Intravenous Vitamin C in Cancer Care

Healthcare Provider Resource

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THE CENTRE FOR HEALTH INNOVATION

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General information:

Proper Name
Ascorbic acid, Ascorbate

Common Name
Vitamin C

Route of Administration
Intravenous (IV)

Common Uses in Cancer Care
IVC is commonly used in cancer care to improve quality of life, reduce cancer-treatment related side effects, 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. 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 per infusion. Proposed mechanisms of action of high dose IVC include generation of hydrogen peroxide creating oxidative stress, enzyme cofactor activities, antioxidant and anti-inflammatory actions, and immune effects. Seventeen prospective clinical trials and 2 interim reports of ongoing clinical trials have been published. These nineteen studies include one randomized placebo controlled trial (RCT), three non-placebo controlled RCTs, and 15 single-arm trials. Most 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

Administration of IV vitamin C has been demonstrated to increase serum, plasma, erythrocyte, and tumor concentrations of ascorbate. 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, 5). 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, 6).

Plasma concentrations of vitamin C varies based on the dose administered, and varies from person to person based on 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 person). Serum levels plateaued at 49mM with the $70g/m^2$ dose, which the authors recommended for dosing in future trials (7). However, most studies to date have used slightly lower doses in the range of 1-1.5g/kg body weight, which typically correlates to dosing of 60 to 100g of ascorbic acid, to achieve plasma concentrations of 20 mM (5, 8-14). Ascorbate has also been found to accumulate in erythrocytes, reaching millimolar levels, and peaking

around 4 hours post-infusion (5). Pharmacokinetics can vary considerably from person to person; therefore in order to obtain optimal therapeutic effect, plasma levels for individuals might need to be measured (15). 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 (15). Vitamin C blood levels in people with cancer, and in particular with advanced disease, may be lower than in healthy individuals (16). Cancer increases oxidative stress and inflammation in the body, which increases ascorbate utilization due to its antioxidant properties (16).

Tumor ascorbate levels increase following administration of IVC (17). In patients with colon cancer, treatment with IVC for 4 days (25g day 1, up to 1g/kg to a maximum of 75g days 2-4) raised tumor ascorbate from 15 ± 6 to 28 ± 6mg/100g tissue.).

Pharmacologic concentrations (0.3 to 20 mM) of vitamin C are cleared within hours by renal filtration and excretion (4). IVC exhibits first order elimination kinetics (18), and has an elimination half-life between 30-120 minutes (7, 18, 19). In one trial, 80% of the administered doses of IVC had been filtered by the kidneys in the 6 hours following infusion (20). Thus, plasma vitamin C concentrations are not maintained in the cytotoxic range for long with bolus IV infusion.

Mechanism of Action

Three primary mechanisms of action have been proposed regarding the possible anticancer effects of high dose IVC: generation of hydrogen peroxide creating oxidative stress, enzyme cofactor activities, and antioxidant and anti-inflammatory functions (21). Additionally, an emerging mechanism is the impact vitamin C has on immune function, particularly T-lymphocytes and natural killer cells (22-24). 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 (3-5). 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 (21).

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 (25). 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 (26-28). 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 (26). High dose ascorbate may be able to reduce expression of tumour hypoxia-inducible factors (HIF) as demonstrated in a small clinical trial in colon cancer (17). 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 six 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) (29). 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 (8). C-reactive protein (CRP) was decreased in 75% of patients in a retrospective study of IVC for patients with variable types of cancer (30). Together, these studies indicate IVC likely has a systemic antioxidant and anti-inflammatory effect, which may contribute to its benefit in patients with cancer.

Immune effects

Two human studies have found an increase in T-lymphocytes with the use of IV vitamin C (22, 23), which may favour anti-tumor immune function (24). Additionally, there is preclinical data to support the potential for IVC to positively impact the function of lymphocytes and natural killer cells (24, 31, 32).

Clinical Evidence Related to Effectiveness

Prospective clinical trials of high dose IVC for cancer efficacy and quality of life outcomes are summarized in Table 1. Note that studies using low doses of IVC (<15g) are summarized separately (Table 2). Results from 17 clinical trials and interim results from two trials have been published at the time of this update. There is one placebo controlled RCT, three non-placebo controlled RCTs and 15 single-arm trials. A variety of cancer types have been studied; the most studied (by number of participants) are breast, lung, prostate, ovarian, and pancreatic cancer. 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 (8, 14, 26, 33) and ovarian (34) 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 IVC 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 clinical trial data has failed to confirm this. Six of the trials in table 1 evaluated IVC as a monotherapy, 5 were single arm (7, 10, 17, 18, 35, 36), and one was an RCT (17).

Quality of life

Most published human studies of IVC monotherapy have included only patients with advanced disease. In three small trials of patients with mixed types of advanced cancers, quality of life remained stable in two (7, 10) and improved in another (35). All three of these studies included patients with various types of advanced cancers who received 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.

One small randomized controlled trial (n=9) administered IVC at a dose of 1g/kg for 4 days prior to colon cancer resection, primarily to evaluate plasma, erythrocyte, and tumor ascorbate levels (17). They followed patients for 30 days post-op and noted that patients in the control arm had a longer length of hospital stay compared to the IVC arm (9.3 days vs 5.8 days, $p = 0.105$). Notably the difference observed between groups

for duration of hospital stay was large but not statistically significant. This may have been due to the small sample size or due to chance.

A retrospective review of all patients receiving IVC at Thomas Jefferson University Hospital over a 7 year period was conducted to analyze IVC adverse effects (AEs) and changes in symptoms (37). 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 (6, 10, 36). Three clinical trials have evaluated IVC as monotherapy for cancer treatment, two failed to demonstrate an objective tumor response (7, 10) and one found a modest response (36). All three trials included people with advanced cancers refractory to conventional therapies. 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 (10). Although adverse events and toxicity were minimal at all doses, no objective anti-tumour 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 (7). Sixteen people completed the study, three of whom demonstrated stable disease and 13 had progressive disease. No objective tumour response was documented.. A small pilot study evaluated the effect of IVC on four patients with locally advanced, extensive basal cell carcinoma (BCC) (36). The included patients, who were not eligible for other treatment, were treated with IVC at doses ranging from 1.1-1.8g/kg 1-3 times weekly for a mean treatment duration of 42 ±23 weeks.. A total of 18 skin lesions were monitored, and 83% responded to treatment (defined as PR + SD) while 17% progressed. There were no complete responses. The overall treatment response was stable disease in three patients and progressive disease in one patient. Treatment was well tolerated with no adverse effects.

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 associated with worse cancer prognosis (30). This study also found 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, bladder cancers, pediatric brainstem glioma, as well as B cell lymphoma suggested that treatment with IVC was associated with tumour regression and remission (38-41). 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 (6). 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 (6) as well as in cancers of the bladder (2), prostate (2, 42), liver (2), breast (2), cervix (2), ovary (6), colon (43) and pancreas (6, 44).

Two studies evaluated IVC alongside modulated electro hyperthermia (mEHT), but without any concomitant standard cancer treatment (45, 46). These studies are described in the section on use with other integrative therapies.

IVC in combination with standard care

Quality of life, side effects, and toxicity

Results from clinical trials of IVC on quality of life are mixed, with two studies finding improvement in QoL (8, 34), two finding no change (12, 13) and one study finding significant but small improvements, which may not be clinically meaningful (47). One clinical trial reported reduced treatment toxicity with the addition of IVC (48). Results from three observational trials demonstrated positive results (49-51). One study reported improved neutrophil to lymphocyte ratio, a marker when elevated that is associated with treatment-induced inflammation.(22)

Clinical trials:

Beneficial effects were found in trials involving participants with breast, pancreatic, and ovarian cancers. The only placebo-controlled RCT to date of IVC was conducted in women undergoing treatment for stage IIa-IIIb breast cancer.(47) In this study, women (n=350), who were receiving adjuvant chemotherapy, radiation, or hormone therapy, were randomized to once weekly IVC at a dose of 25g, or saline placebo, for 4 weeks. The study evaluated seven symptoms using a 4-point visual analogue scale (VAS) administered at baseline and 28 days, and presented that data as changes in the mean with standard deviations. In the treatment arm there were significant reductions (i.e., improvements) in: mean VAS symptom scores for nausea (3.01 ± 0.26 vs 2.78 ± 0.54, $p = 0.0003$), loss of appetite (2.26 ± 0.51 vs 2.11 vs ± 0.52, $p = 0.007$), tumor pain (2.22 ± 0.45 vs 1.99 ± 0.40, $p < 0.0001$), fatigue (3.11 ± 0.32 vs 2.87 ± 0.29, $p < 0.0001$), and insomnia (2.59 ± 0.35 vs 2.32 ± 0.36, $p < 0.0001$). There were no changes in reports of diarrhea or vomiting. There were no significant changes for any outcome in the placebo group. Although these results are statistically significant, they are likely not clinically meaningful given the very small magnitude of effect. A randomized, non-placebo controlled trial administered IVC (75-100g) twice weekly compared to no treatment for 12 months in conjunction with carboplatin/paclitaxel chemotherapy for 25 women with advanced ovarian cancer (48). This study reported significantly fewer grade 1 and 2 toxicities in the treatment group compared to control, and no difference in grade 3 and 4 toxicities. 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 (8) for an average of 6 months. The IVC was well tolerated. Six of the nine participants maintained or improved performance status during treatment, and weight loss was considered minimal compared to usual weight loss (5.3 ± 1.6 kg over 6 months).

Less favourable results were found in a trial of mixed cancers, and a null effect seen in 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 (12). There was large variability in number of IVC infusions (6-173). The study found no improvement in QoL based on questionnaires. In six of 12 patients in whom a response could be evaluated, there was a brief or longer lasting disease stabilization, and in 3 of these 6 there was an unusually favorable response reported. 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 (13). 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:

Three observational studies evaluated quality of life or treatment toxicity. One retrospective cohort study included women with breast cancer, and found that 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 compared to those who used standard care alone (49). 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 (50). Other therapies used in these trials included epirubicin, cyclophosphamide, methotrexate, fluorouracil (49), paclitaxel and cisplatin (50). Finally, a retrospective, matched controlled observational study

evaluated the impact of IVC on efficacy and toxicity in patients with metastatic triple negative breast cancer (TNBC) (51). Thirty-five women receiving IVC every other day during two cycles of gemcitabine + carboplatin chemotherapy were matched to 35 women receiving gemcitabine + carboplatin chemotherapy alone. Adverse events and chemotherapy related toxicities were significantly lower in the IVC arm compared to controls, noted by improvements in anemia, leukopenia, thrombocytopenia, nausea and vomiting, constipation, liver and kidney dysfunction, and peripheral neurotoxicity (all $p < 0.05$). Karnofsky performance status (KPS) score after treatment was significantly higher in the treatment group compared to controls (87.7 ± 4.9 vs 79.4 ± 5.4, $p < 0.0001$). This study suggests that IVC may improve performance status and reduce toxicity of chemotherapy. Data from randomized trials are needed to confirm these findings.

A retrospective observational study compared the neutrophil to lymphocyte ratio (NLR) among women who had been treated with adjuvant radiation with or without IVC(22). NLR is associated with increased inflammation, and higher values have been associated with increased cancer mortality. This study evaluated 424 women, 70 of whom received IVC. IVC was administered 2x/week for at least 4 weeks during radiation. Women were further divided into low dose IVC (<1g/kg, n = 52) and high dose IVC (>1g/kg, n = 18). NLR was measured before radiation, immediately after radiation, and 3 months later. NLR continuously decreased in the high dose IVC group (8.4 ± 1.7, 5.9 ± 1.3, 4.3 ± 1.5, $P_{interaction} = 0.033$), but not in the control or low dose IVC groups (5.5 ± 1.1, 12.5 ± 1.1, and 4.7 ± 1.1 in control, and 7.1 ± 1.4, 14.2 ± 1.2, and 8.9 ± 1.3 in the low dose IVC group). When adjusted for variables including cancer staging, the trend remained in the high dose group, however it's significance became borderline ($P_{interaction} = 0.065$). Lymphocytes were significantly increased in the high dose IVC group compared to the control and low dose group, whereas no significant differences in neutrophils were seen between the three groups. This study indicates that at high doses, (>1g/kg) IVC may suppress inflammation and increase lymphocytes.

Survival, tumor response, and tumor markers

One RCT (48), six single-arm trials (8, 12-14, 26, 33), two preliminary reports (published together) of ongoing single-arm trials (11), and two observational trials (51, 52) have evaluated survival and response rates for IVC concurrent with conventional care. There is limited evidence that IVC may improve survival time or tumor response in women with advanced ovarian cancer and in individuals with pancreatic cancer.

Clinical trials:
In a randomized, non-placebo controlled trial 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 (48). There were 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 (38).

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 (8). 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 ± 7 weeks, and overall survival was 13 ± 2 months. The authors note that these results are considered good when compared to

other clinical trials that have evaluated gemcitabine therapy for stage IV pancreatic cancer in which OS is 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 (14). 57% of participants received all 6 cycles of gemcitabine, and 100% completed radiation therapy which the authors noted as 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 cancer treated patients 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 (33). 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 (26). 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. 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 which is still in progress. Interim results found IVC treatment to be safe, well tolerated, and documented survival outcomes which were superior to historical controls (11). 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. The 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 (11).

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 (12). 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 resistant prostate cancer treated with androgen deprivation therapy were administered 60g IVC weekly for 12 weeks (13). 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 (29). 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 differences were not statistically significant.

Observational studies:
A retrospective, matched controlled observational study evaluated the impact of IVC on efficacy and toxicity in patients with metastatic triple negative breast cancer (TNBC) (51). Thirty-five women receiving IVC every other day during two cycles of gemcitabine + carboplatin chemotherapy were matched to 35 women

receiving gemcitabine + carboplatin chemotherapy alone. The study found that there was no change in tumor response rates (CR, PR, SD) between groups after 2 cycles of treatment. However, the study did find that there was significantly longer PFS and OS in the treatment arm compared to control arm after a median follow up time of 22 months (PFS 7 months (1.5-28.5) vs 4.5 months (1.5-8), p = 0.002, OS 27 months (4-40) vs 18 months (3-26), p = 0.002). Adverse events were significantly lower and KPS score higher in the treatment group. This study suggests that IVC may not alter tumor response, but may improve PFS and OS, improve performance status, and reduce toxicity of chemotherapy. Data from prospective, randomized trials are needed to confirm these findings.

A case series reported the effects of IVC in addition to polymerase inhibitors (PARPi) in a group of eight patients with a mix of progressive stage IV cancers, including prostate (n=2), breast (n=1), pancreatic (n=2), gastric (n=1) and ovarian (n=2)(52). Patients were treated with IVC at a dose of 1-1.5g/kg body weight, 2-4x a week for a minimum of 3 months. Authors reported that 5 patients had a partial response and 3 a complete response. Grade 2 anemia and fatigue were observed, while no grade 3 or 4 toxicities were reported. Toxicities observed were thought to be due to PARPi rather than the IVC. The authors noted that the response rates were reasonable and the tolerability good, and further research is warranted.

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.

Two prospective trials evaluated IVC with modulated electrohyperthermia (mEHT) in people with lung cancer (45, 53). One study 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 (54). 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. The second study evaluated efficacy of IVC + mEHT in a randomized, non-placebo controlled phase II RCT of 97 patients with advanced, treatment-refractory NSCLC (stage IIIB-IV)(45). While the control group received best available supportive care, those in the treatment arm received IVC (1g/kg body weight, 3x/week for a total of 25 treatments) in addition to 60 minutes of mEHT. After a median follow-up of 24 months, the median overall survival was 9.4 months in the treatment arm compared to 5.6 months in the control arm (RR: 0.33, 95% CI: 0.16-0.41, p<0.0001). The median progression-free survival was 3.0 months for the active arm and 1.85 months for the control arm (HR = 0.3294; 95% CI, 0.1222–0.3166; P< 0.0001). Authors report that there were no instances of complete response in either group, with high variability in changes to QOL.

Applications with limited research:

Pediatric use:

There are no clinical trials or observational studies which have included individuals less than 18 years of age. Two case reports describe cases of children treated with IVC; one with neurofibromatosis and another with a brainstem glioma. A report of a 3 year old boy with neurofibromatosis 1 (NF1) treated with IVC had positive outcomes (56). 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. The second case report discussed the effects of a combination of IVC and endolaser therapy on a brainstem glioma in a 6-year-old child.(41) The patient was treated with carboplatin and

vincristine chemo-radiation, and while initially a reduction in tumor size was noted, the tumor began growing again. IVC at a dose of 25g given 2x/week and endolaser was initiated for a total of 18 treatments. After two months there was a 79% reduction in the brainstem glioma.

Hematological malignancies:

Leukemias:
Low dose IVC (1g) has been studied alongside conventional treatments in AML (57, 58), and post-hematopoetic stem cell transplant (59). Details are described in the low dose IVC section and in table 2. 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 (60).

Multiple myeloma:
Only one preliminary study which used low dose IVC alongside bortezomib and arsenic trioxide has been studied, and is described in table 2 (61).

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 (62). 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 (39).

Table 1: Prospective clinical trials of high dose (>15g) intravenous vitamin C for cancer

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Alexander, 2018(14)	Phase I, open label, non-randomized	14 patients with pancreatic adenocarcinoma (stages II, III, IV), eligible for gemcitabine and radiation therapy 19 subjects were enrolled as comparators (no randomization)	IVC dose escalation: 50g, 75g, 100g IVC administered daily with radiation therapy for duration of radiation (average length 5 weeks). Weekly gemcitabine given concomitantly.	Gemcitabine + radiation as per usual care	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 (10)	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	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

Monti, 2012 (33)	Phase I, single arm, 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 given concomitantly	None	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(12)	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. Chemotherapy varied as per usual care.	None	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(62)	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 of CHASER chemotherapy regimen	None	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(34)	RCT - 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, alongside carboplatin/paclitaxel chemotherapy administered for 6 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(29)	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	None	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

			weeks, alongside usual care (chemotherapy in most cases) Cytokines in 8 healthy volunteers were evaluated for comparison			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 (13)	phase II, single arm	20 patients with metastatic castrate-resistant prostate cancer (mCRPC)	IVC 60g once weekly for 12 weeks alongside androgen deprivation therapy. Participants were also given 500mg oral ascorbic acid daily.	None	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(8)	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. Chemotherapy was weekly Gemcitabine on a 4-week cycle	None	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, 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. Administered with modulated electrohyperthermia (mEHT) before, during, or after IVC depending	Different IVC doses and timing of IVC were compared	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,

			on randomization (3 groups of 5 people)			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 (7)	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. All patients received a multivitamin and EPA (2000mg)	None	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 (18)	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	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 (11)	Phase 1, still in progress	13 patients with Glioblastoma multiforme (GBM)	IVC administered 3x/week to target plasma concentrations of >20mM (62-125g), alongside 7 weeks of daily radiation and temozolomide	None	Safety, tolerability, survival	Interim results: IVC safe, well tolerated, no serious AEs attributed to IVC. Median PFS 9.4 months and OS 18.2 months (historical median PFS is 7 months and median OS 14 months)

Schoenfeld, 2017 (11)	Phase II single arm, still in progress	14 patients with non-small cell lung cancer (NSCLC)	IVC administered 2x/week at 75g per infusion for 4 cycles of platinum-doublet chemotherapy	None	Safety, response to treatment	Interim results: 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 (26)	Phase I/IIa single arm	12 patients with metastatic or unresectable 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	None	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.
Banvolgyi 2020 (36)	Pilot single arm	4 patients with basal cell carcinoma who were not eligible for conventional care	IVC at a dose of 1.1-1.8 g/kg, 3 times weekly for a mean of 42 +/- 23.6 weeks	None	Lesion diameter, response (according to adapted RECIST guidelines)	Of 18 lesions monitored, 83% had a response (SD+PR+CR) – 27% PR and 73% SD. No new lesions were detected during the treatment and follow-up period. No AE's reported.
Ou 2020 (45)	RCT - Phase II	97 patients with advanced, refractory, NSCLC (stage IIIB-IV) (n=49 treatment, n=48 control)	A combination of IVC, mEHT, and supportive care was provided	Best supportive care alone	Overall survival, progression free survival, disease control rate, response rate, QOL, safety	Median OS was 9.4 months in the intervention arm compared to 5.6 months for controls (HR: 0.33, 95% CI: 0.16-0.41, p<0.0001). The median PFS was 3.0 months for the treatment

			IVC: 1g/kg, 3x/week, for a total of 25 treatments, infused over 120 minutes. mEHT: HT was applied for 60 minutes.			arm and 1.85 months for the control arm (HR = 0.3294; 95% CI, 0.1222–0.3166;P< 0.0001. No CRs in either group. QOL improvements varied AEs: Thirst was reported by 22/49 participants receiving IVC. One participant experienced severe diarrhea.
Dachs 2021 (17)	RCT	15 patients with colon cancer awaiting surgery (9 in treatment arm, 6 in control arm)	For 4 days prior to surgery, participants received 1g/kg IVC	Surgery alone	Plasma ascorbate levels, erythrocytes, tumor and histologically normal mucosa at diagnostic colonoscopy and at surgery	Tumor ascorbate increased from 15 ± 6 to 28 ± 6mg/100g tissue. Normal tissue increased from 14 ±6 to 21 ± 4mg/100g. Lower ascorbate was evident toward centre of tumor in control and treatment. Lower expression of hypoxia associated proteins was seen in post-infusion tumors compared to controls.
Mansoor 2021 (47)	RCT - Placebo Controlled, Single-Blind,	350 patients with stage IIA-IIIB breast cancer (343 completed study; n = 172 in treatment, 171 in control)	IVC 25g/week (rate of 15g/hour), for 4 weeks alongside conventional care including chemotherapy, radiotherapy and/or tamoxifen	Placebo (saline drip)	Visual Analog Scale assessing nausea, loss of appetite, tumor specific pain, fatigue, insomnia, diarrhea, and vomiting	A significant decrease in the mean score, at day 28 compared to baseline, for: nausea (3.01 ± 0.26 vs 2.78 ± 0.54, p = 0.0003), loss of appetite (2.26 ± 0.51 vs 2.11 vs ± 0.52, p = 0.007), tumor pain (2.22 ± 0.45 vs 1.99 ± 0.40, p < 0.0001), fatigue (3.11 ± 0.32 vs 2.87 ± 0.29, p < 0.0001), insomnia (2.59 ± 0.35 vs 2.32 ± 0.36, p < 0.0001) No significant changes were noted in the control group compared to baseline for any measure

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, , bw = body weight, EPA = eicosapentanoic acid, RECIST = Response Evaluation Criteria in solid tumors, CR = complete response, SD = stable disease, PR = partial response, NSCLC = non-small cell lung cancer, mEHT = modulated electrohyperthermia, GVHD = graft versus host disease

Table 2: Prospective clinical trials of low dose (<15g) intravenous vitamin C for cancer

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Yeom, 2007 (35)	Single arm, open label	39 patients with terminal cancer	10g IVC twice within a 3-day interval, with 4g daily oral vitamin C for 1 week	None	QoL (EORTC QLQ-C30)	Significant improvements after IVC in: Global health scale health 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.
Held, 2013 (61)	Single arm, open label	10 patients with relapsed, refractory myeloma, heavily pre-treated	1g IVC on day 1 and 8 of 21-day cycle for up to 8 cycles, with IV arsenic trioxide and bortezomib	None	Response rate, clinical benefit rate	4 achieved clinical benefit, 1 had durable partial response. No DLTs
Aldoss, 2014 (57)	Single arm, open label	11 patients with relapsed or refractory AML	IVC 1g/day given over 30 minutes, 5 days/week for 5 weeks, IV arsenic trioxide given prior to IVC	None	Response rate	1 CR, 4 CR with incomplete hematological recovery, and 4 patients had disappearance of blasts from peripheral blood and bone marrow. Authors state this was not clinically meaningful.
Zhao, 2018 (58)	RCT	73 elderly patients with AML (39 treatment arm, 34 control arm)	IVC at 50-80mg/kg + DCAG chemotherapy (decitabine + cytarabine + aclarubicin + granulocyte colony stimulating factor)	DCAG chemotherapy alone	Response rate Survival Toxicity	Complete remission rate higher in IVC arm compared to control (79.9% vs 44.1%, $p = 0.004$) after 1 cycle. mOS was higher in IVC arm (15.3 vs 9.3 months, $p = 0.039$). No additional toxicity observed with addition of IVC
Jeon, 2016 (63)	RCT	97 patients with colon cancer undergoing surgery	IVC 50mg/kg administered after anaesthetic before laparoscopic colectomy	IV saline	Post-operative pain, morphine use	IVC decreased postoperative pain during the first 24 hour period ($p < 0.05$), reduced morphine use during the first 2 hours post-op ($p < 0.05$), and there was greater use of rescue analgesics in the placebo group ($p<0.05$)

Simmons 2020 (59)	Phase II, single arm trial with matched historical controls *Interim analysis, no full text available	40 patients including 19 with acute myeloid leukemia, 11 with acute lymphocytic leukemia, and 10 with chronic myeloid leukemia or myelodysplastic syndrome. All underwent Hematopoietic stem-cell transplantation.	IVC administered on days 1-14 post-transplant at a dose of 50mg/kg, then oral vitamin C at a dose of 500mg 2x/day from day 15 post-transplant to 6 months.	Standard care (not described) post hematopoietic stem cell transplant	Primary outcome: Transplant mortality at 1 year, Secondary outcomes: serum ascorbic acid levels, neutrophil and platelet recovery, CD+3 cell counts, rates of acute and chronic graft vs host disease (GVHD), toxicity	All were deficient in vitamin C at day 0, median AA level was 0.3 mg/dL (range: 0.1-0.5); post AA infusion level was normal at 1.6 (1.2-5.7) on day 14. Median neutrophil and platelet recovery was by 12 days (range: 9-15 & 8-21 days respectively) No statistically significant difference was observed in transplant related mortality (AHR 0.6, 95% CI: 0.2-1.5; p-value = 0.27) relapse, (AHR 1.2, 95% CI: 0.3-4.5; p-value = 0.82), grade II-IV acute GVHD (AHR 0.8, 95% CI: 0.7-1.7; p-value = 0.65), grade III-IV acute GVHD (AHR 0.6, 95% CI: 0.2-1.6; p-value = 0.32), and Chronic GVHD (AHR 0.4, 95% CI: 0.1-2.7; p-value = 0.74). No attributable grade 3 - 4 toxicities

Legend: AA = ascorbic acid, AHR = adjusted hazard ratio, AML = acute myeloid leukemia, CR = complete response, DLT = dose limiting toxicity, GVHD = graft versus host disease, IVC = intravenous vitamin C, mOS = median overall survival, OS = overall survival, PR = partial response, QoL = quality of life, RCT = randomized clinical trial.

Low dose Intravenous Vitamin C

Several studies have looked at low doses of IVC for people with cancer (Table 2). 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 $\geq$ 3-4 mM depending on tumour cell type. Typically doses over 15g are required to achieve those plasma concentrations (16). 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 (57). Another study in AML enrolled elderly patients ($\geq$ 60 years) 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 (58). Treatment was continued until disease progression or unacceptable toxicity. This study found that the complete response (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 (61). Lastly, interim results for an ongoing phase III clinical trial evaluating IVC in patients post-hematopoietic stem cell transplant (HSCT) have been reported (59). The study administered IVC at a dose of 50mg/kg on days 1-14 post-transplant in patients with leukemias, then oral vitamin C at a dose of 500mg bid until 6-months. Participants were compared to historical controls using propensity score matching. No full text is available as the abstract was likely from a conference, however given the paucity of data using IVC in a transplant setting, it is included. Forty patients were enrolled, all were deficient in IVC at day 0 (median 17 umol/L). On day 14, all IVC levels were within normal (median 90 umol/L). The median time to neutrophil and platelet recovery was 12 days (9-15 and 8-21 respectively). After a median follow up of 220 days, there was no significant difference in transplant-related mortality, relapse, acute graft vs host disease (GVH) or chronic GVH between IVC group and historical controls. There were no attributable grade III or IV toxicities.

A study in adults with colon cancer looked at IVC given at a dose of 50mg/kg pre-operatively to evaluate the effect on post-operative pain. The study was a randomized, double-blind 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 ($p < 0.05$) (64).

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 of 11 individuals who, after radiation treatment for bone metastases, experienced an increase in pain, further metastatic spread, and/or a worsening of their general condition.(65). 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 retrospective study assessed 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 (66). 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 (67). 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 ($p = 0.0018$) (68). 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.

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 (7, 10, 69). 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%) (70). 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 (37). 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 IVC. 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 (71).

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 (10, 33, 69).

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 (72), carboplatin (73), cisplatin (2, 74, 75), etoposide (2), 5-fluorouracil (2, 74, 76), epirubicin (76), doxorubicin (2, 43, 75), paclitaxel (2, 75), docetaxel (76), and irinotecan (76). 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 (77) was conducted using dehydroascorbic acid – a tightly-regulated, diabetogenic derivative of ascorbic acid (78). The results of this publication are therefore not relevant to the clinical use of vitamin C as it is described here (79).

Other medications:

Poly ADP Ribose Polymerase inhibitors (PARP inhibitors):
One case series combined IVC with PARP inhibitors (niraparib, Olaparib, talazoparib) and reported good response rates and tolerability (52).

Warfarin:
There are two reports of oral vitamin C reducing effectiveness of warfarin (80, 81), but other research has not confirmed this (82). 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 (16, 20), or who have a G6PD deficiency (83). Caution is warranted in patients with a history of kidney stone formation, creatinine > 175 umol/L (16, 20, 84), and those with iron storage diseases (hemochromatosis). Those with diabetes must be informed of the falsely elevated glucometer readings following IVC infusion (85). 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 (10). 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 (84, 86, 87). Further, one participant with a history of kidney stone formation

experienced a recurrence during a trial of continuous IVC infusion (69). Larger prospective studies do not support this association, however, in patients who do not have a history of this condition (88, 89). 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 (20).

Caution is warranted in patients with end-stage renal failure who may be predisposed to hyperoxalemia or hyperoxalosis (84, 90), as this population could be at increased risk for stone formation from IVC treatment (91, 92). However, two case reports document positive outcomes in patients with renal cancer receiving IVC treatment (39, 93), 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 (94, 95). 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 (96), 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 (97). 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 (85, 98). 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 (69), a dose achievable by IV infusion at a rate of 500mg/minute (6, 33). Post-infusion blood levels of vitamin C vary by individual (33) and therefore should be measured to ensure adequate dosing. Low dose IVC has been used in several studies (<15g/infusion), particularly in hematological malignancies and for targeting pain (57-59, 61, 63, 65).

For treatment duration, IVC has been used from 1 week (35) up to 1 year (34) in clinical studies, and in case reports IVC has been used for up to 3 years with a good safety profile (40, 56).

Disclaimer

This monograph provides a summary of available evidence 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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