

# High-Dose Ascorbic Acid and Cancer

John Hoffer, MD, PhD

## Does ascorbic acid have anti-cancer effects in humans?

L. John Hoffer  
Orthomolecular Medicine Today  
Montreal  
May 2, 2009

## RESEARCH

### Intravenously administered vitamin C as cancer therapy: three cases

Sebastian J. Padayatty, Hugh D. Riordan, Stephen M. Hewitt, Arie Katz, L. John Hoffer, Mark Levine

CMAJ March 28, 2006

## COMMENTARY

### High-dose vitamin C therapy: Renewed hope or false promise?

Sarit Assouline, Wilson H. Miller, Jr.

CMAJ March 28, 2006

## Some alternative cancer therapies

- ACID/ALKALINE BALANCE
- DETOXIFICATION
- AMYGDALIN (LAETRIE)
- ANTINEOPLASTONS
- CANCEL/CANTRON (ENTELE)
- ELLAGIC ACID
- ELECTRONIC THERAPIES
- ENZYME THERAPIES
- DIET AND FOOD THERAPIES: Gerson, macrobiotic, vegetarian, wheat grass, etc.
- HERBAL EXTRACTS/PLANT PRODUCTS: Artemisia, chuchuhual tree extract, Essiac tea, Graviola, Hoxsey concoction, Pau D'Arco, Saw Palmetto, etc.
- HYDRAZINE SULFATE
- HYPERTHERMIA
- OXYGEN AND OZONE TREATMENTS: Hydrogen peroxide, hyperbaric oxygen, ozone

- SHARK CARTILAGE
- 714X (Naessen) "Immunostim"
- VACCINES
- ZAPPERS AND ANTI-PARASITIC HERBALS
- ANTIOXIDANTS AND RELATED COMPOUNDS: Vitamins C, A, E, selenium, lipoic acid, melatonin, etc.
- VITAMIN D METABOLITES
- ARSENIC, DMSO, MSM
- GARLIC
- GLANDULARS
- HOMEOPATHY
- LIVE CELL THERAPY
- IMMUNE-SYSTEM BOOSTERS/IMMUNO THERAPIES: Colostrum, MGN3, IP6 (Inositol), Iscador (Mistletoe), mushroom extracts, beta glucan, Carnivora, insulin potentiation therapy (used concurrently with chemotherapy)

## Anti-cancer actions of vitamin C?

- Quackwatch.org's list of dubious cancer therapies lists vitamin C as No. 109, just above wheat grass
- The great majority of researchers and the general public do not regard vitamin C as a proven, effective, anti-cancer agent

# High-Dose Ascorbic Acid and Cancer

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## Supplement use in America

- 50% of Americans use nutritional supplements
- Use by cancer patients is even greater

Journal of Clinical Oncology 2008; 26: 665-673

## Vitamin and Mineral Supplement Use Among US Adults After Cancer Diagnosis: A Systematic Review

Christine M. Velicer CM, Cornelia M. Ulrich CM

From the Cancer Prevention Program, Fred Hutchinson Cancer Research Center; and the Department of Epidemiology, University of Washington, Seattle, WA

## Supplement use after cancer diagnosis

- 64 to 82% of cancer patients use nutritional supplements
- 14 to 32% start supplements after the cancer diagnosis
- Up to 68% of treating physicians are unaware

D'Andrea GM CA: Cancer J Clin 2005; 55:319-21

- *...Mechanistic considerations suggest that antioxidants might reduce the effects of conventional cytotoxic therapies*
- *Clinicians should advise their patients against the use of antioxidant dietary supplements during chemotherapy or radiotherapy*
- *Such caution should be seen as the standard approach for any unproven agent that may be harmful*

## Nutrition and Physical Activity During and After Cancer Treatment: An American Cancer Society Guide for Informed Choices

Doyle C et al CA Clin Cancer J Clin 2006;56:323-53

Antioxidants could repair cellular oxidative damage to cancer cells that contributes to the effectiveness of these treatments. However, the possible harm from antioxidants is only hypothetical... there may be a net benefit to help protect normal cells from the collateral damage associated with these therapies.

**Whether antioxidants or any other dietary supplements are beneficial or harmful during chemotherapy or radiotherapy is a critical question without a clear scientific answer at this time.**

## Canadian Cancer Society 2009

### Antioxidants

Many of the vitamins found in vegetables and fruit act as antioxidants. Antioxidants protect us by destroying free radicals – chemicals that damage cells, which can lead to cancer.

***More research is needed to find out if there are important benefits or harmful effects of using antioxidant supplements during and shortly after treatment.***

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## How does one identify new effective cancer therapies?

- The natural history of cancer is notoriously variable
  - on average, patients get worse faster than their physicians predict
  - a small percentage of patients survive remarkably, sometimes with and sometimes without chemotherapy
  - what accounts for this variability?

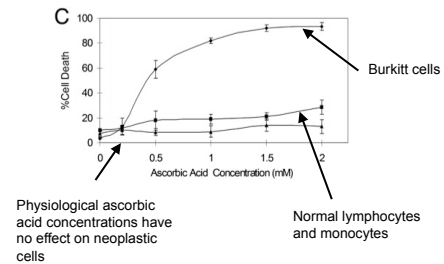
## Today's aims

- Provide a conceptual framework for evaluating the evidence that vitamin C could have a clinically valuable anticancer action
- Discuss the current evidence
- Offer an evidence-based decision algorithm while awaiting more evidence
- Identify urgent research needs

## Specificity

the holy grail of cytotoxic chemotherapy

### Effects of ascorbic acid on human Burkitt lymphoma cells

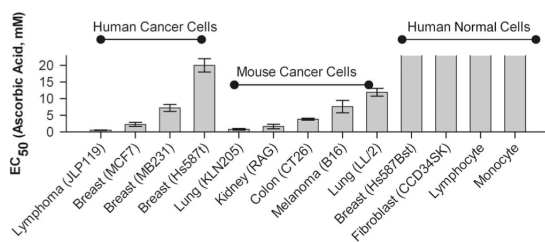


Chen, Qi et al. (2005) Proc. Natl. Acad. Sci. USA 102, 13604-13609

Copyright ©2005 by the National Academy of Sciences

PNAS

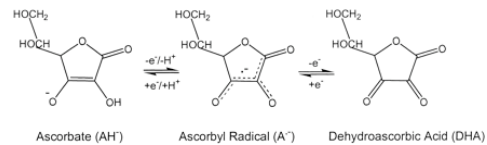
### Effects of pharmacologic ascorbic acid concentrations on cancer and normal cells



Chen, Qi et al. (2005) Proc. Natl. Acad. Sci. USA 102, 13604-13609

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PNAS

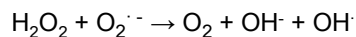
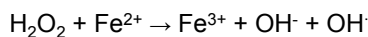
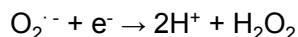
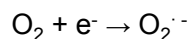


In high concentrations, ascorbic acid generates hydrogen peroxide

# High-Dose Ascorbic Acid and Cancer

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## Reactive Oxygen Species



## Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice

Qi Chen<sup>1\*</sup>, Michael Graham Espey<sup>1,2\*</sup>, Andrew Y. Sun<sup>1\*</sup>, Chaya Pooput<sup>3</sup>, Kenneth L. Kirk<sup>3</sup>, Murali C. Krishna<sup>3</sup>, Deena Betts<sup>4</sup>, Jeanne Drisko<sup>5</sup>, and Mark Levine<sup>1,2\*</sup>

<sup>1</sup>Molecular and Clinical Nutrition Section and <sup>2</sup>Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, and <sup>3</sup>Radiation Biology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892; and <sup>4</sup>Program in Integrative Medicine, University of Kansas Medical Center, Kansas City, KS 66160

PNAS 2008;105:11105-9

## Is vitamin C an antioxidant or a pro-oxidant?

- Antioxidants prevent cancer, whereas pro-oxidants can cause cancer
- Treatments that prevent cancer aren't supposed to cause cancer
- Cancer treatments are not expected to prevent cancer; indeed, they can cause new cancers

## Unifying hypothesis

- In a strongly pro-oxidative environment, redox-active molecules promote or amplify ROS formation
- In a reducing or quiescent environment, redox active molecules are neutral or anti-oxidant

## Unifying hypothesis, ctd.

- Vitamin C is selectively cytotoxic to many cancers but innocuous to normal cells
- Cytotoxic drugs (regardless of mechanism) induce a strongly pro-oxidant environment in their target cells
- Hypothesis: C amplifies the cytotoxicity of chemotherapy for cancer cells while quenching it for normal cells
- Vitamin C could be a **specificity amplifier**

## Evidence

- Safety
- Effectiveness
- Cost
- Convenience



# High-Dose Ascorbic Acid and Cancer

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## Why is evidence needed?

- Vitamin C is GRAS
  - ascorbic acid USP for injection (DIN 02245214)
  - formally approved in ON, AL, BC and widely used elsewhere, including in Montreal
- Safety/efficacy almost totally undocumented
- Major potential risks
  - calcium oxalate nephrolithiasis and nephropathy
  - acute hemolysis in people with *G6PDH* deficiency
  - sodium load
  - osmotic diuresis
- Almost no predictive information about effectiveness

## Phase I clinical trial

- Modeled after Wichita protocol originally described by H.D. Riordan
  - Riordan used iv vitamin C in varying doses, often > 100 g, since 1975
  - the Wichita team published their protocol, case reports and basic research
  - clinical effects were not well documented
    - "It improved patients' sense of well-being, reduced pain, and in many cases prolonged life beyond prognostications of oncologists."

## Support

- Lotte and John Hecht Memorial Foundation
- Anton Kuerti
- Wilson H Miller Jr
- Mark Levine
- Oncologist-collaborators and pharmacists, nurses and support staff in the CRU
- ALVEDA Pharma

## Phase I trial

- Inclusion/exclusion criteria
  - failed all standard therapy
  - good functional status
  - adequate kidney function
  - no oxalate urinary tract stone
  - no *G6PDH* deficiency
  - willing & able to come to CRU 3 times/week for 90 - 120 min infusions

## original article

Annals of Oncology 19: 1969–1974, 2008  
doi:10.1093/annonc/mdn077  
Published online 9 June 2008

### Phase I clinical trial of i.v. ascorbic acid in advanced malignancy

L. J. Hoffer<sup>1,\*</sup>, M. Levine<sup>2</sup>, S. Assouline<sup>1</sup>, D. Melnychuk<sup>1</sup>, S. J. Padayatty<sup>2</sup>, K. Rosadiuk<sup>1</sup>, C. Rousseau<sup>1</sup>, L. Robitaille<sup>1</sup> & W. H. Miller, Jr<sup>1</sup>

<sup>1</sup>Montreal Centre for Experimental Therapeutics in Cancer, Lady Davis Institute for Medical Research, McGill University and the Jewish General Hospital, Montreal, Quebec, Canada; <sup>2</sup>Molecular and Clinical Nutrition Section, Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

**Background:** Ascorbic acid is a widely used and controversial alternative cancer treatment. In millimolar concentrations, it is selectively cytotoxic to many cancer cell lines and has *in vivo* anticancer activity when administered alone or together with other agents. We carried out a dose-finding phase I and pharmacokinetic study of i.v. ascorbic acid in patients with advanced malignancies.

**Patients and methods:** Patients with advanced cancer or hematologic malignancy were assigned to sequential cohorts infused with 0.4, 0.6, 0.9 and 1.5 g ascorbic acid/kg body weight three times weekly.

**Results:** Adverse events and toxicity were minimal at all dose levels. No patient had an objective anticancer response.

**Conclusions:** High-dose i.v. ascorbic acid was well tolerated but failed to demonstrate anticancer activity when administered to patients with previously treated advanced malignancies. The promise of this approach may lie in combination with cytotoxic or other redox-active molecules.



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ScienceDirect

Metabolism Clinical and Experimental 58 (2009) 263–269

Metabolism  
Clinical and Experimental

[www.metabolismjournal.com](http://www.metabolismjournal.com)

Oxalic acid excretion after intravenous ascorbic acid administration  
Line Robitaille<sup>a</sup>, Orval A. Mamer<sup>b</sup>, Wilson H. Miller Jr.<sup>a</sup>, Mark Levine<sup>c</sup>, Sarit Assouline<sup>d</sup>,  
David Melnychuk<sup>d</sup>, Caroline Rousseau<sup>d</sup>, L. John Hoffer<sup>a,b,\*</sup>

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<sup>c</sup>Molecular and Clinical Nutrition Section, Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases,

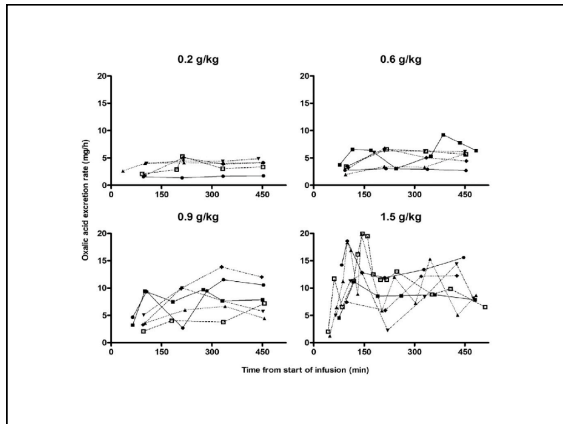
National Institutes of Health, Bethesda, MD 20892, USA

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Received 14 July 2008; accepted 4 September 2008

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Mr R. and M F.

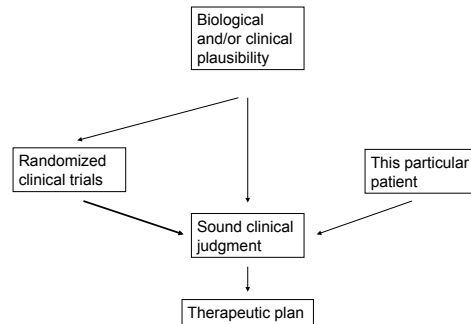
- Their extraordinary responses to chemotherapy could be within the wide range of variability of the natural history of cancer and its response to chemotherapy
- However: it is *biologically plausible* that vitamin C facilitated their chemotherapy
- Plainly, vitamin C did not interfere with their chemotherapy

**Phase I-II Dose-Escalating Study of Intravenous Ascorbic Acid in Combination with Carboplatin and Docetaxel in Previously Untreated Stage IIIB, Stage IV, or Recurrent Non-Small Cell Lung Cancer**

**LJ Hoffer, J Agulnik, V Cohen, WH Miller, D Small**

Lady Davis Institute for Medical Research, McGill University, and the Departments of Medicine and Oncology, Jewish General Hospital, Montreal

## Evidence-based medicine



EBM can be misused

**Randomized clinical trials**

Therapeutic plan

EBM can be misused

- Cookie-cutter medicine
- Off-label prescription
- Fraud

# High-Dose Ascorbic Acid and Cancer

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## Why we need randomized clinical trials

- They speak the language of modern science-based therapeutics
- They hold chaos in check
- They provide the statistical information crucial for assessing any significant therapy

## When is a new RCT *inappropriate*?

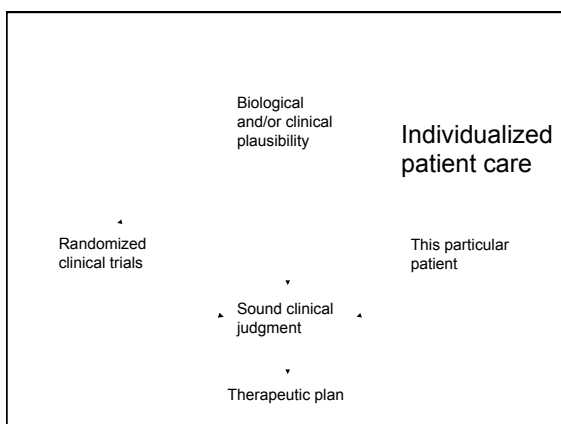
- When the treatment is almost always extremely effective for almost every person
- When the treatment is almost always ineffective for almost every person

## When is a RCT *necessary*?

- In the *intermediate zone*, where the treatment is *possibly* reasonably (or very) effective for many people
- A well-designed and conducted RCT provides crucial probability numbers within the framework of ...
  - a well defined treatment protocol
  - a well defined treatment goal (outcome)
  - in a specific kind of patient...
  - who has a specific disease/stage of disease

## Proceed to RCT when...

- There is credible evidence of biological/clinical plausibility (preferably both)
- The parameters of the treatment have been optimized in preliminary studies
  - the dose and dose regimen are defined and feasible
  - target disease is well identified
  - target outcome specified
    - biomarkers very helpful
  - there is a good notion of the characteristics of the patient who is most likely to respond



## Guidelines for the practice of evidence-based medicine

**Guyatt GH et al. Chest 2008;133:123S-131S**

- Quality of the evidence
  - A (high), B (moderate), C (low)
- Strength of the recommendation
  - strong: "We [strongly] recommend...for/against..."
  - weak: "We suggest using/not using"
- The strength of a recommendation should be based on the degree of confidence one has in the balance between globally desirable and globally undesirable effects of the treatment

# High-Dose Ascorbic Acid and Cancer

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## When is a treatment “effective”?

- A treatment recommendation is “strong” when the evidence is strong that the treatment produces large benefits to most people with the disease
- A treatment recommendation is “weak” when the available evidence is of uncertain reliability, leaving appreciable uncertainty about the magnitude of benefit/harm
- Weak recommendations often pertain to “off-label” use of a drug

## EBM guidelines

- When the recommendation is weak, patient values and preferences loom far larger than for strongly recommended “on-label” treatments
- Clinicians are obliged to provide especially in-depth explanations of the potential benefits, side effects and risks of off-label than on-label treatments, and monitor more rigorously

## Antipsychotic drugs are dangerous

- Rate of agranulocytosis with clozapine is 6.8 events per 1000 patient years
  - Close monitoring protocol mandatory

## Antipsychotic drugs are dangerous

- Atypical antipsychotic drugs (olanzapine, risperidone & quetiapine) increase the risk of sudden death in a dose-related fashion
- Overall risk ~ 3.3 events per 1000 patient years
  - i.e. almost the same risk as for agranulocytosis due to clozapine
- Clinical practice implications
  - avoid off-label use of atypical antipsychotic drugs
  - use minimum effective dose for on-label indications
  - Schneeweiss S, Avorn J, Jan 15, 2009 *N.Engl.J.Med.* pp. 294-6.

**What does EBM instruct when RCTs are unavailable or unreliable?**

Biological and/or clinical plausibility

This particular patient

Sound clinical judgment

Therapeutic plan

## Vitamin C and cancer

- The evidence pertaining to harm or benefit is “low quality”
- *Hence, antioxidant treatment is “off-label”*
- What is one to do while awaiting high quality evidence?



# High-Dose Ascorbic Acid and Cancer

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## General suggestions regarding EBM, antioxidants and cancer

- When the evidence is inconclusive, patient values, preferences and circumstances loom larger than when the evidence is strong
- When chemotherapy is likely to be highly effective and well-tolerated, avoid antioxidants
- When chemotherapy is likely to be ineffective/toxic, concurrent antioxidants seem to offer the best chance
- (As a potential confounder of this analysis, many of the participants in pivotal chemotherapy trials may well have covertly used antioxidants)

## Evidence

- Polished, objective case reports
- Convincing case series
- Disseminate statistics
- Root out fraud
- Develop formal funding mechanisms
- Form information networks
- CAM practitioners and clinical researchers can create pragmatic partnerships in the interest of gathering evidence

## Narrative-interpretive reasoning

- Two kinds of reasoning:
  - Logico-deductive (rational, objective)
  - Narrative-interpretive (context and a “good story”)
- Both are essential in medicine
  - Logico-deductive reasoning establishes facts and relationships
  - Narrative-interpretive reasoning “makes sense,” guides and motivates, is the ground substance of intuition

## Logico-deductive *versus* narrative-interpretive reasoning

- |   |   |
|---|---|
| • Logico-deductive                              | • Narrative-interpretive                |
| – solves puzzles                                | – elucidates mysteries                  |
| – creates algorithms                            | – finds meaning                         |
| – readily formalized                            | – persuasive                            |
| – the major activity of evidence-based medicine | – story and example                     |
|   | – the medium of the “hidden curriculum” |

## The hidden curriculum

*A great deal of what is taught – and most of what is learned – in medical school takes place not within formal course offerings but within medicine’s hidden curriculum.*

FW Hafferty. Academic Medicine, 1998

**“Why are you wasting my time? Just get to the important stuff.”**

Quoted by BJ Good in “Medicine, Rationality, and Experience: An Anthropological Perspective (1995) as cited by FW Hafferty, 1998

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