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Total lymphocyte count in cancer patients with lymphopenia treated with intravenous vitamin C: Results of an observational study

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Abstract

Background: Lymphopenia commonly occurs in cancer patients and predicts poor prognosis. It is caused by radio- and chemotherapy, with malnutrition and treatment-related oxidative stress playing key roles in its pathogenesis. Tumour-related morbidity is reported to be associated with reduced plasma ascorbate, which is a key physiological antioxidant and essential factor in immune function.

Method: A prospective observational study was conducted on 48 cancer patients with lymphopenia (<1500/μL) to investigate the total lymphocyte count (TLC) during four weeks of elective adjuvant treatment with intravenous (iv) vitamin C 7.5 g (Pascorbin®7.5 g) once a week. TLC values at baseline (just prior to start of treatment) and after 4 weeks treatment were compared using descriptive statistics.

Results: After 4 weeks iv vitamin C 7.5 g, TLC increased by a mean of 211/μL ($p = 0.0018$). Subgroup analyses showed that, in patients with severe lymphopenia ($n = 25$) (TLC <1000/μL), the increase in TLC was greater with a mean rise of 368/μL ($p = 0.0004$), than in patients ($n = 23$) with an initial TLC of 1000–1500 (mean rise of 40/μL) ($p = 0.6105$). TLC increased by at least 240/μL in half of the patients with severe lymphopenia and by more than 610/μL in 25% of patients.

Conclusion: Our data indicate that iv high-dose vitamin C treatment increases TLC, which strongly implies improvement of immune function, especially in patients with severe lymphopenia. Appropriately-powered, randomized, placebo-controlled trials of iv high-dose vitamin C are now needed to define more precisely its role in the treatment of cancer-related lymphopenia and how this impacts on the patients' clinical prognosis.

Keywords: Ascorbate, Lymphopenia, TLC, Neoplasms

Background

Severe treatment-related hematological toxicities, such as lymphopenia, occur commonly in many cancers [1]. Drastically reduced TLC increases the risk of various forms of infections [2]. Recent studies reveal an association of post-treatment lymphopenia and decreased survival in patients with solid tumours who underwent chemo- or radiotherapy [1, 3–5]. Adjuvant treatment options are needed to restore this reversible prognostic factor.

Ascorbate, the absorbed form of dietary vitamin C, is an essential factor for immune cells and enhances the immune system in many ways [6, 7]. It enhances leukocyte function and innate immune responses via modulation of chemokinesis and chemotaxis [8]. Leukocytes actively accumulate ascorbate to achieve intracellular concentrations that exceed plasma concentrations by up to 80-fold [9].

Cancer patients are often reported to be vitamin C deficient [10–18]. Particularly serious are the deficiencies in patients with advanced cancer [15, 19, 20], where decreased plasma ascorbate levels are associated with shorter survival and impaired quality of life [21].

Intravenous (iv) instead of oral administration of ascorbate is required in order to achieve the high plasma concentrations [22] that have been shown to have

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potential therapeutic effects [23, 24]. Ten years ago, high dose vitamin C (as sodium ascorbate) was found to have selective tumour cytotoxic effects [25] and its chemotherapeutic potential is still undergoing investigation [26]. Several phase I/IIa studies examined the chemotherapeutic effects of iv high-dose vitamin C as an adjuvant to standard treatment in patients with advanced tumours [27–29]. Another potential benefit of iv vitamin C treatment is the favourable effect on the quality of life of cancer patients [30–32]. Although iv high dose vitamin C is a popular complementary treatment in the management of cancer conditions [23, 24, 33], there is, as far as we are aware, no published data on its effects on lymphopenia.

The aim of this observational study was the evaluation of the effects of iv high-dose vitamin C on lymphopenia in cancer patients.

Methods

The objective of this prospective observational study was to document the use of Pascorbin® 7.5 g (licensed, proprietary medicinal product containing 7.5 g ascorbate for iv infusion; license owner: Pascoe Pharmazeutische Präparate GmbH, Germany) in patients with advanced cancer and lymphopenia, and to monitor its effect on their TLC. Data were collected from those cancer patients attending the ambulatory service of the Clinical Nutrition Department at SOLCA Cancer Hospital, Guayaquil, Ecuador, from February 2012 to October 2014, and who received elective iv ascorbate treatment as an adjuvant to tumour therapy. It was the physicians' decision to use the infusion in accordance to the indication as an adjuvant to tumour therapy with the aims of to speed up postoperative recovery, to reduce the side effects of conventional oncological therapy (such as chemotherapy, radiotherapy), to reduce periods of hospitalization, to prolong the tumour- and recurrence-free intervals and to improve quality of life. As lymphopenia is a chemotherapy or radiation related hematological side effect, the treatment with iv vitamin C is covered by the approved indication.

The study included 48 cancer patients (aged ≥18 years) with lymphopenia, defined as a TLC below 1500/μL blood [2, 34]. Diagnosis of cancer was previously confirmed and documented by the attending physician. Malignant neoplasm of cervix uteri ($n = 11$) was the most common (22.9%) cancer documented in the study group, followed by breast cancer (14.6%), with between 2.1 and 8.3% for other cancer types. The study was a non-interventional study aimed to document the routine clinical use of iv vitamin C. Patients agreed, in a signed statement, to study participation and to release of their data. The criteria for patient selection are listed in Table 1.

Table 1 Patient data eligibility criteria

Inclusion criteria
Aged ≥18
Vitamin C deficiency (due to the underlying cancer disease or treatment)
Previously confirmed cancer diagnosis with previous or current radiation- and/or chemotherapy
Total lymphocyte count <1500/μL
Treatment with iv vitamin C 7.5 g once a week, for a total of 4 doses
Patient's statement of agreement to use and publish their data for the observational study
Exclusion criteria (anamnestic)
Patients who received colony-stimulating factor
Patients not completing all four doses of iv vitamin C
Oxalate-urolithiasis, nephrolithiasis
Renal insufficiency
Iron-storage disease (thalassemia, hämochromatosis, sideroblastic anaemia)
Erythrocytic glucose-6-phosphate-dehydrogenase-deficiency
Pregnancy and lactation

Once a week, patients received iv vitamin C 7.5 g (Pascorbin®), diluted in a suitable carrier solution, such as 100 mL NaCL 0.9%. Data were collected before the start of vitamin C treatment (visit 1, baseline) and after 4 weeks of treatment.

Total lymphocyte count (TLC)

The main study parameter was the change in TLC from baseline to 4 weeks. A quantitative multi-parameter automated hematology analyser (xn 3000 series, sysmex) was used for all patients to measure TLC in peripheral blood samples obtained by venipuncture. The one-sample t-test (two-sided, with $\alpha = 0.05$) was used to test for significance of the mean change. Additional, separate analyses were carried out on data from patients with TLC of <1000/μL (severe lymphopenia) and patients with TLCs of 1000–1500 lymphocytes/μL before start of treatment. The statistical analyses were performed by an independent statistician.

Nutritional status

Due to the lack of an universally accepted definition of malnutrition, our classification of the nutrition status (Table 2) is based on a combination of patient's body mass index (BMI) [35] together with a scored Patient-Generated Subjective Global Assessment (PG-SGA) [36], and the Nutritional Risk Screening (NRS) [37]. The BMI allows us to classify overweight or obese patients. Risk of malnutrion (BMI < 20.5) is defined by NRS and the combination of BMI with the PG-SGA allows us to

Table 2 Baseline demographic and clinical characteristics of patients

Characteristics	Baseline/Visit 1 ($n = 48$)
Age, years mean ± SD; range	
Total	56.4 ± 15.7; 17–84
Male	53.8 ± 15.4; 17–73
Female	57.1 ± 15.9; 24–84
Sex, n (%)	
Male	10 (20.8%)
Female	38 (79.2%)
Nutrition status, n (%)	
Normal	0 (0.0%)
Risk of malnutrition	10 (20.8%)
Mild malnutrition	3 (6.3%)
Moderate malnutrition	17 (35.4%)
Severe malnutrition	12 (25.0%)
Overweight	2 (4.2%)
Obesity Grade 1	4 (8.3%)

differentiate further to mild, moderate or severe malnutrition.

The safety of the vitamin C treatment was assessed by the attending physician in terms of adverse events and possible relatedness of such events to vitamin C treatment.

Results

A total of 48 patients (mean ± standard deviation of age, 56.4 ± 15.7 years; 79.2% female) with previously confirmed neoplasms were included in the study and all were included in our analysis. Of note, more than half of the patients (60.4%) displayed moderate or severe malnutrition (Table 2). The mean TLC increased significantly ($p = 0.0018$) from 902.0/μL (±414/μL) at baseline to 1113/μl (±466/μL) after 4 weeks treatment. This was a mean increase in TLC of 211/μL (±442/μL). In patients with <1000 lymphocytes/μL (severe lymphopenia), the mean increase at 4 weeks was 368/μL (±449/μL) ($p = 0.0004$) compared to an increase of 40/μL (±372/μL) ($p = 0.6105$) in patients with an initial TLC of 1000–1500 lymphocytes/μL ($n = 23$) (Table 3).

Patients in our study group who were at risk of malnutrition or mild malnutrition had initial TLC values of >1000/μL (mean TLC 1046.9/μL and 1270.0/μL, respectively), whereas the initial mean TLC in patients with moderate or severe malnutrition was <1000/μL (846.5/μL and 774.2/μL,

Table 3 Total lymphocytes count (TLC) at start and at end of treatment

	TLC at start of treatment [cells/μL]	TLC at end of treatment [cells/μL]	Difference (end − start)[cells/μL]	probability estimate[a]
All patients n = 48				
Mean value ± SD; range	902 ± 414; 130–1499	1113 ± 466; 220–1135	211 ± 442; −1110–1900	$p = 0.0018$
25% Percentile	532.5	742.5	25.0	
50% Percentile (Median)	920.0	1135.0	115.0	
75% Percentile	1315.0	1440.0	395.0	
Patients with severe lymphopenia (lymphocytes < 1000/μL) $n = 25$				
Mean value ± SD; range	551 ± 212; 130–960	919 ± 447; 380–2420	368 ± 449; −110–1900	$p = 0.0004$
25% Percentile	390.0	585.0	30.0	
50% Percentile (Median)	540.0	820.0	240.0	
75% Percentile	705.0	1180.0	610.0	
Patients without moderate lymphopenia (lymphocytes 1000–1500/μL) $n = 23$				
Mean value ± SD range	1283 ± 161; 1000–1499	1323 ± 396; 220–1870	40 ± 372; −1110–660	$p = 0.6105$
25% Percentile	1120.0	1150.0	20.0	
50% Percentile (Median)	1320.0	1400.0	100.0	
75% Percentile	1180.0	1620.0	180.0	

SD standard deviation

[a]The one-sample t-test (two-sided) with α = 5% was applied for statistical testing of the null hypothesis that the mean changes between start and after 4 weeks of treatment are equal to 0

respectively) (Table 4, Fig. 1). TLC at begin and at end of treatment for each patient are available in Table 5.

In the study group, no adverse effects related to iv vitamin C were observed.

Discussion

Our non-interventianal study provides evidence that iv high-dose vitamin C reverses lymphopenia in cancer patients. We included radiotherapy- or chemotherapy-treated cancer patients with a TLC of <1500/μL, which was our definition of lymphopenia [2]. The data indicated a significant increase in the mean TLC value for the whole group while a subgroup analysis revealed a more significant effect in patients with a TLC of <1000/μL.

Several published reports suggest that lymphopenia is a reversible, predictive factor for earlier tumour progression/relapse and reduced survival, as indicated in several retrospective studies [3–5, 38, 39]. Poor prognosis of cancer patients is indicated by a TLC value of <1000/μL [39] [38] and is more evident with TLC values of <500/μL [3, 5]. More than 35% of our patients with an initial mean TLC of 551/μL (±212) had a TLC of >1000/μL after 4 weeks of iv vitamin C treatment. Given the increased risk of progression and mortality in severe lymphopenia, a TLC increase to >1000/μL is a clinically relevant and significant improvement.

The reasons for lymphopenia can be diverse [40]. In our study group, it is presumably lymphocyte depletion primarily due to radiotherapy and chemotherapy [40]. Severe stress, malnutrition and protein-energy undernutrition can also cause lymphopenia [2]. Moderate-to-severe malnutrition was evident in more than half of the patients (60.4%) in our study group and was probably a contributory factor to the lymphopenia. The small size of our study group may explain the absence of statistical significance of any association between nutritional status and lymphocyte counts at the start of treatment. However, we did observe a correlation between risk of malnutrition and lymphopenia in our study group (Table 4 and Fig. 1).

Table 4 Mean total lymphocytes counts (TLC) for patients of differing nutritional status

Nutrition status	Lymphocytes before therapy mean [cells/μL]	Lymphocytes after therapy mean [cells/μL]	Difference in Lymphocytes mean [cells/μL]
Normal = 0	–	–	–
Risk of malnutrition *n* = 10	1046.9	1334.0	287.1
Mild malnutrition *n* = 3	1270.0	1096.7	−173.3[a]
Moderate malnutrition *n* = 17	846.5	1013.5	167.1
Severe malnutrition *n* = 12	774.2	1013.3	239.2
Overweight *n* = 2	615.0	1620.0	1005.0
Obesity Grade 1 *n* = 4	1025.0	1035.0	10.0
Valid data	48	48	48
Missing data	0	0.0	0

[a]negative values means a decrease of lymphocytes

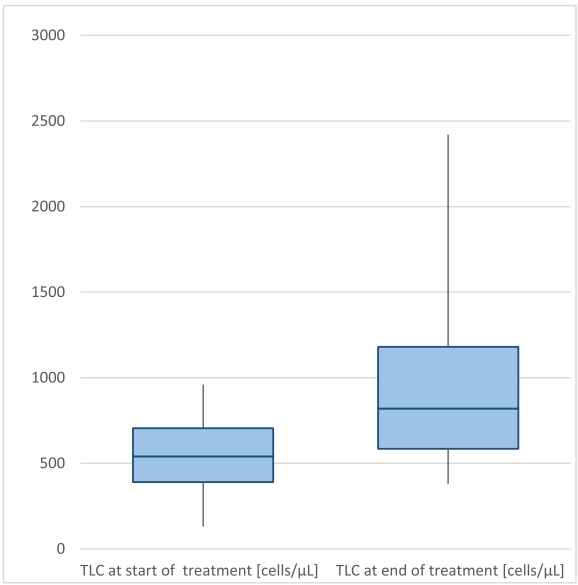

Fig. 1 Total lymphocytes count (TLC) before and after 4-week iv high-dose vitamin C treatment. The Box Plot displays the data of the study group with initial TLC < 1000 μL. Vertical bar indicates standard deviation, box indicates 25%, median, 75% percentile

The beneficial effect of iv vitamin C on TLC values in cancer patients is most likely due to its antioxidant actions counteracting treatment-induced oxidative stress. This was also suggested to explain the positive clinical effects of iv high-dose vitamin C observed in other cancer patients [29, 30, 41]. Oxidative stress is considered to be an underlying cause of lymphopenia of different etiologies [42], such as that caused by intensive exercise [43], end-stage renal disease patients [44] and AZT (3′-azido-2′,3′-dideoxythimidine) (an AIDS treatment). This notion is supported by animal data showing that high-dose antioxidants abrogate experimentally-induced lymphopenia [45].

A contributory factor for the favourable effect of vitamin C could be its function as a cofactor in the synthesis carnitine [46], which supports immune cell function, s predominantly through carnitine-dependent energy metabolism of fatty acids. Carnitine deficiency has been demonstrated in patients with impaired immune responses [47]. The ability of vitamin C to increase endogen carnitine synthesis and thereby improving energy metabolism is supported by animal data [46].

The supportive effect of iv vitamin C on the immune system that we have observed is supported by other

Table 5 TLC at begin and end of treatment for each patient

Lymphocytes at begin	Lymphocytes at end	Lymphocytes - Difference (post - pre)	Lymphocytes - status
1430	1450	20	≥1000
1330	220	−1110	≥1000
880	1460	580	<1000
520	2420	1900	<1000
1499	1620	121	≥1000
1300	1400	100	≥1000
680	920	240	<1000
700	740	40	<1000
1250	1320	70	≥1000
1440	1620	180	≥1000
1350	1630	280	≥1000
1130	460	−670	≥1000
420	880	460	<1000
810	770	−40	<1000
1410	1330	−80	≥1000
550	1280	730	<1000
130	510	380	<1000
1060	910	−150	≥1000
290	1030	740	<1000
1490	1580	90	≥1000
440	1080	640	<1000
660	680	20	<1000
960	1060	100	<1000
1120	1230	110	≥1000
580	750	170	<1000
1420	1710	290	≥1000
760	1310	550	<1000
370	380	10	<1000
1080	1690	610	≥1000
280	1410	1130	<1000
830	720	−110	<1000
630	1290	660	<1000
1250	1380	130	≥1000
1030	1180	150	≥1000
1000	1120	120	≥1000
1420	1670	250	≥1000
530	570	40	<1000
1100	1150	50	≥1000
380	400	20	<1000
490	510	20	<1000
710	820	110	<1000
400	440	40	<1000
540	940	400	<1000
1210	1870	660	≥1000
1320	1400	80	≥1000
1450	1500	50	≥1000
1420	990	−430	≥1000
240	600	360	<1000

published findings (such as, stimulation of natural killer cell activity by high dose vitamin C [48]). Furthermore, our data may relate to the increased quality of life and prolonged survival time observed in in phase I/IIa clinical trials of cancer patients treated with iv vitamin C [28, 29].

Intravenous high-dose vitamin C treatment was well tolerated by our patients, which is consistent with data from other clinical studies and comprehensive clinical surveys indicating the good tolerability of iv high-dose vitamin C up to 0.5 g/kg body weight (in phase-I-trials even up to 1.5 g/kg) when contraindications are complied with [23, 27, 33, 49, 50].

As we are aware, our study provides the first evidence that iv high-dose vitamin C treatment improves the immune status of cancer patients treated in daily clinical practice, and that the treatment is well-tolerated by this patient group. However, the clinical interpretation of our data is limited by the absence of a control group and the small size of our study group.

Conclusion

This study provides "real-life" observational evidence of the use of iv high-dose vitamin C in daily practice in the treatment of cancer patients with lymphopenia. Patients with severe lymphopenia seem to particularly benefit from iv vitamin C with a clinically significant increase in TLC. Appropriately-powered, randomized, placebo-controlled trials of iv high-dose vitamin C are now needed to define more precisely its role in the treatment of cancer-related lymphopenia and how this impacts on the patients' clinical prognosis.

Abbreviations

iv: Intravenous; NIS: Non-interventional stud; TLC: Total lymphocyte count

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Availability of data and materials

TLC at begin and at end of treatment for each patient are available in Table 5 without patient number, because of data protection purposes.

Authors' contributions
DRV conceived and initiated the study and carried out data evaluation. GTM, MMV, and SHM participated in study design, coordination and data evaluation. CV drafted the manuscript and participated in data evaluation. All authors read and approved the final manuscript. The statistical analyses were performed by an independent statistician (Gesellschaft für Therapieforschung mbH, www.gkm-therapieforschung.de, Munich, Germany).

Competing interests
DRV, GTM, MMV, and SHM declare that they have no competing interests and received no funding for this observational study. CV is employed by Pascoe Pharmazeutische Präparate GmbH (Giessen, Germany).

Consent for publication
Not applicable.

Ethics approval and consent to participate
The objective of this prospective observational study was to document the use of an authorized medicinal product. Data were collected from those cancer patients who received elective iv ascorbate treatment as an adjuvant to tumour therapy (non-interventional study; NIS). Because this type of study documents the effects of medical routine without given intervention an ethics committee vote is not necessary. According to the ICMJE definition of a clinical trial purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.
Patients agreed with the study participation and data processing, which was assured by a signed statement.

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