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N08C9 (Alliance): A Phase 3 Randomized Study of Sulfasalazine vs Placebo in the Prevention of Acute Diarrhea in Patients Receiving Pelvic Radiation Therapy

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Abstract

Purpose/Objectives—To provide confirmatory evidence in use of sulfasalazine to reduce enteritis during pelvic radiotherapy (RT), following 2 prior single-institution trials suggestive that benefit existed.

Methods and Materials—A multi-institution, randomized, double-blind, placebo-controlled phase 3 trial was designed to assess the efficacy of sulfasalazine vs placebo in treatment of RT-related enteritis during RT including the posterior pelvis 45.0–53.0 Gy) and conducted through a multi-center national cooperative research alliance. Patients received 1,000 mg sulfasalazine or placebo orally twice daily during and for 4 weeks after RT. Primary end point was maximal severity of diarrhea (Common Terminology Criteria for Adverse Events version 4.0). Toxicity and bowel function were assessed by providers through self-administered bowel function questionnaire taken weekly during RT and for 6 weeks afterward.

Results—Eighty-seven patients were enrolled in the trial between April 29, 2011, and May 13, 2013, with evenly distributed baseline factors. At the time of a planned interim toxicity analysis, more patients with diarrhea grade 3 received sulfasalazine than received placebo (29% vs. 11%;

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$P=.04$). A futility analysis showed that trial continuation would be unlikely to yield a positive result, and a research board recommended halting study treatment. Final analysis of the primary end point showed no significant difference in maximum diarrhea severity between sulfasalazine and placebo arms ($P=.41$).

Conclusions—Sulfasalazine does not reduce enteritis during pelvic RT and may be associated with higher risk of adverse events than placebo. This trial illustrates the importance of confirmatory Phase 3 trials in the evaluation of symptom control agents.

Keywords

chemotherapy; diarrhea; enteritis; radiation therapy

Introduction

Acute diarrhea is an important problem in patients undergoing pelvic radiation therapy (RT). Pelvic RT is used in various clinical settings as either adjuvant or primary treatment of patients with gastrointestinal (GI), gynecologic, and genitourinary cancers, and other tumors. Radiation proctitis and enteritis, manifested primarily with increased stool frequency, represent the major forms of acute toxicity for these patients. Despite advances in treatment delivery and image guidance, enteritis during chemoradiotherapy remains problematic (1).

Sulfasalazine has been investigated as an agent to prevent and treat RT-induced enteritis. Two clinical trials have shown a reduction in treatment-related enteritis during pelvic RT in patients receiving sulfasalazine in comparison to those receiving placebo (2,3).

On the basis of these clinical trials, experts have recommended that sulfasalazine be considered for routine clinical use in prevention of RT-induced diarrhea (4). The randomized phase 3 clinical trial presented herein was designed to provide confirmatory evidence of the efficacy and safety of sulfasalazine. The trial was multi-institutional (Appendix 1-withheld for anonymous review).

Methods and Materials

Participant Eligibility

Patients were eligible for participation if they were 18 years of age or older, had a diagnosis of cancer supporting use of pelvic RT, and were receiving a course of continuous definitive or adjuvant external beam RT to a minimum dose of 45.0 Gy with or without 5-fluorouracil, capecitabine, or oxaliplatin. Patients enrolling in the trial were required to receive a planned dose of 45.0 to 53.5 Gy to the pelvis that included at a minimum the posterior pelvis with conventional fractionation (1.7-2.1 Gy once daily). An additional boost was permitted to structures, such as the prostate or rectal tumor bed, depending on the clinical indication.

Exclusion criteria included metastases beyond pelvic lymph nodes; perineal scar irradiation; lack of a functioning rectum; allergy to sulfasalazine, sulfa drugs, or salicylates; history of any severe bowel disease; grade 3 GI toxicity present before enrollment; chemotherapy

other than that listed in the eligibility criteria; split-course RT; brachytherapy delivered during the course of RT; G6PD deficiency; digoxin use; pregnancy; prior pelvic RT; severe asthma; and hepatic or renal disease showing creatinine or aspartate aminotransferase value greater than 1.5 upper normal limits. Written informed consent was required before enrollment.

Randomization, Treatment, and Assessment

Randomization was performed through the Clinical Trials Support Unit with stratification. in accordance with history of anterior resection of the rectum, total planned RT dose including boost doses (45.0-53.5 Gy vs >53.5 Gy) and concurrent use of radiosensitizing chemotherapy. Radiotherapy technique and normal tissue constraints were not specified. Detailed information on radiotherapy technique and dose-volume limits in normal tissue were not recorded as part of the study. Patients were assigned to either sulfasalazine (arm 1) or placebo (arm 2) in a 1:1 ratio with an algorithm used routinely in clinical trials of the research alliance on the basis of the Pocock and Simon dynamic allocation method. (5).

Arm 1 patients received sulfasalazine 1,000 mg orally twice daily during RT and for 4 weeks afterward. Arm 2 patients received placebo orally twice daily and during RT for 4 weeks afterward. The identity of the study agents were masked to patients and medical providers before dispensing from the site pharmacy. Study treatment was required to begin before the third fraction of RT (Appendix 2).

The maximum severity of diarrhea and the duration of maximum severity of diarrhea, rectal bleeding, abdominal cramping, and constipation were graded according to the CTCAE version 4.0 and for tenesmus (Appendix 3.) each week during RT—and for 6 weeks following RT—by a health care provider. Additionally, whether or not the toxicity was attributable to the study agent, treatment, or other cause was recorded. Bowel function was assessed through a patient self-administered bowel function questionnaire (6) in a quality-of-life booklet filled out by the patient weekly during RT, for 6 weeks following RT completion, and at 12 and 24 months after RT completion. The 12 and 24 months measures will be reported at a later date. Symptomatic treatment of diarrhea was permitted with diet modification and medication, although prescription of sulfasalazine was not permitted. No specific dietary instructions were given to patients.

Statistical Analysis

It was hypothesized that use of sulfasalazine would reduce radiation related enteritis by 1 grade of the CTCA version 4.0 scale in 2/3rds of the patients receiving the drug compared to patients not treated with the study drug. The primary end point was prespecified as the maximal severity of diarrhea toxicity for each patient with all CTCAE version 4.0 assessments during the RT course and for 6 weeks following RT. A 2-sided .05-level Wilcoxon rank sum test was used to test the equality of the distributions of maximum diarrhea severity grades between treatment arms (7). Confidence intervals were constructed for the maximal severity of diarrhea toxicity for each trial arm. The estimated sample size (64 patients per group) provided 1) 99% power to detect an improvement in which diarrhea severity of each patient receiving sulfasalazine is 1 grade lower than it would have been if

the patient had received placebo and 2) 80% power to detect an improvement in which the diarrhea severity of 67% of the patients receiving sulfasalazine is 1 grade lower than it would have been if the patients received placebo. Further confirmatory analyses of these results were undertaken through use of analysis of variance and generalized estimating equations modeling the maximal severity of diarrhea toxicity as the dependent variable. Stratification factors, descriptive factors, and quality-of-life covariates were included in the modeling process.

Analytical procedures detailed for the primary end point were also applied to the secondary end points rectal bleeding, abdominal cramping, tenesmus, and constipation. Analysis of these secondary end points involved Wilcoxon procedures or χ^2 test at each time point, as well as repeated analysis of variance measures and generalized estimating equations modeling with data from all time points. Kaplan-Meier methodology and log-rank test were implemented for time-to-event secondary end points. All analyses were based on the study database frozen on December 17, 2013 (8). Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies.

Role of Funding Source

The trial was designed and conducted and the data were analyzed by the research alliance cooperative group, which is funded by the National Cancer Institute. Sulfasalazine delayed-release tablets were provided by Pfizer Inc. Additional funding for purchase of the placebo was provided by a representative US medical center. The final protocol, amendments, and informed consent documents were approved by local institutional review boards or independent ethics committees.

Results

Trial Participants—Between April 2011 and May 2013, the study enrolled 87 patients (Figure 1). Three patients were excluded from the analyses because of cancellations or protocol violations. Baseline patient characteristics of the study population were similar in the 2 treatment groups (Table 1).

Futility Analysis—In May 2013, a planned interim analysis of 73 patients showed an excess of grade 3 diarrhea toxicity in the sulfasalazine arm vs placebo (28.6% vs 11%; $P=.04$). Although not sufficient to halt the trial through a priori stopping rules, the results raised the possibility that continuing the trial would be futile. A futility analysis showed that even when all future toxicity occurred in the placebo arm, the primary analysis would still provide a nonsignificant P value of .16. For this reason, the research board recommended halting study treatment on May 13, 2013.

Primary Outcome—Toxicity data were available in 84 patients during RT and in 54 patients in the 6 weeks following RT. Wilcoxon rank sum test showed no significant difference between the distribution of maximum diarrhea severity grades between the sulfasalazine arm and the placebo arm ($P=.41$) (Table 2). Ordinal logistic regression

modeling of the maximal severity of diarrhea toxicity confirmed that the sulfasalazine arm had non-significantly increased acute diarrhea in patients receiving pelvic RT (odds ratio=1.35, $P=.46$).

Other Outcomes—The maximum severity and the duration of maximum severity of diarrhea, rectal bleeding, abdominal cramping, and constipation were graded and attributed by a health care provider according to the CTCAE version 4.0 and for tenesmus in accordance with the predefined non-CTCAE grading scale on each week during RT and for 6 weeks following RT. No significant differences were observed in the maximum severity of the listed toxicities before, during, and after RT, except abdominal pain occurring after completion of RT in patients receiving sulfasalazine ($P=.02$) (Table 3). In addition, no significant differences were observed in the duration of maximum severity of the listed toxicities.

No significant differences were observed in the area under the curve summary statistic calculated by combining the individual severity of diarrhea toxicity as measured with the CTCAE version 4.0 during the RT course and for 6 weeks following RT (Supplemental Table 1). No significant differences were observed in the average score for each outcome variable during RT and after RT. No significant differences were observed in the percentage of patients who experienced each outcome variable during RT and for 6 weeks following RT. No significant differences were observed between arms in scores from the Patient Bowel Function Questionnaire during RT and for six weeks after RT.

More patients receiving sulfasalazine required antidiarrheal medications than patients receiving placebo (49% vs 29%; $P=.06$). More patients discontinued sulfasalazine because of bowel toxicity or refusal to continue the medication than discontinued placebo (40% vs 13%; $P=.02$) (Supplemental Table 2).

Discussion

This randomized controlled trial of sulfasalazine vs placebo to reduce enteritis during pelvic RT, with or without concurrent chemotherapy, failed to show a benefit to sulfasalazine use as a prophylactic agent, despite prior evidence suggestive of a benefit. In addition, there was no reduction in secondary toxicities, such as tenesmus, abdominal pain, constipation, maximum grade of diarrhea, or GI hemorrhage, during RT or in the 6 weeks after RT. More patients receiving sulfasalazine had abdominal pain and stopped the medication prematurely in comparison with the placebo.

Although antidiarrheal agents are commonly used with some efficacy in the treatment of this problem, some patients have severe diarrhea despite the medications. Moreover, these agents cannot be used as prophylaxis to prevent radiation-induced diarrhea because of their tendency to cause constipation. A medical regimen capable of preventing or reducing symptoms of acute RT-induced proctitis and enteritis would be useful for patients with a broad range of pelvic cancers for which pelvic RT has a role. Previous trials of prophylactic use of putative antidiarrheals—such as olsalazine, sucralfate, glutamine, and octreotide—

during pelvic RT in the North Central Cancer Treatment Group have not shown a clinical benefit (9-12).

Sulfasalazine was introduced in 1938 as an anti-inflammatory agent for treatment of rheumatoid arthritis (13). It subsequently has been used for treatment of inflammatory bowel disease, psoriasis, and seronegative arthropathies. It has immunosuppressant and immunomodulatory properties, suppressing interleukin production and leukocyte activity. Sulfasalazine has been approved in the United States for treatment of juvenile rheumatoid arthritis (polyarticular course), rheumatoid arthritis, Crohn disease, and ulcerative colitis. Despite the varying underlying pathologic factors associated with rheumatoid arthritis, Crohn disease, and ulcerative colitis, sulfasalazine has been effective in treating these conditions through its action in the clinical setting of chronic inflammation (14-18).

Sulfasalazine has been investigated as an agent to prevent and treat RT-induced enteritis. In 1972, Rauch and Weiland (19), used sulfasalazine in a small, single-arm trial that showed a suggestion of benefit in reducing RT-related enteritis. A more recent randomized clinical trial from Turkey assessed the effectiveness of sulfasalazine for prevention of diarrhea caused by pelvic RT and reported positive results (2,20). Eighty-seven patients receiving pelvic RT were randomly assigned to receive either placebo or 1,000 mg of sulfasalazine twice daily. A statistically significant decrease in the rate of all grades of diarrhea was noted between the groups receiving placebo (86%) and sulfasalazine (55%) ($P=.001$), with CTCAE version 2.0 criteria. Diarrhea of grades 2 to 4 was seen more frequently in the placebo group than the sulfasalazine group (49% vs 27%; $P=.038$). Using the Late Effects of Normal Tissues–Subjective, Objective, Management, and Analytic scale, a statistically significant difference was noted in the maximum grade of diarrhea beginning at week 2 of irradiation and continuing until irradiation was complete. No significant serious adverse events were reported in the study (2,20). A more recent study from India replicated these results in a study of 98 patients receiving pelvic RT for cervical cancer (3). Patients receiving sulfasalazine had only 19% CTCAE version 4.0 grade 2 diarrhea compared with 42% of patients receiving placebo.

On the basis of these data, experts have recommended sulfasalazine for off-label treatment of RT-induced enteritis in the mucositis study section of the Multinational Association of Supportive Care in Cancer (4,21). However, the results of our study contradict this recommendation and show that use of sulfasalazine as a prophylactic agent during pelvic RT will not reduce and may actually worsen acute GI toxicity.

Given the present study's early closure, its interpretation should be limited to the conclusion that sulfasalazine is not superior to placebo in reducing the maximal grade of enteritis during pelvic RT. Patient diet was not controlled during the study and potentially could have affected the outcome. Additionally, the types of cancer included were diverse, although the majority were rectal cancers. Stratification was not performed for type and timing of surgery, nor for type of chemotherapy, both potential confounding factors. Radiotherapy treatment data was not prospectively collected, also, and conceivably could have impacted the rates of enteritis if an imbalance was present between arms. Approximately one-third of patients did not return toxicity data in the 6 weeks after completion of RT. In addition, the study was

halted at approximately one-half of its planned accrual, thereby introducing the possibility that other unrecognized imbalances may have occurred between the patient populations in the 2 arms. Additionally, patients could begin the study drug up until the third day of radiotherapy, raising the possibility that a lack of effect could be related to alterations in the NF- κ B pathway and production of proinflammatory cytokines occurring before the study agent could provide a radioprotective effect. Despite these limitations, a futility analysis showed that, with nearly complete certainty, the study could not have shown a benefit for sulfasalazine.

Our trial was not designed to examine the etiology of the increased diarrhea toxicity found in the sulfasalazine arm, which was unexpected. Inflammatory bowel and acute radiation enteritis share a common symptomatic end point in injury at an organ level, but likely have differing underlying mechanisms at a cellular and cytokine level producing those effects. Sulfasalazine has known gastrointestinal side effects in patient not receiving radiotherapy such as nausea and mucositis. Potentially, radiotherapy and/or chemotherapy acts in a manner yet to be determined to potentiate this effect when used prophylactically during radiotherapy. (22) Additionally, this trial was designed as a pragmatic trial, meant to reflect the continuum of treatment techniques, radiotherapy doses and volumes, and varying chemotherapy regimens used in community cancer centers. It has the strength of modelling how the use of sulfasalazine in general clinical practice might change outcomes, but has the weakness of not providing detailed information on normal tissue dose volume histograms (DVH) and might allow imbalances in treatment and patient characteristics in between arms. The lack of DVH data and detailed information on the chemotherapy regimens utilized create limitations in interpreting this study.

In summary, sulfasalazine should not be considered for prophylactic use to reduce the GI toxicity of pelvic RT. Its inclusion in clinical guidelines should be reconsidered. There is little high level evidence available to support agents currently available for enteritis prophylaxis. Probiotic preparations are actively being studied after initial studies have suggested that they may reduce symptoms from enteritis during pelvic radiotherapy. (23)

The present study also illustrates the critical importance of randomized controlled trials in evaluating the use of new interventions in clinical practice. Despite promising single-institution results, a rigorous multi-institutional, blinded comparison in a randomized controlled manner failed to confirm the earlier suggestions of benefit. These results illustrate the potential pitfalls inherent in determining the relative benefit of new interventions where evidence from multi-institutional phase 3 trials is lacking. The variance between the findings of the prior randomized trials and the negative results of our own trial are consistent with the typical outcome of a symptom control agent's evaluation under increasingly rigorous conditions. Agents found to be promising in single institution trials subsequently are shown to have little to no benefit when tested in a multi-institutional trial setting with sophisticated statistical and regulatory oversight. (10, 12)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CTCAE	Common Terminology Criteria for Adverse Events
GI	gastrointestinal
RT	radiation therapy, radiotherapy

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Short Summary

A multi-institution, randomized, double-blind, placebo-controlled phase 3 trial was performed to assess the efficacy of sulfasalazine vs placebo in preventing enteritis during pelvic radiotherapy. More patients with diarrhea grade 3 received sulfasalazine than received placebo (29% vs 11%; $P=.04$), and the trial was halted. Sulfasalazine does not reduce enteritis during pelvic radiotherapy and may be associated with a higher risk of adverse events than placebo.

Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. *Abbreviation:* AE = adverse event.

Table 1

Baseline Patient Characteristics

Characteristic	Study Participants ^a			P Value
	Placebo Arm (n=42)	Treatment Arm (n=42)	Total (N=84)	
Age, median (range), y	56.5 (37.0-81.0)	59.0 (37.0-84.0)	58.0 (37.0-84.0)	.32 ^b
Race/ethnicity				.61 ^c
White	37 (88)	32 (77)	69 (82)	
Black or African American	3 (7)	6 (14)	9 (11)	
Asian	1 (2)	2 (5)	3 (4)	
American Indian or Alaska Native	1 (2)	1 (2)	2 (2)	
Unknown or patient unsure	0 (0)	1 (2)	1 (1)	
Sex				.50 ^c
Female	18 (43)	15 (36)	33 (39)	
Male	24 (57)	27 (64)	51 (61)	
History of rectum resection				.65 ^c
Yes	3 (7)	2 (5)	5 (6)	
No	39 (93)	40 (95)	79 (94)	
Total cumulative dose, cGy				.80 ^c
4,500-5,350	31 (74)	32 (76)	63 (75)	
>5,350	11 (26)	10 (24)	21 (25)	
Concurrent chemotherapy				.65 ^c
Yes	25 (60)	27 (64)	52 (62)	
No	17 (41)	15 (36)	32 (38)	
Tumor type ^d				
Anal margin	1(2.4)	0(0.00)	1 (1)	
Colon/rectal	23(54.7)	27(64.3)	50 (60)	
Endometrial	6(14.2)	5(10.9)	11 (13)	
Other	1(2.4)	0(0.00)	1 (1)	
Ovarian	1(2.4)	1(2.4)	2 (2)	
Pelvic	1(2.4)	0(0.00)	1 (1)	
Prostate	6(14.2)	9(20.4)	15 (18)	
Uterus	2(4.8)	0(0.00)	2 (2)	
Vaginal vault	1(2.4)	0(0.00)	1 (1)	

^aValues are presented as number (percentage) of patients unless specified otherwise.

^dTumor type provided for total participant cohort.

Table 2

Final Analysis of the Primary End Point for Maximum-Grade Diarrhea

Grade	Placebo Arm (n=42)	Treatment Arm (n=42)	Total (N=84)	P Value (Wilcoxon Rank Sum)
0	10 (24)	10 (24)	20 (24)	.41
1	15 (36)	13 (31)	28 (33)	
2	13 (31)	8 (19)	21 (25)	
3	4 (10)	10 (24)	14 (17)	
4	0 (0)	1 (2)	1 (1)	

Table 3

Maximum Grade of Toxicities

Toxicity Grade	During RT, No. (%)		<i>P</i> Value ^a	After RT, No. (%)		<i>P</i> Value ^a
	Placebo Arm (n=42)	Treatment Arm (n=42)		Placebo Arm (n=29)	Treatment Arm (n=25) [^]	
Tenesmus			.23 ^a			.64 ^a
0	30 (71)	27 (64)		21 (72)	18 (78)	
1	9 (21)	6 (14)		7 (24)	5 (22)	
2	3 (7)	7 (17)		1 (3)	0 (0)	
3	0 (0)	2 (5)				
Abdominal pain			.30 ^a			.02 ^a
0	26 (62)	22 (52)		24 (83)	17 (68)	
1	12 (29)	14 (33)		2 (7)	8 (32)	
2	4 (10)	3 (7)		3 (10)	0 (0)	
3	0 (0)	3 (7)				
Constipation			.70 ^a			.63 ^a
0	27 (64)	26 (62)		22 (76)	19 (76)	
1	13 (31)	12 (29)		6 (21)	6 (24)	
2	2 (5)	4 (10)		1 (3)	0 (0)	
Diarrhea			.44 ^a			.48 ^a
0	11 (26)	10 (24)		14 (48)	11 (44)	
1	14 (33)	13 (31)		10 (35)	12 (48)	
2	13 (31)	9 (21)		3 (10)	2 (8)	
3	4 (10)	9 (21)		2 (7)	0 (0)	
4	0 (0)	1 (2)				
Rectal bleeding			.38			.15 ^a
0	22 (52)	26 (62)		27 (93)	20 (80)	
1	20 (48)	16 (38)		2 (7)	5 (20)	

Abbreviation: RT, radiation treatment.

^a χ^2 test.[^] Data incomplete on two patients