Ther Adv Med Oncol
2020, Vol. 12: 1–11
DOI: 10.1177/1758835919890281

Early intravenous administration of nutritional support (IVANS) in metastatic gastric cancer patients at nutritional risk, undergoing first-line chemotherapy: study protocol of a pragmatic, randomized, multicenter, clinical trial

Riccardo Caccialanza, Emanuele Cereda, Catherine Klersy, Silvia Brugnatelli, Valeria Borioli, Alessandra Ferrari, Marilisa Caraccia, Federica Lobascio, Anna Pagani, Sara Delfanti, Giuseppe Aprile, Michele Reni, Lorenza Rimassa, Davide Melisi, Stefano Cascinu, Luca Battistini, Francesca Candiloro and Paolo Pedrazzoli

Abstract

Background: Malnutrition is common in cancer patients, particularly in those affected by gastrointestinal malignancies, and negatively affects treatment tolerance, survival, functional status, and quality of life (QoL). Nutritional support, including supplemental parenteral nutrition (SPN), has been recommended at the earliest opportunity in malnourished cancer patients. The limited available evidence on the efficacy of SPN in gastrointestinal cancer patients is positive, particularly with regards to QoL, body composition, and energy intake, but the evidence on survival is still scanty. Furthermore, studies regarding the early administration of SPN in combination with nutritional counseling from the beginning of first-line chemotherapy (CT) are lacking. We hypothesize that early systematic SPN in combination with nutritional counseling (NC), compared with NC alone, can benefit patients with previously untreated metastatic gastric cancer at nutritional risk undergoing first-line CT.

Methods: The aim of this pragmatic, multicenter, randomized (1:1), parallel-group, open-label, controlled clinical trial is to evaluate the efficacy in terms of survival, weight maintenance, body composition, QoL and feasibility of cancer therapy of early systematic SNP. This is in combination with NC, compared with NC alone, in treatment-naïve metastatic gastric cancer patients at nutritional risk undergoing first-line CT.

Discussion: Malnutrition in oncology remains an overlooked problem. Although the importance of SPN in gastrointestinal cancer patients has been acknowledged, no studies have yet evaluated the efficacy of early SPN in metastatic gastric patients undergoing CT. The present study, which guarantees the early provision of nutritional assessment and support to all the enrolled patients in accordance with the recent guidelines and recommendations, could represent one of the first proofs of the clinical effectiveness of early intensive nutritional support in cancer patients undergoing CT. This study could stimulate further large randomized trials in different cancer types, potentially resulting in the improvement of supportive care quality.

Trial registration: This study is registered on ClinicalTrials.gov: NCT03949907.

Keywords: body composition, gastric cancer, malnutrition, nutritional counseling, supplemental parenteral nutrition, survival

Received: 26 June 2019; revised manuscript accepted: 29 October 2019.

Correspondence to:
Riccardo Caccialanza
Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Viale Golgi 19, Pavia 27100, Italy
r.caccialanza@smatteo.pv.it

Emanuele Cereda
Valeria Borioli
Marilisa Caraccia
Federica Lobascio
Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Catherine Klersy
Biometry and Clinical Epidemiology Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Silvia Brugnatelli
Alessandra Ferrari
Anna Pagani
Sara Delfanti
Medical Oncology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Giuseppe Aprile
Department of Oncology, San Bortolo General Hospital, Vicenza, Italy

Michele Reni
Department of Medical Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy

Lorenza Rimassa
Medical Oncology and Hematology Unit, Humanitas Clinical and Research Center IRCCS, Rozzano (Milan), Italy

Davide Melisi
Digestive Molecular Clinical Oncology Research Unit, Section of Medical Oncology, Department of Medicine, University of Verona, Verona, Italy

Stefano Cascinu
Department of Oncology and Hematology, University Hospital of Modena, Modena, Italy

Luca Battistini
Francesca Candiloro
Neuroimmunology Unit, IRCCS Santa Lucia Foundation, Rome, Italy

Paolo Pedrazzoli
Medical Oncology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Department of Internal Medicine, University of Pavia, Pavia, Italy

Background

Malnutrition is common in cancer patients, particularly in those affected by gastrointestinal malignancies, and negatively affects treatment tolerance, survival, functional status, and quality of life (QoL).[1–5] It is known that nutritional status tends to worsen over the course of the illness[6] and that inadequate nutritional support may negatively affect not only nutrition and function, but also prognosis in cancer patients.[2,7] In recent years, there has been growing evidence that increased treatment toxicity and poorer prognosis are associated with lean body mass (LBM) loss[8] that leads to sarcopenia in the most common cancer types[9,10] and, consequently, to impaired functional status and QoL.[11–13] Therefore, more proactive or even intensive nutritional support should be considered in this patient population.[14]

The most recently available guidelines recommend the use of supplemental parenteral nutrition (SPN) during nonsurgical therapy if cancer patients are malnourished, hypophagic, or affected by iatrogenic gastrointestinal complications, and if enteral nutrition is not feasible.[3,4] A recent task force of the American Society for Parenteral and Enteral Nutrition, however, has recommended artificial nutrition, including SPN, at the earliest opportunity in malnourished patients.[15] The limited available evidence on the efficacy of SPN in gastrointestinal cancer patients is positive, in particular with regards to QoL, body composition, and energy intake,[16–22] but the evidence on survival is still scant. Furthermore, studies on the effect of early administration of SPN in combination with nutritional counseling (NC) from the start of first-line chemotherapy (CT), are lacking.

The aim of this pragmatic, randomized, multicenter clinical trial (ClinicalTrials.gov identifier: NCT03949907) is to evaluate the efficacy in terms of survival, weight maintenance, body composition, QoL, and feasibility of cancer therapy, of early systematic SPN. This is in combination with NC, compared with NC alone, in patients with previously untreated metastatic gastric cancer at nutritional risk undergoing first-line CT.

Methods/design

Standard protocol approval, registration, and patient consent

This study will be conducted in accordance with good clinical practice and with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by the Fondazione IRCCS Policlinico San Matteo (Pavia, Italy) Ethics Committee (19 April 2019; version 1) and registered on ClinicalTrials.gov (identifier: NCT03949907). Written informed consent will be obtained from every patient entering the study by the medical personnel of the participating institutions and it will be made clear that patients may withdraw from the study at any time without providing a reason and without affecting their current or future care. General practitioners will be kept informed on the study's progress.

Design

This study will be a pragmatic, multicenter, randomized (1:1), parallel-group, open-label, controlled clinical trial. Allocation of patients, fulfilling inclusion criteria to the intervention groups, will be performed at the baseline visit according to a computer-generated randomization list. Concealment will be attained by using a web-based randomization.

Subjects

Consecutive adult patients (18 years old or more) with a histologically confirmed diagnosis of metastatic gastric and gastroesophageal junction cancer will be considered eligible in the presence of: the indication of a first-line CT with a combination of two drugs including platinum derivatives (plus Trastuzumab if HER2+) to be used according to the investigator's choice within the framework of good clinical practice and in agreement with current Italian Association of Medical Oncology guidelines;[23] a measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1);[24] a nutritional risk [Nutritional Risk Screening (NRS) 2002 score of three or more];[25] a permanent venous access (port-a-cath, Groshong, Peripherally Inserted Central Catheter) available; an Eastern Cooperative Oncology Group performance status of two or less.[26] Patients will be excluded in cases of: an indication to complete artificial nutrition support (totally compromised spontaneous food-intake); a contraindication to parenteral nutrition (PN; e.g. abnormal glucose and electrolytes control, hypertriglyceridemia, impaired hemodynamic control, or relevant fluid retention); the presence of jejunostomy for nutritional purposes; an ongoing home artificial nutrition; an unfeasible home parenteral nutrition

(HPN) for social/familial reasons, including the absence of caregivers.

Assessments

In addition to general demographic and clinical data (tumor site, histology, and stage, as well as scheduled anticancer treatment), the following assessments will be performed:

Anthropometry. Body weight (to the nearest 0.1 kg), history of 6-month and 1-month previous unintentional weight loss (WL), height (to the nearest 0.5 cm), and body mass index (BMI) will be recorded.

Nutritional requirements. Energy requirements will be estimated by multiplying the resting energy expenditure (calculated using the Harris–Benedict equation) by a correction factor of 1.5 [in obese patients (BMI >30 kg/m^2) ideal body weight at a BMI $= 23$ kg/m^2 will be used in the equation], while protein requirements will set to 1.5 g/kg of actual body weight (or ideal body weight in obese patients).[3,4,27,28]

Calorie and protein intakes. Calorie and protein intakes from food sources will be estimated at all treatment visits using the 24-h dietary recall method.[28–30] Total intakes throughout the study will be calculated taking into consideration the SPN prescriptions and will be considered achieved when total energy and protein requirements attain $\geqslant$90% of estimated requirements and $\geqslant$1.5 g/kg/day, respectively.

Nutritional risk. This will be assessed at the screening visit using the NRS-2002 screening tool,[25] which is based on the information collected on BMI, 6-month unintentional WL and food intake, as well as on diagnosis and age.

Biochemistry. In addition to standard tests usually performed to monitor CT toxicity, a series of assessments will be considered to monitor potential PN-associated metabolic complications. Accordingly, the following parameters will be evaluated at scheduled visits: glycemia, sodium, potassium, magnesium, calcium, phosphorus, triglycerides, creatinine, urea, liver serum enzymes (aspartate aminotransferase, alanine aminotransferase, gamma glutamyltransferase), total bilirubin, prealbumin, C-reactive protein, total blood count, blood iron, ferritin, vitamin B12, and folates.

Body composition. Whole-body composition will be investigated using the Nutrilab bioimpedance vector assay (BIVA; Akern/RJL). Specifically, resistance and reactance will be measured by calculating phase angle (PhA), standardized PhA (SPA), and hydration index.[31,32]

Muscle mass at lumbar level. The estimation of muscle mass will be performed using computed tomography: muscle area will be quantified on scans at L3,[33] collected at baseline disease staging and subsequent reassessments scheduled by the oncologists for the evaluation of the response to CT.

Muscle strength. Muscle strength [handgrip (HG)] will be measured using a digital hand dynamometer (DynEx™, Akern/MD Systems).[32]

Quality of life. This will be investigated using the European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30, version 3.0) and the dietician will provide instructions for the correct compilation.[34]

Symptoms. Patients will be asked about the presence or onset of symptoms potentially influencing food intake, including anorexia, dysphagia, odynophagia, dysgeusia, nausea, vomiting, and diarrhea.

Adverse complications and events. All adverse complications and events attributable to nutritional interventions (water retention and infectious, cardiac, renal, respiratory, and metabolic complications), including unplanned hospitalizations and their duration, will be recorded.

Immunologic profile. To address this exploratory endpoint in a subgroup of patients [$N = 30$ (15 consecutive patients in each randomization group)], we will integrate measurements obtained using multiple tools, with the aim of analyzing different cell subsets, their functionality, and soluble molecules in the peripheral blood. The analysis will be conducted by the Neuroimmunology Unit of the Santa Lucia Foundation IRCCS (Rome, Italy). Accordingly, blood samples (5 vials with a total volume of 40 ml) will be collected and derived serum and plasma will be analyzed using the Luminex technology for the assessment of 30 soluble factors associated with the inflammatory and immunoregulatory states (CCL2/MCP-1; CCL3/MIP-1 alpha; CCL4/MIP-1 beta; CCL5/

RANTES; CCL11/Eotaxin; CCL20/MIP-3 alpha; CD25/IL-2 receptor alpha; CX3CL1/Fractalkine; CXCL9/MIG; CXCL10/IP-10; Fas; Fas Ligand; GM-CSF; Granzyme B; IFN-gamma; IL-2; IL-3; IL-4; IL-5; IL-6; IL-9; IL-10; IL-12 p70; IL-13; IL-15; IL-17A; IL-17F; IL-22; IL-27; TNF-alpha) together with the patients' cellular immunologic profiles using 18-color flow cytometry.[35,36] The following antibodies will be used: KLRG, CXCR3, CD95, CD39, CD25, CD3, CD45RA, CD123, CD38, IL-1β, IL-12, LAIR, γδ, PD-1, Perforin, Granzyme A, Granzyme B, HLA-DR, GM-CSF, IL-2, INFγ, IL-14, TNFα, CD95, CD56, CD45RA, CCR6, CD4, CD3, CD57, CD27, CD19, CD23, CD69, CD80, CD8; CD158 b1/b2i, CD158a, CD16, NKG2A, CD56, CD4, CD127, CD161, CD11c, CD8, IL-10, IL-17, IL-6, HLA-DR, CD14, Foxp3, CD19, TNFα, Vδ2, IFNα, CD49d, CD83, CD86, live/dead.

A summary of assessments and related endpoints that will be investigated during the study, is provided in Table 1.

Treatment

Patients will be randomized to the following intervention groups:

- NC in combination with systematic early supplemental HPN since diagnosis (SPN group).
- NC alone (NC group).

NC consists of a personalized dietary prescription (including sample meal plans and recipe suggestions) tailored on personal eating patterns and food preferences, in order to achieve estimated protein-calorie requirements and taking into account chewing and swallowing abilities.[28] Regular consultation with a registered dietitian will take place every 10 days by means of face-to-face interviews (at scheduled follow-up visits) and telephone interviews (planned between CT cycles and as required by the patient). In the presence of a significant reduction in food intake, the use of oral nutritional supplements will be also considered.

Supplemental HPN will be prescribed, provided daily, and adjusted throughout the study (approximately every 10 days, until the end of the scheduled first-line CT) depending on the biochemical parameters, the estimated protein-calorie oral intakes (in order to satisfy estimated requirements) and any potential related complications. Specifically, calorie and protein targets should not exceed 40 kcal/kg and 2 g/kg of body weight (real or ideal according to BMI), respectively.[32] HPN will be infused mainly during night hours using multichamber bags containing olive oil-based lipid emulsions when not contraindicated (triglycerides levels $>$300 mg/dl). Supplemental HPN will be continued at least up to the end of first-line CT. Afterwards, it will be progressively reduced in cases showing complete recovery of usual body weight and a protein-calorie food intake $\geqslant$75% of the estimated requirements.

Where body WL exceeds 10% of the weight recorded at enrollment, patients allocated to the NC group will exit the study. They will be treated according to current supportive guidelines, including HPN and followed-up for vital status.

Endpoints

The primary outcome will be a composite of 1-year overall survival (OS) or the absence of unintentional WL $\geqslant$10% of weight recorded at enrollment. Specifically, vital status will be ascertained by means of active follow-up (in-office visits, inquiries by telephone or mail to participants or proxy respondents and linkage to municipal registries), while WL will be regularly documented at scheduled visits.

The following secondary endpoints will be also evaluated: 1-year OS; first-line treatment-related moderate–severe adverse events (grade three or greater) according to Common Terminology Criteria for Adverse Events (v4.0);[37] progression-free survival (PFS) at 12 months; rate of patients with progressive disease receiving second-line CT; total dose (%) of first-line CT administered compared with the treatment plan; objective response rate to first-line CT using RECIST criteria;[24] change in body weight at 12 months; change in handgrip strength at 12 months; change in L3 muscle mass at 4 months and, if feasible, at 12 months evaluated with computed tomography; change in PhA and SPA at 4 months and 12 months evaluated by BIVA; rate of unplanned hospitalizations at 12 months; change in EORTC QLQ-C30 score at 4 months and 12 months.

The safety of SPN will be evaluated by monitoring the incidence of catheter-related bloodstream infections and the occurrence of abnormalities in

Table 1. Summary of scheduled assessments.

Procedures and assessments	Visit 1 Baseline	Visit 2 Month 1	Visit 3 Month 2	Visit 4 Month 3	Visit 5 Month 4	Visit 6 Month 6	Visit 7 Month 9	Visit 8 Month 12
Informed consent form	X							
Demographic and general clinic data collection	X							
Cancer staging	X							
CT scheduling	X							
Inclusion/exclusion criteria	X							
Randomization	X							
Anthropometry	X	X	X	X	X	X	X	X
Calorie and protein requirements	X	X	X	X	X	X	X	X
Calorie and protein intake	X	X	X	X	X	X	X	X
Symptoms	X	X	X	X	X	X	X	X
Biochemistry	X	X	X	X	X	X	X	X
Immunologic profile*	X				X			
Body composition by bioelectric impedance	X		X		X			X
Muscle mass by computed tomography	X				X			X
Muscle strength	X		X		X			X
Total CT received					X			
CT toxicity		X	X	X	X	X	X	X
Quality of life (EORTC QLQ-C30)	X				X			X
Adverse event (safety)		X	X	X	X	X	X	X
Unplanned hospitalization					X			X
HPN compliance*		X	X	X	X	X	X	X
Survival status		X	X	X	X	X	X	X

CT, chemotherapy; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer core quality of life questionnaire version 3.0; HPN, home parenteral nutrition.
*To be assessed only in patients randomized to early HPN.

biochemical parameters (metabolic complications) and all related side effects.

Finally, the levels of soluble effectors and immunoregulatory cells at 1 week and 1 month from the start of CT will be assessed as an exploratory endpoint.

Benefit for participants

All participants will be provided with early nutritional assessment and support. The participants nutritional status will be regularly monitored and their nutritional support will be optimized according to treatment tolerance and possible side-effects.

This study may lead to significant improvements in nutritional care, which will prevent or ameliorate the effect of CT in gastric cancer patients.

Potential risks and burdens for research participants

The participants will have a permanent venous access already available. SPN will be tailored according to oral intake and regularly monitored. Nevertheless, SPN may cause discomfort or expose the patients to an increased risk of PN-associated complications that may also depend on the efficacy of the training provided to patients and caregivers with regards to HPN management. Available data, however, shows that HPN can be safely provided by caregivers and cancer patients.[38,39]

Dissemination

Results of the study will be presented at local, national, and international medical meetings. The findings of the study will be published in peer-reviewed medical/scientific journals and made open access on acceptance. If appropriate, the results of the study will be disseminated by press releases by the Fondazione IRCCS Policlinico San Matteo. Information may also be disseminated to the general public via public engagement and community outreach programs.

Statistics

In the absence of previous studies with a similar design, the calculation of the sample size is based only on the survival component of the primary endpoint. It was performed with the Stata 15.1 software (StataCorp, College Station, TX, USA). According to preliminary data available in the literature, 12-month survival is expected to be around 45% in this type of patient. It is assumed that, based on data on mortality due to malnutrition in advanced cancer patients, NC alone can increase the 12-month survival rate to 50%. Considering a study power of 80%, an alpha error at two tails of 5%, an expected survival in the experimental arm (NC + SPN) of 70%, it will be necessary to enroll about 192 patients (96 per arm) to observe 77 deaths. When this number of events is reached, the study will be discontinued. Estimation of the sample size makes use of the two-sample comparison of survivor functions using the log-rank test (Freedman method).

The analysis will be performed with the Stata 15.1 software (StataCorp, College Station, TX, USA) or subsequent versions. All tests will be 2-sided. A p value <0.05 will be considered statistically significant. For *post-hoc* comparisons and subgroup analyses the Bonferroni correction will be used.

Analysis sets. Patients who have signed informed consent and have carried out at least one planned check will be considered for analysis. The main analysis will be carried out according to the intention to treat principle: the patients of the analysis set will be analyzed (mITT) according to the treatment to which they were randomized, regardless of the treatment actually undergone. A per protocol analysis will also be performed, considering the treatment actually administered, in the absence of major deviations (including, but not restricted to, cross-over to the other arm, early drop out before second assessment, inappropriate SPN prescription and/or management, etc.) from the protocol. These will be identified before the database lock.

Primary endpoint analysis. OS will be compared using the log-rank test. The relative risk and its 95% confidence interval (CI) will be derived from a Cox model. A multivariable secondary analysis of the primary endpoint will also be performed while adjusting for age, gender, BMI, PhA, and hydration index, as confounding factors at recruitment.

In addition, the statistical analysis plan will detail some prespecified subgroup analyses, according to the site of the neoplasm, the stage of neoplasm, HER2 expression, the presence of a gastrectomy and the total number of CT cycles received during the observation period.

Secondary endpoints will be analyzed as follows.

- PFS will be compared among groups, as described for OS.
- The percentage of patients requiring second-line CT will be compared with a logistical model, with odds ratio (OR) and 95% CI calculations.
- The percentage of CT dose administered compared with the planned 4-month dosage will be compared using Student t tests for independent samples (or its nonparametric analog).

- The percentage of patients with dose-limiting toxicity will be compared with a logistic model, with OR and 95% CI calculation.
- The percentage of patients with responses to CT will be compared with a logistic model, with OR and 95% CI calculation.
- The variation over time of secondary efficacy and QoL measures will be compared between the two treatment groups by means of a generalized logistic or linear regression model for repeated measurements (according to the type of dichotomous or continuous endpoint). The test on the interaction time × treatment term will verify the effectiveness of the latter.
- For safety, descriptive statistics will be calculated separately for each treatment group.
- The following dichotomous endpoints will be considered: dose-limiting toxicity, response to CT, and catheter-related bloodstream infections.
- The following continuous endpoints will be considered: weight variations, BMI, PhA, SPA, hydration index, LBM, HG, biochemical parameters, and EORTC QLQ-C30 score.
- Definition and drop-outs management: patients who have left the study (drop-out) before 4 months will not be included in the mITT analysis population. Therefore, a sensitivity analysis will be performed with multiple imputations of missing data for the primary endpoint. Patients leaving the study after 4 months will be censored on the date of leaving for primary endpoint analysis. Every effort will be made to recover the mortality rate.
- Patients who voluntarily discontinue the study or are lost at follow-up will be considered drop-outs.

Study organization

The Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, is responsible for the project management of the trial. The study was planned by the Clinical Nutrition and Dietetics Unit, the Medical Oncology Unit, the Biometry and Clinical Epidemiology Service of the Fondazione IRCCS Policlinico San Matteo, and the board of oncologists from other institutions listed as coauthors. Periodic board meetings will be scheduled (approximately every 6 months) in order to harmonize study procedures and to monitor and share the study progression.

Participating institutes

Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; San Bortolo General Hospital, Vicenza, Italy; Azienda Socio-Sanitaria Territoriale Fatebenefratelli Sacco, Milan, Italy; Veneto Institute of Oncology-IRCCS, Padua, Italy; Azienda Socio-Sanitaria Territoriale of Melegnano e della Martesana, Italy, Milan; University Hospital of Modena, Modena, Italy; IRCCS San Raffaele Scientific Institute, Milan, Italy; Azienda Socio-Sanitaria Territoriale of Pavia, Pavia, Italy; Humanitas Clinical and Research Center IRCCS, Rozzano (Milan), Italy; University Hospital of Verona, Verona, Italy; Neuroimmunology Unit, Santa Lucia Foundation IRCCS, Rome, Italy.

Further institutes will be invited. Researchers and physicians who may be interested in participating in the trial should contact the corresponding author for detailed information.

The study protocol will be submitted to each participating institute's Ethics Committee for approval. Any possible important protocol modifications will be communicated and submitted to the same committees.

Discussion

Malnutrition in oncology still represents an overlooked problem that negatively affects clinical outcomes.[6,40,41] This is particularly marked in gastrointestinal cancer patients.[5,9,13,42–45] The evidence supporting the efficacy of nutritional support in patients affected by gastric cancer is promising, but still scant and mainly focused on the perioperative/postoperative period.[46–50]

Although the importance of PN support in gastrointestinal cancer patients has been acknowledged,[51] there are still no studies evaluating the efficacy of SPN in metastatic patients receiving first-line CT. Evidence suggests a beneficial effect of early and tightly controlled nutritional support in the presence of malnutrition.[52,53] The present study ensures the early provision of nutritional assessment and support to all the enrolled patients, in accordance with recent guidelines and recommendations,[3,4,15] and would help clarify the most appropriate and beneficial nutritional care strategy for metastatic gastric cancer patients.

Toxicity frequently requires the prolongation or reduction of planned systemic treatments, resulting in reduced response rates and poor

prognosis.[5,8,9] Therefore, nutritional support from diagnosis, aimed at satisfying estimated energy requirements in patients at nutritional risk, may enable not only the maintenance/improvement of nutritional status and QoL, but may also have a positive and decisive effect on adherence to anticancer treatment and the related curative intent.

With the present trial, we aim to verify the hypothesis that early SPN from diagnosis in metastatic gastric patients at nutritional risk undergoing first-line CT and receiving NC as standard of care not only improves nutritional status, body composition, functional status, and QOL, but also increases tolerance to CT by maintaining weight, thereby improving OS.

NC itself has been proven effective in improving protein-calorie intake and QoL in malnourished cancer patients,[54] and was recommended for all gastrointestinal cancer patients undergoing anticancer treatment more than 10 years ago.[55] However, data on its efficacy on OS and other primary clinical endpoints in gastric cancer patients are lacking.

Positive results from this trial would stimulate further large randomized trials, also in other cancer types, potentially resulting in the improvement of supportive care quality for the studied patient populations, and in the expansion of the number of patients who may benefit from HPN. In this context, the management of HPN will always require the fulfillment of adequate quality standards and the attentive consideration of any possible ethical issue regarding prescriptions' suitability and treatment interruption.

Finally, the immune response is emerging as a key factor affecting the efficacy of several anticancer treatments.[56] Olive oil-enriched lipid emulsions were shown to have promising and intriguing effects on immune function.[57] To date, the impact of PN, particularly of olive oil-based lipid emulsions, on the immunological profile of cancer patients undergoing CT has not been investigated. Therefore, we will also evaluate the immunological profile and how it changes during nutritional support in gastric cancer patients receiving first-line CT.

This approach may help to clarify the interactions between the immune system and olive oil-enriched PN. This new area of research could lead to the discovery of new molecular mechanisms regulating the immune system during CT and potentially to the development of new therapeutic strategies aimed at enhancing the efficacy of anticancer treatments.

A possible practical critical aspect of the study could be the standardization of nutritional support interventions. To achieve this, however, participating centers would need physicians and dietitians skilled in clinical nutrition and who are following standardized protocols.

Acknowledgment

The authors are grateful to Dr. Paul Baines for assistance in editing the manuscript.

Author's Note

Lorenza Rimassa is also affiliated with Department of Biomedical Sciences, Humanitas University, Pieve Emanuele Milan, Italy.

Author contributions

RC, EC, CK, SB, SD, GA, MR, LR, SC, LB, DM, and PP developed the study concept and protocol. CK, VB, MC, FL, AF, and AP assisted in further development of the protocol. RC, EC, CK, SB, SD, GA, MR, LR, DM, SC, and PP drafted the clinical study protocol, funding, and ethics application. RC, EC, CK, SB, GA, MR, LR, SC, LB, FC, and PP drafted the manuscript. All authors contributed and approved the final manuscript. RC and PP act as guarantors of the study.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: the study was funded by the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy and by an unrestricted grant from Baxter Healthcare Corporation.

Conflict of interest statement

RC has received research funding from Baxter Healthcare Corporation. RC and PP have served as consultants and/or on advisory panels for Baxter Healthcare Corporation. LB has served as scientific lecturer and/or on advisory panels for Baxter Healthcare Corporation, Roche, Merck, Teva, Genzyme and Novartis. RC and PP have participated in speakers' bureaus for Baxter Healthcare Corporation. RC and EC have participated in speakers' bureaus for Akern s.r.l.

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available owing to the Italian privacy law but are available from the corresponding author on reasonable request.

Consent for publication

All authors have approved the submission of this manuscript for publication. No restriction of future publication of data is made by any of the study partners.

Ethics approval and consent to participate

This study has been reviewed as ID 20190028466 by the Institutional Ethics Committee of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, who gave a favorable opinion (19/04/2019; version 1).

The study sponsor is Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. This study is registered on ClinicalTrials.gov Identifier: NCT03949907.

All individuals recruited to the study will participate freely and after fully informed consent.

ORCID iDs

Riccardo Caccialanza https://orcid.org/0000-0002-9379-3569

Lorenza Rimassa https://orcid.org/0000-0001-9957-3615

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