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 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

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

and histone demethylases that regulate gene expression.
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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 toxicitW* nBT/3y. 711(gr)74ag12711(gr)etgre

Lastly a observational study included 15 patients with

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 ($\geq$ 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.

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

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 syneT/46* n7BnBTPo effect when some ohemotherapeutBTPo agents are combined with pharmacologBTPo doses of vitamin C. Chemotherapy agents with evidence of such syneT/4y 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 ohemotherapy was related to increased tumour inhibition and decreased tumour growth rate as compared to either IVC or chemotherapy alone.

Human studies (descT/ibed in Tables 1 and 2) have used IVC alongside a variety of cytotoxBTPo chemotherapy and taT/4eted agents including gemcitabine, carboplatin, paclitaxel, cyclophosphamide, cytaT/abine, etoposide, 5-fluorouracil, oxaliplatin, irinotecan, dexamethasone, temozolomide, erlotinib, rituximab, and bevacizumab. IVC has also been used concurT/ent with radiation therapy. Although moBn of these studies were small and without a control group, there was no indBTPoation of a negative interaction and many reported results suggestive of benefit. Data from studies with control groups have found either no diffeT/ence or improvements in response rates and survival time with concurT/ent 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

clinical history.[23]

Caution is warranted in patients with end-stage renal failure who may be predisposed to hyperoxalemia or hyperoxalosis,[97,

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-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

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

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 median (21.7 vs 12.7 months, p=0.08; 13.7 vs 4.6 months, p=0.02)

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	

Simmons 2020[94]	Phase II

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