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Prevention of irinotecan induced diarrhea by probiotics: A randomized double blind, placebo controlled pilot study

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KEYWORDS
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Summary
Purpose: Diarrhea is one of the dose limiting toxicity of irinotecan. SN-38 is main irinotecan metabolite responsible for diarrhea development, which is excreted in glucuronidated form into the intestine. This study aimed to determine the effectiveness of the probiotics in the prevention of irinotecan induced diarrhea due to reduction of intestinal beta-D-glucuronidase activity.
Methods: Between January 2011 and December 2013, 46 patients with colorectal cancer starting a new line of irinotecan based therapy were included. Patients were randomized 1:1 to probiotics (PRO) or placebo (PLA). Probiotic formula Colon Dophilus™, was administered at a dose of 10×10^9 CFU of bacteria tid, orally for 12 weeks of chemotherapy. The study was prematurely terminated due to slow accrual, when 46 of 220 planned patients were accrued.

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Results: Twenty-three patients were randomized to PRO and 23 patients to PLA. Administration of probiotics compared to placebo led to a reduction in the incidence of severe diarrhea of grade 3 or 4 (0% for PRO vs. 17.4% for PLA, $p = 0.11$), as well as reduction of the overall incidence of diarrhea (39.1% for PRO vs. 60.9% for PLA, $p = 0.24$) and incidence of enterocolitis (0% for PRO vs. 8.7% for PLA). Patients on PRO used less antidiarrheal drugs compared to PLA. There was no infection caused by probiotic strains recorded.
Conclusions: Administration of probiotics in patients with colorectal cancer treated with irinotecan-based chemotherapy is safe and could lead to a reduction in the incidence and severity of gastrointestinal toxicity.

Introduction

Mucositis, is one of the most common side effects of radiation therapy and chemotherapy.[1] It is connected with inflammation and cell loss in the epithelial barrier lining the gastrointestinal tract.[2–4] Clinical symptoms of intestinal mucositis include nausea, vomiting, bloating, constipation, weight loss and diarrhea. Moreover, mucositis is frequently lead to dose reduction of chemotherapeutics or to postpone chemotherapy treatment, leading to a higher mortality. [2–4]

Mucositis is tightly connected with chemotherapy induced diarrhea and have severe impact on quality of life of cancer patients. Several mechanisms are involved in the development of chemotherapy induced diarrhea such as malabsorption induced by mucositis, dysmicrobia induced by chemotherapy and broad-spectrum antibiotics as well as predisposition to infectious diarrhea in immunocompromised patients. Some chemotherapeutic agents and their metabolites also induce diarrhea directly due to effect on the intestinal mucosa.[3,5]

Irinotecan is one of the most potent drugs in the treatment of metastatic colorectal cancer. The incidence of irinotecan induced diarrhea varies between 60 and 90% and severe diarrhea has been reported in 20—40% patients.[6] Diarrhea is one of the most important factors in morbidity and mortality during irinotecan based chemotherapy.[6] Predisposing factors are age over 65 years, ECOG PS of 1 and previous abdominopelvic radiation.[6] The main cause of diarrhea is one of irinotecan metabolites, SN-38 which is in the liver glucuronidated and subsequently expelled into the intestine. It is deconjugated by bacterial enzyme beta-D-glucuronidase in the intestinal lumen. This form causes direct damage of intestinal mucosa associated with malabsorption and the development of diarrhea. Moreover, administration of irinotecan might cause mucositis with induction of several pro-inflammatory cytokines, changes of intestinal mucin composition and subsequent alterations of intestinal microflora.[7–11] Irinotecan induced diarrhea is usually treated with loperamid by decreasing the activity of the myenteric plexus, but dose reduction of irinotecan is often necessary. Several approaches were evaluated in prevention of irinotecan induced diarrhea including administration of broad-spectrum antibiotics and/or beta-D-glucuronidase inhibitors with the aim to reduce activity of intestinal beta-D-glucuronidase.[12] Other approaches are based on modulating the metabolism of irinotecan using cyclosporine and phenobarbital to reduce biliary excretion of SN-38 and induction of glucuronidation. Promising results were shown using activated charcoal, which has resulted in the absorption of SN-38. Other methods, such as oral alkalization, thalidomide and amifostine were tried without success.[6]

Probiotics are live microorganisms, which as drugs or food supplements help to maintain healthy beneficial microbial balance in the digestive tract of a human or other host.[13] Probiotic bacteria reduce activity of intestinal beta-D-glucuronidase,[14,15] and therefore these bacteria could be applied in the prevention of diarrhea in patients treated by irinotecan based therapy. According to MASCC/ISOO (Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology) guidelines probiotic agents containing *Lactobacillus* sp. can be used for the prevention of chemotherapy and radiation therapy induced diarrhea in patients with pelvic malignancy.[16] Given their low toxicity, good tolerability, probiotics may be an important part of supportive therapy of irinotecan based chemotherapy.

The aim of this pilot trial was to determine the effectiveness of the probiotic formula Colon Dophilus™ in the prevention of irinotecan induced diarrhea in metastatic colorectal cancer patients.

Patients and methods

The study protocol was reviewed and approved by the Ethical Committee of the National Cancer Institute of Bratislava, Slovakia. Study was registered to Database of Clinical Trials and ClinicalTrials.gov Identifier was NCT01410955.

Patients

All patients were required to provide written informed consent before enrollment. Eligible patients were men or women, aged 18 years or older with histologically proven colorectal cancer starting new line of chemotherapy based on irinotecan, ECOG PS 0-1 at study entry, life expectancy more than 3 months, with absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule. Exclusion criteria included the following: impossibility to take oral medication, active infection treated by antibiotic therapy, ileostomy, hypersensitivity to study drug, any concurrent malignancy other than non-melanoma skin cancer, no other cancer in past 5 years, serious concomitant systemic disorders or diseases incompatible with the study (at the discretion of investigator).