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High-Dose Vitamin C (PDQ®)

Health Professional Version

PDQ Integrative, Alternative, and Complementary Therapies Editorial Board.

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This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of high-dose vitamin C in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

This summary is reviewed regularly and updated as necessary by the PDQ Integrative, Alternative, and Complementary Therapies Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Overview

This cancer information summary provides an overview of the use of high-dose vitamin C (also known as ascorbate or L-ascorbic acid) as a treatment for people with cancer. This summary includes a brief history of early clinical trials of high-dose vitamin C; reviews of laboratory, animal, and human studies; and current clinical trials.

This summary contains the following key information:

- Vitamin C is an essential nutrient with redox functions at normal physiologic concentrations.
- High-dose vitamin C has been studied as a treatment for cancer patients since the 1970s.
- Laboratory studies have reported that high-dose vitamin C has redox properties and decreased cell proliferation in prostate, pancreatic, hepatocellular, colon, mesothelioma, and neuroblastoma cell lines.
- Two studies of high-dose vitamin C in cancer patients reported improved quality of life and decreases in cancer-related side effects.

- Studies of vitamin C combined with other drugs in animal models have shown mixed results.
- Intravenous vitamin C has been generally well tolerated in clinical trials.

Many of the medical and scientific terms used in this summary are hypertext linked (at first use in each section) to the NCI Dictionary of Cancer Terms, which is oriented toward nonexperts. When a linked term is clicked, a definition will appear in a separate window.

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General Information

Vitamin C is an essential nutrient that has redox functions, is a cofactor for several enzymes, and plays an important role in the synthesis of collagen.[1] A severe deficiency in vitamin C results in scurvy, which is associated with malaise, lethargy, easy bruising, and spontaneous bleeding.[2] One of the effects of scurvy is a change in collagen structure to a thinner consistency. Normal consistency is achieved with administration of vitamin C.

In the mid-20th century, a study hypothesized that cancer may be related to changes in connective tissue, which may be a consequence of vitamin C deficiency.[3] A review of evidence published in 1974 suggested that high-dose ascorbic acid may increase host resistance and be a potential cancer therapy.[4]

Vitamin C is synthesized from D-glucose or D-galactose by many plants and animals. However, humans lack the enzyme L-gulonolactone oxidase required for ascorbic acid synthesis and must obtain vitamin C through food or supplements.[1]

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History

The earliest experience of using high-dose vitamin C (intravenous [IV] and oral) for cancer treatment was by a Scottish surgeon, Ewan Cameron, and his colleague, Allan Campbell, in the 1970s.[1] This work led to a collaboration between Cameron and the Nobel Prize–winning chemist Linus Pauling, further promoting the potential of vitamin C therapy in cancer management.[2,3] As a result, two clinical trials of oral vitamin C were conducted in the late 1970s and early 1980s.[4,5]

(Refer to the Human Studies section of this summary for more information about these early studies.)

Pharmacokinetic studies later revealed substantial differences in the maximum achieved blood concentrations of vitamin C based on the route of administration. When vitamin C is taken orally, plasma concentrations of the vitamin are tightly controlled, with a peak achievable concentration less than 300 µM. However, this tight control is bypassed with IV administration of the vitamin, resulting in very high levels of vitamin C plasma concentration (i.e., levels up to 20 mM).[6,7] Further research suggests that pharmacologic concentrations of ascorbate, such as those achieved with IV administration, may result in cell death in many cancer cell lines.[8]

Health care practitioners attending complementary and alternative medicine conferences in 2006 and 2008 were surveyed about usage of high-dose IV vitamin C in patients. Of the 199 total respondents, 172 had administered vitamin C to patients. In general, IV vitamin C was commonly used to treat infections, cancer, and fatigue.[9]

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Laboratory/Animal/Preclinical Studies

In Vitro Studies

Numerous studies have demonstrated that pharmacological doses of ascorbic acid (0.1–100 mM) decrease cell proliferation in a variety of cancer cell lines.[1-5] Specifically, decreases in cell proliferation after ascorbic acid treatment have been reported for prostate,[6] pancreatic,[7,8] hepatocellular,[9] colon,[10] mesothelioma,[11] and neuroblastoma [12] cell lines.

The potential mechanisms through which treatment with high-dose ascorbic acid may exert its effects on cancer cells have been extensively investigated. Several studies have demonstrated that the *in vitro* direct cytotoxic effect of ascorbic acid on various types of cancer cells is mediated through a chemical reaction that generates hydrogen peroxide.[1,7,13,14] Treating colon cancer cells with 2 mM to 3 mM of ascorbic acid resulted in downregulation of specificity protein (Sp) transcription factors and Sp-regulated genes involved in cancer progression.[10] One study suggested that ascorbate-mediated prostate cancer cell death may occur through activation of an autophagy pathway.[6]

Differences in chemosensitivity to ascorbate treatment in breast cancer cell lines may depend on expression of the sodium-dependent vitamin C transporter 2 (SVCT-2).[15]

Research has suggested that pharmacological doses of ascorbic acid enhance the effects of arsenic trioxide on ovarian cancer cells,[16] gemcitabine on pancreatic cancer cells,[8] and combination treatment of gemcitabine and epigallocatechin-3-gallate (EGCG) on mesothelioma cells.[17]

Findings from one study reported in 2012 suggested that high-dose ascorbate increases radiosensitivity of glioblastoma multiforme cells, resulting in more cell death than from radiation therapy alone.[18]

However, not all studies combining vitamin C with chemotherapy have shown improved outcomes. Treating leukemia and lymphoma cells with dehydroascorbic acid (the oxidized form of vitamin C that increases levels of intracellular ascorbic acid) reduced the cytotoxic effects of various antineoplastic agents tested, including doxorubicin, methotrexate, and cisplatin (relative reductions in cytotoxicity ranged from 30% to 70%).[19] In another study, multiple myeloma cells were treated with bortezomib and/or plasma obtained from healthy volunteers who had taken vitamin C supplements. Cells treated with a combination of bortezomib and volunteers' plasma exhibited lower cytotoxicity than did cells treated with bortezomib alone.[20]

Animal Studies

Studies have demonstrated tumor growth inhibition after treatment with pharmacological ascorbate in animal models of pancreatic cancer,[1,7,8] liver cancer,[3] prostate cancer,[21] sarcoma,[22] mesothelioma,[11] and ovarian cancer.[4]

The effects of high-dose ascorbic acid in combination with standard treatments on tumors have been investigated. In a mouse model of pancreatic cancer, the combination of gemcitabine (30 or 60 mg/kg every 4 days) and ascorbate (4 g/kg daily) resulted in greater decreases in tumor volume and weight, compared with gemcitabine treatment alone.[8] According to a study reported in 2012, ascorbate enhanced the cancer cell–killing effects of photodynamic therapy in mice injected with breast cancer cells.[23] A study of mouse models of ovarian cancer found that ascorbate enhanced the tumor inhibitory effect of carboplatin and paclitaxel, first-line chemotherapy used in ovarian cancer.[24]

Using N-acetylcysteine (NAC) and vitamin C, researchers showed in 2007 that these compounds, both thought to act predominantly as antioxidants, may have antitumorigenic actions *in vivo* by decreasing levels of hypoxia-inducible factor (HIF)-1, a transcription factor that targets vascular endothelial growth factor (VEGF) and plays a role in angiogenesis.[25]

There have also been reports of animal studies in which vitamin C has interfered with the anticancer activity of various drugs. In a study reported in 2008, administration of dehydroascorbic acid to lymphoma-xenograft mice prior to doxorubicin treatment resulted in significantly larger tumors than did treatment with doxorubicin alone.[19] Notably, this study used dehydroascorbate, the oxidized form of vitamin C that is known to be transported actively into cells and then reduced to vitamin C. Treating multiple myeloma xenograft mice with a combination of oral vitamin C and bortezomib resulted in significantly greater tumor volume than did treatment with bortezomib alone.[20] This increase in tumor volume was caused by a chemical reaction that occurs in the gastrointestinal tract but does not appear to be relevant to intravenous administration.

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Human/Clinical Studies

Early Ascorbate-Only Trials

In the early 1970s, a consecutive case series was conducted in which 50 advanced-cancer patients were treated with large doses of ascorbic acid.[1] These patients began ascorbic acid treatment after conventional therapies were deemed unlikely to be effective. Patients received intravenous (IV) ascorbic acid (10 g/day for 10 consecutive days; some patients received higher doses), oral ascorbic acid (10 g/day), or both. The subjects exhibited a wide variety of responses to treatment, including no or minimal response, tumor regression, and tumor hemorrhage. However, the authors noted that lack of controls prevented definitive assignment of any beneficial responses to the ascorbic acid treatment. A case report published in 1975 detailed one of the patients who had experienced tumor regression.[2] Diagnosed with reticulum cell sarcoma, the patient exhibited improvement in well-being and resolution of lung masses after being treated with ascorbic acid. When the patient's daily dose of ascorbic acid was reduced, some of signs of the disease returned; however, remission was achieved again after the patient reverted to the higher initial dose.

A larger case series of terminal cancer patients treated with ascorbate was reported in 1976. In this study, 100 terminal cancer patients (50 of whom were reported on previously) [1] were treated with ascorbate (10 g/day for 10 days IV, then orally) and compared with 1,000 matched controls from the same hospital. The mean survival time for ascorbate-treated patients was 300 days longer than that of the matched controls.[3,4]

Two studies tried to reproduce earlier results. These studies were randomized, placebo-controlled trials in which cancer patients received either 10 g oral vitamin C or placebo daily until signs of cancer progression. At the end of each study, no significant differences were noted between the two ascorbate-treated and placebo-treated groups for symptoms, performance status, or survival.[5,6]

Recent Ascorbate-Only Trials

One study reported three case reports of cancer patients who received IV vitamin C as their main therapy. During vitamin C therapy, the patients used additional treatments, including vitamins, minerals, and botanicals. According to the authors, the cases were reviewed in accordance with the NCI Best Case Series guidelines. Histopathologic examination suggested poor prognoses for these patients, but they had long survival times after being treated with IV vitamin C.[7] Vitamin C was given at doses ranging from 15 g to 65 g, initially once or twice a week for several months; two patients then received it less frequently for 1 to 4 years.

Two studies demonstrated that IV vitamin C treatment resulted in improved quality of life and decreases in cancer-related side effects in cancer patients.[8,9]

Studies have shown that vitamin C can be safely administered to healthy volunteers or cancer patients at doses up to 1.5 g/kg and with screening to eliminate treating individuals with risk factors for toxicity (e.g., glucose-6-phosphate dehydrogenase deficiency, renal diseases, or urolithiasis). These studies have also found that plasma concentrations of vitamin C are higher with IV administration than with oral administration and are maintained for more than 4 hours.[10,11]

Ascorbate-Combination Trials

A phase I study published in 2012 examined the safety and efficacy of combining IV ascorbate with gemcitabine and erlotinib in stage IV pancreatic cancer patients. Fourteen subjects entered the study and planned to receive IV gemcitabine (1,000 mg/m^2 over 30 minutes, once a week for 7 weeks), oral erlotinib (100 mg daily for 8 weeks), and IV ascorbate (50 g/infusion, 75 g/infusion, or 100 g/infusion 3 times per week for 8 weeks). Minimal adverse effects were reported for ascorbic acid treatment. Five subjects received fewer than 18 of the planned 24 ascorbate infusions and thus did not have follow-up imaging to assess response. Three of those patients had clinically determined progressive disease. All of the other nine patients had repeat imaging to assess tumor size, and each met the criteria for having stable disease.[12]

A 2013 phase I clinical study evaluated the safety of combining pharmacological ascorbate with gemcitabine in treating stage IV pancreatic cancer patients. During each 4-week cycle, patients received gemcitabine weekly for 3 weeks (1,000 mg/m^2 over 30 minutes) and twice weekly ascorbate infusions for 4 weeks (15 g over 30 minutes during the first week, followed by weekly escalations in dose until plasma levels reached at least 350 mg/dL [20 mM]). Among nine patients, mean progression-free survival was 26 weeks and overall survival was 12 months. The combination treatment was well tolerated, and no significant adverse events were reported.[13]

In 2014, a phase I/IIA clinical trial evaluated the toxicities of combining IV ascorbate with carboplatin and paclitaxel in stage III/IV ovarian cancer. Twenty-seven patients were randomly assigned to receive either chemotherapy alone or chemotherapy and IV vitamin C concurrently. Chemotherapy was given for 6 months, and IV vitamin C was given for 12 months. The addition of IV vitamin C was associated with reduced chemotherapy-related toxicities.[14]

Trials of high-dose IV vitamin C with other drugs are ongoing.[12,14] A number of studies have included IV ascorbic acid treatment (1,000 mg) with arsenic trioxide regimens, with mixed results. The combination therapies were well tolerated and suggested beneficial effects in multiple myeloma patients, although the specific contribution of vitamin C could not be determined.[15-18] However, similar combination regimens resulted in severe side effects, disease progression, and no anticancer effect in patients with refractory metastatic colorectal cancer [19] and metastatic melanoma.[20] Because these were not placebo-controlled trials, the extent that ascorbate contributed to the toxicity demonstrated in these studies is unclear.

Current Clinical Trials

Check the list of NCI-supported cancer clinical trials for integrative, alternative, and complementary therapies clinical trials on ascorbic acid that are actively enrolling patients.

General information about clinical trials is also available from the NCI website.

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Adverse Effects

Intravenous (IV) high-dose ascorbic acid has been generally well tolerated in clinical trials.[1-8] Renal failure following ascorbic acid treatment has been reported in patients with preexisting renal disorders.[9]

Case reports have indicated that patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency should not receive high doses of vitamin C because of the risk of developing hemolysis.[10-12]

Vitamin C may increase bioavailability of iron, and high doses of the vitamin are not recommended for patients with hemochromatosis.[13]

Drug Interactions

When administered in high doses, vitamin C may result in adverse interactions with some anticancer agents. These interactions have primarily been detected in preclinical studies. A 2013 phase I clinical study evaluated the safety of combining high-dose IV ascorbate with gemcitabine in stage IV pancreatic cancer patients. The combination therapy was well tolerated by patients, and no significant adverse events were reported.[14]

In vitro and *in vivo* animal studies have suggested that combining oral vitamin C with bortezomib interferes with the drug's ability to act as a proteasome inhibitor and blocks bortezomib-initiated apoptosis.[15-17] This interference occurred even with the oral administration of vitamin C (40 mg/kg/day) to animals. Studies in cell culture and performed by adding blood plasma from healthy volunteers given oral vitamin C (1 g/day) also showed a significant decrease in bortezomib's growth inhibitory effect on multiple myeloma cells. Another study found similar results. Plasma from healthy volunteers who took 1 g of oral vitamin C per day was shown to decrease bortezomib growth inhibition in multiple myeloma cells and to block its inhibitory effect on 20S proteasome activity.[17] However, a study that utilized mice harboring human prostate cancer cell xenografts failed to find any significant effect of oral vitamin C (40 mg/kg/day or 500 mg/kg/day) on the tumor growth inhibitory action of bortezomib.[18]

Several studies have been performed to assess the potential synergistic or inhibitory action of vitamin C on certain chemotherapy drugs, with variable results. A series of studies in cell culture and in animals bearing tumors has shown that when given at high concentrations or dosages, dehydroascorbic acid (an oxidized form of vitamin C) can interfere with the cytotoxic effects of several chemotherapy drugs.[19] However, dehydroascorbic acid is generally present only at low concentrations in dietary supplements and fresh foods.

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Changes to This Summary (05/11/2017)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Human/Clinical Studies

Revised text to state that similar combination regimens resulted in severe side effects, disease progression, and no anticancer effect in patients with refractory metastatic colorectal cancer and metastatic melanoma. Also added text to state that because these were not placebo-controlled trials, the extent that ascorbate contributed to the toxicity demonstrated in these studies is unclear.

This summary is written and maintained by the PDQ Integrative, Alternative, and Complementary Therapies Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ® - NCI's Comprehensive Cancer Database pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of high-dose vitamin C in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

This summary is reviewed regularly and updated as necessary by the PDQ Integrative, Alternative, and Complementary Therapies Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for High-Dose Vitamin C are:

- Nagi B. Kumar, PhD, RD, FADA (Fellow of the American Dietetic Association)
- Jeffrey D. White, MD (National Cancer Institute)

Any comments or questions about the summary content should be submitted to Cancer.gov through the NCI website's Email Us. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.

Levels of Evidence

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Integrative, Alternative, and Complementary Therapies Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

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information must be obtained from the owner(s) and cannot be granted by the National Cancer Institute. Information about using the illustrations in this summary, along with many other cancer-related images, is available in Visuals Online, a collection of over 2,000 scientific images.

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