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Continuous ascorbate infusions in the management of the patients with advanced colon cancer

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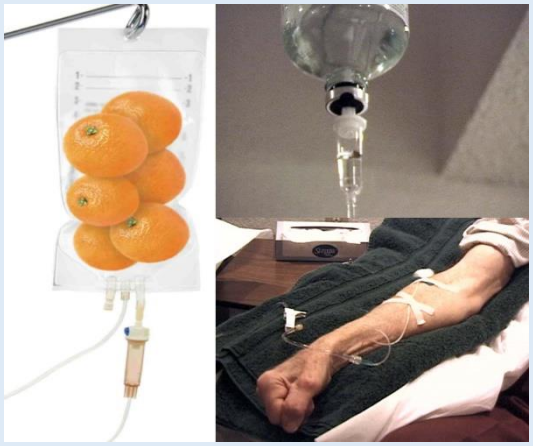
ABSTRACT



Objective: Cytotoxic effect of ascorbic acid on colon cancer cells has been demonstrated in pre-clinical models. In this study, we analyzed data of a previous clinical trial of the treatment of late stage colon cancer patients by continuous ascorbic acid infusions.

Design: The author analyzed the effect of continuous intravenous ascorbic acid (10 g–50 g) administered by injection pumps for 6-8 weeks. Adverse effects, hematologic and blood chemistry parameters, and time to survival were monitored during treatment.

Subjects: 17 terminal colon cancer patients.

Outcome measures: Blood was collected to measure ascorbic acid (AA), absolute lymphocyte count (ALC), neutrophil to lymphocyte ratio (NLR), lactate dehydrogenase concentration (LDH), glucose concentration, ratio of immature neutrophils to total white blood cells (IN/WBC), albumin and creatinine concentrations. Patients' survival time was correlated with measured biomarkers.

Results: The evaluation of the initial blood chemistry parameters as prognostic factors of patients' survival demonstrated strong correlation with survival for lactate dehydrogenase, creatinine, and albumin levels. Continuous ascorbate infusions demonstrated a regulatory effect on ALC, lymphopenia, and NLR, which suggested a benefit of using medium continuous ascorbate doses for improvement of immune functioning. The rate of

growth of LDH in patients with elevated initial levels was decreased in most cases. Treatments were accompanied by reduced serum glucose and uric acid concentrations. In addition, our data demonstrated that continuous IVC can be administered safely.

Conclusions: Continuous IVC infusions show potential to benefit colon cancer patients with minimal side effects. Further research and clinical studies investigating the efficacy of continuous IVC therapy for colon cancer are warranted.

Keywords: continuous infusion, ascorbic acid, colon cancer, survival, lymphopenia, lactate dehydrogenase, neutrophil to lymphocyte ratio.

INTRODUCTION

Colorectal cancer is a major worldwide health problem that, despite recent improvements in treatment, continues to have a low response rate [1]. It is a heterogeneous disease. Roughly forty percent of cases carry a KRAS oncogene mutation, which is associated with poor outcomes, poor overall survival, serious alterations in normal cell metabolism and resistance to chemotherapy [2,3].

Intravenous ascorbic acid administration is being considered as a potential treatment for cancer [4]. Pharmacological concentrations of AA induce antiproliferative, cytotoxic and genotoxic effects on colon cancer cells in vitro [5]. Tumors preferentially accumulate ascorbic acid, possibly by uptake via glucose transporters and by increased expression of AA transporters [6]. Ascorbic acid may interfere with glucose metabolism in colon cancer cells, which rely heavily on the Warburg effect to meet cellular energy needs by blocking essential enzymes or shutting down the pathway that allows KRAS mutation-dependent enhancement of glucose absorption [7].

Other potential mechanisms of action for AA against colon cancer include upregulation of p53 and inhibition of hyaluronidase, an enzyme that aids tumor metastasis by destroying collagen [8,9]. Ascorbic acid is associated with the "normalization" of methylation markers ten-eleven translocation enzymes (TET) and 5-hydroxymethyl cytosine (5-hmCyt), as well as with decreases in hypoxia inducible factor (HIF-1)-activated tumor growth [10,11]. In summary, ascorbic acid at pharmacological concentrations exerts a selectively cytotoxic effect toward tumors, by several potential mechanisms of action.

At the clinical level, AA is associated with improvement of quality-of-life in patients with advanced disease and improved tolerability of standard therapy [7]. In the present publication, we described previously unpublished parameters from the Riordan clinical study of the treatment of colon cancer patients by continuous ascorbic acid infusions, including blood chemistry and blood count parameters that are reportedly related to patient prognosis and degree of inflammation.

MATERIAL AND METHODS

Patient characteristics: Seventeen patients with late stage colon cancer were included in our study. 88% of the patients had a metastatic tumor. Written

informed consent was provided by all patients included in this study. The ethics committees of the Eppley Institute for Research in Cancer and Allied Diseases at the University of Nebraska Medical Center (Omaha. NE) and the IRB of the Riordan Clinic approved the study.

Before participating in this study, all patients had undergone several chemotherapies, some with radiation and some without. A description of all recruited 24 patients and how the Phase 1 IVC continuous infusion clinical trial was conducted was previously given [12,13]. Since 70% of the participants in this study were patients with colon cancer, we decided to analyze this group separately.

For these subjects, information about the type of cancer, metastatic state, dosage during treatment, duration of the treatment, survival and adverse effects during intervention are presented in Table 1.

Table 1. Characteristics of colon cancer patients participating in a phase I clinical trial of continuous IVC infusions.

Subject	Sex	Primary / Metastasis	AA Dose mg/kg/day	Treatment Time (week)	Survival Time (days)	Adverse effects
1	M	Colon / Liver	150	4	69	ED
2	F	Colon / Liver, Lung	710	8	456	none
3	F	Colon / Liver	290	8	143	DM, NA, F
4	M	Colon / Lung, Liver	570	8	397	none
5	F	Colon / Lung	430	7	155	ED, DM
6	M	Colon / Liver	290	2	36	KS, DM
7	F	Colon / Lung	430	3	21	ED
8	M	Colon / Liver	430	8	80	none
9	F	Colon / Liver	150	8	67	NA
10	M	Colon / Liver	430	48	334	SD, NA, K
11	F	Colon	430	6	ND	NA
12	M	Colon / Liver, Lung	710	8	43	F, K
13	M	Colon / Chest-Abd. Wall	150	7	220	DM
14	F	Colon / Liver	290	6	142	none
15	M	Colon / Lung	570	8	ND	ED, BP
16	M	Colon / Liver	710	8	110	IWB
17	M	Colon / Omentum	290	8	173	AX

The abbreviations of side effects are: SD = Stable Disease, IWB = improved well-being, ED - edema, DM – dry mouth, NA - nausea, BP –blood pressure, AX - anorexia, KS – kidney stones and K-hypokalemia. ND- not determined.

Intervention: Patients were divided into groups and given continuous infusions of AA at specified doses: 150 mg/kg/day (3 patients), 290 mg/kg/day (4 patients), 430 mg/kg/day (5 patients), 510 mg/kg/day (2 patients) and 710 mg/kg/day (3 patients). To administer treatment, ascorbic acid was diluted in Lactated Ringers solution and administered continuously with a infusion pump (flow rates 20 ml/hour or 10 ml/hour depending on the dose). Overall, fourteen of the patients received the treatment for at least six weeks. Subject #10 showed stable disease and elected to continue ascorbic acid therapy for an additional forty-eight weeks. Patients' health, adverse events and tumor progression were

monitored during treatment. Samples for routine blood chemistry were collected one week prior to therapy and weekly during treatment.

Statistical analysis: The inter-relationship between survival and blood parameters was examined using Spearman's correlation coefficients and regression analysis. Pairwise comparisons were analyzed by Wilcoxon Signed–Rank test. Two tailed p values < 0.05 were considered statistically significant. Statistical analysis was performed using Systat software (Version 13, Chicago, IL, USA).

RESULTS

Plasma ascorbate concentration: Pre-treatment plasma ascorbic acid concentrations were below normal in two-thirds of the subjects. Kinetic curves of AA concentrations in blood during 21-28 days in the range of doses from lowest 150 mg/kg/day to highest 710 mg/kg/day, averaged for all patients in these dosage groups, are presented in Figure 1.

Plasma AA concentrations increased initially and then appeared to reach of steady state between 1.0 and 1.6 mM. The data for all four doses could be fitted to a single Michaelis-Menten type equation with a calculated maximum level of 1.19 mM and a half-time to maximum of 0.87 days (r = 0.75). Concentrations in this range are shown to be necessary for anti-cancer effect [4,14]. Increasing dosages did not have a dramatic effect on the steady state AA concentrations, which may be explained by the saturation of tubular AA reabsorption and sodium-dependent transporters, leading the body to excrete AA more rapidly [15].

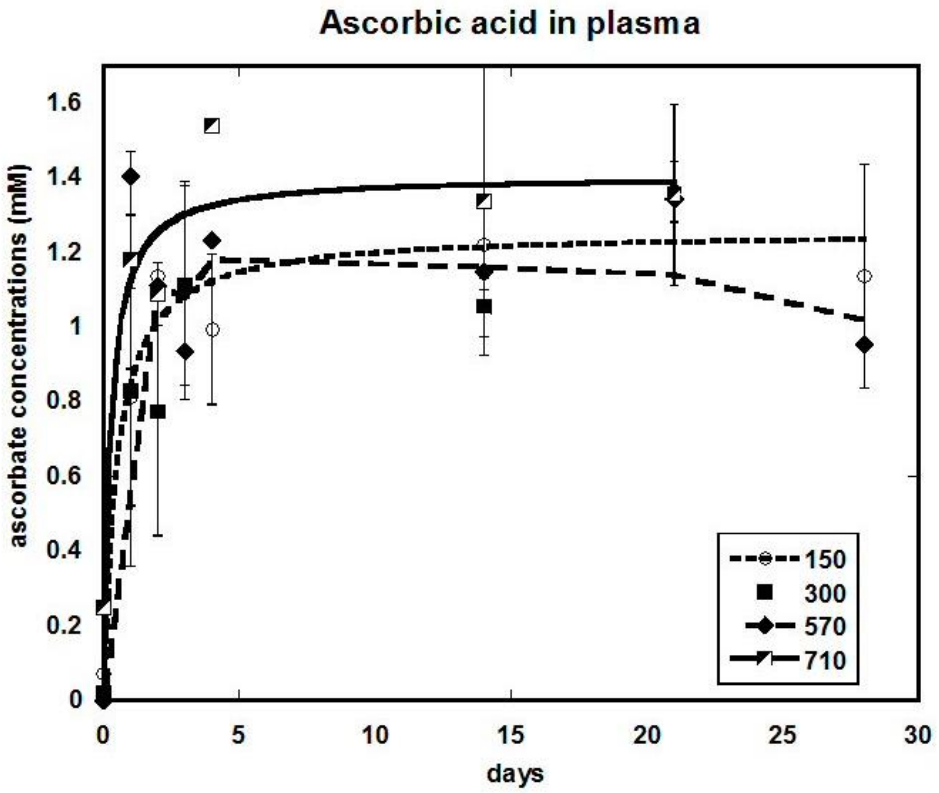


Figure 1: Average ascorbic acid concentrations (mM) for doses of 150 mg/kg, 290 mg/kg, 570 mg/kg, and 710 mg/kg plotted against time

Survival time and blood parameters: Table 2 shows how various blood counts and chemistry parameters measured prior to intravenous ascorbate therapy correlate with patient survival time. The Spearman correlation coefficients between survival and blood tests are presented in Table 2.

LDH showed a negative correlation with survival (r_s = -0.78, $p < 0.04$), while creatinine (r_s = 0.68, $p < 0.006$) and albumin levels (r_s = 0.51, $p<0.02$) showed strong positive correlations with survival. There was weaker negative association between survival, NLR, immature neutrophils, glucose (r_s in range -0.33 to 0.39) and positive association with ALC (r_s = 0.31).

To demonstrate the prognostic value of these parameters, we compared survival times of subjects with normal parameter values to those with parameter values outside the normal range. Results are shown as box and whisker plots in Figure 2.

For each of the parameters depicted, subjects with values in the normal range had significantly better survival rates than those with abnormal parameter values. Survival times were reduced for subjects with ALC below 1000 cells/L, NLR above 3.5, LDH above 250 U/L, IN/WBC above 0.05, creatinine concentrations below 0.8 mg/dL, and albumin levels below 3.5 g/dL. In addition, our data shows the cumulative effect of multiple abnormal parameter values. Survival time was lower for subjects with more abnormal values of these parameters.

Based on this analysis, we investigated the effect of the continuous IVC treatment on parameters correlated with survival.

Table 2. Correlation matrix between measured blood parameters and survival of the patients. Spearman correlation coefficients between patient survival time and parameters measured in colon cancer patients prior to treatment are indicated.

	survival	ALC	NLR	LDH	glucose	IN/WBC	creatinine	uric acid
survival	1							
ALC	0.31	1						
NLR	-0.39	**-0.57**	1					
LDH	**-0.78**	-0.27	0.34	1				
glucose	-0.37	-0.42	0.40	0.13	1			
IN/WBC	-0.33	-0.19	0.13	0.15	0.14	1		
creatinine	**0.68**	-0.04	-0.10	**-0.5**	-0.18	**-0.57**	1	
uric acid	-0.21	-0.01	-0.13	-0.11	0.01	0.07	-0.12	1
A/G ratio	**0.46**	0.25	-0.30	-0.12	-0.03	-0.26	**0.45**	0.06
albumin	**0.51**	0.41	**-0.65**	-0.30	-0.22	-0.33	0.29	0.28

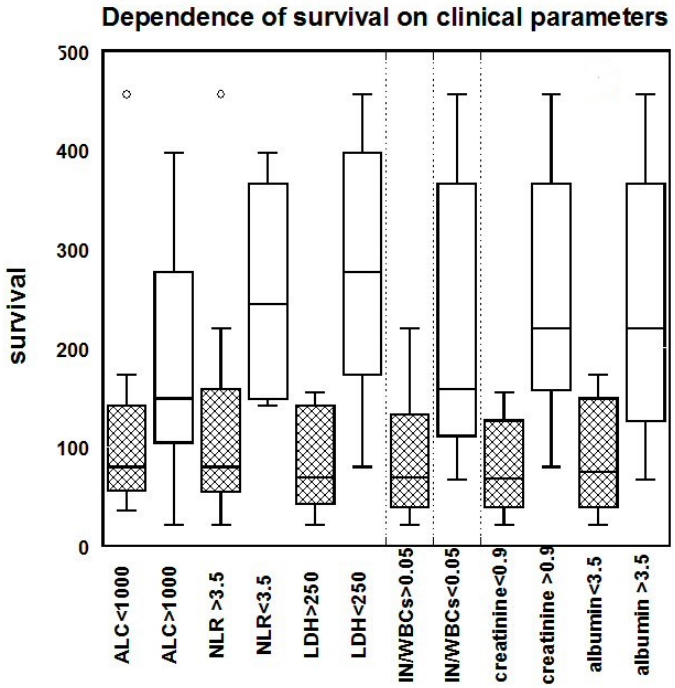


Figure 2. Survival time (days) of colon cancer patients with normal (clear boxes) or abnormal (shaded boxes) blood chemistry parameter values. Normal vs. Abnormal cutoffs: ALC < 1000 cells/ul, NLR < 3.5, LDH < 250 U/L, IN/WBC < 5%, creatinine < 0.8 mg/dl, and albumin < 3.5 g/dl.

Effect of continuous infusion on lymphocyte and neutrophil counts: As lymphocytes and neutrophils have important roles in tumorigenesis and carcinogenesis, we tracked ALC and NLR during intravenous ascorbate infusions.

The effect of continuous infusions on the ALC was analyzed for all terminally ill colon cancer patients. Ten patients enrolled in the study had lymphopenia or ALC values below normal range (1300-4000 cells/µl) with severe lymphopenia (ALC < 1000 cells/µl) observed in seven subjects. Six of the seven with severe lymphopenia had improvement in ALC during ascorbate therapy (at an average increase of 53%). Data for patients' lymphocytes one week before treatments, at the beginning of the treatment, and at the end of the treatment are shown in Table 3.

Distributions of the percent change of ALC and NLR before and after treatment are shown in Figure 3. The percentage of change in ALC was calculated based on the pre-treatment ALC, initial ALC values and the ALC at the end of the treatment.

Data in Figure 3 indicates that ALC values appear to drop in the week leading up to treatments, but then improve during the course of treatment. The average improvement during treatment was 28% (IQR: -20% to 73%) compared an average decrease of -10% (IQR: -25% to 13%) in the week immediately before treatment.

In addition, we calculated the neutrophil-to-lymphocyte ratios, as NLR is useful prognostic factors in a variety of cancers. Table 3 shows the NLRs for each of the seventeen subjects before and during treatment. For NLR, values appear to be rising in the week leading up to therapy, suggesting a poor prognosis for these subjects. Immediately prior to the onset of therapy, 12 subjects had above normal NLR levels (0.78 - 3.53). The improvement in the NLR during treatment is shown as down marks (DN) in the Table 3. Continuous ascorbate infusion resulted in improvement of NLR in seven of the 12 patients who showed abnormal NLR values initially.

Table 3. Time course of ALC and NLR values in colon cancer patient given IVC infusions. ALC_p = value one week pre-treatment; ALC_0 = value at treatment start; ALC_F = value at treatment end; NLR_p= value one week pre-treatment; NLR_0 = value at treatment start; NLR_1 = value after one week treatment; and NLR_4 = values averaged over 4 weeks treatment. " ↓" marks NLR decrease during treatment.

	ALC_P	ALC_0	ALC_F	NLR_P	NLR_0	NLR_1	NLR_4	Trend
subject 1	1230	980	1056	4.73	5.64	5.00	6.22 ± 0.87	
subject 2	1512	972	1055	3.19	6.50	4.29	4.54 ± 0.36	↓
subject 3	ND	1261	755	ND	5.69	5.92	7.46 ± 1.09	
subject 4	1400	1590	1270.2	2.07	1.87	2.46	2.33 ± 0.12	
subject 5	2232	1971	1795.2	1.74	2.07	2.27	2.65 ± 0.33	
subject 6	420	518	897	13.67	12.29	6.23	6.23	↓
subject 7	1296	1560	1044	6.75	15.00	9.11	ND	↓
subject 8	ND	944	1751	ND	4.56	ND	5.86 ± 0.55	
subject 9	1850	1494	3843	2.48	3.89	ND	2.94 ± 0.42	↓
subject 10	4712	4712	7752	2.30	2.00	1.84	2.12 ± 0.39	
subject 11	2048	2205	1610	2.00	1.00	1.88	2.31 ± 0.48	
subject 12	ND	936	915	ND	3.67	2.33	3.86 ± 0.89	
subject 13	2162	1168	1584	2.74	4.31	2.95	2.71 ± 0.40	↓
subject 14	1045	1188	572.5	3.68	3.32	3.85	5.05 ± 0.61	
subject 15	1178	1311	1605	4.05	3.84	3.74	3.27 ± 0.25	↓
subject 16	496	624	1075.2	ND	3.84	ND	3.94	
subject 17	1170	902	2058	4.80	6.91	2.95	4.51 ± 0.52	↓

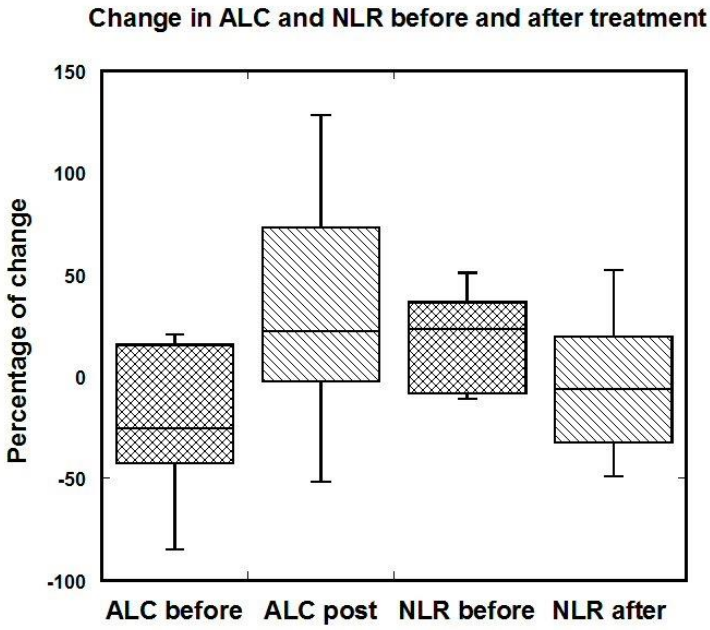


Figure 3. Percent change in ALC and NLR before treatment compared to during IVC therapy in colon cancer patients who began treatment with abnormal values in each parameter.

The percentage of NLR changes are shown in Figure 3 for subjects who started treatment with abnormal levels of each parameter. For these subjects, therapy tended to move parameter values in the direction for improving prognosis. These data suggest that continuous ascorbate treatment can result in the suppression or prevention of the progression of the rate of growth of NLR.

We also evaluated the change in the level of immature granulocytes during intervention. The ratio of immature neutrophils to total white blood cells (IN/WBC) was above normal (2%) in ten patients, with the median IN/WBC in these subjects being 7.5% (IQR = 4.9% to 12.6%). Treatment reduced these values to a median of 3.4% (IQR = 0.4% to 4.6%).

Effect of ascorbic acid on blood chemistry parameters: LDH is elevated in many types of cancers; it has been linked to tumor growth, maintenance, and invasion [16]. Regression analysis (Table 2) demonstrated a significant correlation between colon cancer patient survival time and LDH ($P < 0.004$). Subjects with LDH values within the normal range (140 to 280 U/L) had a median survival time of 277 days (IQR = 150 to 412) while subjects with elevated LDH values had a median survival time of 90 days (IQR = 44 to 143). LDH concentrations before IVC therapy were above the normal range in 56% of the patients. Overall, nine subjects showed continued increases in LDH while six showed an LDH decrease.

Hyperglycemia is common in cancer patients [17]. Sixty percent of the colon cancer patients in our study had above normal blood glucose concentrations (>100mg/dl). The effect of IVC on plasma glucose concentration is shown in Figure 4, where the average percentage of change in glucose concentration from the pre-treatment value is plotted against the initial glucose concentration.

For patients with above-normal pre-treatment glucose concentrations, plasma glucose concentrations decreased by an average of 21% (IQR = -31% to +13%) during treatment. The most dramatic decreases in glucose levels occurred when the initial glucose concentrations were at their highest levels.

Continuous ascorbate treatments corresponded to significant reductions in serum uric acid, noticeable as early as the first week after treatment. Recent evidence has demonstrated that hyperuricemia is associated with excess cancer risk, recurrence, and mortality [18]. During treatment, all patients experienced a significant uric acid lowering effect. The median values of UA were 5.1 mg/dL (IQR = 4.3 to 5.7) before treatment and 2.2 mg/dL (IQR = 1.4 to 2.7) after one week of treatment. The reduction in UA after one week of treatment depended on ascorbate dosage.

Two other blood chemistry parameters that correlate with survival in our study were serum albumin and creatinine. Our data demonstrated high correlations between carnitine and albumin levels and survival colon cancer patients ($r=0.68$ and $r=0.51$). The correlation of initial (pre-treatment) creatinine and albumin levels with survival time is shown in Figure 5(a, b).

Albumin was below normal range (3.5 to 5.0 g/dL) in 7 patients (median = 3.3 g/dL, IQR = 3.2 to 3.4). As it was shown in Table 2 and Figure 2, albumin has a prognostic value in our colorectal cancer patients. Albumin levels were decreasing in most of these subjects prior to therapy and during therapy, and we do not have evidence that treatment affected albumin levels in this study.

The average decrease in creatinine during treatment was 14% (IQR = -4% to -24%), a statistically significant change ($p<0.001$). Thus, intervention did not prevent decreases in creatinine during this study.

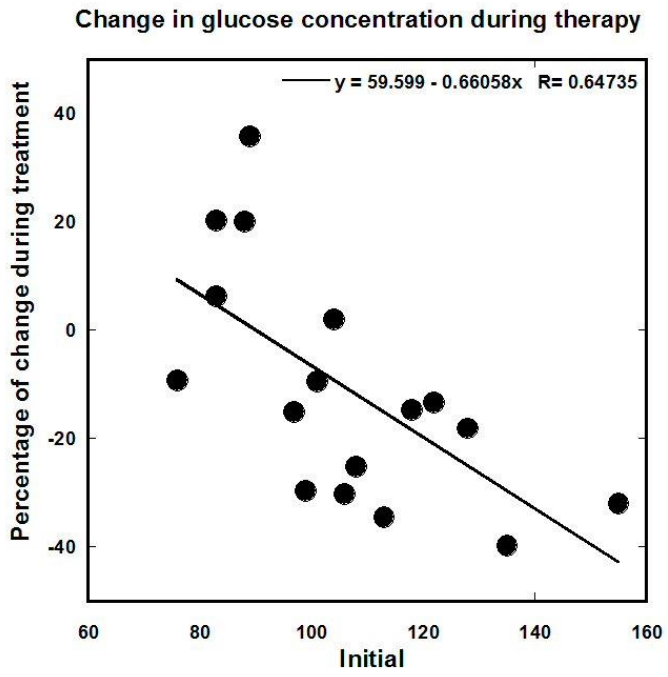


Figure 4. Percentage of plasma glucose concentration change during IVC therapy as function of pre-treatment glucose concentrations (mg/dL). The line represents the linear extrapolation of the data.

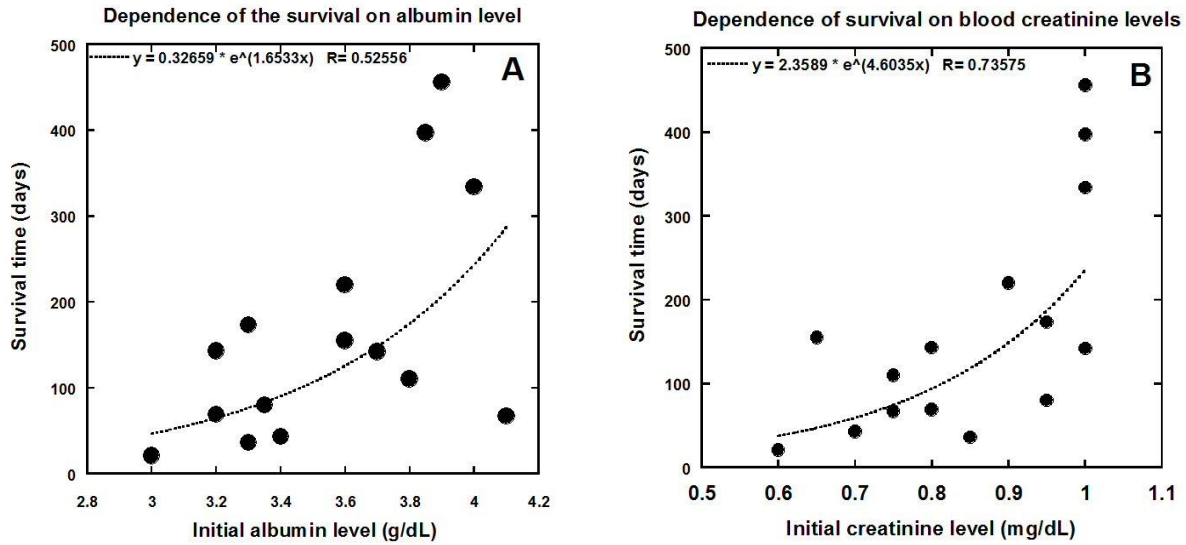


Figure 5 (a, b). Correlation of colon cancer patient survival with initial levels of albumin and creatinine.

DISCUSSION

We analyzed data of seventeen colon cancer patients from the Phase I clinical trial given continuous IVC infusions [12]. The eight-week trial involved terminal patients with poor prognosis. Considering recent interest in potential biological effects of vitamin C on cancer survival and improvements in quality of life, we analyzed previously unpublished data from this study in the subgroup of colon cancer patients. Our purpose was two-fold: to see if these parameters served as prognostic indicators of survival for colon cancer patients in the study and to determine if there

were any improvements in parameter values for these subjects during therapy.

The continuous infusions of ascorbate at doses used in this pilot clinical trial lead to sustained plasma AA concentrations (1.0 to 1.6 mM) that, based on experimental evidence, are sufficient for anti-tumor effects.

In the present study, we evaluated the initial blood chemistry parameters as prognostic factors of patients' survival. According to our data, a strong correlation with survival was found for LDH, creatinine and albumin levels, and survival time was lower for subjects with abnormal values of the measured parameters.

Serum albumin level has been found to be an independent prognostic factor for survival in various cancers including colorectal cancer [19]. In our group of patients, seven patients had level of albumin lower than normal range with tendency to decrease on average on 8.3% during intervention.

Creatinine was found to be another prognostic parameter of survival for late stage colon cancer patients.

Another potential biomarker of patients' survival was the level of lactate dehydrogenase (r=-0.78). Only six patients showed the decrease in the level of LDH during treatment; however, the rate of growth of this parameter in patients with LDH higher than normal range was suppressed in most of patients.

Analysis of white blood cell counts for colon cancer patients in our trial provided two main observations: patient lymphocytes tended to decrease with time prior to therapy; and patients who had below normal lymphocyte counts at the onset of therapy tended to see an increase in lymphocyte numbers during treatment. The present analysis demonstrated the regulatory effect of continuous ascorbate on ALC and lymphopenia and suggested a strategic benefit of using medium ascorbate doses in continuous infusions for improvement immune cell counts.

Analysis of neutrophil-to-lymphocyte ratios also demonstrated a potentially beneficial regulatory effect of treatment on the immune cell population. In the present study, most of the patients entered the trial with above-normal NLRs. Continuous ascorbate therapy decreased NLR in 7 of 12 patients who had initially above-normal NLR levels.

Our analysis also demonstrated an effect of treatment on immature granulocytes. High proportion of immature neutrophils predicts infection [20]. In our study, 60% of the patients had elevated IN/WBCs (averaged for the period before treatment) with a median of 7.5%. During treatment, the median IN/WBCs for these patients decreased to 3.35%. This may indicate a decrease in infection and/or inflammation level in these patients during therapy.

In the present study, continuous ascorbate therapy was associated with decreases in plasma glucose concentrations in patients with hyperglycemia and a reduction in plasma uric acid.

Our data confirmed that continuous IVC can be administered safely. For prevention of hypokalemia, the level of electrolytes should be controlled during treatment and include supplementation. In addition, renal function should be monitored, and patients with the history of kidney disease are not recommended for such treatments. Adverse events were more frequent at the higher IVC doses used [13], and based on the pharmacokinetic data, we can

suggest that higher doses in continuous infusion ascorbic acid therapy may result in more side effects without significant increasing plasma ascorbate concentrations and improvement biomarkers beyond those obtained at lower doses.

This analysis, to our knowledge, is the first clinical study of continuous ascorbate infusion that includes analysis of biological markers correlating with survival and monitors how these markers change during therapy. We conclude that injected doses between 10 – 20 g/day are enough to achieve plasma ascorbate concentrations of 1 mM or higher. This therapy also showed signs of improving blood cell count and chemistry parameters that are prognostic indicators of patient survival.

The weaknesses of the study were low number of patients, late stage of cancer (untreatable, metastatic colon cancer), the lack of a control group, and the likelihood that subjects had immune systems that were damaged by prior treatments such as chemotherapy and irradiation. Future studies should be designed to address these issues.

CONCLUSIONS

In conclusion, the analysis of the parameters that served as prognostic indicators of colon cancer patients' survival and evaluation of the improvements of described parameters' values for these subjects during therapy demonstrated that continuous ascorbate infusions benefit colon cancer patients. The data suggested a regimen of continuous infusions for improving immune functioning and cancer biomarkers. In addition, our analysis demonstrated that continuous ascorbate can be administered safely.

Abbreviations: AA: ascorbic acid; LDH: lactate dehydrogenase; ALC: absolute lymphocyte counts; NLR: neutrophil to lymphocyte ratio; IN/WBC: the ratio of immature neutrophils to white blood cells; A:G: albumin to globulin ratio; UA: uric acid.

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Author' contributions: NM analyzed data, made the statistical calculations, and prepared the manuscript.

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