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Randomized control trials

Immunonutrition improves functional capacities in head and neck and esophageal cancer patients undergoing radiochemotherapy: A randomized clinical trial☆

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SUMMARY

Background & aims: Malnutrition is frequent in head and neck (HN) and esophageal cancer patients and aggravated by radiochemotherapy (RCT), increasing morbi-mortality and treatment toxicity. Our goal was to investigate the effect of immunonutrition consisting of an arginine, omega-3 fatty acid, nucleotides-enriched diet on nutritional status, and functional capacity in HN or esophageal cancer patients undergoing RCT.

Methods: 37 patients were randomized in a double-blind clinical trial. 5 days before and until the end of RCT (5–7 weeks), they received either an Immunomodulating Enteral Nutrition (IEN) or an iso-nitrogenous, isoenergetic Standard Enteral Nutrition (SEN). Anthropometrical parameters, nutritional risk index (NRI), serum albumin, plasma antioxidant capacity, and functional capacity were recorded between the beginning and the end of RCT.

Results: A significant gain in total body weight (+2.1 ± 3.1 kg) was observed in IEN patients. Albuminemia and NRI were improved concomitantly in IEN malnourished patients. Plasma antioxidant capacity was improved (+100 ± 13 μM *Eq*Trolox) in IEN patients. Functional capacity measured by WHO Performance Status and Karnofsky index was maintained in IEN patients but significantly reduced in SEN patients.

Conclusions: These preliminary data show that immunonutrition could improve the nutritional status together with functional capacity in HN and esophageal cancer patients undergoing RCT.

Clinical trial registration: This clinical trial promoted by the University Hospital Center of Clermont-Ferrand has been registered at ClinicalTrial.gov website under the following reference: NCT00333099.

1. Introduction

Malnutrition is present at early stage disease in approximately 30–40% of head and neck (HN) cancer patients[1] and 80% of esophageal cancer patients.[2] The main causes are mechanical obstruction, anorexia, tumor induced cachexia, poor dietary habits, tobacco consumption and excessive alcohol consumption. The anatomic site of the tumor can significantly affect swallowing and

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chewing functions with dysphagia, odynophagia, pain which contribute to a decrease of protein energy intake.[3]

Malnutrition in cancer patients is associated with a longer hospital stay, a reduced response and an increased toxicity of treatment,[4] a worse quality of life and performance status,[5] and a lower survival rate.[6] Malnutrition is also known to have an adverse impact on immune function by inducing T-lymphocytopenia and dysfunction, reduced monocyte HLA-DR expression, reduced prostaglandin concentration.[7]

At present, radiochemotherapy (RCT) is commonly used in patients with upper-third esophageal cancer and seems also to be the most appropriate approach in order to preserve organ functions in patients with advanced HN cancer.[8] RCT is often associated with significant acute and late toxicity effects due to its radiosenzitisation effects. These may cause severe mucositis, dysphagia, odynophagia, loss of sense of taste, xerostomia, nausea, vomiting and loss of appetite which hindered oral feeding and deteriorated functional capacity requiring a break in the radiation treatment.[9] So, enteral nutrition (EN) administered either with nasogastric tube (NG) or percutaneous endoscopy gastrostomy (PEG) before the beginning of RCT is recommended in HN and esophageal cancer treated by RCT.[10] EN allows to prevent or to limit weight loss, treatment interruption and length of hospitalization.[11] Recent studies suggest that the immune, nutritional or inflammatory status may be modulated by the use of pharmaconutrients in RCT-treated cancer patients.[12–14] Arginine, glutamine, omega-3-fatty acids and nucleotides are the most studied and their molecular mechanisms are well explicated in a recent review.[15] Arginine plays a role in the synthesis of nucleotides, polyamines, nitric oxide and proline, stimulates lymphocyte function and improves wound healing. Omega-3 fatty acids and eicosapentanoic acid (EPA) inhibit excessive inflammatory responses with no immunosuppressive effect. Nucleotides are used by cells with high proliferation rate as enterocytes, immune cells and other cells implicated in wound healing.

A diet enriched in immunonutrients could limit deleterious effect of RCT on immune status and so preventing deterioration of nutritional status and functional capacities. To our knowledge, no randomized control trial evaluated the impact of such a diet in radiochemotherapy-treated HN and esophageal cancer patients. Here, we carried out a multicentre prospective randomized trial to investigate the effects of enteral immunonutrition on nutritional and immune status, and functional capacities in these patients.

2. Patients and methods

2.1. Study description

2.1.1. Patients eligibility

Eligible patients were adults who accepted written informed consent, aged more 18 years, with a documented HN or esophageal cancer (epidermoide carcinoma or adenocarcinoma) with a planned treatment by RCT, with or without surgery and an acceptable functional capacity (WHO Performance status $\leq$2 or Karnofsky index >50%). Exclusion criteria were: denied written informed consent, exclusive radiotherapy or exclusive surgery treatment, tonsils cancer, existence of metastases or concomitant cancer, cancer relapse on site, insulin dependent diabetes, thyroid diseases, major surgery or severe infection in the 3 previous months, consumption of omega-3 (or arginine and nucleotides) enriched food or supplements in the previous month, pregnancy, breath feeding and no effective contraceptive mean.

2.1.2. Protocol design

The study was a multicentre, randomized, double blinded, controlled trial, carried out in 3 hospitals. It was approved by French health authorities and local ethical committee. From February 2006 to September 2011, patients who fulfilled the selection criteria were included and randomized to receive either an Immune modulating Enteral Nutrition formula (IEN group) or an isocaloric, isonitrogenous formula (SEN, Standard Enteral Nutrition group), for 5 days before to the end of the RCT (5–7 weeks). A balanced stratified randomization was made using a statistical software "SEM: Statistics Epidemiologie Medecine[16]" managed by an external person not involved in the study.

Initially, the study was designed to assess mucositis occurrence with intention to treat analysis. Because of recruitment difficulties, we did not obtain the required number of patients to evidence the difference expected for this principal criterion (125 patients per arm to observe a 20% reduction in mucositis occurrence). However, the number of recruited patients (13–15 patients per arms) was sufficient to assure robust statistical analyses on secondary endpoints, especially performance status assessed by independent evaluation of Karnofsky index and WHO/ECOG score.

2.1.3. Nutritional intervention

Based on usual habits of each medical center (Clermont-Ferrand, Lyon, Béziers), patients were proposed either a gastrostomy (endoscopic, radiologic or surgical) or a nasogastric tube before the beginning of RCT. If needed, EN was initiated immediately with a usual standard polymeric formula, but in all cases, it was initiated 5 days before RCT at least. At this time, patients in the IEN group received a polymeric formula enriched with arginine (13 g/L), eicosapentaenoic and docosahexaenoic acids (EPA + DHA 3.4 g/L) and ribonucleotides (1.3 g/L, IMPACT®, Nestlé HealthCare Nutrition, Lausanne, Switzerland) (Table 1). Patients in the SEN group received an isocaloric isonitrogenous polymeric formula providing by Nestlé HealthCare Nutrition (Table 1). The 2 EN formulae had identical external features to maintain double blinded. All patients received a minimal volume of 1500 mL which was infused overnight via a pump during a 12–14 h-period. If needed, in order to reach the targeted energy and protein intakes (35–40 kcal/kg per day and 1.5–1.8 g protein/kg per day), the enteral intakes were increased by using a standard polymeric hypercaloric normoproteic formula (isosource energy®, Nestlé HealthCare Nutrition) (Table 1). The EN was conducted at home for 90% of the patients. All non-used EN packs and empty packaging were returned at hospital pharmacy and counted at the end of the study in order to estimate compliance.

Table 1
Composition of enteral nutrition diets.

Components	Units per L	Impact® Nestlé	Isocaloric isonitrogenous formula Nestlé	Isosource Energy® Nestlé
Total proteins (P)	g	56	66	57
L Arginine	g	13.0	15	1.9
Lipids (L)	g	28	28	62
SFA[a]	g	16	16.7	17.3
MUFA	g	5.9	4.4	22.9
PUFA	g	5.8	6.9	21.8
DHA, EPA	g	3.4	0	0
Glucids (G)	g	134	122	200
Mono/di-saccharides	g	4.0	4.3	7.7
Ribonucleotides	g	1.3	0	0
Nitrogen	g	9.0	11.4	9.1
Energy	kcal	1010	1024	1600
%P/L/G	%	22:25:53	28:25:47	14:35:51

[a] Saturated Fatty Acids (SFA), Mono-Unsaturated fatty Acids (MUFA), Poly-Unsaturated Fatty Acids (PUFA).