The efficacy of immunonutrition in improving tolerance to chemoradiotherapy in patients with head and neck cancer, receiving nutritional counseling: study protocol of a randomized, open-label, parallel group, bicentric pilot study

Riccardo Caccialanza (ID)**, Emanuele Cereda, Catherine Klersy, Mariateresa Nardi, Sara Masi, Silvia Crotti, Silvia Cappello, Valentina Caissutti** (ID)**, Carlotta Brovia** (ID)**, Federica Lobascio, Elena Formisano, Sara Colombo, Andrea Riccardo Filippi** (ID)**, Elisabetta Bonzano, Patrizia Comoli, Laura Catenacci, Andrea Alberti, Valeria Musella, Alessandra Ferrari, Ilaria Imarisio, Richard Tancredi, Teresa Monaco, Maria Grazia Ghi, Paolo Bossi and Paolo Pedrazzoli**

Abstract

Background: Nutritional support, including nutritional counseling and oral nutritional supplements (ONSs), has been recommended at the earliest opportunity in head and neck (H&N) cancer patients. The limited available evidence on the efficacy of immunonutrition during chemoradiotherapy (CT-RT) in H&N cancer patients is positive with regard to some secondary endpoints, but is still scanty, particularly with regard to toxicity and treatment tolerance. We hypothesize that early systematic provision of ONSs with a high-protein–high-calorie mixture containing immunonutrients (Impact) compared to standard high-calorie–high-protein nutritional blends, in addition to nutritional counseling, may be beneficial to patients with H&N cancer during CT-RT. Hence, we designed the present study to evaluate the efficacy, in terms of treatment tolerance, toxicity and response, body weight, body composition, protein-calorie intake, quality of life (QoL), fatigue, muscle strength and immunological profile of the early systematic provision of ONSs enriched in immunonutrients compared to isonitrogenous standard blends, in H&N cancer patients undergoing CT-RT.

Methods: This is a pragmatic, bicentric, randomized (1:1), parallel-group, open label, controlled, pilot clinical trial.

Discussion: Many efforts are still to be taken to improve the efficacy of nutritional support in oncology. Immunonutrition represents a promising approach also in H&N cancer patients, but the evidence on its efficacy in improving clinical outcomes during CT-RT is still inconclusive. The present pilot 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 oral immunonutrition in cancer patients undergoing CT-RT and could stimulate further large randomized trials, potentially resulting in the improvement of supportive care quality.

Trial registration: This study is registered on ClinicalTrials.gov Identifier: NCT04611113.

Keywords: chemoradiotherapy, head and neck cancer, immunonutrition, malnutrition, nutritional counseling, treatment tolerance

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
Sara Masi
Silvia Crotti
Silvia Cappello
Valentina Caissutti
Carlotta Brovia
Federica Lobascio
Elena Formisano
Clinical Nutrition and
Dietetics Unit, Fondazione
IRCCS Policlinico San
Matteo, Pavia, Italy

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

Mariateresa Nardi
Clinical Nutrition Service,
Veneto Institute of
Oncology-IRCCS, Padua,
Italy

Sara Colombo
Andrea Riccardo Filippi
Radiation Oncology
Department, Fondazione
IRCCS Policlinico San
Matteo and University of
Pavia, Pavia, Italy

Elisabetta Bonzano
Radiation Oncology
Department, Fondazione
IRCCS Policlinico San
Matteo and University of
Pavia, Pavia, Italy

PhD School in
Experimental Medicine,
University of Pavia, Pavia,
Italy

Patrizia Comoli
Laura Catenacci
Cell Factory and Pediatric
Hematology Oncology,
Fondazione IRCCS
Policlinico San Matteo,
Pavia, Italy

Andrea Alberti
Paolo Bossi
Department of Medical
and Surgical Specialties,

Radiological Sciences and Public Health, University of Brescia, ASST Spedali Civili, Brescia, Italy

Alessandra Ferrari
Ilaria Imarisio
Richard Tancredi
Teresa Monaco
Medical Oncology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Maria Grazia Ghi
Oncology Unit 2, Istituto Oncologico Veneto-IRCCS, Padua, Italy

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

Internal Medicine Department, University of Pavia, Pavia, Italy

Background

At the time of diagnosis, head and neck (H&N) cancer patients already present with a variable impairment of nutritional status.[1,2] The causes of this condition are multiple, attributable both to local factors, related to the location of the neoplasm, and to systemic factors, that is, inflammatory mediators causing tissue wasting, anorexia and weight loss. Anticancer treatments themselves (e.g. radiotherapy, chemotherapy and surgery) can be responsible for nutritional status deterioration through an increase in energy requirements and/or the reduction of food intake and nutrient absorption.[3–8] It is known that an altered nutritional status is associated with a worse prognosis and the more frequent need to suspend anticancer treatments.[3,4,9,10]

The guidelines for the nutritional management of cancer patients agree on the utility of nutritional support whenever it is necessary to improve clinical outcomes, prevent or treat malnutrition, improve the efficacy and tolerability of treatments.[3,4]

Previous studies have shown that nutritional counseling in H&N cancer patients is able to improve protein-calorie intake, prevent the deterioration of nutritional status, and improve quality of life (QoL).[1,5,11]

One recent study suggested that while some H&N cancer patients may have pretreatment normal nutritional status, early nutritional counseling is nevertheless essential for the improvement of treatment tolerance and survival outcomes.[12]

In a recent study, we have also shown that the systematic use of oral nutritional supplements (ONSs) in combination with dietary counseling further favors the maintenance of nutritional status, the recovery of QoL and, more importantly, improves the practicability of chemoradiotherapy (CT-RT).[13] This effect was substantially attributed to the increase in protein-energy intake, but also the possible anti-inflammatory action of omega-3 fatty acids could not be excluded. In this regard, it is known that the modulation of inflammation with omega-3 fatty acids and other nutrients could play a role during cancer treatments.[14] The use of immunonutrition in cancer patients has been progressively gaining attention in the past few years, as a high-calorie–high-protein nutritional blend enriched in immunonutrients (arginine, nucleotides and omega-3 fatty acids; Impact – Nestlè Health Science, Creully Sur Seulles, France) has proved effective in reducing the risk of postoperative complications (e.g. infections, fistulas, etc.) and the length of stay of patients undergoing major cancer surgery (abdominal and H&N).[15,16] In oncology, there is also a growing interest in the modulation of inflammation and immunosuppression at the tumor microenvironment level.[17]

To date, to the best of our knowledge, only one recent phase III trial has investigated the therapeutic efficacy of immunonutrient-enriched ONSs in H&N cancer patients undergoing adjuvant CT-RT in comparison with an isonitrogenous and isocaloric control supplement.[18] The intervention with the immunomodulating formula failed to reduce severe mucositis during CT-RT, but an improvement in overall survival (OS) and progression-free survival (PFS) was observed in patients who were compliant to ONSs. We speculated that the lack of effectiveness of the immunomodulating supplement was likely due to some flaws in the study design,[19] which we aim to overcome by a modified design in our present study.

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 Ethics Committee of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (29/07/2020; prot. N. 20200069594) and by that of Veneto Institute of Oncology-IRCCS, Padua, Italy (25/01/2021; prot. N. 2020/141), and was registered on ClinicalTrials.gov (NCT04611113). 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

The study will be a pragmatic, bicentric, randomized (1:1), parallel group, open label,
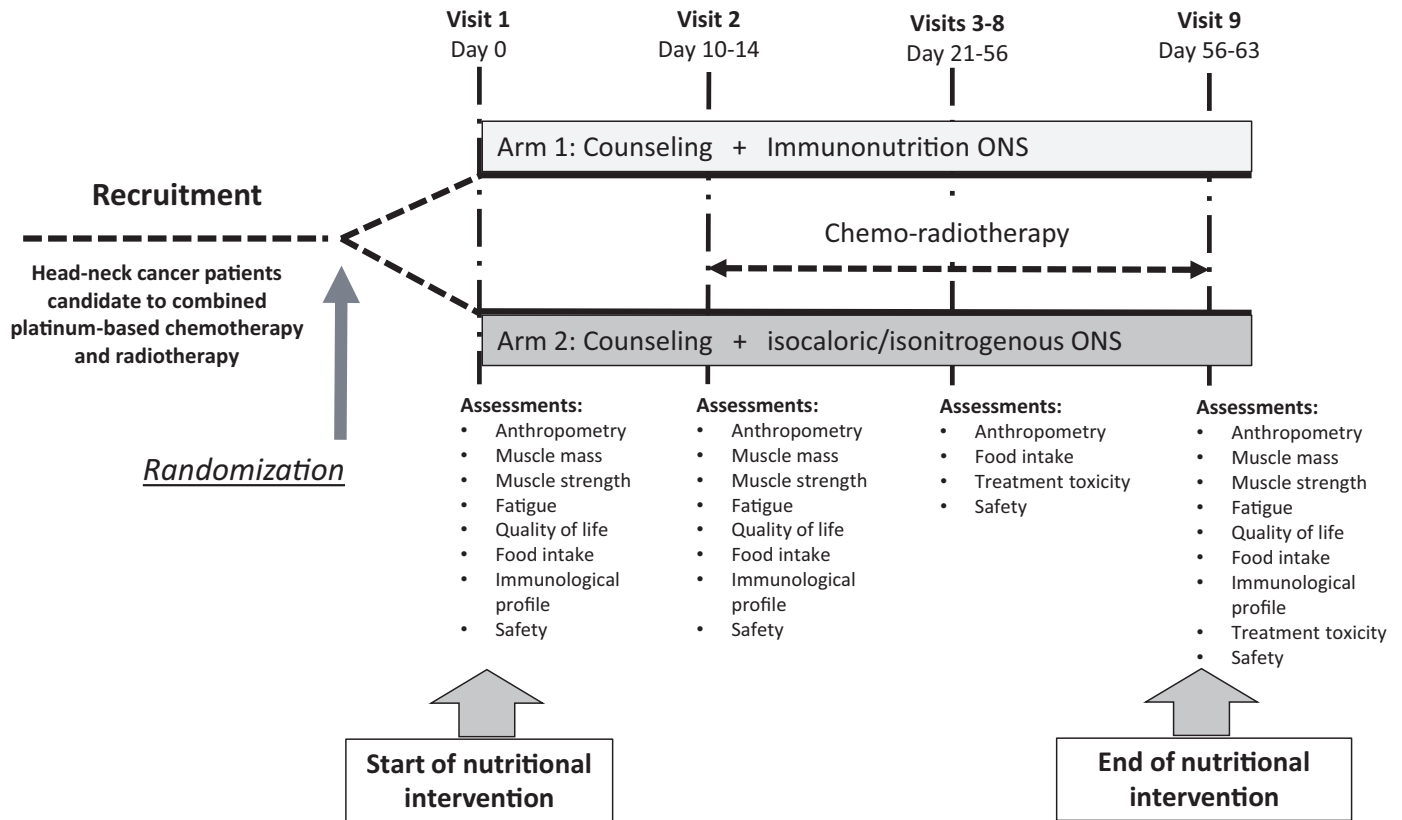
Figure 1. Study flowchart.

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.

The study flowchart is presented in Figure 1.

Subjects

Consecutive adult (≥18 years) patients with a histologically confirmed diagnosis of H&N cancer [any type (International Classification of Disease [ICD] categoriess C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C30, C31, C32), excluding thyroid gland (ICD C73)] and candidate to a platinum-based chemotherapy (CT) regimen and concomitant radiotherapy (RT) for adjuvant or curative purposes, will be considered eligible in presence of an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.[20] Patients will be excluded in cases of indication to or ongoing artificial nutrition support (totally compromised spontaneous

food-intake) and incapacity or unavailability to consume ONSs.

Assessments

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

Anthropometry: Body weight (to the nearest 0.1 kg), height (to the nearest 0.5 cm) and body mass index (BMI) will be measured and calculated according to standard procedures.[21] Information regarding unintentional weight loss (WL) during the last 6 months will be also collected.

Calorie and protein intakes: Calorie and protein intakes from food sources will be estimated at all treatment visits by evaluating a 3-day quantitative food diary, using the 24-h dietary recall method including weekdays and weekends, consulting atlas of food portions and collecting information on brand names of commercial and

ready-to-eat-foods, method of preparation, use of dressings or added fat.[13,22,23] Total intakes throughout the study will be calculated taking into consideration ONS consumption and will be considered achieved when total energy and protein requirements attain $\geq$90% of estimated requirements and $\geq$1.5 g/kg/day, respectively.

As total calorie per bottle is different between the two ONSs, this difference will be considered in the calculation of total daily energy intakes.

Nutritional risk and malnutrition: Nutritional risk will be assessed at the screening visit using the nutrition risk index 2002 (NRS-2002) screening tool, which is based on the information collected on BMI, 6-month unintentional WL and food intake, as well as on diagnosis and age.[24] Presence of malnutrition will be diagnosed according to phenotypic and etiological criteria for malnutrition proposed by the global leadership initiative on malnutrition (GLIM).[25]

Body composition: Whole body composition will be investigated using the Nutrilab Bioimpedance Vectorial Assay (BIVA; NUTRILAB Akern srl; Florence, Italy). Specifically, resistance and reactance will be measured by calculating phase angle (PhA), standardized phase angle (SPA), and hydration index (HI).[26–29] Standardization of the operative procedures and the use of the same devices will be undertaken to ensure a homogenous bioimpedance data collection.

Muscle mass at cervical level: The estimation of skeletal muscle mass (SMM) will also be performed using computed tomography. To this purpose, muscle area will be quantified on scans at C3,[30] collected at baseline disease staging and subsequent reassessments scheduled by the oncologists for the evaluation of response to CT.

Assessment of SMM at the level of C3 is easy and robust and can be performed on routinely available imaging in H&N cancer patients.[31]

Muscle strength: Muscle strength [handgrip (HG)] will be measured using a digital hand dynamometer (DynEx, Akern/MD Systems).[13,26–28]

Quality of life: It will be evaluated at baseline and at the end of treatment using the European Organization for Research and Treatment of Cancer (EORTC) core QoL questionnaire (QLQ-C30) and the EORTC head and neck cancer QoL questionnaire (QLQ-H&N35).[13,32,33]

Fatigue: Self-reported fatigue and its impact on daily activities and function will be assessed at baseline and at the end of treatment using the 40-item functional assessment of chronic illness therapy – fatigue (FACIT-F) scale.[34]

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

Adverse complications and events: All adverse complications and events attributable to nutritional interventions (gastrointestinal side effects), including unplanned hospitalizations and their duration, will be recorded.

Immunological profile: Measurements obtained using multiple tools will be integrated with the aim of analyzing different cell subsets, their functionality, and soluble molecules in the peripheral blood. Blood samples will be analyzed for the assessment of plasma interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-alfa, together with the patients' cellular immunological profiles. In detail, subsets of T effector and regulatory lymphocytes, monocytes, myeloid-derived suppressor cells and dendritic cells will be assessed by labeling with monoclonal antibodies (anti-CD3, -CD4, -CD8, -CD11b, -CD14, -CD15, -CD16, -CD19, -CD25, -CD33, -CD39, -CD56, -CD123, -CD303, and Human leukocyte antigen DR [HLA-DR]; Becton Dickinson, Franklin Lakes, NJ, USA; anti-FOXP3; e-Bioscence Invitrogen, Carlsbad, CA, USA; -Slan-M-DC8; Miltenyi Biotec, Bergisch Gladbach, Germany), and multicolor flow cytometry.[26]

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

Anti-cancer treatments

Chemotherapy will be employed by investigators' choice within the framework of good clinical practice and in agreement with current Italian Association of Medical Oncology guidelines.[35] In particular, standard treatment will consist of cisplatin 100 mg/m² every 3 weeks or 40 mg/m² weekly (only in postoperative setting). Patients

Table 1. Summary of scheduled assessments during the study.

Evaluations	Visit 1 Day: 0	Visit 2 Day: 10–14 start of CT-RT	Visit 3–8 Day: 21–56 CT-RT	Visit 9 Day: 56–63 end of study
Informed consent	X			
Demographic data	X			
Inclusion/exclusion criteria	X			
Randomization	X			
Weight history	X			
Anthropometric evaluation	X	X	X	X
Protein-calorie intake	X	X	X	X
Symptoms	X	X		X
Quality of life (EORTC QLQ-C30)	X	X		X
Fatigue (FACIT-F)	X	X		X
Body composition (BIVA)	X	X		X
Muscle mass (computed tomography)	X			X
Muscle strength (handgrip)	X	X		X
Immunological profile	X	X		X
Toxicity of CT-RT		X	X	X
Adherence to CT-RT		X	X	X
Response to CT-RT treatment				X
Adverse events		X	X	X
Compliance with oral support		X	X	X

BIVA, Nutrilab Bioimpedance Vectorial Assay; CT-RT, chemoradiotherapy; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer core quality of life questionnaire; FACIT-F, functional assessment of chronic illness therapy – fatigue.

ineligible for treatment with cisplatin (age, renal, cardiac, respiratory or neurogenic dysfunction) will receive carboplatin under the curve (AUC) 6 every 3 weeks or area AUC 2 weekly.

Regarding radiation therapy, patients will be treated with intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT).

Gross tumor volume (GTV), clinical target volume (CTV), planned target volume (PTV), and organ at risk (OAR) will be identified and contoured on the planning CT. Treatment volume extent will be based on physical examination, CT, endoscopic findings, and magnetic resonance imaging (MRI). Different doses to different targets will be delivered with a simultaneous integrated boost (SIB) technique. Radiation treatment is scheduled once a day. Prescription dose will be 66–70 Gy to the high-risk PTV and 50–54 Gy to the lower-risk PTV (i.e. to the whole neck negative) in 33–35 fxs/6.5 weeks. It will be determined for each patient to achieve a standard dose consistent with tumor type, stage, site and intent in agreement with the recommendations of the International Commission on Radiation Units and Measurements 83 report (i.e. the PTV should receive 95–107% of the prescribed dose, and PTV coverage should be higher than 95%).[36]

Treatment

All patients will receive nutritional counseling as standard of care[3] and will be randomly assigned to consume two bottles per day of a high-calorie, high-protein ONS enriched in immunonutrients [arginine, nucleotides (RNA) and omega-3 fatty acids; Impact (237 mL per bottle)] or an isonitrogenous standard blend [Meritene Drink (200 mL per bottle); Nestlè Health Science, Creully Sur Seulles, France] for about 9–2 weeks up to the end of CT-RT or until withdrawal.

The detailed composition of the two ONSs is provided in Table 2. Adherence to interventions throughout the study will be assessed and monitored by the caregiver and the dietitian through daily recording on a diary of the bottles consumed. The safety of ONS consumption will also be addressed by monitoring the occurrence of any potential gastrointestinal side effects.

Nutritional counseling will consist of a personalized dietary prescription (including sample meal plans and recipe suggestions) tailored on personal eating patterns, food preferences in order to achieve estimated protein-calorie requirements and taking into account chewing and swallowing abilities, as well as the impact of relevant symptoms (anorexia, dysgeusia, odynophagia, nausea, vomiting, diarrhea, and constipation).[13,26,28] Total daily energy requirements will be calculated by multiplying the estimated resting energy expenditure (Harris–Benedict equation) by a correcting factor of 1.5, while daily protein requirements were set at 1.5 g/kg of actual body weight.[13,26,28] Regular consultation with a registered dietitian will take place every 7 days by means of face-to-face interviews, and food intake will be quantified by means of a 3-day food diary and 24-h recall. The patient will also be given the opportunity to contact the local nutrition clinic by telephone for any specific clarifications and advice.

Efficacy endpoints

The primary outcome will be the difference in incidence of treatment-related moderate to severe adverse events (grade ≥3) according to common terminology criteria for adverse events (CTCAE v5.0).[37]

The following secondary endpoints will also be evaluated: toxicity-free survival (difference in the time to onset of grade ≥3 adverse events); difference in the incidence of any toxicity event; adherence to treatment schedule, defined as difference in the proportion of patients completing the treatment schedule as planned taking into account the percentage of CT and RT dose administered and the percentage of variation in their duration; objective response rate to CT-RT using response evaluation criteria in solid tumors (RECIST) criteria (to be assessed in patients with a measurable disease);[38] change in QoL (EORTC QLQ-C30 and QLQ-H&N35 score), fatigue (FACIT-F score), body weight, protein-calorie intake, muscle strength, muscle mass and body composition parameters at the end of the study; rate of unplanned hospitalizations (one or more) during the study.

Exploratory endpoints

The levels of soluble factors and immunoregulatory effector cells will be assessed at study inclusion, and at the start and completion of anti-cancer treatments.

Benefit for participants

All participants will be provided with early and tight nutritional assessment and support.

Their nutritional status will be regularly monitored and nutritional support will be continuously 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 impact of CT-RT in H&N cancer patients.

Potential risks and burdens for research participants

No risks and burdens for participants are expected in the context of the present research.

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. Information may also be disseminated to the general public *via* public engagement and community outreach programmes.

Table 2. Nutrient contents of the intervention formula.

Characteristic	Immunonutrition Impact		Control formula Meritene Drink	
	100 mL	1 bottle 237 mL	100 mL	1 bottle 200 mL
Macronutrients				
Proteins, g	7.6	18	9.4	18.8
L-arginine, g	1.8	4.3	/	/
Carbohydrates, g	18.9	44.8	14	28
Fats, g	3.9	9.2	3.5	7.0
Saturated fatty acid, g	1.8	4.3	0.5	1.0
MCT, g	1.1	2.6	/	/
Mono-unsaturated fatty acids, g	0.7	1.7	1.7	3.4
Poly-unsaturated fatty acids, g	1.3	3.1	0.7	1.4
Omega-3, g	0.6	1.4	/	/
Omega-6/omega-3 ratio, g	0.9	0.9	/	/
Fiber, g	1.4	3.3	<0.5	<1.0
Energy				
Total, kcal	144	341	125	250
% from proteins	21	21	30	30
% from carbohydrates	53	53	45	45
% from fats	24	24	25	25
Minerals				
Sodium, mg	150	355	80	160
Potassium, mg	190	450	190	380
Chloride, mg	169	401	65	130
Calcium, mg	114	270	120	240
Phosphorus, mg	101	239	100	200
Magnesium, mg	32	76	23	46
Iron, mg	1.7	4	1.5	3.0
Zinc, mg	2.1	5	1.3	2.6
Copper, µg	250	590	170	340
Manganese, µg	30	71	34	68
Fluoride, µg	21	50	12	24
Molybdenum, µg	22.5	53.3	11	22

(Continued)

Table 2. (Continued)

Characteristic	Immunonutrition Impact		Control formula Meritene Drink	
	100 mL	1 bottle 237 mL	100 mL	1 bottle 200 mL
Selenium, µg	6.6	15.6	7.5	15
Chromium, µg	14	33	12	24
Iodine, µg	21	50	17	34
Vitamins				
Vitamin A, µg	139	329	120	240
Vitamin D, µg	0.9	2.2	1.2	2.4
Vitamin E (α-tocopherol), mg	4.2	10	2.3	4.6
Vitamin K, µg	9.4	22.3	10	20
Thiamine, mg	0.17	0.4	0.2	0.4
Riboflavin, µg	25	60	23	46
Niacin, mg	2.2	5.2	0.9	1.8
Pantothenic acid, µg	110	260	65	130
Vitamin B6, µg	21	50	25	50
Folic acid, µg	28	66	35	70
Vitamin B12, µg	0.8	1.9	0.3	0.7
Biotin, µg	10.1	24	5	10
Vitamin C, mg	30	71	16	32
Choline, mg	38	90	/	/
Nucleotides, mg	18	43	/	/

MCT, medium chain triglycerides.

Statistics

Sample size. Sample size calculations are based on the primary endpoint. In this study we will enroll 86 patients (43 in each arm). This sample size accounts for a 15% dropout rate. Calculations are performed following the approach by Cocks and Torgerson,[39] based on the confidence interval. As this is a pilot study that will give elements to help in the decision to proceed with a confirmatory study, we will use a 90% one-tailed confidence interval (type I error of 10%). With this approach, the confidence interval is calculated under the H0 assumption of no difference between arms, using the expected sample size for the pilot study. If the upper limit of the interval excludes the hypothesized treatment effect in a confirmatory study, then consideration can be given to designing a confirmatory study. From previous studies,[13,26] we expect the proportion of patients developing moderate-to-severe toxicity (G3–G5) (primary endpoint) to be approximately 60% in the control arm and 45% in the experimental arm. In a confirmatory study, these assumptions would require enrolling 346 patients (173 per arm) to demonstrate such an absolute difference of 15%, with a power of 80% and a two-tailed first-type error of 5%. According to the Cocks approach, with 86 patients, the upper limit of the 90% confidence interval for the null effect will be 14.8%, a value that excludes the 15% treatment effect estimate.

Analysis set. Patients who, after signing informed consent, will have undergone at least one planned

follow-up represent the analysis set. The main analysis will be carried out according to the modified intention to treat (mITT) principle: patients in the analysis set will be analyzed according to the treatment to which they were randomized, regardless of the treatment actually taken. A per protocol (PP) analysis will also be performed, considering the treatment actually taken with adherence to the planned treatment.

Analysis of the primary endpoint. The proportion of patients developing moderate-to-severe toxicity (G3–G5; assessed according to CTCAE v5.0 criteria) will be compared with a generalized linear model extended to the binomial family. The difference between the proportions and associated 95% confidence interval (95% CI) will be calculated.

Analysis of the secondary endpoints. Time to event endpoints will be compared between treatment arms with the log rank test. Hazard ratios and 95% CI will be derived from a Cox model. Binary endpoints will be analyzed as described for the primary endpoint. Endpoints on a continuous scale will be compared using generalized linear regression models. The mean difference and 95% CI will be presented. Normalizing transformations may be applied.

For all models Huber–White robust standard errors will be computed to account for center.

Dropouts. Deceased patients, patients hospitalized outside the participating centers, patients starting artificial nutrition and patients undergoing oncological surgery during radiotherapy qualify as dropouts. For them the last available value will be carried forward. Multiple imputation may be considered in a sensitivity analysis of the primary endpoint.

Randomization. Patients will be randomly assigned 1:1 by the treating physician to one of the two study arms according to a computer-generated random blocks randomization list. Randomization will be stratified by center, in order to maintain the 1:1 ratio at center level. It will be performed *via* web, using the REDCap at Fondazione IRCCS Policlinico san Matteo. The system will assign the patient to the treatment arm after an initial check on the eligibility criteria to be answered by the treating physician. The randomization list was generated by and is kept at the Clinical Epidemiology and Biometry unit of the coordinating center.

The Stata software (release 16; StataCorp, College Station, TX, USA) is used for sample size calculation, generation of the randomization list and data analysis.

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 and the Clinical Epidemiology and Biometry Unit of the Fondazione IRCCS Policlinico San Matteo and the board of oncologists from other institutions listed as co-authors. Periodic board meetings will be scheduled (approximately every 3 months), in order to harmonize study procedures and to monitor and share the study progression.

Participating institutes

Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Veneto Institute of Oncology-IRCCS, Padua, Italy.

Discussion

Malnutrition in oncology still represents an overlooked problem,[40–42] which negatively affects clinical outcomes, and this is particularly relevant in H&N cancer patients.[1,5,43] The evidence supporting the efficacy of nutritional support in patients affected by H&N cancer is promising, but still scanty and mainly focused on nutritional endpoints,[1,43–45] while the impact on survival and treatment feasibility still requires confirmation.[12,13]

Immunonutrition represents a promising approach in cancer care. It has been gaining attention in past decades particularly in the surgical gastrointestinal setting, where it has been shown to be able to reduce overall infectious complications and length of hospitalization, without affecting mortality.[46,47] In the context of H&N cancer surgery, a recent Cochrane review found that the overall quality of the evidence was low or very low for several outcomes, including length of stay, mortality, wound infection, and adverse events.[15] However, in a recent study on patients undergoing salvage surgery for H&N cancer recurrence, immunonutrition led to a reduction in the risk of overall complications and a decreased length of hospitalization.[48] Furthermore, in a retrospective study on 411 H&N cancer patients,

preoperative immunonutrition was associated with a shorter length of hospital stay and a lower rate for wound infections and local complications, with more pronounced effects in those with previous RT and extensive surgery.[49]

During CT-RT, a controlled, randomized, prospective, double-blind, multicenter study on 111 patients with H&N and esophageal cancer showed that functional capacity and nutritional status were maintained in those receiving an immune-enhanced supplement and reduced in controls receiving a standard enteral diet.[50]

Furthermore, in a small pilot study conducted on 31 non-metastatic stage III or IV H&N cancer patients treated with concomitant CT-RT, immunonutrition provided orally during 5 days before each cycle of CT was shown to be associated with a favorable modulation of inflammatory and oxidative status, and a low incidence of severe acute mucositis was noted.[51]

This study served as a cue for the recently published phase III multicenter, randomized, double-blind study comparing an oral immunomodulatory supplementation with an isonitrogenous, isocaloric control supplement in 180 H&N cancer patients treated surgically and with adjuvant CT-RT.[18] In both intention to treat (ITT) and PP analyses, immunonutrition did not reduce severe mucositis during CT-RT. Interestingly, among subjects with high ($\geqslant 75\%$) compliance to immunonutrient supplementation, both OS (81% compared with 61%) and PFS (73% compared with 50%) were significantly greater in the experimental group than in the controls, but this could have occurred independently of immunonutrition efficacy, as mentioned elsewhere.[19]

Pre-CT-RT nutritional status was recently confirmed to be able to identify H&N cancer patients vulnerable to treatment interruption and treatment complications[52] and, in particular, body composition assessment is crucial to predict clinical outcomes and treatment toxicity.[53]

Beyond overcoming the methodological bias of the IMPATOX trial already discussed,[19] the present pilot study ensures the early provision of nutritional assessment and support to all the enrolled patients, in accordance with recent evidence guidelines and recommendations,[1,3,4,12,13] and would help clarify the hypostasized advantages of immunonutrition during CT-RT for H&N cancer patients.

Toxicity frequently requires the prolongation and/or reduction of planned systemic treatments, resulting in reduced response rates and poor prognosis.[54] Therefore, tight nutritional support with immunonutrients from treatment initiation, aimed at fully, continuously satisfying estimated energy and protein requirements, may enable not only the maintenance/improvement of nutritional status and QoL, but may also have a positive and decisive impact on adherence to anticancer treatment and the related curative intent.

Positive results from this pilot trial would stimulate further larger randomized, hopefully international, trials, potentially resulting in the improvement of supportive care quality for H&N cancer patients, and in the expansion of the number of patients who may benefit from immunonutrition also in the non-surgical oncological setting.

Finally, the immune response is emerging as a key factor affecting the efficacy of treatments also in H&N cancer.[55] Therefore, we will also evaluate how the immunological profile changes during CT-RT, according to the nutritional treatment group.

This approach may help to initiate the exploration of the interactions between the immune system and immunonutrient supplementation. This new area of research could lead to the discovery of new molecular mechanisms regulating the immune system during CT-RT and, potentially, 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 counseling. However, to achieve this, participating center dietitians will share their protocols and will clarify potential discrepancies.

Authors' contributions
RC, EC, CK, ARF, PB and PP developed the study concept and protocol. VC, CF, SC, SC, EB, SM, MN, MGG, AA, AF, VM, SC, II, LC, RT, FL, EF, TM and PC assisted in further development of the protocol. RC, EC, CK, ARF, PB, AF, PC, MGG and PP drafted the clinical study protocol, funding and ethics application. RC, EC, CK, ARF, PB and PP drafted the

manuscript. All authors contributed and approved the final manuscript. RC, ARF and PP act as guarantors of the study.

Conflict of interest statement

The authors have the following conflicts of interest to declare: RC and EC has served on advisory boards for Nestlè Health Science; PB has served on advisory boards for Helsinn.

Ethics approval and consent to participate

This study has been reviewed as ID 20200060578 by the Institutional Ethics Committee of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, (29/07/2020; prot. N. 20200069594) and as ID 2020/141 by that of Veneto Institute of Oncology-IRCCS, Padua, Italy (25/01/2021; prot. N. 2020/141), who gave a favorable opinion.

The study sponsor is Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. This study is registered on ClinicalTrials.gov Identifier: NCT04611113.

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

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.

ORCID iDs

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

Carlotta Brovia (iD) https://orcid.org/0000-0001-7092-1903

Valentina Caissutti (iD) https://orcid.org/0000-0001-5245-2736

Andrea Riccardo Filippi (iD) https://orcid.org/0000-0001-7159-7869

Availability of data and material

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

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