Intravenous Vitamin C in Cancer Care

Healthcare Provider Resource

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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) are 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 cell type. Plasma levels of 20mM are commonly targeted to achieve potentially cytotoxic effects *in vivo*, although several cancer cell lines exhibit cytotoxic responses at much lower concentrations. The dose required to achieve plasma ascorbate levels of 20mM typically ranges between 1-1.5g/kg of body weight per infusion. This monograph focuses on IVC at doses of ≥15g which we have defined as high dose. Proposed mechanisms of action of high dose IVC include generation of hydrogen peroxide creating oxidative stress, enzyme cofactor activities, anti-angiogenic and anti-inflammatory actions, and immune effects. Twenty-three prospective clinical trials have been published using IVC in cancer populations. These 23 studies include five randomized controlled trials (RCT) and 18 single-arm trials. Most published studies have been relatively small. Results from these clinical 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 cancer, ovarian cancer, non-small cell lung cancer, and RAS-mutant colorectal cancers. More research is needed, particularly from larger, randomized and placebo-controlled trials to confirm these findings and 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 compared to when taken orally.[3] Physiologic plasma concentrations of ascorbate range from the µM 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] Thus, only the IV route of administration can achieve sufficient serum levels that may have the proposed cytotoxic effect on cancer cells *in vivo*.[2] Vitamin C induced cancer cell cytotoxicity only occurs at plasma concentrations that range from 1mM to >20mM depending on the tumor cell line evaluated.[4,6]

Plasma concentrations of ascorbate following IVC infusion vary based on baseline plasma levels, the dose administered, body weight, and tumor burden. A pharmacokinetic study from 2021 found that serum ascorbate levels plateaued at infused doses greater than 75g (around 1g/kg in the study population) in both healthy and cancer populations;[7] thus, higher doses may have diminishing returns. In this study, the maximum serum concentration (C_{max}) achieved with a 75g dose in the healthy population was 24.9mM and in the cancer population was 21.6mM. In the same study, a 100g dose achieved a C_{max} of 23.7mM in the healthy population and 23.2mM in the cancer population. Clinical trials and

other pharmacokinetic studies have generally found similar results, although at least one has found higher doses continue to raise serum levels.[8] Most of these trials to date have used doses ranging 1-1.5g/kg body weight, which typically correlates to dosing between 60 and 100g of ascorbate, to achieve plasma concentrations around 20mM.[5,9-16]

Pharmacokinetics of infused ascorbate varies considerably from person to person; therefore in order to obtain optimal therapeutic effect, plasma levels for individuals may need to be measured.[17] 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.[17] Ascorbate plasma levels in people with cancer, and in particular for those with advanced disease, may be lower than in healthy individuals, as cancer increases oxidative stress and inflammation in the body, which increases ascorbate utilization due to its antioxidant properties.[18]

Ascorbate has also been found to accumulate in erythrocytes and tumors. Erythrocyte ascorbate reaches millimolar levels, and peaks around 4 hours post-infusion.[5] Tumor ascorbate levels increase following administration of IVC.[19] 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 of ascorbate are cleared within hours by renal filtration and excretion.[4,7] IVC exhibits first order elimination kinetics,[20] and has an elimination half-life between 30-120 minutes [7,20-22], with the most recent pharmacokinetic study reporting a half-life closer to 120 minutes.[7] Complete renal clearance has been reported as a mean of 24-h following 100g infusion of IVC in one pharmacokinetic study,[7] and in another trial, 80% of the administered doses of IVC had been filtered by the kidneys 6 hours following infusion.[23] Thus, plasma ascorbate concentrations are not maintained in the cytotoxic range for long with bolus IV infusion due to the short half-life of ascorbate and relatively quick renal clearance.

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 anti-inflammatory functions.[24] An emerging proposed mechanism is the supportive impact vitamin C has on immune function, particularly T-lymphocytes and natural killer cells.[25-27] These mechanisms are backed by several preclinical trials, and limited clinical research; however, this area requires 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 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 without hindrance.[24]

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.[28] 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.[29-31] Vitamin C is also a cofactor for various hydroxylases

and histone demethylases that regulate gene expression. Changes in the regulation of these enzymes via increased vitamin C levels in tumours have been shown in many studies.[29] High dose vitamin C may be able to reduce expression of tumour hypoxia-inducible factors (HIF) as demonstrated in a small clinical trial in colon cancer.[19] Vitamin C may be involved in epigenetic changes by acting as a cofactor for DNA and histone demethylases.

Other mechanisms of action:

Reductions in various inflammatory and angiogenic markers have been found in studies of IVC. One study of 12 patients with cancer administered six IVC treatments over a two-week period found non-significant reductions in various inflammatory and angiogenesis promoting cytokines.[32] Common inflammatory markers, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), were reduced following IVC treatment in two studies.[33,34] Neutrophil to lymphocyte ratio, a marker of inflammation, was reduced in a study of women with breast cancer.[25] Preclinical studies suggest ascorbate may have inhibitory effects on angiogenesis, possibly by suppressing nitric oxide and affecting the initial phase of cell migration and tube vessel formation.[35,36] Together, these studies indicate IVC likely has a systemic anti-angiogenic and anti-inflammatory effects, 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,[25,26] which may favour anti-tumor immune function.[27] Additionally, there is preclinical data to support the potential for IVC to positively impact the function of lymphocytes and natural killer cells.[27,37,38]

Clinical Evidence Related to Effectiveness

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 in Table 2. Twenty-three clinical trials (one placebo controlled RCT, four non-placebo controlled RCTs, and 18 single-arm trials) were identified by database searching and are summarized in this monograph. Additionally, a systematic review was published in 2022 which included clinical trials (n = 18) evaluating the impact of vitamins E and C on cancer survival.[39] The review will not be discussed further, as it included studies on both IV and oral administration of vitamin C, however 16 of the 18 studies are reviewed individually in this monograph.

A variety of cancer types have been studied with respect to IVC. The most studied cancer types (by number of participants) are: breast, lung, prostate, ovarian, colorectal, and pancreatic. Overall, IVC concurrent with oxidative therapies such as chemotherapy and radiotherapy seem to produce the greatest likelihood 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 [9,15,29,40] and ovarian cancers,[41] improving objective responses in NSCLC,[42] and improving PFS in patients with RAS mutant colorectal cancer.[43] Further research is needed to explore the effectiveness of IVC for these and other conditions.

IVC monotherapy

Most 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. Seven of the trials, detailed in table 1, evaluated IVC as a monotherapy, 6 of these were single arm[11,20,22,44-46] and one was an RCT.[19]

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 [11,22] and improved in another.[44] 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 may be expected to decrease in a population of patients with advanced disease, however, without a control group this effect cannot be causally determined.

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.[19] The investigators 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.[47] 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 with respect to 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.[11,22,45,46] Four clinical trials have evaluated IVC as monotherapy for cancer treatment; three failed to demonstrate an objective tumor response[11,22,46] and one found a modest response.[45] All four trials included people with advanced or terminal 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.[11] Although AEs 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.[22] Sixteen people completed the study, three of whom demonstrated stable disease and 13 had progressive disease. No objective tumour response was documented. A pilot clinical study included 24 late-stage patients given continuous infusions of 150 to 710 mg/kg/day of IVC for up to eight weeks.[46] One patient had stable disease and continued the treatment for 48 weeks, while the remaining 23 patients progressed. Treatment was generally well tolerated with mild side effects including nausea, edema, and dry mouth or skin. Two grade 3 AEs were reported: a kidney stone and hypokalemia. Finally, a small pilot study evaluated the effect of IVC on four patients with locally advanced basal cell carcinoma (BCC) who were not eligible for other treatment .[45] Researchers cite that at the time of their study initiation, alternative options for patients with metastatic or locally advanced BCC were not available, prompting them to study IVC and its possible benefit in this population. Since then, conventional options have emerged. Participants received 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 (n = 45), IVC treatment after conventional treatment was shown to be associated with a decrease in C-reactive protein in 75% of patients and therefore might have a role in reducing inflammation, a marker associated with worse cancer prognosis.[33] This study also found that IVC treatment

might contribute to decreased levels of some tumour markers, most notably prostate-specific antigen (PSA) levels. PSA was measured before and after IVC therapy in 20 participants, of whom 18 showed a reduced PSA following IVC treatment (95% CI, 77% improvement ± 21%).

Two studies evaluated IVC alongside modulated electro hyperthermia (mEHT), but without any concomitant standard cancer treatment.[48,49] These studies are described in the section on use with other integrative therapies.

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.[50-53] 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] glioblastoma,[6] bladder,[2] prostate,[2,54] liver,[2] breast,[2] cervix,[2] ovary,[6] colon,[55] and pancreatic cancer.[6,56]

IVC in combination with standard care

Quality of life, side effects, and toxicity

Results from clinical trials of IVC on quality of life (QoL), and treatment-related toxicity are mixed, with two studies finding improved outcomes,[57,58] and three finding no change.[13,14,43] Results from three observational trials demonstrated positive results.[59-61] One study reported an improved neutrophil to lymphocyte ratio, a marker that when elevated is associated with treatment-induced inflammation.[25]

Clinical trials:
Beneficial effects were found in trials involving participants with breast,[58] pancreatic,[9] and ovarian[57] cancers. The only placebo-controlled RCT to date of IVC was conducted in women undergoing treatment for stage IIa-IIIb breast cancer.[58] In this study, women (n = 350) receiving adjuvant chemotherapy, radiation, or hormone therapy, were randomized to IVC once weekly 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 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 to 25 women with advanced ovarian cancer.[57] 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 ascorbate levels >20mM) twice weekly during gemcitabine chemotherapy for an average of 6 months.[9] 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 $\pm$ 1.6 kg over 6 months).

Generally neutral effects were found for QoL or treatment toxicity in three trials. In a non-placebo-controlled RCT for patients with metastatic colorectal cancer (n = 442) there were similar rates of treatment-related adverse events (TRAEs) in the experimental arm

(IVC + FOLFOX ± bevacizumab) compared to the control arm (FOLFOX ± bevacizumab); the percentage of all TRAEs was 86.9% and 81.9% respectively, and 11 patients (5.0%) from the IVC group and 9 (4.1%) from the control group discontinued treatment due to TRAEs.[43] This study indicates that although IVC did not increase treatment toxicity, it also did not decrease it. 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.[13] There was large variability in number of IVC infusions (6-173). The study found no improvement in QoL based on questionnaires. 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.[14]

Observational studies:

Three observational studies evaluated QoL or treatment related toxicity. One retrospective cohort study included women with breast cancer, and found that QoL (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.[59] In another prospective uncontrolled observational study, improvements in QoL from both the patient and physician perspective were documented after 2 and 4 weeks of treatment in a group of patients newly diagnosed with cancer.[60] Other therapies used in these trials included epirubicin, cyclophosphamide, methotrexate, fluorouracil,[59] paclitaxel and cisplatin.[60] Finally, a retrospective, matched controlled observational study evaluated the impact of IVC on efficacy and toxicity in patients with metastatic triple negative breast cancer.[61] 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.[25] As mentioned previously, 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 its 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

Two RCTs [43,57], nine single-arm trials,[9,13-16,29,40,42,62] and two observational trials [61,63] 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 advanced ovarian cancer, pancreatic cancer, NSCLC, and RAS mutant colorectal cancer, however more research is needed.

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.[57] 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. 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.[50]

Two studies in metastatic colorectal cancer were conducted by the same group; a phase I single-arm trial[62] and a phase III RCT.[43] The RCT was non-placebo controlled and included 442 patients with metastatic colorectal cancer.[43] Patients were randomized to either high-dose IVC (n = 221) (1.5 g/kg/d on days 1-3 of FOLFOX ± bevacizumab) or FOLFOX ± bevacizumab alone (n = 221). The median duration of treatment in both groups was 4.5 months. There was no significant difference in median PFS between the IVC group vs. control group: 8.6 vs. 8.3 months; HR, 0.86 (95%CI, 0.70–1.05; p=0.19). The objective response rate (ORR) and overall survival (OS) were similar in both groups; ORR, 44.3% vs. 42.1%; p=0.9; median OS, 20.7 vs. 19.7 months; p=0.7). However, a sub- analysis revealed that patients with a RAS mutation had significantly longer PFS (median PFS, 9.2 vs. 7.8 months, HR, 0.67; 95% CI, 0.50–0.91; p=0.01) with IVC + chemotherapy versus chemotherapy alone. There were similar grade 3 or higher treatment-related adverse events; 33.5% vs. 30.3% of patients in the IVC compared to control groups, respectively. Prior to this RCT, the same group completed a phase I study in 36 patients with metastatic colorectal cancer or gastric cancer who received escalating doses of IVC during mFOLFOX6 or FOLFIRI ± bevacizumab.[62] 0.2-1.5 g/kg on days 1-3 of to determine the maximum tolerated dose (MTD). Following this, patients received IVC either at the MTD or at a fixed rate of 0.6, 0.8, or 1 g/min if the MTD was not reached. No MTD was reached, and no dose-limiting toxicities were detected. The recommended phase 2 dose was defined as 1.5 g/kg/day and the subsequent ORR and disease control rate were 58.3%, and 95.8%, respectively. Grade 3 and 4 treatment related adverse events in general were lower than reported with the use of chemotherapy alone.

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 nine patients with metastatic pancreatic adenocarcinoma administered IVC at doses of 50g-125g (to achieve plasma ascorbate levels >20mM) twice weekly during gemcitabine chemotherapy for an average of 6 months.[9] The IVC was well tolerated, with 6/9 who 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 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-IV) administered IVC at 50-100g daily during radiation therapy to 14 individuals who also received gemcitabine chemotherapy.[15] 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 OS 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.[40] Eight of the nine patients who completed the trial had a reduction in the size of their primary tumour and the tumour size was stable in the ninth patient. These results are not typical for treatment with either gemcitabine or gemcitabine plus erlotinib alone. Lastly, a phase I/IIa study applied 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.[29] They found that IVC did not alter the PK of gemcitabine in any clinically significant way, and IVC was safe with only grade 1 nausea and thirst observed. 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.[64]

The only study in which IVC was applied for glioblastoma multiforme (GBM) is a phase I clinical trial in 11 patients receiving radiation and temozolomide.[16] In this study, participants were treated with IVC three times per week after surgery, during concurrent radiotherapy and temozolomide targeting plasma ascorbate levels ≥ 20 mM (15 – 125 g infusion) and then two times per week alongside temozolomide alone . Median PFS was 9.4 months, and median OS was 18 months (the reported historical median as mentioned by the authors was 7 and 15 months, respectively; however, no statistical analysis was performed). No dose-limiting toxicities were reported for the participants and a similar toxicity profile was reported in comparison to historical experience. Adverse events associated with the application of IVC included only dry mouth and chills. Patients with undetectable O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation (n=8) had better median PFS and OS at 10 and 23 months, respectively. The authors found that overall, the combination of radiotherapy, temozolomide, and IVC is safe, and demonstrated promising results.[16]

One study evaluated the use of IVC among non-small cell lung cancer patients (NSCLC). This phase II clinical trial recruited 38 chemotherapy naïve advanced-stage patients who were given IVC at a dose of 75g 2x/week + carboplatin and paclitaxel every three weeks for four cycles.[42] The primary end point of the study was achieved with an objective response rate of 34.2%; significantly better than historical controls of 20% (p=0.03). Partial responses (cPR) were achieved in all patients and the disease control rate (stable disease + cPR) was 84.2%. Median PFS and OS were 5.7 months and 12.8 months, respectively. Further analysis revealed that in patients with PFS ≥ 6 months, immunophenotyping of peripheral blood mononuclear cells demonstrated an increase in effector CD8 T-cells suggesting a more aggressive host immune response. One grade 5 (neutropenic fever) and five grade 4 treatment-related adverse events (cytopenia) were observed within the group. The authors concluded that the addition of IV infused ascorbate alongside platinum-based chemotherapy improved tumor response in advanced NSCLC patients and may have favourably altered the host immune response.

Finally, in a phase I/II single arm trial, 14 patients with heavily pre-treated advanced cancers of various types received IVC at a dose of 1.5g/kg two or three times weekly during usual care chemotherapy.[13] Of the 12 who were evaluable for response, six had a brief or longer lasting disease stabilization. Ultimately in this study, it is difficult to know if this represented a positive or null response.

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.[32] Patients received usual chemotherapy with the addition of IVC escalating from 15g to 50g, 3x/week for 2 weeks. Plasma cytokines and tumor markers were measured before and after the intervention. Following IVC treatment, several favorable changes in cytokines were noted based on average z-scores, including decreases in 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, these differences were not statistically significant. In twenty men with metastatic castrate resistant prostate cancer treated with androgen deprivation therapy, the addition of IVC failed to improve PSA.[14] In this study, patients were administered 60g of IVC weekly for 12 weeks, with no patient achieving a 50% reduction in PSA (indeed: median PSA increased 17ug/L at 12 weeks), and no objective signs of disease remission were found.

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).[61] Thirty-five women receiving IVC every other day during two cycles of gemcitabine + carboplatin chemotherapy were matched to 35 women receiving chemotherapy alone. The study found that there was no change in tumor response rates 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).[63] Patients were treated with IVC at a dose of 1-1.5g/kg body weight, 2-4x a week for a minimum of three months. Authors reported that five patients had a partial response and three 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 the PARPi rather than IVC. The authors noted that the response rates were favourable 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 therapies.

Two prospective trials evaluated IVC with modulated electrohyperthermia (mEHT) in people with lung cancer.[48,65] 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.[66] IVC doses were administered at 1.0, 1.2, and 1.5 g/kg 3x/week for 4 weeks (with 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).[48] 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. Some caution is warranted when interpreting these results due to some potential inaccuracies in the statistical analysis applied.

One controlled observational study included 27 patients with small-cell lung cancer (SCLC), more than half of whom had 'limited stage' SCLC.[67] Twelve patients received IVC; 25-50 g/day every 1 or 2 weeks with carboplatin and etoposide ± radiation therapy, and they received in addition alkalinization therapy in the form of an alkaline diet and bicarbonate therapy. Patients were compared with 15 patients who received similar conventional treatment alone. The median OS for the intervention group was 44.2 months (95% CI = 22.0−not reached), as compared with 17.7 months for the control group (95% CI = 13.5−not reached; p < 0.05). The authors concluded that the combination of IVC and chemotherapy together with alkalinization therapy might be beneficial in SCLC patients receiving chemotherapy.

Lastly a observational study included 15 patients with various stage III/IV cancers (mostly solid tumors) who were following a Ketogenic diet (KD) and received 15-40g of IVC 1-2 times per week.[34] After 1-week of IVC treatment, CRP levels declined from 3.19 ± 3.25 mg/L to 1.06 ± 0.67 mg/L ($P < 0.001$), and ESR levels declined from 64.13 ± 38.83mm/h to 31.6 ± 16.55 mm/h ($P = 0.004$). The authors reported an increase in hemoglobin but did not provide these values. Creatinine levels increased after IVC treatment (0.85 ± 0.23 vs 1.17 ± 0.29 mg/dL, $P < 0.001$) highlighting a potential impact on renal function. Vomiting, hypertension, oliguria and proteinuria were reported in 60%, 40%, 26%, and 30% of patients respectively.

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.[68] 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.[53] The patient was treated with carboplatin and vincristine chemo-radiation. 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. While initially a reduction in tumor size was noted for this child, the tumor began growing again and the combination approach no longer had an effect.

Hematological malignancies

Leukemias:

Low dose IVC (1g) has been studied alongside conventional treatments in AML,[69,70] and post-hematopoetic stem cell transplant.[71] 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.[72]

Multiple myeloma:

One preliminary study, described in Table 2, applied low dose IVC alongside bortezomib and arsenic trioxide.[73]

Lymphoma:

One small phase I study, described in Table 1, included 3 people with B cell lymphoma treated with IVC.[74] One case report of an individual with B cell lymphoma treated with IVC during and after radiation therapy resulted in disease remission that remained stable for 1.5 years until the time of its publication.[51]

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.[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.[69] The treatment was well tolerated, but overall the results were not promising enough to recommend further study of this combination. Another study in AML enrolled elderly patients (≥ 60 years) with newly diagnosed AML who were either unfit for or refused intensive chemotherapy.[70] Patients were randomized to receive decitabine-based chemotherapy alone, or decitabine-based chemotherapy plus low dose IVC at 50-80mg/kg/day. 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.[73] Ten people received this treatment for up to eight 3-week cycles. Four patients had clinical benefit; there were no dose-limiting toxicities. Interim results for an ongoing phase III clinical trial evaluating IVC in patients post-hematopoietic stem cell transplant (HSCT) have been reported.[71] 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 was included in this synthesis. Forty patients were enrolled, all of whom were deficient in ascorbate levels at day 0 (median 17 umol/L). On day 14, all ascorbate 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 the IVC group and historical controls. There were no attributable grade III or IV toxicities. Lastly, a case series reported on four patients with refractory and relapsed multiple myeloma (MM) who received 7.5g IVC 2x/week alongside carfilzomib-lenalidomide-dexamethasone.[77] One patient had a complete response, while the other 3 patients had a very good partial response. The authors concluded that the addition of IVC to conventional chemotherapy might be an effective approach in relapsed refractory MM patients.

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.[78] 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 ($p < 0.05$).

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.[79] 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. The 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.[80] 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.[81] 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 ($p = 0.0018$).[82] 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 that lymphopenia is a potentially reversible, and predictive factor for earlier tumor progression or relapse, this finding 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.[11,22,46] 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%).[83] 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.[47] 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. However, 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.[84]

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

Very common (≥10% of patients): dry mouth, nausea, transient hypertension, hyponatremia

Common (between 1 and 10% of patients): increased thirst, increased urination, diarrhea, fatigue, weakness, headache, light-headedness, dizziness, injection site discomfort, phlebitis, arthralgia/myalgia, chills, anorexia/dysgeusia, hemolysis, hypokalemia, hypomagnesemia, hypocalcemia, hypotension, loss of appetite, neuropathy, hypernatremia

Uncommon (between 0.1 and 1% of patients): abdominal cramping, facial flushing, vomiting, kidney stones, lower urinary tract symptoms, insomnia, abnormal urine colour, hyperglycemia, fever, swelling of feet or lower legs, sweating, ascites, allergic reaction,

acute oxalate nephropathy, renal failure in those with a pre-existing renal condition.

Very rare (<0.01% of patients): atrial fibrillation (one report)

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.[11,40,46]

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,[85] carboplatin,[86] cisplatin,[2,87,88] etoposide,[2] 5-fluorouracil,[2,87,89] epirubicin,[89] doxorubicin,[2,55,88] paclitaxel,[2,88] docetaxel,[89] and irinotecan.[89] 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 (described in Tables 1 and 2) have used IVC alongside a variety of cytotoxic chemotherapy and targeted agents including gemcitabine, carboplatin, paclitaxel, cyclophosphamide, cytarabine, etoposide, 5-fluorouracil, oxaliplatin, irinotecan, dexamethasone, temozolomide, erlotinib, rituximab, and bevacizumab. IVC has also been used 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. Data from studies with control groups have found either no difference or improvements in response rates and survival time with concurrent use of IVC.[42,43,57] 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 was conducted using dehydroascorbic acid, a tightly-regulated, diabetogenic derivative of ascorbic acid.[90,91] The results of this publication are therefore not relevant to the clinical use of vitamin C as it is described here. [92]

Other medications

Poly ADP Ribose Polymerase (PARP) inhibitors

One case series combined IVC with PARP inhibitors (niraparib, olaparib, talazoparib) and reported good response rates and tolerability.[63]

Warfarin

There are two reports of oral vitamin C reducing the effectiveness of warfarin,[93,94] but other research has not confirmed this.[95] Until more is known, caution should be used if patients are on warfarin.

Cautions and Contraindications

High dose IVC should not be administered to patients with renal failure,[18,23] or who have a G6PD deficiency.[96] Caution is warranted in patients with a history of kidney stone formation, creatinine > 175 umol/L[18,23,97], and those with iron storage diseases (hemochromatosis). Those with diabetes must be informed of the falsely elevated glucometer readings following IVC infusion.[98] 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.[11] Finally, IVC use has not been studied for use by pregnant or lactating women, or by children. Caution is warranted in these groups. 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.[97,99,100] Further, one participant with a history of kidney stone formation experienced a recurrence during a trial of continuous IVC infusion.[46] However; larger prospective studies do not support this association in patients who do not have a history of this condition.[101,102] 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.[23]

Caution is warranted in patients with end-stage renal failure who may be predisposed to hyperoxalemia or hyperoxalosis,[97,103,104] as this population could be at increased risk for stone formation or oxalate nephropathy from IVC treatment.[104-106] However, two case reports document positive outcomes in patients with renal cancer receiving IVC treatment,[51,107] therefore renal failure is a contraindication for IVC whereas renal cancer is not necessarily a contraindication.

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.[108,109] 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 oral vitamin C intake.[110] The effect of IVC has not been studied in this population and thus the risk is theoretical. IVC may be used to mobilize iron stores in the treatment of functional anemia among hemodialysis patients and may actually reduce ferritin stores.[111] If IVC is administered to individuals with iron storage diseases, prescribing professionals should consider regular monitoring of iron status, and exacerbation of these conditions may necessitate discontinuing treatment.

Diabetes

IV ascorbate will elevate fingerstick blood glucose monitor readings in most portable glucometers.[98,112] 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 at least 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. Low dose IVC has been used in several studies (<15g/infusion), particularly in hematological malignancies and for targeting pain.[69-71,73,76,79]

For treatment duration, IVC has been used from 1 week[44] up to 1 year[41] in clinical studies, and in case reports IVC has been used for up to 3 years with a good safety profile.[52,68]

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.

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

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Riordan, 2005[58]	Phase I Single arm	24 patients with terminal cancer and no available effective therapies	150-710 mg/kg/day IVC for up to 8 weeks with doses increasing after each 3 enrollments	None	Disease status, adverse events, lab outcomes	1 patient had stable disease, others had progressive disease. Most AEs were grade I or II (nausea, dry mouth, edema, and fatigue were most common); 4 AEs were grade III or IV with 2 possibly related to treatment (kidney stone & hypokalemia). Standard blood count and chemistry profiles remained stable.
Hoffer, 2008 [35]	Phase I Single arm	24 patients with locally advanced, metastatic, or recurrent cancer 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 DLTs	None	Toxicity, preliminary antitumour effects, QoL (FACT-G), and plasma ascorbate levels	AEs and toxicity were minimal at all doses. No objective antitumour 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 [54]	Phase I Single arm	14 patients (9 completed) with metastatic pancreatic cancer receiving gemcitabine and erlotinib	IVC 3x weekly for 8 weeks Cohort 1: 50g Cohort 2: 75g Cohort 3: 100g	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.

Stephenson, 2013 [32]	Phase I Single arm	17 patients with advanced solid tumours refractory to standard therapy	IVC 4x weekly for 4 weeks. Dose escalation protocol: 30, 50, 70, 90, 110 g/m^2 All patients received a multivitamin and EPA (2000mg)	None	Safety, tolerability, PK, QoL (EORTC QLQ-C30), tumour response	7/17 patients experienced grade III or IV AEs (hypokalemia, hypernatremia, headache) Half-life: 2.0 $\pm$ 0.6 h C_{max} and AUC increased proportionately with dose, but reached maximum at 70 g/m^2 (C_{max} 49mM, AUC 219 h mM). No objective tumour responses observed. EORTC scores improved in weeks 3-4 compared to baseline (week 3 N = 7, week 4 N = 2).
Welsh, 2013[22]	Phase I Single arm	9 patients with stage IV pancreatic adenocarcinoma receiving gemcitabine	IVC 2x weekly during chemotherapy; titrated to achieve plasma levels of >20mM (50-125g)	None	Primary: Toxicity (CTCAE v3), plasma ascorbate levels Secondary: performance status, weight, PFS, OS, lab outcomes	No DLTs or SAEs; safe and well tolerated. Mean AA trough levels were significantly higher than baseline 6/9 subjects maintained or improved performance status and mean weight loss was 5.3 ± 1.6kg during treatment. PFS: 26 ± 7 weeks; OS: 13 ± 2 months for those receiving at least 1 month of treatment ↓ F_2-isoprostane levels Stable levels of GSH and E_{hc} in RBCs
Kawada, 2014[90]	Phase I Single arm	3 patients with relapsed B cell non-Hodgkin's lymphoma receiving CHASER regimen	75g IVC administered on days 9, 11, 14, 16, and 18 of 21-day cycle of CHASER	None	Safety, dose (based on plasma AA concentration)	No AEs attributed to IVC Plasma concentration of >15mM achieved by day 9 or 18 with 75g dose. 75g dose recommended for future trials.
Ma, 2014[43]	Phase I/II 2-arm, open label RCT	25 patients with newly diagnosed stage III/IV ovarian cancer receiving carboplatin/paclitaxel for 6 months	IVC + chemotherapy IVC given 2x weekly for 12 months; dosed to achieve plasma concentration of 20-23mM (75g or 100g)	Chemotherapy alone	Safety and toxicity measured by CTCAE v3, PFS	No difference in grade III/IV toxicities between groups, significant reduction in grade I ($p < 0.01$) and II ($p = 0.028$) toxicities in IVC arm Median PFS 8.75 months longer in IVC arm. P values not provided by authors.

Hoffer, 2015[37]	Phase I/II Single arm	14 patients with advanced cancer, for whom standard care chemotherapy would offer <33% likelihood of meaningful response	IVC at 1.5g/kg given 3x weekly on chemo weeks and 2x weekly if no chemo until DLT or disease progression following 2 chemo rounds.	None	AEs, toxicity, QoL (FACT-G, Profile of Mood States-B), objective clinical response	IVC was safe and non-toxic, thirst and increased urination occurred in all patients. No improvement in QoL. 2 patients experienced stable disease while on study, 1 patient had temporarily stable disease. No benefit reported or no conclusions able to be made in 11 patients.
Nielsen, 2015[30]	Phase I Single arm	10 patients with metastatic castrate-resistant prostate cancer	IVC 1x weekly for 4 weeks Week 1: 5g Week 2: 30g Weeks 3 and 4: 60g	None	Pharmacokinetic measurements	IV vitamin C exhibited first order elimination kinetics. 60g dose achieved peak plasma ascorbate concentration of 20.3mM. Elimination half-life 1.87 h, volume distribution 0.19 L/kg, clearance rate 6.02L/hr. No difference in pharmacokinetics between doses.
Mikirova, 2016[53]	Phase I Single arm	12 patients with mixed cancer types receiving standard oncology care	IVC 3x weekly for 2 weeks; dosed per Riordan protocol (15g, then 25g, then individualized dosing up to 50g)	None	Blood analyses for plasma ascorbate, cytokines, tumour 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 tumour markers (CA15-3, CA 19-9, CEA, CA 242).

Nielsen, 2017 [38]	Phase II Single arm	23 patients with metastatic castrate-resistant prostate cancer receiving androgen deprivation therapy; chemotherapy naïve	IVC 1x weekly for 12 weeks. Week 1: 5g Week 2: 30g Weeks 3-12: 60g All participants were additionally given 500mg oral AA daily for 26 weeks.	None	Primary: 50% reduction in PSA Secondary: QoL (EORTC QLQ-C30), safety, imaging, biomarkers (Hgb, LDH, ALP, albumin, CRP) Follow-up at weeks 12, 20, 26, and 52	No patient achieved a 50% reduction in PSA; median PSA increase of 17 µg/L at 12 weeks. Most common AEs were hypertension and anemia. 3 AEs related to the treatment, all likely related to fluid load and not IVC. 11 grade III-V AEs, all likely related to disease burden. No signs of disease remission. ECOG score stable in 16/20 participants; no significant improvement in any biomarkers or QoL questionnaires.
Ou, 2017[91]	Phase I 3-arm, open label randomized	15 patients with stage III/IV NSCLC refractory to standard treatments	Arm 1: 60 min mEHT + 1g/kg IVC 3x weekly for 4 weeks; mEHT preceding IVC Arm 2: 60 min mEHT + 1.2g/kg IVC 3x weekly for 4 weeks; mEHT and IVC given concurrently Arm 3: 60 min mEHT + 1.5g/kg IVC 3x weekly for 4 weeks; mEHT following IVC	None	Plasma AA levels, safety, QoL (EORTC QLQ-C30)	Plasma AA at baseline was lower in the study group than in healthy people (0.05 vs 0.09 mM, $p < 0.05$). 1.5g/kg IVC achieved peak plasma concentrations of 21-25mM. AEs/toxicity: mild (grade I-II) thirst and fatigue, one patient had grade III 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

Polireddy, 2017[15]	Phase I/II 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 II: IVC 3x weekly (75 or 100g) with gemcitabine until tumour progression or patient withdrawal	None	PK, safety, tumour 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.
Alexander, 2018[39]	Phase I 2-arm, 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 treatment duration 5.7 weeks). Weekly gemcitabine given concomitantly.	Gemcitabine + radiation as per protocol	AEs (CTCAE v4), treatment compliance, plasma AA levels, and F2-isoprostane (oxidative stress marker), PFS, OS	Well-tolerated, 3 AEs attributed to IVC (dry mouth, thirst, transient BP elevation). One DLT occurred (esophageal spasm, patient rechallenged without incident and continued trial) 57% received all cycles of gemcitabine, 100% completed radiation; better than historical averages. 57% received all doses of IVC Significant difference in plasma F2-Isoprostanes between week 0 to week 3 (p=0.99) and after completion of chemoradiotherapy (p=0.88) but not in comparators Mean plasma AA concentrations: 50g = 15mM, 75g = 20mM, 100g = 20mM IVC group had better mOS and PFS compared with University of Iowa's institutional median (21.7 vs 12.7 months, p=0.08; 13.7 vs 4.6 months, p=0.02)

Allen 2019[40]	Phase I Single arm	11 patients with GBM after surgery	Phase I: RT + TMZ + IVC *IVC: 3x weekly Phase II: TMZ + IVC *IVC: 2x weekly in an intra-patient escalated manner *Targeting plasma AA levels ≥ 20 mM (15 – 125g infusion)	None	Dose to achieve targeted AA plasma levels, OS, PFS, dose limiting toxicities, AEs	Targeted AA plasma levels of 20 mM were achieved in the 87.5 g group of patients Median PFS was 9.4 months, and median OS was 18 months. No dose-limiting toxicities occurred and there was a similar toxicity profile to the historical group. AEs related to IVC: dry mouth and chills
Wang 2019[56]	Phase I Single arm	36 patients with metastatic colorectal or gastric cancer on mFOLFOX6 or FOLFIRI chemotherapy	Part 1: IVC in escalating doses (0.2-1.5 g/kg daily on days 1-3 of chemotherapy Part 2: IVC at MTD (or 1.5g/kg if MTD was not reached) daily at rates from 0.6-1.0g/min on days 1-3 of chemotherapy	None	MTD from the first phase, DLTs, RP2D, TR, OR, TRAEs, PK, PFS	No MTD was reached, and no DLT was detected The RP2D was 1.5g/kg/day The OR and disease control rate were 58.3%, and 95.8%, respectively Grade 3 TRAEs were neutropenia (13.9%), sensory neuropathy (2.8% (n=1)), vomiting (2.8%), diarrhea (2.8%), and leukopenia (2.8%). One grade 4 TRAE occurred: neutropenia (2.8%) PK: C_{max} and AUC reached maximum values at 1.5g/kg/day Median PFS was 8.8 months with 17 PFS events at follow-up (16 disease progression, 1 death)
Banvolgyi 2020[59]	Phase I 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, 3x weekly. Treatment duration not pre-specified; mean duration was 42 ± 23.6 weeks	None	Lesion diameter, clinical response (according to adapted RECIST guidelines), AEs	Of 18 lesions monitored, 83% had a response (SD+PR+CR) – 27% PR and 73% SD. No new lesions were detected during treatment, however patient 2 developed an intrasellar progression after 4 months. No AEs occurred.

Ou, 2020[49]	Phase II 2-arm, open label RCT	97 patients with advanced, refractory, NSCLC (stage IIIB-IV) (n=49 treatment, n=48 control)	IVC + mEHT + best supportive care IVC: 1g/kg, 3x/week, for a total of 25 treatments mEHT: 60 minutes 3x/week. Best supportive care: antibiotics, analgesics, dietetic advice, or other appropriate treatments at the discretion of the care team	Best supportive care alone	OS, PFS, 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). Median PFS was 3.0 months for the treatment 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, incidence of peripheral neuropathy was lower in the intervention group (p<0.05). AEs: thirst was reported by 22/49 participants receiving IVC. One participant experienced severe diarrhea. Intervention arm had a significantly lower incidence of AEs, including leukopenia (14.3% vs. 25.8%), anemia (11.5% vs. 20%) and thrombocytopenia (17.2 vs 31.4%, p<0.05) Note: IVC and mEHT were both experimental interventions, results cannot be attributed to IVC
Dachs 2021[18]	Phase II 2-arm, open label RCT	15 patients with colon cancer awaiting surgery (n=9 treatment, n=6 control)	IVC at 1g/kg daily x 4 days prior to surgery	Surgery alone	Plasma, tissue, and erythrocyte AA levels, HIF proteins, AEs and QOL, tumour	Tumour 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 tumortumourontrol and treatment. Erythrocyte ascorbate increased significantly post-infusion and continued to increase over the 4-day infusion period (p <0.005) and levels were higher than in plasma (2mM vs. 0.2 mM). Lower expression of hypoxia associated proteins was seen in post-infusion tumours compared to controls. All AEs were grade I. Transient hypertension, peripheral neuropathy, and light-headedness reported. No changes in QOL.

Mansoor 2021[42]	Phase II 2-arm, parallel group, single-blind, placebo-controlled RCT	343 patients with stage IIA-IIIB breast cancer (n=172 treatment, n=171 control)	IVC at 25g once weekly x 4 weeks alongside conventional care (chemotherapy, radiotherapy and/or tamoxifen)	Placebo (saline drip)	Visual Analog Scale (VAS) assessing nausea, loss of appetite, tumour pain, fatigue, insomnia, diarrhea, and vomiting	A significant decrease in the mean VAS 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), tumour 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). Diarrhea and vomiting had nonsignificant decreases: diarrhea (2.65 ± 0.62 vs 2.59 ± 0.68, p = 0.39), vomiting 2.87 ± 0.56 vs 2.77 ± 0.50, p = 0.08) No significant changes were noted in the control group compared to baseline for any measure
Chen 2022[8]	Phase 1 2-arm	Healthy volunteers (n=21) and patients with cancer (n=12) not eligible for conventional treatment at time of enrollment	Healthy volunteers received 1-100g in escalating doses.of IVC and patients with cancer received 25-100g in escalating doses.	None	Characterize the pharmacokinetic profile of IVC Determine MTD Safety and AEs	IVC exhibited first order kinetics up to 100g, is excreted by the kidneys and had complete renal clearance in 24 hours. Mean 24-hour total IVC excretion in urine for all doses was lower in oncology participants (89% of dose) compared to healthy participants at 100g (99%). Serum vitamin C concentration plateaued at doses over 75g (around 1g/kg in this study population) in both groups. Area under the concentration-time curve only plateaued in healthy group. The maximum serum concentration (C_{max}) at a 75g dose was 24.9mM and 21.6mM in the healthy and cancer groups, respectively. 100g dosing achieved a C_{max} of 23.7mM and 23.2mM in the healthy and cancer groups, respectively. Half-lives were reported to be close to 2 hours in both groups. There were no significant AES observed, MTD was not reached.

Furqan 2022[55]	Phase II Single arm	38 chemotherapy naïve patients with advanced-stage NSCLC	IVC 75g 2x weekly + carboplatin and paclitaxel every three weeks x 4 cycles	None (compared to historical controls)	ORR, disease control, PFS, OS and TRAEs	ORR was 34.2% compared to historical control rate of 20% (p = 0.03). All patients were confirmed partial responses (cPR). The disease control rate (stable disease + cPR) was 84.2%. Median PFS and OS were 5.7 months and 12.8 months, respectively. TRAEs: one grade 5 (neutropenic fever) and five grade 4 (cytopenia) events were identified.
Wang 2022[44]	Phase III 2-arm, non-placebo controlled	442 patients with metastatic colorectal cancer (n=221 treatment, n=221 control)	IVC 1.5 g/kg on days 1-3 of FOLFOX ± bevacizumab chemotherapy	FOLFOX ± bevacizumab	ORR, OS, PFS, TRAEs	No significant difference between the IVC and control group in median PFS (8.6 vs.8.3 months; HR, 0.86, 95% CI, 0.70–1.05; p = 0.1 9), ORR (44.3% vs. 42.1%; p = 0.9), or median OS (20.7 vs. 19.7 months; p =0.7). Patients with RAS mutation in the treatment arm (+ IVC) had significantly longer PFS compared to those in receiving FOLFOX ± bevacizumab alone (median PFS, 9.2 vs. 7.8 months, HR, 0.67; 95% CI, 0.50–0.91; p = 0.01). Grade 3 or higher TRAEs; 33.5% and 30.3% of patients in the IVC and control groups, respectively.

Legend: AA = ascorbic acid/ascorbate, AE = adverse events, bw = body weight, CR = complete response, DLT = dose limiting toxicity, EPA = eicosapentanoic acid, GVHD = graft versus host disease, IVC = intravenous vitamin C, mEHT = modulated electrohyperthermia, mOS = median overall survival, MTD = maximum tolerated dose, NSCLC = non-small cell lung cancer, ORR = overall response rate, OS = overall survival, PFS = progression free survival, PK = pharmacokinetics, PR = partial response, QoL = quality of life, RECIST = Response Evaluation Criteria in solid tumours, RPD2 = recommended phase 2 dose, SE = side effect, SD = stable disease, RT= radiotherapy, TMZ = temozolomide, TTP = time to progression

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

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Yeom, 2007[48]	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[79]	Single-arm, open label	10 patients with relapsed, refractory myeloma	1g IVC on day 1 and 8 of 21-day cycle for up to 8 cycles, alongside IV arsenic trioxide and bortezomib	None	Response rate, clinical benefit rate	4 achieved clinical benefit, 1 had durable partial response. No DLTs
Aldoss, 2014[92]	Single-arm, open label	11 patients with relapsed or refractory AML	IVC 1g/day x 5 days/week x 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.
Jeon, 2016[93]	RCT	97 patients with colon cancer undergoing surgery	IVC 50mg/kg administered after anesthetic 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 ($p<0.05$)
Zhao, 2018[93]	RCT	73 elderly patients with AML (39 treatment arm, 34 control arm)	IVC at 50-80mg/kg + DCAG chemotherapy	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.

Simmons 2020[94]	Phase II Single-arm trial with matched historical controls *Interim analysis, no full text available	40 patients including 19 with AML, 11 with ALL, 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	Transplant mortality at 1 year, serum AA levels, neutrophil and platelet recovery, CD+3 cell counts, rates of acute and chronic GVHD, toxicity	All were deficient in AA 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/ascorbate, AHR = adjusted hazard ratio, ALL = acute lymphocytic leukemia, AML = acute myeloid leukemia, CR = complete response, DCAG = decitabine + cytarabine + aclarubicin + granulocyte colony stimulating factor, 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, RR = response rate

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