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Research article

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 extention, 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.

Oral mucositis

Approximately 550,000 people worlwide 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, tipically 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 oncological 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, antimicotical 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 antiflogistic 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-Fluorouracil 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

Partecipants 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 normalty 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-Vaquero 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 sperimental 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.

Abbrevations:

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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References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.
2. Adelstein DJ, Lavertu, P, Saxton JP, et al. Mature results of a phase III randomized trial comparing concurrent chemoradiotherapy with radiation therapy alone in patients with stage III and IV squamous cell carcinoma of the head and neck. Cancer. 2000; 88: 876–883
3. Forastiere AA, Trotti A. Radiotherapy and concurrent chemotherapy: a strategy that improves locoregional control and survival in oropharyngeal cancer. J Nat Cancer Inst. 1999;91:2065–2066.
4. Lee DJ, Cosmatos D, Marcial VA, et al. Results of an RTOG phaseIII trial (RTOG 85-27) comparing radiotherapy plus etanidazole with radiotherapy alone for locally advanced head and neck carcinomas. Int J Radiat Oncol Biol Phys. 1995;32:567–76.
5. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. Int J Radiat Oncol Biol Phys. 2000;48:7–16.
6. Dose AM. The symptom experience of mucositis, stomatitis, and xerostomia. Semin Oncol Nurs. 1995;11:248–55.
7. Aoyagi T, Terracina KP, Raza A, et al. Cancer cachexia, mechanism and treatment. World J Gastrointest Oncol. 2015;7(4):17-29.
8. Groome PA, O'Sullivan B, Mackillop WJ, et al. Compromised local control due to treatment interruptions and late treatment breaks in early glottis cancer: population-based outcomes study supporting need for intensified treatment schedules. Int J Radiat Oncol Biol Phys. 2006;64:1002–1012.
9. Nonzee NJ, Dandade NA, Patel U, et al. Evaluating the supportive care costs of severe radiochemotherapy-induced mucositis and pharyngitis: results from a Northwestern University Costs of Cancer Program pilot study with head and neck and nonsmall cell lung cancer patients who received care at a county hospital, a Veterans Administration hospital, or a comprehensive cancer care center. Cancer. 2008;113(6):1446-52.
10. McGuire DB, Fulton JS, Park J, et al. Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer. 2013;21(11):3165-77.
11. Rosenthal DI, Trotti A. Strategies for managing radiation-induced mucositis in head and neck cancer. Semin Radiat Oncol. 2009;19:29–34.

12. Quinn B, Potting CM, Stone R, et al. Guideline for the assessment of oral mucositis in adult chemotherapy, radiotherapy and haematopoetic stem cell transplant patients. Eur J Cancer. 2008;44:61–72.
13. Mead GM. Management of oral mucositis associated with cancer chemotherapy. Lancet. 2002;359:815–6.
14. Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer. 2007;109(5):820-31.
15. Krebs H. Glutamine metabolism in the animal body. In: Mora J, Palacios R, editors. Glutamine: Metabolism, enzymology and regulation. NewYork: Academic Press; 1980. 319–25.
16. van Zaanen HC, van der Lelie H, Timmer JG, et al. Parenteral glutamine dipeptide supplementation does not ameliorate chemotherapy-induced toxicity. Cancer. 1994. 74: 2879-2884.
17. Lacey JM, Wilmore DW. Is glutamine a conditionally essential amino acid? Nutr Rev. 1990;48:297–309.
18. Sonis ST. The pathobiology of mucositis. Nat Rev Cancer. 2004;4(4):277-84
19. Wernerman J, Hammarqvist F. Glutamine: a necessary nutrient for the intensive care patient. Int J Colorectal Dis. 1999;14(3):137-42.
20. Mates JM, Perez-Gomez C, Nunez de Castro I, et al. Glutamine and its relationship with intracellular redox status, oxidative stress and cell proliferation/death. Int J Biochem Cell Biol. 2002;34(5):439-58.
21. Kaufmann Y, Todorova VK, Luo S, et al. Glutamine affects glutathione recycling enzymes in a DMBA-induced breast cancer model. Nutr Cancer. 2008;60(4):518-25.
22. Coeffier M, Marion R, Ducrotte P, et al. Modulating effect of glutamine on IL-1beta-induced cytokine production by human gut. Clin Nutr. 2003;22(4):407-13.
23. Coeffier M, Marion R, Leplingard A, et al. Glutamine decreases interleukin-8 and interleukin-6 but not nitric oxide and prostaglandins e(2) production by human gut in-vitro. Cytokine. 2002;18(2):92-7.
24. Evans ME, Jones DP, Ziegler TR. Glutamine prevents cytokine-induced apoptosis in human colonic epithelial cells. J Nutr. 2003;133(10):3065-71.
25. Xue H, Sawyer MB, Field CJ, et al. Bolus oral glutamine protects rats against CPT-11-induced diarrhea and differentially activates cytoprotective mechanisms in host intestine but not tumor. J Nutr. 2008;138(4):740-6.
26. Bellon G, Monboisse JC, Randoux A, et al. Effects of preformed proline and proline amino acid precursors (including glutamine) on collagen synthesis in human fibroblast cultures. Biochim Biophys Acta. 1987;930(1):39-47.
27. Rouse K, Nwokedi E, Woodliff JE, et al. Glutamine enhances selectivity of chemotherapy through changes in glutathione metabolism. Ann Surg. 1995;221:420–6.
28. Savarese DM, Savy G, Vahdat L, et al. Prevention of chemotherapy and radiation toxicity with glutamine. Cancer Treat Rev. 2003;29:501–13.
29. Klimberg VS, Kornbluth J, Cao Y, et al. Glutamine suppresses PGE 2 synthesis and breast cancer growth. J Surg Res. 1996;63:293–7.
30. Ziegler TR, Benfell K, Smith RJ, et al. Safety and metabolic effects of L-glutamine administration in humans. JPEN. 14:137S-146S, 1990
31. Ziegler TR, Young LS, Benfell K, et al. Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition following bone marrow transplantation: A double-blind, randomized, controlled trial. Ann Intern Med. 1992; 116:821-828.
32. Chang YH, Yu MS, Wu KH, et al. Effectiveness of Parenteral Glutamine on Methotrexate-induced Oral Mucositis in Children with Acute Lymphoblastic Leukemia. Nutr Cancer. 2017;69(5):746-751.
33. Schloerb PR, Amare M. Total parenteral nutrition with glutamine in bone marrow transplantation and other clinical applications (a randomized, double-blind study). JPEN J Parenter Enteral Nutr. 1993;17(5):407-13.
34. Schloerb PR, Skikne BS. Oral and parenteral glutamine in bone marrow transplantation: a randomized, double-blind study. JPEN J Parenter Enteral Nutr. 1999;23(3):117-22.
35. Vidal-Casariego A, Calleja-Fernández A, de Urbina-González JJ, et al. Efficacy of glutamine in the prevention of acute radiation enteritis: a randomized controlled trial. JPEN J Parenter Enteral Nutr. 2014;38(2):205-13.
36. Zygogianni A, Kyrgias G, Kouvaris J, et al. Impact of acute radiation induced toxicity of glutamine administration in several hypofractionated irradiation schedules for head and neck carcinoma. Head Neck Oncol. 2012;4(5):86.
37. Peterson DE, Jones JB, Petit RG 2nd. Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. Cancer. 2007;109(2):322-31.
38. Huang EY, Leung SW, Wang CJ, et al. Oral glutamine to alleviate radiation-induced oral mucositis: a pilot randomized trial. Int J Radiat Oncol Biol Phys. 2000;46(3):535-9.
39. Anderson PM, Schroeder G, Skubitz KM. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. Cancer. 1998;83(7):1433-9.
40. Skubitz KM, Anderson PM. Oral glutamine to prevent chemotherapy induced stomatitis: a pilot study. J Lab Clin Med. 1996;127(2):223-8.
41. Jebb SA, Osborne RJ, Maughan TS, et al. 5-fluorouracil and folinic acid-induced mucositis: no effect of oral glutamine supplementation. Br J Cancer. 1994;70(4):732-5.
42. Okuno SH, Woodhouse CO, Loprinzi CL, et al. Phase III controlled evaluation of glutamine for decreasing stomatitis in patients receiving fluorouracil (5-FU)-based chemotherapy. Am J Clin Oncol. 1999;22(3):258-61.
43. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-6.
44. White JV, Guenter P, Jensen G, et al. Malnutrition Task Force; A.S.P.E.N. Board of Directors. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). JPEN J Parenter Enteral Nutr. 2012;36(3):275-83.
45. Gupta T, Agarwal J, Jain S, et al. Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: a randomized controlled trial. Radiother Oncol. 2012;104(3):343-8.
46. Marta GN, Silva V, de Andrade Carvalho H, et al.Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiother Oncol. 2014;110(1):9-15.
47. Leung HW, Chan AL. Glutamine in alleviation of radiation-induced severe oral mucositis: A meta-analysis. Nutr Cancer. 2016;68:734–742.
48. Cerchietti LC, Navigante AH, Lutteral MA, et al. Double-blinded, placebo-controlled trial on intravenous L-alanyl-L-glutamine in the incidence of oral mucositis following chemoradiotherapy in patients with head and-neck cancer. Int J Radiat Oncol Biol Phys. 2006;65:1330–1337.
49. Chattopadhyay S, Saha A, Azam M, et al. Role of oral glutamine in alleviation and prevention of radiation-induced oral mucositis: A prospective randomized study. South Asian J Cancer. 2014;3:8–12.
50. Tsujimoto T, Yamamoto Y, Wasa M, et al. L-glutamine decreases the severity of mucositis induced by chemoradiotherapy in patients with locally advanced head and neck cancer: A double-blind, randomized, placebo-controlled trial. Oncol Rep. 2015;33:33–39.
51. Yarom N, Ariyawardana A, Hovan A, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO): Systematic review of natural agents for the management of oral mucositis in cancer patients. Support Care Cancer. 2013;21:3209–3221.

52. Choi K, Lee SS, Oh SJ, et al. The effect of oral glutamine on 5-fluorouracil/leucovorin-induced mucositis/stomatitis assessed by intestinal permeability test. Clin Nutr. 2007;26:57–62.
53. Rubio IT, Cao Y, Hutchins LF, et al. Effect of glutamine on methotrexate efficacy and toxicity. Ann Surg. 1998;227:772–778; 778–780.
54. Cockerham MB, Weinberger BB, Lerchie SB. Oral glutamine for the prevention of oral mucositis associated with high-dose paclitaxel and melphalan for autologous bone marrow transplantation. Ann Pharmacother. 2000;34:300–303.
55. Ward E, Smith M, Henderson M, et al. The effect of high-dose enteral glutamine on the incidence and severity of mucositis in paediatric oncology patients. Eur J Clin Nutr. 2009;63:134–140.
56. Sayles C, Hickerson SC, Bhat RR, et al. Oral Glutamine in Preventing Treatment-Related Mucositis in Adult Patients With Cancer: A Systematic Review. Nutr Clin Pract. 2016;31(2):171-9.
57. Tanaka Y, Takahashi T, Yamaguchi K, et al. Elemental diet plus glutamine for the prevention of mucositis in esophageal cancer patients receiving chemotherapy: a feasibility study. Support Care Cancer. 2016;24(2):933-941.
58. Tanaka Y, Takahashi T, Yamaguchi K, et al. Erratum to: Elemental diet plus glutamine for the prevention of mucositis in esophageal cancer patients receiving chemotherapy: a feasibility study. Support Care Cancer. 2016;24(2):943.
59. Pattanayak L, Panda N, Dash MK, et al. Management of Chemoradiation-Induced Mucositis in Head and Neck Cancers With Oral Glutamine. J Glob Oncol. 2016;2(4):200-206.
60. Lopez-Vaquero D, Gutierrez-Bayard L, Rodriguez-Ruiz JA, et al. Double-blind randomized study of oral glutamine on the management of radio/chemotherapy-induced mucositis and dermatitis in head and neck cancer. Mol Clin Oncol. 2017;6(6):931-936.
61. Yuce Sari S, Yazici G, Yuce D, et al. The effect of glutamine and arginine-enriched nutritional support on quality of life in head and neck cancer patients treated with IMRT. Clin Nutr ESPEN. 2016;16:30-35.
62. Beutheu S, Ghouzali I, Galas L, et al. Glutamine and arginine improve permeability and tight junction protein expression in methotrexate-treated Caco-2 cells. Clin Nutr. 2013;32(5):863-9.
63. Leocádio PC, Antunes MM, Teixeira LG, et al. L-arginine pretreatment reduces intestinal mucositis as induced by 5-FU in mice. Nutr Cancer. 2015;67(3):486-93.

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