Oral mucositis (OM) is a pathological condition that frequently complicates the oncological treatments of the head-neck district cancers (HNC), correlated both to the therapy toxicity and to a defective cell turnover. Chemoradiotherapy (CRT) may induce or worsen oral mucositis due to the combined toxicity of chemotherapy (type and dosage of drugs) and radiotherapy (irradiation site, daily dose, fractionation, irradiated area extension, treatment duration). Furthermore, the OM evolution can also be influenced by the state of the oral mucosa and the overall clinical conditions of the patient before starting treatments, lifestyle (smoking and alcohol), and oral hygienic habits.

The role of glutamina (Gln) has been proposed for years now, but there is not clear evidence yet about its routinely administration in order to prevent CRT-induced OM.

Glutamine Efficacy in Prevention of Oral Mucositis in Head-Neck Cancer Patients Undergoing to Chemo-Radiotherapy

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Abstract

Background and Aims: Oral mucositis (OM) is a serious condition that frequently complicates the oncological treatments of the head-neck district cancers (HNC). Glutamine (Gln) could have a role in preserving and restoring tissue integrity, but there is not clear evidence yet about it’s routinely administration in order to prevent chemo-radiotherapy (CRT)-induced mucositis. Methods: Randomized non-controlled clinical trial involving HNC patients eligible to CRT, at the enrollment (T0) randomized to control arm (CA) or Gln arm (GlnA) receiving best supportive care vs best-supportive care plus oral supplementation with L-glutamine (15 g/day) from the first day up to 15 days after the end of treatment, respectively. Endpoints: prevention of grade 3 and 4 OM onset according to the RTOG/EORTC criteria. Results: Twenty-nine HCN patients were recruited. No differences between the two arms were found for OM at baseline (p 0.8571), that worse both in the CA (linear trend p 0.0001) and in the GlnA (p 0.0006) in course of CRT. OM severity difference at the last visit was only close to significance (p 0.0534), however it was noted a significant linear trend (p 0.0367). Notably, despite a major patients percentage in the GlnA developed grade 2 OM (71.43 vs 53.33%), none developed grade 3 or 4 OM in this group (0 vs 33.33%). Weight loss difference (2.2 and 4.89 kg for CA and GlnA, respectively) was not significant (p 0.19). No patient discontinued the study medication or CRT due to Gln adverse effects, OM, or malnutrition. Conclusions: Oral Gln administration in HNC patients could limit the severity of OM, so improving tolerance to CRT and quality of life, although our results not reached statistically significant evidence. Further well designed studies on larger size samples are necessary in order to investigate the role for Gln in the clinical management of OM.

Keyword: head-neck cancer patients, chemo-radiotherapy, glutamine, mucosite,malnutrition

Introduction

Oral mucositis (OM) is a pathological condition that frequently complicates the oncological treatments of the head-neck district cancers (HNC), correlated both to the therapy toxicity and to a defective cell turnover. Chemoradiotherapy (CRT) may induce or worsen oral mucositis due to the combined toxicity of chemotherapy (type and dosage of drugs) and radiotherapy (irradiation site, daily dose, fractionation, irradiated area extension, treatment duration). Furthermore, the OM evolution can also be influenced by the state of the oral mucosa and the overall clinical conditions of the patient before starting treatments, lifestyle (smoking and alcohol), and oral hygienic habits.

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Oral mucositis

Approximately 550,000 people worldwide are diagnosed with a HNC every year [1]. Radiotherapy (RT) and/or chemotherapy (CT) are first line therapeutic strategies for the treatment of HNC, in order to improve locoregional control and survival in these patients [2,3]. However both RT and CT are burdened with important side effects such as mucositis over a wide area of the oral cavity, pharynx, and larynx, typically beginning on the third week of RT and persisting up to 8–12 weeks after the end of treatment [2]. It has been estimated a mucositis incidence in over 75% patients with HNC undergoing RT, with a severity grade 3 or 4 affecting from 25 to more than 50% of subjects, depending of the cases [4,5]. Furthermore oncological treatments can cause dysgeusia, xerostomia, dysphagia, dermatitis, loss of taste, microbial colonization, and...
osteoradionecrosis, finally leading to hyporexia, undernutrition, and cachexia [2,6]. It is well known that cancer cachexia is associated with poor responses to oncologic therapies and decreased survival, as well as having a dramatic impact on patient’s quality of life [7].

In the specific context, OM can reduce tolerance to oncologic therapies, so leading to a limited duration or discontinuation and a reduced dosage of treatments, and therefore compromising clinical outcomes in terms both of survival and quality of life [8]. The interference with an adequate oral feeding may then require an artificial enteral nutrition in cases of severe hyporexia and malnutrition risk. Moreover, CRT-induced mucositis and pharyngitis play a negative role on the overall clinical conditions, in some cases requiring hospitalization and incremental medical costs [9]. The clinical management of OM has been symptomatic for a long time, but targeted therapies are currently being studied.

Several efforts have been proposed to prevent and to treat mucositis, such as oral care, topic antiseptic oral rinses, antimicrobial gels, but a standard effective treatment has not been established yet [10-13]. In this regard, a systematic review of the literature by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) produced Guidelines on the different therapeutic options, although there are no evidence levels to recommend many of them as a systematic clinical practice [14].

Glutamine

Several Authors focused the role of Gln in the prevention and treatment of OM in oncological treatments. Gln is the most abundant free amino acid in the organism [15]. It can be synthesized by virtually all the body cells as an important metabolic substrate for rapidly replicating cells, particularly gastrointestinal tract mucosa and immune cells, thus playing a role in preserving and restoring tissue integrity [16]. In conditions of increased stress, such as oncological treatments, intracellular Gln storage undergo a drastic depletion and may therefore impair the tissue repair processes thus becoming a conditionally essential amino acid [17]. Gln also neutralizes reactive radicals derived from RT and CRT, thus preventing further DNA damages and protecting tissues [18-21].

Moreover, the rationale of Gln administration in the OM treatment lies even in an antiinflammatory role through down-regulation of cytokines such as prostaglandin E2 (PGE2) and TNF-α, thus closing the pro-inflammatory feedback loop, and in an antiapoptotic role through inhibition of epithelial cells apoptosis at an intracellular level [22-29]. Over the last 25 years, several clinical trials have been conducted to evaluate effects of Gln supplementation in oncological patients.

Although data from the first studies by Ziegler in the 90s, and even a recent trial by Yu-Hsiang C et al. [30,31], reported a positive effect on OM in a pediatric sample, poor evidences were obtained with Gln parenteral administration, without a significant reduction of clinically manifest mucositis in hematological cancer subjects [16,32-34]. On the contrary, oral administration significantly reduced OM severity, duration, and extent, although these beneficial effects have not been confirmed by other studies 35-42].

It is to be noted as studies differed by type and primitive tumor site, staging, oncological treatment regimens, Gln administration protocols (dosage, frequency, therapy duration). The characteristics and results of the main studies since 2007 on oral Gln administration in course of oncologic therapies are reported in Table 1. The aim of this study is to evaluate the effectiveness of oral Gln administration in the prevention of grade 3 and 4 OM and to allow the oncologic treatment completion in patients with HCN undergoing CRT. A secondary endpoint is to evaluate the nutritional status.

Materials and Methods

Patients population and radiotherapy/chemotherapy

We recruited HNC patients, sent to the Dietetic and Clinical Nutrition Service by the oncological team (oncologists, radiotherapists), with preserved oral food intake, undergoing to CRT. Radiation treatment, planned with an ‘intensity-modulated’ approach (IMRT), was administered daily, 5 consecutive days a week for 6–7 weeks. For definitive treatment, the macroscopic disease received 70 Gy/35, the elective lymph nodes volume 63 Gy/35 fractions or 54.25 Gy/35 fractions in relation to primary cancer and the risk of lymph nodes tumour spread. For radical treatment of locally advanced cancer, CT was given as induction treatment using the TPF regimen (Docetaxel 75 mg/m2 body surface area and Cisplatin 100 mg/m2 on day 1 and 5-Fluouracil 1000 mg/m2 as a 24-hours continuous infusion on days 2–5 every 3 weeks. Concurrent CT was given with weekly Cisplatin (30 or 40 mg/m2) or weekly Carboplatin for 6–7 weeks. Mean radiation dose received by oral cavity was 40 Gy (range 6-56).

Patients were randomly assigned to two arms of the trial: 1) best supportive care; 2) best-supportive care plus oral supplementation with L-glutamine (dosage 15 g/day) from the first day up to 15 days after the end of treatment. RT characteristics and primitive locations of tumors are shown in Table 2.

Objective evaluation of OM and nutritional assessment

The assessment of the OM severity was performed according to the RTOG/EORTC criteria [43] by the Oncologist or Radiotherapist at the beginning of the treatment (1st visit), in the middle (2nd visit), and at the end of the treatment. The nutritional assessment, performed by the Dietetic and Clinical Nutrition Service, included: evaluation of nutritional status (anthropometric data), risk of malnutrition (according to NRS-2002), and nutritional history. It was performed at the beginning of the treatment (1st visit), in the middle (2nd visit), at the end (3rd visit), and after 15 days from the end of treatment (4th visit).

In case of an onset of severe OM the nutritional assessment was anticipated and, in case of mild to moderate malnutrition (according to ASPEN 2012 criteria), [44] adequate dietary indications and nutritional supplements were provided. Severe malnourished patients were excluded from the trial and referred to artificial nutrition.

Exclusion criteria
Exclusion criteria were: ECOG performance status >2 and/or Karnofski Index (KI) <70; age <18 and >75 years; renal and/or hepatic failure; uncontrolled diabetes; ulcerated mucositis; lockjaw; active alcohol consumption; active smoking; severe malnutrition.

Statistical analysis

Participants were assigned to the two groups through a block stratified randomization for the variables: age, sex, previous smoking habits, previous potus. The data were analyzed through descriptive statistics. The differences between the two groups were evaluated through the Student t test for independent samples for the continuous variables with a normal distribution, and through the Mann-Whitney U test for variables with non normal distribution. Shapiro-Wilk W test for non normality was used. Mann-Whitney U test and Chi Square Test when appropriate were performed for comparison of nominal and ordinal variables. Statistical significance was assigned to a p value <0.05.

Ethical statements

Study has been conducted in accordance with the Helsinki Declaration, Good Clinical Practice (GCP), and local ethical and legal requirements. The protocol was approved by the Ethic Committee before enrollment of participants into the study (CS/135 on 04/16/2014).

Results

Twenty-nine patients were included in the trial, between 38 and 79 years of age (mean: 61.3 years ± 11.06), 16 male (55.17%) and 13 female (44.83%). Fifteen subjects were allocated in the control and 14 in the Gln group. There were not significant differences between the two groups for age, body weight, BMI, neither at the baseline nor at the last control (Student’s t test). Moreover, groups were homogeneous for treatment parameters such as CT regimens and radiation doses. Mean weight loss were 2.2 and 4.89 in the control and in Gln group, respectively, but this difference was not significant (Mann-Whitney test, p 0.19). No patient discontinued the study medication due to adverse effects. No patient discontinued oncological treatments due to OM or malnutrition incidence, in neither group. Features of patients in each group at baseline and at the last visit are summarized in Table 3.

Differences in the mucositis severity degree between the two groups were not significant at baseline (Mann-Whitney test, p 0.8571), while a significant mucositis worsening was observed both in the control (Chi-square test for linear trend, p 0.0001) and in the Gln group (p 0.0006) in course of CRT, as evidenced in Table 4. The difference in the distribution of the OM severity grades between two groups at the last visit was only close to significance (Chi-square test, p 0.0534), however it has been noted a significant linear trend in the mean scores analysis (Chi-square test for linear trend, p 0.0367). Notably, despite the fact that a major percentage of patients in the Gln group developed grade 2 mucositis (71.43 vs 53.33%), none component of this group developed grade 3 or 4 mucositis (0 vs 33.33%).

Discussion

Recent radiotherapy techniques such as the Three Dimensional Conformal RadioTherapy (3D-CRT) and the Intensity Modulated Radiation Therapy (IMRT) allowed a dose escalation to the tumor and a more preservation of surrounding tissues [45,46]. However mucositis in course of RT and CRT in HNC patients remains a serious complication limiting tolerance to oncologic treatments. Several treatments have been supposed and practiced, but there is still no consensus about which intervention is more and really effective in order to prevent and to treat this distressing and frequent complication.

In this regard, it has been proposed a role for Gln, due to its trophic action on gastrointestinal tract mucosa and antioxidant effect, with discordant and not yet fully conclusive results from clinical trials. While poor and disappointing effects were obtained through the parenteral administration, at least in onco-hematologic patients, role of oral Gln is still investigated and debated in a clinical context [16,33,34].

According to the recent meta-analysis by Leung HW et al. [47], which examined 5 clinical randomized controlled trials, involving a total of 234 patients with HNC underwent to RT alone or CRT, it has been revealed a significant role for oral Gln in reducing the risk and severity of OM in treated patients compared with either placebo or no treatment controls (risk ratio 0.17; 95% CI 0.06–0.47) [35,38,48–50].

A systematic review by Yarom N et Al. of 7 well-designed studies involving solid and hematological cancer patients did not provide unique results [51] since 4 studies confirmed its efficacy, [37, 52-54] while other 4 ones disconfirmed it, [39,41,42,55] so Authors concluded as actual conflicting evidences do not allow to indicate Gln as effective, and to recommend its systematic use. According to the previous considerations, the systematic review by Sayles C et Al. provided a rationale to perform large randomized placebo-controlled studies to further evaluate Gln effectiveness [56]. Beside these, more recent data showed as Gln significantly reduced not only the incidence and the severity of mucositis, [57-59] but also the rates of adverse events such as pain, dysphagia, nausea, edema, cough, and analgesics use [59].

The results of the present study seem to reveal a certain effectiveness of Gln in reducing the severity of OM although we did not reach a statistical significance (p 0.0534), probably due to the small sample of our study. However, we highlighted as beside a significant linear trend for mucositis worsening in both groups, due to the adverse effects of oncological treatment, notably none of the components of the experimental group developed a grade 4 mucositis, unlike the control group (0 vs 33.33%).

Moreover, we confirmed as Gln is safe and well tolerated, since no patient left the protocol due to treatment side effects, and weight loss did not differ significantly between the two groups. Furthermore, we also showed the clinical feasibility of the therapy, since adherence in Gln assumption was respected by all the probands. Our results appear to be similar to those from the recent double-blind randomized trial by Lopez-Vaque-ro D et Al. who involved 50 subjects and administered oral Gln at a higher dosage (30 g/day): Authors observed slight effects in reducing mucositis incidence and severity in the treatment rather than in the placebo group, although not reaching a statis-
tical significance. On the contrary, there was found a significant reduction in the radiation dermatitis onset (p 0.038) and severity (p 0.032) [60].

The comparison of our data appears more complicated with the results from the randomized controlled trial by Yuce Sari S et al. [61] who enrolled a similar size sample but administered Gln at a lower dosage (15 g/day) and associated to arginine, which in previous studies showed a protective action on the intestinal mucosa during CT in cellular [62] and murine experimental cancer models [63]. Furthermore the outcomes were expressed not as quantitative mucositis but as global health status, social functions, pain, appetite, xerostomia, sticky saliva, dysgeusia, and swallowing problems, however all being significantly worse in the control group.

The data provided by the present study appear encouraging to propose Gln employment in a clinical context, however they have to be read in the light of some intrinsic limitations due to reduced sample size, and to the trial design features (randomized but not double-blind placebo-controlled, and single center trial). On the other hand, the strengths of this study were the assessment of the OM through a quantitative validated scale (allowing reproducibility and comparability with other similar trials), the Gln monoadministration (not associated to other molecules with possible confounding effects), and the sample homogeneity by type (HNC) and disease staging (requiring CRT).

Moreover, a specific nutritional competence allowed not only to exclude severe malnutrition at the enrollment and therefore ensuring homogeneity in nutritional conditions at baseline, but also to monitor regularly patients, so ensuring safety and adherence to the treatment. Therefore, it is reasonable to conclude that, according this randomized study, oral Gln administration provided mild effects in reducing the severity of OM in HNC patients underwent to CRT, although it has not been reached a statistically significant evidence.

However this close-to-significance benefit suggests as further confirmatory studies on larger size samples are necessary, in addition to considering Gln effect on secondary outcomes such as dermatitis, pharyngodynia, dysphagia, dysphonia, xerostomia, dental damage, mandibular necrosis, laryngeal edema, and social functions. It would be desirable a greater homogeneity for future trials in terms of histological type and primitive site of tumors, staging, oncological treatment regimens, Gln administration protocols (dosage, frequency, therapy duration), as well as personal features such as age, comorbidities, concurrent drugs assumption, nutritional status, and body composition.

Conclusions

Oral Gln administration in HNC patients undergoing to CRT could have a mild role in order to limit the severity of OM, although in our randomized clinical trial we could not reach statistically significant evidence. Further well designed studies on larger size samples are necessary in order to investigate the possible role of Gln in the clinical management of OM which still remains a serious complication in these subjects.

Abbreviations:

OM: Oral Mucositis; Gln: Glutamina; HNC: Head-Neck District Cancers; CRT: Chemoradiotherapy; IMRT: Intensity Modulated Radiation Therapy

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Statement of Authorship

FC, CA, and OM designed research. FC, CA, OM, MT, CA, AF, and FP conducted research. MFD analysed data and performed statistical analyses. FC and CA wrote the paper. FC had primary responsibility for final content. All Authors read and approved the final manuscript.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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