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MINIREVIEWS

Prevention of pelvic radiation disease

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Abstract

Pelvic cancers are among the most frequently diagnosed cancers worldwide. Treatment of patients requires a multidisciplinary approach that frequently includes radiotherapy. Gastrointestinal (GI) radiation-induced toxicity is a major complication and the transient or long-term problems, ranging from mild to very severe, arising in non-cancerous tissues resulting from radiation treatment to a tumor of pelvic origin, are actually called as pelvic radiation disease. The incidence of pelvic radiation disease changes according to the radiation technique, the length of follow up, the assessment method, the type and stage of cancer and several other variables. Notably, even with the most recent radiation techniques, *i.e.*, intensity-modulated radiotherapy, the incidence of radiation-induced GI side effects is overall reduced but still not negligible. In addition, radiation-induced GI side effects can develop even after several decades; therefore, the improvement of patient life expectancy will unavoidably increase the risk of developing radiation-induced complications. Once developed, the management of pelvic radiation disease may be challenging. Therefore, the prevention of radiation-induced toxicity represents a reasonable way to avoid a dramatic drop of the quality of life of these patients. In the current manuscript we provide an updated and practical review on the best available evidences in the field of the prevention of pelvic radiation disease.

Key words: Pelvic radiation disease; Radiotherapy; Gastrointestinal toxicity; Amifostine; Aminosalicylates; Sucralfate; Beclomethasone dipropionate; Probiotics supplementation; Misoprostol; Mesalazine

Core tip: Radiotherapy is a treatment of choice in the management of several pelvic cancers. Acute and late-onset radiation-induced gastrointestinal toxicity, also known as pelvic radiation disease, is still frequently observed, despite recent improvements in radiation techniques. In the current review we provide an updated overview on the medical therapies that have been investigated with preventive intents, focusing our attention on the best available evidences, primarily randomized controlled studies.

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INTRODUCTION

Pelvic cancers are among the most frequently diagnosed cancers worldwide[1]. Treatment of patients requires a multidisciplinary approach that frequently includes radiotherapy. Healthy intestinal tissue, mainly from distal large bowel and loops of the small intestine, is usually encompassed in the radiation field during radiotherapy for pelvic and abdominal tumors. Gastrointestinal (GI) radiation-induced toxicity is a major complication and the transient or long-term problems, ranging from mild to very severe, arising in non-cancerous tissues resulting from radiation treatment to a tumor of pelvic origin, are actually called as pelvic radiation disease (PRD)[2]. The incidence of PRD changes according to the radiation technique, the length of follow up, the assessment method, the type and stage of cancer and several other variables[3]. Notably, even with the most recent radiation techniques, *i.e.*, intensity-modulated radiotherapy, the incidence of radiation-induced GI side effects is overall reduced but still not negligible. In the last decade, the implementation of radiation techniques able to deliver higher radiation dose to the tumour mass and sparing the surrounding normal tissue have reduced the incidence of acute radiation-induced toxicities[4]. However, larger volumes of normal tissues receive low doses of radiation compared to conventional treatment, *i.e.*, 3D conformal radiotherapy, and the effect of combined chemotherapy and radiotherapy in sensitizing normal tissues to long-term effects are yet largely unknown. In addition, radiation-induced gastrointestinal side effects can develop even after several decades; therefore, the improvement of patient life expectancy will unavoidably increase the risk of developing radiation-induced complications.

Several patient-related risk factors have been identified: diabetes, inflammatory bowel diseases (Crohn's disease and ulcerative colitis) and collagen vascular diseases (scleroderma, systemic lupus erythematous)[3]. All these risk factors represent independent predictor of both acute and late-onset pelvic radiation disease[3]. Tobacco smoking and a body mass index less than 18.5 kg/m^2 increase the risk of developing radiation-induced side effects[3].

Once developed, the management of pelvic radiation disease may be challenging, due to the scarce treatment options and the almost lack of robust and well-performed interventional prospective studies[3]. Radiation toxicity is defined as acute when it occurs during radiotherapy or within 3 mo after treatment, while it is defined as chronic when it develops after longer time periods. The most frequent radiation-related side effects are diarrhea, urgency, rectal bleeding, and fecal incontinence, reported in about 5%-50% of patients[3,5,6]. Therefore, the prevention of radiation-induced toxicity represents a reasonable way to avoid a dramatic drop of the quality of life of these patients.

Aim of the current manuscript is to provide an updated and practical review on the best available evidences in the field of the prevention of pelvic radiation disease.

PATHOGENESIS

The pathogenesis of pelvic radiation disease is complex and includes changes in most sections of the colo-rectal wall. In the acute phase, during and soon after irradiation, mucosal injuries become clear and are primarily the result of apoptotic processes in the crypt epithelium, breakdown of the mucosal barriers and inflammation, thus altering the mucosal permeability. When the mucosal barrier becomes interrupt, bacterial products and other activating and potentially toxic agents, gain access to sub-epithelial intestinal tissue, where they stimulate a variety of immune cells to produce cytokines and other pro- and anti-inflammatory mediators[7,8]. In the late-onset phase, prominent structural changes include atrophy of the mucosa, fibrosis of the intestinal wall, and vascular sclerosis. Radiation-induced endothelial dysfunction leads to loss of thrombo-resistance, resulting in thrombin formation, neutrophil recruitment and activation, and stimulation of mesenchymal cells[7-10]. Thus, the typical chronic aspects are represented by diffuse connective tissue fibrosis, obliterative endoarterites and following neo-angiogenesis with telangiectasias development. Therefore, the development of late-onset, chronic radiation-induced symptoms are strictly related to the fibrotic and ischemic process and to the chronic state of inflammation and alteration of the gut permeability and barrier function.

DRUGS FOR PREVENTING PRD

In the last decades several drugs have been investigated as potential chemopreventive agents (Table 1); in the next paragraphs we will provide a brief overview on these drugs, focusing on the best available evidences and on the effects on both acute and late-onset radiation-induced side effects.

Amifostine

Amifostine is an organic thiophosphate cytoprotective agent[11]. The rationale for the use of amifostine as a radioprotective agent is its capability of detoxifying the reactive metabolites and scavenging reactive oxygen species generated by tissue irradiation. The selective action of amifostine on normal instead of tumoural tissue is attributed to the higher capillary alkaline phosphatase activity, higher pH and better vascularity of normal tissues compared to tumour tissue, resulting in a more rapid generation of the active thiol metabolite[12].

Table 1 Efficacy of drugs as possible preventive agents of pelvic radiation disease

Drug	Route of administration	Type of evidence	Prevention		Comments
			Acute PRD	Chronic PRD	
Amifostine	IV or SC	RCTs	Yes	No	A dose of 340 mg/m^2 IV or 500 SC administered during the whole period of treatment may prevent acute but not late-onset symptoms Nausea and vomiting are common side effects
Amifostine	Rectal	RCTs	Yes	?	Intrarectal administration is feasible and seems safe A dose of 1–2 g/d administered during the whole period of treatment may prevent acute symptoms A dose of 2 g/d seems more effective than 1 g/d No systemic side effects reported No definitive data on long-term effect Large multicenter RCTs are warranted
Sulfasalazine	Oral	RCT	Yes	?	A dose of 1000 mg/d significantly reduces the risk of developing diarrhea during radiation treatment
Balsalazide	Oral	RCT	Yes	No	Daily dose of 6 capsules may reduce compliance to the preventive treatment in clinical practice Possible beneficial effect Large multicenter RCTs are warranted
Mesalazine	Oral or rectal	RCTs	No	?	No beneficial or even harmful effects on acute symptoms
Beclomethasone	Rectal	RCT	No	Yes	Possible preventive effect on late-onset rectal bleeding and cost-effective preventive strategy
Sucralfate	Oral	RCTs	No	No	No beneficial or even harmful effect as preventive agents on both acute and late-onset symptoms Useful for treating rectal bleeding
Probiotics	Oral	RCTs Meta-analysis	Yes	?	Large multicenter RCTs are warranted

IV: Intravenous; SC: Subcutaneous; RCT: Randomized controlled trial; PRD: Pelvic radiation disease.

Amifostine can be administered intravenously, subcutaneously or intrarectally. Several randomized controlled trials have investigated the efficacy of amifostine treatment for the prevention of pelvic radiation disease[13-19].

Effect on acute PRD: Overall, amifostine preventive treatment has shown to be effective in the prevention of acute, early-onset radiation-induced disease, particularly when administered intrarectally[13].

Athanassiou *et al*[14] enrolled 205 patients with pelvic cancer, 110 treated with daily intravenous amifostine (340 mg/m^2 in 3-5 min, 15-30 min before RT) and 95 controls. Grade 2-3 acute toxicity, according to the EORTC/RTOG clinical scale, was reported in 5.5% of patients in the amifostine group against 22.1% in the control group (P = 0.001). Katsanos *et al*[15] demonstrated in a randomized controlled trial that the subcutaneous administration of amifostine was feasible and effective. Forty-four patients with either rectal or uterine cancer were enrolled: 21 patients were assigned to the active arm (daily s.c. amifostine at a dose of 500 mg, 20-30 min before radiotherapy) and 23 were randomized to the control group. Four patients (17.4%) in the control group developed acute colitis whilst none of the patients in the active group developed acute colitis (P = 0.05)[15].

In order to increase patient compliance and acceptance, the intrarectal route has been investigated as an alternative to the intravenous or subcutaneous routes. Kouloulias *et al*[16] in a randomized controlled trial evaluated 67 patients, 33 of whom were treated with daily intrarectal amifostine at a dose of 1.5 g administered as an aqueous solution in a 40-mL enema *vs* 34 controls and found that amifostine treatment significantly reduced acute rectal toxicity from 44% (Grades Ⅰ-Ⅱ) to 15% (Grade Ⅰ) (P = 0.026). Singh *et al*[17] investigated in a non-randomized comparative study the efficacy of a higher dosage of intrarectal amifostine (2 g) *vs* a lower dosage (1 g). After assigning 18 patients to 1 g and 12 patients to 2 g, the authors found that patients treated with higher dosage did not experience radiation-related toxicity, while 33% of patients in the 1-g group reported Grade 2 toxicity; however, the difference was not statistically significant (P = 0.06)[17].

The intrarectal route of administration of amifostine turned out to be more effective than the subcutaneous one[13]. Kouloulias *et al*[13] investigated in a randomized comparative study 27 patients treated with daily intrarectal amifostine at a dose of 1.5 g *vs* 26 patients treated with daily subcutaneous amifostine at a dose of 500 mg and found a lower incidence of Grades Ⅰ-Ⅱ rectal radiation morbidity in the intrarectal group (11% *vs* 42%, P = 0.04)[13].

Effect on chronic PRD: The efficacy of amifostine preventive treatment on late-onset, chronic pelvic

radiation disease is still unclear and data conflicting. One pilot study, based on 29 patients with localized prostate cancer, showed a significant reduction of late rectal bleeding after daily intrarectal high-dosage amifostine (1.5-2.5 g) *vs* low-dosage amifostine (0.5-1 g) (P = 0.0325)[18]. Singh *et al*[17] in a non-randomized, controlled study considered 30 patients with pelvic cancer, 18 of whom received low-dosage intrarectal amifostine (1 g daily) *vs* 12 patients receiving high-dosage intrarectal amifostine (2 g daily) and found that the higher dosage significantly reduced late-onset, chronic pelvic radiation disease at 12 mo (P = 0.04). On the other hand, Katsanos *et al*[15] in the previously mentioned randomized controlled trial did not report any efficacy for subcutaneous amifostine to prevent late-onset toxicity. Based on the available data, it is not clear whether the administration route influences the efficacy of amifostine-based preventive treatment. Well-performed, prospective, large sample trials, comparing different routes of administration should be performed to clarify the effect on late-onset radiation-induced toxicity.

Amifostine can be considered as a safe drug and side effects have been described only when the intravenous and subcutaneous routes of administration were performed. Nausea, vomiting, severe asthenia, transient hypotension and local erythema and pruritus have been the most frequently reported side effects (5.5%-27.8%)[15,19]. Infrequently, severe hypotension and systemic allergic reaction with cutaneous rash and dyspnea have been described[14]. No life-threatening adverse events have ever been reported. Notably, intrarectal amifostine seems to be safer and systemic side effects have not been reported since now.

Aminosalicylates

Aminosalicylates are compounds that contain 5-aminosalicylic acid (5-ASA), which is a potent inhibitor of the synthesis and release of pro-inflammatory mediators (*e.g.*, nitric oxide, leukotrienes, thromboxanes, and platelet activating factor) and also inhibits the function of several cells implicated in the acute inflammatory and immune response (*e.g.*, natural killer cells, mast cells, neutrophils, mucosal lymphocytes, and macrophages)[20]. As the pathophysiology of early pelvic radiation disease is mainly mediated by eicosanoid inflammatory mediators[21], the administration of aminosalicylates in order to prevent acute radiation-induced rectal injury has been investigated.

The available aminosalicylates can be distinguished into pro-drugs (sulfasalazine and balsalazide) and active compound (mesalazine).

Sulfasalazine

Sulfasalazine is a pro-drug that is metabolized to its active component, 5-ASA, by intestinal microflora, therefore ensuring a high concentration of the active drug to the distal colon.

Kiliç *et al*[22] considered in a randomized, placebo-controlled, double-blind trial, 87 patients, 44 of whom were assigned to the active group (two tablets of 500 mg of sulfasalazine twice a day) against 43 patients allocated in the control group. During irradiation, diarrhea occurred in 55% of the sulfasalazine and 86% of the placebo group, and this difference was found to be statistically significant (P < 0.001)[22]. Additionally, sulfasalazine significantly decreased the severity of radiation-induced symptoms as evaluated by LENT-SOMA score after the first week of radiotherapy: precisely, in the second (P = 0.003), third (P < 0.001), fourth (P < 0.001) and fifth (P < 0.001) weeks.

Pal *et al*[23] enrolled in a randomized, placebo-controlled trial 98 patients with carcinoma of the cervix, 49 of whom were assigned to the active arm (oral sulfasalazine 1 g twice daily from the day of starting of radiotherapy to 1 wk after completion of treatment) *vs* 49 patients allocated to the placebo group. Sulfasalazine showed to significantly reduce the occurrence of acute radiation-induced toxicity as evaluated by Common Toxicity Criteria (CTC); the incidence of grade Ⅱ or higher gastrointestinal toxicity was 19.1% (9/47) in the active arm *vs* 41.7% (20/48) in the control group (P = 0.017). None of the previously cited trials reported any considerable side effect due to sulfasalazine.

Most of the existing evidence supports the role of sulfasalazine as a preventive treatment of acute, early-onset PRD. The Mucositis Study Group of Multinational Association of Supportive Care in Cancer (MASCC), an international multidisciplinary organization dedicated to research, policy and programs to improve the quality of life of patients and caregivers touched by cancer[24], suggests the use of sulfasalazine orally twice daily to reduce the incidence and severity of radiation-induced enteropathy in patients receiving external-beam radiotherapy to the pelvis[25]. However, there are no definitive data on its long-term efficacy in the prevention of chronic PRD.

Balsalazide

Balsalazide is a pro-drug of mesalazine chemically similar to sulfasalazine but lacking the sulfapyridine moiety in favor of a less antigenic carrier, 4-aminobenzoyl-β-alanine, which yields a high concentration of active drug (5-ASA) to the distal colon being metabolized by colonic microflora[20].

Jahraus *et al*[26] performed the only randomized, placebo-controlled, double-blind trial aiming to evaluate the preventive effect of balsalazide on acute radiation-induced side effects. Twenty five patients were enrolled and randomized to active treatment (3 capsules of 750 mg of balsalazide 2 times a day) or to identical-looking placebo. Patients started drugs

or placebo intake 5 d before the beginning of the radiation treatment and continued it until 14 d after the completion of RT. After a follow-up conducted throughout RT and concluded 2 wk after the end of radiation treatment, balsalazide significantly reduced the frequency of acute radiation-induced pelvic disease (P = 0.04) according to the CTC scale, in particular of proctopathy symptoms, when compared to placebo. Of note, 3 patients in the balsalazide group and 1 patient in the placebo group withdrew from the trial, because of the high number of pills to intake, thus the proposed way of administration might affect patient compliance in the clinical practice. Nausea and limited vomiting are the only adverse reactions to balsalazide reported so far[26].

Up to now, these data have not been confirmed by further investigational trials, and the efficacy of balsalazide for the prevention of late-onset pelvic radiation disease has not yet been evaluated.

Mesalazine

Mesalazine (5-ASA) is the active compound of aminosalicylates. Freund *et al*[27] considered in a randomized, placebo-controlled trial 16 patients with prostate cancer, 8 of whom received mesalazine as rectal suppositories (250 mg three times a day) *vs* 8 patients assigned to the placebo arm. The study was prematurely stopped because of severe side effects in the 5-ASA group: 75% of patients treated with 5-ASA reported symptoms of severe proctopathy while only one patient in the placebo group. Additionally, Baughan *et al*[28] enrolled in a randomized controlled trial 73 patients with pelvic cancer and found that diarrhea occurred in a higher proportion of patients in the 5-ASA arm than the placebo arm (91.2% *vs* 73.7%, P = 0.01). Resbeut *et al*[29] considered in a randomized, placebo-controlled trial 153 patients, 74 of whom receiving two tablets four times a day of mesalazine 500 mg (daily dose 4 g) *vs* 79 patients assigned to the placebo arm throughout the pelvic irradiation period. No significant difference regarding either the occurrence and the duration of diarrhea was observed, while the severity of diarrhea considered after two weeks from the beginning of radiation therapy was significantly higher in the 5-ASA group (P = 0.006).

Based on the available evidences, there is no evidence supporting the administration of mesalazine in the prevention of acute, early-onset PRD. Moreover mesalazine has repeatedly shown in RCTs to worsen symptoms in comparison with placebo and thus mesalazine should be avoided as a preventive agent.

Beclomethasone dipropionate

The inflammatory process plays a pivotal role in the early phases of radiation-induced damages[3]. Therefore, reducing or abolishing the initial inflammatory process could be a reasonable preventive strategy of radiation-induced alterations. Glucocorticosteroids are the most effective anti-inflammatory agents available for several inflammatory diseases, but their prolonged use is limited by the development of severe side effects. Beclomethasone dipropionate (BDP) is a nonsystemic glucocorticoid with a different and safer pharmacokinetic profile.

In 2011, the preventive efficacy of BDP has been investigated in a double-blind, placebo-controlled randomized trial[30]. Patients with a diagnosis of prostate cancer and scheduled for radiation treatment were treated with a 3-mg BDP enema or identical-looking placebo the evening before each radiation session, for the entire duration of radiotherapy. Immediately after the end of radiotherapy, patients stopped the enema formulation and received two 3-mg BDP suppositories, or identical placebo, for 4 more weeks. Between June 2007 and October 2008, 120 patients were randomized, 60 patients in the BDP arm and 60 patients in the placebo arm. After 12 mo of follow-up, patients treated with BDP presented a significant reduction of the post-radiation risk of bleeding (OR = 0.38; 95%CI: 0.17-0.86) and of rectal mucosal changes. In particular, actively treated patients presented fewer rectal angiectasias in comparison to non-treated patients. Most importantly, at the end of follow-up, patients on BDP presented a higher Quality of Life score, in particular BDP preventive treatment seemed to better preserve the patient's emotional status (*e.g.*, anger, depression, irritability), which was less frequently altered.

At the moment, this represents the only available RCT showing a beneficial effect of BDP treatment as chemopreventive agent. Further studies are warranted to confirm these encouraging results.

Misoprostol

Misoprostol is a methylester analog of prostaglandin E1 that is used to prevent gastric ulcers, to treat missed miscarriage, to induce labor and to induce abortion. The rationale for its use as a radioprotective agent lies on its capability to stimulate mucus production, to prevent cellular shedding and lysosomal enzyme release[31]. Additionally, misoprostol seems to induce the production of sulfhydryl compounds, which may act as free radical scavengers[32].

Few randomized trials have investigated the efficacy of intrarectal misoprostol in preventing PRD and overall the results are contrasting. Khan *et al*[33] enrolled in a randomized, placebo-controlled, double-blind trial, 16 patients who underwent pelvic irradiation, 9 of whom received one rectal suppository of 400 μg of misoprostol one hour before each radiotherapy session, *vs* 7 patients taking placebo. According to a non-validated clinical scale-considering bowel movements per day, rectal tenesmus, rectal bleeding and general well-being-misoprostol significantly reduced the occurrence and

severity of acute, early-onset PRD ($P < 0.01$) and also decreased the incidence and severity of chronic rectal toxicity ($P < 0.01$). On the other hand, Hille et al randomized 100 patients with prostatic cancer, 50 of whom received one rectal suppository of 400 μg of misoprostol one hour before each radiotherapy session, *vs* 50 patients taking placebo[34,35]. As assessed by the validated RTOG and LENT/SOMA clinical scales, misoprostol did not reduce the incidence and severity of radiation-induced acute PRD nor the occurrence and gravity of chronic, late-onset PRD. Furthermore, misoprostol increased the incidence of grade 1 and 2 acute rectal bleeding ($P = 0.03$) and also favored late rectal bleeding.

In conclusion, as the existing evidence concerning the efficacy of misoprostol in the prevention of PRD is conflicting, misoprostol should not be considered as a treatment of choice in the clinical setting, as also discouraged by the MASCC panel[25].

Sucralfate

Sucralfate is an alkaline aluminum hydroxide of sulfated sucrose. The rationale for the administration of sucralfate in the prevention of PRD lies on its supposed property to protect mucosa by forming a viscous superficial coating and to stimulate mucosal healing by its angiogenic effect[36,37]. Sucralfate can be administered either orally or as a rectal enema.

Effect on acute PRD: The efficacy of sucralfate in the prevention of acute, early-onset PRD has been investigated by several randomized, controlled trials[38-42]. Overall, sucralfate as a preventive treatment on acute radiation-induced toxicity seems not to be effective.

In 1991, Henriksson *et al*[38] published a randomized, double-blind placebo-controlled trial based on 66 patients with localized pelvic cancer and found encouraging results; indeed, 1 g of sucralfate taken 6 times a day significantly improved diarrhea ($P = 0.003$), frequency of defecation ($P = 0.04$), stool consistency ($P = 0.04$) and loperamide consumption ($P = 0.003$) as evaluated by patient diary. However, these data were not subsequently confirmed by several RCTs. Martenson *et al*[39] enrolled in a randomized double-blind placebo-controlled trial 123 patients with pelvic cancer, 62 receiving oral sucralfate 1.5 g four times a day *vs* 61 receiving placebo, and found that sucralfate did not decrease acute pelvic RT-related bowel toxicity and even seemed to worsen some gastrointestinal symptoms. Indeed, patients receiving sucralfate had an increased frequency of fecal incontinence (34% *vs* 16%, $P = 0.04$), need for protective clothing (23% *vs* 8%, $P = 0.04$), and an increased occurrence and severity of nausea ($P = 0.03$). Similarly, Stellamans *et al*[40] evaluated in a randomized double-blind placebo-controlled trial 80 patients, 38 of whom received oral sucralfate four times a day, twice 1 g and twice 2 g *vs* 42 patients taking placebo, and did not find any significant difference in the incidence and severity of acute radiotherapy-induced discomfort, diarrhea and in the number of stools per day. Moreover, Hovdenak *et al*[41] enrolled in a randomized, placebo-controlled trial 51 patients with localized pelvic tumor during 7-wk radiotherapy, 24 of whom were randomized to oral sucralfate 2 g three times a day *vs* 27 receiving placebo, and found in an interim analysis that sucralfate significantly increased acute RT-induced diarrhea ($P = 0.033$) so that the trial was stopped. The finding of the above mentioned RCTs was further confirmed by a meta-analysis that showed no significant beneficial effect of sucralfate on the prevention of acute radiation-induced symptoms[41]. The rectal administration of sucralfate was tested too. In a randomized, placebo-controlled trial, O'Brien *et al*[42] enrolled 86 patients with localized prostate cancer and assigned 43 of them to receive once daily enema of 3 g of sucralfate in 15 mL suspension, given during and for 2 wk after the end of radiotherapy *vs* 43 patients receiving placebo, and found that sucralfate did not substantially reduce the incidence of symptoms associated with irradiation.

Based on the available evidences, the MASCC panel recommends oral sucralfate not to be used to prevent acute rectal side effects induced by radiotherapy[25].

Effect on chronic PRD: As far as chronic, late-onset PRD is concerned, its prevention with oral sucralfate has been investigated in several randomized controlled trials with conflicting results. In the previously reported trial, Henriksson *et al*[43] found that 1 g of sucralfate taken 6 times a day was again significantly effective in reducing the frequency of defecation ($P = 0.01$), of mucus discharge ($P = 0.01$) and weight loss ($P = 0.04$) in comparison to the placebo group, and also observed a trend in diminishing the occurrence of blood in the stools ($P = 0.11$) and loperamide consumption ($P = 0.11$). At opposite, Kneebone *et al*[44] evaluated in a randomized, double-blind placebo-controlled trial 298 patients with localized prostate cancer, 143 of whom received 3 g of oral sucralfate twice a day *vs* 155 patients taking placebo, and found no significant reduction in the incidence of late rectal toxicity in patients receiving sucralfate; indeed, the cumulative incidence of RTOG Grade 2 or worse late rectal toxicity at 2 years, was 28% for placebo and 22% for the sucralfate arm ($P = 0.23$) and there were no differences concerning bowel frequency ($P = 0.99$), mucus discharge ($P = 0.64$), or fecal incontinence ($P = 0.90$)[44].

O'Brien *et al*[45] enrolled in a randomized, placebo-controlled trial 86 patients with localized prostate cancer and assigned 43 of them to receive once daily enema of 3 g of sucralfate in 15 mL suspension *vs* 43 receiving placebo and found that rectal

sucralfate did not reduce the occurrence of chronic PRD, as the occurrence of late Grade 2 RTOG/EORTC toxicity was 5% in the sucralfate arm *vs* 12% in the placebo group ($P = 0.26$), and the incidence of late rectal bleeding was not different between the two arms of randomization (54% for sucralfate *vs* 59% for placebo).

Concerning the existing evidence, sucralfate seems to be safe and no serious adverse events have been reported. Fecal incontinence, nausea and constipation are the only side effects reported so far, in about 15%-34% of patients[39,41].

Probiotic supplementation

After pelvic radiation treatment it has been observed a change in the microbial ecosystem of the large intestine, which can contributes to the development of radiation-induced GI side effects[46,47]. Therefore, it has been suggested that probiotics supplementation during radiation treatment might reduce the development of radiation-induced side effects, in particular of diarrhea. Indeed, probiotics might have a role in the prevention and treatment of radiation-induced diarrhea, because their mechanisms of action include modification of composition of indigenous intestinal flora, enhancement of mucosal barrier function, prevention of bacterial overgrowth, and colonization of pathogens, and stimulation of hosts immune defenses[48].

Up to now, only few studies have been performed with the intent to ascertain the preventive effect of probiotics supplementation during radiation-treatment[49,50]. Overall, these studies have concluded for a possible preventive effect. In particular Fuccio *et al*[50] performed a double-blinded, placebo-controlled trial to investigate whether a preparation of probiotics, VSL#3, could reduce the incidence and severity of radiation-induced diarrhea. Each sachet of VSL#3 administered during the trial contained 450 billions/g of viable lyophilized bacteria, including several different strains of lactobacilli (*L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbruekii* subsp. bulgaricus), 3 strains of bifidobacteria (*B. longum*, *B. breve* and *B. infantis*) and 1 strain of Streptococcus salivarius subsp. thermophilus. During a 6-year period of enrollment, 482 patients who underwent adjuvant postoperative radiation therapy for sigmoid, rectal or cervical cancers were evaluated; 243 patients were randomized to receive probiotic supplementation and 239 patients were randomized in the placebo group. Radiation-induced diarrhea was less frequent in the active group (31.6% of patients) than in the placebo group (51.8%) ($P < 0.001$); furthermore, diarrhea was also consistently less severe in the probiotic supplementation group. Indeed, in the placebo group, 55.4% of patients that developed diarrhea presented a grade 3 severity (requiring treatment) or 4 (presence of hemorrhage or dehydration), compared with only 1.4% of patients in the active group ($P < 0.001$). Finally, the mean daily number of bowel movements was significantly lower in the active group compared with the placebo group ($P < 0.001$), whereas the mean time of use of rescue medication (loperamide) was significantly longer ($P < 0.001$). Finally, probiotic supplementation was well tolerated without reporting moderate or severe side effects.

These encouraging results, however, have not yet been confirmed and further well-performed, high-quality studies should be performed on this highly interesting issue.

CONCLUSION

Pelvic radiation disease is a multifactorial disease with a wide range of clinical spectrum. Several risk factors and subgroups of patients at increased risk of developing radiation-induced toxicity have been identified. Since endothelial dysfunction, inflammation, and connective tissue alterations have an important role in the pathogenesis of pelvic radiation disease[3], patients with diabetes, inflammatory bowel diseases (Crohn's disease or ulcerative colitis), and collagen vascular disease (scleroderma, systemic lupus erythematosus) have an increased risk of developing severe acute and late toxicities. Patients with these clinical conditions might have the maximum beneficial effect from a preventive treatment with several agents (*e.g.*, intrarectal amifostine, beclomethasone dipropionate and oral probiotics), for which well-performed RCTs have showed a beneficial effect for the prevention of acute and/or late-onset radiation-induced toxicities. Further studies should be performed to increase the literature concerning this issue, focusing on the identification of subgroups of patients for which a preventive strategy should be advised.

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