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RAPID COMMUNICATION

Use of probiotics for prevention of radiation-induced diarrhea

P Delia, G Sansotta, V Donato, P Frosina, G Messina, C De Renzis, G Famularo

P Delia, G Sansotta, V Donato, P Frosina, G Messina, C De Renzis, G Famularo, Institute of Radiology, Oncologic Radiotherapy Unit, Azienda Ospedaliera Universitaria, Messina and Department of Internal Medicine, San Camillo Hospital, Rome, Italy
Correspondence to: Dr. Giuseppe Famularo, Department of Internal Medicine, San Camillo Hospital, Circonvallazione Gianicolense, 00152 Rome,
Italy. gfamularo@scamilloforlanini.rm.it
Telephone: +39-6-58704325 Fax: +39-6-58704557
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Abstract

AIM: To investigate the efficacy of a high-potency probiotic preparation on prevention of radiation-induced diarrhea in cancer patients.

METHODS: This was a double-blind, placebo-controlled trial. Four hundred and ninety patients who underwent adjuvant postoperative radiation therapy after surgery for sigmoid, rectal, or cervical cancer were assigned to either the high-potency probiotic preparation VSL#3 (one sachet *t.i.d.*,) or placebo starting from the first day of radiation therapy. Efficacy endpoints were incidence and severity of radiation-induced diarrhea, daily number of bowel movements, and the time from the start of the study to the use of loperamide as rescue medication.

RESULTS: More placebo patients had radiation-induced diarrhea than VSL#3 patients (124 of 239 patients, 51.8%, and 77 of 243 patients, 31.6%; $P < 0.001$) and more patients given placebo suffered grade 3 or 4 diarrhea compared with VSL#3 recipients (55.4% and 1.4%, $P < 0.001$). Daily bowel movements were 14.7 ± 6 and 5.1 ± 3 among placebo and VSL#3 recipients ($P < 0.05$), and the mean time to the use of loperamide was 86 ± 6 h for placebo patients and 122 ± 8 h for VSL#3 patients ($P < 0.001$).

CONCLUSION: Probiotic lactic acid-producing bacteria are an easy, safe, and feasible approach to protect cancer patients against the risk of radiation-induced diarrhea.

Key words: Probiotics; Radiation therapy; Diarrhea

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INTRODUCTION

Almost all regimens of radiation therapy may disturb the colonization resistance of the indigenous gut flora. This is the main mechanism underlying the pathophysiology of acute radiation-induced enteritis and colitis, which are a common and potentially severe complication among cancer patients treated with radiation therapy. Attempts to treat this complication with antibiotics, sucralfate, anti-inflammatory drugs such as mesalazine and balsalazide, glutamine, octreotide, proteolytic enzymes, and hyperbaric oxygen have so far provided inconclusive clinical results with failure of treatment occurring in a substantial proportion of patients[1-9]. Furthermore, prophylactic use of sucralfate does not reduce the burden of radiation-induced bowel toxicity but rather, is associated with more severe gastrointestinal symptoms including bleeding and fecal incontinence[10,11]. In the light of these contradictory findings, we urgently need innovative approaches that target other steps in the pathophysiology of radiation-induced diarrhea.

The term probiotic refers to a product or preparation containing viable and defined microorganisms in a number thought to be sufficient to alter by implantation or colonization the host's microflora and thereby exert beneficial effects[12,13]. Experimental studies in animal models and clinical trials of patients with inflammatory bowel disease (IBD) have consistently shown that use of probiotic organisms may effectively down-modulate the severity of intestinal inflammation through altering the composition and the metabolic and functional properties of gut indigenous flora[12,13]. Experience with probiotic organisms for the prevention of enteritis and colitis in cancer patients receiving radiation therapy is limited, however we have recently shown in a small pilot trial of feasibility and safety that both the incidence and severity of radiation-induced diarrhea were appreciably reduced with pre-emptive treatment with VSL#3, a new high potency preparation of probiotic lactobacilli, during adjuvant radiotherapy after surgery for abdominal and pelvic cancer[14]. The present study was undertaken to assess and compare the benefits of probiotic therapy with VSL#3 on clinically relevant endpoints in a greater sample of 490 patients, including 190 subjects we enrolled in our earlier trial.

MATERIALS AND METHODS

Four hundred ninety consecutive patients attending the outpatient clinics of the Cancer X-Ray Unit of the University of Messina, Italy, from May 1999 to December 2005, who had received adjuvant postoperative radiation therapy after surgery for sigmoid, rectal, or cervical cancers were randomly assigned to either treatment with VSL#3 (VSL Pharmaceuticals, Fort Lauderdale, MD), one sachet *t.i.d.*, or a VSL#3-identical appearing placebo starting from the first day of radiation therapy until the end of the scheduled cycles of radiation therapy. The design of the study was approved by the Ethics Committee of our hospital, and all patients gave written informed consent to participate. The study was double-blind, parallel-group, and placebo-controlled and was performed in accordance with the Declaration of Helsinki and standards of good clinical practice.

Each sachet of VSL#3 contained 450 billions/g of viable lyophilized bacteria, including four strains of lactobacilli (*L. casei, L. plantarum, L. acidophilus, and L. delbruekii subsp. bulgaricus*), three strains of bifidobacteria (*B. longum, B. breve, and B. infantis*), and one strain of *Streptococcus salivarius subsp. thermophilus*. Patients were eligible for inclusion if they had no contraindication for probiotic or antibiotic therapy or radiation therapy. We excluded by randomization patients with a Karnofsky performance score $\leqslant$ 70, a life expectancy $\leqslant$ 1 year, persistent vomiting or diarrhea, fistulizing disease, known Crohn's disease or ulcerative colitis, intra-abdominal abscesses or fever (more than 37.5℃) at the time of enrolment, or clinical, microbiological, or imaging evidence of sepsis syndrome, and requirement for continuous antibiotic treatment or use of antibiotics in the last 2 wk before initiation of VSL#3 therapy.

At base-line, patients provided a medical history and had a physical examination (consisting of vital signs, 12-lead electrocardiogram, neurological examination, and laboratory testing). The study subjects were followed up weekly during the scheduled cycle of radiation therapy and then 1 mo after completion of radiation therapy. At each visit, clinical symptoms, concomitant medications, and any adverse events were reviewed, and a physical examination and laboratory studies were performed. Efficacy endpoints were incidence and severity of radiation-induced diarrhea, number of patients who discontinued radiotherapy because of diarrhea, daily number of bowel movements, and the time from the start of the study to the use of loperamide as rescue medication for diarrhea. The randomization was balanced between treatment groups in terms of sex, age, nodal involvement, tumor grade and size, local invasion at operation, invasion of contiguous structures at histology, and postoperative complications. The total X-ray dose the patients were given was between 60 and 70 Gy. We measured the severity of gastrointestinal toxicity according to World Health Organization grading, with grade 0 indicating no toxicity, grade 1 indicating self-limited toxicity lasting less than 2 d, grade 2 indicating self-limited symptoms lasting more than 2 d, grade 3 referring to symptoms requiring treatment, and grade 4 indicating severe toxicity with dehydration and/or hemorrhage.

Statistical analysis

Statistical analysis of results was performed using Kaplan-Meier estimates. $P < 0.05$ was taken as significant.

RESULTS

Two hundred thirty nine out of 245 patients in the placebo group (97.5%) completed the study as 6 patients were withdrawn after a few sessions of radiation therapy due to the occurrence of severe diarrhea resistant to loperamide and the usual standard of care; these patients were excluded from the analysis of results. Two hundred forty three among the 245 patients in the VSL#3 group (99.1%) completed the study, one patient withdrew his consent after the first session of radiation therapy, and one patient died of myocardial infarction after three sessions of radiation therapy; both patients were excluded from analysis of the results.

More patients in the placebo group had radiation-induced enteritis and colitis compared with the VSL#3 group (124 of 239, 51.8%, versus 77 of 243 patients, 31.6%; $P < 0.001$). Furthermore, patients given the placebo suffered more severe toxicity compared with VSL#3 recipients as grade 3 or 4 diarrhea was documented in 69 of 124 (55.4%) placebo-treated patients and 8 of 77 (1.4%) VSL#3-treated patients ($P < 0.001$), whereas 50 of 124 placebo-treated patients had grade 1 or 2 diarrhea compared with 34 of 77 VSL#3 recipients (NS). Even though the difference did not reach statistical significance, there was clearly a trend in favor of the treatment with VSL#3 compared with the placebo.

The mean daily number of bowel movements for patients with radiation-induced diarrhea was 14.7 $\pm$ 6 and 5.1 $\pm$ 3 among placebo and VSL#3 recipients, respectively ($P < 0.05$), and the mean time to the use of loperamide as rescue medication for diarrhea was 86 $\pm$ 6 h for patients receiving placebo versus 122 $\pm$ 8 h for patients receiving VSL#3 ($P < 0.001$).

No tumor- or treatment-related deaths or deaths from other causes were recorded in either group during the period of radiation therapy, and no case of bacteremia, sepsis, or septic shock due to the probiotic lactobacilli was reported among the VSL#3 recipients during the treatment period with the probiotic preparation or during the six months beyond active treatment. Likewise, no case of bacteremia, sepsis, or septic shock due to organisms other than the probiotic lactobacilli was recognized during the period of active treatment. We did not recognize any other toxicity reasonably attributable to VSL#3.

DISCUSSION

We have clearly demonstrated in a large sample of patients the benefits of probiotic therapy with VSL#3 for the prevention and/or reduction of both the incidence and severity of enteritis and colitis associated with adjuvant radiation treatment after surgery for abdominal and pelvic cancer. Significantly fewer patients treated with VSL#3 had grade 3 or 4 diarrhea during the period of radiation treatment compared with patients given placebo, in

addition to the usual standard of care. We also observed a trend in favor of VSL#3 in terms of reduced incidence in grade 1 or 2 intestinal toxicity, even though the difference between the two groups did not reach statistical significance.

The findings of this study have reiterated those of our early pilot trial[14] and strongly support our working hypothesis that using probiotic lactobacilli may be an easy, cheap, safe, and feasible approach to effectively protect patients against the risk of radiation-induced diarrhea, which is a severe and potentially lethal complication of radiation therapy for abdominal and pelvic cancer. However, apart from our two studies with VSL#3, experience with probiotic organisms in this setting is limited. Our Medline search yielded indeed only one other study with probiotics, i.e. the double-blind and randomized trial by Urbancsek and colleagues who reported favorable results with *Lactobacillus GG* treatment[15]. In contrast, we used VSL#3, which is a high-potency preparation with unique characteristics compared with traditional probiotics, in particular, because of the enormously high bacterial concentration and the presence of a consortium of different bacterial species with potential synergistic relations between different strains that may greatly enhance the suppression of potential pathogens[12]. Whether treatment with VSL#3 could be more effective than using *Lactobacillus GG* or other probiotic organisms is unknown for several reasons, including the lack of a well-designed head-to-head comparison between the different probiotic preparations. However, the composite mixture of VSL#3 with a large number of probiotic strains possessing very different and specialized metabolic and immunoregulatory activities is a unique feature of this preparation, and may explain its wide spectrum of biological activities. One additional important point is that results of experimental studies and double-blind placebo-controlled clinical trials have consistently validated VSL#3 as a therapeutic tool to down-modulate intestinal inflammation in several animal and human models of IBD[13]. In contrast, clinical trials of *Lactobacillus GG* treatment for IBD patients have provided conflicting results and the true clinical efficacy of this probiotic strain is still substantially unclear[16-18].

Clinical and experimental studies of VSL#3 in patients with ulcerative colitis and animal models of IBD have provided insights into the mechanisms underlying the efficacy of probiotic lactobacilli of VSL#3 to protect patients against radiation-induced diarrhea. VSL#3 lactobacilli lower the production of proinflammatory cytokines and several other effectors of inflammation and tissue injury, such as nitric oxide and metalloproteinases, interfere with the pro-inflammatory signal transduced by toll-like receptors, exert a significant protection upon the integrity of the intestinal epithelial barrier, and down-modulate the process of apoptosis. This latter mechanism is of utmost importance because the triggering of an unregulated process of apoptosis is regarded as the main factor ultimately responsible for the radiation-induced injury of the intestinal epithelium[19]. Furthermore, probiotic bacteria up-regulate the innate immune response in the gut and are thus part of a protective mechanism against invasive organisms, which is important when ileal and colonic protection against invading organisms is severely impaired as a result of exposure to radiation. All these mechanisms are likely to synergistically contribute to the down-modulation of gut inflammation and host protection against intestinal colonization by invasive pathogens and their subsequent translocation into portal circulation also in patients irradiated for therapeutic purposes.

Treatment with VSL#3 proved in our study to be remarkably safe and we did not recognize any toxicity reasonably attributable to VSL#3 over the time-span of probiotic treatment. Furthermore, we observed no case of bacteremia, sepsis, or septic shock due to the probiotic lactobacilli of VSL#3, which is in agreement with results of other clinical trials of VSL#3 in IBD patients. Previous clinical experience with this probiotic preparation has indeed demonstrated the remarkable safety of VSL#3 bacteriotherapy even with dosages significantly greater than those used in this trial. This does strongly reinforce the view that probiotic treatment with VSL#3 should be regarded as remarkably safe even in the setting of intestinal inflammation associated with severely altered barrier function as it may occur in patients with radiation-induced enteritis and colitis.

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