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Supplemental ascorbate in the supportive treatment of cancer: Reevaluation of prolongation of survival times in terminal human cancer*

(vitamin C)

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ABSTRACT **A study has been made of the survival times of 100 terminal cancer patients who were given supplemental ascorbate, usually 10 g/day, as part of their routine management and 1000 matched controls, similar patients who had received the same treatment except for the ascorbate. The two sets of patients were in part the same as those used in our earlier study [Cameron, E. & Pauling, L. (1976) *Proc. Natl. Acad. Sci. USA* 73, 3685–3689]. Tests confirm that the ascorbate-treated patients and the matched controls are representative subpopulations of the same population of "untreatable" patients. Survival times were measured not only from the date of "untreatability" but also from the precisely known date of first hospital attendance for the cancer that eventually reached the terminal stage. The ascorbate-treated patients were found to have a mean survival time about 300 days greater than that of the controls. Survival times greater than 1 yr after the date of untreatability were observed for 22% of the ascorbate-treated patients and for 0.4% of the controls. The mean survival time of these 22 ascorbate-treated patients is 2.4 yr after reaching the apparently terminal stage; 8 of the ascorbate-treated patients are still alive, with a mean survival time after untreatability of 3.5 yr.**

A year and a half ago we reported (1) the results of a clinical trial in which 100 terminal cancer patients were given supplemental sodium ascorbate (usually 10 g/day) as part of their routine management, with their progress compared with that of 1000 similar patients who were treated identically (by the same clinicians in the same hospital) except that they received no supplemental ascorbate. The reported mean survival time after the patient had been recognized to be terminal ("untreatable" in Scottish medical practice) was more than 210 days for the ascorbate subjects and 50 days for their matched controls. Analysis of the survival-time curves indicated that deaths occur for about 90% of the ascorbate-treated patients at one-third the rate for the controls and that the other 10% have a much greater survival time. The results seemed clearly to indicate that this simple and safe form of medication is of definite value in the treatment of patients with advanced cancer.

Several experienced investigators in this field have expressed to us their doubt as to whether the ascorbate-treated patients and their controls comprised representative subpopulations of the same population and whether comparable times of untreatability had been assigned to the two groups. We decided to investigate these questions.

A new set of control patients was selected, and tests were carried out, as described in the following paragraphs, to answer the questions that had been raised. Our conclusion is that the results previously reported are valid, and, in fact, the increase in life expectancy of ascorbate-treated patients with terminal cancer is found to be somewhat larger than was previously reported.

Selection of the controls

The original group of matched controls was selected by senior members of the Medical Records Staff in Vale of Leven Hospital, who were asked to produce records of 10 patients for each ascorbate-treated patient matched as to sex, age (to within 5 yr), and tumor type (site of the primary cancer and histological type), without regard as to whether or not death had occurred. The individual case records were then examined by a physician employed for this purpose, Frances Meuli, who first determined the date of untreatability by such conventional standards as the establishment of inoperability at laparotomy, the abandonment of any definitive form of anti-cancer treatment, or the date of admission for terminal nursing care and then calculated the survival time from that date until the factually recorded date of death. In carrying out her survey, Meuli was unaware of the survival times of the 100 ascorbate-treated test patients. In order to avoid possible bias, we did not supervise her work closely or attempt to refine it.

When we decided to check some of the other characteristics of these patients in more detail, as listed below, our examination of the records showed that, for some of the controls, the date of untreatability selected by Meuli was unreliable, sometimes because of incompleteness of the records and sometimes because of the death of these registered cancer patients from some intercurrent illness. Moreover, for some of the 100 original ascorbate-treated patients (no. 68, 77, 84, 89, 90, 91, 92, 93, 95, and 98), mostly with rather rare forms of cancer, the selected controls were found not to match sufficiently closely. We have accordingly replaced these 10 ascorbate-treated patients with 10 others, as determined by the availability of suitable controls, randomly selected from the more than 500 terminal cancer patients who have now received ascorbate treatment in Vale of Leven Hospital.

A fresh selection of a set of 1000 matched controls was then carried out. The new set, which overlaps largely with the first one, was again selected by the Medical Records Staff, and the selection was checked by one of us (E.C.) and our research assistant, Anita McLaren, who carefully studied each invididual case record to determine its suitability as a control and to establish for each patient, whenever possible, the following recorded dates: (*i*) appearance of first symptom or sign of cancer; (*ii*) first hospital attendance because of the cancer that eventually reached the terminal stage; (*iii*) when any form of definitive anticancer treatment, believed at that time to be po-

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tentially curative, was instituted; (*iv*) when any form of definite anticancer treatment, recognized at that time to be only palliative, was instituted; (*v*) classification as untreatable, when treatment, other than for control of pain and general nursing care, had been discontinued; and (*vi*) death. Such dates were established for both the ascorbate group and the control group. In addition, for the ascorbate group the date when supplemental ascorbate was commenced was noted (usually coincident with or a few days later than the date of untreatability).

Comparison of ascorbate-treated patients and their matched controls

In table 1 of our earlier paper, the survival times (after the date of untreatability) of each of the 1100 subjects of that study were given. The corresponding values with the new set of controls are very similar, and we present in Table 1 of the present paper only the survival times of the ascorbate-treated patients after the date of first hospital attendance for the cancer that became untreatable, their survival times after the date of untreatability, and the corresponding mean values for the matched controls. (In 2.6% of the selected controls the records did not permit the date of untreatability to be reliably determined; these are patients whose date of death has been established but who had been lost to hospital follow-up in the intervening period. These controls were not used in determining the mean value of the second survival time.) The survival times of the patients who are still living are for the date 15 May 1978.

A test of the controls

As would be expected, there is a considerable difference in the survival times of patients with different primary cancers. We have accordingly divided the 100 ascorbate-treated patients into nine groups: 17 with colon as the site of the primary cancer (with 170 controls), 13 stomach, 17 bronchus, 11 breast, 8 kidney, 7 rectum, 7 bladder, 6 ovary, and 14 others. The treatment with ascorbate was begun only at the time when the patient was deemed untreatable; before that date, the history of those patients was no different from that of their controls. If the ascorbate-treated patients and their controls constitute representative subpopulations of the same population–that is, if they were randomly selected and if, in addition, the date of untreatability was determined in the same way for the two groups–the number of days between the date of first hospital attendance and the date of untreatability would be the same for the two groups, except for statistical fluctuations. We have accordingly made this comparison in several ways. In every trial, the calculation has provided no basis for the rejection of the null hypothesis with statistical significance. For example, the time between date of first hospital attendance and date of untreatability is greater than 1 yr for 27% of the ascorbate-treated group and for 23% of their controls; these numbers are not significantly different.

We carried out the nonparametric Wilcoxon matched-pairs signed-ranks test for each of the nine groups mentioned above in the following manner. The position, −5 to +5, of each ascorbate-treated patient in the individual set of 11 (the patient and 10 controls) as determined by the number of days from first hospital attendance to untreatability was taken as the magnitude of the difference between the two members (patient and controls) of the matched pair, and the Wilcoxon procedure was used to calculate the value of P. For eight of the nine groups, the value of P (two-tailed) was greater than 0.10, and for the ninth (cancer of the rectum), a value $P = 0.07$ was obtained. Inasmuch as with nine trials it is expected that one will give $P < 0.11$ because of statistical fluctuation, this result does not contradict the null hypothesis.

We conclude that the ascorbate-treated patients and their controls do represent randomly selected subpopulations of the same population of terminal cancer patients and that no systematic error has been made in the determination of the dates of untreatability.

The effect of ascorbate

Information about the progress of 100 terminal cancer patients who received supplemental ascorbate and 1000 matched controls (treated identically but without supplemental ascorbate) as selected in this second study is presented in Table 1. Because of the statistical and other reasons already given, we contend that this information provides an even better basis for comparison than the pilot-study information reported in our previous communication (1).

Columns C and D of Table 1 list the survival time of each ascorbate-treated cancer patient and the mean survival time of their 10 individually matched controls measured from the date of untreatability. (The distributions of values for the new sets of 10 controls are broadly similar to those for the old sets, as given in table 1 of ref. 1, and it is not necessary to publish individual values.) Columns A and B of Table 1 list the corresponding survival times as measured from the date of first hospital attendance; there can be no uncertainty about these dates, which are systematically recorded on each individual case record. The survival times measured from them accordingly provide a useful check on those measured from the date of untreatability.

Values of average survival times measured from each of the two reference dates are given for ascorbate-treated patients and matched controls in the nine categories (colon, bronchus, stomach, breast, kidney, bladder, rectum, ovary, and others) in Table 2. In every category and for both reference dates, the mean survival times are greater for the ascorbate-treated patients than for their controls. The probability that this would occur through a chance statistical fluctuation is only 4×10^{-6} The extension of survival time by ascorbate relative to the date of first hospital attendance (column E) is greater than that relative to the date of untreatability (column F) in four categories and smaller in five. The differences between the values in these two columns are not statistically significant; they can be accounted for as resulting from a few very large values of the time between first hospital attendance and untreatability. For example, if patients 62 and 63 had the same survival time as the average for the other five in the bladder carcinoma group, the value in column E of Table 2 would be 328+ and thus only slightly less than the corresponding value in column F, rather than greater. This change would also decrease the value for all patients in column E from 321+ to 248+, just about equal to that in column F. There are eight values greater than 2000 days in column A of Table 1 and only two in column C; the chance of a large fluctuation is accordingly somewhat greater for the average survival time measured from the date of first hospital attendance than for the average survival time measured from the date of untreatability. On the other hand, the date of first hospital attendance is quite definite, whereas there is some uncertainty (in our opinion, however, not very great) in the date of untreatability so that it seems reasonable to assign equal weights to the values in columns E and F. We thus obtain the mean value 288+ days as the increase in survival time of the ascorbate-treated patients relative to their matched controls in the present study. The standard error of this mean, calculated on the unreliable assumption of a standard distribution of the values in Table 2, is about 50 days.

The values in column G relate to the ascorbate patients and controls previously reported (1), adjusted to include the addi-

Table 1. Comparison of times of survival of 100 cancer patients who received ascorbate and 1000 matched patients with no treatment (second set), by site of primary cancer*

Case	Sex	Age, yr	Survival, days† A	B	C	D
			Stomach			
1	F	61	124	264	124	38
2	M	69	42	62	12	18
3	F	62	25	149	19	36
4	F	66	45	18	45	12
5	M	63	412	180	257	64
6	M	79	51	142	23	20
7	M	76	1112	35	128	13
8	M	54	46	299	46	51
9	M	62	103	85	90	10
10	F	69	876+	69	876+	19
11	M	46	146	361	123	52
12	M	57	340	269	310	28
95	F	59	396	130	359	55
			Bronchus			
13	M	74	81	72	74	33
14	M	74	461	134	423	18
15	M	66	20	84	16	20
16	M	52	450	98	450	58
17	F	48	246	48	87	13
18	F	64	166	142	115	49
19	M	70	63	113	50	38
20	M	77	64	90	50	24
21	M	71	155	30	113	18
22	M	70	859+	56	857+	18
23	M	39	151	260	38	34
24	M	70	166	116	156	20
25	M	70	37	87	27	27
91	M	55	223	69	218	32
93	M	74	138	100	138	27
97	M	69	72	315	39	39
98	M	73	245	188	231	65
			Colon			
28	F	76	248	292	135	18
29	F	58	377	492	50	30
30	M	49	189	462	189	65
31	M	69	1843	235	1267	17
32	F	70	180	294	155	57
33	F	68	537	144	534	16
34	M	50	519	643	502	25
35	F	74	455	301	126	21
36	M	66	406	148	90	17
37	F	76	365	641	365	42
38	F	56	942	272	911	40
77	M	65	776+	198	743+	14
84	F	74	372	37	366	28
90	M	58	163	199	156	31
92	F	60	101	154	99	28
99	M	77	20	649	20	33
100	M	38	283	162	274	80
			Rectum			
39	F	56	185	422	62	38
40	F	75	479	82	226	10
41	F	57	875	551	437	62
42	M	56	115	140	85	13
43	M	68	362	106	122	36
44	M	54	244	645	198	80
45	M	59	2175	407	759	64
			Ovary			
46	F	49	1234	307	230	64
47	F	68	89	690	88	21
48	F	52	201	285	196	129
49	F	67	356	244	337	58
50	F	56	2970	371	154	66
96	F	51	456	368	91	70
			Breast			
51	F	56	1235	796	10	45
52	F	57	24	977	24	68
53	F	53	1581	1623	580	23
54	F	68	1166	555	747	12
55	F	68	40	1304	39	52
56	F	53	727	1165	87	28
57	F	75	3808	675	633	62
58	F	68	791	871	251	75
59	F	55	1804	916	389	104
60	F	43	3460+	1311	2270+	41
61	F	53	719	978	322	64
			Bladder			
62	M	93	4288	464	260	29
63	F	70	3658	694	305	22
64	F	77	51	221	37	21
65	F	72	278	490	109	16
66	M	44	548	433	37	11
67	M	64	1607+	484	1320+	14
68	M	63	1250+	152	419+	32
			Kidney			
71	F	71	205	332	8	91
72	F	63	538	377	96	47
73	F	51	203	147	190	35
74	M	53	296	500	64	34
75	M	57	870	299	260	19
76	M	73	331	585	326	37
78	M	69	1685	1056	46	15
79	M	74	2060+	647	2060+	44
			Gallbladder			
69	F	71	31	91	21	17
70	M	67	256	169	245	68
			Esophagus			
26	M	69	199	103	60	25
27	F	80	838	90	44	11
			Reticulum cell sarcoma			
80	M	44	1664+	367	1659+	23
81	M	65	86	427	86	45
			Prostate			
82	M	48	1306	467	255	77
89	M	68	331	944	122	15
			Uterus			
83	F	62	1273	497	86	44
			Brain			
85	M	49	47	296	34	59

(*Continued on following page.*)

Table 1. (*Continued*)

Case	Sex	Age, yr	Survival, days† A	B	C	D	Case	Sex	Age, yr	Survival days† A	B	C	D
			Pancreas							Chronic lymphatic leukemia			
86	M	77	465	56	342	20	94	F	59	3281	237	889	30
87	M	67	27	60	27	24							
88	F	60	83	99	16	58							

* The + following the survival time of an ascorbate-treated patient indicates that the patient was alive on 15 May 1978.

† A, survival time of the ascorbate patient, measured from the date of first hospital attendance for the cancer that reached the terminal stage; B, the corresponding mean survival time of that patient's 10 matched controls; C and D, survival times for ascorbate patient and controls, respectively, measured from the dates of untreatability.

tional periods of survival of the 18 ascorbate patients still alive on 10 August 1976. It is apparent that there is reasonably good agreement with the values reached in our present more detailed study.

Comparison of the survival times of ascorbate-treated cancer patients and their matched controls measured from the date of untreatability is shown for eight of the nine groups in Figs. 1 and 2. The median increase is about 140 days, which is about 50% of the mean increase, the difference being caused by some ascorbate-treated patients with very long survival times, as was discussed in our previous communication (1).

In that earlier paper, the ratio of average survival time after untreatability of the ascorbate-treated group to that of controls was given as 4.2; this value has now increased to 5.6 because of the continuing survival of some of the original patients. The corresponding ratio in the present study is 7.7.

Although the matched controls were selected without consideration of the date of death or whether death had occurred, none was still living at the time when Table 1 was compiled. The explanation of this fact is that cancer patients who reach a terminal stage have a life expectancy of only a few months at most. Nevertheless, it seems worthwhile to compare the controls with the 92 ascorbate-treated patients who had also died when Table 1 was prepared, measuring survival time in both groups from date of first hospital attendance to date of death, the two reference dates that are exactly known. This comparison gives 251 days as the increase in average survival time of the ascorbate-treated subjects over the value for the controls, compared to 321+ days when all 100 treated subjects are included.

Of the 1000 control patients, 370 were completely concurrent with the ascorbate-treated patients. The mean value of the survival times of these completely concurrent control patients was 327 days measured from the date of first hospital attendance and 42 days measured from the date of untreatability, compared with 379 and 36 days, respectively, for the overlapping and historical controls. The values of the increase in survival time of the ascorbate-treated patients over that for the completely concurrent controls are 354+ days (from date of first hospital attendance) and 257+ days (from date of untreatability); the average is 306+ days. These values, with use of the 370 completely concurrent controls, are a little larger than those with use of all 1000 controls (average 288+ days for the two reference dates). The average of the values for the concurrent controls and all controls, equally weighted, is 297+ days.

Statistical tests show that the survival times of the ascorbate-treated patients are significantly greater than those of their matched controls. The nonparametric Wilcoxon matched-pairs signed-ranks test was carried out for each of the nine groups in Table 2, for both survival time after first hospital attendance and survival time after date of untreatability. Each of the 18 tests led to rejection of the null hypothesis of the same distribution function for survival times of ascorbate-treated patients and of their controls at a highly significant level [P (one-tailed) <0.01 or 0.001].

Table 2. Differences in average survival times of ascorbate-treated patients and matched controls

Primary tumor type	Patients, no. Test	Controls	Mean survival times, days: From first hospital attendance A Test	B Control	From date of untreatability C Test	D Control	Increased survival times of ascorbate-treated patients, days* E A − B	F C − D	G
Colon	17	170	458+	316	352+	33	142+	319+	324
Bronchus	17	170	219+	118	186+	31	101+	155+	184+
Stomach	13	130	286+	159	182+	32	127+	150+	134+
Breast	11	110	1396+	1020	487+	52	376+	435+	378+
Kidney	8	80	774+	492	381+	39	282+	342+	348+
Bladder	7	70	1669+	420	355+	21	1249+	334+	226+
Rectum	7	70	634	336	270	43	298	227	247
Ovary	6	60	884	366	183	69	518	114	157
Others	14	140	706+	279	278+	37	427+	241+	189+
All	100	1000	681+	360	293+	38	321+	255+	234+

* E, calculated as A − B; F, calculated as C − D; G, additional survival time of first set of ascorbate-treated patients with first set of controls ref. (1) to 15 May 1978, when seven of them were still living (measured from the date of untreatability). The + following a number indicates that one patient in the group (two in the bladder group) continued to survive after 15 May 1978.

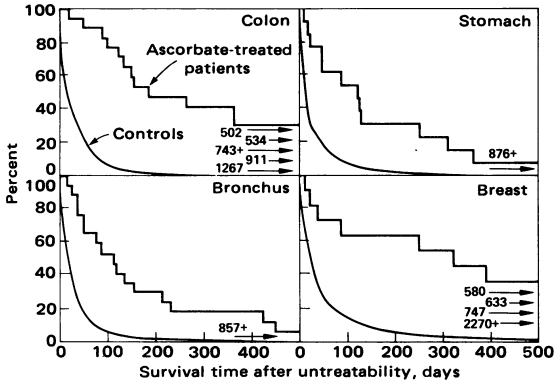

FIG. 1. Fraction of survivors at times after date of onset of terminal stage (untreatability) of ascorbate-treated patients with primary cancer of colon, stomach, bronchus, or breast, compared with that for matched controls (10 per ascorbate-treated patient).

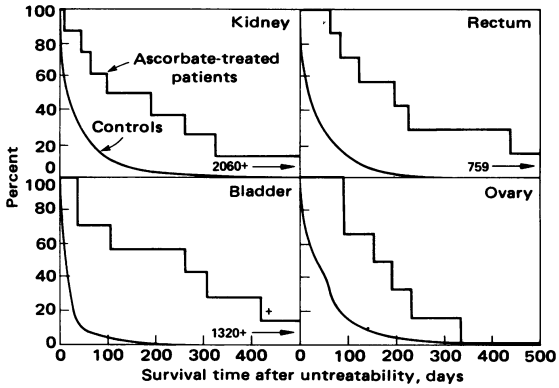

FIG. 2. Fraction of survivors at times after date of onset of terminal stage (untreatability) of ascorbate-treated patients with primary cancer of kidney, rectum, bladder, or ovary, compared with that for matched controls (10 per ascorbate-treated patient).

Conclusion

From examination of the case records for a revised set of 100 ascorbate-treated patients with terminal cancer [mostly the same as those reported in our earlier study (1)] and a new set of 1000 matched controls, and using the precisely known date of first hospital attendance and date of death as reference points, we conclude again that there is strong evidence that treatment of patients in Scotland with terminal (untreatable) cancer with about 10 g of ascorbate per day increases their survival significantly (by an average of about 300+ days). Larger amounts might have a greater effect. Eight of the 100 ascorbate-treated patients were still alive on 15 May 1978, even though they had been judged, at the time when administration of ascorbate was initiated, to have reached the terminal stage of their illness; their mean survival time after the date of untreatability is 3.5+ yr. Survival times greater than 1 yr after the date of untreatability were observed for 22 of the 100 ascorbate-treated patients, 55 times the fraction (4/1000) for the matched controls. These 22 ascorbate-treated patients had on 15 May 1978 survived an average of 2.4 yr after reaching the apparently terminal stage.

There is little doubt, in our opinion, that treatment with ascorbate in amounts of 10 g/day or more is of real value in extending the life of patients with advanced cancer. Moreover, as has been pointed out before (2), the quality of life of the patients is improved by the administration of ascorbate. Also, we continue to believe that the addition of ascorbate to treatment regimens at an earlier stage might well have a much greater effect, increasing the average survival time by several years.

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1. Cameron, E. & Pauling, L. (1976) *Proc. Natl. Acad. Sci. USA* **73**, 3685–3689.
2. Cameron, E. & Campbell, A. (1974) *Chem. Biol. Interact.* **9**, 285–315.