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Lactobacillus brevis CD2 lozenges prevent oral mucositis in patients undergoing high dose chemotherapy followed by haematopoietic stem cell transplantation

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ABSTRACT

Background Oral mucositis is a common inflammatory complication in patients undergoing high-dose chemotherapy and radiation followed by haematopoietic stem cell transplantation (HSCT). Lactobacillus brevis CD2 has been proven efficacious in preventing chemoradiotherapy-induced oral mucositis in squamous cell carcinoma of head and neck.

Methods This phase II study aimed to evaluate the safety and efficacy of L. brevis CD2 lozenges in preventing oral mucositis in patients undergoing HSCT. Eligible patients received four to six lozenges of L. brevis CD2 per day, beginning from 4 to 7 days before initiation of chemotherapy and continuing until resolution of mucositis or till day +24.

Results Of 31 patients enrolled, 7 (22.6%) patients did not develop any mucositis, 6 (19.4%) patients developed grade 1, 12 (38.7%) patients developed grade 2, 4 (12.9%) and 2 (6.5%) patients developed grade 3 and grade 4 mucositis, respectively. Median time to onset and for resolution of mucositis were 6 days and 8 days, respectively. No adverse events were reported with usage of study drug. However, one patient died of Klebsiella sepsis.

Conclusion Promising results from the study encourage the use of L. brevis CD2 lozenges as a supportive care treatment option; however, a randomised, double-blind, multicentric trial in a larger population is warranted.

Trials registration number NCT01480011 at https://www.clinicaltrials.gov (Registered on Nov 04, 2011).

Key questions

What is already known about this subject?

- Severe oral mucositis (OM) has been reported to occur in about 60%–100% of patients undergoing haematopoietic stem cell transplantation (HSCT) after myeloablative chemotherapy.
- The Multinational Association for Supportive Care in Cancer recommends palifermin and low-level laser therapy as a preventive measure for severe OM in HSCT subjects.

What does this study add?

- Lactobacillus brevis CD2 lozenges have been proven efficacious in preventing chemoradiotherapy-induced oral mucositis in squamous cell carcinoma of head and neck, but this was the first study to test the safety and efficacy of same preparation in patients with haematological malignancies receiving high-dose chemotherapy and radiation followed by HSCT.
- Of 31 patients enrolled, only six (19.4%) patients developed severe OM (grades 3 and 4); the median time to onset and for resolution of mucositis were 6 days and 8 days, respectively.

How might this impact on clinical practice?

- L. brevis CD2 lozenges are to be taken orally, therefore imparts convenience to oncologist and patient.
- L. brevis CD2 lozenges may be considered as a supportive cancer care for management of OM in patients with haematological malignancies undergoing high-dose chemotherapy followed by HSCT.

BACKGROUND

Chemotherapy and/or radiation induced oral mucositis (OM) is a pathological process characterised by mucosal damage, ranging from mild inflammation to deep ulcerations affecting one or more parts of the alimentary tract, from the mouth to the anus.[1] This may lead to devastating effects such as opportunistic infections, fever, oral ulcerations, anorexia, haemorrhage, pain, dysphagia and dysgeusia, longer period of hospitalisation and increasing the cost of therapy.[2]

Studies have demonstrated that severe OM (grades 3 and 4) occur in about 60%–100% of patients undergoing haematopoietic stem cell transplantation (HSCT), the highest incidence being reported for

regimens that combine total body irradiation (TBI) with chemotherapy.[3–10] Our site reported an incidence of grade 3/4 mucositis in 67% of patients receiving bis-chloroethylnitrosourea (BCNU), etoposide, ara-c, melphalan (BEAM) or lomustine, etoposide, ara-c, melphalan (LEAM) for lymphoma.[11] Currently, various strategies and agents have been described for the prevention of OM, including routine oral care, mucosal surface protectants, anti-inflammatory drugs, growth factors, certain antimicrobial formulations, laser therapy, oral cryotherapy and specific natural and miscellaneous agents.

The Multinational Association for Supportive Care in Cancer recommends palifermin and low-level laser therapy (LLLT) as a preventive measure in such situations.[12 13] Palifermin was reported to be superior to placebo in reducing the duration of grade 3/4 OM in a multicentre, placebo-controlled trial in 212 patients with haematological malignancies who received myelotoxic therapy requiring HSCT with TBI.[14] Palifermin is expensive and is currently not available in India while LLLT needs special equipments and expertise, thus not available at all cancer hospitals.

Indications and availability of centres offering high-dose chemotherapy have expanded significantly. Cancer therapy induced OM still remains a significant problem in patients receiving high-dose chemotherapy followed by HSCT. Trials with new agents with better efficacy and lesser side effects are needed. Probiotics have been extensively studied in the gut and new perspectives are opening up for applications in oral care, where the manipulation of the oral microflora may have a significant impact on attenuating the inflammatory conditions of the mouth. *Lactobacillus brevis* CD2 strain is a normal inhabitant of the mouth and intestinal flora and is also commonly found in dairy products. In an earlier randomised, double-blind, placebo-controlled trial in 200 patients with head and neck squamous cell carcinoma, we reported a much lower incidence of grade 3/4 OM in patients receiving *L. brevis* CD2 lozenges as compared with placebo.[15] Some strains of *L. brevis* species (CD2) are endowed with high levels of arginine deiminase (AD) and sphingomyelinase enzymes.[16] AD plays a major role in metabolism of arginine by converting it to citrulline and ammonia by competitive inhibition. It reduces the availability of arginine within the oral cavity to arginase, thus decreasing the production of polyamines, and tonitric oxide synthase, thus reducing the production of nitric oxide and leading to the attenuation of the inflammatory markers (cytokines interleukin (IL) 1 alpha, IL-6, IL-8, tumour necrosis factor-alpha, interferon-gamma, prostaglandin E2 (PGE2) and matrix metalloproteinases).[17] Bacterial sphingomyelinase is known to hydrolyse the platelet-activating factor,[18] a potent phospholipid mediator of inflammation, which has been reported for its role in inflammation and tissue injury associated with mucositis during radiation therapy.[19] Previous studies have also demonstrated the efficacy of *L. brevis* CD2 in the management of inflammation in periodontal and gingival diseases.[17 20] In another study, significant decrease in oral ulcers in patients with Behçet Disease was observed after 1 and 2 weeks of therapy with *L. brevis* CD2 lozenges.[21]

The current phase II study was designed to test the safety and efficacy of *L. brevis* lozenges in patients with haematological malignancies receiving high-dose chemotherapy and radiation followed by HSCT.

METHODS

Design

This was a single-arm, single-centre, phase II clinical study conducted at Department of Medical Oncology, Dr BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India from January 2012 to October 2012. The investigational drug has already been approved by Food and Drug Administration (FDA), India for prevention and treatment of oral mucositis in patients undergoing cancer therapy. However, it has never been tried in patients with haematological malignancies undergoing high-dose chemotherapy followed by HSCT. Therefore, sample size calculation was not done, and a phase II, pilot study involving about 30 patients receiving myeloablative high-dose chemotherapy as a conditioning regimen for allogeneic or autologous HSCT was designed. The protocol was approved by the Institute Ethics Committee (Ref. No. IEC/NP-231/2011 dated 9 September 2011), and signed informed consent was collected from all study participants or guardians in case of minors (<18 years). The study was registered with www.clinicaltrials.gov with NCT01480011 as identifier.

The primary endpoint of the study was the incidence of severe OM defined as grades 3 and 4 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V.3.0 toxicity grading (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Secondary endpoints included incidence of all grades of OM and dysphagia as per NCI-CTCAE V.3.0, time duration for resolution of oral mucositis and requirement of intravenous antibiotics.

Analysis was done using SPSS V.16.0 (IBM, New York, USA).

Participants

Patients with confirmed histological diagnosis of cancer/leukaemia and with Karnofsky Performance Score ≥70%, in the age group 10–70 years, with adequate organ functions (serum creatinine <1.8mg/dL, total bilirubin <2mg/dL, liver enzymes within three times of normal limit) and an expected survival >6 months were included. Patients with autoimmune disease, with history of HIV or with any neurological disorders were excluded from the study.

Intervention

The study drug contained not less than 2×10^9 (2 billion) viable cells of *L. brevis* CD2 as the active ingredient. The study drugs were supplied by CD Pharma India, New Delhi. The intended daily dose of trial medication was

Table 1 Baseline characteristics and conditioning regimen of enrolled patients

Variable	n	Mean (SD) or %	Median (range)
Age (years)	31	35.42 (19.38)	29 (10–64)
<18 years	8	25.8	
Sex			
Male	19	61.3	
Female	12	38.7	
Diagnosis			
MM	11	35.5	
HL	7	22.6	
AML	6	19.4	
NHL	4	12.9	
CML	1	3.2	
ALL	1	3.2	
RMS	1	3.2	
Type of transplant			
Autogenic	22	71	
Allogenic	9	29	
Conditioning regimen			
High dose melphalan	12	38.7	
BEAM	6	19.4	
CBV	6	19.4	
Flu Mel	5	16.1	
FLU BU	1	3.2	
Mel Treo	1	3.2	
Haemoglobin (g/dL)	31	11.51 (2.17)	12 (7.4–14.9)
Platelets (×10^3/µL)	31	162 (70.7)	162 (64–298)
TLC (/µL)	31	8952.26 (8246)	5320 (2100–35800)
ANC (/mm^3)	31	6119.35 (7773)	3100 (200–30700)

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BEAM, BCNU, etoposide, ara-C and melphalan; CBV, cyclophosphamide, etoposide, BCNU; CML, chronic myeloid leukaemia; Flu Bu, fludarabine and busulfan; Flu Mel, fludarabine and melphalan; HL, Hodgkin's Lymphoma; Mel Treo, melphalan and treosulfan; MM, multiple myeloma; NHL, Non-Hodgkin's Lymphoma; RMS, rhabdomyosarcoma.

four to six lozenges per day, one lozenge to be taken every 2 to 3 hours and to be dissolved in the mouth. Patients were requested not to chew the lozenge and not to eat or drink for at least 30 min before and after the medication in order to maximise the enzymatic activity of the bacteria contained in the lozenge. The treatment was started 4 to 7 days prior to initiation of conditioning chemotherapy and was continued till resolution of mucositis or Day +24 poststem cell infusion, whichever occurred earlier.

Assessments

Patients/donors were mobilised using granulocyte colony-stimulating factor (G-CSF) at a dose of 10 µg/kg body weight daily, and stem cells were harvested on day 5 with targeted stem cells collection of at least 2.5×10^6/kg CD 34+ cells per kg of recipient body weight. Patients were examined once daily, starting 7 days before scheduled chemotherapy and continuing till day +24 after stem cell infusion or complete healing of mucositis, whichever occurred earlier. Haemoglobin, absolute neutrophil counts (ANC), and platelets were measured daily. Biochemical parameters (liver function tests and renal functions) were assessed every alternate day. In case of febrile episodes, blood cultures and gram staining were performed. Our standard practice for management of neutropenic fever is usage of cefoperazone/sulbactam with either amikacin or levofloxacin. All patients were given fluconazole or itraconazole prophylaxis and allogenic transplant patients were prescribed acyclovir prophylaxis. Adverse events including mucositis and dysphagia were assessed daily by two independent persons as per NCI-CTCAE V.3.0. Mucosal lesions were characterised according to their number, localisation in the oral cavity, and presence or absence of bleeding or ulceration. Photographs of the mucosal lesions in the oral cavity were taken weekly. Adherence to study medication was assessed daily and entered in a patient diary. Unused lozenges and bottles were collected and recorded.

RESULTS

Patient characteristics

Thirty-one patients scheduled for myeloablative high-dose chemotherapy and stem cell rescue (autologous or allogenic) were enrolled into this phase II study. All cases involved peripheral blood stem cell transplantation. Baseline characteristics, diagnosis and conditioning regimen are listed in table 1. Study included eight minors, all patients ranged in age between 10 and 64 years, with median age of 29 years. Median number of daily dose of study medication was 3 (range 1–5). Conditioning regimens were as per-published standard myeloablative high-dose chemotherapy protocols. Melphalan at a dose of >180 mg/m^2 was used for patients with multiple myeloma.

Engraftment and safety aspects

All patients were engrafted, one patient died of *Klebsiella* pneumoniae sepsis followed by multiple organ failure after engraftment. Median time for neutrophil engraftment was 12 days (range 9–18) and for platelet engraftment was 15 days (range 5–24). Median duration of G-CSF administration was 14 days (range 6–34). All patients developed febrile neutropenia. Median duration of antibiotic therapy was 10 days (range 4–19). Twenty patients required more than one line of antibiotic therapy for persistent fever. Twelve patients required

Table 2 Engraftment and use of supportive care

Parameters	n (%)	Days, median (range)
ANC engraftment	31 (100)	12 (9–18)
Platelet engraftment	29 (93.5)	15 (5–24)
Duration of G-CSF	31 (100)	14 (6–34)
Documented infections	6 (19.4)	
Requirement for IV antibiotics		10 (4–19)
IV antibacterial only	6 (19.4)	
Requirement of IV antibacterial and non- prophylactic antifungal	16 (51.6)	
Requirement of IV antibacterial and non- prophylactic antifungal and antiviral	9 (29)	
Requirement of >1 line of antibiotics	20 (64.5)	
Use of supportive care		
None	22 (71)	
BG paint	8 (25.8)	
N-acetyl Cysteine	1 (3.2)	

ANC, absolute neutrophil count; BG paint, boro-glycerine paint (containing 30 mL boro-glycerine solution, 2 × 400mg metronidazole tabs, 2 × 10mg clotrimazole lozenges and 2 × 250mg tetracyclinecapsules; Mix all ingredients, prepare the solution and apply locally); G-CSF, granulocyte colony-stimulating factor; IV, intravenous.

systemic antifungal drugs for suspected fungal infections though no proven fungal infection was documented. Six patients had documented infections (blood, 3; urine, 1; chest, 1 and soft tissue, 1). No blood culture was positive for *lactobacillus* (table 2).

Assessment of endpoints

Mucositis and dysphagia grade assessments are shown in table 3. Severe oral mucositis was observed in six patients (19.4%). Out of 31 patients, 7(22.6%) patients did not develop mucositis, 6(19.4%) developed grade 1, and 12(38.7%) patients developed grade 2 mucositis. Patients with grade 3/4 mucositis also required parenteral nutrition for a varying period of time. Median time to onset and for resolution of mucositis was 6 days (range 3–9) and 8 days (range 5–18), respectively, from the day of stem cell infusion. Of the 11 myeloma patients who received high-dose melphalan (>180 mg/m^2), 5(45.5%) developed grade 3/4 mucositis. Eleven (35.5%) patients required narcotic analgesics for a variable period of time to control pain. Twenty-two patients did not use any supportive therapy for management of OM (table 2). Dysphagia was reported by over two-thirds of patients with the median of 1 (range 0–4) for the maximum grade of dysphagia (table 3).

DISCUSSION

The current study was designed as an open-label, phase II pilot study to determine the safety and efficacy of *L. brevis* CD2 lozenges in preventing OM in leukaemia patients undergoing high-dose chemotherapy followed

Table 3 Incidence of mucositis and dysphagia

	Mucositis		Dysphagia	
Parameters	n (%)	Median (range)	n (%)	Median (range)
Grade 0	7 (22.6)		9 (29)	
Grade 1	6 (19.4)		8 (25.8)	
Grade 2	12 (38.7)		7 (22.6)	
Grade 3	4 (12.9)		6 (19.4)	
Grade 4	2 (6.5)		1 (3.2)	
Severity				
Mild to moderate (Grades 1 and 2)	18 (58.1)		15 (48.4)	
Severe (Grades 3 and 4)	6 (19.4)		7 (22.6)	
Time to onset of mucositis (days)		6 (3–9)		
Time for resolution of mucositis (days)		8 (5–18)		
Maximum grade of dysphagia				1 (0–4)

by HSCT. This study was planned as stepping stone for larger phase III studies. Few large phase III studies using other agents have been conducted till date for the prevention of chemotherapy/radiotherapy-induced oral mucositis, and the recommendations for management of mucositis have usually been formulated on basis of these studies. In the current phase II study, only 19.4% patients developed severe OM (grade 3/4), which is much less than reported in earlier studies using various interventions.

In a landmark phase III study, Speilberger *et al* reported palifermin to be an effective treatment option for OM in patients receiving autologous HSCT after an intensive conditioning regimen using cyclophosphamide and etoposide with TBI.[14] WHO grades 3 or 4 oral mucositis occurred in 63% of the palifermin-treated group compared with 98% in the placebo group. Median duration of grades 3 and 4 OM was reported as 6 and 9 days in palifermin and placebo groups, respectively. Subsequently, palifermin was approved by US-FDA for OM prevention in patients with haematological malignancies receiving myelotoxic therapy requiring HSCT.

Studies using LLLT, amifostine, oral cryotherapy and zinc sulphate have also been reported.[22–26] LLLT has been reported efficacious for prevention of OM in patients undergoing HSCT. Ferreira *et al* randomised 35 patients to receive either laser or to simulated laser (sham). No statistically significant difference was found in overall incidence of OM; however, incidence of severe OM was significantly lower (p=0.015).[22] In an earlier randomised, double-blind, placebo controlled study, 70 patients were randomised to receive either 650 nm wavelength, 780 nm wave length or placebo. The authors reported that 650 nm wavelength reduced the severity of oral mucositis and pain scores, was safe and well tolerated.[23] In a prospective trial by Spencer *et al* 90 myeloma patients undergoing autologous stem cell transplantation were randomised to receive amifostine or no amifostine prior to melphalan 200 mg/m^2 regimen. Use of amifostine was associated with a reduction in severe (WHO grade 3 or more) mucositis (12% vs 33%, p=0.02), but no difference was observed in the requirement for analgesics or parenteral nutrition between the two arms.[24] In another randomised, double-blind study involving 60 patients undergoing HSCT, use of zinc sulphate did not reduce or prevent severe OM as compared with placebo. Twenty-three per cent of patients in the zinc sulphate group and 27% in the placebo group developed grade 3 mucositis; none of the patients in the zinc or placebo group developed grade 4 mucositis.[25]

In the current phase II study, four minors developed OM, only one had severe mucositis. The median number of probiotic lozenges taken by the patients was three lozenges per day, and not as per the intended dose of 4–6 lozenges per day. The reasons behind poor adherence are not entirely clear. Some of the concerns expressed by patients were taste, the number of other medications which they felt were more essential and maintaining a gap between study intervention and other medicines. Whether adhering to the intended dose of four to six lozenges daily would have resulted in better outcomes is unclear. However, adherence will be monitored strictly and more carefully in the proposed phase III study. The study was performed with utmost care considering the history of reports of septicaemia with usage of probiotics in severely immunocompromised subjects. One patient succumbed to *Klebsiella pneumoniae* sepsis, but there were no adverse events attributable to study drug, suggesting the study intervention to be safe for usage even in severely neutropenic population. On the other hand, there was no reduction in incidence of neutropenic fever or requirement of antibiotics;perhaps the cause of fever/infection could have been due to other factors and not directly related to OM.

It is well known that microbiota structure within a host is determined by both host and environment factors. A recent study conducted in children with acute lymphoblastic leukaemia (ALL) revealed structural imbalance of the oral microbiota, characterised by decreased diversity and abundance alterations of certain bacteria. A few of these bacterial strains may be possibly involved in systemic infections, namely, endocarditis, bacteraemia and so on.[27] OM was earlier considered to be merely the result of basal cell damage induced by chemotherapy and radiotherapy on rapidly dividing epithelial cells. However, it has now been recognised that mucositis is actually the consequence of various complex and dynamic array of biological events involving multiple signalling pathways and interactions between the epithelium, the underlying submucosa, supportive connective tissues and cancer therapy/drugs.[28] An interaction between the oral microenvironment and the development of mucositis has also been discussed in the past. Incidence and severity of OM during the cancer therapy cycle is influenced by changes in resident oral flora and by changes in the physiology of oral epithelium. Oral micro-organisms are believed to be involved in the ulceration phase, and thus, may have an influence on the development of mucosal toxicity associated with cancer treatment. Several other host–microbe interactions are reported to be occurring during the development of mucositis. These interactions involve the release of nuclear factor kappa B (a transcription factors involved in the production of messaging and effector proteins including the proinflammatory cytokines and enzymes), as well as toll-like receptor and mitogen-activated protein kinase signalling, indicating the role oral microbiota in mucosal damage occurring as a result of cancer treatment.[29] In a hamster model of radiation-induced mucositis, Sonis *et al* reported higher abundance of microbiota in the ulcerated epithelium and bacterial colonisation that peaked synchronously with mucositis score (Day 21). They found that bacteria on the ulcerated surface contributed to the mucositis process by release of endotoxins, causing the polymorphonuclear leucocytes and macrophages to release pro-inflammatory cytokines and thus, increasing inflammation.[30] Some of the bacteria present in the microflora of the mouth have a rich array

of enzymes which, as a result of their metabolic activity, allow modification or modulation of the surrounding environment. Caluwaerts *et al* reported AG013, a mouth rinse formulation of *Lactococcus lactis* secreting human Trefoil Factor 1, to be a safe and efficacious therapeutic tool for treating oral mucositis.[31] *L. brevis* CD2 is rich in arginine deiminase, an enzyme by virtue of its activity downregulates production of nitric oxide, which is known to modulate the production of inflammatory cytokines, PGE2 and matrix metalloproteinases..[9 17 21 32–34]

These observations strongly support the use of specifically selected bacteria with characteristic enzymatic activity in modulating the oral microflora of these patients and thus arresting or attenuating the inflammatory processes induced by the chemotherapy agents. The current study suggests *L. brevis* to be safe (even in children) and effective in preventing oral mucositis induced by myeloablative chemotherapy in patients undergoing HSCT. Study population and regimens were not uniform, which is a limitation of our study.

If the findings of this study are confirmed, this may allow doses of certain cytotoxic drugs to be increased where mucositis is the dose-limiting toxicity factor, for example increasing the dose of melphalan beyond 200mg/m^2 for multiple myeloma patients undergoing high-dose chemotherapy and autologous stem cell transplant. Based upon the promising safety and efficacy results of this study, *L. brevis* CD2 lozenges appear to be a useful companion for patients and warrant conduct of a randomised, double blind, placebo-controlled, multi-centric phase III study.

CONCLUSIONS

L. brevis CD2 lozenges may be considered as a supportive cancer care for management of oral mucositis in patients with haematological malignancies undergoing high-dose chemotherapy followed by HSCT. Larger studies are indicated to confirm results.

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Contributors AS designed the protocol, contributed to subject enrolment and smooth conduct of study, performed statistical analysis and interpreted the results, and wrote the manuscript. SB, LK and VR contributed to study design, subject enrolment, interpretation of results, and critically reviewed the manuscript. TT, SP, and RS contributed to study conduct, subject enrolment, data collection, data analysis and drafting the manuscript. ST contributed towards radiological investigations, data analysis and drafting of the manuscript. RG contributed towards performance of all laboratory investigations, data analysis and wrote the manuscript.

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Competing interests None declared.

Patient consent Obtained.

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