling.[16] Furthermore, treatment with 1 and

3 mM of ascorbic acid for 60 min preferentially inhibited the growth of human tongue carcinoma HSC-4 cells over non-tumorigenic tongue epithelial dysplastic oral keratinocyte cells.[17]

In vivo human studies also demonstrate efficacy of vitamin C in addressing cancer and cancer-related pathology and symptomatology. In a study involving stages III to IV ovarian cancer patients who had undergone debulking surgery, IV vitamin C twice weekly for 6 months with chemotherapy (paclitaxel, carboplatin) and then for six months post-chemotherapy resulted in IV vitamin C patients reporting five-fold fewer adverse treatment effects, including neurotoxicity, myelosupression, infection, hepatobiliary/pancreatic toxicity, and toxicities of the renal, pulmonary, and gastrointestinal systems relative to controls who received chemotherapy alone.[18]

In similar studies involving individuals with a variety of solid tumors including breast, colorectal, pancreatic, liver, lung, and skin, IV vitamin C was administered using a dose escalation design—50, 70, 90, 110 g/m^2 of IV vitamin C, four days per week for four weeks.[19] Quality of life, as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer (EORTC QLQ-C30), remained stable for the first two weeks then improved at weeks three to four for the patients who completed the questionnaire.

Another controlled trial recruited patients with metastatic stage IV pancreatic cancer and administered IV vitamin C using a dose escalation design—50, 75, 100 grams of IV vitamin C, 3 days per week for 8 weeks.[20] Patients were also receiving gemcitabine and erlotinib. Researchers reported reductions in tumor mass from 10% to 42% in 8 of the 9 patients who completed the study. There was no evidence of increased toxicity with the addition of IV vitamin C to the regimen. Patients did report transient, mild nausea and light-headedness due to osmotic load during their infusions.

In another study, 39 terminally ill cancer patients were administered 10 grams of vitamin C twice with a three-day interval and an oral intake of four grams of vitamin C per day for a week.[21] Patients' quality of life was evaluated using the EORTC QLQ-C30. Researchers noted improvements in the global health score, with score improving from 36±18 to 55±16 after administration of vitamin C. In the functional scale, patients reported significantly higher scores for physical, role, emotional, and cognitive function. They also reported improvements in fatigue, nausea/vomiting, pain, and loss of appetite after administration of IV vitamin C. While

this trial was uncontrolled and of short duration, researchers reported that the findings suggest that IV vitamin C may be a safe and effective therapy to improve quality of life in terminal cancer patients.

Dose-limiting toxicities associated with high-dose IV vitamin C therapy include grade 4 hypernatremia and grade 3 hypokalemia.[19] Adverse effects included, most commonly, nausea and mild headache, and, infrequently, hypertension, insomnia, abnormal urine color, decreased appetite, fatigue, chills, and hyperglycemia,[19] as well as dry skin and mouth, edema, fatigue, and one incident of a kidney stone.[22]

In conclusion, the existing body of research suggests that while oral administration of vitamin C may not be significantly beneficial in addressing cancer, intravenous administration of vitamin C appears to be beneficial in improving quality of life, reducing tumor size, and improving chemotherapy- and disease-related adverse effects in a variety of forms of cancer.

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