Integrative Cancer Therapies

Intravenous Vitamin C and Cancer: A Systematic Review

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Abstract

Background. Intravenous vitamin C (IVC) is a contentious adjunctive cancer therapy, widely used in naturopathic and integrative oncology settings. We conducted a systematic review of human interventional and observational studies assessing IVC for use in cancer patients. *Methods*. We searched MEDLINE, EMBASE, The Cochrane Library, CINAHL, and AMED from inception to April 2013 for human studies examining the safety, effectiveness, or pharmacokinetics of IVC use in cancer patients. *Results*. Of 897 records, a total of 39 reports of 37 studies were included: 2 randomized controlled trials (RCTs), 15 uncontrolled trials, 6 observational studies, and 14 case reports. IVC dosing ranged from 1 g to more than 200 g ascorbic acid per infusion, typically administered 2 to 3 times weekly. IVC does not appear to increase toxicity or interfere with antitumor effects of gemcitabine/erlotinib therapy or paclitaxel and carboplatin. Based on 1 RCT and data from uncontrolled human trials, IVC may improve time to relapse and possibly enhance reductions in tumor mass and improve survival in combination with chemotherapy. IVC may improve quality of life, physical function, and toxicities associated with chemotherapy, including fatigue, nausea, insomnia, constipation, and depression. Case reports document several instances of tumor regression and long-term disease-free survival associated with use of IVC. *Conclusion*. There is limited high-quality clinical evidence on the safety and effectiveness of IVC. The existing evidence is preliminary and cannot be considered conclusive but is suggestive of a good safety profile and potentially important antitumor activity; however, more rigorous evidence is needed to conclusively demonstrate these effects. IVC may improve the quality of life and symptom severity of patients with cancer, and several cases of cancer remission have been reported. Well-designed, controlled studies of IVC therapy are needed.

Keywords

ascorbic acid, cancer, chemotherapy, interactions, integrative oncology, intravenous vitamin C, naturopathic oncology, quality of life, systematic review, vitamin C

Introduction

Intravenous vitamin C (IVC) is a commonly used therapy among naturopathic doctors and other integrative oncology health care practitioners. A survey published in 2010 evaluating the use of IVC among health care practitioners attending annual complementary medicine conferences found that 84% of complementary medicine practitioners (172 of 199 respondents) reported using IVC in more than 11 000 patients for various conditions, including cancer.[1] In addition to widespread use, a body of evidence is emerging on the biological effects of IVC in cancer patients. In 2006, the *Canadian Medical Association Journal* published 3 reports of objectively verified cases of cancer remission associated with IVC therapy.[2] Since then there has been an explosion of new research on the use of IVC, with 4 phase I trials as well as other reports published in the last 3 years alone.[3-8] Based on emerging data, IVC appears to have therapeutic potential in cancer patients; however, there is a lack of an unbiased synthesis of data on its safety and effectiveness.

IVC as a therapy for cancer was first developed in the 1970s by Nobel Prize winner Linus Pauling.[9] Cameron and Pauling published preliminary studies as case series and uncontrolled trials. Their work found longer survival times among advanced cancer patients treated with vitamin C given orally and intravenously, compared to controls who were not given the vitamin C, and when compared to expected survival times based on disease stage.[10,11] These studies have since been criticized for weak methodology; however, they sparked wider interest in vitamin C as a therapeutic agent for cancer care. More recent clinical and laboratory-based studies have investigated the effects of IVC on tumor growth, quality of life (QOL), potential interactions with chemotherapy, and mitigation of side effects from chemotherapy.[3,7] Laboratory studies demonstrate that vitamin C in high concentrations has antitumor and chemosensitizing effects.[12-14] Studies in humans have shown improvements in QOL and cancer-related symptoms.[6,8] Evidence to date while inconclusive is promising that IVC may represent an important emerging therapy with a spectrum of benefit for patients with cancer.

The mechanisms of high-dose IVC are distinct from those of orally administered vitamin C.[15] Oral dosing achieves a maximum serum concentration of less than 250 µM (0.25 mM) due to the limited absorptive capacity of the gastrointestinal tract.[15,16] Intravenously administered vitamin C will increase serum levels more than 100-fold: up to 30 mM.[15] In a study comparing a low dose of 1.25 g oral and IV vitamin C administration, there was a 6.6-fold greater plasma concentration achieved by the IV route over the oral route. Based on pharmacokinetic modeling, intravenous doses of 50 and 100 g were expected to yield plasma concentrations of approximately 13 to 15 mM, compared to 220 µM concentrations achieved by the maximum tolerated oral dose, 3 g 4 times daily.[17] When present at such high serum concentrations, vitamin C generates the cytotoxic reactive oxygen species, hydrogen peroxide.[18-22] In normal cells, hydrogen peroxide is metabolized to water and oxygen according to the following reaction, by the enzyme catalase: $2H_2O_2 \rightarrow 2H_2O + O_2$.[19] Tumor cells lack catalase, leaving them vulnerable to the cytotoxic effects of hydrogen peroxide and resulting in preferential cytolytic activity associated with high concentrations of vitamin C.[18-21,23,24] In addition to the inability to convert hydrogen peroxide, tumor cells selectively take up more vitamin C compared to normal cells through facilitated transport by glucose transporters (GLUT),[25-29] a process upregulated in tumor cells due to their increased metabolic need for glucose.[30,31]

With an apparently high safety profile, and preliminary evidence suggesting plausible biological activity, this inexpensive and unpatentable agent deserves closer examination for its potential anticancer effects. We conducted a systematic review of the literature describing the use and pharmacokinetics of IVC therapy in patients with cancer. Our goal was to review and summarize this body of literature according to the safety and effectiveness of IVC use in cancer care, as well considering potential interactions with conventional chemotherapy or radiation therapy.

Methods

Search Strategy

Electronic search strategies were developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. Using the OVID platform, we searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, AMED (Allied and Complementary Medicine), and

PsycINFO. We also searched the Cochrane Library (including CENTRAL, Cochrane Database of Systematic Reviews, DARE, HTA, and NHS EED). The original searches were performed March 29, 2010, and updated to April 29, 2013.

Strategies used a combination of controlled vocabulary (eg, "Ascorbic Acid," "Injections, Intravenous") and keywords (eg, intravenous vitamin c, IV vitamin c). Vocabulary and syntax were adjusted across databases. There were no language or date restrictions on any of the searches. Additional references were also sought through hand-searching the bibliographies of relevant items. Authors were contacted to obtain details of unpublished studies.

Specific details regarding the search strategies appear in the appendix.

Inclusion Criteria

For inclusion, evidence had to come from human studies published in English, including clinical trials, uncontrolled trials, observational studies, case series, or case reports. Studies had to assess the safety and/or effectiveness of IVC in cancer patients with respect to one or more of the following: (*a*) antitumor effects, including tumor response; (*b*) survival, including overall survival and time to relapse or disease-free survival; (*c*) impact on side effects associated with chemotherapy or radiation therapy and/or cancer-related symptoms; (*d*) impact on QOL; or (*e*) interactions with conventional chemotherapy or radiation therapy. Studies assessing clinical surrogate outcomes were included if they examined endpoints directly related to cancer risk or tumor activity, such as tumor markers, or objective markers assessing healthy bodily function, such as hematological or immune function in cancer patients. IVC could be used as a single, adjuvant, or cyclic agent in studies. We included controlled and uncontrolled studies; controlled studies had to compare patients with cancer receiving IVC to patients with cancer not receiving IVC. We excluded studies assessing oral vitamin C exclusively. In vitro and in vivo studies were excluded due to the high risk for confounding and previous work showing a lack of correlation between preclinical and clinical results.[32]

Record Screening and Selection

First pass record screening was conducted independently by 3 researchers (HF, GF, MC) based on title review, with second pass conducted on abstracts and/or full text where uncertainty existed. Disagreement between researchers was resolved by consensus. Reports published in English were included for full analysis if they met inclusion criteria.

Data Extraction

We piloted data extraction forms and conducted extraction in triplicate for 30% of studies to assess interresearcher reliability (HF, GF, MC). No major inconsistencies in data extraction were found. Extraction sheets were prepared based on the Consolidated Standards of Reporting Trials (CONSORT) statement for clinical trials and the Newcastle-Ottawa scale (NOS) for observational studies.[33-35] Randomized controlled trials (RCTs) were assessed for quality using the Cochrane Risk of Bias tool,[36] and observational studies were assessed for quality using the NOS.[35]

Results

Of 897 records screened, 39 records were included for full analysis and review. Figure 1 shows a flowchart of the literature search and study selection. Studies of IVC were categorized according to whether they consisted of high or low doses of vitamin C. Higher doses were considered 5 g or more, whereas studies using only 1 g were considered low dose. No studies used intermediate doses between 1 and 5 g. While studies using higher dosages are more reflective of common clinical practice when using IVC for anticancer purposes, we included low-dose studies as well for their data on the safety of IVC alongside specific chemotherapy regimens.
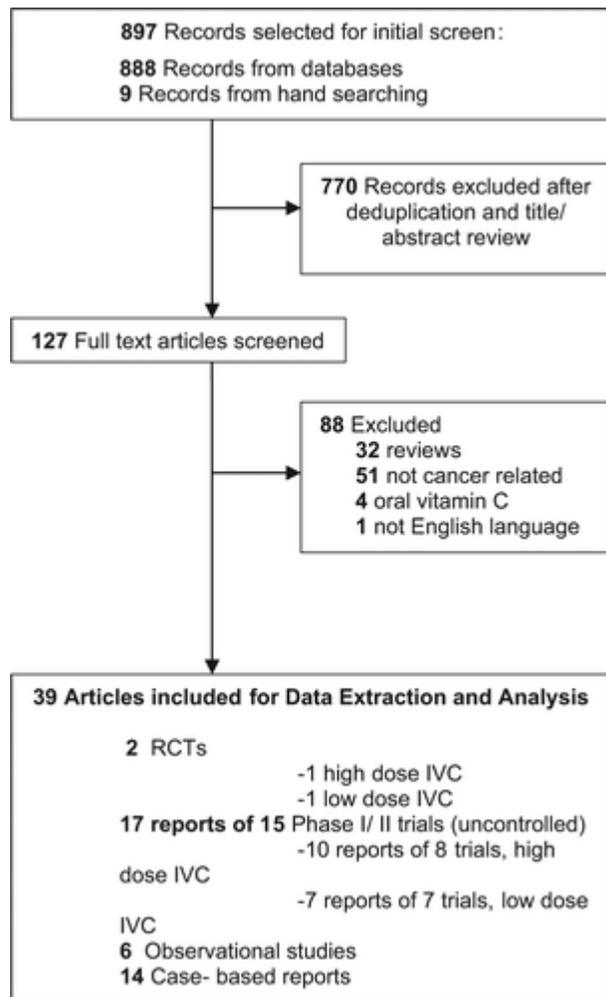
Figure 1. Literature flowchart.

High-Dose IVC

We included 1 RCT, 7 uncontrolled phase I/II trials, 6 observational studies, and 14 case reports wherein high-dose IVC was employed.

Randomized Controlled Trials

A 2014 pilot RCT investigated the use of high-dose IVC in chemonaive patients with stage III-IV ovarian cancer.[37] The dosing schedule for IVC consisted of gradual dose escalation up to a target of either 75 g or 100 g vitamin C per infusion, depending on peak plasma concentration of vitamin C per individual; the target concentration was between 20 and 23 nM (350-400 mg/dL). IVC was given twice weekly. A total of 27 women with newly diagnosed stage III-IV ovarian cancer, who had undergone debulking surgery and who were currently receiving paclitaxel and carboplatin chemotherapy, were randomized to receive high-dose IVC twice per week for 12 months, or chemotherapy alone. IVC was given alongside chemotherapy for the first 6 months and then continued for another 6

months following the completion of chemotherapy, for a total 12 months of treatment. The study showed that IVC did not increase the toxicity of chemotherapy; women who received IVC treatment reported fewer side effects/toxicities related to chemotherapy in almost all categories of toxicity, including neurotoxicity, bone marrow toxicity, infection, hepatobiliary/pancreatic toxicity, toxicities in the renal/genitourinary, pulmonary, and gastrointestinal systems, as well as dermatological. There was no difference in lymphatic or cardiac toxicities. Patients receiving IVC reported ≤50% of the average number of grade I and II adverse events per encounter (visit), compared to the control group. Finally, patients were followed for survival for 5 years. Those who received IVC had a nonsignificant trend toward improved overall survival as well as the median time to disease progression or relapse. Median time to disease progression or relapse was 8.75 months longer in the IVC group (25.5 vs 16.75 months). The authors suggest the reason for lack of statistically significant findings with respect to this outcome was the small sample size, as the study was not adequately powered to detect efficacy. There may be a higher risk of bias in reporting of chemotherapy-associated side effects, given their often subjective nature; however, there is likely lower risk of bias with respect to hard outcomes such as time to relapse.

Phase I/II and Uncontrolled Studies

We included 7 uncontrolled phase I/II studies assessing high-dose IVC, described in Table 1.[3,5,7,38-42] These studies evaluated the maximum blood concentrations of vitamin C that can be achieved through IVC dosing, adverse events, dose-limiting toxicities, and safety in combination with chemotherapy and included preliminary estimates of tumor response, survival, and QOL.

Click to view table
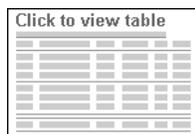
Table 1. Description of Human Trials of High-Dose Intravenous Vitamin C (HD-IVC) Use in Cancer Patients.

Pharmacokinetics

Four trials and 1 observational study showed that blood concentrations of approximately 20 to 25 mM vitamin C can be achieved by administering the equivalent of between 50 and 70 g IVC.[3-5,7,38] Higher doses appear capable of achieving higher levels, with the equivalent of ~140 g ($70 g/m^2$) achieving 49 mM,[3] and 100 g achieving 31.9 mM[5]; however, there seems little additional benefit from higher dosages with respect to maximum blood concentrations (C_{max}). Stephenson et al evaluated doses of 50, 70, 90,

and 110 g/m^2 (approximately equal to 100, 140, 180, and 220 g for a 6-foot, 180-lb male) and found that the serum concentrations plateaued at 49 mM with the 140 g dose (70 g/m^2); therefore, 70 g/m^2 was recommended for further investigation by future studies.[3] In addition, Stephenson et al found that each of the 3 highest dose groups were able to maintain plasma vitamin C level between 10 and 20 mM for 5 to 6 hours. Vitamin C was eliminated by first-order kinetics, and the elimination half-life ($t_{1/2}$) was approximately 2 hours, with a range of between 1.7 and 2.5 hours among the different dose cohorts.[3]

Tumor response

Two studies assessed tumor response. Of these, one reported no objective tumor response among 17 patients with solid tumors not receiving chemotherapy or radiation, when IVC 100 to 220 g was given 4 days weekly over a period of 4 weeks.[3] In this study, 13 patients had progressive disease (PD), 3 had stable disease (SD), and 1 withdrew from the study for reasons not described. The second study was of 8 weeks duration and used 50, 75, or 100 g IVC 3 times per week alongside gemcitabine and erlotinib in patients with stage IV, metastatic pancreatic cancer.[5] This study showed preliminary effects on tumor response.[5] Of the 9 patients who completed this study, 7 had SD and 2 had PD. Three patients died during the study, and when these were included in the count, 5 patients had PD. Assessment of computed tomography or positron emission tomography–computed tomography scans by a blinded radiologist showed a decrease in tumor size in 8 of 9 patients completing the trial; in these patients, tumor mass decreased between 10% and 42%.[5] There was no evidence of increased toxicity from chemotherapy with the addition of IVC.[5] There was some mild transient nausea and lightheadedness during the IVC infusion due to osmotic load; however, other reported adverse events were consistent with those expected from the chemotherapy regimen and are listed in Table 1.

Survival

Two trials reported survival metrics, both in patients with stage IV pancreatic cancer on gemcitabine with or without erlotinib.[5,7] Monti et al reported that mean progression-free survival was 89 days, and overall survival was 182 days among 14 patients receiving high-dose IVC (50, 75, or 100 g 3 times per week for 8 weeks).[5] Welsh et al reported that of the 9 patients completing at least 1 cycle (4 weeks) of the chemotherapy, with IVC dosed between 50 and 125 g twice per week until progression, mean survival was 13 months, and time to progression was 26 weeks.[7]

Quality of life

Three trials assessed QOL measures, collectively suggesting a positive impact of IVC use on QOL.[3,38,42] Stephenson et al found that QOL as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer (EORTC-QLQ-C30) questionnaire remained stable for the first 2 weeks among patients receiving IVC; at weeks 3 and 4, QOL seemed to improve for the small number of patients who completed the questionnaire at these time points.[3] Hoffer et al evaluated the effects of various dosing regimens and found that those patients who received 0.6 g/kg (approximately 42 g for a 70-kg male) or more had stabilization of their physical function as measured by the Functional Assessment of Cancer Therapy–General questionnaire, whereas those patients receiving lower doses had significant deterioration in their physical function ($P < .01$).[38] Similarly, Yeom et al found that among stage IV cancer patients, administration of even 10 g IVC twice within a 3-day period resulted in significant improvements in global health score ($P = .001$), physical, role, emotional, and cognitive function ($P < .05$ for all), and improvements in the following symptoms: fatigue, nausea/vomiting, pain, and loss of appetite ($P < .005$ for all).[42] These findings should be interpreted with caution due to the short duration and uncontrolled nature of the studies.

DLTs and adverse events

Dose-limiting toxicities (DLTs) reported by Stephenson et al were 3 incidents of grade 4 hypernatremia in 2 of 3 patients in the third dose cohort (90 g/m^2 or ~180 g for a 6-foot male) and 1 of 3 patients in the fourth dose cohort (110 g/m^2 or ~220 g for a 6-foot male), as well grade 3 hypokalemia in 2 of 3 patients in the third dose cohort (90 g/m^2 or ~180 g).[3] No DLTs were reported by Welsh et al using dosages up to 125 g IVC twice weekly.[7] Mild to moderate adverse events most commonly reported among other phase I trials included nausea and headache,[3,5,38] which may be due in part to the osmotic load. Other infrequent adverse events are listed in Table 1.

Three reports of 2 phase I trials assessed biochemistry and kidney function during IVC and found no sign of impaired kidney function or other abnormalities associated with high-dose IVC therapy.[38,40,43] Hoffer et al found that IVC was associated with a small increase in 6-hour urinary oxalate excretion (81.3 mg, normal = 10-60 mg), equivalent to excretion of less than 0.5% of a 100 g IVC dose as oxalic acid, but there was no incidence of related adverse events and no trend to increased serum creatinine.[38,43] Riordan et al found that IVC therapy was not associated with any significant changes in blood cell

counts (CBC), blood urea nitrogen (BUN), or serum creatinine.[40] There was a small decrease in serum uric acid during IVC therapy. One incident of a kidney stone in a patient with a previous history of kidney stones and one incident of reversible hypokalemia in a patient with concurrent diarrhea were reported.[40]

Risk of bias

Due to the uncontrolled nature of these trials, and the lack of a standardized tool for risk of bias assessment of such studies, we were unable to assess any particular risk of bias score for the phase I/II studies. Given the nature of the endpoints, there is likely to be a lower risk of bias for reports of pharmacokinetic parameters, survival and tumor response, and higher risk of bias in the reports on QOL and adverse events. It should be noted that efficacy data from these studies should be interpreted with caution due to their uncontrolled design, small sample size, and inherent risk of bias.

Observational Studies

We included 6 observational studies of high-dose IVC, described in Table 2.[4,6,8,11,44,45] Two recent studies showed improvements in QOL and cancer and/or chemotherapy-related symptoms,[6,8] and one study showed an effect on inflammatory and tumor markers in particular C-reactive protein (CRP) and prostate-specific antigen (PSA),[4] while 3 older studies reported a survival advantage associated with use of oral plus IV vitamin C therapy.[11,44,45]
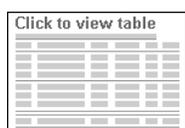
Table 2. Description of Observational Studies of High-Dose Intravenous Vitamin C (HD-IVC) Use in Cancer Patients.

Pharmacokinetics

A retrospective cohort studyby Mikirova et al reported that concentration of plasma vitamin C achieved through administration of high-dose IVC range (50 g infusion) was ~18 mM.[4]

Quality of life and side effects of chemotherapy

Takahashi et al reported on a prospective observational study (Japan) of 60 newly diagnosed patients with advanced cancer who received high-dose IVC.[8] The largest subgroup by cancer type was lung cancer (n = 14), followed by breast (n = 8), stomach (n = 8), and colon (n = 6) cancers. The Riordan IVC protocol was used, wherein patients

were started with ~15 g vitamin C per infusion for the first dose, followed by 25 g for the second dose and 50 g for the third dose. Thereafter, the dose was adjusted to achieve blood vitamin C concentrations between 350 and 400 mg/dL immediately after infusion. Infusions were given twice weekly for a total of 4 weeks. Oral vitamin C was supplemented at a dose of 2 to 4 g per day. A total of 34 patients (56.7%) received concomitant chemotherapy. After 4 weeks, there were significant improvements in overall QOL as measured by the EORTC-QLQ-C30 questionnaire, which improved from 44.6 ± 27.8 to 61.4 ± 24.3 ($P < .001$). There were also significant improvements in fatigue scores (from 42.4 ± 28.7 to 28.4 ± 25.7, $P < .01$), insomnia scores (31.1 ± 32.1 to 16.4 ± 23.7, $P < .01$), as well as pain scores (17.8 ± 25.7 to 10.0 ± 13.9, $P < .05$) and constipation (21.1 ± 31.3 to 11.7 ± 22.3, $P < .05$) when compared to baseline. The clinical global impression of change as assessed by patients' oncologists was "minimally" to "much improved" in 60% of patients. IVC therapy was well tolerated and no patients discontinued treatment due to adverse events. Possible side effects reported were all mild (grade I) and included headache (n = 5), nausea (n = 5), angialgia (irritation at site of injection; n = 2), dry mouth (n = 1), tumor site pain (n = 1), and dysuria (n = 1).

Vollbracht et al conducted a retrospective cohort study (in Germany) of 125 early stage (IIa-IIb) breast cancer patients, of whom 53 were treated with 7.5 g IVC weekly for a minimum of 4 weeks in addition to standard therapies, compared to 72 patients who were treated with standard therapy alone.[6] Chemotherapy regimens included epirubicin/cyclophosphamide (56%), cyclophosphamide/methotrexate/fluorouracil (20%), and fluorouracil/epirubicin/cyclophosphamide (15.2%). There was a statistically and clinically significant reduction in severity of chemotherapy-related side effects in the IVC group. Patients in the control group had almost 2-fold higher symptom severity with respect to nausea, loss of appetite, fatigue, depression, sleep disorders, dizziness, and hemorrhagic diathesis. Each of these outcomes was significant compared to the control group ($P < .05$). The differences between groups were evident during concomitant chemotherapy and during the postchemotherapy phase. Patients who received IVC also had higher performance scores during chemotherapy (mean Karnofsky index of 80% compared to 71% in the control group, $P < .001$) as well as postchemotherapy (87% vs 78%, $P < .001$). No side effects related to IVC were observed.

Tumor markers

Mikirova et al conducted a retrospective cohort study assessing the impact of IVC on tumor and inflammatory markers.[4] Among 45 patients attending the Riordan clinic, data on CRP, PSA, and other tumor and inflammatory markers were analyzed. The median

number of IVC treatments was 9 (interquartile range = 5-18). Most patients (76%) had a reduction in CRP while on IVC; for those with under 10-day intervals between IVC treatments, this number increased to 95%. Among patients with elevated CRP at baseline (>10 mg/L), there was a mean reduction of 80%. In prostate cancer patients, lowered CRP correlated with reductions in PSA, suggesting an impact on disease activity. In addition, 53% of patients had reduction in CEA, CA 27.29, CA 15.3, but these changes were not significant. Among a subgroup (n = 11), there were also reductions in IL-2 and tumor necrosis factor-α (TNF-α) that were noticeable after 6 treatments.

Survival

Cameron and Pauling reported findings from 3 retrospective cohort studies.[11,44,45] These studies included 294, 100, and 100 terminally ill cancer patients receiving vitamin C therapy, compared to 1532, 1000, and 1000 historic controls, respectively, who were identified from the hospital records of 3 district hospitals in Scotland over a 4.5-year period (1978-1982). Vitamin C therapy consisted of 10 to 45 g (most commonly 10 g) IVC for the first 10 days, followed by 10 g daily oral dosing given indefinitely thereafter.[10,11] The first study of 100 terminally ill cancer patients and 1000 controls (also terminally ill cancer patients) reported a 4.2-fold longer survival time associated with vitamin C therapy: mean survival was 210 days in the vitamin C group compared to 50 days in the control group.[11]

Responding to concerns regarding an appropriate control group,[45] a second study was conducted using a matched design. This study reported a survival advantage of 300 days for vitamin C therapy compared to the control group.[45] Survival times greater than 1 year after the date of "untreatability" were observed for 22% (n = 22) of the vitamin C group, compared to 0.4% (n = 4) of the control group. The 22 patients in the vitamin C group had a mean survival of 2.4 years, and at the time of evaluation, 8 were still alive (mean survival of 3.5+ years), whereas no one had survived in the control group. Finally, the third study comparing records from 294 terminally ill cancer patients treated with vitamin C to 1826 matched controls from the same Scottish hospitals found that vitamin C–treated patients had an almost 2-fold increase in overall survival, 343 days compared with 180 days in the control patients.[44]

Risk of bias

The cohort studies scored between 4 and 7 on an 8-point scale for risk of bias.[4,6,8] There was high risk of bias in the representativeness of the cases, as studies were based on cases that had self-selected to obtain IVC treatment; in 2 studies there was a lack of

control group. However, 2 studies were multicenter studies,[6,8] increasing the probability of the cases being more representative of a wider demographic. One study was single center and lacked a control arm.[4] The case–control studies, despite being older reports, had a relatively low risk of bias according to our assessment, scoring between 7 and 8 on an 8-point scale. All 3 reports were by Cameron and Pauling.[11,44,45] The first study lacked adequate definition of controls[11]; however, subsequent studies had clearer definitions of the controls and used an independently conducted matching process.[44,45] Outcomes data were based on hospital records.

Case Reports

We included 14 case reports pertaining to 221 separate cases, described in Table 3.[2,10,46-56] One of these studies was a case-based review of 153 cases observed over 16 years of clinical practice, and primarily summarized safety data.[52] Excluding this report, the remaining 13 case reports detailed the effectiveness of high-dose IVC in a population consisting of 68 patients with the following cancer types: colorectal (n = 10), breast (n = 8), bladder (n = 7), kidney (n = 7), lung (n = 8), lymphomas (n = 8), ovarian (n = 5), stomach (n = 5), pancreatic (n = 3), gallbladder (n = 2), brain (n = 1), melanoma (n = 1), and others (n = 3).
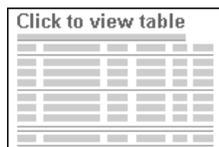
**Table 3.** Case Reports of High-Dose Intravenous Vitamin C (HD-IVC) Use in Cancer Patients.

Collectively, the case reports documented 1 or more of the following outcomes: (*a*) cancer remission and long-term cancer-free survival; (*b*) survival considerably beyond life expectancy; (*c*) initial disease stabilization but recurrence or death after IVC was decreased or stopped; (*d*) tumor stabilization and/or regression based on circulating tumor markers (eg, CA-125), CT scans, x-ray, bone scans, or other imaging techniques; and (*e*) improvements in pain related to bone metastasis and a reduction in the need for pain medication.[2,10,46,48,49,51,55,57] The first published case series, by Cameron in 1974, documented a 16% survival rate at 1 year associated with use of IVC among a population of 50 terminally ill cancer patients not responding to conventional therapy.[10]

One early report of 3 cases described adverse reactions to high-dose IVC in 2 patients with advanced Hodgkin's lymphoma and 1 with bronchial carcinoma.[56] The reactions consisted of worsening of dyspnea, shortness of breath, and mediastinal compression in 2

cases and the incidence of acute fever and pain at the tumor site in 1 case. This appeared to be associated with administration of high doses of IVC without a gradual dose escalation period and may have been related to tumor necrosis in advanced disease. In the first 2 cases, symptoms were rapidly relieved by emergency chemotherapy, and in the third case, symptoms resided after 48 hours, after which IVC was reinstituted starting gradually at 4 g, gradually increasing to 10 g per day, which was well tolerated. None of the other case-based data reported any serious adverse reactions.

Low-Dose IVC

Low-dose IVC (1 g) has been studied for its immunological effects[58] in addition to as part of a chemotherapy regimen for multiple myeloma featuring arsenic trioxide as well as secondary drugs including bortezomib, melphalan, decitabine, and dexamethasone.[7,59-61] See Table 4.
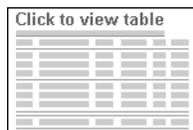
Table 4. Description of Human Trials of Low-Dose IVC in Patients With Multiple Myeloma (MM) or Leukemia.

Randomized Controlled Trials

In one study, an RCT in 51 chemonaive patients with multiple myeloma, 2 g IV cefodizime (a cephalosporin antibiotic) was compared with 1 g IV vitamin C for effects on nonspecific immune function, with each being given daily for 7 days. In this study, cefodizime but not IVC resulted in significant increases in neutrophil activity and phagocytosis.[58]

Phase I/II and uncontrolled studies

Seven studies assessed low-dose IVC for reducing toxicity of arsenic trioxide based chemotherapy regimens. Although arsenic trioxide is no longer commonly used, these studies provide additional information about the possible safety of IVC alongside this and the secondary drugs, such as bortezomib, melphalan, dicitabine, and dexamethasone. In these studies, 1 g intravenously administered vitamin C was given on the days of arsenic trioxide administration in order to improve tolerability. In general, the addition of vitamin C to this regimen appeared to be well tolerated, with most adverse events attributed to the chemotherapy regimen. The therapeutic effects of IVC were difficult to determine due to lack of a control group and simultaneous administration of multiple chemotherapy drugs; however, the authors commented that the addition of low-dose IVC to this regimen appeared to be well tolerated.[60-62]

Interactions

Existing evidence suggests safety of IVC when given alongside most chemotherapy agents, with possible synergistic effects seen in some studies, such as those with gemcitabine and paclitaxel/carboplatin.[5,7,37] Ma et al evaluated high-dose IVC in ovarian cancer patients receiving paclitaxel and carboplatin and found that there was a reduction in chemotherapy-related side effects, as well as a trend toward longer time to relapse compared to chemotherapy alone (RCT).[37] Monti and Welsh evaluated high-dose IVC in combination with gemcitabine and/or erlotinib and found reductions in tumor mass and possible improvements in survival in stage IV pancreatic cancer patients, and no evidence of increased toxicity with the addition of vitamin C (phase I).[5,7] Vollbracht et al investigated 7.5 g IVC alongside standard therapies in early-stage breast cancer patients, where the standard therapies were epirubicin/cyclophosphamide (56%), cyclophosphamide/methotrexate/fluorouracil (20%), and fluorouracil/epirubicin/cyclophosphamide (15%). In the study, IVC significantly reduced side effects without any evidence of increased toxicity compared to patients receiving standard therapies alone.[6] One case report of a patient with advanced colorectal cancer reported complete remission with high-dose IVC therapy alongside 5-fluoruracil and leucovorin.[49] Trials of low-dose IVC suggest that it does not increase the toxicity of arsenic trioxide, melphalan, bortezomib, or dexamethasone.[59-61] Overall, there is a lack of evidence for any negative interactions; however, further evaluation in this area is needed.

Discussion

The results of our review suggest that there is limited, high-quality research on high-dose IVC. Though it suffers largely from bias and gaps in reporting, the existing literature suggests that high-dose IVC may be a safe and effective adjunctive therapy in the treatment of cancer. There are no data suggesting that high-dose IV Vitamin C can be used effectively as a stand-alone anticancer agent. Existing data coming from heterogeneous trial methodologies and populations precludes meta-analysis at this point. Preliminary data from 1 RCT indicate that the addition of IVC to standard chemotherapy for ovarian cancer may improve time to relapse as well as reduce the side effects of chemotherapy.[37] Data from phase I/II trials and observational studies are promising though not conclusive, suggesting improvements in QOL, reductions in the side effects of chemotherapy and/or disease-related symptoms, as well as possible improvements in

survival.[5-8,11,44,45] These studies are not conclusive due to their methodological limitations, such as the uncontrolled nature of the trials, small sample size, or observational design. Although a weaker grade of evidence, case reports demonstrate several instances of cancer remission associated with high-dose IVC, supported by objective assessments.[2,46-50] To date, studies investigating the safety of IVC alongside standard chemotherapy regimens have yielded encouraging results, with no evidence of increased toxicity, and in some cases suggesting improved outcomes.[5-7,37] Existing evidence shows consistency between studies and across study designs regarding outcomes associated with IVC, including consistent documentation of improvements (or stabilization) of QOL, reduction in side effects and cancer-related symptoms, as well as early suggestions of a positive impact on survival and tumor response. We did not evaluate for publication bias, and there is a possibility that this may have inflated our findings of positive reports. Further investigation is warranted to better elucidate the effects of this therapy in controlled settings, given an apparent excellent safety profile, low cost, and potential for both anticancer activity and improving QOL.

Survival Time in Phase I/II Studies

Uncontrolled studies[5,7] provide some data that the addition of IVC to chemotherapy may enhance tumor response in advanced-stage cancer patients, specifically pancreatic cancer, and increase survival. The authors of one study noted that compared to other reports of stage IV pancreatic cancer treated with gemcitabine, preliminary results achieved with the addition of adjunctive IVC therapy were superior to gemcitabine alone, where median progression-free survival was 9 weeks, and overall survival was 6 months.[7,63] The IVC study results pertain to mean survival, rather than median survival, the outcomes reported (mean survival 13 months, and time to progression 26 weeks) are consistent with a better than expected survival time for this patient population. This is consistent with findings from the first RCT evaluating IVC in patients with advanced ovarian cancer, with a trend toward longer time to relapse. Based on these preliminary data, there is an urgent need for more rigorous, adequately powered evaluations to assess the effects of IVC on hard outcomes such as tumor response and particularly overall survival using randomization and ideally blinding in study design.

Symptom Management and Quality of Life

Results reported by the single RCT, cohort studies, as well as early data from phase I trials suggest that IVC may have a beneficial effect in maintaining or improving QOL,[3,8]

maintaining physical function,[38,42] and reducing symptoms associated with chemotherapy or disease progression.[6,8,37] Although these outcomes are important in themselves, improving patients' tolerance to treatment may also help maximize the anticancer effects of chemotherapy. Patients who tolerate chemotherapy may be more likely to continue with the recommended number of cycles and may have fewer dose reductions and treatment delays. Similarly, increased tolerability and reduced toxicity of chemotherapy may allow patients to substantially surpass the expected maximum number of ongoing chemotherapy treatments that they can safely tolerate, again potentially allowing patients to receive greater benefit from the anticancer effects of chemotherapy.

The single RCT evaluating both side effects and survival indicates 2-fold less chemotherapy related side effects as well as a trend toward longer time to relapse in advanced stage ovarian cancer patients. Although positive findings need to be replicated, it does suggest that the reduction in side effects seen with IVC therapy may not be attributable to a reduction in the effectiveness of chemotherapy. This lack of negative interaction is consistent with in vivo data.[64-66]

Mechanism of Action

The primary mechanism of high-dose IVC appears to be as a prodrug for the formation of hydrogen peroxide.[7] In extracellular fluid, vitamin C as ascorbate dissociates into the ascorbate radical ($AscH^{\cdot-}$), effectively reducing iron to the ferrous form according the reaction: $AscH^- + Fe^{3+} \rightarrow Fe^{2+} + AscH^{\cdot-} + H^+$.[15] The ferrous iron from this complex reacts with oxygen, producing the superoxide anion ($O2^{\cdot-}$) that then reacts with hydrogen to form hydrogen peroxide (H_2O_2).[15] According to Fenton chemistry, transition metals such as iron or copper function as efficient electron carriers, accepting and transferring electrons between other substances. Having received an electron from ascorbate, iron in the ferrous form (Fe^{2+}) reacts with hydrogen peroxide (H_2O_2) to yield the highly reactive hydroxyl radical ($OH\cdot$) in the classic Fenton reaction: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^-$.[15]

According to Levine, the downstream targets of reactive oxygen species (ROS) generated from H_2O_2 are diverse, and the precise type of damage effected differs by cancer cell and tissue type.[15] This feature may in part explain the broad activity of IVC across many cancer types.[22] In laboratory models, high concentrations of vitamin C have consistently

been shown to generate extracellular H_2O_2 in several cell lines, and diverse downstream targets associated with ROS production,[22,67] including cell cycle arrest (G_0/G_1)[22] and/or inhibition of cell growth and division,[68] caspase-independent autophagy mediated by beclin-1 and LC3 II,[69] apoptosis via induction of apoptosis-inducing factor (AIF),[70] induction of oxidative DNA damage,[71] apoptosis mediated by Bax protein signaling, release of cytochrome C from the mitochondria, activation of caspase 9 and caspase 3, and cleavage of poly[ADP-ribose] polymerase.[72]

Laboratory studies have shown that high concentrations of vitamin C induce cytotoxicity and apoptosis in prostate cancer,[73] pancreatic cancer,[24] lung cancer,[74] and colorectal cancer cells[75]; suppress hypoxia inducible factor (HIF)[76,77]; can reactivate p53[78]; induce caspase-independent death[24,69]; and have been shown to suppress tumor growth and prolong survival in xenograft models.[21,24,79] Vitamin C has also been shown to sensitize cancer cells to chemotherapy such as gemcitabine, resulting in a synergistic cytotoxic response.[80] Of note, vitamin C's selective cytotoxic activity appears to be influenced by tumor expression of sodium-dependent vitamin C transporter 2 (SVCT-2); in human breast cancer cells, expression of SVCT-2 resulted in attainment of higher intracellular vitamin C concentrations and greater ROS damage leading to caspase-independent autophagy.[69] SVCT-2 expression appears to sensitize cells to autophagic damage and may serve as a future biomarker in identifying those breast cancer patients most likely to benefit from IVC therapy.

In addition to ROS generation with consequent cytotoxic effects, and chemosensitization, vitamin C has been shown to inhibit angiogenesis and decrease inflammation through suppression of COX-2 and NF-κB.[81-84] A study in melanoma cells showed that vitamin C suppressed VEGF RNA expression and transcription, likely through regulation (inhibition) of cyclooxygenase (COX)-2 expression and mitogen-activated protein kinases (MAPK) signaling.[83] MAPKs are an important signaling molecule in the production of VEGF.[83] Another study showed similar results, with vitamin C suppressing proliferation of human melanoma cells via the downregulation of insulin-like growth factor (IGF-II), followed by activation of p38 MAPK and the inhibition of COX-2 expression.[85] Another study assessed the effects of high-dose vitamin C injections in mice carrying sarcoma xenografts: not only did the survival rate increase by 20% in the vitamin C group, compared to the controls, but there was a significant reduction in the expression of 3 angiogenesis-related genes, bFGF,

VEGF, and MMP2.[86] Several preclinical studies demonstrate the ability of vitamin C to inhibit TNF-α induced activation of NF-κB in cancer cells.[81,82,87]

The reason why some patients appear to respond favorably to IVC therapy, such as those documented in case reports, while others have not is unclear. SVCT-2 expression has been suggested as a possible biomarker for cellular vitamin C uptake and responsiveness to therapy.[69] There may be other interindividual variations in vitamin C metabolism, including factors that affect maximal intracellular vitamin C concentrations, that have not yet been identified, as well as differential susceptibility to vitamin C among tumor subtypes. Tumor cell catalase expression is one factor that has been identified as mediating vitamin C resistance, and silencing of catalase expression has been shown to reverse vitamin C resistance in BT-20 breast cancer cells.[88] In addition, genetic variations in vitamin C transporters has been shown to modify risk of certain cancers,[89-91] and it is possible that such variations may also be influential in determining an individual's response to IVC therapy.

Safety

When precautions are taken, IVC appears to have a relatively good safety profile. Adverse effects reported in the studies we included were largely attributable to chemotherapy; however, the more commonly reported side effects attributable to IVC include transient nausea due to osmotic load, headache, lightheadedness, and dry mouth.[3,5,7,40] According to Riordan, IV fluid osmolality of less than 1200 mOsm is generally well tolerated.[92] Less commonly reported side effects may include grade I-II fatigue, diarrhea, insomnia, hypertension, decreased appetite, chills (likely due to cold temperature infusion), and hyperglycemia.[3,5,7,38,40] High-dose IVC has also been shown to falsely elevate glucose on blood testing.[93] DLTs included electrolyte imbalances, including hypernatremia and hypokalemia. Many dosing protocols combine high-dose IVC with calcium chloride, magnesium chloride, and potassium chloride to offset these shifts.[3,94] High-dose IVC is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to risk of hemolysis; therefore, red blood cell G6PD screening is required.[49] Patients with brain metastasis, rapidly growing tumors, or a heavy tumor load may be at increased risk of tumor necrosis, based on an early report in the literature of tumor necrosis accompanied by acute fever, dyspnea, and mediastinal compression following IVC therapy that was given without gradually escalated doses.[56] A graduated dosing schedule is now generally recommended for all patients, with 10 to 15 g used as a

starting dose, and increased to 25 g or more if well tolerated.[23,92] High-dose IVC is contraindicated in patients with renal insufficiency or on hemodialysis, as well as forms of iron overload due to risk of worsening these conditions.[92] Some concern has been raised with respect to risk of kidney stone formation in patients with a history of previous kidney stones, due to vitamin C increasing urinary oxalate excretion[38,43]; however, only one incident of kidney stones was reported among the studies included here.[40] Because magnesium has been shown to help inhibit oxalate stone formation in recurrent stone formers,[95,96] magnesium is often added to the IVC formula.[92]

Interactions

Among the studies included here, IVC was examined alongside several chemotherapy drugs. Studies showed that IVC in combination with paclitaxel and carboplatin[97] as well as gemcitabine and erlotinib[5,7] may improve time to relapse, survival, and tumor mass reductions compared to chemotherapy alone. One of these studies also demonstrated a large decrease in chemotherapy-related side effects,[97] demonstrating that while there appears to be no negative impact on efficacy based on relapse rates, there may well be a protective effect on normal tissue from the use of IVC. One study of IVC alongside epirubicin, cyclophosphamide, methotrexate, and fluorouracil showed no evidence of increased toxicity and decreases in chemotherapy-associated side effects; however, effects on survival or tumor mass were not assessed.[6] Data from one case report showed complete remission with high-dose IVC therapy alongside 5-fluoruracil and leucovorin. Although preliminary, available data suggest that IVC therapy may be safe when used alongside these drugs.[49] IVC also does not appear to increase the toxicity of arsenic trioxide, melphalan, bortezomib, or dexamethasone, although effects on survival are not known.[59-61] Overall, the documentation is suggestive of positive interactions between IVC and other cancer agents, although details of coadministration are varied and sometimes unclear.

Intravenously administered vitamin C has a relatively short half-life, approximately 2 hours in cancer patients given varying doses.[3] It has been suggested that where evidence on interactions between natural substances and chemotherapy drugs are unknown, an appropriate dosing protocol may be the spacing of both therapies 5 half-lives apart.[98] Since 5 half-lives is the accepted length of time for a substance to be eliminated from the body, this would minimize the risk of direct interactions during the time when chemotherapy is exerting its biological effects. In the absence of clinical data, it may be

necessary to carefully examine preclinical data in order to establish the existence of additive effects, interference, or no interaction between vitamin C and chemotherapeutic agents. Although not exhaustive, high concentrations of vitamin C havebeen shown to have additive effects in combinationwith the following chemotherapy agents: cisplatin,[12,99-103]cyclophosphamide,[104] doxorubicin,[104-107] etoposide,[108] fluorouracil,[12,14,100] gemcitamine,[80,109] irinotecan,[14] paclitaxel,[99,110,111] tamoxifen,[112] vincristine,[111,113,114] and FOLFIRI[14] and FOLFOX[14,65] regimens. Conversely, IVC may interfere with the effects of bortezomib[115,116] and methotrexate[100] based on in vitro data.

There is a report of oral vitamin C increasing prothrombin time in a patient who was stable on warfarin therapy.[117] However, a subsequent study involving 19 patients with escalating doses from 3 to 10 g per day for 7 days concluded that vitamin C had no impact on the pharmacodynamic actions of warfarin.[118] There is also a single report of possible resistance to warfarin; however, this was associated with low-dose oral vitamin C in a patient who was reportedly also taking several other self-prescribed, over-the-counter supplements, and has not been reported to be a special risk of IV administration.[119]

Dosing protocols varied among the studies included in our review. In addition to vitamin C, the inclusion of calcium chloride, magnesium chloride, and potassium chloride in the IV formula may improve tolerability and reduce potential electrolyte imbalances as well as risk of kidney stones. Dosing schedules vary from weekly up to 4 times weekly[3,6]; however 2 to 3 times weekly appears to be most common among the studies reviewed here including among studies showing antitumor effects.[5,7,8,97] A test dose of IVC is given as the first treatment, 10 to 15 g, and if well tolerated a medium dose of 25 to 30 g is often given next, with the third dose in the range of 50 g or more.[3,4,8,92] According to Riordan, this protocol should be followed for at least a year for antitumor effects, although studies have shown preliminary antitumor effects (time to relapse, tumor size, response rate) even after 6 months and 8 weeks of treatment.[7,97] This is an area needing further study as well as prudent clinical judgment. Certainly case-based data support the long-term use of IVC, with many patients continuing less frequent but still regular treatments for several years in their efforts to maintain remission.

Limitations

The primary limitation of our review is related to the quality of the evidence, with much of the evidence on IVC consisting of uncontrolled studies and case reports. Assessments of

risk of bias of all studies were relatively high due to design and reporting, most importantly small sample size and lack of use of an appropriate control group. This limits our ability to draw conclusions regarding effectiveness, including the magnitude of the effect if any, optimal dosing schedule, and in comparison with other therapies. On the other hand, controlled studies consisted of 2 RCTs, 1 cohort study, and 3 case–control studies, and the outcomes reported by these studies were consistent with reports of uncontrolled studies.[6,11,44,45,58,97]

Strengths

To our knowledge, this review is the first systematic review of the literature examining the use of intravenously administered vitamin C therapy. Our review is broad in scope, and we have drawn on data from case reports, phase I trials, uncontrolled studies, as well as more rigorous evidence from RCTs. This is a critical first step in advancing an emerging field of research. We report not only on effectiveness in relation to tumor response and survival but also evaluate QOL, symptom scales, and tolerability in combination with standard therapies. There is a surprising amount of data available in these areas despite the inherent limitations of funding and conducting this type of research, as well as several ongoing trials assessing IVC in refractory non-Hodgkin's lymphoma (Clinicaltrials.gov NCT00626444); in combination with gemcitabine for pancreatic cancer (NCT01654861); and in combination with irinotecan for colorectal cancer (NCT01550510). There is also currently a multicenter, prospective cohort study ongoing at the Ottawa Integrative Cancer Centre and the Canadian College of Naturopathic Medicine examining QOL and survival parameters, which will further add to the body of evidence on IVC.

In conclusion, high-dose IVC is a promising investigational therapy. Insufficient evidence exists to draw conclusions, though the literature does suggest IVC has a good safety profile as an adjunctive therapy in the treatment of cancer. High-quality evidence with large sample sizes and rigorous follow-up is lacking. Preliminary evidence suggests that IVC may have the potential to improve tumor response and survival time, as well as improve QOL and side effects of chemotherapy or cancer-related symptoms; however, there is an urgent need for rigorous and well-controlled evaluations of IVC as an adjunctive treatment for cancer before definite conclusions can be drawn.

Appendix

Search Strategies (Updated in April 2013)

Click to view table
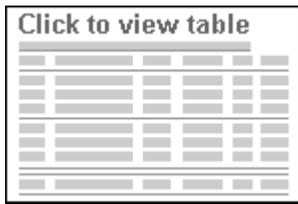
Ovid MEDLINE(R) 1950 to March Week 2 2010

Database: EMBASE, Ovid MEDLINE(R)

Search Strategy:

_____

1 (intravenous vitamin c or IV vitamin c).tw.

2 exp Ascorbic Acid/ (68934)

3 intravenous drug administration/

4 2 and 3

5 ((vitamin c or ascorbic acid or l-ascorbic acid or sodium ascorbate or magnesium ascorbicum or magnorbin or ferrous ascorbate or hybrin) adj3 (intravenous$ or intra-venous$ or IV)).tw.

6 1 or 4 or 5

7 human/

8 6 and 7

9 remove duplicates from 8

The Cochrane Library

(vitamin c or ascorbic acid or l-ascorbic acid or sodium ascorbate or magnesium ascorbicum or magnorbin or ferrous ascorbate or hybrin) adj (intravenous$ or intra-venous$ or IV)

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