Vitamin C as Cancer Therapy: An Overview

L.J. Hoffer, M.D., Ph.D.;[1] C. Tamayo, M.D.;[2] M.A. Richardson, Dr.PH[2]

Introduction

The popularity of complementary/alternative therapies (CAM) is an international phenomenon with 25% of UK residents,[1] 50% of the German, French[1], and Australian[2] populations, and 42-69% of Americans using these approaches.[3,4] CAM has been a major growth industry in Europe,[5-7] and that trend is mirrored in the United Staes. Since 1990, prevalence of use increased 33.8% and visits to CAM practitioners rose 47.3% from 427 to 629 million, with out-of-pocket estimates at $34.4 billion.[3,8] Among cancer patients, however, prevalence of use is upwards of 50%[9-11] and most of that use is in combination with conventional therapies. A summary of research on CAM use for cancer across 13 countries estimated prevalence of use at 31.4% (range 7-64%).[12]

In Canada, an estimated 129,200 new cancer diagnoses and 62,700 deaths are expected for 1998. Since 1988, the incidence rate has increased by one-third. Similarly, the mortality rate has increased by one-fifth.[13] In the United States, approximately one-third of Americans living today, almost 75 million, will be diagnosed with cancer in their lifetime.[14] During 1997, over 1.4 million individuals received a cancer diagnosis, 1500 died daily, and 7.4 million were living with a history of cancer. The direct medical, morbidity, and mortality costs of cancer for our nation were estimated at $104 billion.[15] Although cancer is second to heart disease as the leading cause of death in the United States, by the year 2000, cancer deaths will surpass those from heart disease in the United States and in most developed nations,[16,17] despite the decline in age-adjusted mortality rates due to smoking cessation.[18] Currently, one of every four deaths in the United States is attributed to cancer.[15] As cancer incidence and survival time increase, the population seeking alternative approaches is expected to increase. The benefits of CAM remain uncertain in the absence of interpretable clinical data, thus, rigorous scientific research and investigators focused on CAM are needed.

1. Dept. of Medicine, Sir Mortimer B. Davis Jewish General Hospital, Montreal, PQ H3T 1E2
2. Center for Alternative Medicine Research in Cancer, Univ. of Texas-Houston School of Public Health, Houston, TX.

How Does One Measure the Effects of Unconventional Cancer Therapies?

Most physicians think that people who use unconventional or alternative cancer therapies are not guided by scientific considerations; however, the effectiveness of many mainstream therapies are not evidence based. Despite the implausibility of some unconventional therapies, the continued use by cancer patients should be examined.[19]

CAM approaches are generally considered unproven and unaccepted by the medical community at large, primarily because they have not been subjected to scientific testing or are promoted by individuals outside of mainstream medicine. Regardless of their level of acceptance into mainstream medicine or reluctance by some to invest resources into CAM research[20-23] these therapies have infiltrated every aspect of health care. Cancer patients want more information,[24] and some patients believe access to these alternative/complementary approaches should be part of standard oncologic treatment.[25]

The recent upswing of interest in alternative cancer therapies is interesting because it implies real concerns about our modern medical-scientific culture. Patients are increasingly more dissatisfied with the side effects, poor results of most conventional cancer therapies, and the perceived lack of a wholistic approach that accompanies the mechanistic orientation of bio-

medicine. This interest in CAM also accompanies an era when patients increasingly want to participate in the decision-making process regarding their treatment.

Regardless of the reasons, unconventional cancer therapies are held in high esteem by large segments of the public. This shift has implications for health care providers who, despite criticism, have been dedicated to introducing new wholistic approaches as cancer therapy. Historically, information on unconventional cancer therapies focused on strategies to steer patients back to mainstream medicine. With the recent emergence of interest in unconventional cancer therapies, however, this focus is changing.[26] Public interest in unconventional therapies has evoked support from elected representatives in government, funding agencies that rely on public support, and, of course, manufacturers of products. The interest in CAM shows no sign of abating. Accompanying the increasing public interest[3,4,27] is the demand for systematic evaluations of safety and efficacy.[20,21,28,29]

The medical and scientific communities must respond even though some group may be reluctant to invest resources into CAM. Scientific testing is the next logical step, and we must begin building "...bridges, not moats, between thoughtful and careful science and CAM therapies."[30,31]

The Research Agenda to Assess CAM

In October, 1996, a national conference on research methodologies for unconventional cancer therapies was sponsored by the Canadian Breast Cancer Research Initiative (CBCRI). The CBCRI determined that women with breast cancer were interested in unconventional cancer therapies: Are they safe? Are they effective? How do they interact with conventional cancer treatments? Interest was focused on anticancer effects and improved tolerance of standard cancer treatments. Such clear, logical questions are consistent with other reports.[26]

In the United States, the Office of Alternative Medicine (OAM) was established at NIH in 1992 by Congressional mandate. In a first initiative, OAM issued a Request for Applications and funded 30 pilot proposals in 1993. The response was the largest in the history of NIH, with over 6,000 requests for applications, 800 letters of intent, and 452 applications. Given the overwhelming national interest, OAM expanded the research base by funding 10 exploratory research centers at major medical centers in 1995. With continued national interest, OAM was upgraded to the National Center for CAM (NC-CAM) in 1998 and again expanded their research initiative by funding three new exploratory centers as program grants.

Evaluating Unconventional Cancer Therapies

It has been suggested by the U.S. Office of Technology Assessment (OTA) that alternative cancer therapies should be evaluated through "best case series" reviews. However, few practitioners have the data to assemble a best case series. The fact that unconventional cancer therapies are used as adjuncts rather than alternatives to conventional therapy makes the interpretation of apparent tumor regressions problematic. Mainstream oncologists reviewing such cases are aware of the wide variability in the natural history of cancer even when patients with the same type and stage of cancer receive the same therapy. There is understandable skepticism about the meaning of highly selected best cases that may well merely represent extremes in the natural history of a cancer rather than a specific response to an unconventional therapy.

On the other hand, proponents of unconventional therapies claim that it is precisely these unknown factors that unconventional therapies are altering. If this is correct, then it is inappropriate for skeptics to require dramatic, "unexplainable" re-

sponses to a given unconventional therapy before taking it seriously. Rather, it ought to suffice to observe a statistically (and clinically) significantly greater proportion of patients treated with unconventional therapies who have outcomes outside the usual range of response. Those diseases with the greatest unpredictability in natural history could be the very ones most amenable to unconventional therapy. The emergence of bisphosphonates as anticancer drugs illustrates the difficulties involved in evaluating truly novel cancer treatments. It is now generally accepted that bisphosphonates reduce the frequency of breast cancer spread to bone by approximately 50%. This effect was predictable from the known effects of this class of drugs, and testing for it was possible because of the anticipated financial return to the pharmaceutical industry. Yet nearly twenty years of research was needed to convincingly demonstrate this large benefit. The long delay was apparently due to the difficulties involved in clinical studies in patients with advanced cancers, for whom the interpretation of therapeutic effects is complicated by the existence of a large number of confounding variables.[32] Yet these are the kind of patients for whom unconventional cancer therapies are frequently prescribed. If demonstration of such a large and specific treatment effect is so difficult, what can be expected of the smaller, less specific, less predictable, but nonetheless important benefits that might be associated with unconventional cancer therapies?

Appropriate Measures of Response

The specific goals of unconventional cancer therapies are rarely as specific as bisphosphonates. Nevertheless, a fair evaluation requires that the selection response criteria be appropriate for the therapy selected. For therapies presumed to work like biologic response modifiers (BRM), intermediate biologic markers, such as measures of immune responsiveness, or serum tumor markers could provide directions as to which cancer patient will most likely respond.[33] A parallel example is high-dose antioxidant therapy, an approach that for many years was unconventional but which recently graduated to conventional status. Controlled clinical trials with these substances will not be definitive until appropriate indications for therapy and effective types, combinations, and doses of antioxidant therapy are determined. The use of intermediate markers of effect, such as the urinary excretion of F2 isoprostanes, is an appropriate clinical research approach.[34] These measures, although labor and time intensive, may be a better strategy to assess alternative cancer therapies than the simple examination of standard outcomes like survival, tumor size, recurrence rates, pain control, or functional status in an unselected heterogenous group of cancer patients. For wholistic therapies, patient-oriented outcomes including measures of quality of life are appropriate and important.

Vitamin C as Alternative Cancer Therapy

Among the unconventional cancer therapies, high-dose vitamin C therapy is the most rigorously studied, most biologically plausible, and most controversial. Both the United States Congress OTA Report, Unconventional Cancer Treatments (1990)[35] and the task force on alternative therapies formed by the Canadian Breast Cancer Research Initiative (1996)[36] concluded that the limited preclinical and clinical evidence indicates that vitamin C has potential as an anticancer agent. However, there is a lack of understanding of the mechanisms.

Most conventional cancer authorities accept that vitamin C is based on controlled clinical trials that were published in 1979 and 1985. More recent developments however suggest the situation should be reassessed. First, there has accumulated a large body of scientific evidence suggesting that ascorbic acid has immune activat-

ing properties in humans and anticancer properties in certain cell culture and animals system. Second, our increasing knowledge and understanding of the mode of action of BRMs has clarified that the clinical trials that failed to show a clinical anticancer effect of vitamin C were methodologically flawed.

If vitamin C has anticancer effects, it is acting, not as a standard cytotoxic chemotherapy, but rather as a BRM. BRMs are known to potentate host immune mechanisms through stimulation of certain lymphocytes such as T cells, natural killer cells and antigen presenting cells. They also stimulate the secretion of soluble factors of the immune system such as cytokines that mediate the attack and destruction of malignant tissue.[37] There is currently much interest in the use of BRMs such as interleukin-2 (IL-2) to treat certain types of cancer, however, the research approaches differs greatly from that used to screen and test cytotoxic drugs.[33] There is evidence that vitamin C effects could be mediated by cytokines.[38] Therefore, it would be important to build on the existing research expertise of IL-2 and other BRMs. In addition, a recent report indicates that IL-2 therapy induces a precipitous and profound reduction in circulating vitamin C levels in cancer patients.[39] This effect may have implications both for vitamin C therapy and for improving IL-2 therapy. Understanding the biologic effects of vitamin C would also provide information on the interactions of vitamin C and cytotoxic therapies.

Thus, there is need for a careful reassessment of the original and newer clinical information on vitamin C effects in human cancer patients by (1) practitioners skilled in the vitamin C administration, (2) experts in vitamin C biology and pharmacology, (3) experimental oncologists with experience in evaluation of anticancer drugs (especially BRMs) who are willing to implement suitable clinical trials in their medical centres, (4) clinical trial methodologists. Realizing the need for a clinical evaluation of vitamin C therapy in cancer and the great difficulties in designing appropriate clinical trial protocols to do this, we have organized a research workshop to bring together the above mentioned experts. The goal of the workshop process is to reach a consensus among the experts on the most rational approach to assess the mechanism of action and clinical impact of vitamin C. The specific objectives of the workshop process are to reach a consensus on the following: 1) The most rigorous, scientific clinical trial design to test high dose vitamin C as a cancer treatment; 2) An appropriate cancer population with inclusion/exclusion criteria, and 3) Biological outcomes to determine the mechanism of action and clinical response outcomes to objectively determine cancer response of vitamin C.

We will examine the evidence that megadose vitamin C, possibly together with other nutrients, may be beneficial for cancer patients, markers to predict which patients with which cancers are most likely to respond to vitamin therapy, and the types of response.

High dose vitamin C therapy is based on a biological rather than a psychological hypothesis, yet its evaluation presents many of the same problems that will have to be addressed when any unconventional cancer therapy is evaluated. It is simple in that one is looking for a direct biological effect. But it is complex in that the selection of the type of response, type of cancer, and type of patients likely to respond need to be sorted out. Other unconventional therapies are even more difficult in that both the presumed mode of action and the response are problematic. We therefore regard this workshop as a useful test of the experience of gathering experts to bridge the gaps between conventional and unconventional practice and develop valid and decisive clinical protocols, as envisioned in the Office of Technology Assessment report, National Center for Complementary,

and Alternative Medicine and University of Texas Center for Alternative Medicine. Can the evaluation of vitamin C as a cancer therapy provide a simpler paradigm on the road to developing techniques for evaluating other, more complicated unconventional cancer therapies?

References

1. Fisher P, Ward A: Complementary medicine in Europe. *BMJ,* 1994; 309: 107-111.
2. MacLennan AH, Wilson DH, Taylor AW: Prevalence and cost of alternative medicine in Australia. *Lancet,* 1996; 347: 569-73.
3. Eisenberg D, Davis R, Ettner S, et al. Trends in Alternative Medicine Use in the United States, 1990-1997 Results of a Follow-up National Survey. JAMA, 1998; 280: 1569-1575.
4. Haskell W, Alles W, Metz RD: Americans mingle complementary techniques with traditional medical services, survey shows September 21, 1998-Stanford. *Business Wire Health Wire,* 1998.
5. McGinnis LS: Alternative therapies, 1990. An overview. *Cancer,* 1991; 67: 1788-93.
6. Campion EW: Why unconventional medicine? *N Engl J Med,* 1993; 328(4): 282-283.
7. Smith T: Alternative Medicine. *BMJ,* 1983; 287: 307-8.
8. Eisenberg D, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL: Unconventional medicine in the United States: Prevalance, costs, and patterns of use. *N Engl J Med,* 1993; 328: 246-252.
9. Cassileth BR, Lusk EF, Strouse TB, Bodenheimer BJ: Contemporary unorthodox treatments in cancer medicine: A study of patients, treatments, and practitioners. *Ann Intern Med,* 1984; 101: 105-112.
10. American Cancer Society. Unproven methods of cancer management - macrobiotic diets for the treatment of cancer. *CA: A Cancer Journal for Clinicians*, 1989; 39: 248-251.
11. *Lerner IJ, Kennedy BJ:* The prevalence of questionable methods of cancer treatments in the United States. *Cancer,* 1992;42:181-191.
12. Ernst E, Cassileth BR: The prevalence of complementary/alternative medicine in cancer. A systematic review. *Cancer,* 1998; 83: 777-782.
13 National Cancer Institute of Canada. Canadian Cancer Statistics -1998. Toronto, Canada; 1998.
14. American Cancer Society. *Cancer Facts and Figures.* Atlanta, GA: American Cancer Society, Inc.; 1994.
15. American Cancer Society. *Cancer facts & figures -1997.* 1997; 97-300M-No. 5008.97.
16. Cole P: *Of Light Bulbs and Wine Glasses: Risk Factors and Mortality Trends. In: Maulitz RC, Ed. Unnatural Causes: The Three Leading Killer Diseases in America.* New Brunswick, NJ: Rutgers University Press; 1988:83-91.
17. Sondik EJ: Progress in cancer prevention and control. The three leading killer diseases in America. In eds. Maulitz RC: *Unnatural Causes: The Three Leading Killer Diseases in America,* New Brunswick, NJ: Rutgers University Press; 1988: 111-134.
18. Cole P, Amoateng-Adjepong Y: Cancer Prevention: Accomplishments and Prospects. *Am J Public Health,* 1994; 34: 8-10.
19. Lerner M: *Choices in Healing: Integrating the Best of Conventional and Complementary Approaches to Cancer,* Cambridge, MA: MIT Press; 1994.
20. Tannock IF, Warr DG: Unconventional therapies for cancer: a refuge from the rules of evidence? *CMAJ,* 1998; 159: 801-802.
21. Angell M, Kassirer P: Alternative medicine - the risks of untested and unregulated remedies. *N Engl J Med,* 1998; 339: 839-841.
22. Halperin EC: Let's abolish the office of alternative medicine of the National Institutes of Health. *N Carolina Med J,* 1998; 59: 21-23.
23. Stalker DF: Evidence and alternative medicine. *The Mount Sinai J Med.* 1995; 62: 132-143.
24. Richardson MA, Ramirez T, Nanney K, Singletary SE: Alternative/complementary medicine: implications for patient-provider communication. (Abstract). 35th Annual ASCO Meeting. 1998.
25. Coss RA, McGrath P, Caggiano V. Alternative care: patient choices for adjunct therapies within a cancer center. *Cancer Practice,* 1998; 6: 176-181.
26. Jacobs JJ: Unproven alternative methods of cancer treatment. In eds. Devita Jr, VT, Hellman, S, Rosenberg, SA: *Cancer: Principles and Practices of Oncology,* Philadelphia, PA: Lippincott-Raven Publishers; 1997: 2993.
27. Astin JA: Why patients use alternnative medicine. Results of a national study. *JAMA,* 1998; 279: 1548-1553.
28. Fontanarosa PB: Alternative medicine meets science. *JAMA,* 1998;280:1618-1619.
29. DiPaola RS, Zhang H, Lambert GH, et al: Clinical and biologic activity of an estrogenic herbal combination (PC-SPES) in prostate cancer. *NEJM*, 1998; 339: 785-791.
30. Hoey J: The arrogance of science and the pitfalls of hope. *CMAJ,* 1998; 159: 803-804.
31. Jonas WB: Alternative Medicine - learning from the past, examining the present, advancing the future. *JAMA,* 1998;280:1616-1618.
32. Mundy GR, Yoneda T: Bisphosphonates as anti-

cancer drugs. *N Engl J Med,* 1998; 339: 398-400.
33. Hawkins MJ, Hoth DF, Wittes RE: Clinical development of biological response modifiers: comparison with cytotoxic drugs. *Sem Oncol,* 1986; 13: 132-40.
34. Witztum JL: To E or not to E - how do we tell? *Circulation,* 1998; 50: 2785-2787.
35. US Congress OTA. *Vitamin C.* Washington DC: Reprinted by the U.S. Congress Office of Technology Assessment, 1990.
36. Canadian Breast Cancer Research Initiative. Essiac: An information package. Toronto CBCRI Pamphlet, *http://www.Breast.Cancer.Ca/English/e_Frame.Htm. 1996.*
37. Parkinson DR: Present status of biological response modifiers in cancer. *Am J Med,* 1995; 99: 54S-56S.
38. Hoffer LJ: Nutrients as biologic response modifiers. Quillin P, Williams RM, Eds. *Adjuvant Nutrition in Cancer Treatment.* Arlington Heights, IL: Cancer Treatment Research Foundation; 1993: 55-79.
39. Marcus SL, Petrylak DP, Dutcher JP, et al: Hypovitaminosis C in patients treated with high-dose interleukin-2 and lymphokine-activated killer cells. *Am J Clin Nutr,* 1991; 54: 1292S-1297S.