FAILURE OF HIGH-DOSE VITAMIN C (ASCORBIC ACID) THERAPY TO BENEFIT PATIENTS WITH ADVANCED CANCER

A Controlled Trial

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Abstract One hundred and fifty patients with advanced cancer participated in a controlled double-blind study to evaluate the effects of high-dose vitamin C on symptoms and survival. Patients were divided randomly into a group that received vitamin C (10 g per day) and one that received a comparably flavored lactose placebo. Sixty evaluable patients received vitamin C and 63 received a placebo. Both groups were similar in age, sex, site of primary tumor, performance score, tumor grade and previous chemotherapy. The two groups showed no appreciable difference in changes in symptoms, performance status, appetite or weight. The median survival for all patients was about seven weeks, and the survival curves essentially overlapped. In this selected group of patients, we were unable to show a therapeutic benefit of high-dose vitamin C treatment. (N Engl J Med 301:687-690, 1979)

THE possible role of vitamin C in both the pathogenesis and therapy of malignant disease has been suggested by a variety of laboratory and clinical data. A deficiency of ascorbate has been reported in association with dissolution of the intercellular matrix, which might facilitate local infiltration and dissemination of neoplastic cells.[1] Studies in laboratory animals have shown that ascorbate seems to concentrate in malignant tissue and thus depletes systemic reserves.[2-4] Moreover, in patients with skin carcinoma, concentrations of vitamin C are higher in the tumor than in surrounding normal tissue.[5] Lymphocytes, mediators of cellular immunity, contain relatively high amounts of ascorbate, and immune responsiveness has been enhanced by ascorbate administration in mice.[6] Moreover, there have been some apparent regressions of adenomas after administration of ascorbate by mouth in persons with familial polyposis coli, a known premalignant condition.[7]

Several nonrandomized studies have suggested that high-dose vitamin C (10 g per day by mouth) might enhance survival and improve symptoms of patients with advanced cancer. Cameron and Campbell studied 50 such patients who had not received chemotherapy and reported five tumor regressions (10 per cent).[8] These authors also reported that most patients experienced some subjective benefit.[8] In a later report, 50 patients who had previously received irradiation and chemotherapy were combined with the first group, and the survival of all 100 patients was compared with that of 1000 historical control cases in the records at the Vale of Leven Hospital, Loch Lomondside, Scotland.[9] For each ascorbate-treated patient, 10 controls were matched on the basis of age, sex, site and histologic features of the primary tumor. The mean survival of patients given ascorbate was 210 days, as compared with 50 for the selected controls. Since this was not a randomized study, doubt has been raised concerning the comparability of ascorbate-treated patients and the control population.[10] Cameron and Pauling therefore revised the original study group to exclude 10 ascorbate-treated patients with unusual cancers; they substituted 10 other patients randomly selected from the records of ascorbate-treated patients at the Vale of Leven Hospital.[11] In addition, a new group of 1000 controls was selected because data on some of the initial control patients were considered unreliable and incomplete. Most of the new controls, however, were drawn from the original control population. This revised and updated analysis showed that the mean survival of patients given vitamin C was greater than 293 days, as compared with 38 for the controls.

Since bias is possible in nonrandomized studies including selected controls, we conducted a randomized, controlled double-blind trial to evaluate the effect of vitamin C on symptoms and survival in patients with advanced and preterminal cancer.

PATIENTS AND METHODS

All patients had histologically documented advanced cancer, and all were able to take medications by mouth. All were unsuitable for treatment with systemic chemotherapy, either because of progression of disease after previous efforts or because their general condition precluded cytotoxic regimens.

Relatively few pediatric patients met the eligibility criteria. No patients had leukemia. Patients were stratified on the basis of a performance score of 2 versus 3 or 4 on the Eastern Cooperative Oncology Group scale (in which a score of 0 indicates a fully active patient, whereas 4 indicates bedridden); patients with a score of 3 or 4 were grouped as one stratum. The patients were also classified on the basis of site of primary tumor (colon, stomach, lung, pancreas, breast and other) and then randomized to one of two groups: those given vitamin C (10 g per day by mouth in four divided doses, or a total of twenty 0.5-g capsules daily) and those given the same number of capsules containing a comparably flavored lactose placebo. Both drugs were given as identical capsules, dispensed in bottles of 1000, which were identified only by code number. The drug supply was renewed at six-week intervals as needed. Neither patient nor investigator knew which drug was being administered. Treatment was continued until death or until the patient was no longer able to take medications by mouth. At two-week intervals, patients reported the amount and frequency of the drug taken, the status of their symptoms and body weight.

A total of 150 patients were entered into the clinical trial. Patient and tumor characteristics for the 123 patients who took the study medication are listed in Tables 1 and 2. Twenty-seven patients elected not to participate after randomization, but before taking the

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Table 1. Patient Characteristics.

Characteristic	Vitamin C Group	Placebo Group
No. of patients	60	63
Age, yr		
≤45	2	4
46–65	26	27
>65	32	32
Sex		
Male	37	39
Female	23	24
Performance score*		
2	12	13
3	39	43
4	9	7

*Eastern Cooperative Oncology Group score: 0 (fully active) to 4 (totally disabled).

first dose of vitamin C or placebo. These patients (12 assigned randomly to the placebo group and 15 to the vitamin C group) were considered unevaluable for comparative drug effects but were analyzed separately for survival. Their characteristics are shown in Table 3.

Chi-square tests of homogeneity were performed to compare the distributions of the following five pretreatment clinical characteristics between the two treatment groups: age, sex, site of primary tumor, initial performance score and previous treatment. Kaplan–Meier survival curves were plotted separately for the two treatment groups and tested for inequality by use of the Gehan–Wilcoxon and log-rank tests. A Cox covariate analysis was performed, using the survival data from the 123 treated patients.[12]

Results

Survival

The survival curves for the 123 patients treated with vitamin C and with placebo are shown in Figure 1. There was no significant difference in survival between the two groups (log-rank test; $P = 0.61$). We were unable to show any survival benefit according to tumor site. Note that the two treatment groups are evenly balanced in age, sex, site of primary tumor, initial performance status and previous treatment (Tables 1 and 2).

Table 2. Tumor Characteristics and Previous Treatment.

Characteristic	Vitamin C Group	Placebo Group
No. of patients	60	63
Site		
Colorectal	24	26
Pancreas	12	12
Lung	6	6
Stomach	5	3
Other	13	16
Grade of anaplasia (Broder's)		
1, 2	29	27
3, 4	17	23
Not stated	14	13
Previous treatment		
None	5	4
Radiation therapy	17	18
Chemotherapy	52	56

Cox covariate analysis showed that none of the six potentially prognostic factors was significantly associated with survival in the 123 treated patients. Only performance score was even marginally associated ($P = 0.08$) after taking into account the effects of the remaining factors.

The one long-term survivor in this study is a patient with metastatic islet-cell carcinoma, massive hepatomegaly and jaundice who had shown no response to many previous attempts at chemotherapy. After entering the study, he showed improvement in symptoms and some reduction in serum bilirubin. He was still alive 63 weeks after entering the study. This patient received the lactose placebo.

Table 3. Characteristics of 27 Patients Who Took No Study Drug.

Characteristic	No. of Patients
Age, yr	
≤45	1
46–65	13
>65	13
Sex	
Male	19
Female	8
Performance score*	
2	3
3	19
4	5
Previous treatment	
None	7
Radiation therapy	9
Chemotherapy	17
Site of primary tumor	
Colorectal	4
Pancreas	4
Lung	4
Stomach	4
Other	11
Grade of anaplasia (Broder's)	
1, 2	6
3, 4	16
Not stated	5

*Eastern Cooperative Oncology Group score: 0 (fully active) to 4 (totally disabled).

Symptom Reduction and Side Effects

Fifty-eight per cent of the patients given the placebo and 63 per cent of those given vitamin C claimed some improvement in symptoms during treatment. There were no statistically significant differences in symptoms between the two treatment groups (Table 4).

Mild nausea and vomiting were the most frequent toxic reactions, affecting about 40 per cent of patients, but there were no statistically significant differences in

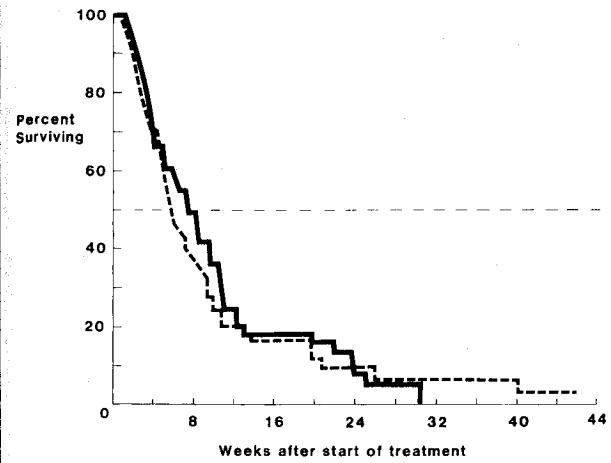

Figure 1. High-Dose Vitamin C versus Placebo and Survival Results in Patients with Advanced Cancer.

The solid line shows survival in 60 patients given vitamin C. The dashed line shows survival in 63 patients given the lactose placebo.

the number of episodes between the two groups (Table 4). There was no noteworthy excess of heartburn or other upper-gastrointestinal-tract symptoms in patients given vitamin C, nor was there any documented occurrence of renal calculi.

Analysis of Untreated Patients

An interesting group of patients in this study are those who accepted randomization but subsequently elected not to participate. These patients, in a nonrandomized study, would be presumed to be included only in the nontreated historical controls (Table 3). These patients were excluded from the above analysis because they would not show evidence of the effect of vitamin C or placebo.

The 27 patients who did not receive treatment had a significantly worse (log-rank test; $P = 0.017$) survival than the 123 patients who did take the medication. The median survival in the untreated patients was 25 days, as compared with 51 for treated patients.

Discussion

We were unable to demonstrate any statistically significant benefit of high-dose vitamin C in selected patients with advanced cancer. It should be noted, however, that only nine of our 123 patients had not previously received chemotherapy or radiation therapy. It is therefore impossible to draw any conclusions about the possible effectiveness of vitamin C in previously untreated patients. In Cameron and Campbell's report of a 10 per cent regression rate in 50 patients with widely disseminated cancer, none had received definitive prior treatment and presumably were more immunocompetent than our patients. Since vitamin C may have an impact on host resistance to cancer,[13] we recognize that earlier immunosuppressive treatment might have obscured any benefit provided by this agent. Nevertheless, the nonrandomized study[9] that showed a fourfold enhancement of survival with vitamin C included patients who had received conventional cancer treatment (i.e., cytotoxic agents and radiation therapy). This improvement could not be substantiated by our study.

There is evidence that vitamin C maintains immunocompetence. Although patients with advanced cancer who have previously been treated with irradiation or chemotherapy are indeed immunosuppressed, they are not totally incapable of mounting an immune response. In two previous studies of patients with advanced cancer who were selected on the basis of essentially the same criteria used in this study, we found that 80 per cent were capable of responding to recall skin tests (O'Connell MJ, O'Fallon JR, Ritts RE, et al: unpublished data), and 56 per cent responded to dinitrochlorobenzene.[14] One might expect, therefore, that vitamin C would exert some restorative influence in patients whose immune apparatus has been compromised by earlier treatment efforts. If such an effect did occur in our patients, it was not seen in their clinical improvement.

Table 4. Symptomatic Results and Side Effects.

	Vitamin C Group		Placebo Group	
	no.	%	no.	%
Improvement				
Appetite	14/53	26	12/52	23
Strength	14/53	26	7/53	13
Activity level	22/53	42	22/53	42
Pain control	12/49	24	7/48	15
Toxicity				
Nausea	27/60	45	27/63	43
Vomiting	22/60	37	22/63	35
Heartburn	16/60	27	15/63	24
Diarrhea	20/60	33	20/63	32
Leg swelling	34/60	57	28/63	44
Other	30/60	50	26/63	41

We cannot recommend the use of high-dose vitamin C in patients with advanced cancer who have previously received irradiation or chemotherapy.

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SPECIAL ARTICLES

LEARNING IN MEDICINE

D. C. TOSTESON, M.D.

"MEDICINE begins in philosophy; philosophy ends in medicine" is an aphorism attributed to Aristotle. I like its demand to connect our thinking as physicians with our thinking in other dimensions. I begin by asking the question: If medicine begins in philosophy, what is the philosophy? I do so in the belief that we stand in serious need of revised designs for medical education and that any such designs must be based on an answer to this question.

I will develop the thesis that practicing medicine is a kind of problem solving. Physicians help their patients to face, define and solve problems that threaten their health and lives. Words like "diagnosis," "treatment" and "management" make the point. I take problem solving to be another name for learning. Medicine, then, is certain kinds of learning. The philosophy in which medicine begins is a devotion to learning — a devotion built on the faith and hope that we can do something about the problems that limit our lives. Several lines of reflection lead me to this conclusion.

Each medical encounter is unique in a personal, social and biologic sense. Each patient and physician is an individual person reminded by the episode that brings them together that "brass, nor stone, nor earth, nor boundless sea, but sad mortality o'ersways their power."[1] Each patient lives in a specific social context. Each patient is the expression of a genome that has never existed before. All these aspects of uniqueness impose on both physician and patient the need to learn about the always new situation, to find the plan of action that is most likely to improve the health of that particular patient at that particular time. In this way of thinking, a doctor is a teacher helping the patient to learn about possibilities for living in a healthier way.

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The importance of learning in medicine also derives from the vast breadth and depth of the subject. It is hard to identify an element of human inquiry that falls clearly outside the scope of medicine. It spans the natural sciences, the social sciences, the humanities and other professions, such as law and business. The breadth of medicine means that no individual physician can continually store the entire range of information that may be important in a particular clinical problem. It is usually necessary to search for, to learn, the relevant information.

Medicine is not only broad but also deep. For example, the conclusion of Frederick Sanger's Dunham Lectures this year at the Harvard Medical School was the revelation that the code in the circular DNA of a bacteriophage reads out in three phases[2] — an insight of as yet obscure but potentially great importance for the future of medicine. On the other hand, there are no more profound ethical issues than those surrounding in vitro fertilization and implantation of human embryos. To explore these depths is the essence of higher learning.

Finally, medicine is clearly not in a static state but, rather, in a very dynamic state. The rate of accumulation of new knowledge is increasing because of the cooperative nature of learning. The dynamism of medicine demands continuing learning from those who would practice competently. For these and other reasons, I believe that medicine is best understood as a kind of learning and that this philosophy should animate medical education.

It follows that the goal of medical education is to prepare persons to learn in medicine. I will describe three important elements in this process, which I think are inadequately addressed at present and should be included in revised designs for medical education: defining more clearly the ideas that we expect all physicians to share, placing greater emphasis on the technics of information management and problem solving, and giving more encouragement to the desire of doctors to continue learning in medicine.