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ORIGINAL ARTICLE

Open phase II study on efficacy and safety of an oral amino acid functional cluster supplementation in cancer cachexia

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Abstract The aim of the present study was to test the efficacy and safety of an oral amino acid functional cluster (AFC) supplementation in cachectic cancer patients. From April 2008 to March 2009, we carried out an open non-randomized phase II study on 25 cachectic advanced (all stage IV) cancer patients with tumor at different sites who received an oral AFC supplementation for 8 weeks. Efficacy was assessed on the basis of improvement of some nutritional/functional (weight, body mass index, lean body mass and grip strength), quality of life (fatigue) and laboratory (albumin, fibrinogen, C-reactive protein, proinflammatory cytokines, leptin and reactive oxygen species) variables. Safety was evaluated according to the NCI-CTCAE version 3. Patients supplemented with the AFC achieved an increase in grip strength ($P < 0.0001$) and total serum albumin ($P = 0.0003$) and a decrease in ROS levels ($P = 0.001$). Moreover, our study showed a trend toward an increase in body weight and leptin and a decrease in CRP and IL-6. In conclusion, the results of the present study suggest that amino acid supplementation may be a significant rational tool for the treatment of cancer cachexia. Our preliminary data should be confirmed in a larger sample size and by a properly designed randomized clinical trial. According to our longstanding experience, a potential area of further research may be to integrate amino acid supplementation into a multi-dimensional approach based on diet, nutritional support and molecularly targeted drugs for the management of cancer cachexia.

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Introduction

Cancer-related anorexia/cachexia syndrome (CACS), which often precedes death, is complex and is characterized by progressive weight loss with depletion of host reserves of skeletal muscle and, to a lesser extent, adipose tissue, anorexia, reduced food intake, poor performance status, and quality of life. At diagnosis, 80% of patients with upper gastrointestinal cancers and 60% with lung cancer have already experienced substantial weight loss [10].

Changes in nutrient metabolism have been reported in patients with cancer-associated cachexia. Increased turnover of liver and muscle proteins, gluconeogenesis from amino acids of muscle origins and acute phase protein (APP) synthesis in the liver are thought to contribute to the rapid muscle wasting seen in CACS [3].

Proinflammatory cytokines including interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, play a central role in the pathogenesis of metabolic alterations that occur in cachexia [4]. Moreover, plentiful evidence has been provided about the mechanisms linking oxidative stress and cancer cachexia [24].

Alterations in protein and amino acid metabolism appear to play a major role in the pathogenesis of CACS. Several factors contribute to changes in the amino acid metabolism in cancer, including reduced dietary intake, chronic inflammation that stimulates hepatic protein synthesis as a part of acute phase response, increased oxidation of branched-chain amino acids (BCAA: leucine, isoleucine and

valine) and net catabolism of skeletal muscle through a reduction in protein synthesis and activation of proteolysis. Indeed, in cachexia an extremely high amino acid amount is consumed to maintain energy. In fact, amino acids: (a) are rapidly absorbed regardless of pancreatic activity [33], (b) reduce insulin resistance [40], (c) induce the hepatic synthesis of anabolic molecules such as growth hormone and insulin-like growth factor [16] and (d) modulate the catabolic hormone-mediated effects on adipocytes [34].

The predominant features of CACS, i.e., progressive loss of muscle mass and function, have been shown to be affected only minimally by the nutritional or pharmacologic tools currently available [29]. Unfortunately, although much progress has been made in the understanding of the pathophysiologic mechanisms leading to CACS/OS, the development of early and effective interventions aimed at preventing and/or reversing the metabolic changes ultimately leading to muscle wasting is far from being attained [9].

Exogenous amino acid supplementation has been used as a complementary or alternative therapy to counteract cachexia. The best suitable qualitative and quantitative amino acid composition for an alternative and/or complementary nutritional therapy is still being studied in different research areas [35]. Among amino acids, BCAA, in particular, have been used to improve nitrogen balance, particularly muscle protein metabolism [5]. BCAA may also be useful to counteract anorexia by competing for tryptophan, the precursor of brain serotonin, across the blood–brain barrier and thus blocking increased hypothalamic activity of serotonin [19]. Oral supplementation of BCAA successfully decreased the severity of anorexia in cancer patients [11].

Many different approaches exist for developing dietary supplementation with formulation of amino acids targeting specific metabolic changes. However, the number of different combinations is so great that no satisfactory mathematical model actually exists to accomplish it, although attempts of outstanding quality have been published [31, 43]. A potentially useful approach may be to develop clusters of amino acids which according to their chemical structure can be used as intermediate molecules to trigger physiologic metabolic pathways driven to energy production. This allows to create an amino acid-composed functional cluster that contains amino acids whose reciprocal stoichiometric ratios have been calculated to match the energy needs of the metabolism and the maintenance of protein synthesis in hypercatabolic states [13].

Aim of the study

Aim of the present study was to test the efficacy and safety of an amino acid functional cluster (AFC) (containing also BCAA) in cachectic patients with advanced cancer at different sites. As efficacy variables we evaluated nutritional/functional [body weight, body mass index (BMI), lean body mass and grip strength], fatigue and laboratory variables [albuminemia, proinflammatory cytokines IL-6 and TNFα, C-reactive protein (CRP), leptin and ROS].

Patients and methods

Eligibility criteria were: advanced histologically confirmed tumor at any site; weight loss ≥5% of ideal or pre-illness body weight in the last 3 months before study enrolment plus at least one of the following signs or symptoms associated with cancer cachexia (anorexia, fatigue, anemia, high levels of inflammatory mediators, i.e. IL-6, CRP). Exclusion criteria were: significant comorbidities; mechanical obstruction to feeding; medical treatments inducing significant changes of patient metabolism or body weight. All patients gave their written informed consent to participate in the study.

Study design

Open non-randomized phase II study carried out from April 2008 to March 2009, approved by the Institutional Ethics Committee. Patients were evaluated at baseline and after treatment (8 weeks) for all variables (nutritional, quality of life and laboratory). After baseline assessment patients started the AFC treatment (AMINOTROFIC, Errekappa Euroterapici, Milan, Italy) for 8 weeks.

Treatment plan

Patients received the AFC (AMINOTROFIC, Errekappa Euroterapici, Milan, Italy) containing L-leucine 1,250 mg, L-lysine 650 mg, L-isoleucine 625 mg, L-valine 625 mg, L-treonine 350 mg, L-cystine 150 mg, L-histidine 150 mg, L-phenylalanine 100 mg, L-tyrosine 30 mg, L-tryptophan 20 mg, vitamin B6 0.15 mg and vitamin B1 0.15 mg per sachet. The planned treatment was 1 sachet twice a day for 8 weeks. Patients were instructed to mix the entire content of the sachet with 200 ml of water and mix it for 1 min to produce an orange flavor drink. This drink was taken twice a day: in the morning immediately after breakfast and in the evening immediately after dinner. Compliance with treatment was ascertained by asking each participant to return unopened sachets. All participants were instructed to maintain their habitual dietary habits throughout the study.

Outcome measures

Nutritional/functional status (weight, BMI, lean body mass by bioelectric impedance analyzer and grip strength),

fatigue by the multidimensional fatigue symptom inventory-short form (MFSI-SF) and laboratory variables (albumin, hemoglobin, absolute lymphocyte count, CRP, proinflammatory cytokines and ROS) were assessed at baseline and immediately after treatment.

Nutritional/functional assessment

BMI was calculated as body mass (kg)/height squared (m^2). LBM measurement was carried out with a bioelectric impedance analyzer (Bioelectric Impedance Analyser, BIA, 101, Akern Spa) using the standard four-electrode arrangement at 800 mA and 50 kHz. Body composition data analyzed by bioelectrical impedance analyzer are derived from correlations of resistance and reactance. During measurement with a bioelectrical impedance analyzer, the subject lies supine with arms and legs angled outward so that the medial surfaces of the limbs do not touch each other. For conventional whole-body measurement, electrodes are placed between the hand and the foot of the dominant side.

Grip strength was measured by a dynamometer (Jamar hand dynamometer; Jamar, Chicago, IL). Patients were asked to sit comfortably with shoulders adducted and elbow flexed at 90° and to squeeze the hand at maximum strength. Each test was repeated three times.

Fatigue assessment

Fatigue assessment was performed with the Italian version of the MFSI-SF QoL questionnaire [41, 42]. The MSFI-SF, a self-administered questionnaire, consists of 30 items designed to assess the multidimensional nature of fatigue. The patients indicate to what extent they have experienced each symptom during the preceding 1-week period on a five-point scale rating from 0 (not at all) to 4 (extremely). The MFSI-SF consists of five subscales and each subscale includes six items: general scale, physical scale, emotional scale, mental scale, and vigor scale. Fatigue by MFSI-SF is calculated by a numerical score: the possible total fatigue score ranges from −20 to 96. The first four MFSI-SF subscale scores (general, physical, emotional, and mental fatigue) are added, and the vigor scale score is subtracted to generate the total fatigue score. The highest MFSI-SF scores are associated with higher levels of fatigue.

Laboratory variables

Plasma albumin concentration was also measured by a nephelometric technique. Routine laboratory analysis of hemoglobin, absolute lymphocyte count and CRP concentration was carried out. The coefficient of variation for these methods, over the range of measurement, was less than 5% as established by routine quality control procedures.

Proinflammatory cytokines (IL-6 and TNF-α) were assessed by enzyme linked immunosorbent assay (Immunotech, Marseille, France) using monoclonal antibodies for two different epitopes of the cytokine molecules. Absorbance of the sample was analyzed by spectrophotometer at 450 nm. Serum leptin levels were determined with an enzyme linked immunosorbent assay using a monoclonal antibody specific for human leptin [Diagnostic Systems Laboratories, Webster (TX) USA]. Absorbance was measured by spectrophotometer at 450 ± 10 nm.

ROS were determined on fresh blood samples using the FORT-test (Callegari, Catellani Group, Parma, Italy), which is based on the Fenton reaction. When 20 µl of blood sample is dissolved in an acidic buffer, the hydroperoxides react with the transition metal ions liberated from the proteins in the acidic medium and are converted to alkoxy and peroxy radicals. The radical species produced by the reaction that are directly proportional to the quantity of lipid peroxides present in the sample interact with an additive (phenylenediamine derivative) that forms a radical molecule evaluable by spectrophotometer at 505 nm (Form CR 2000, Callegari, Parma, Italy). Results are expressed as FORT U (Fort Units) where 1 FORT U corresponds to 0.26 mg/l of H_2O_2. More details about these techniques have been reported in our previous studies [25, 26].

Safety

Adverse events were classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events $(CTCAE)_{v3.0}$ criteria [1].

Statistical analysis

Results are reported as mean ± standard deviation (M ± SD). Differences between baseline and post-treatment values were assessed by the two-tailed Student's *t* test for paired data or Wilcoxon signed-rank test for non-parametric variables. $P \leq 0.05$ was considered statistically significant.

Results

Patient characteristics

From April 2008 to March 2009, 25 patients were enrolled in the study (male-to-female ratio 13:12, mean age 65.8 years, range 55–70); their clinical characteristics are reported in Table 1. The most represented sites were head

Table 1 Patient clinical characteristics

	Number of patients
Enrolled	25
M/F ratio	13/12
Age (years) (mean ± SD)	65.8 ± 11.4
Range	55–70
Weight (kg) (mean ± SD)	59.3 ± 3.15
Range	50–65
Height (cm) (mean ± SD)	166 ± 3.49
Range	160–175
Tumor sites (%)	
Head and neck	9 (36)
Lung	5 (20)
Ovary	4 (16)
Colon	3 (12)
Stomach	1 (4)
Breast	1 (4)
Endometrium	1 (4)
Pancreas	1 (4)
Stage (%)	
IV	25 (100)
ECOG PS (%)	
0	2 (8)
1	11 (44)
2	12 (48)

ECOG PS Eastern Cooperative Oncology Group Performance Status

and neck, lung and ovarian cancer. All patients had metastatic disease (100% stage IV): the metastatic sites were 40% of hepatic and 60% extra hepatic. ECOG performance status was 2 in 48% of patients, 1 in 44% of patients and 0 in 8% of patients. The patient weight loss was >5 and ≤10%. Almost all patients (>90%) during the study were given antineoplastic treatment. Approximately 50% of patients were treated with analgesics for pain relief: the majority of them were given strong opioids. No patients were treated with albumin replacement during the study.

All patients received the planned treatment without dose reduction and completed the planned evaluation.

Nutritional/functional assessment

Body weight, BMI and LBM did not change significantly during treatment (Table 2). The baseline BMI of patients (19.7) is just over the limit of malnutrition (<18.5), but it should be taken into account that several patients had lost weight and some of them at a considerable extent.

Grip strength evaluated by dynamometry increased significantly (28.2 ± 9.5 vs. 30.4 ± 9.2, $P < 0.0001$) after treatment.

Fatigue assessment

Fatigue improved, i.e. MFSI-SF score decreased, but not significantly (25 ± 8.1 vs. 22 ± 7.3, $P = 0.181$) (Table 2).

Laboratory variables

Albumin increased significantly (2.99 ± 0.67 vs. 3.6 ± 0.3 g/l, $P = 0.0003$) while ROS decreased significantly (447.3 ± 152.1 FORT U vs. 371.3 ± 162.2 FORT U, $P = 0.001$) after treatment (Figs. 1, 2). Proinflammatory cytokines and CRP levels decreased but not significantly (IL-6: 21.3 ± 16.4 vs. 13.7 ± 4 pg/ml, $P = 0.157$; TNFα: 22.1 ± 11.9 vs. 19.5 ± 7.6 pg/ml, $P = 0.526$; CRP: 24.7 ± 18.1 vs. 17 ± 11.4, $P = 0.066$), while leptin levels showed a borderline increase (3.6 ± 4.5 vs. 10.8 ± 11.7 ng/ml, $P = 0.052$) (Table 3).

Safety

According to the NCI-CTCAE, no toxicity of any grade was observed nor adverse events possibly related to the AFC administration were reported for any patient. Treatment was well tolerated by all patients and no patient had to discontinue it.

Discussion

The present open phase II study is one of the few studies aiming to assess the effect of a balanced AFC on some key nutritional/functional and laboratory variables of CACS. It demonstrates that cancer patients supplemented with the AFC achieved an increase in grip strength and total serum albumin and a decrease in ROS blood levels. Moreover, our study shows a trend toward an increase in leptin and a decrease in CRP. However, these changes were not statistically significant probably due to the small patient

Table 2 Change of nutritional/functional and quality of life parameters during treatment

Parameters	Baseline	After treatment	*P* value
Weight (kg)	53.1 ± 10.6	54.2 ± 11.1	0.056
BMI	19.7 ± 2.8	19.8 ± 2.9	0.119
Lean body mass (kg)	41.2 ± 8.3	42.6 ± 6.7	0.221
Grip strength (kg)	28.2 ± 9.5	30.4 ± 9.2	**0.0001**
Fatigue (MFSI-SF)	25 ± 8.1	22 ± 7.3	0.181

Difference between mean was calculated by Student *t* test for paired data. Results were considered significant if $P < 0.05$

BMI body mass index, *MFSI-SF* multidimensional fatigue symptom inventory-short form

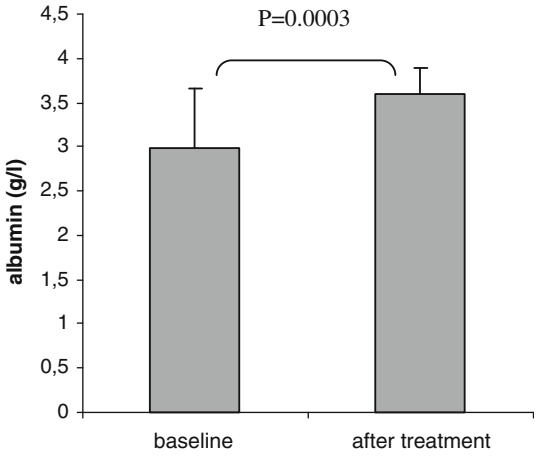

Fig. 1 Change of albumin levels (g/l) during amino acid supplementation treatment. Difference between mean was calculated by Student *t* test for paired data. Results were considered significant if $P < 0.05$

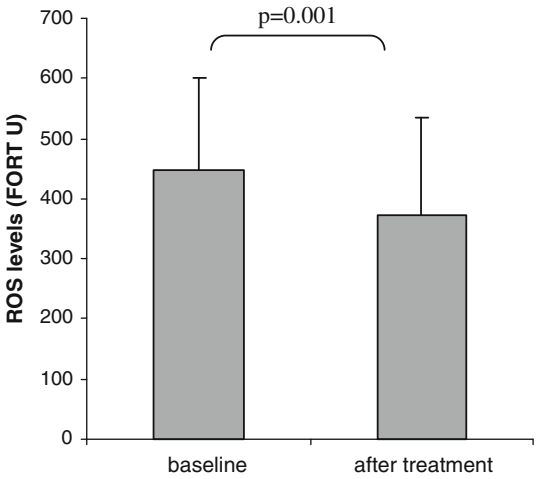

Fig. 2 Blood levels of reactive oxygen species (ROS) before and after treatment with amino acid supplementation. Difference between mean was calculated by Student *t* test for paired data. Results were considered significant if $P < 0.05$

sample size. Additionally, it is to be taken into account that the treatment duration was 8 weeks. It may be hypothesized that a more prolonged treatment duration could lead to a significant improvement of LBM, quality of life variables and a decrease in proinflammatory cytokines [24, 27].

Although recent studies have increasingly suggested that a combined treatment (dietary, nutritional supplementation and pharmacologic) seems to have the potential to reverse CACS and improve the associated symptoms that affect QL [2, 24, 27], the single agent nutritional approach used in the present study has an interesting rationale.

Indeed, amino acids act as specific positive signals for the maintenance of muscular protein stores through several mechanisms. First, amino acids may reduce the negative

Table 3 Change of serum levels of albumin, inflammatory and oxidative stress parameters during treatment

Parameters	Baseline	After treatment	*P* value
Albumin	2.99 ± 0.67	3.6 ± 0.30	**0.0003**
Hemoglobin (g/dl)	10.7 ± 1.5	11.2 ± 1.6	0.894
Absolute lymphocyte count (1 μl^{-1})	1,473 ± 559	1,673 ± 872	0.284
CRP	24.7 ± 18.1	17 ± 11.4	0.066
IL-6 (pg/ml)	21.3 ± 16.4	13.7 ± 4	0.157
TNF alpha (pg/ml)	22.1 ± 11.9	19.5 ± 7.6	0.526
Leptin (ng/ml)	3.6 ± 4.5	10.8 ± 11.7	0.052
ROS (FORT U)	447.3 ± 152.1	371.3 ± 162.2	**0.001**

Difference between mean was calculated by Student *t* test for paired data. Results were considered significant if $P < 0.05$

BMI body mass index, *MFSI-SF* multidimensional fatigue symptom inventory-short form

influence of hormone-mediated catabolic stimuli. In addition, at high physiologic concentrations, amino acids activate different important steps of protein synthesis [33]: in animals and humans acute intravenous infusion of an amino acid mixture stimulated protein synthesis in skeletal muscle but not in the liver [32, 36]. It has been suggested that protein synthesis can occur through an additional metabolic pathway involving the insulin-like growth factor-1 (IGF-1): amino acid flow through the portal vein is the signal for IGF-1 secretion which is, in turn, responsible for the activation of growth hormone that promotes protein synthesis and counteracts hypercatabolic states [16]. In addition, IGF-1 seems to reduce skeletal muscle protein catabolism under stressful conditions. Moreover, recent data suggest that amino acids directly act on protein synthesis through a post-transcriptional control [33]. Additionally, recent findings have shown that leucine-enriched essential amino acids can influence the mTORC1 signaling pathway which plays an important role in controlling muscle protein synthesis in response to nutrients and exercise [15].

Indeed, amino acids are direct and/or indirect sources of energy, regulating ATP production and utilization. Carbon skeleton of amino acids has two major destinations: (1) conversion to glucose and then to tissue glycogen and (2) oxidation to CO_2 via the tricarboxylic acid (Krebs) cycle. The amino acid metabolic pathway produces basic intermediates for energy production and utilization, such as pyruvate and dicarboxylic intermediates of the Krebs cycle, including acetyl-coenzyme A (CoA), citrate, α-ketoglutarate, succinylCoA, fumarate and oxaloacetate. In addition, specific amino acids play a key role for the synthesis of molecules that regulate ATP synthesis, such as creatine and carnitine, and counteract free radical damage, such as glutathione [33]. Vice versa, in hypercatabolic states, such

as CACS, the altered energy and single nutrient metabolism and the related insulin resistance cause muscle protein catabolism and amino acid release which are used by the liver cells to produce glucose through gluconeogenesis.

Therefore, a selected and balanced AFC supplementation may be a powerful tool in counteracting muscle wasting and nutritional/functional impairment of cachectic patients.

All amino acids present in the proposed cluster may have pharmacological properties to counteract the metabolic, nutritional and functional abnormalities of CACS. In detail, a specific role in controlling protein synthesis has been attributed to leucine, an essential ketogenic amino acid of the BCAA family. High amounts of leucine blunt catabolism and promote protein synthesis [23]. Leucine is metabolized mostly for energy production in peripheral muscles rather than in the liver. Moreover, BCAA stimulates the synthesis of glutamine and alanine (especially from valine) which are then exported to the liver to form glucose and to the gut as energy substrates [37]. On the basis of the available data BCAA appear to exert significant antianorectic and anticachectic effects: by interfering with brain serotonergic activity and by inhibiting the overexpression of muscle proteolytic pathways, they have been shown to induce beneficial metabolic effects in different chronic diseases [22].

Besides BCAA, other amino acids should also be present to maximally exert a cooperative messenger role in promoting availability in energy substrate. Moreover, an imbalanced supply of non-essential amino acids may differently influence glucose-dependent energetic metabolism [13].

In the proposed AFC an important role is also played by cystine which is the stable disulfide form of cysteine. Moreover, humans can synthesize cysteine from the sulfur-containing amino acid methionine. Several clinical studies on cysteine supplementation, most of them performed with either *N*-acetylcysteine or a naturally derived cysteine-rich protein isolate, have demonstrated many positive effects: (1) increase in intracellular glutathione concentration in human lymphocytes [30] and heart muscle tissue [6]; (2) increase in grip strength evaluated by dynamometer [18] or by a whole leg isokinetic test [21]; (3) an amelioration of the loss of body cell mass in cancer patients [17]; (4) a significant decrease in serum levels of several proinflammatory cytokines [27]. These findings are in keeping with the decrease in ROS levels, which is clearly related to the increased antioxidant capacity, i.e. GSH, and the improvement of muscle strength observed in the present study.

Albumin is the preferred source of amino acids by cells by being the most abundant protein in circulating plasma, and accounting for about 50–70% of the human plasma protein reserve. The marked decrease of albumin is often seen in almost all catabolic conditions, including cancer cachexia. Both in elderly subjects [7] and in patients with wasting syndrome [39] a low plasma albumin was found to be a strong predictor for loss of muscle mass and short survival. Hack et al. [17] have also shown in cancer patients that the amino acid cysteine supplementation increased the (otherwise low) plasma albumin levels. As albumin is present in plasma in both the reduced and the oxidized form, which has a higher catabolic rate [20], the effect of cysteine supplementation may be explained by the conversion of oxidized albumin into its more stable reduced form [14].

The increase in plasma albumin observed in the present study after AFC supplementation may have also influenced the decreased oxidative stress since albumin substantially contributes to the redox buffer of the blood [17].

Despite a large amount of encouraging experimental studies on animal models of cachexia [5], to date very few clinical trials have tested the efficacy of amino acid supplementation in cachectic patients.

In detail, some authors tested the efficacy of a beta-hydroxy-beta-methylbutyrate (HMB) (a precursor metabolite of leucine), arginine and glutamine mixture supplementation on cachectic cancer patients [8, 29, 38]. Rathmacher [38] showed that the amino acid mixture supplementation resulted in an improvement of the emotional profile, decreased feeling of weakness, correction of anemia (increased red blood cells count and hemoglobin) and lymphocytopenia when compared with placebo. More recently, Berk [8] was unable to adequately test the ability of the amino acid mixture to improve LBM, weight, fatigue and QL in a population of advanced cancer patients with cachexia: only 37% of the 472 randomized patients completed the treatment and they showed just a strong trend toward an increased LBM. Moreover, May et al. [29] in 32 cachectic patients with tumors at different sites observed that the above mixture of amino acids was effective in inducing a significant increase in fat free mass: while the mechanism of action is unclear, the authors hypothesized that arginine and glutamine supplementation enhances net protein synthesis while HMB supplementation minimizes protein breakdown.

Outside cancer cachexia, a randomized study in AIDS-associated wasting patients indicated that an oral supplementation of the amino acids glutamine, arginine and HMB increased patient muscle mass and body weight, besides $CD3^+$ and $CD8^+$ lymphocyte count [12]. Moreover, a more recent study on 40 patients with rheumatoid cachexia showed that two different amino acid mixtures administered for 12 weeks were both able to significantly improve fat free mass, total body protein and physical functioning [28]. The most recent study, carried out in 41 elderly

subjects with sarcopenia, showed that an oral amino acid mixture supplementation, very similar to that tested in the present study, was able to significantly increase LBM assessed by DEXA and induce a significant decrease of some indexes of insulin resistance as well asTNFα [40].

In conclusion, the results of the present study and the current available literature suggest that amino acid supplementation may be a significant rational tool for the treatment of cancer cachexia. It can be hypothesized that amino acid supplements, taken together with effective, targeted and possible causal anticachectic therapies, may improve muscle protein metabolism and cell functions [34]. Regarding specifically head and neck cancer patients, who represented 36% of the sample studied, the AFC supplementation may have acted both in increasing nutritional intake and through its beneficial metabolic effect.

Our preliminary data warrant to be confirmed in a larger sample size in a properly designed randomized phase III clinical trial. According to our longstanding experience, a potential area of further research may be to integrate amino acid supplementation into a multi-targeted approach based on diet, nutritional support and molecularly targeted drugs for the management of cancer cachexia.

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Conflict of interest None.

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