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

A Controlled Trial

EDWARD T. CREAGAN, M.D., CHARLES G. MOERTEL, M.D., JUDITH R. O'FALLON, PH.D., ALLAN J. SCHUTT, M.D., MICHAEL J. O'CONNELL, M.D., JOSEPH RUBIN, M.D., AND STEPHEN FRYTAK, M.D.

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

From the Division of Medical Oncology and the Cancer Statistics Unit, Mayo Clinic, Rochester, MN 55901, where reprint requests should be addressed to Dr. Creagan.

Supported in part by a contract (CM 02066) with the National Institutes of Health.

D-12

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

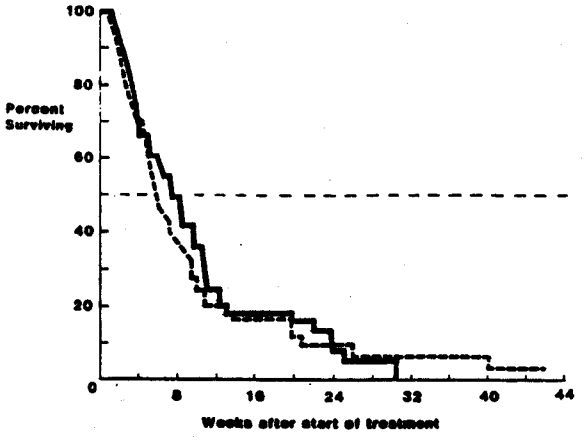

Figure 1. High-Dose Vitamin C versus Placebo and Survival Results in Patients with Advanced Cancer.

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.

We are indebted to Mrs. H. Golenzer, Mrs. T. Hu and Mrs. R. Rogers for their support and cooperation.

References

1. Cameron E, Pauling L, Leibovitz B: Ascorbic acid and cancer: a review. Cancer Res 39:663-681, 1979
2. Boyland E: The selective absorption of ascorbic acid by guinea-pig tumour tissue. Biochem J 30:1221-1224, 1936
3. Sure B, Theis RM, Harrelson RT: Influence of Walker carcinosarcoma on concentration of ascorbic acid in various endocrines and organs. Am J Cancer 36:252-256, 1939
4. Watson AF: The chemical reducing capacity and vitamin C content of transplantable tumours of the rat and guinea-pig. Br J Exp Pathol 17:124-134, 1936
5. Moriarty MJ, Mulgrew S, Malone JR, et al: Results and analysis of tumour levels of ascorbic acid. Ir J Med Sci 146:74-78, 1977
6. Siegel BV, Morton JI: Vitamin C and the immune response. Experientia 33:393-395, 1977
7. DeCosse JJ, Adams MB, Kuzma JF, et al: Effect of ascorbic acid on

rectal polyps of patients with familial polyposis. Surgery 78:608-612, 1975
8. Cameron E, Campbell A: The orthomolecular treatment of cancer. II. Clinical trial of high-dose ascorbic acid supplements in advanced human cancer. Chem Biol Interact 9:285-315, 1974
9. Cameron E, Pauling L: Supplemental ascorbate in the supportive treatment of cancer: prolongation of survival times in terminal human cancer. Proc Natl Acad Sci USA 73:3685-3689, 1976
10. Comroe JH Jr: Experimental studies designed to evaluate the management of patients with curable cancer. Proc Natl Acad Sci USA 75:4543, 1978
11. Cameron E, Pauling L: Supplemental ascorbate in the supportive treatment of cancer: reevaluation of prolongation of survival times in terminal human cancer. Proc Natl Acad Sci USA 75:4538-4542, 1978
12. Cox DR: Regression models and life-tables. J R Stat Soc (B) 34:187-220, 1972
13. Cameron E, Pauling L: The orthomolecular treatment of cancer. I. The role of ascorbic acid in host resistance. Chem Biol Interact 9:273-283, 1974
14. Moertel CG, Ritts RE Jr, Schutt AJ, et al: Clinical studies of methanol extraction residue fraction of *Bacillus Calmette-Guérin* as an immunostimulant in patients with advanced cancer. Cancer Res 35:3075-3083, 1975

NEJM 301(25):1399 DEC. 20, 1979

VITAMIN C THERAPY OF ADVANCED CANCER

To the Editor: This letter is written out of courtesy to Dr. Linus Pauling, who has requested that we clarify an introductory statement in our article pertaining to vitamin C therapy for advanced cancer.[1]

In the 1976 report covering their nonrandomized observations of 100 terminal cancer patients treated with high-dose vitamin C, Cameron and Pauling stated "All of the patients are treated initially in a perfectly conventional way, by operation, use of radiotherapy, and administration of hormones and cytotoxic substances."[2]

On the basis of this statement, we stated that their patients had received radiation and chemotherapy. Drs. Pauling and Cameron have subsequently informed us that because of the prevailing standards of cancer treatment in Scotland at that time, only four of their 100 patients had actually received chemotherapy, and only 20 had received irradiation. Therefore, our study differs from that of Cameron and Pauling, not only because our study was randomized, double-blind and placebo controlled, but also because our study included a greater proportion of patients previously given chemotherapy. Dr. Pauling believes that prior chemotherapy may have negated the benefits of vitamin C.

We must of course stand by our conclusions that high-dose vitamin C is of no value in patients who have been treated in a conventional manner according to accepted standards of cancer management in the United States today. Any contention that previous chemotherapy prevented our patients from achieving the extraordinary survival increase claimed by Drs. Cameron and Pauling must be considered highly speculative at best. Our patients were entered into the study only when they were well beyond any acute immunosuppressive effects of previous therapy. Our earlier studies in patients similarly selected indicated that the great majority are capable of mounting a definite immune response to both recall antigens and de novo sensitization.[3] Nevertheless, as we stated in our manuscript, the results of our investigation can be applied directly only to the population we studied.

On the basis of available evidence, we do not consider it conscionable to withhold oncologic therapy of known value to give the cancer patient large amounts of vitamin C. Any claims for benefit from high-dose vitamin C at any stage of malignant disease remain to be established by properly designed prospective, randomized, and concurrently controlled studies. We hope that Drs. Pauling and Cameron will agree that such scientifically acceptable evidence should be obtained before this treatment is publicly advocated for clinical use.

EDWARD T. CREAGAN, M.D.
CHARLES MOERTEL, M.D.
Mayo Clinic
Rochester, MN 55455

1. Creagan ET, Moertel CG, O'Fallon JR, et al: Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer: a controlled trial. N Engl J Med 301:687-690, 1979
2. Cameron E, Pauling L: Supplemental ascorbate in the supportive treatment of cancer: prolongation of survival times in terminal human cancer. Proc Natl Acad Sci USA 73:3685-3689, 1976
3. Moertel CG, Ritts RE Jr, Schutt AJ, et al: Clinical studies of methanol extraction residue fraction of *Bacillus Calmette-Guérin* as an immunostimulant in patients with advanced cancer. Cancer Res 35:3075-3083, 1975

EXCERPTED FROM DiPalma, JR & McMichael, R.
"THE INTERACTION OF VITAMINS WITH CANCER CHEMOTHERAPY." CA- A CANCER JOURNAL FOR CLINICIANS
29(5): 280-286 (1979)

Vitamin C

The so-called "Orthomolecular Therapy" of cancer with "megadoses" of vitamin C (up to 10 grams a day) has received a great deal of popular attention. The beneficial actions claimed are:

- relief of pain from skeletal metastases;
- reduction of opiate dosage;
- correction of high urinary hydroxyproline;
- tumor regression and prolonged life expectancy.[19-22]

However, evidence for benefit is based on uncontrolled and non-randomized clinical trials. While therapeutic actions remain unconfirmed by other researchers or by a well-conducted clinical trial, there has been considerable effort expended to discover a secure experimental basis. It is claimed that vitamin C either slows down or stops the growth of malignant cells by inhibiting the action of hyaluronidase, the substance necessary for cell division, proliferation and migration.[23] Recently, all the possible mechanisms of potential beneficial action have been reviewed.[24]

In lung cultures, the addition of either L-cysteine or ascorbic acid to the medium protects against the abnormal growth and malignant transformation induced by exposure to smoke from tobacco or marijuana cigarettes. This protection was afforded to both young and old cultures.[25] Decrease of DNA synthesis and neoplastic cell proliferation have been observed for ascorbic acid in tumor cell lines in culture.[26] A mutagenic action of vitamin C has been demonstrated in fibroblast cultures.[27] Tumor bearing guinea pigs require ascorbic acid for tumor growth.[28] Thus, it is seen even in this brief review that at least experimentally there is ample evidence of an interaction of vitamin C with both neoplastic cells and carcinogenic agents.

It is not entirely true that vitamin C therapy is without risk. When taken in daily gram amounts for prolonged periods, vitamin C can be toxic.[8] Perhaps its most serious reaction is the depression of B_{12} serum levels that may lead to bone marrow changes.[29-31] The utilization and distribution of B_{12} is a factor in carcinogenesis. Consequently, the effect of vitamin C upon Vitamin B_{12} may be indirectly involved in the problem of carcinogenesis.

The relationship of vitamin C therapy to the radiosensitivity of neoplastic tissues is also significant because inhibition of cellular oxidation protects tumors against radiation to a considerable degree. The chemical reaction of ascorbate with radiation induced radicals and the resulting additional oxygen consumption may produce a greater degree of hypoxia and subsequent radioprotection. Drugs such as metronidazol and Flagyl (which inhibit cellular oxygen consumption) cause reoxygenation of tumor tissue and hence increase radiosensitivity.[32] Obviously, patients taking large amounts of ascorbic acid are subject to an inhibiting interaction with radiosensitizing drugs and this should be guarded against.

REFERENCES

8. ANN REV PHARMACOL TOXICOL 17: 133-147 (1977)
19. CHEM BIOL INTERACT 9: 285-315 (1974)
20. RES COMMUN SYSTEMS (8/1973)
21. CHEM BIOL INTERACT 11: 387-393 (1975)
22. EUR. J. CANCER 10: 507-511 (1974)
23. ONCOLOGY 27: 191-192 (1973)
24. CANCER RES 39: 663-681 (1979)
25. BR. J. EXP. PATHOL 58: 625-631 (1977)
26. ONCOLOGY 35: 160-162 (1978)
27. NATURE 260: 722-724 (1976)
28. BR. J. CANCER 35: 448-453 (1977)
29. JAMA 230: 241-242 (1974)
30. JAMA 234: 24 (1975)
31. AM J. CLIN NUTR 31: 253-258 (1978)
32. BR. J. RADIOL 50: 644-646 (1977)

D-15

NEJM 302,5:1980 298-300

VITAMIN C FOR CANCER

To the Editor: In their article on high-dose vitamin C in patients th advanced cancer,* Creagan and his colleagues note only in passing that the patients who cooperated in the experiment, whether subjects or controls, had a statistically significant increased survival time (almost double) over that of clinically comparable patients who chose not to participate. The nonparticipants would be a very interesting group to know about. Were there other, unidentified differences in their clinical status that led them to withdraw before the study? Were there demonstrable or observable psychologic differences? Specifically, did they resign themselves to illness and imminent demise? Did those who withdrew receive different or even less active medical care?

MARTIN L. ROSSMAN, M.D.
WILLIAM S. BROSTOFF, M.D.
University of California
San Francisco, CA 94143 School of Medicine

To the Editor: The authors of the recently published Mayo Clinic trial claim to have shown no significant benefit from high-dose vitamin C in patients with advanced cancer. In my judgment, their findings could lead to exactly the opposite conclusion.

Of the 150 patients initially selected for study, 27 elected not to participate in the Mayo Clinic trial. These nonparticipants were initially indistinguishable from the remainder on the basis of age, sex, performance score, previous treatment, site of primary tumor, and grade of anaplasia; yet their survival time proved to be very much shorter than that of either the test or control groups. Thus, 60 patients with advanced cancer given ascorbate lived on the average somewhat longer than 63 similar patients given a lactose placebo, but both these groups lived more than twice as long as comparable patients given no treatment. I would suspect very strongly that among those patients dying of cancer who gave informed consent to take part in a study to determine whether vitamin C had any value in advanced cancer, many took the precaution of ensuring that they were not in the control group by simply purchasing vitamin C at the corner drugstore. This is a perfectly understandable human response; it could so easily have been checked by simple blood or urine tests to identify who in fact was ingesting high levels of vitamin C irrespective of randomization. If my suspicions are correct, the Mayo Clinic findings are positive and important, indicating that, in spite of heavy preceding radiation therapy and chemotherapy, a group of 123 patients with advanced cancer, the majority of whom may have been ingesting high levels of vitamin C, lived more than twice as long as a smaller group of untreated but otherwise identical controls.

I trust that our colleagues at the Mayo Clinic and elsewhere will continue their studies to determine the truth of this most important issue.

Alexandria, G83 OUA, Scotland
EWAN CAMERON, M.D., F.R.C.S.
Vale of Leven District General Hospital

To the Editor: We were surprised that Creagan and his coauthors failed to attach any importance to their finding that the 123 treated patients, those who received either placebo or vitamin C, lived twice as long as the 27 untreated pateints (51 days vs. 25 days). In addition, they failed to discuss the fact that more than half the treated population reported symptomatic improvement in appetite, strength, activity level, or pain control during treatment.

We view these as very important results that demonstrate that vitamin C does influence the course of advanced cancer. The fact that a placebo yields similar results offers a clue to the possible mechanism of vitamins and other alternative therapies in the treatment of cancer. We are referring to the placebo effect. In an earlier article in the *Journal*, the important role of the placebo effect in relieving anginal pain was discussed.* Dr. Creagan and his coworkers have demonstrated in their article that the placebo effect can also be important in the treatment of cancer patients.

DAVID SMALL
EDITH S. GERINGER
State University of New York at Buffalo
Buffalo, NY 14214 School of Medicine

*Benson H, McCallie DP Jr. Angina pectoris and the placebo effect. N Engl J Med. 1979; 300:1424-9.

To the Editor: The study by Creagan and his co-workers cannot be taken as proof that vitamin C is ineffective in cancer patients or that the successful results achieved by Cameron are not reproducible. Creagan et al. studied patients with terminal cancer whose average survival time proved to be seven weeks from the start of the study. At this advanced stage, the secretion of digestive juices is diminished, and absorption is impaired. The disintegration of capsules and the absorption of their contents is therefore affected; this is well known in cytostatic therapy. For example, the biologic availability of 5-fluorouracil in capsules varies more than that of the drug in oral solution.

Whereas Cameron gave vitamin C in oral solution containing sorbitol (a sugar that enhances absorption of vitamins*), Creagan et al. administered vitamin C in 20 capsules daily and did not even determine the blood levels to confirm absorption. Moreover, it is questionable whether the patients really did take this large number of capsules daily.

Conclusion: Further investigations must be made to elucidate the action of vitamin C and sorbitol in patients with cancer.

CLEWIN H. ZAESLEIN, M.D.
CH-4056 Basel, Switzerland 112 Mittlere Strasse

*The Merck index. 9th ed. Rahway, N.J.: Merck, 1976:1126-7.

The New England
Journal of Medicine

Volume 312 JANUARY 17, 1985 Number 3

HIGH-DOSE VITAMIN C VERSUS PLACEBO IN THE TREATMENT OF PATIENTS WITH ADVANCED CANCER WHO HAVE HAD NO PRIOR CHEMOTHERAPY

A Randomized Double-Blind Comparison

CHARLES G. MOERTEL, M.D., THOMAS R. FLEMING, PH.D., EDWARD T. CREAGAN, M.D., JOSEPH RUBIN, M.D., MICHAEL J. O'CONNELL, M.D., AND MATTHEW M. AMES, PH.D.

Abstract It has been claimed that high-dose vitamin C is beneficial in the treatment of patients with advanced cancer, especially patients who have had no prior chemotherapy. In a double-blind study 100 patients with advanced colorectal cancer were randomly assigned to treatment with either high-dose vitamin C (10 g daily) or placebo. Overall, these patients were in very good general condition, with minimal symptoms. None had received any previous treatment with cytotoxic drugs. Vitamin C therapy showed no advantage over placebo therapy with regard to either the interval between the beginning of treatment and disease progression or patient survival. Among patients with measurable disease, none had objective improvement. On the basis of this and our previous randomized study, it can be concluded that high-dose vitamin C therapy is not effective against advanced malignant disease regardless of whether the patient has had any prior chemotherapy. (N Engl J Med 1985; 312:137-41.)

IN 1974 a report by Cameron and Campbell raised the possibility that high-dose vitamin C might be [illegible]value in the treatment of advanced cancer.[1] It stat[illegible] that among 50 patients who were treated with vitamin C at a daily dose of 10 g, 5 had objective tumor regressions. Later, Pauling joined Cameron in reporting an expansion of this series to 100 patients.[2] They compared their treated patient group with 1000 historical control patients drawn from a review of records at the Vale of Leven Hospital, Loch Lomonside, Scotland. They claimed a striking survival advantage for their patients treated with vitamin C, who had a mean survival of 210 days as compared with 50 days for the selected control patients. In a later report they revised their study by replacing 10 of their initial treated patients with 10 new ones and replacing approximately 50 per cent of their 1000 historical controls.[3] In this revised version, the survival of patients taking vitamin C, from the date when their disease became untreatable, was increased to a mean of 293 days or more, and that of the controls was decreased to 38 days. This extraordinary survival gain with simple and relatively nontoxic therapy, particularly when reported by a Nobel laureate (Pauling), quite naturally attracted considerable public attention as well as causing widespread use of this treatment by patients with advanced cancer. The validity of this therapeutic claim, however, could be subject to question because historically controlled studies in the treatment of both malignant and nonmalignant diseases have frequently produced results that could not be confirmed by more scientifically rigorous prospective and randomized studies.

We had previously attempted to validate the results of Cameron and Pauling in a prospective randomized trial that was double blinded to prevent any inadvertent bias.[4] We selected patients for study according to the published criteria of Cameron and Pauling: i.e., all the patients had proved terminal cancer and "all were treated initially in a perfectly conventional manner by operation, use of radiation therapy, and administration of hormones and cytotoxic substances."[2] The survival curves of our vitamin C–treated and our placebo-treated patients were essentially identical.

In the randomized double-blind study mentioned above, patients were chosen to match the published description of the patients chosen by Cameron and Pauling — i.e., all the patients had previously been treated by conventional means, including the use of cytotoxic drugs. The majority of patients in that randomized study had received prior chemotherapy. In discussions of our initial study, Dr. Pauling stated that, in fact, only 4 of their 100 patients had been treated with cytotoxic drugs, since chemotherapy was not frequently employed at the Vale of Leven Hospital.[5] He speculated that our study did not duplicate the strongly positive results he had reported because "the cytotoxic drugs damage the body's protective mechanisms, and vitamin C probably functions largely by potentiating these mechanisms." Although the

From the Mayo Clinic and Mayo Foundation, Rochester, Minn. Address reprint requests to Dr. Moertel at the Mayo Clinic, Rochester, MN 55905.

Supported in part by a Public Health Service grant (CA 31224) and a Research Career Development Award (CA 00755 [Dr. Ames]) from the National Cancer Institute.