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TOPIC HIGHLIGHT

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Recent advances in the management of radiation colitis

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Abstract

Radiation colitis, an insidious, progressive disease of increasing frequency, develops 6 mo to 5 years after regional radiotherapy for malignancy, owing to the deleterious effects of the latter on the colon and the small intestine. When dealing with radiation colitis and its complications, the most conservative modality should be employed because the areas of intestinal injury do not tend to heal. Acute radiation colitis is mostly self-limited, and usually, only supportive management is required. Chronic radiation colitis, a poorly predictable progressive disease, is considered as a precancerous lesion; radiation-associated malignancy has a tendency to be diagnosed at an advanced stage and to bear a dismal prognosis. Therefore, management of chronic radiation colitis remains a major challenge owing to the progressive evolution of the disease, including development of fibrosis, endarteritis, edema, fragility, perforation, partial obstruction, and cancer. Patients are commonly managed conservatively. Surgical intervention is difficult to perform because of the extension of fibrosis and alterations in the gut and mesentery, and should be reserved for intestinal obstruction, perforation, fistulas, and severe bleeding. Owing to the difficulty in managing the complications of acute and chronic radiation colitis, particular attention should be focused onto the prevention strategies. Uncovering the fibrosis mechanisms and the molecular events underlying radiation bowel disease could lead to the introduction of new therapeutic and/or preventive approaches. A variety of novel, mostly experimental, agents have been used mainly as a prophylaxis, and improvements have been made in radiotherapy delivery, including techniques to reduce the amount of exposed intestine in the radiation field, as a critical strategy for prevention.

Key words: Radiation colitis; Acute; Chronic; Prevention; Intestinal obstruction; Perforation; Fistula; Bleeding

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INTRODUCTION

Radiation colitis is an insidious, progressive disease of increasing frequency. It is usually iatrogenic and unavoidable and frequently develops 6 mo to 5 years after regional radiotherapy for malignancy[1,2]. About half of all patients with malignancies undergo irradiation as part of their therapy. Considerable morbidity and mortality accompany radiation treatment because of the deleterious effects on adjacent normal tissues, mainly the colon and the small intestine. The type and extent of injury, depending on the dose of the radiation and the radiation sensitivity of the gut and the duration, is highly variable, ranging from 3 mo to 30 years[1,3]. Serious consequences may develop after years of gestation, and the disease, its treatment, and the disability produced are formidable. Apart from acute radiation colitis, manifestations of chronic radiation injury include proctitis, hemorrhages, fistulas, abscesses with signs of sepsis, perforations, strictures, and even cancer. Therefore, novel means to increase resistance of the intestine to radiation damage and effective therapeutic strategies are needed to prevent and manage this disease.

MANAGEMENT OF COLITIS CAUSED BY IRRADIATION

In general, prior to start, each treatment should be

individualized, and any predisposing factor should be identified during its course in order to early recognize and treat complications. Once complications have arisen, it is best to deal with the irradiated tissue by the most conservative modality, because the areas of intestinal injury do not tend to heal. This may require early diversion or resection as conservative therapy, because fistulas and bleeding will become recurrent and intractable. The effectiveness of non-surgical approaches remains far from desirable, and bleeding recurrence represents a major drawback that leads to a need for consecutive therapeutic sessions and combination of techniques[4]. If diversion fails to control bleeding, resection is necessary, even if it involves an abdominoperineal resection.

From another general viewpoint, there is a similarity in the activation of mucosal cytokines between inflammatory bowel disease (IBD) and radiation proctosigmoiditis. Indeed, as in the case of IBD patients, the mucosal levels of interleukin (IL)-2, -6, and -8 are significantly higher in both diseased and normal segments of colon in patients with radiation proctitis, compared with normal controls. In addition, IL-1β levels are significantly higher in diseased segments, compared with endoscopically normal-appearing segments in radiation proctitis. Tumor necrosis factor-alpha (TNF-α) levels are also significantly elevated in irradiated mice compared with non-irradiated controls[5]. These data may partially explain the beneficial effects of similar systemic and topical drugs including mesalamine compounds and steroids when used in radiation-induced proctosigmoiditis[6].

ACUTE RADIATION COLITIS (TABLE 1)

Empirical-experimental management

The majority of acute radiation colitis is self-limited, and only supportive management is required[7]. It must be emphasized, however, that acute radiation syndrome with a threshold dose of 8 Gy in man, represents a lethal clinical-pathological unit, enteritis and proctocolitis necro-hemorrhagica, with unknown causal therapy. In this respect, the detection of phospho-Elk-1, a protein acting as a transcription factor activating specific genes, might be considered as a suitable and very sensitive marker of acute radiation-induced injury of large and small intestine[8]. Whether Elk-1 inhibitors, such as the compound A (CpdA) or the protective agent U0126 [1,4-diamino-2,3-dicyano-1,4-bis(2-aminophenylthio)-butadiene], the effect of which probably results from the IL-1β mRNA reduction *via* the inhibition of ERK pathway, can be used in the management of this syndrome remains to be investigated[9,10].

Inflammatory cell infiltration of the colon is observed at an early stage of radiation-induced colitis. The migration of inflammatory cells from the circulation requires interactions between cell adhesion molecules on the vascular endothelium and molecules on the surface of leukocytes. Specifically, circulating leukocytes are recruited to sites of inflammation by a well-regulated and coordinated process that largely occurs in postcapillary venules. Adhesion molecules are expressed on the surface of endothelial cells, and leukocytes are involved in an orderly sequence of cell-cell interactions that include leukocyte adherence to vascular endothelium and the subsequent transendothelial migration into the inflamed tissue. Finally, reactive oxygen metabolites produced by activated leukocytes can induce damage to various cellular components, including structural and regulatory proteins, carbohydrates, lipids, DNA and RNA. In this respect, upregulation of intercellular adhesion molecule (ICAM)-1 and the accumulation of inflammatory myeloperoxidase-positive cells have been observed during acute radiation colitis prior to an overt radiation-induced ulcer, thereby playing important roles in the development of radiation-induced colonic ulcer[11]. Moreover, there is direct *in vivo* evidence that antioxidant mechanisms of the intestinal mucosa are not mobilized during the acute tissue radiation response; four days after exposure, during the inflammatory phase, superoxide dismutases (SOD) and catalase are decreased and glutathione peroxidases and metallothioneins are induced. Dexamethasone treatment modulates only glutathione peroxidase expression and does not influence either metallothionein or SOD expression. These experimental data indicate that during the radiation-induced acute inflammatory response, an imbalance of the antioxidant network of intestinal mucosa occurs[12].

In view of the aforementioned data, modulation of the leukocyte recruitment and activation pathway seems to be a potential therapeutic strategy against acute radiation colitis. Further supporting this consideration, experimental studies have demonstrated that leukocyte rolling is mediated by P-selectin and that firm leukocyte adhesion is supported by lymphocyte function antigen-1 in radiation-induced colitis. P-selectin-dependent leukocyte rolling is a precondition for subsequent leukocyte adhesion in radiation-induced intestinal damage. Therefore, targeting P-selectin and/or lymphocyte function antigen-1 might protect against pathologic inflammation in the colon induced by radiotherapy[13]. Moreover, Cu/Zn-SOD1 supplementation in an

Table 1 Management of acute radiation colitis

Management of acute radiation colitis
Supportive management
Anti-diarrheal medications and by reducing fat and lactose intake; In intractable cases hospitalization is required for parenteral feeding and elementary diet
Elk-1 inhibitors
Compound A (CpdA)
U0126 [1,4-diamino-2,3-dicyano-1,4-bis(2-aminophenylthio) butadiene]
Modulation of leukocyte recruitment and activation pathway
Targeting P-selectin and/or lymphocyte function antigen-1
Cu/Zn-SOD1 supplementation
Synthetic somatostatin analog octreotide
Other measures
Antiemetics
Steroid-containing suppositories
Recombinant granulocyte colony-stimulating factor in neutropenia
Epidermal growth factor

experimental model of radiation-induced intestinal inflammation has also been shown to decrease oxidative stress and adhesion molecule upregulation in response to abdominal irradiation. Specifically, a significant increase in the flux of rolling leukocytes and number of firmly adherent leukocytes in intestinal venules is observed after irradiation. Although administration of SOD1 has no effect on leukocyte rolling, it decreases leukocyte adhesion to intestinal venules significantly and in a dose-dependent way. Treatment with SOD1, at doses that reduce leukocyte recruitment, abrogates the increase in hydroperoxides in intestinal tissue and ICAM-1 upregulation in intestinal endothelial cells. The inflammatory score, but not a combined histology damage score, is also significantly reduced by SOD1[14].

Diarrhea associated with acute radiation colitis frequently resolves with anti-diarrheal medications and by reducing fat and lactose intake. The diarrhea rarely requires discontinuation of treatment unless chemotherapy is given concurrently with radiation[15]. Intractable diarrhea during the combined treatment may require hospital admission for administration of parenteral feeding. Elementary diet may also be introduced as an alternative to parenteral nutrition[16].

Patients refractory to anti-diarrheal medications may benefit from administration of the synthetic somatostatin analog octreotide[7]. Specifically, it has been shown that subcutaneous octreotide administration (150 μg t.i.d.) for 5 d is apparently an effective, well-tolerated treatment modality for concurrent chemoradiotherapy-induced diarrhea refractory to loperamide[17]. Octreotide appears to be more effective than conventional therapy with diphenoxylate and atropine in controlling acute radiation-induced diarrhea and eliminating the need for radiotherapy interruptions[18].

Apart from anti-diarrheal medications, other measures of general management of acute radiation enteropathy include administration of antiemetics. Steroid-containing suppositories may be helpful in the treatment of patients with anorectal inflammation[7]. Severe neutropenia from chemotherapy might require growth factors, such as recombinant granulocyte colony-stimulating factor (G-CSF, filgrastim) or granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim) to shorten the period of neutropenia, and avoid excessively delayed therapy from the bone marrow depression[19]. G-CSF is a cytokine known to activate neutrophils *in vivo* and GM-CSF mediates its effects on the neutrophil lineage through its effects on phagocytic accessory cells and its synergy with G-CSF[20,21].

Epidermal growth factor, an endogenous peptide, trophic to the gastrointestinal tract, significantly decreases the acute clinical manifestations of experimental radiation enteritis[22]. Therefore, it may be effective in human acute radiation colitis[23].

CHRONIC RADIATION COLITIS (TABLE 2)

Empirical-experimental management

Chronic radiation colitis is recognized as a frequent and clinically important sequel of abdominal and pelvic irradiation treatment for malignant disease. Since radiotherapy is now being used more than ever before in the therapy of solid organ neoplasms of the abdomen and the pelvis, the incidence of radiation colitis is likely to increase in the future[24-26]. Importantly, it is a precancerous lesion: Radiation-associated rectal cancer originates from dysplasia due to radiation colitis and has a tendency to be diagnosed at an advanced stage and to bear a dismal prognosis[27,28]. Therefore, management of chronic radiation colitis remains a major challenge owing to the progressive evolution of the disease that includes development of fibrosis, endarteritis, edema, fragility, perforation, partial obstruction, and even cancer. Patients with this condition are commonly managed conservatively. Because the obstruction is only partial, decompression is easily achieved by nasogastric suction and parenteral support. The patient is then often discharged on a liquid-to-soft diet. However, this therapeutic regimen does nothing for the underlying pathology. Although total parenteral nutrition corrects denutrition and facilitates deferred surgery in some patients, severe radiation enteritis remains a poorly predictable progressive disease with numerous relapses[29]. The problem, sooner or later, will return with the patient further depleted by the chronic radiation colitis. In a recent meta-analysis assessing the incidence and significance of malnutrition and examining the efficacy of therapeutic nutritional interventions used to manage gastrointestinal side effects in patients undergoing pelvic radiotherapy, it has been shown that there is no evidence favoring the use of nutritional interventions to prevent or manage bowel symptoms attributable to radiotherapy[30]. Regarding the underlying

Table 2 Management of chronic radiation colitis (IL; TNF-α)

Management of chronic radiation colitis
Empirical-experimental management
Total parenteral nutrition
Anti-IL-6R
Cyclooxygenase-2 inhibitors
Rho kinase inhibitors
Small molecular inhibitors of TNF-α
Targeting cadherin-catenin complex pathways
Recombinant human IL-11
Low-residue diet combined with bismuth subsalicylate or opiate drugs, such as loperamide or diphenoxylate (for mild diarrhea)
Aminosalicylates
Prostaglandin-inhibiting compounds
Oral steroids (for severe cases)
Probiotics (Lactobacillus bulgaricus)
Antioxidants
Colestyramine Balsalazide (in radiation-induced proctosigmoiditis)
Peroxisome proliferation-activated receptor activators
Sucralfate enemas
Short-chain fatty acids
Hyperbaric oxygen
Control of bleeding (by endoscopic cauterization using a heater, BICAP probe, Nd: YAG or argon laser)
Surgery (indicated in intestinal obstruction, perforation, fistulas, and severe bleeding)

pathology, vascular damage consisting of fibrin thrombi, fibrinoid necrosis and subintimal thickening of the arterioles leads to persistent local ischemia, which results in diffuse fibrosis of the lamina propria and submucosa. The diffuse fibrosis, in turn, accelerates vascular damage and further worsens local ischemia, forming a vicious cycle, finally leading to ulceration of the bowel wall and serious complications including massive gastrointestinal hemorrhages and perforations[31]. Therefore, surgical intervention appears to be appropriate when the diagnosis of chronic radiation colitis is confirmed[32].

Nevertheless, chronic changes in cytokine levels after abdominal irradiation in rodents have recently been documented[33]. Structural injury of the bowel wall and mesentery were scored and correlated with the levels of TNF-α, IL-6, transforming growth factor (TGF)-β1, -β2, -β3 and interferon (IFN)-γ mRNA in large and small bowel of mice 18-25 wk after whole abdominal irradiation with 12.5 and 13.5 Gy. Abdominal irradiation seems to induce considerable bowel damage associated with increased levels of all cytokines compared with sham-irradiated (0 Gy) mice. These experimental data demonstrate long-term cytokine expression changes in the bowel wall after irradiation that parallel the responses noticed in other tissues prone to radiation-induced fibrosis, such as cutaneous and pulmonary tissues, thereby having implications for the prediction, treatment and/or prevention of chronic radiation colitis. For instance, chronic IL-6 elevations, even prior to the start of irradiation, may predict patients at risk of radiation fibrotic bowel damage in the same way that IL-6 baseline elevations have been shown to identify patients with an increased risk of radiation pneumonitis and pulmonary fibrosis following thoracic irradiation[33]. Since studies in animal models of IBD have shown that various antibodies to pro-inflammatory cytokines and their receptors, such as IL-6 receptor (IL-6R) or TNF, appear to suppress chronic intestinal inflammation by inducing T-cell apoptosis[34], it is reasonable to assume that such antibodies (anti-IL-6R) might also be used to manage radiation colitis. In addition, reduction in cytokine expression with cyclooxygenase (COX)-2 inhibitors and small molecular inhibitors of TNF-α may reduce the frequency and severity of long-term bowel damage. There is some evidence that the COX-2 pathway is implicated in radiation-induced gut injury[31,35,36]. COX-2 and nuclear factor κB (NF-κB) expression have been associated with histopathological changes in the human colon and rectum following abdominal radiotherapy[31].

Besides, in radiation colitis involving aberrant glands, cellular proliferation increases and spotted oncogene p53 expression is noticed. Therefore, radiation colitis and aberrant glands with p53 overexpression might predict malignant potential of this condition[37].

Three typical phases of radiation proctitis are defined on histological grounds (acute damage, and early and late regenerative phases), essentially correlating with the time interval between radiotherapy and surgery. Such characteristics are mirrored by alterations in cadherin-catenin expression and localization in rectal crypts; morphology at both cellular and glandular levels in the large bowel is dependent to an extent on cell-cell adhesion mediated by cadherin-catenin complexes. In this regard, P-cadherin is highly expressed in the acute radiation damage and early regenerative phases, with a decreased level of expression during late regeneration. E-cadherin and associated catenins are translocated from the membrane to the cytoplasm in degenerating crypts, with return to normal membranous expression in regenerating crypts. Therefore, radiation-induced proctitis represents an *in vivo* model of mucosal damage and regeneration, thereby providing a valid model to study events during epithelial injury and repair: altered cadherin and associated catenins expressions appear to be predictive indicators closely associated with these processes[38]. On the other hand, because the E-cadherin-catenin complex plays a critical role in the maintenance of normal tissue architecture, mutation of any of its components is believed to result in loss of cell-cell adhesion, thereby contributing to neoplasia development. In this respect, adenomatous polyposis coli (APC) gene abnormalities, found to be the "gate-keeping" event for the initiation of colorectal neoplasia, may lead to a disruption of normal cell-cell adhesion through altered association with catenins and the cell adhesion molecule E-cadherin that binds catenins[39]. Translocation of the β-catenin protein, a key downstream effector of the Wnt signal transduction pathway, is frequently found in colorectal cancer. This protein is also observed in the cytoplasm and/or nucleus of non-neoplastic irradiated colonocytes. Nuclear translocation of β-catenin correlates with loss of APC and gain of cyclin D1 expression, suggesting the activation of the Wnt pathway during radiation-induced colorectal carcinogenesis. Because the translocation of β-catenin is found in irradiated-colonic mucosa as well as in colon cancer, the disruption of the β-catenin expression may be one of the early events in radiation-induced colonic oncogenesis[40]. Based on these data, interventions on cadherin-catenin complex pathways may also be used against chronic radiation colitis and radiation-induced colonic carcinogenesis. Finally, in a novel mouse model of radiation-induced colitis, a combination of high-dose γ-irradiation and lack of major histocompatibility complex (MHC) class Ⅱ expression on cells of hematopoietic origin results in the development of radiation colitis. Therefore, protection and/or inhibition from radiation-induced colitis seems to require MHC class Ⅱ antigen expression by cells of hematopoietic origin[41]. In this regard, administration of the recombinant pleiotropic human cytokine IL-11, which stimulates bone marrow stem cells to proliferate, has been shown to decrease intestinal mucosal injury produced by radiation in animals, thereby providing a potential therapeutic regimen for the treatment and/or prevention of chronic radiation colitis[42].

Diarrhea, with or without abdominal cramps, is the most common symptom of chronic radiation colitis[26]. The etiology of chronic radiation-induced diarrhea may be attributable to accelerated small and large

bowel transit, bacterial overgrowth, increased intestinal permeability, malabsorption of bile salts, lactose, fat and carbohydrate, and pancreatic insufficiency, all of which can exist with or without small bowel or large bowel strictures[43,44]. In case of colonic strictures, spurious diarrhea can occur. Moreover, the above mentioned microvascular changes in the bowel wall lead also to mucosal atrophy and a non-specific chronic inflammatory cell infiltrate, which has resulted in a mistaken diagnosis of celiac sprue[45]. However, in most cases, the pathophysiology of the diarrhea is uncertain. While changes in intestinal absorption and motility, unrelated to bacterial overgrowth, have been implicated in the etiology of diarrhea, there has been no comprehensive evaluation of gastrointestinal function in chronic radiation colitis. Perhaps partly as a result of this, present approaches to treatment have often been empirical. A low-residue diet (i.e. a low-fiber diet poor in foods that increase bowel activity) combined with bismuth subsalicylate or opiate drugs, such as loperamide or diphenoxylate, might be sufficient for mild diarrhea[1]; loperamide-N-oxide slows small intestinal transit, increases bile acid absorption, and is effective in the treatment of diarrhea associated with chronic radiation colitis[26]. Other antidiarrheal agents can be administered, including aminosalicylates and prostaglandin (PG)-inhibiting compounds[46,47]. In severe cases of radiation colitis, oral steroids have been tried with limited success[48]. Randomized controlled trials are not available, and all treatment regimens are based on evidence from small pilot studies, including the administration of sulfasalazine[49], glutathione (GSH)[50], and antioxidants[51]. Furthermore, antibiotics are indicated if there is small bowel bacterial overgrowth syndrome[52,53]. Preliminary results suggest that probiotics may also be useful for treatment of radiation bowel disease, although no robust data exist[54]. Other studies suggested that colestyramine, an agent that binds bile acids in the colonic lumen, might be effective in preventing radiation-induced diarrhea if administered in dosages of 4 g t.i.d. during radiation therapy[55]. In the presence of low serum magnesium levels, intravenous administration of magnesium sulfate, together with low residue diet and antidiarrheals, may also ameliorate the diarrhea[56].

Anti-diarrheal and bulk-forming agents have a role in the management of rectal urgency, frequency, and fecal incontinence, which might be induced by radiation damage of the myenteric plexus of the rectum and internal anal sphincter[57]. Sulfasalazine, 5-aminosalicylic acid (5-ASA) preparations and corticosteroid enemas have minimal or no effects on rectal tenesmus or bleeding[48].

However, recent pilot studies indicate that balsalazide, a new 5-ASA drug that yields a high concentration of active drug to the distal colon, is able to prevent or reduce symptoms of radiation-induced proctosigmoiditis[58]. In addition, irradiation-induced inflammatory response could be modulated pharmacologically based on the anti-inflammatory properties of 5-ASA, which is a peroxisome proliferation-activated receptor (PPAR) activator. PPAR agonists are now emerging as therapeutic drugs for various inflammatory diseases characterized by impaired PPAR expression: Irradiation drastically reduces mRNA and protein levels of PPAR-α and -γ. Specifically, 5-ASA treatment normalizes both PPAR-α and PPAR-γ during the post-irradiation period (after 7 and 3 d, respectively). By promoting PPAR expression and its nuclear translocation, 5-ASA interferes with the NF-κB pathway, both reducing irradiation-induced NF-κB p65 translocation/activation and increasing the expression of NF-κB inhibitor (IκB) mRNA and protein. Therefore, 5-ASA prevents irradiation-induced inflammatory processes as well as expression of TNF-α, monocyte chemotactic protein-1, inducible nitric-oxide synthase, and macrophage infiltration. In addition, 5-ASA restores the IFN-γ/signal transducer and activator of transcription (STAT)-1 and STAT-3 concentrations that were impaired at 3 and 7 d post-irradiation and are correlated with suppressor of cytokine signaling-3 repression. Collectively, these data suggest that PPAR agonists might be effective in the prevention of inflammatory processes and immune responses during and after pelvic radiotherapy[59].

Fecal incontinence appears to be a late complication that causes symptoms years after radiation treatment. The specific mechanisms that cause incontinence are changes in anal resting tone, squeeze pressure, and rectal volume or rectal compliance. Other aspects associated with incontinence include further disorders such as proctitis, colitis, and other disturbances involving the lower digestive tract. The therapeutic options mainly comprise management of associated aspects, such as proctitis or diarrhea; surgical intervention should be the absolute exception[60].

It has been reported that sucralfate treatment has a protective effect against experimental radiation colitis. Sucralfate enemas prior to radiation lead to reduction in: (a) the number of apoptotic colonic crypt cells; (b) the number of caspase-3 positive cells; (c) oncogene p53 accumulation and p21 expression; and (d) proapoptotic Bax/anti-apoptotic Bcl-2 ratio in rats. Therefore, the protective effects of sucralfate against radiation colitis might be partially due to the suppression of radiation-induced apoptosis in the colon and the protection of the colonic epithelial stem cell region[61]. Sucralfate administration may be also effective in human radiation proctocolitis[62]. In addition, when compared with oral sulfasalazine plus rectal prednisolone enemas, sucralfate enemas give a better clinical response in human proctosigmoiditis, are better tolerated, and, because of the lower cost, they might be the preferred short-term regimen[48]. Moreover, topical sucralfate induces a lasting remission in the majority of patients with moderate to severe rectal hemorrhage due to radiation proctosigmoiditis[63].

Clinically, short-chain fatty acids (SCFAs) have been proposed as possible therapeutic agents in several conditions including radiation proctitis. Although some promising effects have been observed in uncontrolled studies, a specific therapeutic role for SCFAs remains to be defined[64].

Hyperbaric oxygen

Hyperbaric oxygen application appears to be a very effective means of treatment of chronic radiation colitis and non-healing wounds in the involved anorectal region[65]. Hyperbaric oxygen therapy can be considered as a treatment option after failure of standard treatments in patients with severe radiation proctopathy[66]. The rationale for hyperbaric oxygen is the creation of an oxygen gradient in hypoxic tissue that stimulates the creation of new blood vessels. Neoangiogenesis improves the blood supply and reduces the ischemia and necrosis responsible for severe complications. In a retrospective study of patients with severe radiation colitis refractory to medical management, hyperbaric oxygen therapy provided clinical relief and can thus prove to be a useful alternative to conventional treatment in patients with chronic radiation-induced necrosis of the digestive tract[67]. Moreover, in a systematic review of the literature on the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries, all but seven of the 74 publications analyzed reported positive results when hyperbaric oxygen was delivered as treatment for or prevention of delayed radiation injury. These results are particularly impressive in the context of alternative interventions[68]. Hyperbaric oxygen may also be helpful in management of bleeding due to chronic radiation colitis in patients not controlled with conservative measures such as formalin and laser therapy[69,70]. Hyperbaric oxygen treatment and infusion of PG E1 abolishes completely tarry stools and hematuria, and reverses the endoscopic findings of radiation colitis and cystitis[71].

Control of bleeding

Rectal bleeding due to radiation colitis usually results from telangiectasias. It is frequently minor, but blood transfusions may be required. Endoscopic cauterization using a heater, BICAP probe, Nd:YAG or argon laser can reduce bleeding.

Argon plasma coagulation therapy appears to be a simple, safe, and effective technique in the management of hemorrhagic radiation-induced proctosigmoiditis and is now generally accepted as the treatment of choice followed by local application of formalin if this fails[31,72,73]. Argon plasma coagulation, a non-contact thermal coagulation technique that reduces rectal bleeding in 80%-90% of cases, is applied endoscopically, with a probe passing through the endoscope that delivers a field of argon gas to the mucosal surface, where it is ionized by a high-voltage filament resulting in superficial mucosal heating and coagulation of friable blood vessels. Topical formalin therapy depends on direct application of a 4% concentration of the chemical soaked in gauze to the hemorrhagic areas under direct vision using a rigid sigmoidoscope. Thrombosis of the neovasculature and coagulation necrosis of the superficial mucosa ensues, with a complete response rate of 78%. While topical formalin appears to be slightly less effective than argon plasma coagulation therapy, formalin application alone or a combination of the two treatments has been advocated for severe cases of hemorrhagic radiation proctitis. Although formalin installation may be effective in controlling refractory bleeding due to radiation-induced proctitis, the procedure is not risk-free and may induce major complications such as acute colitis[74]. Preliminary results of a randomized study of the two therapeutic interventions, however, show equivalent efficacy but an absence of effect of either treatment on anorectal dysfunction.

Another approach to treat hemorrhagic radiation proctitis involves use of low-dose thalidomide, a potent inhibitor of (neo)angiogenesis, following a case report with successful outcome[75]. In addition, hormone therapy consisting of an estrogen-progesterone combination might provide a promising new additional symptomatic therapy for bleeding radiation colitis[76].

Rectal strictures should be managed initially non-operatively with a low-fiber diet, stool softeners, mineral oil enemas, and analgesics. Manual or endoscopic dilations of rectal strictures might be required. Short strictures with minimal angulation can be dilated by transendoscopic balloons or other dilators, albeit with considerable risk of perforation. Long, tortuous strictures should be managed operatively[77].

Surgery

About one third of patients with chronic radiation enteritis will need to be operated during follow-up. Surgical intervention is indicated in intestinal obstruction, perforation, fistulas, and severe bleeding. Surgery should be performed by an experienced team familiar with the treatment of radiation colitis. It is difficult to perform surgery for chronic radiation colitis because of the diffuse process of fibrosis and alterations in the gut and mesentery. The risk of anastomotic leak is high if the anastomosis is performed using irradiated tissue[78]. The risk can be lowered if at least one limb of the anastomosis did not receive prior radiotherapy[79]. It is difficult to distinguish between the normal tissue area and the irradiated area of the gut by gross evaluation during operation even when the fresh tissue is sent for frozen section. The accuracy in localizing injured intestine may be improved by intraoperative endoscopic evaluation, which can detect radiation-induced mucosal injury[80].

Resection of the affected intestine is significantly better than an enteric bypass procedure in overall outcome. However, extensive surgical resection of the diseased bowel may lead to short bowel syndrome and increase the need for total parenteral nutrition. Moreover, because of the progressive evolution of the fibrosis, the patient may require additional surgery. Surgical bypass of the damaged bowel is associated with a blind loop syndrome, and the patient may be still at risk of perforation, bleeding, abscess, and fistulae due to the persistence of the affected bowel. Bypass procedures should be performed when resection is not possible or as a temporary management before resection at a later date. Limited resection of the diseased intestine is the goal, but if the lesion is too diffuse, a bypass procedure

might be attempted.

Management of a pelvic fistula (e.g. vaginal or bladder fistula) is also complex and requires fecal diversion before the corrective surgery. Patients with fistulae frequently present with additional challenges such as electrolyte imbalance, malnutrition and infections. Many surgical techniques have been described to repair fistulae, but corrective surgery is best done when the patient is medically stable and enough time has elapsed after the surgical diversion. This permits the healing and decreased inflammation of the affected tissues[81,82].

In cases with severe fibrotic strictures, surgical intervention with establishment of a primary anastomosis may be required[83]. Strictureplasty may be an effective and safe tool to conserve intestinal length in certain highly selected patients with chronic radiation colitis and small-bowel strictures, namely those with limited intestinal reserve where strictures are located within long segments of diseased bowel which, if resected or bypassed, would have significant nutritional or metabolic consequences. Strictureplasty is not indicated for the treatment of perforation, hemorrhage, fistula, or short segments of disease in patients with adequate intestinal reserve[84].

Surgical complications of chronic radiation colitis such as intestinal obstruction, enterocutaneous fistula, intestinal stenosis, intestinal bleeding, severe proctocolitis and intestinal perforation should be managed operatively[85].

It is important to note that vigorous preoperative and postoperative nutritional support and evaluation are vital because of the poor healing qualities of the irradiated gut.

If conservative measures and local intervention to control bleeding prove unsuccessful, resection or ligation of the affected area(s) is preferred over a bypass procedure because the latter will allow the hemorrhage to continue and may lead to a higher mortality rate[86]. A promising surgical approach is small bowel transplantation, which may be considered in the pediatric population with radiation colitis.

PREVENTION OF RADIATION COLITIS

Based on the above data, it appears that the management of radiation bowel damage can be difficult and problematic; chronic radiation colitis is complex and rarely curable. Recent advances in the approaches to its prevention or amelioration are therefore particularly encouraging. Research to uncover the mechanisms of fibrosis and the molecular events underlying radiation bowel disease could lead to the development of new therapeutic and/or preventive approaches and provide the basis for predicting the risk of bowel damage and oncogenesis using levels and expressions of the mentioned cytokine IL-6, oncogene p53 or cadherin-catenin complexes, and for amelioration of bowel damage through inhibition, for example, of the COX-2 and Rho/Rho kinase pathways[33,87]. In this regard, the COX-2 inhibitor Rofecoxib® has been shown to suppress cytokine expression and to reduce acute bowel damage in rodents following abdominal irradiation[36]. In addition, piroxicam (a nonsteroidal anti-inflammatory agent) significantly decreases the incidence of colonic neoplasia in general and also delays the endoscopic appearance of colonic neoplasia in rats after pelvic irradiation[88]. Moreover, specific inhibition of Rho kinase is a promising approach for the amelioration of radiation fibrotic gut damage, as reported by a study investigating molecular pathways involved in the maintenance of fibrosis of the bowel wall of late radiation colitis patients[87]. Alterations in expressions of genes coding for Rho proteins was first established by molecular profile analysis of ileal biopsies. Primary cultures of gut smooth muscle cells derived from the ileal biopsies are associated with retention of fibrogenic differentiation *in vitro* and exhibit a typical cytoskeletal network, a high constitutive connective tissue growth factor level, increased collagen secretory capacity and altered expression of genes coding for the Rho family. Rho kinase blockade induces a simultaneous reduction in the number of actin stress fibers, α-smooth muscle actin and heat shock protein (Hsp) 27 levels. It also reduces connective tissue growth factor levels, the latter probably through NF-κB inhibition, leading to decreased expression of the type 1 collagen gene[87]. These observations show the involvement of the Rho/Rho kinase pathway in radiation fibrosis and intestinal smooth muscle cell fibrogenic differentiation, suggesting the potential role of Rho kinase inhibitors in ameliorating the radiation bowel damage.

Additional biomarkers potentially playing a role in the prediction, reduction or prevention of radiation colitis include genetic alterations of the cellular radiation response genes, such as the ataxia telangiectasia gene, and micronutrients, such as selenium and zinc. Genetic variants of the ataxia telangiectasia gene have been correlated with the risk of rectal hemorrhage associated with chronic radiation proctitis among prostate cancer patients who received the full brachytherapy prescription dose to defined volumes of the rectum[89]. The ataxia telangiectasia sequence alterations lead to an approximately sevenfold increase in mild to moderate (Radiation Therapy Oncology Group grades 1 and 2) radiation proctitis among patients who had received the full prescription dose to either low (< 0.7 mL) or moderate (0.7-1.4 mL) volumes of their rectum. Patients contemplating this increasingly popular radiation treatment modality for early prostate cancer should not only be better informed about the risks of bowel complications, but could also have their radiation dose prescriptions individualized based on genetic profiling.

Dietary supplementation of selenium and zinc may be useful in reducing anorectal sequelae after pelvic radiotherapy; an indirect relationship between baseline plasma levels of these micronutrients and abnormalities in anorectal function one year after radiotherapy for prostate cancer has been suggested. Notably, the heavy metal zinc induces Hsps, also known as stress proteins and molecular chaperones, which play a central role in protecting cellular homeostatic processes from environmental and physiologic insults by preserving the

structure of normal proteins and repairing or removing damaged ones. Lowering Hsps in cancer tissues can amplify the effectiveness of chemo- or radiotherapy[90].

Importantly, improvements in the delivery of radiotherapy, including techniques to reduce the amount of exposed intestine in the radiation field, also represent a critical strategy for prevention. The ideal radiation toxicity preventive therapy must have high efficacy, low toxicity, low cost, and not afford cancer protection. Unfortunately, the currently available therapy often does not fulfill all of these objectives and there is a need to identify patients who may truly benefit from preventive therapies. Specifically, the radiation therapy technique plays an essential role in reducing the rate of complications; particular attention should be paid to optimizing radiotherapy technique and dose prescriptions. The use of only anterior and posterior fields for pelvic radiation should be avoided, if possible, because of the high dose and large volume of intestine irradiated. A higher operative mortality was reported in trials using this technique preoperatively for rectal cancers[91,92]. The toxicity of radiation is directly related to the volume of small bowel being irradiated[93]. In many patients, therapy in the prone position with a special "belly" board allows the protrusion of the small intestine out of the radiation field[94,95]. Patients should be instructed to maintain a full bladder during the radiation session, which mechanically displaces the intestine out of the pelvis[96].

Modern radiation treatment techniques, such as three-dimensional treatment planning, also optimize the treatment technique by developing more accurate dose distributions. Notably, three-dimensional conformal radiotherapy techniques, including intensity-modulated radiotherapy, may not reduce late intestinal toxicity because margins around the cancer may not be able to be safely reduced and because of the prescription of higher radiation doses[97,98]. Brachytherapy, alone or as a supplement to external beam radiotherapy, is now increasingly being utilized to decrease normal tissue toxicity, without compromising treatment efficacy, in the management of prostate carcinoma[99,100]. Brachytherapy is a kind of radiotherapy whereby the source of radiation is located either within the malignant tissue (interstitial brachytherapy) or within a cavity in its immediate vicinity (intracavitary brachytherapy), rather than at a distance (typically 100 cm) from the center of the neoplasm target, as it is the case with external beam radiotherapy. Brachytherapy exploits the physical characteristics inherent with this modality of radiotherapy, whereby the high radiation dose is limited to the neoplasm target, while the surrounding normal tissues are spared from radiation by the rapid dose reduction (with the square of the distance). Brachytherapy alone, in the therapy of low-risk prostate carcinoma, is well tolerated, even in patients with a history of IBD[101].

Another related treatment, such as intensity-modulated radiotherapy (IMRT), uses sophisticated planning techniques to avoid critical structures. IMRT uses multiple segments of beams to shape the dose distribution to a desired result.

Operation, as a major risk factor, leads to the prolapse of the small intestine into the pelvis, exposing it to a full dose of radiation. Postoperative bowel adhesions also increase the volume of gut irradiated compared with normal intestine, usually mobile and able to move out of the radiation field. With gut adhesions, the intestine is trapped and is more likely to receive a high dose of radiation. If radiation therapy is anticipated after surgery, every attempt should be made at the time of surgery to displace the bowel outside of the radiation field[102]. One simple technique is the surgical placement of a polyglycolic, biodegradable mesh that moves the intestine out of the pelvis[103,104]. The procedure has negligible morbidity and it does not increase the operating time significantly. It also does not require a second operation to remove the mesh because it is absorbed 3 to 4 mo postoperatively. MRI can be used post-operatively to verify the position of the mesh, the small bowel, and its disappearance. Placement of a mesh during surgery allows a higher dose of radiation to be given postoperatively when indicated, thereby decreasing by 50% the volume of the small bowel exposed to the radiation[105,106]. Other techniques such as pelvic reconstruction, omentoplasty, and transposition of the large bowel also reduce the volume of gut at risk for radiotherapy up to 60%[106-109].

Amifostine (WR-2721) is an amino-thiol with well-established radioprotective effects. Recent studies have documented its effectiveness in protection of the salivary glands in patients receiving radiotherapy for head-and-neck cancer[110]. It has also been investigated for the prevention of chronic radiation colitis. According to preclinical studies, amifostine protects both the small and large intestine[111]. Specifically, it is converted intracellularly to an active metabolite, WR-1065, which in turn binds to free radicals and protects the cell from radiation damage[112]. In a randomized study, the late effects of radiation were significantly reduced in the group receiving parenterally administered amifostine. However, the median follow-up was quite short (24 mo), and longer follow-up is necessary to confirm the benefits of this medication because the incidence of late complications increases with time[113]. There is also evidence suggesting that intrarectal application of amifostine directly onto the rectum may reduce the risk of proctitis in patients undergoing radiotherapy for prostate cancer[114]; its intrarectal application is feasible and well tolerated. Systemic absorption of amifostine and its metabolites is negligible, and close monitoring of patients is not required after rectal administration[115]. Systemic administration of amifostine, used concurrently with radiotherapy in advanced rectal cancer, has been reported to reduce acute and late pelvic radiation toxicity[113]. Other investigators[116], however, were not able to demonstrate any protection afforded by amifostine.

Since cytotoxic effects of ionizing radiation on gastrointestinal epithelium may be related to oxidative stress, a number of agents have been used as a prophylaxis

treatment. Eicosanoids and free radicals release have been implicated in the pathogenesis. Selenium and/or vitamin E pretreatments are shown to improve post-irradiation disturbances in pro-oxidant-antioxidant balance, such as increased intestinal lipid peroxide and decreased GSH levels, increased intestinal SOD and GSH peroxidase activities and decreased glutathione transferase activity. This amelioration has been confirmed by histopathological findings[117]. In another study, the early side effects of radiation were suggested to be prevented by vitamin A supplementation[118].

PGs have been investigated as potential radioprotectors. PGE2 and the PG analogs enprostil and misoprostol (Cytotec®) display radiation protection in animal studies[119-122]. Misoprostol suppositories also reduced symptoms of acute radiation colitis in patients undergoing radiation therapy for prostate cancer[123]. With respect to the mechanism of action, PGE2 has pro-proliferative and anti-apoptotic effects on epithelial cells in gastrointestinal injury. PGE2 decreases radiation-induced apoptosis and increases crypt survival[124].

Experimental data indicate that in control animals, glucagon-like peptide-2 (GLP-2) induces an increase in intestinal mucosal mass, along with an increase in villus height and crypt depth. GLP-2 administration before and after irradiation completely prevents the acute radiation-induced mucosal ulcerations and strikingly reduces the late radiation damage. Microscopic observations show an improved organization of the intestinal wall and an efficient wound healing process, especially in the smooth muscle layers. This therapeutic effect is mediated through an increased mucosal mass before tissue injury and the stimulation of still unknown mechanisms of tissue response to radiation damage. Although these preliminary results still need to be confirmed, GLP-2 might be a way to limit patient discomfort during radiotherapy and reduce the risk of consequential late effects[125].

Irradiated intestine consistently exhibits increased immunoreactivity of transforming growth factor (TGF)-β1. It has been demonstrated that mucosal barrier breakdown is closely associated with increased TGF-β immunoreactivity in subsequent radiation enteropathy. The highly significant correlation between TGF-β expression levels and alterations in late-responding tissue compartments also suggest a role for TGF-β in primary radiation colitis. A recent preclinical study showed a role for possible anti-TGF-β1 interventions to reduce delayed radiation fibrosis and enteropathy[126].

Preliminary studies also suggest that IFN-γ may be effective in the treatment of patients with radiation-induced cutaneous fibrosis. IFN-γ should be considered in Phase Ⅰ-Ⅱ studies to assess its toxicity and efficacy in the treatment of patients with radiation colitis[127].

Many special diets and nutrients, such as the mentioned fiber, elemental diets, SCFAs and amino acids like glutamine, may reduce small-bowel radiation toxicity. Specifically, probiotics (*Lactobacillus bulgaricus* strain isolated from yogurt) added as substrates can be given by an oral or enteral route to patients who undergo radiotherapy to prevent radiation-induced colitis and related malnutrition[128].

Glutamine and arginine support the mucosal barrier in several ways. In experimental studies, a 7-d glutamine- or arginine-enriched diet administered both pre- and post-irradiation showed that they have protective effects on gut mucosa in the post-irradiation state. However, pre- and post-irradiation administration together do not provide superior protection compared to post-irradiation administration alone[129].

Administration of insulin-like growth factor (IGF)-I immediately following abdominal irradiation increases small-intestinal mass and improves indicators of mucosal integrity, suggesting acceleration of small-intestinal mucosal recovery from radiation injury[130]. More recently, growth hormone and IGF-I have been demonstrated to protect intestinal cells from radiation-induced apoptosis both *in vitro*, by inhibiting apoptosis of the cells and preserving the mucosal integrity[131], and *in vivo*[132], utilizing IGF- I transgenic mice.

Pancreatic enzymes can exacerbate acute intestinal radiation toxicity, and suppressing pancreatic secretion with synthetic somatostatin receptor analogs, such as octreotide, can reduce both early and delayed radiation colitis[133]. Of note, in an experimental model, irradiation significantly increased intestinal and pancreatic myeloperoxidase activities and intestinal malondialdehyde levels of intestinal tissues, and octreotide treatment improved this elevation. The histopathologic evaluation of the mucosal structure was also preserved in the octreotide-treated group. Inflammation of pancreatic tissue was also confirmed with histopathological examinations. Moreover, irradiation seems to induce NF-κB overexpression, and octreotide treatment decreases the end organ damage and inflammation of the small intestine. Thus, octreotide appears to have beneficial effects on intestinal and pancreatic damage in abdominal irradiation through the inflammatory process[134].

Despite the aforementioned promising agents used in acute and chronic radiation colitis, further understanding of the pathophysiological mechanisms involved in the pathogenesis of acute and chronic irradiation colitis and the interaction of the molecular events controlling mainly apoptosis and fibrosis may assist in the development and establishment of new therapeutic approaches.

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