FEATURE

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Intravenous Vitamin C in Cancer Management;

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Intravenous vitamin C is an effective cancer therapy delivering independent cytotoxic effects to tumour cells, as well as enhancing cytotoxicity of several conventional chemotherapeutic drugs. While many medical professionals condemn the therapy, recent advances have shown a very large increase in the use of intravenous vitamin C among several leading oncology units across North America. The following review highlights the basis for intravenous route of administration, preclinical evidence of selective cytotoxicity to tumour cells while sparing non-cancerous cells, evidence of safety regarding combination antioxidant therapy and chemotherapy, as well as a selection of controlled human trials of intravenous vitamin C in cancer management.

ORIGINS OF VITAMIN C IN CANCER THERAPY

The landmark study of Cameron and Pauling outlining success of vitamin C for cancer management in 100 patients relative to 1,000 disease matched controls (Cameron 1976) is often credited as the origins of investigation into vitamin C as a complementary cancer therapy. In their book, Cancer and Vitamin C, Cameron and Pauling outline the work of Dr. W.J.

McCormick through the 1950's, a Canadian Physician who formulated the hypothesis that cancer is a collagen disease, secondary to a deficiency of vitamin C (Cameron 1993). Dr. McCormick recognized that the generalized stromal changes of scurvy were consistent with the local stromal changes observed in the immediate vicinity of invading neoplastic cells. Dr. McCormick surmised that the nutrient (vitamin C) that is known to be capable of preventing such generalized changes in scurvy might have similar effects in cancer. Evidence that cancer patients are commonly depleted of ascorbate (vitamin C) supported this view.

Cameron and Pauling stated the following: "Most important of all, we are led to the conclusion that the administration of this harmless substance, ascorbic acid (vitamin C), might provide us with an effective means of permanently suppressing neoplastic cellular proliferation and invasiveness, in other words an effective means of controlling cancer. Ascorbic acid (vitamin C) in adequate doses might prove to be the ideal cytostatic agent." (Cameron 1993).

PRECLINICAL EVIDENCE RELATING TO VITAMIN C IN CANCER THERAPY

From a mean baseline of 70micromol/L, repeated oral dosing achieves plasma vitamin C concentrations of 220micromol/L. Intravenous administration of large dosages (18+g of vitamin C) can achieve plasma vitamin C concentrations of up to 14000micromol/L. In vitro models have demonstrated that concentrations of 1,000- 5,000micromol/L of vitamin C are selectively toxic to several cancer cell lines (Padayatty 2006).

Ten cancerous cell lines and four normal cell lines were exposed to varying concentrations of vitamin C in vitro. EC50 values (concentration of vitamin C required to reduce cell survival by 50%) were calculated for each cell line. Human lymphoma cells proved to be highly sensitive to vitamin C, with an EC50 value of 0.5micromol/L. Five additional cell lines demonstrated EC50 values of less than 4.0micromol/L, a concentration easily achieved through I.V. administration of vitamin C. 20micromol/L of vitamin C was incapable of significantly reducing survival in normal cell lines, highlighting that cytotoxic effects of vitamin C appear to be confined to cancerous cells (Chen 2005).

Guinea pigs bearing intradermal L-10 hepatocarcinoma tumors received oral or subcutaneous (SC) injections of vitamin C, with tumour mass and intra-tumour vitamin C concentrations determined at necropsy. Tumour burden reached nearly 50g in untreated animals. SC injections of ascorbate (500mg/kg/day) inhibited tumour growth by as much as 65%. "Tumor growth correlated inversely with intratumour ascorbate concentration, the latter exceeding 2mM in some cases. Ascorbate concentrations sufficient to kill tumour cells can be safely achieved in solid tumours in vivo, suggesting a possible role for high dose intravenous ascorbate in treating cancer." (Casciari 2005).

At low concentrations in cell culture (less than 500micromol/L), vitamin C appears to inhibit intra- tumour generation of oxygen radical species. Endogenous catalase appears readily able to quench ascorbate-derived radical formation. The ascorbate-derived radical, however, inhibits catalase in a dose-response manner. Once concentrations in cell culture reach 2,000micromol/L or greater, catalase appears to be incapable of preventing the formation of ascorbate radical (Nemoto 1997, Asano 1999, Sakagami 2000). Taken in context with the evidence presented above, it appears as though 2000 micromol/L is the lowest target plasma concentration of vitamin C, which would be desirable for use of vitamin C as a chemotherapeutic agent. Such a concentration is readily achieved through intravenous administration of vitamin C.

INTRAVENOUS VITAMIN C IN CANCER THERAPY; A SYNOPSIS

- I.V. vitamin C increases quality of life.
- I.V. vitamin C prolongs survival.
- I.V. vitamin C works synergistically with conventional cancer therapies.
- I.V. route of administration achieves plasma levels of vitamin C consistent with concentrations demonstrated in vitro to be cytotoxic to several cancer cell lines.
- I.V. vitamin C inhibits hyaluronidase, an enzyme produced by cancer cells responsible for the breakdown of healthy tissue facilitating tumour progression and metastasis.
- I.V. vitamin C increases intracellular hydrogen peroxide. Hydrogen peroxide is directly cytotoxic to tumour cells. At concentrations achieved through I.V. administration, vitamin C overwhelms the ability of tumour cells to suppress hydrogen peroxide production.
- I.V. vitamin C corrects an ascorbate deficiency, often seen in cancer patients.
- I.V. vitamin C helps prevent systemic free radical injury.

INTERACTION OF VITAMIN C WITH CHEMOTHERAPY

A recent systematic review examined evidence from randomized controlled trials of supplemental antioxidant nutrients administered concurrently with conventional cancer treatments. The paper included 19 controlled human trials of single or combination antioxidant therapies in combination with chemotherapeutic regimes (Block 2007). The authors conclude, "From the 19 studies included in this review, no evidence was found that supported concerns that antioxidant supplementation given concurrently with ROS-generating chemotherapy diminished the efficacy of the chemotherapy in study populations comprising mostly advanced or relapsed patients. In contrast, 17 of the RCTs included in this review showed either a statistically significant advantage or non-statistically higher survival and/or treatment response in those patients given antioxidants."

A separate review included preclinical evidence in addition to evidence from controlled human trials. Over 280 peer-reviewed papers are presented, including 50 human trials of collectively over 8,500 subjects, approximately 5,000 of whom were actively receiving antioxidant therapies. Again, a comprehensive review of the area highlights a lack of adverse interaction from combined antioxidant and chemotherapy intervention. Studies collectively including almost 4,000 patients actively receiving antioxidant therapy find increased survival as a treatment outcome (Simone 2007).

INTRAVENOUS VITAMIN C AS CANCER TREATMENT; CONTROLLED HUMAN TRIALS

Table 1 presents 12 controlled human trials of intravenous vitamin C for the management of several cancer types. In some reports the specific cancer types are poorly defined, while in others, a clearly defined protocol of combined chemotherapy and intravenous vitamin C is described.

One paper presented (Padayatty 2006), published in the Canadian Medical Association Journal, highlights what is likely to become the future of intravenous Vitamin C therapy in cancer. The paper includes contributions from the National Cancer Institute, the National Institute of Health, Centers for Cancer Research, and McGill University. The paper presents only three cases, however each case is of advanced, incurable cancer, documented with the highest standard of objective histopathological assessment. All three cases achieved long-term remission, with intravenous vitamin C the likely basis for the observed outcomes. The authors call for a reevaluation of intravenous vitamin C as a complementary tool for cancer management.

Since the publication of this paper, several leading cancer clinics across North America have begun adding intravenous vitamin C to various cocktails used for the treatment of refractory multiple myeloma (See table 1). Please refer to table 2 for a commonly implemented protocol of intravenous vitamin C in complementary cancer management.

While it may remain the generally held opinion of oncologists across the country that intravenous use of vitamin C is inappropriate for cancer treatment, leading oncology units in North America have revived interest in this safe, non-toxic and effective chemotherapeutic strategy. It will invariably take several decades for the medical masses to become aware of recent successes of I.V. vitamin C in various clinical settings. Thankfully, the Naturopathic community never lost interest in this treatment strategy, and such therapies have remained available to patients since the pioneering work of Pauling and Cameron.

CONCLUSION

The ability of vitamin C to prolong survival, improve quality of life, and reduce adverse effects of conventional cancer therapies has been reproducibly demonstrated over several decades. Recent research efforts of leading cancer clinics strongly supports previous reports of profound positive impact from the intervention.

Opposition to the use of intravenous vitamin C by oncologists is frustrating. It forces us to question the motives of such practitioners; is the ultimate goal best-possible patient care, or compliance with rigorously controlled trials of experimental chemotherapeutic drugs. The use of complementary strategies confounds results of such studies, and is ultimately a common basis for discouraging the use of complementary medicine in cancer management.

The ultimate decision regarding the course of patient care lies in the hands of the patient. As the use of intravenous vitamin C and other complementary strategies in cancer management become more commonplace, medical practitioners will invariably be compelled to reexamine the evidence as it pertains to such strategies. ■

Table 1: IV VITAMIN C FOR CANCER MANAGEMENT; EVIDENCE SUMMARY

Reference	Description	Outcomes
Systematic review of single or combination antioxidant therapy		
Block KI, Koch AC, Mead MN, Tothy PK, Newman RA, Gyllenhaal C. Impact of antioxidant supplementation on chemotherapeutic efficacy: a systematic review of the evidence from randomized controlled trials. Cancer Treat Rev. 2007; 33(5):407-18.	Systematic review of 19 studies examining single or combination antioxidant therapy in combination with chemotherapeutic treatment regimes.	"From the 19 studies included in this review, no evidence was found that supported concerns that antioxidant supplementation given concurrently with ROS- generating chemotherapy diminished the efficacy of the chemotherapy in study populations comprising mostly advanced or relapsed patients. In contrast, 17 of the RCTs included in this review showed either a statistically significant advantage or non- statistically higher survival and/ or treatment response in those patients given antioxidants."
Systematic review of single or combination antioxidant therapy		
Berenson et al. A phase I/II study of arsenic trioxide/bortezomib/ ascorbic acid combination therapy for the treatment of relapsed or refractory multiple myeloma. Clin Cancer Res. 2007; 13(6):1762-8.	22 patients with multiple myeloma having failed 3-9 prior therapies received in open label design arsenic trioxide, bortezomib, and a fixed dose of ascorbic acid (1 g) i.v. on days 1, 4, 8, and 11 of a 21-day cycle for a maximum of eight cycles.	Objective responses were observed in 6 (27%) of subjects. 12- months progression- free survival rate was 34%. Overall survival rate was 74%.
Yeom CH, Jung GC, Song KJ. Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration. J Korean Med Sci. 2007;22(1):7-11.	39 terminal cancer patients were administered 10000mg IV vitamin C twice over a one- week period, with coadministration of 4000mg per day oral vitamin C. EORTC QLQ-C30 quality of life scale served as the main endpoint measure.	Functional scores demonstrating statistically significant improvement included physical, emotional, and cognitive function. Symptom scores demonstrating significant improvement included fatigue, nausea/ vomiting, pain, and appetite loss. Other function and symptom scales were not significantly improved following administration of vitamin C.
Berenson JR, Boccia R, Siegel D, et al. Efficacy and safety of melphalan, arsenic trioxide and ascorbic acid combination therapy in patients with relapsed or refractory multiple myeloma: a prospective, multicentre, phase II, single-arm study. Br J Haematol. 2006;135(2):174-83.	65 multiple myeloma patients who failed at least two previous therapies received melphalan, arsenic trioxide (ATO) and ascorbic acid (AA) (1 g i.v) (MAC) combination therapy. The intervention was administered twice weekly for 6 weeks.	Objective responses occurred in 31 of 65 (48%) patients, including two complete, 15 partial and 14 minor responses. Median progression-free survival and overall survival were 7 and 19 months respectively. Twenty-two patients had elevated serum creatinine levels (SCr) at baseline, and 18 of 22 (82%) showed decreased SCr levels during treatment. Specific grade 3/4 haematological (3%) or cardiac adverse events occurred infrequently.
Padayatty SJ, Riordan HD, Hewitt SM, Katz A, Hoffer LJ, Levine M. Intravenously administered vitamin C as cancer therapy: three cases. CMAJ. 2006;174(7):937-42.	The paper reviews the basis for intravenous versus oral route of administration for vitamin C, and reports on 3 cases of advanced cancer demonstrating exceptionally long survival following intravenous vitamin C.	"Recent evidence shows that oral administration of the maximum tolerated dose of vitamin C (18 g/d) produces peak plasma concentrations of only 220 _mol/L, whereas intravenous administration of the same dose produces plasma concentrations about 25-fold higher. Larger doses (50–100 g) given intravenously may result in plasma concentrations of about 14 000 _mol/L." "At concentrations above 1000 _mol/L, vitamin C is toxic to some cancer cells but not to normal cells in vitro." "We found 3 well-documented cases of advanced cancers, confirmed by histopathologic review, where patients had unexpectedly long survival times after receiving high-dose intravenous vitamin C therapy. We examined clinical details of each case in accordance with National Cancer Institute (NCI) Best Case Series guidelines. Tumour pathology was verified by pathologists at the NCI who were unaware of diagnosis or treatment. In light of recent clinical pharmacokinetic findings and in vitro evidence of anti-tumour mechanisms, these case reports indicate that the role of high-dose intravenous vitamin C therapy in cancer treatment should be reassessed." A clinical response was seen in 8 of 20 patients (40%). The median duration of response was 5 months. The median progression free survival was 4 months and the median overall survival was 11 months. -

Reference	Description	Outcomes
Wu KL, Beksac M, van Droogenbroeck J, Amadori S, Zweegman S, Sonneveld P.Phase II multicenter study of arsenic trioxide, ascorbic acid and dexamethasone in patients with relapsed or refractory multiple myeloma. Haematologica. 2006;91(12):1722-3.	20 patients having failed 1-8 prior therapies (mean 4) were assigned to receive arsenic trioxide, dexamethasone, and ascorbic acid combination therapy for 4, 4 week cycles. 1000mg intravenous vitamin C was administered on 5 separate days during week one of the first cycle, and on 2 separate days each week thereafter.	A clinical response was seen in 8 of 20 patients (40%). The median duration of response was 5 months. The median progression free survival was 4 months and the median overall survival was 11 months.
Abou-Jawde RM, Reed J, Kelly M, Walker E, Andresen S, Baz R, Karam MA, Hussein M. Efficacy and safety results with the combination therapy of arsenic trioxide, dexamethasone, and ascorbic acid in multiple myeloma patients: a phase 2 trial. Med Oncol. 2006;23(2): 263-72.	Twenty patients in whom no more than two previous therapies had failed were enrolled. The regimen consisted of 14- or 15-wk cycles, with the first cycle considered induction, followed by one or two consolidation cycles with a reduced steroid schedule and then a maintenance cycle in responding patients	The overall response rate was 30%, with at least stable disease in 80% of patients. Median progression- free survival was 316 d in all patients and 584 d in those with a response. The regimen was well tolerated, with most adverse events being mild or moderate.
Riordan HD, Casciari JJ, González MJ, Riordan NH, Miranda-Massari JR, Taylor P, Jackson JA.A pilot clinical study of continuous intravenous ascorbate in terminal cancer patients. P R Health Sci J. 2005;24(4):269-76.	Twenty-four late stage terminal cancer patients were given continuous infusions of 150 to 710 mg/kg/day vitamin C for up to eight weeks.	The most common adverse events reported were nausea, edema, and dry mouth or skin; and these were generally minor. One patient with a history of renal calculi developed a kidney stone after 13 days of treatment. Blood creatinine, BUN, glucose, and uric acid concentrations decreased or remained stable during therapy, suggesting that ascorbate infusions did not adversely affect renal function.
Drisko JA, Chapman J, Hunter VJ. The use of antioxidants with first-line chemotherapy in two cases of ovarian cancer. J Am Coll Nutr. 2003;22(2):118-23.	2 cases of remission of advanced stage ovarian cancer (one patient had Stage IIIC papillary serous adenocarcinoma, and the other had Stage IIIC mixed papillary serous and seromucinous adenocarcinoma) are presented. 60g intravenous vitamin C was administered twice weekly complimentary to carboplatinum/ paclitaxel chemotherapy.	Both patients had remained disease free at the time of publication. One patient had been followed for 3.5 years, the other patient for 3 years.
Bahlis et al. Feasibility and correlates of arsenic trioxide combined with ascorbic acid-mediated depletion of intracellular glutathione for the treatment of relapsed/refractory multiple myeloma. Clin Cancer Res. 2002;8(12):3658-68.	Six patients with stage IIIA relapsed/refractory myeloma were studied. 0.25 mg/kg/day arsenic trioxide + 1,000 mg/day IV ascorbic acid (AA) was administered for 25 days over a 35 day period.	Two patients had partial responses; four patients achieved stable disease. Dose- limiting toxicity did not occur in any patient. The coadministration of ascorbic acid did not alter the pharmacokinetics of Arsenic trioxide. Serial in vitro studies demonstrated continued sensitivity of patient myeloma cells to arsenic trioxide + AA.
Cameron E, Campbell A. Innovation vs. quality control: an 'unpublishable' clinical trial of supplemental ascorbate in incurable cancer. Med Hypotheses. 1991;36(3):185-9.	Over a 4.5 year treatment period at three different cancer treatment centers, 1826 cases of "incurable" cancer were followed with 294 of these patients administered vitamin C orally, IV, or both. Oral protocol called for 10000mg per day. IV protocol called for cycles of 10000mg per day for 10 days. Standard practice in these treatment centers was not to administer chemotherapeutic agents for most adult cancers.	Mean survival was calculated as date of first hospital admittance until date of study conclusion (among subjects still alive) or death. Kaplan- Meier survival curves revealed mean survival among control patients of 180 days. Mean survival among vitamin C supplemented patients was 343 days. Identical dosing regimes produced significant variability in plasma ascorbate levels achieved. A clear linear relationship was observed for maximum plasma ascorbate level achieved and survival time. Plasma ascorbate levels greater than 3mg/dl were considered "particularly desirable".

Reference	Description	Outcomes
Campbell A, Jack T, Cameron E. Reticulum cell sarcoma: two complete 'spontaneous' regressions, in response to high-dose ascorbic acid therapy. A report on subsequent progress. Oncology. 1991;48(6):495-7.	A case report of terminal reticulum cell sarcoma managed with intravenous vitamin C is presented.	Spontaneous regression of a case of histologically proven widely disseminated reticulum cell sarcoma was observed, with 17 years of disease free follow- up at the time of publication of the report.
Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. Proc Natl Acad Sci U S A. 1976;73(10):3685-9.	100 patients with "untreatable" cancers were managed with a course of intravenous vitamin C (10g per day for 10 days) followed by oral dosing of 10g per day thereafter. Survival times were compared to 1000 disease matched controls.	The mean survival time for vitamin C treated subjects was 210 days, versus 50 days in disease matched controls. 90% of vitamin C treated subjects had survival times approximately 3-fold greater than controls. 10% of vitamin C treated subjects had survival times more than 20-fold greater than controls.

Table 2; Commonly administered protocol of intravenous vitamin C in complimentary cancer management

Introductory dosing regime:

• 250ml	Sterile Water	• 20 ml	Ascorbic Acid (500mg/ml)
• 4ml	Magnesium Sulphate (500mg/ml)	• 5ml	Potassium Chloroide (2meq/ml)
• 2ml	B12 (1000mcg/ml)	• 1ml	B-Complex (100mg/ml)
• 2ml	B6 (100mg/ml)	• 4ml	Sodium Bicarbonate 8.4%

If the formula is well- tolerated, increase dosages of constituents as follows;

• 500ml	Sterile Water (drain 100ml)	• 100 ml	Ascorbic Acid (500mg/ml)
• 20ml	Calcium Gluconate (100mg/ml)	• 4ml	Magnesium Sulphate (500mg/ml)
• 5ml	Potassium Chloroide (2meq/ml)	• 2ml	B5 (250mg/ml)
• 2ml	B12 (1000mcg/ml)	• 2ml	B-Complex (100mg/ml)
• 2ml	B6 (100mg/ml)	• 2ml	Selenium (200mcg/ml)
• 2ml	Multitrace (Zn 1mg, Cu .4mg, Mn .lmg, Cr 4mcg, Se 20mcg, I 25mcg, Mo 25mcg)		
• 1ml	Zinc Sulphate (10mg/ml)		

If the formula is well- tolerated, increase dosages of constituents as follows;

• 1000ml	Sterile Water (drain 250ml)	• 150 ml	Ascorbic Acid (500mg/ml)
• 25ml	Calcium Gluconate (100mg/ml)	• 6ml	Magnesium Sulphate (500mg/ml)
• 7.5ml	Potassium Chloroide (2meq/ml)	• 2ml	B5 (250mg/ml)
• 2ml	B12 (1000mcg/ml)	• 2ml	B-Complex (100mg/ml)
• 2ml	B6 (100mg/ml)	• 2ml	Selenium (200mcg/ml)
• 2ml	Multitrace (Zn 1mg, Cu .4mg, Mn .lmg, Cr 4mcg, Se 20mcg, I 25mcg, Mo 25mcg)		
• 1ml	Zinc Sulphate (10mg/ml)		

Therapy is initiated at low dosage, slow infusion, gradually working up to 50- 75g of vitamin C. Dosages greater than 50g should only be administered if access is available to a PICC line. Larger dosages into peripheral veins will result in sclerosis. Therapy is performed three times per week, pending objective demonstration of improvement (blood work, ultrasound, CAT scan, MRI). Treatment is reduced to twice weekly, and again to once weekly, as objective demonstration of improvement progresses. Once weekly treatment is typically maintained for at least months.

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