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Professional Resource: Intravenous Vitamin C (IVC)

Proper Name
Ascorbic acid, Ascorbate

Common Name
Vitamin C

Common Uses in Cancer Care
IVC is most commonly prescribed to improve quality of life, to slow cancer progression and to reduce cancer-treatment related symptoms, for example fatigue, nausea and lack of appetite.

Route of Administration
Intravenous (IV)

Pharmacokinetics
The administration of IVC results in far higher serum levels of vitamin C than oral administration of an identical dose (1). Intravenous infusion may raise serum levels of vitamin C 70-fold compared to those that may be achieved through oral dosing alone. IV administration bypasses the tight controls within the body that prevent the absorption of this amount of vitamin C when taken orally (2). Only the IV route of administration has been documented to achieve sufficient serum levels to observe a cytotoxic effect *in vivo* (3).

Pharmacologic concentrations (0.3 to 15 mM) of vitamin C are cleared within hours by renal filtration and excretion (4). The half-life of high doses of vitamin C (>70uM) is estimated to be approximately 30 minutes (5). In one trial, 80% of administered doses of IVC had been filtered by the kidneys in the 6 hours following the IV (6).

Mechanism of Action
Two mechanisms of action have been proposed regarding the effectiveness of IVC to slow cancer progression. Both mechanisms are supported by several preclinical studies, although both require further study.

H_2O_2 Production
One proposed mechanism involves this nutrient acting as a prodrug for the formation of hydrogen peroxide (H_2O_2). Administration of IVC has been shown to cause measurable increases in extracellular H_2O_2, which has been shown to cause cell death in numerous cancer cell lines by pyknosis/necrosis while

leaving normal human cells unharmed (4). Extracellular H_2O_2 is thought to kill cancerous cells through a number of mechanisms that result in the depletion of ATP (2, 7). As normal cells rely upon aerobic mechanisms for ATP generation rather than anaerobic ATP metabolism, they may be less sensitive than cancer cells to ATP depletion through H_2O_2 exposure. In addition, the mitochondria of normal cells may be less sensitive than cancerous cells to the toxic effects of H_2O_2 (2). The mechanisms protecting normal cells from H_2O_2 have not been completely explained but *in vitro* studies clearly demonstrate little sensitivity of non-cancerous cells to IVC treatment (8).

Pro-oxidant effect

Despite vitamin C's known action as an antioxidant when taken orally (9), the high plasma concentrations of vitamin C that result from IV administration (0.3 to 15 mM) lead to the generation of free radicals in the extracellular fluid (2), causing the infused vitamin C to behave as a pro-oxidant compound *in vivo*. The actions of a pro-oxidant are the opposite to an antioxidant in that the pro-oxidant will generate free radicals, rather than quench them.

Clinical Evidence related to Effectiveness

IVC MONOTHERAPY

Quality of life

The few clinical trials that have been published have included only patients with advanced disease. These studies have assessed the impact of IVC on quality of life, with mixed results. In one trial, quality of life remained stable (10) while quality of life improved in another (11). In a retrospective cohort study, breast cancer patients who used IVC in combination with standard care demonstrated improved quality of life as compared to those who used standard care only (12). These results are notable, as quality of life would otherwise be expected to decrease in this population of patients with advanced disease.

Slow cancer progression

IVC is not considered a curative monotherapy for cancer (8, 10), and the human intervention literature is limited. A handful of well-documented case reports suggest that treatment with IVC is associated with tumour regression and remission, and unexpectedly long survival times (13, 14). These outcomes are supported by animal studies conducted using high doses of vitamin C obtainable by IV infusion that demonstrate reduced tumour size (3) and decreased tumour growth rate (8). Similarly, *in vitro* evidence demonstrates sensitivity of a number of cell lines to treatment with vitamin C. Benefit has been identified in cell-line studies of lymphoma (4) and glioblastoma (8) as well as in cancers of the bladder (3), prostate (3, 15), liver (3), breast (3), cervix (3), ovary (8), colon (16) and pancreas (8, 17).

IVC IN COMBINATION WITH STANDARD CARE

Symptom management

Recent clinical studies have studied the combination of IVC with concurrent chemotherapy based on hypotheses that IVC may reduce the toxicity of standard treatment, improve treatment response, or both (10). In one retrospective cohort study that included women with breast cancer, cancer-related symptoms and treatment side effects were reduced in those women who were treated with IVC (12). In a separate pilot randomized controlled trial conducted in women with ovarian cancer, women who received IVC treatment reported fewer side effects and a trend towards benefit in disease-related outcomes (18). Other therapies used in these trials included epirubicin, cyclophosphamide, methotrexate, fluorouracil (12), paclitaxel and cisplatin (18).

Slow cancer progression
A recent Phase I trial included people newly diagnosed with stage IV pancreatic cancer who were treated with IVC in combination with gemcitabine and erlotinib as first line treatment. Eight of the 9 patients who completed the trial had a reduction in the size of their primary tumour and tumour size was stable in the ninth patient, results that are not typical for treatment with either gemcitabine or gemcitabine plus erlotinib alone (19).

Animal and cell-line studies suggest a synergistic effect when some chemotherapeutic agents are combined with pharmacologic doses of vitamin C. Published evidence appears to support concurrent use of IVC with: gemcitabine (20), carboplatin (21), cisplatin (3, 22, 23), etoposide (3), 5-fluorouracil (3, 22, 24), epirubicin (24), doxorubicin (3, 16, 23), paclitaxel (3, 23), docetaxel (24), and irinotecan (24). 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.

It is notable that one *in vitro* study that demonstrated detrimental interactions between vitamin C and numerous chemotherapeutic agents (25) was conducted using dehydroascorbic acid – a tightly-regulated, diabetogenic derivative of ascorbic acid (26). The results of this publication are therefore not relevant to the clinical use of vitamin C as it is described here (27).

IVC IN COMBINATION WITH NATURAL AGENTS

There is limited research regarding the effects of IVC in combination with other natural agents. One *in vitro* study suggests that the anti-oxidant compound alpha-lipoic acid (ALA) may enhance the cytotoxic effect of IVC (16), and thus that co-administration of these agents may be beneficial. Separate preclinical evidence indicates that the cytotoxicity of vitamin C is impaired by concurrent IV glutathione administration (28).

Adverse Events and Side Effects

The majority of IVC studies report only mild and rare side effects and collectively demonstrate a positive safety profile for doses up to 1.5g/kg, three times a week (10, 29). 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%) (30). Common side effects include nausea, dizziness, dry mouth, fatigue, perspiration and weakness, although these effects may be attributed to the infusion of a high osmolarity solution. Further, these reactions appear to be limited or prevented by drinking fluids before and during treatments (10, 19, 29).

Cautions and Contraindications

IVC should not be administered to patients with renal failure (creatinine > 175 umol/L) (6), a history of kidney stone formation or those with a deficiency of G6PD. Caution is warranted in patients with iron storage diseases. Furthermore, the action of IVC as an osmotic diuretic may mean that it is not suitable for patients with anuria, dehydration, severe pulmonary congestion/edema or low cardiac output (10). Finally, IVC use has not been studied for use by pregnant or lactating women, or by children. Caution is warranted in these groups and IVC should only be used under the guidance of trained health professionals.

Kidney stones and renal failure
A few case reports cite vitamin C intake as a cause of kidney stones and renal failure (31, 32). Further,

one participant with a history of kidney stone formation experienced a recurrence during a trial of continuous IVC infusion (29). Larger prospective studies do not support this association, however, in patients who do not have a history of this condition (33, 34). 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 (6).

Caution is warranted in patients with end-stage renal failure who may be predisposed to hyperoxalemia (35), as this population could be at increased risk for stone formation from IVC treatment (36, 37). However, two case reports document positive outcomes in patients with renal cancer receiving IVC treatment (14, 38).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Cases of potentially fatal hemolysis have been reported when high doses of IVC are administered to individuals with a deficiency of G6PD (39, 40). A deficiency of this enzyme causes serum H_2O_2 levels to rise, leading to cell destruction (4). Patients that are candidates for IVC treatment must be screened for adequate levels of G6PD if dosing is to exceed 15 grams per IV session.

Iron storage diseases

Patients with hemochromatosis should avoid excessive vitamin C intake (41), although the effect of IVC has not been studied in this population and thus the risk is hypothetical. IVC may be used to mobilize iron stores in the treatment of functional anemia among hemodialysis patients and may actually reduce ferritin stores (42). If IVC is administered to individuals with iron storage diseases, regular monitoring of iron status is recommended and exacerbation of these conditions may necessitate discontinuation of IVC therapy.

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. Recent dosing studies suggest that a target dose of approximately 22mM (400mg/dL) is optimal (29), a dose achievable by IV infusion at a rate of 500mg/minute (8, 19).Post-infusion blood levels of vitamin C vary by individual (19) and therefore should be measured to ensure adequate dosing.

Patients at the OICC typically receive between 40g and 75g per infusion to achieve these levels. Treatments are generally administered 2-3 times per week and a glucometer is used as a surrogate measuring device to assess serum saturation levels.

Disclaimer

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

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