1. Lung Cancer Survival With Herbal Medicine and Vitamins in a Whole-Systems Approach: Ten-Year Follow-up Data Analyzed

Abstract: Complementary and alternative medicines are used by up to 48% of lung cancer patients but have seen little formal assessment of survival efficacy. In this 10-year retrospective survival study, the authors investigated Pan-Asian medicine + vitamins (PAM+V) therapy in a consecutive case series of all non-small-cell lung cancer patients (n = 239) presenting at a San Francisco Bay Area Chinese medicine center (Pine Street Clinic). They compared short-term treatment lasting the duration of chemotherapy/radiotherapy with long-term therapy continuing beyond conventional therapy. They also compared PAM+V plus conventional therapy with conventional therapy alone, using concurrent controls from the Kaiser Permanente Northern California and California Cancer Registries. They adjusted for confounding with Kaplan-Meier, Cox regression, and newer methods --propensity score and marginal structural models (MSMs), which when analyzing data from observational studies or clinical practice records can provide results comparable with randomized trials. Long-term use of PAM+V beyond completion of chemotherapy reduced stage IIIB deaths by 83% and stage IV by 72% compared with short-term use only for the duration of chemotherapy. Long-term PAM+V combined with conventional therapy reduced stage IIIA deaths by 46%, stage IIIB by 62%, and stage IV by 69% compared with conventional therapy alone. Survival rates for stage IV patients treated with PAM+V were 82% at 1 year, 68% at 2 years, and 14% at 5 years. PAM+V combined with conventional therapy improved survival in stages IIIA, IIIB, and IV, compared with conventional therapy alone. Prospective trials using PAM+V with conventional therapy for lung cancer patients are justified.

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Abstract: Since the discovery of vitamin C, the number of its known biological functions is continually expanding. Both the names ascorbic acid and vitamin C reflect its antiscorbutic properties due to its role in the synthesis of collagen in connective tissues. Ascorbate acts as an electron-donor keeping iron in the ferrous state thereby maintaining the full activity of collagen hydroxylases; parallel reactions with a variety of dioxygenases affect the expression of a wide array of
genes, for example via the HIF system, as well as via the epigenetic landscape of cells and tissues. In fact, all known physiological and biochemical functions of ascorbate are due to its action as an electron donor. The ability to donate one or two electrons makes AscH(-) an excellent reducing agent and antioxidant. Ascorbate readily undergoes pH-dependent autoxidation producing hydrogen peroxide (H(2)O(2)). In the presence of catalytic metals this oxidation is accelerated. In this review, we show that the chemical and biochemical nature of ascorbate contribute to its antioxidant as well as its prooxidant properties. Recent pharmacokinetic data indicate that intravenous (i.v.) administration of ascorbate bypasses the tight control of the gut producing highly elevated plasma levels; ascorbate at very high levels can act as prodrug to deliver a significant flux of H(2)O(2) to tumors. This new knowledge has rekindled interest and spurred new research into the clinical potential of pharmacological ascorbate. Knowledge and understanding of the mechanisms of action of pharmacological ascorbate bring a rationale to its use to treat disease especially the use of i.v. delivery of pharmacological ascorbate as an adjuvant in the treatment of cancer.


3. High-Dose Parenteral Ascorbate Enhanced Chemosensitivity of Ovarian Cancer and Reduced Toxicity of Chemotherapy

Abstract: Ascorbate (vitamin C) was an early, unorthodox therapy for cancer, with an outstanding safety profile and anecdotal clinical benefit. Because oral ascorbate was ineffective in two cancer clinical trials, ascorbate was abandoned by conventional oncology but continued to be used in complementary and alternative medicine. Recent studies provide rationale for reexamining ascorbate treatment. Because of marked pharmacokinetic differences, intravenous, but not oral, ascorbate produces millimolar concentrations both in blood and in tissues, killing cancer cells without harming normal tissues. In the interstitial fluid surrounding tumor cells, millimolar concentrations of ascorbate exert local pro-oxidant effects by mediating hydrogen peroxide (H_2O_2) formation, which kills cancer cells. We investigated downstream mechanisms of ascorbate-induced cell death. Data show that millimolar ascorbate, acting as a pro-oxidant, induced DNA damage and depleted cellular adenosine triphosphate (ATP), activated the ataxia telangiectasia mutated (ATM)/adenosine monophosphate–activated protein kinase (AMPK) pathway, and resulted in mammalian target of rapamycin (mTOR) inhibition and death in ovarian cancer cells. The combination of parenteral (intravenous) ascorbate with the conventional chemotherapeutic agents carboplatin and paclitaxel synergistically inhibited ovarian cancer in mouse models and reduced chemotherapy-associated toxicity in patients with ovarian cancer. On the basis of its potential benefit and minimal toxicity, examination of intravenous ascorbate in combination with standard chemotherapy is justified in larger clinical trials.
4. Effect of high-dose intravenous vitamin C on inflammation in cancer patients

Abstract: An inflammatory component is present in the microenvironment of most neoplastic tissues. Inflammation and elevated C-reactive protein (CRP) are associated with poor prognosis and decreased survival in many types of cancer. Vitamin C has been suggested as having both a preventative and therapeutic role in a number of pathologies when administered at much higher-than-recommended dietary allowance levels. Since in vitro studies demonstrated inhibition of pro-inflammatory pathways by millimolar concentrations of vitamin C, we decided to analyze the effects of high dose IVC therapy in suppression of inflammation in cancer patients.

Methods: 45 patients with prostate cancer, breast cancer, bladder cancer, pancreatic cancer, lung cancer, thyroid cancer, skin cancer and B-cell lymphoma were treated at the Riordan Clinic by high doses of vitamin C (7.5 g -50 g) after standard treatments by conventional methods. CRP and tumor markers were measured in serum or heparin-plasma as a routine analysis. In addition, serum samples were collected before and after the IVCs for the cytokine kit tests.

Results: According to our data positive response to treatment, which was demonstrated by measurements of C-reactive protein, was found in 75% of patients and progression of the inflammation in 25% of patients. IVC treatments on all aggressive stage cancer patients showed the poor response of treatment. There was correlation between tumor markers (PSA, CEA, CA27.29 and CA15-3) and changes in the levels of C-reactive protein.

Our test of the effect of IVC on pro-inflammatory cytokines demonstrated that inflammation cytokines IL-1α, IL-2, IL-8, TNF-α, chemokine eotaxin and CRP were reduced significantly after treatments.

Conclusions: The high dose intravenous ascorbic acid therapy affects C-reactive protein levels and pro-inflammation cytokines in cancer patients. In our study, we found that modulation of inflammation by IVC correlated with decreases in tumor marker levels. In summary, our data support the hypothesis that high dose intravenous ascorbate treatments may reduce inflammation in cancer patients. Our results suggest that further investigations into the use of IVC to reduce inflammation in diseases where inflammation is relevant are warranted.

5. Intravenous Vitamin C Administration Improves Quality of Life in Breast Cancer Patients during Chemo-/Radiotherapy and Aftercare: Results of a Retrospective, Multicentre, Epidemiological Cohort Study in Germany

Abstract. Aim: The aim of the study was to evaluate under praxis conditions the safety and efficacy of intravenous (i.v.) vitamin C administration in the first postoperative year of women with breast cancer. Patients and Methods: Epidemiological multicentre cohort study, including 15 gynaecologists and general practitioners representatively distributed in Germany. Data from 125 breast cancer patients in UICC stages IIa to IIIb were selected for the study. A total of 53 of these patients were treated with i.v. vitamin C (supplied as Pascorbin® 7.5 g) additional to standard tumour therapy for at least 4 weeks (study group) and 72 without this additional therapy (control group). Main outcome measures were efficacy in regard to outcome and severity of disease- or therapy-induced complaints during adjuvant chemo- and radiotherapy and aftercare. Results: Comparison of control and study groups revealed that i.v. vitamin C administration resulted in a significant reduction of complaints induced by the disease and chemo-/radiotherapy, in particular of nausea, loss of appetite, fatigue, depression, sleep disorders, dizziness and haemorrhagic diathesis. After adjustment for age and baseline conditions (intensity score before adjuvant therapy, chemotherapy, radiotherapy), the overall intensity score of symptoms during adjuvant therapy and aftercare was nearly twice as high in the control group compared to the study group. No side-effects of the i.v. vitamin C administration were documented. Discussion: Oxidative stress and vitamin C deficiency play an important role in the etiology of adverse effects of guideline-based adjuvant chemo-/radiotherapy. Restoring antioxidative capacity by complementary i.v. vitamin C administration helps to prevent or reduce disease, or therapy-induced complaints in breast cancer patients. Conclusion: Complementary treatment of breast cancer patients with i.v. vitamin C was shown to be a well tolerated optimization of standard tumour-destructive therapies, reducing quality of life-related side-effects.

6. Pharmacological ascorbate with gemcitabine for the control of metastatic and node-positive...
pancreatic cancer (PACMAN): results from a phase I clinical trial

Abstract

Background: Treatment for pancreatic cancer with pharmacological ascorbate (ascorbic acid, vitamin C) decreases tumor progression in preclinical models. A phase I clinical trial was performed to establish safety and tolerability of pharmacological ascorbate combined with gemcitabine in patients with biopsy proven stage IV pancreatic adenocarcinoma.

Design: Nine subjects received twice-weekly intravenous ascorbate (15–125 g) employing Simon’s accelerated titration design to achieve a targeted post-infusion plasma level of C350 mg/dL (C20 mM). Subjects received concurrent gemcitabine. Disease burden, weight, performance status, hematologic and metabolic laboratories, time to progression and overall survival were monitored.

Results: Mean plasma ascorbate trough levels were significantly higher than baseline (1.46 ± 0.02 vs. 0.78 ± 0.09 mg/dL, i.e., 83 vs. 44 lM, p < 0.001). Adverse events attributable to the drug combination were rare and included diarrhea (n = 4) and dry mouth (n = 6). Dose-limiting criteria were not met for this study. Mean survival of subjects completing at least two cycles (8 weeks) of therapy was 13 ± 2 months.

Conclusions: Data suggest pharmacologic ascorbate administered concurrently with gemcitabine is well tolerated. Initial data from this small sampling suggest some efficacy. Further studies powered to determine efficacy should be conducted.

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7. Pharmacological ascorbate induces cytotoxicity in prostate cancer cells through ATP depletion and induction of autophagy

Abstract: Recent studies have revealed the scientific basis for the use of intravenous (i.v.) vitamin C or ascorbic acid (ascorbate) in treating cancers, and raised the possibility of using i.v. ascorbate as a prooxidant anticancer therapy. Through the production of \( \text{H}_2\text{O}_2 \), pharmacologic ascorbate can induce some cancer cell death in vitro and inhibit a number of types of tumor growth in animal models. However, the mechanism of cell death triggered by ascorbate is not well understood. In this study, we investigated the cytotoxicity of pharmacological concentrations of ascorbate to human prostate
cancer cells and the mechanisms involved. The results showed that ascorbate in the millimolar range induced cytotoxicity in five of the six tested prostate cancer cell lines. The IC\textsubscript{50} values in the sensitive prostate cancer cells ranged from 1.9 to 3.5 mmol/l, concentrations clinically achievable with i.v. ascorbate use. All tested androgen-independent cells were sensitive to ascorbate treatment. The ascorbate-insensitive cell line LaPC4 is hormonally dependent. Whereas the reasons for sensitivity/resistance to ascorbate treatment need to be investigated further, cell death in sensitive cells was dependent on H\textsubscript{2}O\textsubscript{2}. Ascorbate treatment depleted ATP and induced autophagy in sensitive prostate cancer cells, resulting in cell death. Taken together with previous studies, high-dose ascorbate has the potential to be a novel treatment option to hormone-refractory prostate cancer.