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Observational Study on the Effectiveness of L-Arginine Plus Vitamin C in the Management of Cancer-related Fatigue

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Abstract

Background/Aim: Cancer-related fatigue is one of the most distressing symptoms reported by patients with neoplastic disease. L-Arginine has a positive effect on physical performance in healthy individuals, on fatigue in diseases other than cancer, and on immune response in patients with cancer.

Patients and Methods: Forty-four patients with cancer undergoing medical treatment were treated orally with 1.66 g L-arginine and 500 mg of vitamin C *b.i.d*. Cancer-related fatigue and health-related quality of life were recorded before treatment and after 15 and 30 days of supplementation employing a visual analog scale and the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) respectively.

Results: Daily oral supplementation with L-arginine and vitamin C ameliorated cancer-related fatigue in a statistically significant manner. Health-related quality of life remained mostly unchanged despite patients having advanced cancer and being administered medical treatments including chemotherapy, immunotherapy and biological agents. No effect on appetite preservation was observed, except in a small percentage of patients.

Conclusion: Our exploratory study suggests a positive effect of oral supplementation with L-arginine plus vitamin C on cancer-related fatigue without significant worsening of quality of life. Due to the heterogeneity of the patient sample, further studies are needed including more clinically homogenous groups of patients.

Keywords: L-Arginine, vitamin C, cancer-related fatigue, appetite, quality of life.

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Introduction

Patients with cancer commonly experience several symptoms linked to their disease and the side-effects of treatments, which negatively impact their quality of life (QoL). Cancer-related fatigue (CRF) is one of the most common and debilitating symptoms reported by patients and can profoundly affect QoL and physical functioning (1, 2). CRF is characterized by an overwhelming sense of tiredness and exhaustion that does not improve with rest or sleep. It is a distressing, persistent, and subjective experience that interferes with daily activities and overall functioning. Unlike normal fatigue, CRF is often not proportional to recent activity and can affect physical, emotional, and cognitive well-being. Several strategies have been employed to counteract CRF, such as corticosteroids, progestins, physical therapies, cognitive-behavioral therapy, acupuncture, nutrition counseling, and a wide range of oral supplements (3, 4).

Levo- (L)-arginine is an oral supplement with ergogenic properties that promotes muscle hypertrophy and strength gains in healthy individuals while preventing muscle wasting in conditions that lead to atrophy, such as aging or periods of lack of use (5). L-Arginine is a dibasic, cationic, semi-essential amino acid synthesized endogenously from glutamine, glutamate, and proline. It participates in various metabolic functions, including protein synthesis, immune system support, and circulation enhancement (6, 7). L-Arginine is an intermediate in the urea cycle and a precursor for proteins, polyamines, and creatine. Additionally, it is the sole precursor for the biosynthesis of the multifunctional messenger nitric oxide (NO), whose biological effects are complex and depend on various regulatory factors. L-Arginine can be metabolized into NO and L-citrulline by inducible NO synthase or into urea and L-ornithine by the type 1 isoform of cytosolic arginase, which is primarily expressed in the liver as part of the urea cycle (6, 7). NO has vasodilator activity, enhancing circulation and enabling the delivery of more oxygen and nutrients to muscular tissues, which may lower weariness, particularly during physical activity (6, 7). Improved sleep quality is one possible indirect benefit, as enhanced circulation and nutrient delivery support the body's rest and recovery, which can help reduce asthenia. L-Arginine supplementation may improve physical performance and recovery by diminishing exercise-induced fatigue (5-7). However, individual health issues, dietary preferences, and physical activity levels can all affect outcomes. L-Arginine is classified among supplements with evidence B level, *i.e.*, mixed evidence and/or few randomized clinical trials, suggesting caution since high doses (3-20 g/day) may cause gastrointestinal side-effects and reduce arterial blood pressure (8).

While NO was initially identified in endothelial cells, it is now recognized as being produced by various cell types, including several tumor cell lines and solid human tumors. L-Arginine has complex relationships with cancer metabolism and is still under research (9, 10). Unfortunately, the precise role of NO in cancer remains poorly understood; however, some evidence suggests that it may influence tumor initiation, promotion, progression, tumor-cell adhesion, apoptosis, angiogenesis, differentiation, chemosensitivity, radiosensitivity, and tumor-induced immunosuppression) (9, 10). L-Arginine may also support immune function, which is crucial for combating cancer cells (10). In fact, L-arginine is involved in several cellular functions, including immunomodulation, which regulates T-lymphocyte and natural killer cell activity, pro-inflammatory cytokine levels, and the anti-tumor response (11-13). L-Arginine-induced NO production enhances immune cells' ability to target and kill cancer cells. L-Arginine depletion can impair T-cell response in the tumor microenvironment, while L-Arginine supplementation may enhance the anti-tumor immune response (11-13). Moreover, L-arginine is involved in the urea cycle and helps remove ammonia from the body, potentially reducing fatigue and improving energy levels (7).

In medical literature, clinical research on L-arginine, specifically for CRF, is limited. Most evidence derives from its general effects on energy metabolism and physical performance. This exploratory, basket study examines

the impact of L-arginine combined with vitamin C in a cohort of patients with CRF undergoing antineoplastic treatments.

Patients and Methods

Study design. This was a prospective observational study on the effect of L-arginine plus vitamin C on cancer-related fatigue, QoL, and appetite. The study was approved by the Ethics Committee of the Kore University of Enna, Enna, Italy (protocol code P11/2023, approved in November 2023). Informed consent was obtained from all patients involved in the study. Six institutions participated in the study.

The primary endpoint included evaluating the effect of L-arginine/liposomal vitamin C on CRF starting from the first evaluation of fatigue before the beginning treatment (T0) and after 15 (T1), 30 (T2), and 60 (T3) days. The effects on QoL and appetite were evaluated at T0, T2 and T3.

Eligibility criteria. Eligible patients had to fulfill the following inclusion criteria: Diagnosis of advanced solid tumor undergoing chemotherapy and/or immunotherapy; age ≥18 years; absence of heart failure, chronic breathing impairment requiring oxygen supplementation, end-stage renal disease, severe intestinal inflammatory diseases, uncontrolled metabolic, neurological or psychiatric diseases; hemoglobin level >10 g/dl; or known allergy to soy.

Treatment. Patients received 1.66 g of L-arginine and 500 mg of vitamin C (Bioarginina C® Orale; Damor Farmaceutici S.p.A., Naples, Italy) orally in 20 ml solution twice daily. They were required to electronically report all adverse events, such as increased stool frequency or diarrhea.

Activity evaluation. The treating oncologists prescribed visits at their discretion, evaluating each case individually. The single-question assessment is the most used and valuable methodology; therefore, enrolled patients self-evaluated their fatigue using the fatigue visual analog scale (VAS), scoring it from 0 (no fatigue) to 10 (extreme fatigue), as previously described. A variation of 1 point on the fatigue VAS was considered a minimally significant difference for symptom improvement. The treating oncologist, nurse, or data manager queried the VAS from patients during visits at T0, T1, T2, and T3.

Health-related quality of life (HR-QoL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Q30 (EORTC QLQ-C30) questionnaire, which includes five functional scales (physical, role, emotional, cognitive, and social), nine symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and global health status/QoL. HR-QoL was assessed using a standardized score for global health status/QoL, ranging between 0 and 100, with a high standardized score representing a high HR-QoL level. The minimal significant difference was defined as a change of 10 points, with an increase of at least 10 points considered a clinically significant improvement in HR-QoL at both the individual and group levels (13). A VAS ranging from 0 (not hungry at all) to 10 (very hungry) was employed to measure self-reported patients' appetite at T0, T2, and T3. Patients and their caregivers were asked to report their satisfaction regarding the effect of oral supplementation (dissatisfied, mild satisfaction, highly satisfied).

Statistical analysis. Descriptive data were reported as absolute numbers with their relative percentages rounded to the nearest unit or, in the case of intermediate values, to the highest one. Comparison between points was carried out employing a two-way analysis of variance test, with means adjusted to the nearest decimal unit. GraphPad statistical software (GraphPad, Boston, MA, USA) was employed for statistical analysis and graph creation.

Results

Patient population. Table I shows the main clinical and demographic characteristics of enrolled patients. Briefly, there were 44 patients enrolled in six different institutions from

January to June 2024. Patients were 20 males and 24 females with a median of 59 years (range=28-79) and a median Eastern Cooperative Oncology Group performance status of 1 (range=1-2). Primary tumors were breast cancer (45%), 10 lung cancer (23%), prostatic cancer (18%), colorectal cancer (9%), and renal carcinoma (5%). Anticancer treatments concomitant with oral supplementation with L-arginine/vitamin included chemotherapy in 27 patients (61%), tyrosine kinase inhibitors in four patients (0.9%), simultaneous chemoradiation in two patients (5%), androgen receptor signaling inhibitors in four cases (0.9%) and immunotherapy in three cases (7%). Table I also shows all treatment regimens employed.

Effect of l-arginine/vitamin C supplementation. Figure 1 shows the effect of L-arginine/vitamin C on CRF and on HrQoL. The mean basal fatigue score according to the VAS scale was 6.3 (range=4-9). After 15, 30, and 60 days, the fatigue score was 4.4 (range=3-7), 4.3 (range=2-8), and 3.9 (range=2-7), respectively. The score declined over time and the difference between time points was statistically significant (p<0.001). The mean basal HrQoL score was 64.3 (range=40-88). At T2 and T3 mean HrQoL scores were 61.4 (range=43-82), and 59.3 (range=40-82). Despite a slight decrease, the observed difference was not statistically significant (p=0.2658). Therefore L-arginine /vitamin C supplementation was not associated with a deterioration in QoL.

Figure 2 shows the effect of L-arginine /vitamin C on self-reported patients' appetite. The basal appetite score was 6.27 (range=4-9). At T2 and T3, the appetite score was 4.36 (range=3-7), and 4.29 (range=2-8), respectively. The appetite score remained stable or slightly improved in eight patients (18%), while it decreased in 82% of cases. Overall, 50% of patients and their primary caregivers reported being highly satisfied, whilst 16% were dissatisfied.

Safety. No patient reported any significant side-effect. Looser stools were reported by two patients who were only treated with capecitabine (5%). Cancer treatment-related toxicity was within the expected range without any suspicious reaction.

Table I. *Patients' demographic and clinical characteristics.*

Parameters		Value
Patients, n		44
Age, years	Median (range)	59 (28-79)
Sex, n (%)	Male	20 (45%)
	Female	24 (55%)
ECOG PS	Median (range)	1 (1-2)
Primary tumor, n (%)	Breast	20 (45%)
	Colorectal	4 (9%)
	Kidney	2 (5%)
	Prostate	8 (18%)
	Lung	10 (23%)
Disease status, n (%)	Disease-free*	18 (41%)
	Metastatic	26 (59%)
Anticancer therapy, n (%)**	Chemotherapy	24 (54.5%)
	Chemoradiotherapy	2 (4.5%)
	Chemoimmunotherapy	3 (6.8%)
	TKI	4 (9.1%)
	CDKI	4 (9.1%)
	ARSI	7 (16%)
Regimen, n (%)	Epirubicin/cyclophosphamide +paclitaxel±trastuzumab ±pertuzumab	10 (23%)
	Carboplatin/paclitaxel	3 (7%)
	Cisplatin/vinorelbine	4 (9%)
	Pemetrexed/platinum salts	4 (9%)
	Capecitabine/oxaliplatin	4 (9%)
	Nivolumab+ cabozantinib	2 (5%)
	Osimertinib	2 (5%)
	Docetaxel	4 (9%)
	Enzalutamide+LHRH	7 (16%)
	CDKI+aromatase inhibitor or fulvestrant	4 (9%)
Basal fatigue (VAS)	Median (range)	6.3 (4-9)
Basal HrQoL	Median (range)	64.3 (40-88)
Appetite, VAS	Median (range)	6.27 (4-9)

ARSI: Androgen receptor signaling inhibitor; CDKI: cyclin-dependent kinase inhibitor; ECOG PS: Eastern Cooperative Oncology Group performance status; LHRH: luteinizing hormone-releasing hormone; TKI: tyrosine kinase inhibitor; VAS: visual analog scale; HrQoL: health-related quality of life. *Receiving adjuvant chemotherapy and anti-human epidermal growth factor receptor agents with trastuzumab plus perzutumab for breast cancer, or capecitabine and oxaliplatin for colorectal cancer. **Some patients simultaneously received diverse treatment.

Discussion

CRF is a common and debilitating symptom that most patients with cancer experience during treatment and often for significant periods afterward (1). The impact of CRF on patients' psychosocial and cognitive functioning

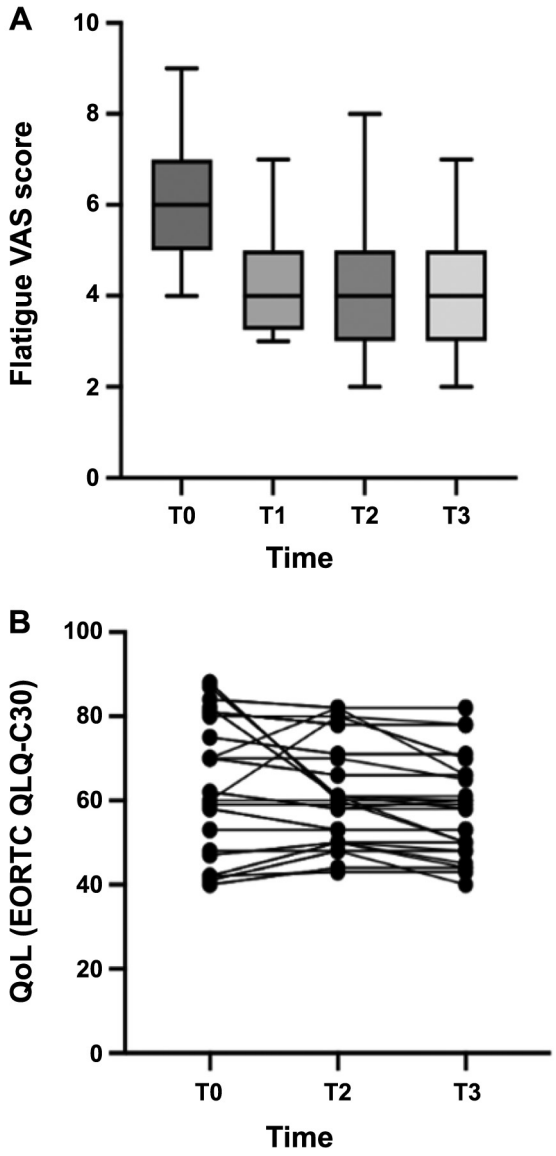

Figure 1. *Effects of L-arginine/vitamin C supplementation on cancer -related fatigue (A) and on health-related quality of life (QoL) (B) over time, at the beginning of treatment (T0) and after 15 (T1), 30 (T2) and 60 (T3) days. Boxes represent the median fatigue Visual Analog Scale (VAS) score with its range; bars indicate the standard error; lines connect the quality-of-life scores at different times from the beginning of treatment. EORTC QLQ-C30: European Organization for Research and Treatment of Cancer quality of life questionnaire.*

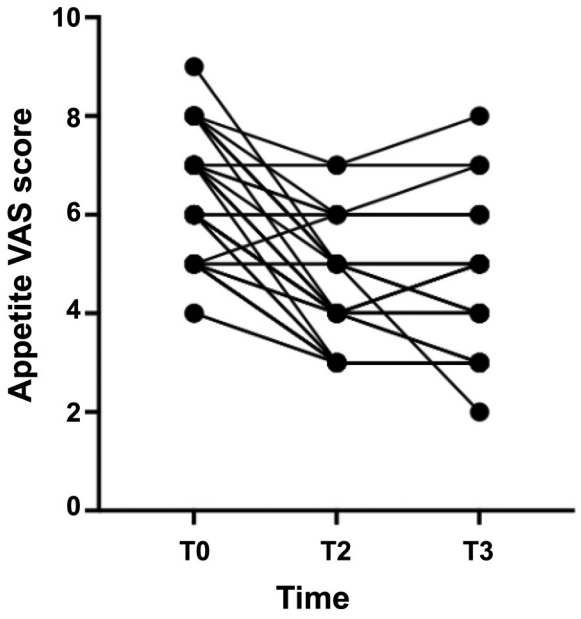

Figure 2. *Effects of L-arginine/vitamin C supplementation over time on self-reported appetite in patients with cancer at the beginning of treatment (T0), and at 30 (T2) and 60 (T3) days respectively. VAS: Visual analog scale.*

and QoL has led to the development of a wide array of assessment tools for screening and diagnosing CRF (3). A comprehensive and critical review of CRF identified more than 20 different fatigue measures that investigate unidimensional or multidimensional aspects of the issue (14). Unidimensional measures typically consist of single-question scales designed to capture the incidence and severity of CRF. In contrast, multidimensional measures evaluate the broader impact of CRF across physical, emotional, and cognitive domains (14).

Despite the recommendations of most international guidelines for patients to receive information and education about CRF before starting treatment–screening and assessing which should be done using rating scales or questionnaires–patients remain poorly informed about this issue (3, 15, 16). Exercise or regular physical activity is the most employed method to alleviate CRF, often motivated by individual initiative rather than medical advice, which typically favors prescribing pharmacological agents such as steroids, whose chronic use can lead to severe toxicity (4, 14). Other mindfulness practices or physical therapy are only occasionally implemented, and psychological support alone seems ineffective (4, 14).

Patients with cancer exhibit systemic inflammation, which increases protein catabolism and encourages the release of free amino acids to assist muscle protein remodeling and metabolism (17, 18). Malnutrition is a result of inflammation linked to tumor growth, and this raises the risk of cachexia and is related to fatigue. Therefore, nutritional therapies have gained popularity as a prophylactic strategy to manage cachexia caused by cancer (19). Hence, the rationale for using oral supplementation is the assumption that oral nutritional supplements may confer an ergogenic effect and enhance exercise capacity above and beyond that received through diet food ingestion alone (20).

In some clinical settings, such as infection, burns, and surgery, the demand for arginine cannot be fully met by *de novo* synthesis and regular dietary intake. Arginine and glutamine may act by reducing inflammation and infection progression, thus promoting improvements in food intake (18, 20, 21). Creatine exerts anabolic activity, acting as an immediate energy substrate to support muscle contraction and further increase lean mass, mainly due to greater water uptake by muscle (22, 23). Orally supplemented L-arginine has been shown to improve endothelial dysfunction and reduce respiratory support and length of in-hospital stay *versus* placebo in patients hospitalized for severe COVID-19 (22, 23). A prospective study examined the effects of two L-arginine-based supplements on 500 patients with COVID-19 infection-related fatigue (24). The fatigue level assessed by the Fatigue Assessment Scale significantly decreased, suggesting that supplements with L-arginine may be proposed as a remedy to restore physical and mental performance affected by the fatigue burden in people with COVID-19.

Perioperative immune-nutrition with added L-arginine was shown to significantly reduce the length of hospital stay and the incidence of infectious complications in patients with cancer (25, 26)Several recent studies have indicated that vitamin-C alleviates cancer and chemotherapy-related symptoms, such as fatigue, insomnia, loss of appetite, nausea, and pain (27). Improvements in physical, role, cognitive, emotional, and social functioning and overall health were also observed. Therefore, vitamin C is a potential partner for L-arginine. It has been reported that high NO levels in endothelial cells can enhance exercise performance. In murine models, supplementation with a combined extract containing L-arginine (along with L-glutamine, vitamin C, vitamin E, folic acid, and green tea extract) significantly increased serum NO levels in a dose-dependent manner and reduced fatigue (28).

In the medical literature, the reports of the role of L-arginine supplementation in patients with cancer are limited. Eighty-eight patients receiving concurrent chemoradiotherapy for head and neck, esophageal, and cervical cancer were randomized to receive either a standard diet or a diet supplemented with L-arginine, glutamine, and fish oil (29). Patients who received the supplements had a higher completion rate, fewer grade 3-4 hematological toxicities, and longer survival compared to those who did not receive.

Saligan *et al.* measured FACT-F fatigue scores before and during treatment and plasma arginase type 1 gene expression in 30 patients with non-metastatic prostate cancer receiving external-beam radiation therapy (30). Fatigue significantly worsened from baseline to the end of treatment, and its intensity was linked to the upregulation of plasma arginase type 1 gene expression. In contrast, genes associated with the adaptive immune functional pathway [cluster of differentiation 28 (*CD28*), *CD27*, C-C chemokine receptor type 7 (*CCR7*), CD3 δ subunit of T-cell receptor complex (*CD3D*), *CD8A*, and major histocompatibility complex, class II, DO β (*HLA-DOB*)] were significantly downregulated. Radiation-induced upregulation of the plasma arginase type 1 gene may be crucial in intensifying fatigue through arginine deficiency and suppressing T-cell proliferation pathways.

The present non-comparative study demonstrates a statistically significant positive effect of oral L-arginine/vitamin C supplementation on CRF and HR-QoL scores. On the other hand, there was no positive effect of oral L-arginine/vitamin C supplementation on appetite except in a minority of cases. However, our study has some limitations. The patient sample was relatively small and included various tumor types,

disease stages, and types of antineoplastic treatments, which are confounding factors since they may influence responses to supplementation with L-arginine/vitamin C. Therefore, we are planning to test L-arginine /vitamin C supplementation in larger series selected for specific oncological diseases with more standardized entry criteria.

Conclusion

The reported data support the use of L-arginine /vitamin C in counteracting CRF and maintaining QoL. This agent is very well tolerated and accepted by patients and their caregivers. However, further studies are needed in patient populations homogeneous for cancer type, antitumor therapy, clinical setting, and comorbid diseases such as diabetes.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Conceptualization, VG and MRV; methodology, VG; formal analysis, DS; investigation, AC, IF, DA, GS, DS, RV; data curation, MG, VG; writing–original draft preparation, VG and DS; writing–review and editing, VG and MRV. All Authors read and agreed to the published version of the manuscript.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine-learning software, were used in the preparation, analysis, or presentation of this manuscript.

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