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REVIEW ARTICLE

Intravenous vitamin C in the supportive care of cancer patients: a review and rational approach

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ABSTRACT

This article reviews intravenous vitamin C (IV C) in cancer care and offers a rational approach to enable medical oncologists and integrative practitioners to safely provide IV C combined with oral vitamin C to patients. The use of IV C is a safe supportive intervention to decrease inflammation in the patient and to improve symptoms related to antioxidant deficiency, disease processes, and side effects of standard cancer treatments. A proposed rationale, together with relevant clinical safety considerations for the application of IV C in oncologic supportive care, is provided.

Key Words Vitamin C deficiency, intravenous vitamin C, ascorbate, supportive care, quality of life

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INTRODUCTION

Historically, Cameron and Campbell[1] and Cameron and Pauling[2] investigated oral and intravenous vitamin C (IV C) treatment in patients with advanced malignancy. Phase I trials in which IV C doses of 75–220 g (up to 1.5 g/kg or 110 mg/m^2) were given to patients with advanced malignancies alone and in combination with chemotherapy demonstrated both safety and tolerability, providing some reduction in symptoms, but did not allow for conclusions to be drawn about tumour response or overall treatment efficacy[3–8].

Extensive literature demonstrates that cancer patients experience vitamin C deficiency correlated with reduced oral intake, inflammation, infection, disease processes, and treatments such as radiation, chemotherapy, and surgery[9–29]. Studies report reductions in inflammatory markers and suggest some improvement in symptoms, with a possible benefit in quality of life (QOL) when IV C alone or in combination with oral vitamin C is used in oncologic care[30–34].

We propose a pragmatic approach for the administration of IV and oral vitamin C as a supportive therapy, including recommendations to ensure safety before and after chemotherapy. In the post-adjuvant and advanced incurable settings, IV C with radiation treatment is not discussed.

METHODS

Using the OVID platform in MEDLINE, a scoping review was conducted current to October 2016 to address these questions:

- What are the pharmacokinetics of IV C and how would administration affect cancer patients?
- Do cancer patients, compared with healthy subjects, experience vitamin C deficiency?
- Is it safe to administer IV C to cancer patients during and after chemotherapy? Does IV C have the potential to improve QOL?

Overall, the literature to date has not supported the efficacy of IV C as monotherapy in anticancer treatment, and our research questions therefore did not address that topic. Instead, we set out to address the potential value of vitamin C in supportive care. To be included in the review, studies had to be conducted in humans, to be published in English, and to provide information about the safety of IV C in malignant conditions, about any reductions in side effects or cancer-related symptoms, or about the effect for QOL. We included controlled, uncontrolled, and nonrandomized studies. We excluded studies assessing oral ascorbate only and included those that assessed IV C or IV C combined with oral vitamin C administration.

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The first search used key terms relevant to pharmacokinetics in cancer patients ("ascorbate metabolism," "renal clearance of vitamin C," "vitamin C and kidney function"). It resulted in the selection of eight studies for their reporting about the storage, use, and clearance of vitamin C.

A second search for "vitamin C blood levels in cancer patients" and "vitamin C deficiency in cancer patients" used key search terms ("plasma vitamin C," "antioxidant status," "serum antioxidant levels") in combination with "cancer." Articles about vitamin C deficiency were included if they reported vitamin C plasma levels in humans, tumour type, stage of disease, and comparisons with healthy control subjects. All others were excluded. The search identified 142 records for screening, of which 14 are included in the present report (Tables I and II).

A third search pertaining to the safety of IV C use in cancer patients identified 147 records for screening. The search strategy used key word searches according to population ("cancer," "oncology," "neoplasm," "malignancy") and intervention ("ascorbic acid," "ascorbate," "vitamin C," "intravenous vitamin C," "IVC"). Of the 147 records screened, 138 were selected for extraction. Of the 138 records extracted, 24 were related to human studies in patients receiving I VC and are reported on in this paper: 1 randomized controlled trial, 6 controlled trials, 7 uncontrolled trials, 6 observational studies, and 4 case-based reports.

Our scoping review did not include articles pertaining to use of IV C during radiation therapy.

RESULTS

Vitamin C: Oral and IV Pharmacokinetics

Vitamin C (ascorbic acid or ascorbate) is required for the biosynthesis of collagen, L-carnitine, and some neurotransmitters[37,38]. Humans have a mutated gene encoding for ascorbate biosynthesis, making vitamin C an essential nutrient to prevent deficiency leading to disease[37,39,40]. Vitamin C increases the intestinal absorption of non-heme iron from dietary sources and is involved in the metabolism of tyrosine and in the maximization of activity for the hormones cholecystokinin, oxytocin, vasopressin, and alpha-melanotropin[37]. Vitamin C deficiency interferes with collagen synthesis, catecholamine formation, prostaglandin metabolism, and cellular immunity[37].

The total human body store of vitamin C can range between 300 mg (at severe depletion such as scurvy) and 2 g[14,38]. The bioavailability of vitamin C is moderated by intestinal absorption, tissue stores, renal resorption, renal excretion, and the health status of the individual[9,15,26,34,41]. Ascorbate is transported by sodium-dependent transporters Slc23a1 and Slc23a2 in the small intestine and proximal renal tubule[42,43]. The normal range for ascorbate in human blood plasma is 0.70–1.4 mg/dL (40–80 μmol/L)[44]. Oral consumption of vitamin C creates maximal serum levels of 1.3–4.0 mg/dL (73.8–227.1 μmol/L)[44–49]; IV C can increase concentrations to more than 350 mg/dL or 20–49 mmol/L[5,7,44]. The unit conversion for reporting vitamin C levels is 1 mg/dL = 56.78 μmol/L[50].

In a study of advanced cancer patients who were administered 15 g IV C over a period of 30 minutes, average vitamin C levels before and after IV C were 0.6 ± 0.1 mg/dL and 57.0 ± 6.0 mg/dL respectively[15]. Table III illustrates the relationship of IV C dose to plasma level in several studies. Above steady-state blood levels, IV C is rapidly cleared by the renal system, proportional to concentration[4,45,47,52,53].

Duconge *et al.*[54] reported the saturation point of renal tubular resorption for vitamin C to be 70 μmol/L. Graumlich *et al.*[41] described the saturation point at the proximal renal tubule as V_{max} 126 mg/h, after which clearance of vitamin C approaches the glomerular filtration rate. Compared with healthy subjects, cancer patients excrete less vitamin C from all intake sources, including IV C[15,17,41,48,49,53]. Estimates for the clearance time of IV C range from 30 minutes to 2 hours[4,7,41,49,54].

TABLE I Vitamin C blood levels in healthy subjects

Reference	Participants (*n*)	Vitamin C blood level	
		Reported units	Conventional units (mg/dL)
Bodansky *et al.*, 1952[17]	23	0.79 mg/dL	0.79
Romney *et al.*, 1987[28]	56	0.69±0.27 mg/dL	0.69±0.27
Schectman *et al.*, 1989[35]	5009	1.15 mg/dL	1.15
Torun *et al.*, 1995[13]	156	0.88±0.47 mg/dL	0.88 ± 0.47
Schorah *et al.*, 1996[21]	34	61.8 μmol/L	1.08
Khanzode *et al.*, 2003[26]	40	0.65±0.01 mg/dL	0.65±0.01
Gan *et al.*, 2008[20]	159	49.2±25.0 μmol/L	0.86±0.440
Mahdavi *et al.*, 2009[11]	22	0.89±0.07 mg/dL	0.89±0.07
Emri *et al.*, 2012[25]	59	49.1±0.4 μmol/L	0.86±0.01
	35	32.7±0.6 μmol/L	0.58±0.10
	24	49.1±0.7 μmol/L	0.86±0.10
Suh *et al.*, 2012[36]	141	1.21±0.0.49 mg/dL	1.21±0.0.49
Mehdi *et al.*, 2013[27]	30	0.92±0.06 mg/dL	0.92±0.06

TABLE II Vitamin C blood levels in cancer patients[a]

Reference	Cancer type	Pts (*n*)	Vitamin C blood level (mg/dL)	*p* Value
Bodansky *et al.,* 1952[17]	Gynecologic, GI, breast	69	0.48	<0.01
Torun *et al.,* 1995[13]	Breast	25	0.50±0.43	<0.05
	Head and neck	22	0.37±0.21	<0.05
	Genitourinary	24	0.40±0.22	<0.05
	Lung	5	0.42±0.14	<0.05
	GI	13	0.36±0.21	<0.05
Ramaswamy *et al.,* 1996[12]	Breast, stage I	20	1.00±0.3	<0.001
	Breast, stage II	30	0.80±0.2	<0.001
	Breast, stage III	40	0.40±0.1	<0.001
	Breast, stage IV	10	0.30±0.1	<0.001
	Cervical, stage I	20	0.61±0.2	<0.001
	Cervical, stage II	30	0.50±0.23	<0.001
	Cervical, stage III	40	0.44±0.24	<0.001
	Cervical, stage IV	10	0.37±0.13	<0.001
Khanzode *et al.,* 2003[26]	Gastric	30	0.52±0.01	<0.001
Gupta *et al.,* 2009[19]	Mixed, late stage	17	0.27±0.08	<0.001
Mahdavi *et al.,* 2009[11]	GI, head and neck, lung	57	0.17±0.02	<0.0001
Emri *et al.,* 2012[25]	Malignant mesothelioma	42	0.53±0.01	<0.001
Mehdi *et al.,* 2013[27]	Multiple myeloma	30	0.68±0.09	<0.001
	Multiple myeloma	30	0.74±0.06	<0.001
Mikirova *et al.,* 2013[15]	Mixed, advanced	193	0.11±0.02	<0.01

[a] Note that, as the disease stage advances, vitamin C levels decline in comparison with earlier stages and with healthy subjects.
Pts = patients; GI = gastrointestinal.

TABLE III Relationship of intravenous vitamin C (IV C) dose with plasma vitamin C level

Reference	IV C dose (g)	Peak plasma level (mmol/L)
Drisko *et al.,* 2003[51] and Riordan *et al.,* 2005[3]	10	1–5
Hoffer *et al.,* 2008[4]	1.5/kg	>10
Monti *et al.,* 2012[5]	100	25–32

Vitamin C Deficiency and Oxidative Stress

Vitamin C deficiency is reported to occur more frequently in patients with chronic disease and major depression and in hospitalized patients, postsurgical patients, and smokers[18,20–23,25–27,29,55–61]. Tables I and II summarize vitamin C blood levels measured in cancer patients and in healthy control subjects, reporting lower levels for cancer patients with advanced-stage compared with early disease.

Hypovitaminosis C is described as depletion at less than 0.5 mg/dL and as deficiency at less than 0.2 mg/dL[18]. A diagnosis of hypovitaminosis C is established by clinical findings and low serum ascorbic acid level[18,23,24,62]. Fasting vitamin C blood levels are reported to best represent body stores[24]. Scurvy occurs within 1–3 months of depletion and is diagnosed by vitamin C levels less than 0.2 mg/dL[62]. Symptoms of vitamin C deficiency include fatigue, myalgia, weakness, poor wound healing, follicular hyperkeratosis, perifollicular hemorrhages, ecchymoses, xeroses, and lower extremity edema[14,18,62]. Gingival swelling, oral hemorrhage, pain in the back and joints, hemorrhage into the soft tissue and joints, syncope, and sudden death can also occur with persistent deficiency[18,62].

Cancer patients experience increased oxidative stress and inflammation[11,15,34,51,60,63–65] known to increase utilization of ascorbate. That increase in utilization correlates with low vitamin C blood levels in patient populations[9–13,17–23,25,28,29,34,35,58,59,65,66]. Vitamin C is consumed during inflammation as it reduces free radical activity. When an antioxidant destroys a free radical, the antioxidant itself becomes oxidized. Antioxidant resources must therefore constantly be restored in the body. When inflammation consumes vitamin C such that stores become low, the kidneys slow excretion so that vitamin C from dietary consumption can be retained. However, decreased excretion might not be well compensated oral intake during high levels of inflammation. In cancer patients, IV C has been shown to decrease inflammation through suppression of cox-2 and nuclear factor κB[15,34]. Mikirova *et al.*[34] reported that advanced cancer patients receiving doses of 7.5–50 g IV C showed reductions in C-reactive protein; interleukins 1α, 2, and 8; tumour necrosis factor α; and eotaxin. In a study of 193 patients, inflammatory markers were comparatively higher

and vitamin C levels were lower in those with metastatic compared with localized tumours[15]. Although increased oxidative stress might contribute to vitamin C deficiency independent of dietary intake[11,35,57,59,67], cancer patients with impaired oral intake or a history of surgery or radiation affecting absorptive surfaces might also experience hypovitaminosis C[9]. Several studies reported that micronutrient deficiencies, including for vitamin C, are not corrected by total parenteral nutrition; hence, IV C could be useful to consider as supportive care[21,29,66].

Factors associated with vitamin C deficiency include the metabolic state of the malignancy and its effects on host metabolism, the catabolic effects of antineoplastic therapy, and the physiologic stresses of disease processes[9]. Studies combining oral and IV C show safety, decreased inflammation, and repletion of vitamin C levels[1,2,31]. Thus, clinicians might find it useful, depending on individual factors, to consider a regimen of both oral and IV C in supportive care.

IV C and QOL

Clinical trials using IV C in cancer patients conducted by Hoffer *et al.*[4], Stephenson *et al.*[7], and Ma *et al.*[8] collected QOL data, but did not report a statistically significant benefit. Yeom *et al.*[31], Vollbracht *et al.*[30], Takahashi *et al.*[33], and Carr *et al.*[32] investigated the effect of IV C on QOL for cancer patients, reporting a benefit for that outcome.

Yeom and colleagues[31] conducted a prospective study of 39 patients with metastatic cancer, providing 10 g IV C twice (with a 3-day interval between doses), together with 4 g oral ascorbate daily for 1 week and reported a significant improvement in QOL. Drawbacks of the study were the small sample size, the short duration of the study, and the lack of a control group.

The observational retrospective study conducted by Vollbracht and colleagues[30] evaluated breast cancer patients (stages IIA–IIIB) attending 15 treatment centres. Their comparison of 53 patients treated with 7.5 g IV C weekly for 4 weeks, plus standard therapy (surgery, chemotherapy, radiation, and hormonal treatment) and 72 control subjects matched for age, stage, and type of treatment found that appetite, fatigue, depression, and sleep disorders during and after adjuvant therapy were significantly improved in the group receiving IV C plus standard treatment. Compared with the control subjects, patients receiving IV C also had significantly better mean Eastern Cooperative Oncology Group performance status scores during adjuvant treatment and after 6 months had elapsed. Tolerability for IV C administration during adjuvant chemotherapy was reported to be excellent (86.8%) and good (13.2%) for those receiving IV C before and after treatment, and no significant interactions between vitamin C therapy and adjuvant therapy were observed during the study. One major limitation of the study was its lack of randomization and the potential expectation bias that could have been introduced. The study also did not report survival outcomes.

The prospective interventional study by Takahashi *et al.*[33] investigated health-related QOL in 60 patients with newly diagnosed advanced cancer, including those undergoing chemotherapy, who received doses of 12.5–100 g IV C given at a rate of 0.5–1.0 g per minute twice weekly for 4 weeks in addition to oral vitamin C doses of 2–4 g daily. Findings from the study included significant decreases in fatigue, insomnia, and constipation after 2 weeks, and a reduction in pain after 4 weeks. The 30-question Core Quality of Life Questionnaire from the European Organisation for Research and Treatment of Cancer was completed before IV C treatment and after 2 and 4 weeks of twice-weekly IV C, daily oral vitamin C, and standard-of-care therapy. Clinical Global Impression of Change assessments were conducted throughout the study by physicians. Significant improvements in physical, emotional, and social functioning were reported after 2 weeks of treatment, and improvement in cognitive function was reported after 4 weeks. The baseline mean global health status score of 44.6 improved to 61.4 after 4 weeks of IV and oral ascorbate given in addition to standard treatment. No adverse events were reported. Although the study lacked a control group, the results suggest that administration of vitamin C can improve QOL, including a reduction in fatigue, for cancer patients. It is notable that, during the study period, 55.0% of the patients were receiving concomitant chemotherapy. The authors proposed that vitamin C might have improved QOL by relieving fatigue and other symptoms caused by a state of chronic vitamin C deficiency in combination with inflammatory processes. Despite design flaws and lack of a control group, the study provided valuable data about the safety of vitamin C and improvement in QOL outcomes.

Safety of IV C

Phase I studies of IV C alone and in combination with chemotherapy have reported excellent safety profiles[1–8,33]. A survey of providers who used IV C for 9328 patients reported an adverse event rate of 1.0%[68]. Reported side effects of IV C used in clinical trials include nausea, dizziness, dry mouth, perspiration, and weakness[6,7]. Suggestions for prevention of side effects include giving plenty of oral fluids before and during treatment[3–5,7].

Conditions for which screening is recommended for all dosage levels of IV C include glucose 6 phosphate dehydrogenase (G6PD) deficiency, iron and copper storage diseases, renal failure, history of kidney stones or oxaluria, and pregnancy or lactation. Doses of IV C greater than 75 g or those leading to blood concentrations exceeding 10 mmol/L might be contraindicated for patients with renal failure, history of oxalosis, anuria, dehydration, severe pulmonary edema, or low cardiac output; use of lower doses of IV C could be appropriate at the discretion of the clinician[4]. Clinical trials providing IV C to cancer patients reported oxaluria that uneventfully returned to baseline[4,69].

Caution is advised for the use of IV C in cancer patients with end-stage renal failure predisposed to oxaluria[70,71]. In contrast, two studies in patients with chronic renal failure undergoing frequent hemodialysis found that, alone and in combination with erythropoietin, single applications of IV C (0.3 g and 0.5 g) are a safe way to mobilize iron stores and to increase hemoglobin levels in patients with functional anemia[72,73]. Several case reports have pointed to vitamin C intake as a possible cause of kidney stones and renal failure[3,74,75]; however, prospective trials have not supported the association[76,77]. Several case reports suggest vitamin C can cause hemolytic events in patients in whom G6PD is deficient; hence, testing for G6PD deficiency before

IV C administration is warranted[78,79]. High serum concentrations of ascorbate in the presence of G6PD deficiency have the potential to cause a red blood cell hemolytic crisis[80,81]. Levels of G6PD can also be higher after hemolytic episodes or transfusion of red blood cells, which might mask deficiency, and therefore testing 8–12 weeks after transfusion is recommended[80,81]. Normal G6PD levels range from 4.6 U/g hemoglobin to 13.5 U/g hemoglobin[80].

DISCUSSION

Our review shows that vitamin C depletion might occur more readily in patients with cancer because of lack of oral intake, decreased bioavailability, increased tissue utilization, and increased oxidative stress. Inflammation attributable to disease processes, standard anticancer treatments, and vitamin C deficiency can cause symptoms that might be ameliorated by IV C. Review of the data suggests that a combination of oral vitamin C and IV C as supportive care is safe, and hence we provide a rational approach for administration in cancer patients as supportive care during, for example, the post-adjuvant or the incurable advanced setting.

Because of theoretical concerns about the administration of intravenous antioxidant treatment during curative chemotherapy and any possible reduction in treatment efficacy, we recommend an approach that allows for clearance of IV C before chemotherapy administration. Giving 5–25 g IV C over a period of 30–120 minutes is safe for cancer-affected adults of any sex and body mass to decrease inflammation, allow for optimal repletion of the body's antioxidant stores, and possibly support QOL. In addition, 500–4000 mg oral vitamin C daily is safe during the intervals between IV C treatments and could support continued oral repletion, as observed in studies combining oral and IV C in adults with cancer[1,2,31].

Temporary or long-term barriers to oral repletion during cancer treatment make IV C a plausible consideration in oncology care. Slower infusion times as described in Table IV could allow for maximal incorporation of vitamin C into the body's antioxidant stores. Symptoms correlated with deficiency such as fatigue, myalgia, arthralgia, and nonspecific anemia present an opportunity to consider whether IV C could potentially be used to reduce symptoms and support health. Such an approach could be beneficial if coordinated with cancer treatments of noncurative intent, in which the goal is to support the patient, prevent interruptions to standard treatment, and possibly improve QOL. Vitamin C could also be considered for potential activity in the tumour microenvironment, which contains inflammatory proteins such as vascular endothelial growth factor, interleukin 8, and other cytokines that favour malignant processes[34,82–85]. Vitamin C might also take part in stromal activity to decrease the hospitality of the stroma to the malignant entity[83].

Doses of IV C greater than 15 g given over a period of 30 or fewer minutes have been found *in vitro* and *in vivo* to have a pro-oxidative effect[86–88] when blood concentrations exceed 3–4 mm/L[86,88–90]. Preclinical studies that demonstrate plasma concentrations greater than 10 mmol/L and an antitumour effect[86,90] propose that a pro-oxidative effect is created by the generation of hydrogen peroxide (H_2O_2) and ascorbyl radicals in the extracellular space[44,54,91]. Mikirova *et al.*[65] reported that single doses of 15–25 g IV C increase the total antioxidant capacity of the blood and that single IV C doses greater than 25 g decrease total antioxidant capacity. Figure 1 depicts those findings. Mikirova and colleagues also reported that IV C doses of 15–25 g create no pro-oxidant effect on plasma lipids and proteins. Although studies providing IV C at more than 30 g have been conducted [achieving blood levels of 20–30 mm/L (400 mg/dL)], human data reporting clinical benefit are lacking. A case report by Mikirova *et al.*[92] describes a child who at 14 months was diagnosed with neurofibroma and optic pathway tumours. The child received treatment with carboplatin and vincristine for 1 year, after which disease progression continued. At 4 months after chemotherapy completion, the child began treatment with IV C (7–15 g weekly). After 30 months of IV C, magnetic resonance imaging demonstrated a significant reduction of the tumours and disease stability over time. The patient experienced no complications from IV C and continued receiving IV C up to age 5, when the case was published.

Vitamin C is stored and used by the body in varying amounts depending on disease status. Human studies

TABLE IV Suggested intravenous vitamin C doses, infusion times, and osmolarity

Sterile water (mL)	Vitamin C (g)	Osmolarity (mol/L)	Infusion duration (min)
150	5	375	30
250	10	440	30–60
350	15	469	30–60
500	20	440	60–90
500	25	540	60–120

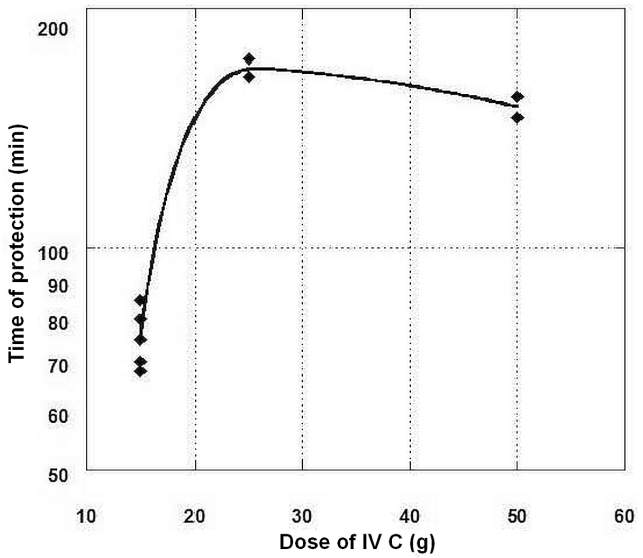

FIGURE 1 At doses less than 25 g, intravenous vitamin C maximally adds to the antioxidant value of blood plasma. Reprinted, with permission, from Mikirova *et al.,* 2007[65].

indicate that IV C is rapidly cleared by the kidneys and that blood levels return to steady state within several hours after administration[4,7,41]. Increasing the IV C dose without extending the infusion time can drive plasma levels to peak, creating a differential gradient and driving ascorbate into the tissue space, theoretically stimulating pro-oxidant behaviour. We hypothesize that there are no absolute low and high doses of IV C, but rather "low-dose behaviour" and "high-dose behaviour," which we identify as functions of the administered dose, the infusion time, and the disease status of the individual. We postulate that high-dose behaviour might yield pro-oxidative effects and could potentially be created with IV C given at higher doses over shorter infusion times. Those effects are further discussed in a systematic review by Fritz *et al.*[93]. High-dose behaviour requires the infusion of larger volumes of fluid in hyperosmolar concentrations, which can create side effects in patients as previously described. In contrast, low-dose behaviour potentially increases total antioxidant capacity, requires less fluid volume for administration, and can be given at near physiologic osmolarity, maximizing exposure to tissue stores and obviating the side effects described in the studies using high-dose behaviour. Based on the 2007 study by Mikirova and colleagues[15], we identify the optimal gram doses of IV C to be between 5 g and 25 g. Based on that postulate and pharmacokinetic data[4,44,46,54], we propose a defined infusion time between 30 minutes and 2 hours to allow for optimal repletion of antioxidant stores and potential benefit for inflammation and symptoms, thus improving QOL.

In a randomized phase I/IIA pilot study in 27 patients with stages III and IV ovarian cancer[8], one group was treated with carboplatin–paclitaxel and IV C, and another group was treated with carboplatin–paclitaxel only. The authors, Ma *et al.,* reported a statistically significant decrease in grades 1 and 2 toxicities in the IV C treatment group based on the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events,* version 3. Although the sample size was too small to analyze for antitumour effect, the reported reduction in chemotherapy-related side effects with the addition of IV C is promising.

A possible criticism of our proposed approach is the potential for a placebo effect. Another potential criticism is the question of whether antioxidant vitamin C would interfere with pro-oxidative therapies such as chemotherapy. A further criticism could be the lack of outcomes data for the combination of IV C with conventional therapies. However, in the noncurative clinical setting, we propose that patients with a potentially increased need for vitamin C and those with presumed deficiencies could benefit from IV C and oral vitamin C to optimize homeostasis though anti-inflammatory support, potentially resulting in symptom reduction and improved QOL. We propose giving 5–25 g IV C away from or before chemotherapy (followed by a 30- to 60-minute break to allow for clearance of additional vitamin C by the kidney and to normalize blood levels before chemotherapy administration).

In a systematic review of IV C and oral vitamin C given to cancer patients, the authors (Jacobs *et al.*[73]) concluded that most of the relevant studies have failed to report an antitumour effect, and that the studies thus far report a possible QOL benefit for patients, including effects on symptoms such as fatigue, pain, and insomnia. In a review of vitamin C and cancer-related fatigue conducted by Carr *et al.*[32], the authors noted that some other types of standard treatments for cancer-related fatigue are prescribed despite limited evidence for efficacy.

The systematic review by Jacobs *et al.* suggests that the time required for vitamin C infusion is a possible issue for patients. In our experience, patients receiving IV C for 1- to 2-hour infusions once or twice weekly are willing to use this relatively low-cost but time-intensive therapy because of the perceived benefits. We recommend that clear information be provided to patients that the effects of adding IV C to chemotherapy are unknown with respect to overall efficacy and that vitamin C could potentially decrease treatment efficacy despite any positive effect on symptoms (Table V). If the decision is made to provide IV C in supportive care, we recommend that it be given before chemotherapy, followed by a 30- to 60-minute break, or that it be given 12–72 hours after chemotherapy with attention to the half-life and clearance of the chemotherapy. Table V illustrates doses, osmolarity, and infusion times for the safe administration of IV C according to the proposed rational approach. Caution is recommended to minimize any potential interaction between chemotherapy and excess circulating vitamin C. We propose to combine IV C and oral vitamin C in a continuous manner to prevent deficiencies that could lead to side effects and reduced QOL. In the supportive care setting, IV C given 1–3 times per week for 1–4 months in combination with oral vitamin C—for example, during post-adjuvant treatment—could improve or prevent deficiency, promote wound healing, lessen inflammation, improve QOL or performance status, and potentially lessen the side effects of systemic treatment. Our rational approach to safely providing IV C is presented in Table V.

CONCLUSIONS

In doses up to 25 g, IV C can safely be used to treat presumptive ascorbate deficiency based on symptoms and could favourably affect clinical parameters such as inflammation, fatigue, and QOL. Using a rational, evidence-based approach such as that presented in Table V, clinicians can safely provide IV C as supportive care to patients with cancer.

The potential synergy of IV C with chemotherapy or radiation treatment, and the effect on overall outcomes, including survival, of a combined treatment approach, warrant further study. Studies that have already explored the effects of IV C in supportive care have design flaws such as small sample sizes and lack of a control group; thus, future studies could add a placebo control in a parallel-arm or crossover design. Studies that include blood biomarkers are also needed. How long any potential effect of an individual IV C treatment lasts is unknown. Studies designed to test that factor could be useful in creating evidence-based guidelines for optimal or sustained improvement in QOL. Studies measuring vitamin C status before and during standard-of-care treatment could elucidate whether ongoing or intermittent deficiencies exist and whether such deficiencies could be related to symptoms that affect QOL. Additional research is needed to study the roles of IV C and oral ascorbate with respect to dose, metabolic clearance,

TABLE V Rational approach for using intravenous (IV) and oral vitamin C in the supportive care of cancer patients

Key points
■ Provide clear information to patients: The effect of adding IV vitamin C (IV C) to chemotherapy is unknown in terms of overall efficacy and could potentially reduce treatment efficacy despite any positive effects.
■ Low-dose IV C could be given before chemotherapy, followed by a break of at least 30–60 minutes, depending on the dose, to allow for clearance and to avoid any significant interaction with chemotherapy.
■ At the discretion of the provider and depending on chemotherapy metabolism and clearance time, IV C could be given after chemotherapy—specifically, 12–72 hours after chemotherapy.
■ An IV C dose of 5–25 g or less can be given at a rate of 10-15 g/h.
■ Test each patient for quantitative and total red blood cell glucose 6 phosphate dehydrogenase (G6PD) deficiency before treatment with IV C.
■ No IV C is given to patients with G6PD deficiency. Check for recent history of hemolysis and transfusion; if present, retest for G6PD within 8–12 weeks. Use caution with oral vitamin C in G6PD deficiency.
■ The renal system rapidly excretes IV C; thus, adequate kidney function is required for higher doses. Use caution when giving IV C to patients with a history of kidney stones or oxaluria.
■ At the discretion of the provider, IV C could be given 30–60 minutes before IV iron.
■ An indwelling venous access system or port can be used for the administration of IV C.
■ Oral hydration should be encouraged during and after infusion.
■ The osmolarity of IV C should be kept as close to physiologic as possible (see Table IV).
■ Do not administer IV C within 12–24 hours before positron-emission tomography imaging.
■ Use caution when considering the use of IV C during adjuvant therapy with curative intent; data about the effect of IV C on treatment efficacy are limited.
■ Ascorbic acid for injection (USP 50 mL vial, 500 mg/mL) can be sourced from tapioca, beet, and corn.
■ Ascorbate for IV administration is combined with sterile water before administration.
■ Because ascorbate in solution can degrade with light exposure and time, a bag drape is recommended.
Indications
■ Presumptive vitamin C deficiency or depletion, together with fatigue, anemia of chronic disease, reduced oral intake, history of surgery or radiation to the gastrointestinal tract, history of malabsorption, treatment with chemotherapy having intestinal or mucosal side effects, slow wound healing, or infection
■ Symptoms of fatigue, muscle weakness, arthralgia, myalgia, neuropathy, bleeding gums, poor wound healing, lower extremity edema, poor oral intake, loss of appetite, pain, or depression
■ Cancer patients in supportive care—such as those in the post-adjuvant or advanced and noncurative treatment settings receiving chemotherapy—and, with cautious consideration, patients receiving adjuvant treatment who might be experiencing symptoms that limit continuation of treatment or that interfere significantly with quality of life
Contraindications
■ Deficiency of G6PD (normal: 4.6–13.5 U/g hemoglobin)
■ Uncontrolled serum glucose above 300 mg/dL (16.7 mmol/L)
Precautions
■ Renal insufficiency: use of IV C is at the discretion of the provider if creatinine exceeds 2.0 mg/dL.
■ Hypercalcemia or oxaluria: use of IV C is at the discretion of the provider.
■ Metal storage diseases: In the presence of hemochromatosis or Wilson disease, regular monitoring is recommended. Exacerbation of those conditions might necessitate discontinuation of IV C.
■ Iron overload because of a history of frequent transfusion.
■ Caution should be used during adjuvant therapy with curative intent because of limited data about treatment efficacy.
Possible side effects
■ Finger-stick glucose monitoring could be abnormal for 1–6 hours after IV C.
■ Side effects reported in clinical trials providing high-dose IV C have included nausea, dizziness, dry mouth, fatigue, perspiration, and weakness. Such effects are not likely to occur with 5–25 g (low-dose) IV C; however, caution is advised.
Frequency and duration
■ During chemotherapy and for 1–4 months after, IV C could be given 1–3 times weekly.
■ Suggested dosing for oral vitamin C: 250–2000 mg twice daily, ongoing at the discretion of the provider.

and infusion time. The role of target vitamin C plasma levels in relation to objective treatment response in humans requires further investigation as well. Although caution is warranted with respect to the use of IV C with surgery, chemotherapy, and radiation in the curative setting, vitamin C is a low-cost, safe therapy for the supportive care setting that might be an effective tool for improved supportive care.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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