

# Intravenous Vitamin C in Cancer Care: Evidence Review and Practical Guidance for Integrative Oncology Practitioners



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## ABSTRACT

Intravenous vitamin C (IVC) is a common therapy used by naturopathic doctors and other licensed integrative practitioners. With several proposed mechanisms of action related to cancer care, it is often used in integrative oncology settings. Despite its common use, there are no published evidence-based resources on the efficacy, safety, and procedural considerations for the use of IVC in practice. The objectives of this review are to summarize the evidence on high-dose IVC in supportive cancer care and to provide a resource of practical clinical guidance for IVC application. In cancer care, IVC is most commonly used at doses high enough to achieve a potential cancer cell cytotoxicity. This review focuses on IVC at doses of  $\geq 15$  g which we have defined as high-dose. To date, there are 23 published clinical trials evaluating the use of high-dose IVC in cancer support. Based on data from these clinical studies, IVC used concurrently with oxidative therapies, such as chemotherapy and radiotherapy, seems to produce the greatest likelihood for improvements in quality of life and additive anti-tumour effects compared with IVC as monotherapy or with non-oxidative therapies. IVC has shown promise in improving quality of life in patients with breast cancer and advanced pancreatic and ovarian cancers. Limited evidence suggests survival and/or tumour response may be improved with the inclusion of IVC in patients with advanced pancreatic cancer, non-small cell lung cancer, and RAS-mutated colorectal cancer. IVC does not offer curative potential, and further research is needed to explore its effectiveness relevant to mortality outcomes. Practical guidance including assessment, monitoring, dosing, safety, and communication with other healthcare providers is discussed.

**Key Words** Supportive cancer care, intravenous therapy, naturopathic medicine

## INTRODUCTION

Intravenous vitamin C (IVC) gained interest as a therapy for cancer after studies published by Cameron, Campbell, and Pauling in the 1970s suggested it could improve outcomes.<sup>1-3</sup> However, subsequent controlled trials using oral supplementation showed no benefit,<sup>4,5</sup> and vitamin C received minimal attention for the next couple of decades. Following additional research and a better understanding of the differences between oral and IV administration, interest in IVC was renewed in the early 2000s.

IVC is commonly used by naturopathic and integrative practitioners in the integrative oncology setting. An observational study of people with breast cancer being treated by naturopathic doctors (NDs) in Washington State reported that 12.3% of patients were treated with IVC, making it the most commonly used injectable therapy in this cohort.<sup>6</sup> A survey of complementary and integrative medicine practitioners published in 2010 reported that 172/199 respondents administered IVC,<sup>7</sup> although this included indications related to conditions outside of cancer. Finally, data from the

Canadian/US Integrative Oncology Study (NCT02494037), the largest observational study of integrative oncology administered by NDs in North America, found that IVC was recommended to 67% of patients with advanced-stage cancer (Mark Legacy, Study Coordinator, email communication, April 2023). These data are set to be published in 2024.

IVC has been studied in a range of doses for people with cancer. The effects likely differ based on dose, as only higher doses have been shown to achieve the proposed pro-oxidative and cytotoxic effects. There is no accepted definition of low-dose versus high-dose IVC, as the exact dose whereby these effects occur is unknown. A dose of 15 g was decided on by the authors as qualifying as high-dose based on 2 factors. Firstly, a 15 g dose is expected to achieve plasma concentrations between 2 and 5 mM,<sup>8</sup> thus reaching pro-oxidant and cytotoxic levels for some, but not all cell lines, as demonstrated in preclinical research.<sup>9,10</sup> Secondly, 15 g is a common cut-off dose for safety when glucose 6 phosphate dehydrogenase (G6PD) enzyme status is unknown or deficient. Deficiency in this enzyme can lead to hemolytic anemia due to impaired clearance of

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hydrogen peroxide, indicating a pro-oxidative process is occurring. This is discussed further in the safety section.

Given the use of IVC in cancer settings, NDs and other integrative practitioners should be aware of the evidence around efficacy and safety. This narrative review provides an up-to-date evidence-based resource for integrative practitioners on the use of IVC in cancer populations.

### Mechanism of Action

Several mechanisms of action have been proposed for IVC in cancer care. These include IVC generating a pro-oxidant effect, enzyme cofactor activities, anti-inflammatory activities, immune effects, and correcting hypovitaminosis C.

#### Pro-Oxidant Effect

Although vitamin C acts as an antioxidant via the donation of electrons, high concentrations can cause the formation of hydrogen peroxide ( $H_2O_2$ ), which has a pro-oxidant effect inducing cytotoxicity by pyknosis and/or necrosis.<sup>9,11,12</sup> This is thought to impact cancer cells more than healthy cells; the tumour microenvironment contains more free transition metal ions, which allows more  $H_2O_2$  to be produced, and cancer cells lack enzymes such as catalase, glutathione peroxidase, and peroxiredoxin-2 to break down  $H_2O_2$ .<sup>13</sup> Preclinical studies have found this pro-oxidant and cytotoxic effect to occur at plasma concentrations that range from 1 mM to greater than 20 mM, depending on the tumour cell line evaluated.<sup>9,10</sup>

#### 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 administration.<sup>14</sup> As a cofactor for collagen synthesis, *in vivo* studies have found increased collagen encapsulation and decreased metastases in cancer models with low-dose vitamin C.<sup>15-17</sup> Vitamin C is a cofactor for various hydroxylases and histone demethylases that regulate gene transcription.<sup>15</sup> High-dose IVC may be able to reduce expression of tumour hypoxia-inducible factors (HIF) as demonstrated in a small clinical trial in colon cancer.<sup>18</sup> Vitamin C may therefore be involved in epigenetic changes by acting as an enzyme cofactor.

#### Anti-Inflammatory Activities

Studies in adults with cancer using IVC have found reductions in several inflammatory markers, including C-reactive protein, erythrocyte sedimentation rate,<sup>19,20</sup> neutrophil-to-lymphocyte ratio,<sup>21</sup> and F2-isoprostanes.<sup>22</sup> This is particularly important and highlights an indication for use of IVC in cancer settings, given that those with cancer are documented to have increased inflammation.<sup>23</sup>

#### Immune Effects

Two human studies found an increase in T-lymphocytes with the use of IVC,<sup>21,24</sup> which may favour anti-tumour immune function.<sup>25</sup> This corroborates preclinical data, which demonstrate a positive impact on the function of lymphocytes and natural killer cells.<sup>25-27</sup>

### Correcting Hypovitaminosis C

Adults with cancer, and particularly those with advanced disease, are at risk of hypovitaminosis C (plasma levels  $<28 \mu\text{mol/L}$ ).<sup>23</sup> This is multifactorial, but likely driven by increased oxidative stress and inflammation, which increases the rate of utilization of vitamin C.<sup>23</sup> Hypovitaminosis C can cause ill-effects, including fatigue, myalgia, impaired wound healing, edema, and ecchymoses, thus impacting quality of life and physical health.<sup>23</sup>

### Pharmacokinetics

Administration of IVC results in far higher serum ascorbate levels than oral administration of an identical dose<sup>28,29</sup> as it bypasses gastrointestinal limitations to absorption.<sup>11</sup> Pharmacologic concentrations of serum ascorbate are defined as 0.3 mM and higher, which are achievable through IV administration but not through oral ingestion.<sup>9,12</sup> Pharmacologic concentrations of ascorbate exhibit first-order elimination kinetics.<sup>30</sup> The elimination half-life is short, ranging from 30–120 minutes<sup>30-33</sup> through renal excretion;<sup>9,33</sup> thus, concentrations in the theoretical cytotoxic range are not maintained for long.

A pharmacokinetic study from 2021 found that serum ascorbate levels started to plateau at IVC doses over 75 g (around 1 g/kg in the study population) in both healthy and cancer populations;<sup>33</sup> thus, higher doses may have diminishing returns. In this study, the maximum serum concentration ( $C_{\text{max}}$ ) at a 75-g dose in the healthy population was 24.9 mM and in the cancer population was 21.6 mM. This is generally consistent with previous studies, which used doses ranging from 1 to 1.5 g/kg (typically correlating to doses of 60–100 g) to achieve serum concentrations around 20 mM.<sup>12,22,34-40</sup> Vitamin C pharmacokinetics are impacted by tumour burden and baseline serum levels. It has been demonstrated that those with advanced disease may require higher doses to achieve similar serum levels, possibly due to lower baseline levels and higher inflammation and oxidative stress.<sup>23,41</sup>

### Clinical Evidence for High-Dose IVC in Cancer Care

Twenty-three clinical trials, including one placebo-controlled randomized controlled trial (RCT), four non-placebo-controlled RCTs, and 18 single-arm trials, have been published for high-dose IVC (defined here as  $\geq 15$  g) and cancer. Findings from these studies are reported in Table 1. A variety of cancer types have been studied; the most studied (by number of participants) are breast, lung, prostate, ovarian, colorectal, and pancreatic cancer. The main focus of this paper is high-dose IVC as doses  $<15$  g are not likely to achieve plasma levels in the theoretical cytotoxic range as described above. However, several studies have evaluated low-dose IVC ( $<15$  g). These are reported separately in Table 2 but will not be discussed further.

### Impact on Quality of Life and Treatment Toxicity

When used alongside conventional cancer treatments, clinical trial data demonstrate mixed results for the impact of IVC on quality of life (QoL) or treatment toxicity. Studies of IVC in breast,<sup>42</sup> pancreatic,<sup>22</sup> and ovarian<sup>43</sup> cancers have reported benefits in these outcomes, whereas studies in colorectal,<sup>44</sup> prostate,<sup>38</sup> and

**TABLE 1 (Part 1 of 6)** Clinical Trials of High-Dose (>15 g) Intravenous Vitamin C for Cancer

Reference	Study Design	Participants	Intervention	Control	Outcomes and Measures	Results
<b>Riordan, 2005<sup>58</sup></b>	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 enrolments	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. AEs and toxicity were minimal at all doses.
<b>Hoffer, 2008<sup>35</sup></b>	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 1.5 g/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	No objective antitumour effects observed. No change in social, emotional, or functional parameters of QoL, physical function deteriorated in 0.4 g/kg group but not in others. Peak plasma concentration was 26.2 mM with 1.5 g/kg dose; 1.5 g/kg recommended dose for future trials
<b>Monti, 2012<sup>54</sup></b>	Phase I Single arm	14 patients (9 completed) with metastatic pancreatic cancer receiving gemcitabine and erlotinib	IVC 3x weekly for 8 weeks Cohort 1: 50 g Cohort 2: 75 g Cohort 3: 100 g	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.
<b>Stephenson, 2013<sup>32</sup></b>	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 <sup>2</sup> All patients received a multivitamin and EPA (2000 mg)	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±0.6 h C <sub>max</sub> and AUC increased proportionately with dose but reached maximum at 70 g/m <sup>2</sup> (C <sub>max</sub> 49 mM, AUC 219 h mM).
<b>Welsh, 2013<sup>22</sup></b>	Phase I Single arm	9 patients with stage IV pancreatic adenocarcinoma receiving gemcitabine	IVC 2x weekly during chemotherapy; titrated to achieve plasma levels of >20 mM (50–125 g)	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 significantly higher than baseline 6/9 subjects maintained or improved performance status and mean weight loss was 5.3±1.6 kg during treatment. PFS: 26±7 weeks; OS: 13±2 months for those receiving at least 1 month of treatment
<b>Kawada, 2014<sup>90</sup></b>	Phase I Single arm	3 patients with relapsed B cell non-Hodgkin's lymphoma receiving CHASER regimen	75 g IVC administered on days 9, 11, 14, 16, and 18 of 21-day cycle of CHASER	None	Safety, dose (based on plasma AA concentration)	↓ F <sub>2</sub> -isoprostane levels Stable levels of GSH and E <sub>1c</sub> in RBCs No AEs attributed to IVC Plasma concentration of >15 mM achieved by day 9 or 18 with 75 g dose. 75 g dose recommended for future trials.

**TABLE 1 (Part 2 of 6)** Clinical Trials of High-Dose (>15 g) Intravenous Vitamin C for Cancer

Reference	Study Design	Participants	Intervention	Control	Outcomes and Measures	Results
<b>Ma, 2014</b> <sup>43</sup>	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 2x weekly for 12 months; dosed to achieve plasma concentration of 20–23 mM (75 g or 100 g)	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. <i>P</i> values not provided by authors.
<b>Hoffer, 2015</b> <sup>37</sup>	Phase I/II Single arm	14 patients with advanced cancer, for whom standard care chemotherapy would offer <33% likelihood of meaningful response	IVC at 1.5 g/kg 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.
<b>Nielsen, 2015</b> <sup>30</sup>	Phase I Single arm	10 patients with metastatic castrate-resistant prostate cancer	IVC 1x weekly for 4 weeks Week 1: 5 g Week 2: 30 g Weeks 3 and 4: 60 g	None	Pharmacokinetic measurements	IV vitamin C exhibited first order elimination kinetics.  60 g dose achieved peak plasma ascorbate concentration of 20.3 mM.  Elimination half-life 1.87 h, volume distribution 0.19 L/kg, clearance rate 6.02 L/hr.  No difference in pharmacokinetics between doses.
<b>Mikrova, 2016</b> <sup>53</sup>	Phase I Single arm	12 patients with mixed cancer types receiving standard oncology care	IVC 3x weekly for 2 weeks; dosed per Riordan protocol (15 g, then 25 g, then individualized dosing up to 50 g)	None	Blood analyses for plasma ascorbate, cytokines, tumour markers	Plasma ascorbate ranged from 5 mM (15 g infusion) to 15 mM (50 g infusion).  Several favorable changes in cytokines noted, including decreases in several inflammatory and angiogenesis-promoting cytokines (e.g., FGF-6, IL-1B, TGF-1), and tumour markers (CA 15-3, CA 19-9, CEA, CA 242).
<b>Nielsen, 2017</b> <sup>38</sup>	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: 5 g Week 2: 30 g Weeks 3–12: 60 g  All participants were additionally given 500 mg 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 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.

**TABLE 1 (Part 3 of 6)** Clinical Trials of High-Dose (>1.5 g) Intravenous Vitamin C for Cancer

Reference	Study Design	Participants	Intervention	Control	Outcomes and Measures	Results
<b>Ou, 2017<sup>91</sup></b>	Phase I 3-arm, open label randomized	15 patients with stage III/IV NSCLC refractory to standard treatments	<p>Arm 1: 60 min mEHT + 1 g/kg IVC 3x weekly for 4 weeks; mEHT preceding IVC</p> <p>Arm 2: 60 min mEHT + 1.2 g/kg IVC 3x weekly for 4 weeks; mEHT and IVC given concurrently</p> <p>Arm 3: 60 min mEHT + 1.5 g/kg IVC 3x weekly for 4 weeks; mEHT following IVC</p>	None	Plasma AA levels, safety, QoL (EORTC QLQ-C30)	<p>Plasma AA at baseline was lower in study group than in healthy people (0.05 vs 0.09 mM, <math>p &lt; 0.05</math>). 1.5 g/kg IVC achieved peak plasma concentrations of 21–25 mM.</p> <p>AEs/toxicity: mild (grade I–II) thirst and fatigue, one patient had grade III diarrhea at 1.5 g/kg and was removed from trial. No hematological or creatinine abnormalities.</p> <p>QoL, on symptom subscale: significant within person improvement after 4 weeks in fatigue, dyspnea, insomnia, appetite, diarrhea, and financial problems (<math>p &lt; 0.05</math>). On function subscale only physical function improved significantly.</p> <p>Note: IVC and mEHT were both experimental interventions, results cannot be attributed to IVC</p>
<b>Poivreddy, 2017<sup>15</sup></b>	Phase I/II Single arm	12 patients with metastatic or unresectable pancreatic cancer who declined combination chemotherapy or progressed on a non-gemcitabine regimen	<p>Phase I: IVC alone dose escalated to 100 g, then combined (same day) with gemcitabine to evaluate PK</p> <p>Phase II: IVC 3x weekly (75 or 100 g) with gemcitabine until tumour progression or patient withdrawal</p>	None	PK, safety, tumour response, survival	<p>Half-life (<math>T_{1/2}</math>) of gemcitabine was shortened by 9% when combined with IVC, but, given the short half-life of gemcitabine (0.28 H), change (to 0.25 H) likely not clinically significant.</p> <p>AEs attributed to IVC were grade I nausea and thirst.</p> <p>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.</p>
<b>Alexander, 2018<sup>99</sup></b>	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)	<p>IVC dose escalation: 50 g, 75 g, 100 g;</p> <p>IVC administered daily with radiation therapy for duration of radiation (average treatment duration 5.7 weeks).</p> <p>Weekly gemcitabine given concomitantly.</p>	Gemcitabine + radiation as per protocol	<p>AEs (CTCAE v4), treatment compliance, plasma AA levels, and F2-isoprostane (oxidative stress marker), PFS, OS</p>	<p>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)</p> <p>57% received all cycles of gemcitabine, 100% completed radiation; better than historical averages. 57% received all doses of IVC</p> <p>Significant difference in plasma F2-isoprostanes week 0 to week 3 (<math>p = 0.99</math>) and after completion of chemoradiotherapy (<math>p = 0.88</math>) but not in comparators</p> <p>Mean plasma AA concentrations: 50 g = 15 mM, 75 g = 20 mM, 100 g = 20 mM</p> <p>IVC group had better mOS and PFS compared with University of Iowa's institutional median (21.7 vs 12.7 months, <math>p = 0.08</math>; 13.7 vs 4.6 months, <math>p = 0.02</math>)</p>



**TABLE 1 (Part 4 of 6)** Clinical Trials of High-Dose (>15 g) Intravenous Vitamin C for Cancer

Reference	Study Design	Participants	Intervention	Control	Outcomes and Measures	Results
<b>Allen 2019<sup>40</sup></b>	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 (15–125 g infusion)	None	Dose to achieve targeted AA plasma levels, OS, PFS, dose limiting toxicities, AEs	Targeted AA plasma levels of 20 mM achieved in 87.5 g group of patients  Median PFS 9.4 months, mOS 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
<b>Wang 2019<sup>46</sup></b>	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 1.5 g/kg if MTD was not reached) daily at rates from 0.6–1.0 g/min on days 1–3 of chemotherapy	None	MTD from the first phase, DLTs, RP2D, ORR, TRAEs, PK, PFS	No MTD reached, no DLT detected  RP2D was 1.5 g/kg/day  ORR and disease control rate 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 IV TRAEs occurred: neutropenia (2.8%)  PK: C <sub>max</sub> and AUC reached maximum values at 1.5 g/kg/day  Median PFS was 8.8 months with 17 PFS events at follow-up (16 disease progression, 1 death)
<b>Banvolgyi 2020<sup>49</sup></b>	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 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.
<b>Ou, 2020<sup>49</sup></b>	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: 1 g/kg, 3x weekly, for total of 25 treatments  mEHT: 60 minutes 3x weekly  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 9.4 months in intervention arm compared with 5.6 months for controls (HR: 0.33; 95% CI: 0.16–0.41, p<0.0001). Median PFS 3.0 months for treatment arm and 1.85 months for control arm (HR: 0.33; 95% CI: 0.12–0.32, 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 reported by 22/49 participants receiving IVC. One participant experienced severe diarrhea. Intervention arm had 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

**TABLE 1 (Part 5 of 6)** Clinical Trials of High-Dose (>15 g) Intravenous Vitamin C for Cancer

Reference	Study Design	Participants	Intervention	Control	Outcomes and Measures	Results
<b>Dachs 2021</b> <sup>18</sup>	Phase II 2-arm, open label RCT	15 patients with colon cancer awaiting surgery ( <i>n</i> =9 treatment, <i>n</i> =6 control)	IVC at 1 g/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±6 mg/100 g tissue. Normal tissue increased from 14±6 to 21±4 mg/100 g. Lower ascorbate was evident towards centre of tumour control and treatment. Erythrocyte ascorbate increased significantly post-infusion and continued to increase over the 4-day infusion period ( <i>p</i> <0.005) and levels were higher than in plasma (2 mM vs. 0.2 mM).  Lower expression of hypoxia-associated proteins seen in post-infusion tumours compared with controls.  All AEs were grade I. Transient hypertension, peripheral neuropathy, and light-headedness reported. No changes in QoL.
<b>Mansoor 2021</b> <sup>42</sup>	Phase II 2-arm, parallel group, single-blind, placebo-controlled RCT	343 patients with stage IIA–IIIB breast cancer ( <i>n</i> =172 treatment, <i>n</i> =171 control)	IVC at 25 g 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	Significant decrease in mean VAS score, at day 28 compared with baseline, for: nausea (3.01±0.26 vs. 2.78±0.54, <i>p</i> =0.0003), loss of appetite (2.26±0.51 vs. 2.11±0.52, <i>p</i> =0.007), tumour pain (2.22±0.45 vs. 1.99±0.40, <i>p</i> <0.0001), fatigue (3.11±0.32 vs. 2.87±0.29, <i>p</i> <0.0001), insomnia (2.59±0.35 vs. 2.32±0.36, <i>p</i> <0.0001). Diarrhea and vomiting had nonsignificant decreases: diarrhea (2.65±0.62 vs. 2.59±0.68, <i>p</i> =0.39), vomiting 2.87±0.56 vs. 2.77±0.50, <i>p</i> =0.08)  No significant changes were noted in the control group compared to baseline for any measure
<b>Chen 2022</b> <sup>8</sup>	Phase I 2-arm	Healthy volunteers ( <i>n</i> =21) and patients with cancer ( <i>n</i> =12) not eligible for conventional treatment at time of enrollment	Healthy volunteers received 1–100 g in escalating doses of IVC and patients with cancer received 25–100 g in escalating doses.	None	Characterize the pharmacokinetic profile of IVC  Determine MTD  Safety and AEs	IVC exhibited first order kinetics up to 100 g, is excreted by the kidneys with 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 with healthy participants at 100 g (99%).  Serum vitamin C concentration plateaued at doses over 75 g (around 1 g/kg in this study population) in both groups. Area under the concentration-time curve only plateaued in healthy group.  Maximum serum concentration (C <sub>max</sub> ) at 75 g dose was 24.9 mM and 21.6 mM in healthy and cancer groups, respectively. 100 g dosing achieved C <sub>max</sub> of 23.7 mM and 23.2mM in healthy and cancer groups, respectively.  Half-lives reported to be close to 2 H in both groups.  No significant AEs observed, MTD not reached.

**TABLE 1 (Part 6 of 6)** Clinical Trials of High-Dose (>15 g) Intravenous Vitamin C for Cancer

Reference	Study Design	Participants	Intervention	Control	Outcomes and Measures	Results
<b>Furquan 2022</b> <sup>55</sup>	Phase II Single arm	38 chemotherapy-naïve patients with advanced-stage NSCLC	IVC 75 g 2x weekly + carboplatin and paclitaxel every three weeks x 4 cycles	None (compared with historical controls)	ORR, disease control, PFS, OS and TRAEs	ORR 34.2% compared with historical control rate of 20% ( $p=0.03$ ). All patients were confirmed partial responses (cPR). Disease control rate (stable disease + cPR) was 84.2%. Median PFS and mOS were 5.7 months and 12.8 months, respectively. TRAEs: one grade V (neutropenic fever) and five grade IV (cytopenia) events were identified.
<b>Wang 2022</b> <sup>44</sup>	Phase III 2-arm, non-placebo controlled RCT	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 IVC and control group in mPFS (8.6 vs. 8.3 months; HR: 0.86, 95% CI: 0.70–1.05; $p=0.19$ ), ORR (44.3% vs. 42.1%; $p=0.9$ ), or mOS (20.7 vs. 19.7 months; $p=0.7$ ). Patients with RAS mutation in treatment arm (+ IVC) had significantly longer PFS compared with those receiving FOLFOX ± bevacizumab alone (mPFS: 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 IVC and control groups, respectively.

AA = ascorbic acid; AE = adverse event; ALP = alkaline phosphatase; AUC = area under the curve; BP = blood pressure; BW = body weight;  $C_{max}$  = peak concentration; CTC/AE = Common Terminology Criteria for Adverse Events; CA = cancer antigen; CEA = carcinoembryonic antigen; CI = confidence interval; CR = complete response; CRP = C-reactive protein; CHASER = rituximab + cyclophosphamide + cytarabine + etoposide + dexamethasone; DLT = dose limiting toxicity;  $E_{10}$  = intracellular redox status; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EPA = eicosapentaenoic acid; FACT-G = Functional Assessment of Cancer Therapy – General; FOLFOX = folinic acid + fluorouracil + oxaliplatin; FGF = fibroblast growth factor; GBM = glioblastoma multiform; GSH = glutathione; GVHD = graft versus host disease; HIF = hypoxia-inducible factor; HR = hazard ratio; Hgb = hemoglobin; IL = interleukin; IVC = intravenous vitamin C; LDH = lactate dehydrogenase; mEHT = modulated electrohypercemia; mOS = median overall survival; mPFS = median progression-free 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; PSA = prostate-specific antigen; QoL = quality of life; RBC = red blood cell; RCT = randomized controlled trial; RECIST = Response Evaluation Criteria in Solid Tumours; RPD2 = recommended phase 2 dose; RT = radiotherapy; SAE = serious adverse event; SD = stable disease; SE = side effect; TGF = tumour growth factor; TRAE = treatment-related adverse event; TMZ = temozolomide; TTP = time to progression.



**TABLE 2** Clinical Trials of Low-Dose (<15 g) Intravenous Vitamin C for Cancer

Reference	Study Design	Participants	Intervention	Control	Outcomes and Measures	Results
<b>Yeom, 2007<sup>48</sup></b>	Single arm, open label	39 patients with terminal cancer	10 g IVC twice within a 3-day interval, with 4 g 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 not significantly changed.
<b>Held, 2013<sup>79</sup></b>	Single arm, open label	10 patients with relapsed, refractory myeloma	1 g 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
<b>Aldoss, 2014<sup>92</sup></b>	Single arm, open label	11 patients with relapsed or refractory AML	IVC 1 g daily 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.
<b>Jeon, 2016<sup>93</sup></b>	RCT	97 patients with colon cancer undergoing surgery	IVC 50 mg/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 ( $p<0.05$ )
<b>Zhao, 2018<sup>93</sup></b>	RCT	73 elderly patients with AML (39 treatment arm, 34 control arm)	IVC at 50–80 mg/kg + DCAG chemotherapy	DCAG chemotherapy alone	Response rate, survival, toxicity	Complete remission rate higher in IVC arm compared with control (79.9% vs. 44.1%, $p=0.004$ ) after 1 cycle.  mOS higher in IVC arm (15.3 vs. 9.3 months, $p=0.039$ ).  No additional toxicity observed with addition of IVC.
<b>Simmons 2020<sup>94</sup></b>	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 50 mg/kg, then oral vitamin C at a dose of 500 mg 2x daily 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, CD3+ 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 were both achieved at day (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; $p=0.27$ ); relapse (AHR: 1.2, 95% CI: 0.3–4.5; $p=0.82$ ), grade II–IV acute GVHD (AHR: 0.8, 95% CI: 0.7–1.7; $p=0.65$ ), grade III–IV acute GVHD (AHR: 0.6, 95% CI: 0.2–1.6; $p=0.32$ ), and chronic GVHD (AHR: 0.4, 95% CI: 0.1–2.7; $p=0.74$ ). No attributable grade III–IV toxicities

AA = ascorbic acid; AHR = adjusted hazard ratio; ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CD = cluster of differentiation; CR = complete response; DCAG = decitabine + cytarabine + aclarubicin + granulocyte colony stimulating factor; DLT = dose limiting toxicity; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; 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.

mixed cancers<sup>37</sup> have reported no benefit. Observational studies have been more supportive of IVC, with two studies evaluating breast cancer<sup>45,46</sup> and one in mixed cancers,<sup>47</sup> all showing benefit. Data from studies using IVC as monotherapy show similar findings; in three small single-arm trials of patients with mixed types of advanced cancers, QoL remained stable in two<sup>32,35</sup> and improved in another.<sup>48</sup> Given the advanced stage of these patients,

stable QoL may be a desirable outcome; however, without a control group, these outcomes are difficult to interpret.

Three studies used IVC in combination with another integrative intervention and evaluated QoL outcomes. The first two studies used IVC with modulated electrohyperthermia (mEHT) in patients with advanced non-small cell lung cancer (NSCLC).<sup>34,49</sup> One was a phase I study using IVC and mEHT in patients refractory to

standard treatments and noted symptom subscale improvements at 4 weeks in fatigue, dyspnea, insomnia, appetite, diarrhea and financial problems.<sup>34</sup> The second was a phase II study by the same authors, and they noted varying QoL improvements compared with best supportive care only. Incidence of peripheral neuropathy was lower in the IVC plus mEHT group.<sup>49</sup> The third study used IVC with a ketogenic diet in patients with advanced cancers and noted decreases in inflammatory markers.<sup>20</sup> Due to the multimodal interventions, it is difficult to know what impact IVC had compared with the other treatments.

Due to the small number of studies, heterogeneity in outcome measures used (e.g., patient-reported outcome measures, physician-assessed symptoms, performance status, blood tests), and mixed results, it is not possible to state what specific symptoms, toxicities, or aspects of QoL may improve with the use of IVC. From studies reported in Table 1, there have been noted improvements for specific symptoms (including nausea, dyspnea, insomnia, loss of appetite, weight loss, pain, fatigue, and neurotoxicity),<sup>42,50,51</sup> performance status,<sup>51,52</sup> and blood tests (including hematological toxicities such as anemia, leukopenia, and thrombocytopenia, inflammation, and liver and kidney function).<sup>51,53</sup>

Although some research indicates IVC may help improve patient QoL, there is still equipoise from the published research. More rigorous and well-controlled clinical trials are needed to clarify the impact of IVC on QoL and treatment side effects. No studies have reported worsening QoL or increased treatment toxicity with the use of IVC.

### Impact on Cancer Outcomes

Two RCTs,<sup>43,44</sup> nine single-arm trials,<sup>15,22,37-40,54-56</sup> and two observational trials<sup>46,57</sup> have evaluated survival and tumour response rates for IVC concurrent with conventional care. The clinical trials are described in Table 1. Given that the majority of these studies are single arm, evaluating the impact on these outcomes is difficult. There is preliminary evidence that IVC may improve survival time and/or tumour response when combined with conventional treatment in pancreatic cancer,<sup>15,39,52,54</sup> NSCLC,<sup>55</sup> and RAS-mutant colorectal cancer;<sup>44</sup> however, more research is needed to confirm these findings.

Clinicians should be aware of the two RCTs that have assessed IVC for treatment outcomes. The first was a non-placebo controlled RCT in which 25 people with stage III or IV ovarian cancer receiving carboplatin and paclitaxel were randomized to IVC or control.<sup>43</sup> The median time to disease progression was 8.75 months longer in the treatment arm compared with the control, but the results were not statistically significant (no *p* value was calculated by the authors).<sup>43</sup> The second RCT was also not placebo controlled and evaluated 442 patients with metastatic colorectal cancer randomized to FOLFOX ± bevacizumab with or without IVC.<sup>44</sup> There were no significant differences in objective response rates, median progression-free survival (PFS), or overall survival between groups; however, a sub-analysis revealed that patients with a RAS mutation had significantly longer PFS (9.2 vs. 7.8 months, hazard ratio [HR] 0.67; 95% confidence interval [CI]: 0.50–0.91; *p* = 0.01) with IVC and chemotherapy versus chemotherapy alone.

Four clinical trials have evaluated IVC as monotherapy for cancer treatment; three failed to demonstrate an objective tumour response<sup>32,35,58</sup> and one found a modest response.<sup>59</sup> All four trials included people with advanced or terminal cancers refractory to conventional therapies. It is important for clinicians to know that IVC monotherapy is not considered a curative cancer treatment.

Finally, two studies used IVC as part of a multimodal integrative intervention and evaluated survival time. One RCT used IVC with mEHT in patients with advanced NSCLC,<sup>49</sup> and a second controlled observational study used IVC with an alkaline diet and bicarbonate alongside chemo-radiation.<sup>60</sup> In both studies, survival time was superior for those in the treatment arm compared with the control arm. Due to the multimodal intervention, it is difficult to know what impact IVC had compared with the other treatments.

No studies have reported worsening response rates or survival outcomes with the use of IVC.

### Impact on Primary and Secondary Cancer Prevention

No studies have evaluated IVC as a treatment to reduce the risk of developing cancer or cancer recurrence. Thus, using IVC as a prevention strategy is not recommended based on current evidence.

### IVC as Monotherapy vs. Combination Therapy

Most studies in cancer have used IVC alongside conventional cancer treatments, primarily chemotherapy. Of the 23 clinical trials identified for high-dose IVC (Table 1), only seven evaluated IVC as a monotherapy; six were single-arm<sup>30,32,35,48,58,59</sup> and one was an RCT.<sup>18</sup> The findings of studies that have used IVC as monotherapy have generally been unremarkable; however, it must be noted that these studies also enrolled patients with advanced disease who had often exhausted conventional treatment options. Good outcomes for any intervention are unlikely in this heavily pretreated population. Nonetheless, it is important for practitioners to realize that the most evidence-based approach to the use of IVC is one which combines it with conventional cancer treatments, particularly chemotherapy.

### Safety of IV Therapy in Cancer-Affected Populations

#### Side Effects

The majority of IVC studies, as documented in Table 1, report only mild side effects and collectively demonstrate a positive safety profile for doses up to 1.5 g/kg three times per week.<sup>32,35,58</sup> This clinical data is supported by observational and survey data.<sup>7,61</sup> A low adverse event rate was documented through a large survey of practitioners who use this therapy (101/9328 infusions, or 1.0%).<sup>7</sup> 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 3,034 doses of IVC ranging from 50 to 150 g.<sup>61</sup> Adverse events were reported in less than 5% of all infusions and less than 3% in patients receiving IVC alone.

Based on the literature, including the clinical trials reported in Table 1, observational studies,<sup>61</sup> a large clinician survey,<sup>7</sup> and the clinical experience of the authors, the following adverse events are

expected among patients receiving IVC. 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.<sup>35,54,58</sup>

- Very common ( $\geq 10\%$  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, hypokalemia, hypomagnesemia, hypocalcemia, hypotension, neuropathy
- 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)

## Cautions and Contraindications

### Renal Function

A few case reports cite vitamin C intake as a cause of kidney stones and renal failure;<sup>58,62-64</sup> however, larger prospective studies do not support this association in patients who do not have a history of these conditions.<sup>65,66</sup> 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.<sup>67</sup> It is recommended that IVC not be administered to patients with renal failure who may be predisposed to hyperoxalemia or hyperoxalosis,<sup>64,68,69</sup> as this population could be at increased risk for stone formation or oxalate nephropathy from IVC treatment.<sup>69-71</sup> Additionally, caution is recommended in patients with a history of kidney stone formation or compromised renal function. Although there is no definitive cut-off for renal function, creatinine levels  $> 175 \mu\text{mol/L}$  or eGFR  $< 45 \text{ mL/min}$  have been proposed and are a rational approach.<sup>23,64,67,69</sup>

### 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.<sup>72,73</sup> A deficiency of this enzyme causes plasma  $\text{H}_2\text{O}_2$  levels to rise when high doses of vitamin C are administered, leading to destruction of healthy cells. The common convention is to avoid doses of vitamin C exceeding 15 g in those with unknown or deficient G6PD status, although data to support the cut-off dose are lacking.

### Diabetes

IVC administration will elevate fingerstick blood glucose monitor readings in most portable glucometers.<sup>74,75</sup> 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 should not be relied on for accurate blood sugar measurements until approximately 8 hours after IVC administration.

### Iron Storage Diseases

Patients with hemochromatosis should avoid excessive vitamin C intake,<sup>76</sup> although the effect of IVC has not been studied in this population and 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.<sup>77</sup> If IVC is administered to individuals with iron storage diseases, monitoring of iron status is recommended.

### Fluid Concerns

IVC is administered as a hypertonic solution and typically infused in 500 mL or more of fluid. The high osmolarity implies cautions similar to those of other osmotic diuretics; thus, it may not be suitable for patients with dehydration or anuria. The fluid volume may make IVC unsuitable for those with severe pulmonary congestion, ascites, edema, or low cardiac output.<sup>35</sup>

### Pregnancy and Lactation

The safety of IVC has not been demonstrated in the mother, fetus, or newborn baby.

### Interactions with Cancer Treatments

To date, there are no known negative interactions between commonly used cancer treatments and IVC based on clinical trial data. 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, 5-fluorouracil, oxaliplatin, irinotecan, dexamethasone, temozolomide, erlotinib, rituximab, and bevacizumab. Preclinical studies have suggested the potential for a negative interaction between vitamin C and the targeted agent bortezomib.<sup>78</sup> Despite the small clinical trial by Held et al.,<sup>79</sup> which showed clinical benefit in 4/10 patients receiving low-dose IVC and bortezomib, caution with bortezomib and other boron-based proteasome inhibitors (e.g., ixamib) is warranted until we have more definitive clinical evidence.

Based on antioxidant supplements being discouraged during radiation treatment, IVC was thought to have a theoretical interaction; however, it has been safely used concurrently with radiation therapy without any reported decreases in efficacy. Although most of these studies were small and without a control group, there was no indication of a negative interaction, and many reported results were suggestive of benefit. The data from studies with control groups have shown either no difference or improvements in response rates and survival time with concurrent use of IVC.<sup>43,44,55</sup> See Table 1 for details on these studies.

Preclinical data corroborate the limited clinical data, suggesting a synergistic effect when some chemotherapy agents are combined with IVC. Chemotherapy agents with evidence of synergy

combined with IVC include: gemcitabine,<sup>80</sup> carboplatin,<sup>81</sup> cisplatin,<sup>29,82,83</sup> etoposide,<sup>29,82,83</sup> 5-fluorouracil,<sup>29,82,84</sup> epirubicin,<sup>84</sup> doxorubicin,<sup>29,83,85</sup> paclitaxel,<sup>29,83</sup> docetaxel,<sup>84</sup> and irinotecan.<sup>84</sup> In these studies, the combination of IVC plus chemotherapy was related to increased tumour inhibition and decreased tumour growth rate compared with either IVC or chemotherapy alone.

To date, very few studies have evaluated IVC with monoclonal antibodies<sup>86</sup> or oral targeted therapies (e.g., tyrosine kinase inhibitors).<sup>54</sup> Thus, the safety profile of IVC with these agents is not clear.

## Knowledge Gaps

Although IVC has been commonly used by NDs and other integrative practitioners since the early 2000s, there remain significant gaps in the knowledge around its efficacy. Most studies to date have been small, single-arm, and heavily focused on safety and dosing. Thus, research on clinical effectiveness is sparse. More RCTs, particularly those with a placebo control, are needed. The Patterson Institute for Integrative Oncology Research, together with The Ottawa Hospital Research Institute, are conducting a double blind, placebo-controlled RCT of IVC in patients with incurable NSCLC. This study will help to address this gap, but studies in other cancer types are needed. A description of the trial is available at <https://clinicaltrials.gov>, NCT05849129.

There are no published clinical studies evaluating IVC with newer cancer agents, such as immunotherapy (e.g., PD1 and CTLA4 inhibitors) and cell-based gene therapies (e.g., CAR T-cell therapies) which are increasingly being used in cancer control. In terms of IVC in specific cancer populations, there is a lack of data on hematological malignancies and pediatric populations, as well as on early-stage disease; thus, whether there are benefits and in which populations the benefit is greatest are not known.

## Practical Considerations for Integrative Practitioners

This section offers practical guidance for integrative practitioners providing IV therapy to patients with cancer, and specific considerations for IVC administration.

### IV Therapy Monitoring Considerations

Providing IV care to individuals with a cancer diagnosis can present some unique challenges. Certain impacts of cancer and its treatment can affect the tolerance and suitability of IV therapy. Practitioners should be aware of the side effects and toxicities of chemotherapy and other conventional treatments, such as myelosuppression, renal toxicity, nausea and vomiting, and

hypertension. Fluid management issues are also a consideration, including increased edema, ascites, hydronephrosis, and pleural effusion. Practitioners should be aware of these issues and know how to accommodate them. This section outlines considerations for monitoring patients with cancer receiving IVC.

### Initial Physical Exam and Functional Status

Prior to initiating IVC, a physical exam is recommended to assess weight, fluid burden, cardiovascular and respiratory health, and general vital signs. Table 3 shows suggested minimum requirements for care. In general, patients with severely compromised vitals should not be administered IVC due to the potential presence of a condition which may require acute or emergency treatment.

Overall functional status should also be assessed using a validated tool such as the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale. It is recommended to only administer IVC to patients with an ECOG score of 3 or lower.

### Baseline Laboratory Assessment

Table 4 describes suggested laboratory tests with suggested minimum requirements to initiate and maintain IVC treatment, as well as parameters for additional monitoring.

### Ongoing Evaluation

In addition to a baseline physical exam and laboratory testing, ongoing monitoring of laboratory tests, vital signs, weight, and functional status should be completed at regular intervals. Patients should be asked about new symptoms or treatments and tolerance of previous infusions at each visit. For example, rapid weight gain or loss should require evaluation for cachexia or ascites. In general, it is recommended that blood tests be repeated every 3 months. More frequent testing (e.g., monthly) is recommended in patients who have had recent results outside the parameters outlined in Table 4. These values are informed by the Common Terminology Criteria for Adverse Events, version 5.0.

### Dosing and Frequency of Use

IVC is typically administered 1 to 3 times weekly, with twice weekly being the most common dosing schedule in clinical trials. It is common for practitioners to dose IVC to achieve plasma concentrations around 20 mM. This is based on preclinical data which have shown that while some cancer cell lines exhibit apoptosis at concentrations as low as 1 mM of IVC, other cell lines require concentrations as high as 20 mM.<sup>9,10</sup> Two commonly used

**TABLE 3** Recommended Vital Sign Requirements for Administering Intravenous Vitamin C

	Minimum Requirements for Care*	Rationale for Refusing Care Outside of Minimum Requirement
<b>Heart rate</b>	40–130 BPM	Possible presence of underlying pathology that may be worsened by IV fluid administration
<b>Blood pressure</b>	SBP 80–180 mmHg DBP <110 mmHg	Presence of condition that requires emergency treatment (e.g., hypertensive crisis, septic shock)
<b>Respiratory rate</b>	12–25 breaths per minute	Underlying conditions causing tachy/bradypnea require evaluation prior to IV administration
<b>Temperature</b>	35–38°C	Underlying condition requiring urgent evaluation (e.g., febrile neutropenia, medication side effect)
<b>Oxygen Saturation</b>	>92%	Underlying pathology causing hypoxia requires evaluation (e.g., pneumonia)

\*Symptomatic patients with values within these cut-offs may also be refused treatment based on clinical judgment. Ranges above are suggested guidelines only. BPM = beats per minute; IV = intravenous; SBP = systolic blood pressure; DBP = diastolic blood pressure.



**TABLE 4** Recommended Laboratory Requirements for Administering Intravenous Vitamin C

	Minimum Requirements for Care	Parameters for Additional Monitoring	Rationale for Refusing Care Outside of Minimum Requirement
<b>G6PD</b>	Normal (qualitative)  Within normal range provided by lab (quantitative)	No further testing needed	Hemolytic anemia may result from high dose IVC administration in the context of G6PD deficiency. <sup>73</sup>
<b>Hemoglobin</b>	80 g/L	80–99 g/L	Transfusion may be required to prevent sequelae
<b>Platelets</b>	50 x 10 <sup>3</sup> /μL	50–75 x 10 <sup>3</sup> /μL	Elevated bleeding risk
<b>Absolute neutrophil count</b>	0.5 x 10 <sup>9</sup> /L	0.5–1.0 x 10 <sup>9</sup> /L	Presence of severe neutropenia and increased risk of infection
<b>Creatinine</b>	<175 μmol/L	Above normal limit	Severely decreased kidney function may affect metabolism/elimination of vitamin C and may increase risk of renal stones and oxalate nephropathy
<b>Estimated glomerular filtration rate</b>	45 mL/minute	45–60 mL/minute	Severely decreased kidney function may affect metabolism/elimination of vitamin C and may increase risk of renal stones and oxalate nephropathy
<b>Sodium</b>	130–150 mmol/L	130–135 mmol/L or 145–150 mmol/L	Consequences of hypo/hyponatremia, IVC may affect electrolyte balance, and intervention may be needed beyond these values
<b>Potassium</b>	3.0–5.5 mmol/L	3.0–3.5 mmol/L or 5.0–5.5 mmol/L	Consequences of hypo/hyponatremia, IVC may affect electrolyte balance, and intervention may be needed beyond these values

G6PD = glucose-6-phosphate dehydrogenase; IVC = intravenous vitamin C

methods of dosing IVC are a weight-based approach and the fingerstick glucose method (FSGM); both methods attempt to target the theoretical cytotoxic ascorbate concentrations.<sup>87</sup> Weight-based approaches typically range from 1 to 1.5 g/kg of body weight (~50–125 g per infusion), which is common in clinical trials. As described in the pharmacokinetics section, doses around 1 g/kg have typically been found to achieve concentrations in the theoretical cytotoxic range.<sup>33</sup> The FSBG method is used as an approximation of plasma ascorbate concentrations without correction.<sup>87</sup> Dosing is escalated to achieve a 400 mg/dL (22.2 mmol/L) difference in patients' glucometer readings pre- and immediately post-IV treatment. In addition to total dose, infusion rate also impacts peak plasma concentrations. Based on existing research, infusion rates ranging from 0.5 to 1.0 g/min are recommended.<sup>33,88</sup>

### Goals of Care and Informed Consent

Patients may request IVC treatments expecting that this therapy can replace curative conventional options. It is important for clinicians to inform patients that IVC is not considered a curative treatment for cancer. An evidence-informed discussion with patients about treatment expectations should be conducted prior to the initiation of IVC treatment. This will allow patients to provide fully informed consent for IV care and help manage expectations with regard to treatment. In addition, treatment impacts should be reviewed with the clinician regularly. Treatment should be discontinued if no clinical evidence of benefit on disease progression or quality of life can be seen.

In addition, informed consent for an intervention that requires significant time and cost for the patient should be given thorough consideration given the potential of financial toxicity. While there may be benefit for patients that use this therapy, it is important not to overstate the evidence nor to create false expectations,

particularly with respect to outcomes associated with prolonging survival. In determining utility, the perspective of the patient and their personal reasons for choosing such a therapy needs to be modulated by the evidence that exists and how it aligns with their clinical picture. To maintain informed consent, ongoing evaluation and discussion on continued use of this therapy is critical to preserve the goals of care and best interests of the patient.

### Communication with Oncologists and Other Healthcare Providers (HCPs)

IVC is not supported by all practitioners, and oncologists and other HCPs may raise concerns about its use. This issue is beyond the scope of this paper, but it is advisable for the conscientious practitioner to make efforts to bridge the gap among HCPs. One tool to support this process is writing a clinical consult note with the provision of evidence and rationale for the use of IVC, and providing consideration of how safety and clinical evaluation will be maintained. If integrative practitioners adhere to principles of care and jurisdiction-dependent regulatory framework, they will be in a solid place to provide ethical care that is centered on patient well-being. It is recommended that NDs review the Principles of Care Guidelines published by the Oncology Association of Naturopathic Physicians for further discussion on patient management and communication.<sup>89</sup>

### CONCLUSION

IVC in the context of cancer is a developing and promising clinical application that deserves consideration in cases of active disease. Results from clinical trials demonstrate that IVC is generally well-tolerated, with minimal and mild side effects. Some, but not all, studies have found benefit for quality of life, symptom



## CLINICAL PEARLS

### Tips on access

- Peripheral veins may be small and/or scarred. To improve access, consider: applying heat, movement (squeezing stress ball), dependent arm position and appropriate tourniquet application. Use of a small catheter (e.g., 24 g) may also facilitate peripheral access.
- Central line access points (port-a-cath or peripherally inserted central catheter (PICC) lines) are common in people receiving active treatment. Consider using these devices if you have the regulation, knowledge, and skill to do so. Some provinces require NDs to have a delegation for heparin from a nurse practitioner or medical doctor.

IVs, blood draws and blood pressure measurements should not be conducted on the side of axillary lymph node removal.

### Accommodations for people in treatment

- Nausea/vomiting: have ginger tea and emesis bags available
- Cancellations: implement flexible cancellation policies for patients who may unexpectedly cancel appointments due to illness/hospitalization
- Infection risk: consider separate rooms/dividers between patients

### Safety

- Patients monitoring glucose levels, such as those with diabetes, *must* be informed that point-of-care glucometers will produce falsely elevated readings following IVC treatment. Insulin dosing must not be adjusted based upon these false readings or life-threatening hypoglycemia could result.

management, and treatment-related toxicities alongside cancer treatments and, to a lesser degree, as monotherapy. There is promising preliminary research for IVC administered in addition to standard treatments for tumour response and/or survival outcomes in advanced pancreatic cancer, NSCLC, and RAS-mutant colorectal cancers. The adjunctive use of IVC in cancer requires more rigorous research from larger, randomized, and placebo-controlled trials to confirm these findings and study its impact in other cancers. Within the context of thorough and ongoing informed consent, IVC has the potential to improve management of cancer. Judicious application with strategies to ensure safety is essential. Keeping abreast of new developments and research in the field is critical for any clinician practicing in integrative oncology settings, and especially necessary for a higher-cost and more invasive therapy like IVC.

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### CONFLICTS OF INTEREST DISCLOSURE

We have read and understood the *CAND Journal's* policy on conflicts of interest and declare that we have none.

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