Research Article

Retrospective Evaluation of Clinical Experience With Intravenous Ascorbic Acid in Patients With Cancer

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Abstract

Background. Intravenous ascorbic acid (IV AA) has been used extensively in cancer patients throughout the United States. Currently, there are limited data on the safety and clinical effects of IV AA. The purpose of this study was to expand the current literature using a retrospective analysis of adverse events and symptomatic changes of IV AA in a large sample of cancer patients. *Methods.* We conducted a retrospective chart review of all patients receiving IV AA for cancer at the Thomas Jefferson University Hospital over a 7-year period. We assessed all reports of adverse events, laboratory findings, and hospital or emergency department admissions. We also reviewed quality-of-life data, including fatigue, nausea, pain, appetite, and mood. *Results.* There were 86 patients who received a total of 3034 doses of IV AA ranging from 50 to 150g. In all, 32 patients received only ascorbic acid as part of their cancer management (1197 doses), whereas 54 patients received ascorbic acid in conjunction with chemotherapy (1837 doses). The most common adverse events related to ascorbic acid were temporary nausea and discomfort at the injection site. All events reported in the ascorbic acid alone group were associated with less than 3% of the total number of infusions. Patients, overall, reported improvements in fatigue, pain, and mood while receiving ascorbic acid. *Conclusions.* The results of this retrospective analysis support the growing evidence that IV AA is generally safe and well tolerated in patients with cancer, and may be useful in symptom management and improving quality of life.

Keywords

ascorbic acid, cancer, intravenous, vitamin C, adverse effects, quality of life, safety

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Introduction

A large number of cancer patients reportedly receive intravenous ascorbic acid (IV AA) with or without concomitant chemotherapy, often in nonconventional health care settings.[1] Although IV AA generally is regarded as safe, there are limitations to the currently available data. Clinically, ascorbic acid has been administered intravenously in doses as high as 200 g/d without adverse consequences.[2] We have previously published initial safety data for doses of 75 and 100 g IV AA in patients with metastatic pancreatic cancer receiving the combination of gemcitabine, erlotinib, and IV AA.[3] We did not find significant adverse events beyond what was expected from the chemotherapy alone.

A phase I study at McGill University[4] of 24 patients with terminal cancers reported no toxicity at IV AA doses of up to 125g. Another study involved 9 patients with metastatic pancreatic cancer who received gemcitabine, and IV AA showed no dose-limiting toxicity at similar doses.[5] A more recent phase I-II study by Hoffer et al[6] evaluated adverse events in 14 patients with advanced cancers receiving high-dose IV AA in combination with cytotoxic chemotherapy. The authors reported that the IV AA was overall safe and well tolerated, though some patients had transient adverse events such as nausea or vomiting during or shortly after IV AA infusions.

Because ascorbic acid is broken down to oxalic acid, there has been concern that high-dose IV AA could potentially cause oxalate kidney stones, especially in patients

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with preexisting renal dysfunction. Renal dysfunction would lead to longer dwell time of ascorbate in the high pH environment of the renal extracellular fluid and urinary space with consequent calcium oxalate precipitation. A large epidemiological study of 48 850 men by Thomas et al[7] showed that individuals taking oral ascorbic acid were at an increased risk for developing kidney stones and that the incidence increased in men taking the highest doses. The most recent large epidemiological study based on the Health Professionals Follow-up Study has similarly shown that higher daily vitamin C intake is associated with an increased risk of developing kidney stones in men, but not in women.[8] There have been several case reports of renal failure associated with oxalate crystal formation in patients with preexisting kidney disorders who received high doses of oral vitamin C[9] and IV vitamin C.[10,11] It is not determined if these data indicate an increased risk of developing kidney stones in patients with normal renal function receiving intermittent high IV doses. However, it is essential to measure creatinine in patients prior to receiving IV AA and to intermittently monitor kidney function throughout the time period while receiving infusions to ensure that kidney function is not affected.

A few reports and reviews suggest that IV AA might improve clinical symptoms such as fatigue or nausea associated with either the cancer itself or resulting from the effects of chemotherapy medications.[12-14] A phase I study showed improvements in global, physical, emotional, and social well-being as well as reduction in fatigue, nausea, pain, dyspnea, and insomnia.[15] However, these measures were not evaluated for statistical significance.

Overall, the available data suggest that serious adverse events related to high-dose IV AA are uncommon, though caution is warranted in patient subgroups, such as those with renal disease. The phase I and safety studies to date have either focused on a particular patient group and/or have very small numbers. This article provides the first analysis of safety data for IV AA in a large, heterogeneous population of cancer patients in a setting that may be more representative of common clinical practice. We also provide a secondary analysis of impact on clinical symptoms. Our goal in presenting these data is to provide additional information on safety of current practices and to inform next steps of clinical investigation.

Methods

This retrospective study was approved by the Thomas Jefferson University Institutional Review Board (IRB No. 13D.154, originally approved on April 1, 2013) as a retrospective evaluation of existing clinical data and was conducted according to the principles expressed in the Declaration of Helsinki.

This was a retrospective study covering a 7-year period from 2007 to 2014 of all cancer patients presenting to the Marcus Institute of Integrative Health, Thomas Jefferson University, who received treatment with IV AA. Patients included had a diagnosis of cancer and had received at least 5 doses of IV AA. We established a minimum of 5 doses to ensure sufficient use of the IV AA to evaluate directly related effects. The dosage range was 50 to 150 g. For all patients, the ascorbic acid was mixed in a 1-L bag of 5% dextrose in water with enough fluid removed in order to mix in the ascorbic acid along with magnesium chloride and calcium gluconate. The IV AA was infused over 2 to 3 hours as tolerated by the patient. The dose was determined by the clinical judgment of the treating physician.

All patients had a normal glucose-6-phosphate dehydrogenase (G6PD) level prior to initiating the IV AA. It is the Marcus Institute clinical policy to check the G6PD enzyme level because of its role in the production of reduced nicotinamide adenine dinucleotide phosphate in the hexose-monophosphate shunt[16] and subsequently in the generation of reduced glutathione in the red cell for protection against oxidative stress. Because high doses of IV AA result in the production of hydrogen peroxide, those individuals without the G6PD enzyme will experience significant hemolysis of the red blood cells.[17] All patients had kidney function checked prior to initiating IV AA. The clinic policy requires all patients to have a normal creatinine level and monitored creatinine levels at regular intervals depending on the frequency of infusions. The clinic guidelines also exclude patients with a history of recurrent kidney stones.

The standard IV AA infusion was performed using the following general procedures. When patients arrived, their blood pressure, heart rate, respiratory rate, and temperature were obtained at baseline. The IV was started either peripherally or through an indwelling port. Infusions were prepared with the prescribed dose of IV AA mixed with approximately 1 g of magnesium chloride and 1 g of calcium gluconate. The infusion was run in over 2 to 3 hours. The speed of the infusion was adjusted to tolerance by the patient because the large hyperosmolar load can result in symptoms such as thirst, polyuria, and abdominal or chest discomfort. When patients experienced symptoms such as these or nausea or lightheadedness, the infusion rate was slowed until the symptoms improved. If the symptoms improved, the infusion proceeded at a lower rate. If the symptoms did not improve, that particular infusion was stopped, and the patient was evaluated prior to restarting future infusions. Vital signs were monitored throughout the infusion period and then once more after the infusion was completed and the IV removed. The patients were assessed for any adverse effects and then discharged.

Data were obtained through a thorough chart review, including physician and nursing notes, laboratory values (complete metabolic profile, complete blood count, and liver function tests when available), imaging studies,

Table 1. Types of Cancer in Patients Receiving High-Dose IV AA.

Cancer Type	Patients With IV AA Alone (n)	Patients With IV AA Plus Chemotherapy (n)
Bladder	1	0
Breast	4	6
Colon	5	3
Endometrial	2	0
Ewing's	0	1
Chronic lymphocytic leukemia	1	1
Hepatocellular carcinoma	4	1
Lung	2	5
Lymphoma	2	1
Mesothelioma	1	1
Ovarian	1	3
Pancreatic	1	29
Penile	1	0
Prostate	4	1
Total	32	54

Abbreviations: IV AA, intravenous ascorbic acid.

emergency room visits, and hospital admissions during the treatment period. Adverse events were evaluated by standard National Cancer Institute clinical criteria 4.0.[18]

Analyses

The number of adverse events in the patients receiving IV AA alone compared with those receiving ascorbic acid in combination with chemotherapy was compared using a Fisher exact test. We also performed a qualitative assessment of clinical symptoms such as fatigue, mood, or appetite, which were evaluated based on patient reports described in the clinical charts. Patients are routinely asked at each visit for any changes in their symptoms. For each symptom reported initially (ie, prior to starting IV AA), we evaluated whether patients reported improved, stable, or worsening of that symptom. We included only symptoms that were initially reported by patients; so if a person had no nausea to begin with and did not develop any, then that symptom is not included in the table. Any symptoms that arose during treatment were considered to represent worsening (ie, the new onset of edema). For mood, we utilized clinical report data routinely collected as part of the Marcus Institute clinical procedures, including the subjective report of mood, depressed feelings, anxiety, major stressors, or other psychosocial issues. Patients who develop symptoms are routinely asked whether their symptoms were improved, stable, or worse compared with the prior visit. Appetite/weight loss was reported and measured in all patients. If there was no change in reported appetite and if the weight was within 5% during the period that the patient was receiving IV AA, it was regarded as stable. Weight gain and appetite improvement are reported as "improved," whereas the new onset of weight loss or loss of appetite are reported as "worsening" (no patients were found who were purposely trying to lose weight during their treatment period). In addition, the number of patients reporting improved or stable symptoms in each symptom category was compared with the number of patients reporting worsening symptoms using the Fisher exact test.

Results

Overall, 86 cancer patients were treated between 2007 and 2014, with a total of 3083 doses of IV AA given (median number of doses per patient was 27). There were 56 women and 30 men with a median age of 60 years (range 19-87). This was a heterogeneous patient group in terms of cancer diagnosis and staging. The cancer types for the entire cohort are shown in Table 1. A total of 54 patients received the IV AA in combination with chemotherapy (which included drugs such as paclitaxel, carboplatin, sorafenib, irinotecan, and gemcitabine). The other 32 patients only received the ascorbic acid. There were no significant differences in cancer types, although all the pancreatic cancer patients but one received chemotherapy.

Adverse events for the entire group, divided into those receiving ascorbic acid alone and also in combination with chemotherapy, are provided in Table 2. The table reveals adverse events common in those patients receiving chemotherapy such as reductions in platelets and hemoglobin. These adverse events are known to be associated with the chemotherapy regimens received. Only 2 patients receiving IV AA alone had mild reductions in hemoglobin levels, and both had a history of anemia prior to receiving the infusions. Furthermore, their low hemoglobin levels improved without transfusions and while still receiving IV AA.

The most common adverse events were nausea and vomiting, headache, and discomfort at the injection site. Most of these symptoms were self-limited to the time of individual infusions. For all patients, adverse events were reported in less than 5% of all infusions. In patients receiving only the IV AA, adverse events were reported in less than 3% of all infusions.

Patients with underlying diabetes did not have additional adverse effects, but administration of the ascorbic acid is known to falsely elevate glucometer readings,[19,20] and this was observed in 3 patients. One potentially problematic issue, observed in 5 patients (3 in conjunction with chemotherapy and 2 with IV AA alone), was worsening of baseline ascites or edema. With regard to laboratory assessments that were available on 71 patients, there were no significant changes in electrolytes, blood urea nitrogen, creatinine, or

Table 2. Adverse Event Chart for Patients Divided Into Those Receiving Chemotherapy and Those Not Receiving Chemotherapy (Based on Standard NCI Criteria).

Adverse Event	IV AA + Chemotherapy, Number of Events (n = 54, 1837 doses)	IV AA Alone, Number of Events (n = 32, 1197 doses)
Pain at injection site		
Grade 1	7	8
Headache		
Grade 1	6	4
Cold/Chills		
Grade 1	4	1
Allergic reaction		
Grade 1	2	0
Grade 3	0	2
Platelet count decreased		
Grade 1	9	0
Grade 2	6	0
Grade 3	2	0
Anemia		
Grade 2	12	1
Grade 3	3	1
Neutrophil count decreased		
Grade 2	1	0
Grade 3	5	0
Hyponatremia		
Grade 3	0	1
Hypokalemia		
Grade 4	1	0
Elevated glucose		
Grade 2	3	0
Blood pressure		
Hypotension (grade 3)	2	1
Hypertension (grade 2, found on monitoring but without clinical symptoms)	5	4
Renal failure		
Grade 2	1	0
Grade 3	0	1
Renal colic		
Grade 1 (kidney stone)	0	1
Ascites		
Grade 2	3	2
Gastrointestinal		
Nausea/Vomiting		
(Grade 1)	15	6
(Grade 3)	2	0
Biliary obstruction		
(Grade 2)	1	0
(Grade 3)	3	0
Obstruction/Ileus (grade 3)	1	0
Gastric hemorrhage		
(Grade 2)	1	0
Colonic hemorrhage		
(Grade 3)	1	0
Ascites (grade 2)	1	0

(continued)

Table 2. (continued)

Adverse Event	IV AA + Chemotherapy, Number of Events (n = 54, 1837 doses)	IV AA Alone, Number of Events (n = 32, 1197 doses)
Infection		
Conjunctival (grade 2)	1	0
Urinary tract infection (grade 3)	2	1
Pneumonia (grade 3)	2	1
Thromboembolic event		
Grade 3	2	0
Grade 4	3	0
Myocardial infarction		
Grade 4	2	0
Total	109	35

Abbreviations: IV AA, intravenous ascorbic acid; NCI, National Cancer Institute.

liver function tests when the entire cohort of patients was evaluated as a whole or divided into ascorbic acid alone or in combination with chemotherapy. Decreases in total blood cell counts were observed in patients receiving chemotherapy but generally not in those receiving ascorbic acid alone. No serious adverse events were observed in blood cell counts.

One potential concern with IV AA is the formation of oxalate crystals in the urine, which could lead to kidney stones or even oxalate nephropathy.[10,11] In our cohort, there was 1 patient who developed an elevated creatinine while receiving ascorbic acid, but the workup, including urinalysis and imaging, suggested that the worsening kidney function was related to recurrent infections and progressive lymphoma resulting in obstruction. No crystals were detected in the urine, and ascorbic acid was continued during this time as determined by the medical oncology team, urologist, and patient because there were no other alternative treatments available. Another patient presented to the hospital with nausea and vomiting and was found to have an elevated creatinine, which normalized in 2 days after medical management that included IV hydration. A third patient was reported to have developed a kidney stone while on IV AA, but this was not associated with any renal problems.

The results with regard to symptomatic response are provided in Table 3. For all patients receiving IV AA, there was a significant improvement or stability in fatigue, bowel habits, and pain symptoms ($P < .05$). A small number of patients with mood disturbances, such as depression, also generally reported improvements in their overall mood. Appetite and weight loss was improved in 15 patients and was not substantially altered in 70 patients. There were only 2 reports in which appetite was worsened or weight loss accelerated in the entire group.

Discussion

IV AA as cancer therapy was largely discarded several decades ago when 2 randomized trials of oral vitamin C therapy failed to demonstrate therapeutic benefit.[21,22] However, more recent pharmacokinetic modeling indicates that IV administration of ascorbic acid produces a 25-fold or greater plasma concentration than the same dose given orally.[23] Chen et al[24] have reported that ascorbic acid levels achievable in vivo only by IV infusion are selectively cytotoxic in vitro to various cancer cell lines but not to normal cells by a mechanism involving formation of hydrogen peroxide. This action of IV AA is consistent with a growing literature that reactive oxygen species play an important role in the mechanism of action of proven cancer treatments and that impaired oxygen-reduction balance in cancer cells might cause induced reactive oxygen species to selectively kill cancer cells.[25,26] We recently confirmed this previous work with a series of cell line experiments and also observed that ascorbate deregulates cellular calcium homeostasis, thereby promoting cell death.[27] There are also other proposed mechanisms of action. Ascorbate functions as a cofactor for a group of enzymes (Fe and 2-oxoglutarate-dependent dioxygenases) such as hypoxia inducible factor (HIF) hydroxylases, which affect HIF protein levels through marking HIF for proteosomal degradation and also cotranscription factor binding. High levels of ascorbate result in lower expression of HIF, which decreases tumor growth and increases sensitivity of cancer cells to the toxic effects of vitamin C.[28] Ascorbate also increases the ten-eleven translocation enzyme activity associated with DNA demethylation, hence regulating gene transcription associated with cancer formation.[29] Thus, it is possible that this mechanism represents an additional role for ascorbate in modulating genome activity that could affect tumor cells and growth.

Several small studies, including a phase I study by our group, have reported on the initial safety and effectiveness of IV AA, given either alone or with other agents.[3,4,6] Overall, these studies have suggested that high-dose IV AA is relatively safe and well tolerated, with or without concomitant chemotherapy. In this article we reported on a clinical experience of administering IV AA that may be reflective of a

Table 3. Number of Patients Reporting Improvement, Stability, or Worsening of Specific Symptoms (n = 86 Total Cancer Patients).

Change in Symptoms	Fatigue	Diarrhea/ Constipation	Pain	Appetite/ Weight Loss	Ascites/ Edema	Mood
Worse	5	2	4	2	4	0
Stable	15	5	9	69	1	1
Improved	20	6	11	15	0	6
n = 54 Cancer patients receiving chemotherapy (1837 doses)						
Worse	4	2	3	1	3	0
Stable	10	3	7	44	1	1
Improved	10	6	10	9	0	4
n = 32 Cancer patients without chemotherapy (1197 doses)						
Worse	1	0	1	1	1	0
Stable	5	2	2	25	0	0
Improved	10	0	1	6	0	2

more typical environment and patient population for this treatment versus a more controlled research environment. For this reason, we retrospectively evaluated all patients with cancer treated with IV AA at the Marcus Institute over a 7-year period. The results of the present analysis are based on 86 patients who received IV AA in doses between 50 and 150 g. The total number of doses received was 3034.

In regard to adverse events, IV AA was generally well tolerated, with only 3% to 5% of all infusions associated with an adverse event. The most common adverse event was nausea and vomiting which was self-limited during infusions and resolved quickly afterward. Although the mechanism of these symptoms is not known, the anecdotal clinical experience has been that eating lightly helps mitigate them. Another common adverse effect was pain or discomfort at the injection site. Common clinical practices to mitigate this issue is slowing the infusion rate. In patients expected to receive a substantial number of IV AA doses, consideration of a port-a-cath or permanent line is warranted. Patients in the group receiving chemotherapy plus IV AA were found to have reductions in their blood counts consistent with the effect of chemotherapy. There was no evidence that IV AA alone had an impact on measured blood counts.

The 2 most potentially problematic adverse events relate to fluid collection and renal function. We had 5 patients with existing ascites or edema who experienced worsening of this symptom. Whereas the worsening may have simply been related to the progression of their disease, third spacing is a clinical condition that should be watched carefully in patients receiving IV AA, which is a hypertonic solution typically given in a large quantity of fluid (ie, 750-1000 mL). On the other hand, a report by Hoffer et al[4] described a case in which IV AA substantially reduced a patient's ascites by acting as an osmotic diuretic, and Ma et al[30] also indicated a reduction in ascites with vitamin C in combination with chemotherapy in ovarian cancer. Given that our patients had worsening ascites and edema, future studies will have to better assess the impact of IV AA on patients with substantial third spacing of fluids.

Particular care should be taken when patients have preexisting impairment in renal function, which would make them unable to clear a hypertonic fluid load. Although this was not the case in our cohort, care should be taken when treating patients with known third spacing, particularly if it is associated with lymphadenopathy that impairs venous return from the legs or is associated with a pericardial effusion. Additionally, given the potential for an osmotic diuresis, we noted that 2 patients had electrolyte abnormalities: one with hyponatremia and one with hypokalemia. Given the potential effect of IV AA on electrolytes, it is important to evaluate electrolytes at regular intervals, particularly in those patients with a history of impaired renal function, patients on diuretics or other medications that might affect electrolytes, and patients with a known history of electrolyte disturbances.

It is known that ascorbic acid increases urine oxalate, which suggests a potential risk for developing kidney stones.[31] Furthermore, several studies have demonstrated an increased risk of kidney stone formation with oral supplementation, particularly in men. However, other studies have suggested that high doses of AA may even be protective.[32] Pharmacokinetic studies have also explored whether high doses of vitamin C might increase the risk of forming kidney stones. For example, one study of 16 patients with advanced cancer found that when studied using correct procedures for handling, storing, and analyzing the urine, less than 0.5% of a large IV dose of ascorbic acid in people with normal renal function was found as oxalic acid.[33]

In the medical literature, several cases of acute oxalate nephropathy were reported in patients with preexisting renal insufficiency given large IV doses of vitamin C.[9,10,11]

In our evaluation, we found 2 patients with increased creatinine, and both cases were explained by causes other than ascorbic acid effects. We also had 1 patient who reported developing a kidney stone while receiving IV AA. The type of stone could not be ascertained, and thus, it is possible that the IV AA contributed to the formation of the kidney stone in this patient. However, it should be noted that the overall prevalence of kidney stones in the general population is 1% to 2%.[34] Nonetheless, patients should be monitored regularly for the possibility of developing renal impairment or kidney stones during the course of receiving IV AA.

It is noted that care must be taken in patients with diabetes because AA can falsely elevate glucometer readings substantially (ie, values can range greater than 400 mg/dL).[35] Pharmacokinetic studies have generally observed an elimination half-life of approximately 2 hours,[15,36] with the implication that glucometer readings could remain abnormal for 6 to 8 hours postinfusion. Thus, it is important to remind patients with diabetes to be cautious with regard to treating themselves with added insulin if readings remain elevated after receiving IV AA. Patients should typically wait until the following morning (ie, at least 6-8 hours) to recheck their glucose levels when the AA has been substantially eliminated, so as not to interfere with glucose measurement.

The adverse events analysis of this retrospective study will hopefully add more safety data regarding the use of IV AA in patients with cancer. The comparison of patients receiving IV AA with and without concomitant chemotherapy also helps demonstrate which adverse events are more specifically attributable to the ascorbic acid rather than the chemotherapy. As expected, there were fewer toxicities in the group that received IV AA alone. It is not known if the group receiving both had fewer toxicities from the addition of IV AA, though a study by Ma et al[30] of 25 ovarian cancer patients showed that those treated with IV AA along with carboplatin and paclitaxel had fewer grade 1 and 2 adverse events compared with those treated with the chemotherapy agents alone.

In terms of symptoms, this heterogeneous patient cohort, receiving IV AA alone or in combination with chemotherapy, qualitatively described improvements in energy, nausea, pain, and mood. These are common symptoms in cancer patients and have been a target for studies on the potential beneficial effect of ascorbic acid. For example, one prospective study of 60 patients with advanced cancer found that IV AA (25-100 g/session) administered twice a week resulted in statistically significant decreases in fatigue, insomnia, and constipation after 2 weeks, based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and a reduction in pain after 4 weeks.[37] It also should be noted that fatigue worsened in 5 patients after stopping ascorbic acid (3 were in the chemotherapy group and 2 were in the nonchemotherapy group). A systematic review of quality-of-life studies using vitamin C also showed some evidence for beneficial effect.[13] These studies and the findings from the present retrospective analysis all have limitations that make it impossible to draw conclusions regarding effects on clinical symptoms. In addition, the Mg included in our infusions has also been suggested to improve mood in patients, although a recent randomized crossover trial of 4 g Mg (whereas our infusions typically have 1 g Mg) did not find any benefit in patients with treatment-resistant depression.[38] Future prospective studies that are randomized and controlled with strong statistical analyses will be necessary to better assess any potential benefits of IV AA in cancer patients.

Limitations for this retrospective analysis include inherent problems reviewing past clinical charts, which restricts the analysis to data that are available in those charts. Doses were determined based on the clinical decision of the treating physician, but future approaches to determining ways of standardizing the doses will be important for both research and clinical applications. As mentioned, complete laboratory data were not available on 16 patients, but there was no clinical evidence that these patients experienced untoward medical events that might have been related to laboratory abnormalities. Symptomatic reporting is also limited to what was reported by the patient and the physician. Because the patients were seen clinically, it was important to assess for adverse events, so it is unlikely that there is an underreporting of negative effects of the IV AA. However, it is certainly possible that symptomatic changes, for better or worse, were not included in the charts, thus preventing any firm conclusions. Furthermore, we might expect reporting bias in patients receiving the IV AA, and therefore, future studies should utilize more formal questionnaires and scales for the evaluation of subjective symptoms such as fatigue, mood, and pain. In addition, because this was a retrospective evaluation, there was no control group (ie, a placebo IV with just saline), which might have yielded similar symptomatic changes. However, the ability to compare patients receiving IV AA with and without chemotherapy provides some knowledge as to which adverse events are more specific to the IV AA.

The results, and limitations, that arise from this retrospective analysis suggest the need for larger-scale randomized controlled trials to determine the ability of IV AA to improve the quality of life in cancer patients, especially those receiving chemotherapy.

Conclusion

In this systematic retrospective evaluation of 86 patients with cancer who were given a total of 3034 doses of IV AA, the treatment was found to be generally well tolerated and safe, with few adverse events reported. Also observed were subjective improvements in symptoms such as fatigue,

pain, and mood. Future studies should more specifically evaluate the mitigating effect of IV AA on adverse events related to chemotherapy and improvements in valid quality-of-life measures as well as the potential effectiveness in the management of different types of cancer.

Declaration of Conflicting Interests

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References

1. Padayatty SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. *PLoS One*. 2010;5:e11414. doi:10.1371/journal.pone.0011414
2. Riordan HD, Hunninghake RB, Riordan NH, et al. Intravenous ascorbic acid: protocol for its application and use. *P R Health Sci J*. 2003;22:287-290.
3. Monti DA, Mitchell E, Bazzan AJ, et al. Phase I evaluation of intravenous ascorbic acid in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *PLoS One*. 2012;7:e29794. doi:10.1371/journal.pone.0029794
4. Hoffer LJ, Levine M, Assouline S, et al. Phase I clinical trial of i.v.ascorbic acid in advanced malignancy. *Ann Oncol*. 2008;19:1969-1974.
5. Welsh JL, Wagner BA, van't Erve TJ, et al. Pharmacological ascorbate with gemcitabine for the control of metastatic and node-positive pancreatic cancer (PACMAN): results from a phase I clinical trial. *Cancer Chemother Pharmacol*. 2013;71:765-775.
6. Hoffer LJ, Robitaille L, Zakarian R, et al. High-dose intravenous vitamin C combined with cytotoxic chemotherapy in patients with advanced cancer: a phase I-II clinical trial. *PLoS One*. 2015;10:e0120228. doi:10.1371/journal.pone.0120228
7. Thomas LD, Elinder CG, Tiselius HG, Wolk A, Akesson A. Ascorbic acid supplements and kidney stone incidence among men: a prospective study. *JAMA Intern Med*. 2013;173:386-388.
8. Ferraro PM, Curhan GC, Gambaro G, Taylor EN. Total, dietary, and supplemental vitamin C intake and risk of incident kidney stones. *Am J Kidney Dis*. 2016;67:400-407.
9. McHugh GJ, Graber ML, Freebairn RC. Fatal vitamin C-associated acute renal failure. *Anaesth Intensive Care*. 2008;36:585-588.
10. Lawton JM, Conway LT, Crosson JT, Smith CL, Abraham PA. Acute oxalate nephropathy after massive ascorbic acid administration. *Arch Intern Med*. 1985;145:950-951.
11. Wong K, Thompson C, Bailey RR, McDiarmid S, Gardner J. Acute oxalate nephropathy after a massive intravenous dose of vitamin C. *Aust N Z J Med*. 1994;24:410-411.
12. Fritz H, Flower G, Weeks L, et al. Intravenous vitamin C and cancer: a systematic review. *Integr Cancer Ther*. 2014;13:280-300.
13. Carr AC, Vissers MC, Cook JS. The effect of intravenous vitamin C on cancer- and chemotherapy-related fatigue and quality of life. *Front Oncol*. 2014;4:283. doi:10.3389/fonc.2014.00283.
14. Carr AC, Vissers MC, Cook J. Relief from cancer chemotherapy side effects with pharmacologic vitamin C. *N Z Med J*. 2014;127:66-70.
15. Stephenson CM, Levin RD, Spector T, Lis CG. Phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics of high-dose intravenous ascorbic acid in patients with advanced cancer. *Cancer Chemother Pharmacol*. 2013;72:139-146.
16. Dacie J. *The Haemolyic Anaemias*. 3rd ed. Edinburgh, Scotland: Churchill Livingstone; 1985.
17. Rees DC, Kelsey H, Richards JD. Acute haemolysis induced by high dose ascorbic acid in glucose-6-phosphate dehydrogenase deficiency. *BMJ*. 1993;306:841-842.
18. National Cancer Institute. Cancer Therapy Evaluation Program. http://ctep.cancer.gov. Accessed May 28, 2009.
19. Moatti-Sirat D, Velho G, Reach G. Evaluating in vitro and in vivo the interference of ascorbate and acetaminophen on glucose detection by a needle-type glucose sensor. *Biosens Bioelectron*. 1992;7:345-352.
20. Jackson JA, Hunninghake R, Krier C. False positive finger stick blood glucose readings after high-dose intravenous vitamin C. *J Orthomol Med*. 2006;21:188-190.
21. Creagan ET, Moertel CG, O'Fallon JR, et al. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patient with advanced cancer: a controlled trial. *N Engl J Med*. 1979;301:687-690.
22. Moertal CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy: a randomized double-blind comparison. *N Engl J Med*. 1985;312:137-141.
23. Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann Intern Med*. 2004;140:533-537.
24. Chen Q, Espey MG, Krishna MC, et al. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. *Proc Natl Acad Sci U S A*. 2005;102:13604-13609.
25. Leung PY, Miyashita K, Young M, Tsao CS. Cytotoxic effect of ascorbate and its derivatives on cultured malignant and nonmalignant cell lines. *Anticancer Res*. 1993;13:475-480.
26. Sakagami H, Satoh K, Hakeda Y, Kumegawa M. Apoptosis-inducing activity of vitamin C and vitamin K. *Cell Mol Biol (Noisy-le-grand)*. 2000;46:129-143.
27. Rouleau L, Antony AN, Bisetto S, et al. Synergistic effects of ascorbate and sorafenib in hepatocellular carcinoma: new insights into ascorbate cytotoxicity. *Free Radic Biol Med*. 2016;95:308-322.

28. Mastrangelo D, Pelosi E, Castelli G, Lo-Coco F, Testa U. Mechanisms of anti-cancer effects of ascorbate: cytotoxic activity and epigenetic modulation. *Blood Cells Mol Dis*. 2018;69:57-64. doi:10.1016/j.bcmd.2017.09.005
29. Minor EA, Court BL, Young JI, Wang G. Ascorbate induces ten-eleven translocation (Tet) methylcytosine dioxygenase-mediated generation of 5-hydroxymethylcitosine. *J Biol Chem*. 2013;288:13669-13674.
30. Ma Y, Chapman J, Levine M, Polireddy K, Drisko J, Chen Q. High-dose parenteral ascorbate enhanced chemosensitivity of ovarian cancer and reduced toxicity of chemotherapy. *Sci Transl Med*. 2014;6:222ra18.
31. Massey LK, Liebman M, Kynast-Gales SA. Ascorbate increases human oxaluria and kidney stone risk. *J Nutr*. 2005;135:1673-1677.
32. Gerster H. No contribution of ascorbic acid to renal calcium oxalate stones. *Ann Nutr Metab*. 1997;41:269-282.
33. Robitaille L, Mamer OA, Miller WH Jr, et al. Oxalic acid excretion after intravenous ascorbic acid administration. *Metabolism*. 2009;58:263-269.
34. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Rev Urol*. 2010;12:e86-e96.
35. Ma Y, Sullivan GG, Schrick E, et al. A convenient method for measuring blood ascorbate concentrations in patients receiving high-dose intravenous ascorbate. *J Am Coll Nutr*. 2013;32:187-193.
36. Nielsen TK, Højgaard M, Andersen JT, Poulsen HE, Lykkesfeldt J, Mikines KJ. Elimination of ascorbic acid after high-dose infusion in prostate cancer patients: a pharmacokinetic evaluation. *Basic Clin Pharmacol Toxicol*. 2015;116:343-348.
37. Takahashi H, Mizuno H, Yanagisawa A. High-dose intravenous vitamin C improves quality of life in cancer patients. *Pers Med Universe*. 2012;1:49-53.
38. Mehdi SM, Atlas SE, Qadir S, et al. Double-blind, randomized crossover study of intravenous infusion of magnesium sulfate versus 5% dextrose on depressive symptoms in adults with treatment-resistant depression. *Psychiatry Clin Neurosci*. 2017;71:204-211.