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Lactobacillus brevis CD2 lozenges reduce radiation- and chemotherapy-induced mucositis in patients with head and neck cancer: A randomized double-blind placebo-controlled study ☆,☆☆

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ABSTRACT

Background: Oral mucositis is a frequent and serious complication in patients receiving chemo-radiotherapy for head and neck squamous cell carcinoma. This study evaluated the effects of administering *Lactobacillus brevis* CD2 lozenges on the incidence and severity of mucositis and tolerance to chemo-radiotherapy.

Methods: Two hundred patients suitable for chemo-radiotherapy were enrolled in a randomised, double-blind study to receive daily treatment with lozenges containing either *L. brevis* CD2 or placebo. Anticancer therapy was RT 70 Grays/35 fractions over 7 weeks with weekly Inj. Cisplatin 40 mg/m^2. The study treatment was given during, and for 1 week after completion of anticancer therapy. Primary end-points were the incidence of grade III and IV oral mucositis and the percentage of patients able to complete anticancer treatment.

Findings: The efficacy analysis included the 188 patients who received $\geqslant$1 week of study treatment. Grade III and IV mucositis developed in 52% of patients in the *L. brevis* CD2 arm and 77% in the placebo arm ($P < 0.001$). Anticancer treatment completion rates were 92% in the *L. brevis* CD2 arm and 70% in the placebo arm ($P = 0.001$). A larger proportion of patients remained free of mucositis when treated with *L. brevis* CD2 (28%) compared to the placebo (7%).

Interpretation: *L. brevis* CD2 lozenges reduced the incidence of grade III and IV anticancer therapy-induced oral mucositis and were associated with a lower overall rate of mucositis and a higher rate of anticancer treatment completion.

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1. Introduction

Chemotherapy and radiotherapy are widely used therapeutic interventions for head and neck squamous cell carcinoma (HNSCC), and are often associated with severe side-effects resulting in morbidity and mortality. Oral complications that arise with these therapies include mucositis, xerostomia, bacterial, fungal, or viral infection (particularly in neutropenic patients), dental caries, loss of taste, and osteoradionecrosis.[1] Virtually all patients who receive chemo-radiotherapy (CRT) to the head and neck area develop oral complications and oral mucositis. Grade III and IV mucositis, the most distressing condition, is reported in 40–70% of patients receiving CRT.[2–6]

Mucositis is painful and may result in dose reductions, treatment delays, or treatment discontinuation, which in turn can affect the outcome of anticancer therapy.[1] Furthermore, extensive mucositis may limit adequate nutritional intake and necessitate hospitalisation for parenteral nutrition and narcotic analgesics, increasing the cost of anticancer therapy and impairing the patient's quality of life (QoL).

Management of oral mucositis generally involves good oral hygiene, systemic analgesics, and preventive care such as benzydamine. For haematopoietic stem cell transplantation, palifermin is recommended. Various topical agents such as antimicrobial mouth rinse, L-glutamine, mucosal coating agents, and prostaglandin E2 (dinoprostone) are used, but there is no unequivocal evidence that these agents have any significant effect on mucositis.[7] Thus there is a strong need for well-designed, randomised, placebo-controlled trials in this population to evaluate the safety and efficacy of new agents.

In the normal microflora of the mouth, it is possible to isolate several thousand microbial species. Some of these bacteria have a rich array of enzymes, which enables them, through metabolic activities, to modify their surrounding environment. The report of a successful treatment of the symptoms associated to the gut mucositis with the probiotic preparation VSL#3 has focused the attention towards the benefits consequent to the process of microflora manipulation.[8]

In particular, the strain of *Lactobacillus brevis*, *L. brevis* CD2, produces high levels of arginine deiminase and sphingomyelinase.[9] Eukaryotic human cells can convert arginine into nitric oxide and polyamines by the actions of nitric oxide synthase and arginase, respectively. Arginine deiminase of bacterial origin competes with nitric oxide synthase and converts arginine to ammonia and citrulline; downregulating its conversion to nitric oxide, leading to a reduction in the levels of some of the known inflammatory parameters (cytokines IL-1α, IL-6, IL-8, TNF-α, IFN-y, PGE2 and matrix metalloproteinases).[10] Bacterial sphingomyelinase can hydrolyse the platelet activating factor (PAF),[11] a potent inflammatory cytokine, known to be associated with oral mucositis in radiation therapy.[12]

Previously, small studies demonstrated the efficacy of *L. brevis* CD2 in the prevention of inflammation. One study showed that *L. brevis* CD2 had anti-inflammatory effects in periodontal disease.[10] Lozenges containing *L. brevis* CD2 were also used in the treatment of oral ulcers in Behçet's syndrome, with a significant decrease in oral ulcers after 1 and 2 weeks of therapy.[13]

In view of the characteristics and potential benefits of *L. brevis* CD2, the present study was undertaken to test the *in vivo* efficacy of these bacteria in patients with head and neck cancer who were likely to develop therapy-induced mucositis. The study evaluated the efficacy of *L. brevis* CD2 lozenges in preventing oral mucositis in patients receiving CRT for HNSCC.

2. Methods

2.1. Study design

This was a randomised, double-blind, single centre, placebo-controlled study. It was conducted at the Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi. The Principal Investigator and the study sponsor, CD Pharma India Pvt. Ltd., jointly designed the study.

2.2. Ethics

The study data were gathered and informed consent was obtained in accordance with the Declaration of Helsinki. Study conduct was approved by the Institute's ethics committee. All patients were given a written explanation of the study and provided written informed consent before participating.

2.3. Patient population

Patients with a confirmed diagnosis of HNSCC stage II–IVA (resectable) attending the head and neck cancer clinic at the study centre were examined by head and neck surgeons, radiation, and medical oncologists. Subjects eligible for receiving CRT and meeting other inclusion criteria were enrolled in the study. Inclusion criteria included normal bone marrow (haematological), renal, and liver function.

2.4. Randomisation and masking

Patients were randomly assigned to either of the treatment arms in a 1:1 ratio through a computer-generated randomisation list consisting of randomly permuted blocks of 10 patient numbers. All patients were enrolled by the investigator and assigned to treatment arm according to the randomisation number. The study products were pre-packaged by the sponsor as per the randomisation codes and dispensed accordingly. The *L. brevis* CD2 lozenges and placebo were supplied by CD Pharma India Pvt. Ltd. and were identical in physical appearance, taste and colour.

2.5. Anticancer treatment

All patients received radical radiotherapy at a dose of 70 Gy in 35 fractions over 7 weeks (at 5 fractions per week; standard fractionation) by linear accelerator, with parallel-opposed lateral fields and spinal cord shielding at 44 Gy. Concurrent chemotherapy consisted of cisplatin (DDP) 40 mg/m^2 weekly for 7 doses (days 1, 8, 15, 22, 29, 36, 43) beginning on day 1 of radiation treatment. Patients receiving less than 30 fractions of

radiotherapy or less than 6 doses of cisplatin were classified as not having completed anticancer therapy. A delay of up to 1 week for scheduled radiation or chemotherapy doses was allowed.

2.6. Study investigational product

The *L. brevis* CD2 lozenges contained not less than 2×10^9 (2 billion) viable cells of *L. brevis* CD2 as the active ingredient.[14] Placebo lozenges contained a mixture of the sugars and salts used as excipients in the active formulation. The daily dose was 6 lozenges per day, 1 lozenge every 2–3 h to be dissolved in the mouth and then swallowed. Hot beverages (e.g. tea, coffee, milk, etc.) were avoided for at least half an hour before and after study treatment administration, as higher temperature could reduce the efficacy of the *L. brevis* CD2. The study treatments (active or placebo) were started from the first day of CRT, and continued until 1 week after the last CRT administration. Compliance with study treatment was recorded in patients' diaries.

2.7. Safety and efficacy evaluation

Enrolled subjects were examined once every week, starting from the first day of therapy until 1 week after the last CRT administration.

Primary end-points were determination of the incidence of grade III and IV oral mucositis in patients with head and neck cancer undergoing CRT and the percentage of patients able to complete the anticancer treatment. Secondary end-points were determination of the incidence of grade I and II oral mucositis among the same group of patients, and QoL assessment using a disease-specific instrument, the Functional Assessment of Cancer Therapy Head and Neck questionnaire (FACT-HN).

All patients who received at least 1 dose of study medication were analysed for safety. Patients who discontinued study investigational product within 1 week were excluded from efficacy analysis.

Additional clinical parameters such as use of analgesics, weight loss, need for parenteral feeding, and time to develop oral mucositis were recorded and analysed. Patients that were included in the efficacy analysis were followed up in the clinic up to June, 2010 for the survival estimate.

2.8. Response assessment

Mucositis grade assessment according to NCI CTC version 2.0 was done every week by same observer for characterisation of the lesions (number, localisation in the oral cavity, bleeding, erythema and ulceration). Adverse events also were graded as per NCI CTC version 2.0 criteria.[15]

Photographs of the oral cavity were taken during each study visit. Saliva samples were collected at the start and end of study treatment for analysing the levels of pro-inflammatory cytokines, IgA antibodies and matrix metalloproteinases. The analysis of this will be reported separately.

QoL was assessed using the FACT-HN questionnaire, Version 4.

2.9. Statistical methods

The sample size was calculated assuming rates of grade III and IV mucositis of 50% in the *L. brevis* CD2 arm and 70% in the placebo arm, respectively that would have $\alpha = 0.05$ (2-sided log rank test) and $\beta = 0.20$. Under these conditions, 150 patients were required (75 per treatment arm). Two hundred subjects were recruited to allow for losses to follow-up and protocol violations.

An independent biostatistician analysed the study data. For continuous variables, comparisons between the treatment and placebo groups were performed using unpaired *t*-tests; if data were not normally distributed, the comparison was performed using the Wilcoxon Mann–Whitney test. For within-group comparisons over time, we performed paired *t*-tests or non-parametric Wilcoxon signed rank-sum tests. Between-group comparisons for categorical variables were performed by Chi-square tests (or the Fisher exact test in case of expected cell counts less than 5).

Survival curves were plotted using Kaplan–Meier method.

P values of .05 or less were considered statistically significant. The data were analysed by using SPSS statistical software version 12.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patient disposition

From January 2007 to February 2009, 210 patients were enrolled, of whom 10 were screen failures. An efficacy evaluable population was defined by exclusion of the 12 subjects (8 in the *L. brevis* CD2 arm and 4 in the placebo arm) who discontinued within 1 week of starting the study treatment. Patient disposition is displayed in Fig. 1.

3.2. Baseline characteristics

Patients' baseline characteristics are summarised in Table 1. The treatment groups were well balanced with regard to age and distribution of sex, clinical stage of cancer, and primary site of cancer. All patients received concurrent chemoradiotherapy.

3.3. Efficacy

The oral mucositis incidence and severity distribution differed markedly between patients treated with *L. brevis* CD2 lozenges and those who received the placebo. As shown in Table 2, the proportion of patients with grade III or IV mucositis was lower in the *L. brevis* arm than in the placebo arm (52% versus 77%), while the proportions with grade I and II mucositis were similar (19% versus 15%), and the proportion remaining free of oral mucositis was greater in the *L. brevis* arm (28% versus 7%). Taken together, these findings were highly significant ($P < .001$).

A higher percentage of patients in the *L. brevis* CD2 arm were able to complete planned CRT compared to the placebo arm, 92% versus 70% ($P = .001$), as shown in Table 3. This represents a 31% higher proportions of patients in the *L. brevis*

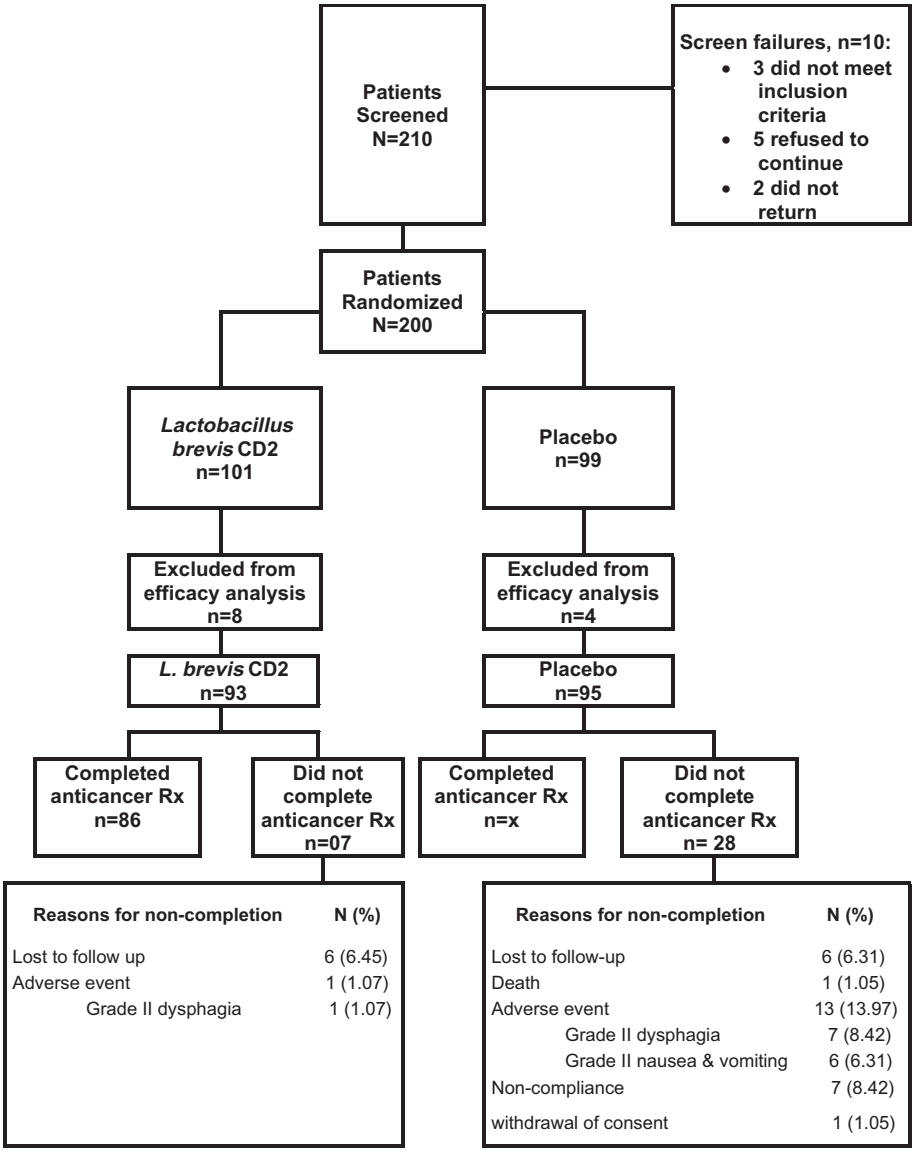

Fig. 1 – Patient disposition.

CD2 arm were able to complete anticancer treatment compared to the placebo arm.

3.4. *Other parameters*

The numbers of patients requiring analgesics to control pain associated with mucositis (narcotics and non-narcotics) were 28 (30%) in the *L. brevis* CD2 arm and 43 (45%) in the placebo arm ($P = .02$). Of these, 11 in the *L. brevis* CD2 arm and 21 in the placebo in arm required narcotic analgesics ($P = .08$).

A total of 51 patients (23 in the *L. brevis* CD2 arm and 28 in the placebo arm) required administration of parenteral nutrition or insertion of a Ryle's tube to maintain adequate nutrition ($P = .31$). Among those who completed the anticancer treatment, 19 of 86 in the *L. brevis* CD2 arm (22%), and 23 of 67 (34%) in the placebo arm received parenteral nutrition or insertion of Ryle's tube ($P = .09$).

The treatment groups were similar with respect to mean body weight at baseline: 55.5 kg (SD 13.1) in the *L. brevis* CD2 arm and 56.02 kg (SD 16.2) in placebo arm ($P = .11$). Unfortunately, there were too many missing end-of-study weights for valid interpretation of weight loss in two arms at end of the treatment (data were available for 54 patients only).

Median time to onset of mucositis was 22 days (SD 13.2) in the *L. brevis* CD2 arm and 18 days (SD 11.6) in the placebo arm (P = ns). Median time to resolution or healing of mucositis was 43 days in both groups (P = ns).

QoL was assessed before and after treatment. Though there was a trend towards improvement in QOL in the *L. brevis* CD2 arm compared to placebo, it was not statistically significant (0.09).

A survival estimate was not a planned end-point in this study, but was undertaken for exploratory purposes. The median follow-up of 17 months was relatively short, and no statistical difference between treatments was observed ($P = .15$). Median overall survival was 42 months in the placebo arm but yet to reach in the study arm. The Kaplan–Meier plot

Table 1 – Baseline characteristics of study patients.

Variable	*L. brevis* CD2 (*N* = 101)	Placebo (*N* = 99)	*P* value
Percentage of total enrollment	50.5	49.5	0.94
Male:female, *n*:*n* (%:%)	94:07 (93.1:6.9)	91:08 (91.9:8.1)	0.758[a]
Age (year), mean ± SD	52.35 ± 9.433	50.09 ± 10.038	0.105[b]
Weight (kg), mean ± SD	56.23 ± 13.125	55.90 ± 14.822	0.868[b]
Height (cm), mean ± SD	164.31 ± 7.167	164.76 ± 12.213	0.754[b]
Head and neck cancer stage, *n* (%)			
I	3 (2.97)	5 (5.1)	0.775[a]
II	6 (5.9)	4 (4.0)	
III	45 (44.6)	41 (41.4)	
IV	47 (46.5)	49 (49.5)	
Site of primary, *n* (%)			
Nasopharynx	11 (10.9)	11 (11.1)	0.977[a]
Oropharynx	48 (47.5)	50 (50.5)	
Hypopharynx	29 (28.7)	28 (28.3)	
Larynx	12 (11.9)	9 (9.1)	
Others	1 (1.0)	1 (1.0)	

[a] Pearson chi square test.
[b] Student *t* test.

Table 2 – Incidence of oral mucositis in efficacy evaluable population.

Oral mucositis grade	*L. brevis* CD2 lozenges *N* = 93 *n* (%[a])	Placebo *N* = 95 *n* (%[a])	*P* value
0	26 (28)	7 (7)	0.002
I	10 (11)	10 (10)	
II	8 (8)	5 (5)	
III	2 (2)	8 (8)	
IV	47 (50)	65 (69)	
0	26 (28)	7 (7)	<0.001
I–II	18 (19)	15 (15)	
III–IV	49 (52)	73 (77)	

[a] Rounded.

Table 3 – Anticancer treatment completion status in efficacy evaluable population.

Status	*L. brevis* CD2 lozenges *n* (%[a])	Placebo *n* (%[a])	*P*-value
Completed	86 (92)	67 (70)	0.001
Did not complete	7 (8)	28 (30)	
Total	93 (100)	95 (100)	

[a] Rounded.

is shown in Fig. 2, which suggests a separation of the curves later in the follow-up period.

3.5. *Safety*

The incidence and frequency of adverse events attributable to CRT (xerostomia, nausea, dysphagia, dysgeusia and vomiting) were similar in both treatment arms.

One patient in the *L. brevis* CD2 arm developed acute myocardial infarction after 4 weeks of anticancer therapy. Cisplatin was discontinued and the patient completed radiotherapy. One patient in the placebo arm died after developing grade IV neutropenia and sepsis. Both of these events were attributed to anticancer treatment.

No serious adverse events attributable to study product or placebo were observed during the study period.

4. Discussion

Oral mucositis is an important, noxious, common complication of cancer treatments such as chemotherapy and radiotherapy. It is usually the dose-limiting factor for treating HNSCC patients. In a large ($n = 450$) retrospective review of stage III or IV head and neck cancer patients undergoing radiation therapy, 83% developed mucositis. Significantly more patients with mucositis (59%) required unplanned delays/breaks in therapy than did those without mucositis (16%).[16]

Oral mucositis is a consequence of physical and chemical damage to the epithelium. Radiation and chemotherapy lead to activation of several biological messengers that mediate release of inflammatory cytokines and cytokine mediators. Further mucosal injuries lead to the loss of epithelial cell renewal, apoptosis, atrophy, and ulcer formation.[17]

Palifermin, a recombinant human keratinocyte growth factor, was found to be superior to the placebo in reducing the duration of grade III and IV mucositis (median 6 days versus 9 days) in a phase III placebo-controlled trial in patients undergoing peripheral blood stem cell transplant after receiving high-dose chemotherapy and total body irradiation. Grade III or IV mucositis was seen in 63% of patients who received the active drug compared to 98% of patients in the placebo group.[18] However, palifermin is not an oral preparation and has been approved only for the prevention of oral mucositis in patients undergoing peripheral blood stem cell transplant after receiving high-dose chemotherapy and radiation. In a phase II randomised study in head and neck cancer, no difference in duration of $\geqslant$grade II mucositis, treatment morbidity,

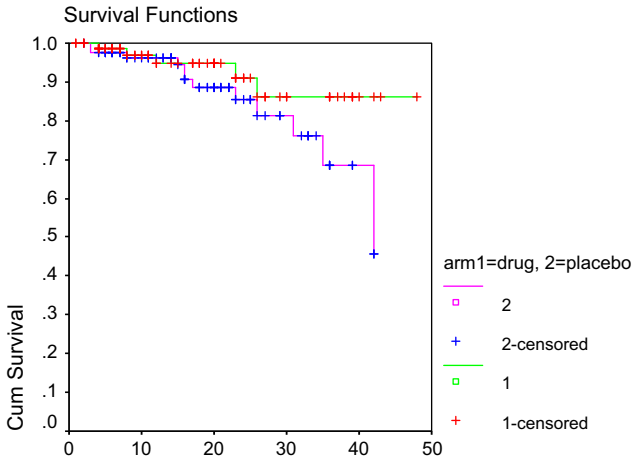

Fig. 2 – Overall survival in months.

response, or survival could be demonstrated between palifermin and placebo.[19] Moreover, wider application is restricted as its efficacy for other cancer treatment-associated mucositis is still under investigation. Also the high costs associated with the use of palifermin make its use a less attractive option in developing countries.

While many studies have been conducted in patients undergoing stem cell transplant, large studies to address the issue of mucositis in HNSCC patients receiving CRT are yet to be reported. The only study with a somewhat adequate number of patients with HNSCC investigated recombinant human epithelial growth factor (rhEGF) and involved 113 patients. In this study responders were defined as having Radiation Therapy Oncology Group (RTOG) grade II or lower mucositis at the 4th or 5th week examination. Topical application of rhEGF as a spray was associated with significantly reduced incidence of RTOG grade III or IV mucositis at the 4th and 5th week of radiotherapy (64% response rate with active treatment compared to 37% with placebo).[20] However, since cancer treatment in the study consisted of radiotherapy with or without chemotherapy; there are limitations to extrapolating the data to combination therapy. In a randomised study involving 130 patients, Ryu et al. reported that there was no difference in either incidence or severity of radiation-associated mucositis in patients treated with granulocyte–macrophage colony-stimulating factor or the placebo.[21]

The present study is probably the largest randomised controlled trial involving HNSCC patients undergoing CRT, for whom no intervention has heretofore been found useful in reducing the severity of mucositis. This study provides evidence that the probiotic *L. brevis* CD2 significantly reduces the incidence and severity of oral mucositis associated with CRT in HNSCC patients. The incidence of grade III and IV mucositis was about 50% higher in the placebo group, while 28% of patients who received *L. brevis* CD2 lozenges remained free of mucositis compared to 7% in the placebo group; these differences in distribution were highly significant ($P < .001$). Treatment with *L. brevis* CD2 was associated with more subjects completing their anticancer therapy. A 31% greater proportion of patients could tolerate and complete anticancer therapy in the *L. brevis* CD2 arm than in the placebo arm ($P = .001$). Most importantly, fewer patients in the *L. brevis* CD2 arm discontinued anticancer treatment due to radiotherapy- or chemotherapy-associated side-effects such as dysphagia and nausea/vomiting ($P = .001$).

In recent years, various clinical/experimental studies and extensive reviews elucidated that commensal bacteria have pivotal role in the development and/or progression of gut mucosits in patients receiving anticancer treatment to suggest that manipulation of gut flora can be considered as plausible strategy to prevent and manage the gastrointestinal mucositis associated with anticancer treatment.[22]

With the use of *L. brevis* CD2, significantly fewer patients required analgesics for mucositis-associated pain compared to the placebo. Despite the reduced incidence of grade III and IV mucositis, the requirement for parenteral nutrition or Ryle's tube insertion was similar in both treatment groups. A possible explanation may be that since more patients were able to complete anticancer therapy in the *L. brevis* CD2 arm, other events such as other toxicity of CRT, and declining general well-being could have contributed to the need for nutritional supplementation in these patients. However, among those patients who were able to complete the anticancer treatment, the requirement for parenteral nutrition or Ryle's tube insertion trended lower in the *L. brevis* CD2 arm. Similarly, the trend towards better QoL in the *L. brevis* CD2 arm did not reach statistical significance, and we speculate that those patients had more likelihood of reporting lower QoL in view of the higher proportion of patients exposed to anticancer treatment for the entire planned CRT treatment period.

In summary, *L. brevis* CD2 lozenges proved to be safe and efficacious in reducing the incidence of severe oral mucositis in patients with HNSCC undergoing combination radiation and chemotherapy. Its relative cost-effectiveness permits its use developed and developing countries alike.

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Conflict of interest statement

None declared.

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REFERENCES

1. Naidu MUR, Ramana GV, Rani PU, et al. Chemotherapy-induced and/or radiation therapy-induced oral mucositis complicating the treatment of cancer. *Neoplasia* 2004;**6**:423–31.
2. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for

locally advanced head and neck cancer. *N Engl J Med* 1998;**338**:1798–804.
3. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst* 1999;**91**:2081–6.
4. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;**349**:2091–8.
5. Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Nat Cancer Inst* 2005;**97**:536–9.
6. Sharma Atul, Mohanti Bidhu Kalyan, Thakar Alok, Bahadur Sudhir, Bhaskar Suman, Amit Bahl. Concomitant chemoradiation versus radical radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: a phase II randomized trial. Ann Oncol 2010; <doi:10.1093/annonc/mdq219>.
7. Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007;**109**:820–31.
8. Delia P, Sansotta G, Donato V, et al. Prevention of radiation-induced diarrhea with the use of VSL#3, a new high-potency probiotic preparation. *Am J Gastroenterol* 2002;**97**(8):2150–2.
9. Di Marzio L, Russo FP, D'Alò S, et al. Apoptotic effects of selected strains of lactic acid bacteria on a human T leucemia cell line are associated with bacterial arginine deiminase and/or sphingomyelinase activities. *Nutr Cancer* 2001;**40**:185–96.
10. Riccia DN, Bizzini F, Perilli MG, et al. Anti-inflammatory effects of *Lactobacillus brevis* (CD2) on periodontal disease. *Oral Dis* 2007;**13**(4):376–85.
11. Rui-Dong Duan. Alkaline sphingomyelinase: an old enzyme with novel implications. Biochim Biophys Acta (BBA) – Mol Cell Biol Lipids 2006;1761:281–91.
12. McManus LM, Ostrom KK, Lear C, et al. Radiation-induced increased platelet-activating factor activity in mixed saliva. *Lab Invest* 1993;**68**:118–24.
13. Tasli ML, Mat C, De Simone C, et al. Lactobacillus lozenges in the management of oral ulcers of Behcet's syndrome. Clin Exp Rheumatol 2006; 24(5 Suppl 42):83–6.
14. Marshall RT. Microbiological count methods. In: *Standard methods for the examination of dairy products*. 16th ed. American Public Health Association; 1992 [chapter 6]. p. 213–6.
15. https://webapps.ctep.nci.nih.gov/webobjs/ctc/webhelp/Common_Toxicity_Criteria_CTC_v2.htm.
16. Vera-Llonch M, Oster G, Hagiwara M, et al. Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma: risk factors and clinical consequences. *Cancer* 2006;**106**:329–36.
17. Sonis ST. Pathobiology of oral mucositis: novel insights and opportunities. *J Support Oncol* 2007;**5**:3–11.
18. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *New Engl J Med* 2004;**351**:2590–8.
19. Brizel DM, Murphy BA, David I, Rosenthal DI, et al. Phase II study of palifermin and concurrent chemoradiation in head and neck squamous cell carcinoma. *J Clin Oncol* 2008;**26**:2489–96.
20. Wu HG, Song SY, Kim YS, et al. Therapeutic effect of recombinant human epidermal growth factor (rhEGF) on mucositis in patients undergoing radiotherapy, with or without chemotherapy, for head and neck cancer: a double-blind placebo-controlled prospective phase 2 multi-institutional clinical trial. *Cancer* 2009;**115**:3699–708.
21. Ryu JK, Swann S, LeVeque F, et al. The impact of concurrent granulocyte macrophage- colony stimulating factor on radiation-induced mucositis in head and neck cancer patients: a double-blind placebo-controlled prospective phase III study by Radiation Therapy Oncology Group 9901. *Int J Radiat Oncol Biol Phys* 2007;**67**:643–50.
22. van vilet MJ, Harmsen HJ, de Bont ES, et al. The role of intestinal microbiota in the development and severity of chemotherapy-induced mucositis. *PLos Pathog* 2010;**6**(5):e1000879.