Diarrhea is a common problem in patients receiving pelvic irradiation with concurrent chemotherapy. Virtually all patients develop diarrhea of varying severity during the course of the treatment. The incidence and severity of diarrhea vary with the chemotherapy type and dose, radiotherapy field size, daily fraction size, and total dose of radiation given. Diarrhea (any grade) occurs in 30% to 87% of patients receiving chemotherapy and in 20% to 49% of patients receiving pelvic radiotherapy. The incidence of severe and life-threatening (grade 3/4) diarrhea ranges from 20% to 40% in patients receiving combined chemoradiotherapy.

Radiation-induced diarrhea can be severe and life threatening. It is obvious that by reducing the chemoradiation-induced bowel symptoms, the patient’s quality of life during (and following) therapy can be enhanced. Additionally, minimizing the severity of radiation-induced enteritis may increase the probability of completing the planned treatment without interruption and improve the outcome. It is also expected that effective management/prevention of severe diarrhea would avoid hospitalization for complications such as dehydration, fluid and electrolyte imbalance, or nutritional decline. Incidence of diarrhea may increase as more aggressive therapeutic regimens are developed and employed.

The pathophysiology of radiation enteritis is not well understood. Radiation-induced mucosal damage results in decreased absorption of water and electrolytes, causing diarrhea. Another possible mechanism is decreased bile acid absorption in the ileum (due to mucosal damage).[1] When passing through the bowel, the excess bile acid irritates and damages the protective mucosal cap of the intestine. This results in transudation of fluid and electrolytes into the lumen and causes diarrhea.

Octreotide (Sandostatin), a somatostatin analog, is very effective in controlling grade 3 diarrhea associated with chemotherapy.[2] Octreotide seems to control diarrhea by decreasing intestinal motility and increasing absorption of water and electrolytes. It also reduces bile secretion. Petrelli et al treated 16 patients with colorectal carcinoma who received fluorouracil (5-FU) and high-dose leucovorin and who had National Cancer Institute (NCI) grade 3/4 diarrhea that did not respond to the maximum dose of diphenoxylate.[3] Patients were treated with continuous octreotide infusion 50 to 150 µg/h, and complete resolution of diarrhea was seen in 94% of patients.[3]

Cascinu et al conducted a randomized comparison of subcutaneous octreotide to loperamide in patients having grade 3 diarrhea secondary to therapy with 5-FU.[4] Complete resolution of diarrhea occurred in 90% of patients who received octreotide compared with 15% of patients who received loperamide.[4] Gebbia et al also showed 80% complete response of 5-FU-induced grade 3 diarrhea in patients treated with octreotide compared with 30% response in the loperamide arm.[5] Octreotide has also been shown to be effective in controlling severe radiation-induced diarrhea not responding to loperamide.[6] In a randomized study of octreotide vs diphenoxylate for patients receiving pelvic radiation, octreotide was found to be significantly more effective in controlling diarrhea.[7] Conventional antidiarrheal agents fail to prevent the onset of grade 3/4 diarrhea.

The role of octreotide in the prevention of grade 3 diarrhea has not been studied in patients receiving radiation therapy. Currently we are developing a randomized, placebo-controlled, phase III...
study through the Radiation Therapy Oncology Group (RTOG) using octreotide LAR depot for prevention or reduction in the incidence of severe diarrhea in patients receiving combined chemoradiotherapy for rectal/anal cancer. In this study, patients will be given a test dose of subcutaneous octreotide and then randomized to receive either octreotide LAR depot 30 mg (arm 1) or placebo (arm 2). The first dose will be given within 7 days of initiation of radiotherapy. The second dose will be given on day 22 of radiotherapy concurrent with chemotherapy. All patients will receive a minimum of 5,000 cGy to the pelvis, using a field size greater than 10 × 10 cm. Radiotherapy will be given once a day. Diarrhea will be graded weekly using the NCI Common Toxicity Criteria score during the course of therapy and every 3 months during follow-up for 12 months. The primary objective of the study is to show a 50% reduction in the incidence of grade 3 diarrhea using octreotide LAR depot. We anticipate that octreotide LAR depot will be cost-effective in terms of antidiarrheal medication use and hospitalizations secondary to complications of diarrhea. Use of octreotide LAR depot might reduce treatment delays and interruptions secondary to diarrhea. Tools for assessment of diarrhea and change in quality of life of patients treated with octreotide LAR depot will also be validated.

The North Central Cancer Treatment Group is currently conducting a study using octreotide LAR depot for the prevention of acute diarrhea in patients receiving pelvic radiation for rectal, prostate, and gynecologic cancers. This is a study to assess the role of long-acting somatostatin analogs in radiation-induced diarrhea, even though the use of 5-FU is allowed. The dose of octreotide LAR depot is lower (20 mg) then in the planned RTOG trial. The study will evaluate the role of octreotide LAR depot in reducing acute as well as late bowel dysfunction from pelvic radiotherapy. The above studies will provide useful information regarding the role of octreotide LAR depot in the prevention and treatment of radiation enteritis associated with pelvic radiotherapy alone or in conjunction with chemotherapy.

References:


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