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Healthcare Provider Resource: Intravenous Vitamin C (IVC)

Proper Name
Ascorbic acid, Ascorbate

Common Name
Vitamin C

Route of Administration
Intravenous (IV)

Common Uses in Cancer Care
IVC is most commonly used in cancer care to improve quality of life, reduce cancer-treatment related symptoms, and possibly to slow cancer progression and improve cancer treatment outcomes.

Summary
Pharmacological levels of plasma ascorbate (≥0.3mM) is achievable only through IV administration. Cytotoxicity of vitamin C to cancer cells in vitro occurs at plasma levels ranging from 1mM to >20mM depending on cancer type; thus plasma levels of 20mM are commonly targeted to achieve potential cytotoxic effects *in vivo*. The dose required to achieve plasma ascorbate levels of 20mM typically ranges between 1-1.5g/kg of body weight (BW) per infusion. Proposed mechanisms of action of high dose IVC include generation of hydrogen peroxide creating oxidative stress, enzyme cofactor activities, and antioxidant and anti-inflammatory actions. Sixteen prospective trials which include two randomized trials and 14 single-arm trials of IVC have been published. There have been no randomized placebo-controlled trials, and all published studies have been relatively small. Results from these trials as well as from observational studies demonstrate that IVC is generally safe and well tolerated, with minimal and mild side effects. Some but not all studies have found benefit for quality of life and symptom management alongside cancer treatments or as monotherapy. There is promising preliminary research for IVC administered in addition to standard treatments for tumour response and survival outcomes in advanced pancreatic and ovarian cancers. More research is needed, particularly from larger, randomized and placebo controlled trials to confirm these findings and better study its impact in other cancers.

Pharmacokinetics

The administration of IVC results in far higher serum levels of vitamin C (between 30 to 300 fold) than oral administration of an identical dose (1, 2). IV administration bypasses the limitations of gastrointestinal absorption present when taken orally (3). Physiologic plasma concentrations of ascorbate are in the uM range, up to 0.2mM with maximal oral ingestion. Pharmacologic concentrations

of ascorbate are defined as 0.3mM and higher, which are not achievable by oral intake but are easily achievable through IV administration (4). Only the IV route of administration has been documented to achieve sufficient serum levels to observe a cytotoxic effect on cancer cells *in vivo* (2). Cytotoxicity of pharmacologic vitamin C to cancer cells occurs at plasma concentrations that vary from 1mM to >20mM depending on the tumor cell line evaluated (4, 5).

Plasma concentrations of vitamin C vary based on dose administered, and can vary from person to person based on their body weight, tumor burden, and baseline plasma vitamin C levels. One phase I trial evaluated serum levels of vitamin C in individuals with advanced cancer after doses of 30, 50, 70, 90, and 110 g/m^2 (approximately equal to 60, 100, 140, 180, and 220g for a six foot, 180lb male). Serum levels plateaued at 49mM with the $70g/m^2$ dose, which the authors recommended for dosing in future trials (6). However, most studies to date have used slightly lower doses in the range of 1-1.5g/kg BW, which typically correlates to dosing of 60 to 100g of ascorbic acid, to achieve plasma concentrations of 20 mM (7-13). Pharmacokinetics can vary considerably from person to person; therefore in order to obtain optimal therapeutic effect, plasma levels for individual people might need to be measured (14). People with a higher tumour burden may require a higher dose to achieve plasma levels of the same magnitude as those with a smaller tumour burden (14).

Pharmacologic concentrations (0.3 to 20 mM) of vitamin C are cleared within hours by renal filtration and excretion (4). IV vitamin C exhibits first order elimination kinetics (15), and has an elimination half-life between 30-120 minutes (6, 15, 16). In one trial, 80% of the administered doses of IVC had been filtered by the kidneys in the 6 hours following infusion (17). Thus, plasma vitamin C concentrations are not maintained in the cytotoxic range for long with bolus IV infusion.

Vitamin C blood levels in people with cancer, and in particular with advanced disease may be lower than in healthy individuals (18). Cancer increases oxidative stress and inflammation in the body, which increases ascorbate utilization due to its antioxidant properties (18).

Mechanism of Action

Three primary mechanisms of action have been proposed regarding the possible anticancer effects of IVC: generation of hydrogen peroxide creating oxidative stress, enzyme cofactor activities, and antioxidant and anti-inflammatory functions (19). These mechanisms are supported by several preclinical trials, although all require further study.

Pro-Oxidant Effect

Although vitamin C acts as an antioxidant via the donation of electrons, high concentrations can cause the formation of hydrogen peroxide (H_2O_2) in tumour cells, which has a pro-oxidant effect (3, 4). High concentrations of vitamin C increase the reduction of transition metal ions, which can generate superoxide radicals that react to form H_2O_2. H_2O_2 enhances oxidative stress through the generation of free radicals and causes cell death by pyknosis/necrosis. Normally, transition metals (such as copper and iron) are bound to proteins and thus are not able to be reduced by vitamin C. It is thought that the tumour microenvironment contains more free transition metal ions, allowing more H_2O_2 to be produced. Healthy cells also combat the oxidative stress of H_2O_2 by producing various enzymes (catalase, glutathione peroxidase, and peroxiredoxin-2) that work to break it down. These enzymes are thought to be deficient in cancer cells, allowing the H_2O_2 to exert its pro-oxidative activities (19).

Enzyme Cofactor Activities

Vitamin C exerts various effects on transcription factors and cell signaling pathways, which can affect the cell cycle, angiogenesis, and cell death pathways even at concentrations achievable through oral and low dose parenteral administration (20). Vitamin C is a cofactor for enzymes essential for collagen structure. *In-vivo* studies show increased collagen encapsulation and associated decreased metastases in various cancer models following supplementation with low-dose vitamin C (21-23). Vitamin C is also a cofactor for various hydroxylases and histone demethylases that regulate gene transcription. Changes in the regulation of these enzymes and increased vitamin C levels in tumours have been shown in many studies (21). Vitamin C may therefore be involved in epigenetic changes by acting as a cofactor for DNA and histone demethylases.

Antioxidant and anti-inflammatory activities:

Reductions in various inflammatory, oxidative, and angiogenesis markers have been found in studies of IVC. One study of patients with cancer administered 6 IVC treatments over a two-week period and found reductions in various inflammatory and angiogenesis-promoting cytokines. However, the pre-versus-post treatment changes were not statistically significant which the authors attributed to their small sample size (n= 12) (24). Angiogenesis and inflammation play a role in cancer initiation and progression, and thus are possible targets of cancer therapy. Another study found reductions in a marker of oxidative stress (F2-isoprostanes) in patients with pancreatic cancer who received high dose IVC (7). C-reactive protein (CRP) was decreased in 75% of patients in a retrospective study of IVC for patients with variable types of cancer (25). Together, these studies indicate IVC likely has a systemic antioxidant and anti-inflammatory effect, which may contribute to its benefit in patients with cancer.

Clinical Evidence Related to Effectiveness

Prospective clinical trials of IVC for cancer are summarized in Table 1. Results from 16 prospective trials have been published at the time of this update. None were double blind placebo controlled trials, two were randomized controlled trials and 14 were single-arm trials. A variety of cancer types have been studied and the most studied (by number of participants) are prostate, ovarian, pancreatic, lung, and glioblastoma. Overall, IVC concurrent with oxidative therapies such as chemotherapy and radiotherapy shows greater promise for improvements in quality of life and additive anti-tumour effects compared to IVC as monotherapy or with non-oxidative therapies (e.g. androgen deprivation therapy). IVC has shown promise in improving survival and quality of life in patients with advanced pancreatic (7, 13, 21, 26) and ovarian (27) cancers, and further research should be done to explore its effectiveness for these and other conditions.

IVC MONOTHERAPY

The majority of prospective studies to date have evaluated IV vitamin C alongside conventional cancer treatments such as chemotherapy and radiation therapy. Although preclinical data and case reports have indicated a possible role for IVC monotherapy as a cancer treatment, the limited available prospective data has failed to confirm this. Four of the studies in table 1 evaluated IVC as a monotherapy, none were randomized (6, 9, 15, 28).

Quality of life

Most published human studies of IVC monotherapy have included only patients with advanced disease. In three small prospective trials of patients with mixed types of advanced cancers, quality of life remained stable in two (6, 9) and improved in another (28). All three of these studies included patients with various types of advanced cancers whoreceived IVC 1-3 times weekly over the course of 1-4 weeks. These results are notable, as quality of life would otherwise be expected to decrease in this population of patients with advanced disease.

A retrospective review of all patients receiving IVC at Thomas Jefferson University Hospital over a 7 year period was conducted to analyze adverse effects (AEs) of IVC, and symptom changes in patients receiving IVC (29). The review included 86 people with various types and stages of cancer; 32 patients received IVC alone (1197 doses), and 54 received both IVC (1837 doses) and chemotherapy (including paclitaxel, carboplatin, sorafenib, irinotecan, and gemcitabine). Significant improvements were reported for patients receiving IVC for fatigue, bowel habits, and pain ($p<0.05$). Non-significant improvements were found in mood, and 15/85 patients had improved weight and appetite, and only 2/85 had worsening appetite or weight.

Survival, Tumour Response, and Tumour markers

IVC is not considered a curative monotherapy for cancer (5, 9). Only two prospective trials have evaluated IVC as monotherapy for cancer treatment and neither demonstrated an objective tumor response (6, 9). Both trials included people with advanced cancers refractory to conventional therapies, and both used IVC at variable but escalating doses for 4 weeks. One study enrolled 24 people with advanced solid cancers or hematological malignancies refractory to standard therapy and treated them with IVC in a dose escalation protocol from 0.4g/kg up to 1.5g/kg 3x/week for 4 weeks (9). Although adverse events and toxicity were minimal at all doses, no objective antitumour effects were observed. In a Phase I trial, 17 people with advanced or metastatic cancer refractory to standard treatment were treated with IVC using a dose escalation design beginning at 30 g/m^2, increasing by 20 g/m^2 until a maximum tolerated dose was found (6). Sixteen people completed the study, of whom 3 demonstrated stable disease and 13 had progressive disease. No objective tumour response was documented in this advanced population.

In a retrospective chart review, IVC treatment after conventional treatment was shown to be associated with a decrease in C-reactive protein (CRP) in 75% of patients and therefore might have a role in reducing inflammation, a marker for poor prognosis (25). This study also suggests that IVC treatment might contribute to decreased levels of some tumour markers, most notably prostate-specific antigen (PSA) levels.

A handful of well-documented case reports in patients with pancreatic, ovarian, renal, and bladder cancers, as well as B cell lymphoma suggested that treatment with IVC was associated with tumour regression and remission (30-32). These outcomes are supported by animal studies conducted using high doses of vitamin C obtainable by IV infusion that demonstrate reduced tumour size (2) and decreased tumour growth rate (5). Similarly, *in vitro* evidence demonstrates sensitivity of a number of cell lines to treatment with vitamin C. Benefit has been identified in cell-line studies of lymphoma (4) and glioblastoma (5) as well as in cancers of the bladder (2), prostate (2, 33), liver (2), breast (2), cervix (2), ovary (5), colon (34) and pancreas (5, 35).

IVC IN COMBINATION WITH STANDARD CARE

Quality of life, Side effects, and Toxicity

Results from prospective trials of IVC on quality of life are mixed, with two studies finding improvement in QoL (7, 27), and two finding no change(11, 12). Results from two observational trials demonstrated positive results (36, 37).

Prospective trials:
Beneficial effects were found for studies in advanced pancreatic and ovarian cancer. A phase 1 trial (PACMAN trial) of 9 patients with metastatic pancreatic adenocarcinoma administered IVC at doses of 50g-125g (to achieve plasma ascorbic acid levels >20mM) twice weekly during gemcitabine chemotherapy (7) for an average of 6 months. The IVC was well tolerated. Six of nine maintained or improved performance status during treatment, and weight loss was considered minimal compared to usual weight loss (5.3 $\pm$1.6 kg over 6 months). In a randomized pilot phase I/II trial of women with newly diagnosed stage III/IV ovarian cancer, women received carboplatin/paclitaxel chemotherapy with or without IVC at 75g or 100g twice weekly for 12 months (27). In the 25 participants, there were no differences in grade 3 and 4 toxicities between both groups, but a significant reduction in grade 1 and 2 toxicities was seen in the IVC arm.

Less positive results were found in a trial of mixed cancers, and a trial for metastatic prostate cancer. A 2015 study enrolled 14 patients with mixed types of advanced cancer receiving usual care chemotherapy, and provided them with IVC at 1.5g/kg 3 times weekly until disease progression or unacceptable toxicity (11). There was large variability in number of IVC infusions (6-173). The study found no improvement in QoL based on questionnaires. Six of 12 whose response could be evaluated had a brief or longer lasting disease stabilization, and 3 of the 6 had an unusually favorable response. In 20 men with metastatic castrate resistant prostate cancer treated with androgen deprivation therapy administered 60g IVC weekly for 12 weeks, ECOG score remained stable for the majority of men (16/20), but there was no significant improvement in QoL questionnaires (12). None of the men achieved a 50% reduction in PSA (median PSA increased 17ug/L at 12 weeks), and no objective signs of disease remission were found.

Observational studies:
In one retrospective cohort study that included women with breast cancer, quality of life (as measured by intensity of cancer-related symptoms and treatment side effects) improved in those women who were treated with IVC in combination with standard care as compared to those who used standard care alone (36). In another prospective uncontrolled observational study, improvements in quality of life, from both the patient and physician perspective, were documented after 2 and 4 weeks of treatment in a group of newly diagnosed cancer patients (37). Other therapies used in these trials included epirubicin, cyclophosphamide, methotrexate, fluorouracil (36), paclitaxel and cisplatin (37).

Survival, Tumour Response, and Tumor Markers

In the only randomized trial to date in which IVC was given in conjunction with chemotherapy, the time to disease progression for women with advanced ovarian cancer was 8.75 months longer in the treatment arm compared to the control, but the results were not statistically significant. The small trial randomized 25 women with newly diagnosed stage III/IV ovarian cancer to carboplatin/paclitaxel chemotherapy with or without IVC at 75g or 100g twice weekly for 12 months (27). There were statistically significantly fewer grade 1 and 2 toxicities in the treatment group compared to control, and

no difference in grade 3 and 4 toxicities. The authors suggest the reason for lack of statistically significant findings with respect to disease free survival may have been the small sample size. Prior to this study, two case reports had been published documenting longer than expected survival times in women with ovarian cancer treated concurrently with IVC, carboplatin and paclitaxel (30).

Four studies in individuals with pancreatic cancer have evaluated the impact of IVC on cancer outcomes with encouraging results. A phase 1 trial (PACMAN trial) of 9 patients with metastatic pancreatic adenocarcinoma administered IVC at doses of 50g-125g (to achieve plasma ascorbic acid levels >20mM) twice weekly during gemcitabine chemotherapy for an average of 6 months (7). The IVC was well tolerated, 6/9 maintained or improved performance status during treatment, and weight loss was considered minimal compared to usual weight loss. Time to progression was 26 $\pm$ 7 weeks, and overall survival was 13 $\pm$ 2 months. The authors note that these results are considered good when compared to other clinical trials of gemcitabine therapy for stage IV pancreatic cancer which have reported OS as low as 6 months. Another study in patients with pancreatic cancer (stages II, III, IV) administered IVC at 50-100g daily during radiation therapy to 14 individuals who also received gemcitabine chemotherapy (13). 57% of participants received all 6 cycles of gemcitabine, and 100% completed radiation therapy which the authors note are better than historical averages. The median overall survival (mOS) and progression free survival (PFS) were better than the University's institutional average (21.7 vs 12.7 months, p=0.08; 13.7 vs 4.6 months, p=0.02 respectively). A phase I trial in people newly diagnosed with stage IV pancreatic were treated with IVC in combination with gemcitabine and erlotinib as first line treatment. Eight of the 9 patients who completed the trial had a reduction in the size of their primary tumour and tumour size was stable in the ninth patient, results that are not typical for treatment with either gemcitabine or gemcitabine plus erlotinib alone (26). Lastly, a phase I/IIa study used IVC at 75g or 100g with gemcitabine chemotherapy in people with metastatic or non-resectable pancreatic cancer to evaluate safety, pharmacokinetics (PK) with gemcitabine, and tumour response. They found that IVC did not alter the PK of gemcitabine in any clinically significant way; IVC was safe with only grade 1 nausea and thirst attributed to IVC. Six of 12 participants survived over 1 year; mOS was 15.1 months, which was superior to published results of gemcitabine, and gemcitabine + nab-paclitaxel treatments.

The only study to date in glioblastoma multiforme (GBM) is a phase I trial of IVC alongside radiation and temozolomide. This trial found IVC treatment to be safe, well tolerated, and documented survival outcomes which were superior to historical controls (10). Following resection or biopsy, 13 patients were treated with daily radiation, temozolomide, and thrice weekly IVC for 7 weeks, followed by temozolomide and IVC for an additional 28 weeks. Plasma ascorbate target was 20mM (doses ranged 62-125g). IVC was safe and well tolerated in all 13 participants; no serious AEs were attributed to IVC. Median PFS was 9.4 months, and OS was 18.2. Historical medians were 7 months and 14 months for PFS and OS respectively.

A preliminary report on a phase II trial of IVC for patients with non-small cell lung cancer (NSCLC) treated with platinum-doublet chemotherapy found a disease control rate of 93% and objective response rate of 29% compared to historical controls with 40% disease control and 15-19% objective response rates in the first 14 subjects (10).

While the prospective trials for survival described above are encouraging, not all studies have had promising results. In a phase I/II single arm trial, 14 patients with heavily pre-treated advanced cancer received IVC at 1.5g/kg 3 times weekly during usual care chemotherapy (11). Of the 12 who were evaluable for response, 6 had brief or longer lasting disease stabilization. Overall it is difficult to know if this represents a positive or null response. Twenty men with metastatic castrate resistance prostate

cancer treated with androgen deprivation therapy were administered 60g IVC weekly for 12 weeks (12). No patient achieved a 50% reduction in PSA (median PSA increased 17ug/L at 12 weeks), and no objective signs of disease remission were found.

Some studies have looked at inflammatory markers and tumor markers in those treated with IVC. One study enrolled 12 people with late-stage, pre-treated cancer (24). Patients received usual chemotherapy with the addition of IVC escalating from 15g to 50g, 3x/week for 2 weeks, and plasma cytokines and tumor markers were measured before and after the intervention. Following IVC treatment several favorable changes in cytokines were noted including decreases in several inflammatory and angiogenesis promoting cytokines (e.g. FGF-6, IL 1B, TGF-1), and tumor markers (CA 15-3, CA 19-9, CEA, CA 242), however results were not statistically significantly different.

IVC IN COMBINATION WITH OTHER COMPLEMENTARY THERAPIES

There is limited research regarding the effects of IVC in combination with other natural agents or complementary agents.

One prospective trial randomized 15 people with stage III/IV NSCLC who had progressed on chemo and/or radiotherapy to IVC with modulated electrohyperthermia before, during, or after IVC (38). IVC doses were administered at 1.0, 1.2, and 1.5 g/kg 3x/week for 4 weeks (5 people in each dosage cohort). Significant within-person improvements in QoL measured by the EORTC QLQ-C30 were found after 4 weeks for fatigue, dyspnea, insomnia, appetite, diarrhea, financial problems, and physical function.

One *in vitro* study suggests that the anti-oxidant compound alpha-lipoic acid (ALA) may enhance the cytotoxic effect of IVC (34), and thus that co-administration of these agents may be beneficial. Separate preclinical evidence indicates that the cytotoxicity of vitamin C is impaired by concurrent IV glutathione administration (39).

Applications with limited research:

Children
There are no prospective or observational trials which have included individuals less than 18 years of age. One case report describes the treatment of a 3 year old boy with neurofibromatosis 1 (NF1) with IV vitamin C with positive outcomes (40). The boy was diagnosed at 14 months with optic glioma, and despite chemotherapy the tumor continued to progress. At the age of 3 amidst ongoing progression and increasing treatment toxicity chemotherapy was discontinued and he started IVC (7-15g/week). Over the course of 30 months of IVC there was reduction and stabilization of tumors of the optic chiasm, hypothalamus, and left optic nerve, and the right sided optic nerve mass disappeared.

Hematological malignancies:
Leukemias:
Low dose IVC (1g) has been studied alongside conventional treatments in AML, and are discussed elsewhere (41, 42). A case report of a women with relapsed AML who was treated with IVC at 70g/infusion 2x/week alongside several natural health products resulted in disease remission with stabilization of platelets, WBCs, and QoL (43).

Multiple myeloma:

Only one preliminary study which used low dose IVC alongside bortezomib and arsenic trioxide has been studied, and is described in table 1 (44).

Lymphoma:
One small phase I study of 3 peopled with B cell lymphoma treated with IVC has been published and is described in table 1 (45). One case report of an individual with B cell lymphoma treated with IVC during and after radiation therapy but without chemotherapy resulted in disease remission and remained stable for 1.5 years until the time of writing (31).

Table 1: Prospective clinical trials of high dose intravenous vitamin C (IVC) for cancer

Reference	Study design	Participants	Intervention	Concomitant treatment	Outcomes and measures	Results
Alexander, 2018(13)	Phase I	14 patients with pancreatic adenocarcinoma stages (II, III, IV), eligible for gemcitabine and radiation therapy 19 subjects were enrolled as comparators	IVC dose escalation: 50g, 75g, 100g IVC administered daily with radiation therapy for duration of radiation (average length 5 weeks)	Radiation (IVC given simultaneously), and weekly IV gemcitabine	AEs (CTCAE v4), treatment compliance, blood draws for plasma ascorbate and F2-isoprostane (oxidative stress marker), OS	Safe, well tolerated, 3 AEs attributed to IVC (dry mouth, thirst, transient BP elevation). 57% received all cycles of gemcitabine, 100% completed radiation; better than historical averages. Plasma F2-Isoprostanes decreased in IVC group but not in comparators. Mean plasma concentrations: 50g = 15mM, 75g = 20mM, 100g = 20mM IVC group had better mOS and PFS compared with University of Iowa's institutional average (21.7 vs 12.7 months, p=0.08; 13.7 vs 4.6 months, p=0.02)
Hoffer, 2008 (9)	Phase I, single centre	24 patients with advanced solid cancers or hematologic malignancy refractory to standard therapy	IVC dose escalation: sequential cohorts of 0.4, 0.6, 0.9, and 1.5g/kg bw 3 times weekly. 4 weeks per dosage level, escalation of dose if no DLT	None, IVC monotherapy	Toxicity, preliminary antitumor effects, QoL (FACT-G), and plasma ascorbate levels	AEs and toxicity were minimal at all doses. No objective antitumor effects observed. No change in social, emotional, or functional parameters of QoL, physical function deteriorated in 0.4g/kg group but not in others. Peak plasma concentration was 26.2 mM with 1.5g/kg dose. 1.5g/kg recommended dose for future trials
Yeom, 2007 (28)	Single arm, open label	39 patients with terminal cancer	10g IVC twice within a 3 day interval, with 4g	None, IVC monotherapy	QoL (EORTC QLQ-C30)	Significant improvements after IVC in: Global health scale health

			daily oral vitamin C for 1 week			score (p = 0.001), physical, role, emotional, and cognitive function(p < 0.05), lower scores for fatigue, nausea/ vomiting, pain, and appetite loss (p < 0.005). Other function and symptom scales were not significantly changed.
Monti, 2012 (26)	Phase I, dose escalation	14 patients (9 completed) with metastatic pancreatic cancer	8 weeks of IVC administered 3x/week, with dose escalation design Cohort 1: 50g Cohort 2: 75g Cohort 3: 100g	Gemcitabine and erlotinib	Response to treatment (RECIST 1.0 criteria)	7/9 subjects had stable disease, 2/9 progressive disease. Mean PFS from start of IVC was 89 days, OS 182 days. All AEs were attributed to disease progression or gemcitabine/ erlotinib.
Hoffer, 2015(11)	Phase I/II, single-arm	14 patients with advanced cancer, for whom chemotherapy would offer <33% likelihood of meaningful response.	IVC at 1.5g/kg 3x/week on chemo weeks and 2x/week if no chemo, until unacceptable toxicity or disease progression following 2 chemo rounds	Various chemotherapy agents as per usual care	AEs, toxicity, objective clinical response, QoL (FACT-G, Profile of Mood States-B), Pk	Number of IVC infusions ranged from 6-173. IVC was safe and non-toxic, thirst and increased urination common SEs. No improvement in QoL. Variable clinical responses; 6/12 whose response could be evaluated experienced either brief or longer lasting disease stabilization with symptomatic improvement, 3 of these 6 had an unusually favorable response.
Kawada, 2014(45)	Phase I, single-arm	3 patients with relapsed B cell non-Hodgkin's lymphoma	IVC 75g administered on days 9, 11, 14, 16, and 18 of 21-day cycle	CHASER chemotherapy regimen (21 day cycle)	Safety/AEs, dose (based on serum AA concentration)	IVC well tolerated, no AEs attributed to the IVC. Serum concentration of >15mM achieved in all patients on days 9 and 18. 75g dose recommended for future trials.
Ma, 2014(27)	Randomized, pilot phase I/II trial	25 patients with newly diagnosed stage III/IV ovarian cancer, randomized to chemotherapy alone (n=12) or chemotherapy + IVC (n=13).	IVC at dose of 75g or 100g (to achieve plasma concentration of 20-23mM) twice weekly for 12 months	Carboplatin/ paclitaxel chemotherapy for 6 months	Safety and toxicity measured by CTCAE v3, survival to 5 years	No difference in grade 3/4 toxicity between groups, significant reduction in grade 1 and 2 toxicities in IVC arm (P <0.01, P = 0.028 respectively). Trend toward improved OS in IVC arm, median time to disease progression was 8.75 months longer in IVC arm compared to

						chemotherapy alone arm.
Mikirova, 2016(24)	Open label pilot trial	12 patients with late-stage, pretreated cancer	IVC as per Riordan protocol (15g, then 25g, then individualized dosing up to 50g), 3 infusions/week for 2 weeks Cytokines in 8 healthy volunteers were evaluated for comparison	Usual care (chemotherapy in most cases)	Blood analyses for plasma ascorbate, cytokines, tumor markers	Plasma ascorbate ranged from 5mM (15g infusion) to 15mM (50g infusion). Several favorable changes in cytokines were noted including decreases in several inflammatory and angiogenesis promoting cytokines (e.g. FGF-6, IL-1B, TGF-1), and tumor markers (CA15-3, CA 19-9, CEA, CA 242).
Nielsen, 2017 (12)	phase II, single arm	20 patients with metastatic castrate-resistant prostate cancer (mCRPC)	IVC 60g once weekly for 12 weeks (participants also given 500mg oral ascorbic acid daily)	Androgen deprivation therapy. No chemo (if participant started chemo, IVC was discontinued)	Primary: PSA (target was 50% reduction) Secondary: QoL (EORTC QLQ-C30), safety, imaging, biomarkers (several including: Hgb, LDH, ALP, albumin, CRP). Follow-up at weeks 12, 20, 26, and 52	No patient achieved a 50% reduction in PSA, there was a median PSA increase of 17 ug/L at 12 weeks. No signs of disease remission, ECOG score stable for majority of patients (16/20), no significant improvement in any biomarkers or QoL questionnaires. 3 AEs related to AA – all related to fluid load.
Welsh, 2013(7)	Phase I, open label	9 patients with stage IV pancreatic adenocarcinoma	IVC to achieve plasma AA of >20mM (50-125g), administered 2x/week during chemotherapy	Gemcitabine chemotherapy, 4 week cycle (3 weekly infusions, 1 week rest)	Primary: Toxicity of IVC (CTCAE v3), plasma ascorbate levels Secondary: Response (RECIST), performance status, weight, TTP, OS, hematologic/ metabolic labs	No DLTs or SAEs; safe and well tolerated. 6/9 subjects maintained or improved performance status during treatment, average tx duration was 6 months. Time to progression was 26 $\pm$ 7 weeks, and OS 13 $\pm$ 2 months for those receiving at least 8 weeks of treatment
Ou, 2017 (46)	Phase I, randomized single blind trial	15 patients, stage III/IV NSCLC who progressed on radio and/or chemotherapy	IVC dose escalation: 1.0, 1.2, and 1.5g/kg administered 3x/week for 4 weeks. Each dosage level was administered 4 times and if no DLTs then dose increased	Modulated electrohyperthermia (mEHT) before, during, or after IVC depending on randomization (3 groups of 5 people)	Plasma ascorbate, DLT, QoL(EORTC QLQ-C30)	Plasma AA at baseline was lower in the study group than in healthy people (0.05 vs 0.09 mM, $p < 0.05$). The 1.5g/kg dose achieved peak plasma concentrations of 21-25mM. AEs/toxicity: mild (grade 1-2) thirst and fatigue, one patient had serious diarrhea at 1.5g/kg and was removed from trial. No

						hematological or creatinine abnormalities. QoL: On symptom subscale: significant within person improvement after 4 weeks in fatigue, dyspnea, insomnia, appetite, diarrhea, and financial problems ($p<0.05$). On function subscale only physical function improved significantly. Note: IVC and mEHT were both experimental interventions, results cannot be attributed to IVC
Stephenson, 2013 (6)	Phase I PK study	17 patients with advanced solid tumors who had not responded to standard therapy	IVC dose escalation protocol, 5 cohorts: 30, 50, 70, 90, 110 g/m^2 Treatment administered 4x/week for 4 weeks at each dosage level	No standard conventional therapy. All patients received a multivitamin and EPA (2000mg)	Safety, tolerability, and PK of IVC, QoL (EORTC QLQ-C30)	Half-life: 2.0 $\pm$ 0.6 h Cmax and AUC increased proportionately with dose, but reached maximum at 70 g/m^2 (Cmax 49mM, AUC 219 h mM). No objective tumor responses observed. Several EORTC scores improved slightly in weeks 3-4 compared to baseline. IVC was well tolerated, SEs were mild except 3 participants experienced moderate to severe hypokalemia, and 2 experienced hypernatremia.
Nielsen, 2015 (15)	Phase I PK study	10 patients with metastatic castrate-resistant prostate cancer	IVC administered once weekly for 4 weeks at fixed doses of 5g (week 1), 30g (week 2), and 60g (weeks 3 and 4)	None, IVC monotherapy	Pharmacokinetic measurements	IV vitamin C exhibits first order elimination kinetics. 60g dose achieved peak plasma ascorbate concentration of 20.3mM. Elimination half-life 1.87h, volume distribution 0.19 L/kg, clearance rate 6.02L/hr. No difference in pharmacokinetics between doses.
Schoenfeld, 2017 (10)	Phase 1	13 patients with Glioblastoma	IVC administerd 3x/week to target	7 weeks of daily radiation and	Safety, tolerability, survival	IVC safe, well tolerated, no serious AEs attributed to IVC.

		multiforme (GBM)	plasma concentrations of >20mM (62-125g)	temozolomide		Median PFS 9.4 months and OS 18.2 months (historical median PFS is 7 months and median OS 14 months)
Schoenfeld, 2017 (10)	Phase II single arm	14 patients with Non-small cell lung cancer (NSCLC)	IVC administered 2x/week at 75g per infusion for 4 cycles of chemotherapy	Platinum-doublet chemotherapy	Safety, response to treatment	No grade 3 or 4 toxicities related to ascorbate. Partial responses in 4, stable disease in 9, progression in 1. Disease control rate of 93% and objective response rate of 29% which is better than historical controls (40% disease control rate and 15-19% objective response)
Polireddy, 2017 (21)	Phase I/IIa single arm	12 patients with metastatic or unrescectable pancreatic cancer who declined combination chemotherapy or progressed on a non-gemcitabine regimen	Phase I: IVC alone dose escalated to 100g, then combined (same day) with gemcitabine to evaluate PK Phase IIa: IVC 3x/week (75 or 100g) with gemcitabine until tumor progression or patient withdrawal	Gemcitabine chemotherapy	Safety, PK, tumor response, survival	Half-life (T1/2) of gemcitabine was shortened by 9% when combined with IVC, but given the short half- life of gemcitabine (0.28H) the change (to 0.25H) is likely not clinically significant. AEs attributed to IVC were grade 1 nausea and thirst. 6/12 (50%) survived over 1 year, 1/12 (8.3%) survived over 2 years post-diagnosis. mOS 15.1 months, mPFS 3 months. mOS was superior to published results of gemcitabine, and gemcitabine + nab-paclitaxel.

Legend: IVC = intravenous vitamin C, AA = ascorbic acid, OS = overall survival, PFS = progression free survival, TTP = time to progression, mOS = median overall survival, AE = adverse events, SE= side effect, DLT = dose limiting toxicity, MTD = maximum tolerated dose, PK= pharmacokinetics, QoL = quality of life, AA = ascorbic acid, bw = body weight, EPA = eicosapentanoic acid,

Low dose Intravenous Vitamin C

Several studies have looked at low doses of IV vitamin C for people with cancer. While there is no standard definition of low dose versus high dose IVC, in general low doses are those not expected to have a pro-oxidant or cytotoxic effect. The *in vivo* pro-oxidant concentration is thought to occur at plasma levels ≥ 3-4 mM depending on tumour cell type. Typically doses over 15g are required to achieve those plasma concentrations (18). Therefore, doses below 15g are included here as low dose IVC interventions.

Several studies in hematological malignances have used low dose IVC combined with standard therapies. A small open-label, single arm study in 11 people with relapsed acute myeloid leukemia (AML) who were unfit for standard induction chemotherapy were given IV arsenic trioxide and 1g IVC for 5 days/week for 5 weeks. The treatment was well tolerated, but overall the results were not promising enough to recommend further study of this combination (41). Another study in AML enrolled elderly patients (≥ 60 yoa) with newly diagnosed AML who were either unfit for or refused intensive chemotherapy. Patients were randomized to receive decitabine-based chemotherapy alone, or decitabine-based chemotherapy plus low dose IVC at 50-80mg/kg/day (42). Treatment was continued until disease progression or unacceptable toxicity. This study found that the CR rate after one and two induction cycles was higher in the IVC arm (79% vs 44%, P = 0.004 and 84.6% vs 70.6%, P = 0.148), and at a median follow up of 13.8 months the IVC arm had better median OS (15.3 vs. 9.3months, HR 0.47, P = 0.039). The OS at 3 years in the IVC group was 28.6% and 12.5% in control group (p <0.001). There was no significant difference in adverse events between groups. This same study did an *in vitro* analysis that found that decitabine in combination with low-dose vitamin C has a synergistic anti-neoplastic action against AML cells through modulation of TET2 expression and activity. Another study looked at 1g IVC alongside IV arsenic trioxide and bortezomib once weekly for people with relapsed/refractory multiple myeloma. Ten people received this treatment for up to eight 3-week cycles. Four patients had clinical benefit; there were no dose-limiting toxicities (44).

One study looked at IVC given at a dose of 50mg/kg (e.g. 3.75g for a 75kg adult) pre-operatively for patients with colon cancer to evaluate the effect on post-operative pain. The study was a randomized, double blinded trial with 97 participants who were administered either IVC or IV saline (placebo) after induction with anaesthesia prior to laparoscopic colectomy. Compared to placebo, IVC decreased postoperative pain during the first 24 hour period ($p < 0.05$), and reduced morphine use during the first 2 hours post-surgery ($p < 0.05$), and there was greater use of rescue analgesics in the placebo group ($p<0.05$) (47).

Two retrospective studies have looked at 2.5g doses of IVC for pain in individuals with bone metastases with promising results. The first was a small pilot study in 11 individuals with bone metastases experiencing pain, who experienced increasing pain, increasing bone metastases, or deterioration of general condition following radiation therapy (48). Individuals received IVC at a 2.5g dose with 3-10 infusions given at 1 week intervals or at times of increasing pain. Six of the 11 experienced a 50%-100% reduction in pain, 1/11 experienced a 25% reduction in pain (64% had a positive response), 2/11 had no change, and 2/11 had worsening pain. Median response was a 55% reduction in pain. The second was a retrospective study of a cohort of patients who received 2.5g IVC during periods of increased pain, to evaluate effect on pain, performance status, and survival in patients with bone metastases unresponsive to radiotherapy (49). Thirty-nine patients were enrolled; 15 received chemotherapy, 15 IVC, and 9 were untreated controls. IVC was administered only during periods of intensifying pain. Performance status improved in 27% of patients in the IVC group compared to 7% in the chemotherapy group and 0% in the

control group. There was a median pain reduction of 50% with use of IVC. Median survival was 10 months in the IVC group compared to 2 months in the chemotherapy and control groups ($p < 0.001$ and $p= 0.002$ respectively).

A retrospective cohort study evaluated the impact of low dose IVC on survival in patients with hepatocellular carcinoma (HCC) following curative hepatectomy (50). This dose was selected as it achieved plasma concentrations of 1.5mM which the authors found was sufficient to have cytotoxic effects on HCC cells *in vitro*. Of 613 patients treated for HCC, 339 (55.3%) received 2g IVC for 4 or more days after hepatectomy. The 5 year disease-free survival for patients in the IVC group was 24% vs 15% for no IVC ($p<0.001$). Median DFS for IVC group was 25.2 vs 18 months for non IVC uses ($P < 0.001$). Multivariate analysis found that IVC administration was an independent factor for improved DFS (adjusted HR 0.622, 95% CI 0.487 – 0.795, $p < 0.001$).

An observational study of patients with cancer and lymphopenia (total lymphocyte count (TLC) < 1500/uL) found that IVC increased the TLC by a mean of 211/uL ($p = 0.0018$) (51). The effect was greater in those with severe lymphopenia (TLC <1000/uL) where the mean increase was 386/uL ($p = 0.0004$) compared to a rise of 40/uL in those at 1000-1500/uL. This prospective observational trial included 48 patients with mixed cancers, receiving various cancer treatments (chemotherapy, radiotherapy) who received 7.5g IVC once weekly for four weeks. Of note, 55% of participants were classified as having moderate or severe malnutrition. Given lymphopenia is a potentially reversible, and predictive factor for earlier tumor progression or relapse, this is an important consideration. Further study is warranted.

Adverse Events and Side Effects

The majority of IVC studies report only mild side effects and collectively demonstrate a positive safety profile for doses up to 1.5g/kg, three times per week (6, 9, 52). This clinical data is supported by a low adverse event rate documented through a large survey of practitioners who use this therapy (101/9328 or 1.0%) (53). A retrospective review of all patients receiving IVC at Thomas Jefferson University Hospital over a 7 year period included 86 people who received a total of 3034 doses of IVC ranging from 50-150g (29). Thirty-two patients received IVC alone (1197 doses), and 54 received IVC and chemotherapy (1837 doses of IVC; chemotherapy included paclitaxel, carboplatin, sorafenib, irinotecan, and gemcitabine). To evaluate for AEs, internal comparisons were made between the IVC alone group and IVC with chemotherapy group. There were fewer toxicities in the group that received IVC alone compared to those receiving IVC with chemotherapy. AEs were reported in less than 5% of all infusions, and less than 3% in patients receiving IVC alone. Most common AEs related to IVC were temporary nausea, and discomfort at the injection site. The IVC infusions were safe and well tolerated in this population.

Although mild and transient, hypertension has been seen in some studies associated with IV C. An observational study evaluating the effect of IVC on blood pressure found a modest reduction (8-9mmHg) in blood pressure in the 26 patients evaluated (54).

The following side effects have been reported in clinical trials, observational studies, and clinician surveys that may be attributed to IVC infusion:

More common (≥5%): Thirst, increased urination, dry mouth, transient hypertension, hypertension, diarrhea, nausea, fatigue, weakness, headache, light-headedness, dizziness, injection site discomfort (peripheral insertion), phlebitis.

Rare (≤4%): Abdominal cramping, facial flushing, vomiting, kidney stone, lower urinary tract symptoms, hypokalemia, hypernatremia, insomnia, abnormal urine colour, loss of appetite, chills, hyperglycemia, tumour fever, pedal edema, perspiration, worsening edema or ascites, allergic reaction.

Rare but serious (1-4%): Hemolysis (only if G6PD deficient), renal failure (only observed in those with pre-existing renal impairment).

Many of these side effects may be attributed to the infusion of a high osmolarity solution. Further, many of these reactions appear to be mitigated by drinking fluids before and during treatments (9, 26, 52).

Interactions with cancer treatments and other medications

Chemotherapy and radiation therapy:
Animal and cell-line studies suggest a synergistic effect when some chemotherapeutic agents are combined with pharmacologic doses of vitamin C. Chemotherapy agents with evidence of such synergy include: gemcitabine (55), carboplatin (56), cisplatin (2, 57, 58), etoposide (2), 5-fluorouracil (2, 57, 59), epirubicin (59), doxorubicin (2, 34, 58), paclitaxel (2, 58), docetaxel (59), and irinotecan (59). In these studies, the combination of IVC plus chemotherapy was related to increased tumour inhibition and decreased tumour growth rate as compared to either IVC or chemotherapy alone

Human studies have used IVC alongside a variety of chemotherapy agents including: gemcitabine, erlotinib, carboplatin, paclitaxel, rituximab, cyclophosphamide, cytarabine, etoposide, dexamethasone, temozolomide, and concurrent with radiation therapy. Although most of these studies were small and without a control group, there was no indication of a negative interaction and many reported results suggestive of benefit. See table 1 for details of these studies.

It is notable that one *in vitro* study that demonstrated detrimental interactions between vitamin C and numerous chemotherapeutic agents (60) was conducted using dehydroascorbic acid – a tightly-regulated, diabetogenic derivative of ascorbic acid (61). The results of this publication are therefore not relevant to the clinical use of vitamin C as it is described here (62).

Warfarin:
There are two reports of oral vitamin C reducing effectiveness of warfarin (63, 64), but other research has not confirmed this (65). Until more is known, caution should be used if patients are on warfarin.

Cautions and Contraindications

IVC should not be administered to patients with renal failure (17, 18), or who have a G6PD deficiency (66). Caution is warranted in patients with a history of kidney stone formation, creatinine > 175 umol/L (17, 18), and those with iron storage diseases (hemochromatosis). Those with diabetes must be informed of the falsely elevated glucometer readings following IVC infusion. Furthermore, the action of IVC as an osmotic diuretic, as well as the IV fluid volume may mean that it is not suitable for patients with anuria, dehydration, severe pulmonary congestion/edema or low cardiac output (9). Finally, IVC use has not been studied for use by pregnant or lactating women, or by children. Caution is warranted in these groups and IVC should only be used under the guidance of trained health professionals.

Kidney stones and renal failure
A few case reports cite vitamin C intake as a cause of kidney stones and renal failure (67, 68). Further, one participant with a history of kidney stone formation experienced a recurrence during a trial of

continuous IVC infusion (52). Larger prospective studies do not support this association, however, in patients who do not have a history of this condition (69, 70). Oxalic acid excretion is transiently increased in a dose-dependent fashion by IVC treatment, but this is not suspected to contribute significantly to stone formation in patients without a clinical history (17).

Caution is warranted in patients with end-stage renal failure who may be predisposed to hyperoxalemia (71), as this population could be at increased risk for stone formation from IVC treatment (72, 73). However, two case reports document positive outcomes in patients with renal cancer receiving IVC treatment (31, 74), therefore renal failure not renal cancer is a contraindication for IVC.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Cases of potentially fatal hemolytic anemia have been reported when high doses of IVC are administered to individuals with a deficiency of G6PD (75, 76). A deficiency of this enzyme causes serum H_2O_2 levels to rise, leading to destruction of healthy cells at doses of IVC exceeding 15 grams (4). Thus, patients that are candidates for IVC treatment must be screened for adequate levels of G6PD if dosing is to exceed 15 grams per IV session.

Iron storage diseases

Patients with hemochromatosis should avoid excessive vitamin C intake (77), although the effect of IVC has not been studied in this population and thus the risk is hypothetical. IVC may be used to mobilize iron stores in the treatment of functional anemia among hemodialysis patients and may actually reduce ferritin stores (78). If IVC is administered to individuals with iron storage diseases, regular monitoring of iron status is recommended and exacerbation of these conditions may necessitate discontinuation of IVC therapy.

Diabetes

IV ascorbic acid will elevate fingerstick blood glucose monitor readings in most portable glucometers (79). Those with diabetes must be informed of this and be advised that insulin must not be administered on the basis of post-treatment glucometer readings. Glucometer readings can remain elevated for several hours post-infusion and should not be relied on for accurate blood sugar measurements until 8 hours after the IVC administration has finished.

Dosing, frequency and length of treatment

A wide range of vitamin C dosages are used clinically, based on different concentrations documented within the clinical and pre-clinical literature. Doses up to 1.5g/kg three times weekly have demonstrated a positive safety profile, and common dosing in clinical trials is 1-1.5g/kg, or 50-125g per infusion. Recent dosing studies suggest that a target dose of approximately 22mM (400mg/dL) is optimal (52), a dose achievable by IV infusion at a rate of 500mg/minute (5, 26).Post-infusion blood levels of vitamin C vary by individual (26) and therefore should be measured to ensure adequate dosing.

For treatment duration, IVC has been used from 1 week (28) up to 1 year (27) in clinical studies, and in case reports IVC has been used for up to 3 years with a good safety profile (32, 40).

Patients at the OICC typically receive between 40g and 75g per infusion to achieve adequate serum levels. Treatments are generally administered 1-3 times per week and a glucometer is used as a surrogate measuring device to assess serum saturation levels. Patients may receive treatment for weeks to months, or in some cases longer term.

Disclaimer

The OICC has prepared this monograph, as part of a series of monographs, to share a review of the research literature related to common therapies and products used within integrative cancer care. The monograph is designed to provide evidence-based research and neither advocates for nor against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published. Prior to using a new therapy or product, always consult a licensed health care provider. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a qualified health care provider.

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