Randomized Trial of Omeprazole or Ranitidine Versus Placebo in the Prevention of Chemotherapy-Induced Gastroduodenal Injury

By Sergio Sartori, Lucio Trevisani, Ingrid Nielsen, Davide Tassinari, Ilaria Panzini, and Vincenzo Abbasciano

Purpose: **Anticancer drugs may induce acute mucosal injury to stomach and duodenum. This study was planned to evaluate the efficacy of omeprazole or ranitidine in preventing such an injury.**

Patients and Methods: **Two hundred twenty-eight cancer patients with normal stomach and duodenum or with less than three erosions, who were selected to be treated with cyclophosphamide, methotrexate, and fluorouracil (90 breast carcinoma patients) or fluorouracil alone (138 colon carcinoma patients), were randomly assigned to treatment with omeprazole 20 mg, ranitidine 300 mg, or one placebo tablet a day. Seven days after the second course of chemotherapy (CT), the patients underwent a further esophagogastroduodenoscopy to evaluate the mucosal injury. Endoscopic findings were quantified on the basis of an arbitrary score, and the occurrence of epigastric pain or heartburn was assessed weekly.**

Results: **A significant difference was found among the three groups ($P = .0032$), as well as between pre- and postCT endoscopic findings ($P = .00001$). Endoscopic scores after CT were significantly higher than pretreatment scores in the placebo ($P = .003$) and ranitidine ($P = .003$) groups but not in the omeprazole group ($P = .354$). Acute ulcers were significantly less frequent in patients receiving omeprazole or ranitidine than in those receiving placebo ($P = .0001$ and $P = .0315$, respectively). Epigastric pain and/or heartburn were significantly less frequent in patients receiving omeprazole ($P = .00124$) or ranitidine ($P = .038$) than in those receiving placebo.**

Conclusion: **Omeprazole is effective in preventing chemotherapy-induced gastroduodenal injury. Ranitidine is effective in reducing the frequency of ulcers and upper gastrointestinal symptoms but is not effective in preventing the global endoscopic worsening caused by chemotherapy. The different efficacy of omeprazole and ranitidine can be explained by their different pharmacodynamics.**

J Clin Oncol 18:463-467.

ANTINEOPLASTIC chemotherapy (CT) can frequently induce damage to upper gastrointestinal (GI) tract mucosa.[1-4] Although the injury is often self-limiting, and its clinical relevance has been questioned,[4] life-threatening complications can sometimes occur.[1,5-7] Moreover, upper GI symptoms after CT are significantly more frequent in patients with CT-induced ulcers or erosions[8,9] and can impose the temporary discontinuation of the anticancer treatment.[10]

The prevention of CT-induced gastroduodenal injury has been scarcely investigated in the past years, and most studies were not well-designed or gave disappointing results.[11-13] More recently, in a placebo-controlled pilot study, we showed that omeprazole is effective in preventing the CT-induced damage to the upper GI tract, whereas misoprostol, a prostaglandin analogue, is not.[9] In another controlled study, famotidine was also reported to have a good prophylactic efficacy.[8] The present study was planned to compare the efficacy of two classes of inhibitors of gastric acid secretion (the proton pump inhibitor omeprazole and the H2-blocker ranitidine) in the prevention of CT-induced gastroduodenal mucosal injury.

PATIENTS AND METHODS

Patients Selection

The study was designed and carried out according to the principles of the Declaration of Helsinki and approved by our local ethical committee. Patients signed an informed consent before participating in the study. Patient selection consisted of two phases. In the former phase, 300 patients with breast or colon carcinoma, selected to be treated with cyclophosphamide, methotrexate, and fluorouracil (CMF) (breast carcinoma patients) or fluorouracil alone (5-FU) (colon carcinoma patients), were screened on the basis of the following eligibility criteria: no previous administration of other anticancer drugs; absence of upper GI symptoms (epigastric pain, heartburn, and vomiting); absence of symptoms or diseases requiring administration of corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs); absence of brain metastases; absence of clinical, biochemical, and instrumental evidence of liver cirrhosis or other causes of portal hypertension; no administration of antibiotics or antisecretory drugs in the last 2 months; a performance status of at least 2 (according to the Eastern Cooperative Oncology Group World Health Organization Classification[14]; and absence of contraindications to esophagogastroduodenoscopy (EGDS).

In the second phase of patient selection, the 300 patients formerly selected underwent EGDS 1 week before starting CT. Only those with

From the Divisione di Medicina Interna e Oncologia Medica, Azienda Ospedaliera S Anna; Istituto di Medicina Interna II, Università di Ferrara, Ferrara; and Servizio di Oncologia, Ospedale Civile, Rimini, Italy.

Submitted March 15, 1999; accepted August 30, 1999.

Address reprint requests to Sergio Sartori, MD, II Divisione Medica, Azienda Ospedaliera S Anna, corso Giovecca 203, I-44100 Ferrara, Italy; email srs@unife.it.

0732-183X/00/1803-463

Table 1. Endoscopic Score

Grade	Description
0	No visible lesion
1	Less than 3 erosions
2	3-15 erosions
3	More than 15 erosions or ulcer with a greatest dimension of <2 cm
4	Giant ulcer (>2 cm) or multiple ulcers with cumulative diameter >2 cm

normal endoscopic appearance or less than three *Helicobacter pylori*–negative erosions and without endoscopic evidence of esophageal or gastric varices were definitively admitted to the study. *Helicobacter pylori* status was assessed by rapid urease test, carried out on two biopsies taken from the gastric body and antrum and monitored for color change (from yellow to red) up to 24 hours. A total of 228 patients (89 men and 139 women, aged 34 to 65 years; 138 with colon cancer and 90 with breast cancer) fulfilled such a definitive criterion of eligibility and were entered onto the study.

Study Design

The 228 patients definitively enrolled onto the study were randomly assigned to prophylactic treatment with omeprazole 20 mg once a day, ranitidine 300 mg once a day, or one placebo tablet once a day. A stratified randomization by type of CT regimen was performed. The drugs were administered in their commercially available form; however, the patients were not told which drug they were receiving. Randomization was performed and medications were administered by a member of our department not participating in the study. All investigators were unaware of which drug each patient had received.

One week after EGDS and randomization, CT was started. Cyclophosphamide 600 mg/m^2 body surface area (bsa), methotrexate 40 mg/m^2 bsa, and 5-FU 600 mg/m^2 bsa were given intravenously on days 1 and 8 every 28 days to breast cancer patients. 5-FU 370 to 400 mg/m^2 bsa preceded by leucovorin 200 mg/m^2 bsa was given intravenously for 5 consecutive days every 28 days to colon cancer patients. Seven days after the second course of CT, EGDS was performed again. Prior studies have shown that mucosal damage is quite evident at this time.[1,2,9] Endoscopic findings were clustered into five categories, quantified according to the arbitrary score (Table 1) used in our prior study,[9] and obtained by modifying the combined endoscopic scoring system of Lanza et al.[15] Biopsies were performed only when gastric lesions were observed to exclude the presence of epithelial atypias. Both preliminary and postCT EGDS were carried out by the same endoscopist, who was unaware of the prophylactic treatment given to patients.

The patients were asked weekly about NSAIDs use and evaluated to assess the onset of epigastric pain or heartburn; vomiting was not considered because several different antiemetic drugs (with the exception of corticosteroids) were given during CT administration. If some patients needed to take NSAIDs during the period of observation, they discontinued the study and were considered in the final analysis according to the intent-to-treat principle. Finally, the number of cases that needed to postpone the next course of CT for at least 1 week because of upper GI troubles was recorded.

Statistical Analysis

Statistical analysis was performed under the intent-to-treat principle. Analysis of variance was performed to compare the three treatment arms before and after CT, adjusting for CT regimen and time. Pre- and postCT endoscopic findings observed in each arm were then compared by using paired Student's *t* test, adjusted for multiple comparisons by using the Bonferroni method.

The number of patients developing ulcers in the placebo group versus each active treatment; the frequency of postCT epigastric pain and heartburn in relation to the prophylactic treatment administered and in relation to the degree of gastroduodenal injury; and the number of cases in which CT had to be postponed because of upper GI troubles, were analyzed using Fisher's exact test.

RESULTS

Two hundred ten out of 228 patients who enrolled finished the study. Eighteen patients dropped out: six refused postCT EGDS (three in placebo, two in ranitidine, and one in omeprazole group); seven patients needed to take NSAIDs during the period of observation (three in placebo, two in ranitidine, and two in omeprazole group); and five patients discontinued CT after the first course for causes independent of upper GI toxicity (one in placebo, three in ranitidine, and one in omeprazole group). CT regimens and patients assigned to each prophylactic treatment are reported in Table 2.

A significant difference was observed among the three treatment groups ($P = .0032$), as well as between pre- and postCT endoscopic findings ($P = .00001$). Table 3 reports in detail the pre- and postCT endoscopic findings observed in the three groups. PostCT endoscopic score resulted significantly higher than pretreatment score in the placebo ($P = .003$) and ranitidine ($P = .003$) groups but not in the omeprazole group ($P = .354$).

The frequency of ulcers was significantly higher in patients receiving placebo (11 gastric and seven duodenal ulcers) than in those receiving ranitidine (five gastric and

Table 2. Chemotherapies and Composition of the 3 Treatment Arms

	No. of Patients					
Treatment Arm	CMF	Dropouts	5-FU	Dropouts	Total	Dropouts
Placebo	30	2	45	5	75	7
Ranitidine	30	2	47	5	77	7
Omeprazole	30	2	46	2	76	4
Total	90	6	138	12	228	18

162.129.220.240

Table 3. Endoscopic Findings Before and After CT*

	CMF (no. of patients)							5-FU (no. of patients)							Total (no. of patients)						
	PreCT Score		PostCT Score					PreCT Score		PostCT Score					PreCT Score		PostCT Score				
	0	1	0	1	2	3	4	0	1	0	1	2	3	4	0	1	0	1	2	3	4
Placebo	22	8	12	4	4	6	2	36	9	20	3	7	6	4	58	17	32	7	11	12	6
Dropout	1	1						3	2						4	3					
Ranitidine	24	6	17	2	5	3	1	40	7	27	4	7	2	2	64	13	44	6	12	5	3
Dropout	1	1						3	2						4	3					
Omeprazole	23	7	21	3	3	1	0	36	10	34	4	5	1	0	59	17	55	7	8	2	0
Dropout	1	1						1	1						2	2					

*Expressed as endoscopic scores.

three duodenal ulcers, $P = .0315$) or omeprazole (one gastric and one duodenal ulcer, $P = .0001$). Four bleeding lesions were observed in the placebo group (one erosive-hemorrhagic gastritis lesions and two gastric ulcers and one duodenal ulcer) and one in the ranitidine group (one duodenal ulcer). In all cases, bleeding was mild, and no blood transfusion was necessary.

Forty-eight patients suffered from epigastric pain or heartburn. Forty patients had postCT endoscopic worsening; eight patients did not ($P = .0001$). The symptoms were significantly more frequent in the placebo arm (24 cases) than in the ranitidine (13 cases, $P = .038$) and omeprazole arms (11 cases, $P = .00124$). Twenty-four of 28 patients with mucosal injury with an endoscopic score of 3 or 4 had symptoms versus 16 of 51 patients with injury with endoscopic score of 1 or 2 ($P = .0001$). CT was postponed for six patients in the placebo group, for two patients in the ranitidine group, and for no patients in the omeprazole group ($P = .036$ *v* placebo).

DISCUSSION

Unlike other GI side-effects caused by anticancer drugs, such as vomiting or diarrhea, poor attention is generally paid by oncologists to the CT-induced injury to upper GI mucosa. However, acute lesions of the esophagus,[16,17] stomach, and duodenum[1,2,18-20] are not infrequently observed. 5-FU, cytarabine, actinomycin D, vinca alkaloids, and methotrexate are commonly considered to be the most injurious agents,[1,21,22] and major complications can sometimes occur, in particular when dose-intensive treatments are administered[1,5,6,23] or concomitant factors concur to make the injury worse.[7,24] Recently, a study investigating patients undergoing high-dose CT and bone marrow transplantation questioned the clinical relevance of CT-induced gastroduodenal complications.[4] However, the conclusions of this study seem to be questionable in some degree. In fact, the prophylactic therapy with H2-blockers and sucralfate, given empirically to all patients, suggests that the study design paid some attention to the toxic effects of CT on upper GI mucosa. Moreover, overt (even though not disastrous) GI bleeding was observed in 7.4% of patients, despite such a prophylaxis. Many oncology units are in the habit of giving gastroprotective drugs on an empirical basis to patients undergoing anticancer treatments, but, in our opinion, the prevention of CT-induced gastroduodenal mucosal injury is worthy of being investigated in controlled trials. Recently, we showed that omeprazole is effective in preventing such an injury, whereas misoprostol was shown as not effective,[9] according to another report demonstrating that misoprostol is not useful in the prophylaxis of high-dose CT-induced mucositis.[25] Indeed, anticancer drugs seem to exert their toxic effects on the neck and foveolar epithelium of the body and fundus of the stomach, as well as on the surface epithelium of the antrum and duodenum, sparing the glandular compartment of the gastric body and fundus.[1] It follows that acid secretion is substantially preserved during CT administration,[8,9,26] whereas gastric mucosal barrier is impaired. In such a situation, the inhibition of acid secretion induced by omeprazole can counterbalance, at least in part, the imbalance between protective and aggressive factors induced by anticancer drugs.[9] In another study,[8] the H2-blocker famotidine was also reported to be effective in the prevention of CT-induced gastric mucosal injury, and the pH of the gastric juice was significantly higher in famotidine-treated patients than in placebo-treated patients, suggesting an important prophylactic role of the inhibition of acid secretion.

In the present study, we compared two drugs representative of the two main antisecretory classes, proton pump inhibitors and H2-blockers. The results confirm the prophylactic efficacy of omeprazole, although they appear partially unsatisfying in regard to ranitidine. Indeed, ranitidine was effective in reducing the frequency of acute ulcers and upper GI symptoms but, unlike omeprazole, failed in

preventing the global mucosal injury caused by CT. The possible difference in the efficacy of the two drugs can be explained by their pharmacodynamic characteristics. Omeprazole 20 mg has been shown to reduce intragastric acidity by 97% and to maintain gastric pH above 3 for 18 to 20 hours.[27-29] Conversely, the time spent above pH 3 is 8 to 10 hours after administration of ranitidine 300 mg, and intragastric acidity is reduced by only 57%.[27,28,30] The results of our study suggest that such a duration and degree of inhibition of acid secretion may be enough to protect the CT-injured gastroduodenal mucosa against the development of major lesions (ulcers), but the global prevention of the endoscopic worsening observed after CT administration is likely to need the stronger and longer antisecretory effect exerted by omeprazole. However, no dangerous or life-threatening complications were observed in our study, and both drugs were shown to be effective in significantly reducing the frequency of upper GI symptoms, making patients' quality of life and compliance better during CT administration, even though only omeprazole significantly prevented the need of postponing the next course of CT. Indeed, epigastric pain and heartburn were significantly more frequent in presence of mucosal injury scored as 3 or 4, and ranitidine was shown to be effective in preventing such an injury. Consequently, it might be supposed that ranitidine also would have been useful in limiting the temporary discontinuation of CT if a larger series of patients had been investigated.

In conclusion, our results do not allow the inference that the greater prophylactic efficacy of omeprazole can translate into clinical benefits actually more considerable than those of ranitidine. Further studies (investigating preferably dose-intensive anticancer regimens rather than standard doses) are needed to evaluate this issue, as well as the cost-effectiveness of the prevention of CT-induced gastroduodenal mucosal injury.

REFERENCES

1. Slavin RE, Dias MA, Saral R: Cytosine arabinoside induced gastrointestinal toxic alterations in sequential chemotherapeutic protocols: A clinical-pathological study of 33 patients. Cancer 42:1747-1759, 1978

2. Sartori S, Nielsen I, Maestri A, et al: Acute gastroduodenal mucosal injury after cisplatin plus etoposide chemotherapy. Oncology 48:356-361, 1991

3. Wang LS, Chi KH, Hu MH, et al: Management for patients with advanced T4 epidermoid carcinoma of the esophagus. J Surg Oncol 62:22-29, 1996

4. Kaur S, Cooper G, Fakult S, et al: Incidence and outcome of overt gastrointestinal bleeding in patients undergoing bone marrow transplantation. Dig Dis Sci 41:598-603, 1996

5. Van Schil PE, Brutel de la Riviere A, Knaepen PJ, et al: Second primary lung cancer after bronchial resection: Treatment and results in eleven patients. J Thorac Cardiovasc Surg 104:1451-1455, 1992

6. Naunhein KS, Petruska P, Roy TS, et al: Preoperative chemotherapy and radiotherapy for esophageal carcinoma. J Thorac Cardiovasc Surg 103:887-893, 1992

7. Liaw CC, Huang JS, Wang CM, et al: Spontaneous gastroduodenal perforation in patients with cancer receiving chemotherapy and steroids. Cancer 72:1382-1385, 1993

8. Mori K, Tominaga K, Yokoama K, et al: Efficacy of famotidine in patients with acute gastric mucosal injury after continuous infusion of cisplatin plus vindesine. J Cancer Res Clin Oncol 121:367-370, 1995

9. Sartori S, Trevisani L, Nielsen I, et al: Misoprostol and omeprazole in the prevention of chemotherapy induced acute gastroduodenal mucosal injury: A randomized, placebo-controlled pilot study. Cancer 78:1477-1482, 1996

10. Ogata Y, Shirouzu K, Akagi Y, et al: Hepatic arterial chemotherapy for liver metastases from colorectal cancer. Kurume Med J 43:41-47, 1996

11. Polloni A, Marchi S, Bellini M, et al: Use of antisecretory drugs for gastroprotection during antiblastic chemotherapy. Drugs Exp Clin Res 11:303-306, 1985

12. Mavligit GA, Faintuch J, Levin B, et al: Gastroduodenal mucosal injury during hepatic arterial infusion of chemotherapeutic agents: Lack of cytoprotection by prostaglandin E1 analogue. Gastroenterology 92:566-569, 1987

13. Jewell LD, Fields AL, Murray CJW: Erosive gastroduodenitis with marked atypia after hepatic arterial infusion chemotherapy. Am J Gastroenterol 80:421-424, 1985

14. Oken MM, Creech RH, Tormey DC: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

15. Lanza FL, Graham DY, Davis RE, et al: Endoscopic comparison of cimetidine and sucralfate for prevention of naproxen-induced acute gastroduodenal injury: Effect of scoring method. Dig Dis Sci 35:1494-1499, 1990

16. Sartori S, Nielsen I, Trevisani L, et al: Barrett esophagus after antineoplastic chemotherapy. Endoscopy 22:152, 1990 (letter)

17. Sartori S, Trevisani L, Nielsen I, et al: Barrett's esophagus after continuous 5-fluorouracil infusion: A case report. Gastrointest Cancer 2:163-165, 1997

18. Lubitz L, Ekert H: Reversible changes in duodenal mucosa associated with intensive chemotherapy followed by autologous marrow rescue. Lancet 2:532-533, 1979

19. Brinker H: Treatment of therapy-resistant acute myeloid leukemia with 7 and 8 cytostatics. Scand J Haematol 14:35-41, 1975

20. Suda K, Seki T, Kano Y, et al: Continuous 5-fluorouracil infusion causing acute gastric mucosal lesions. Endoscopy 25:426-427, 1993

21. Lewis JH: Gastrointestinal toxicity due to medicinal agents. Am J Gastroenterol 81:819-834, 1986

22. Mitchell EP: Gastrointestinal toxicity of chemotherapeutic agents. Semin Oncol 5:566-579, 1992

23. Lewkow L, Hooker J, Raab M, et al: Phase I–II study of dose-intensive mitoxantrone and cyclophosphamide with autologous bone-marrow transplantation in metastatic breast cancer. Proc Am Soc Clin Oncol 9:98 1990 (abstr 145)

24. Sheperd FA, Laskey J, Evans WK, et al: Cushing's syndrome associated with ectopic corticotropin production and small-cell lung cancer. J Clin Oncol 10:21-27, 1992

25. Duenas Gonzalez A, Sobrevilla Calvo P, Frias Mendivil M, et al: Misoprostol prophylaxis for high-dose chemotherapy-induced mucositis: A randomized double-blind study. Bone Marrow Transplant 17:809-812, 1996

26. Kakinuma S, Ohwada S: Gastric mucosal blood flow and gastric secretion following intravenous administration of 5-fluorouracil in anesthetized rats. Cancer Chemother Pharmacol 39:357-360, 1997

27. Lanzon-Miller S, Pounder RE, Hamilton MR: Twenty-four intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine or omeprazole. Aliment Pharmacol Ther 1:239-251, 1987

28. Olbe L, Cederberg C, Lind T, et al: Effect of omeprazole on gastric acid secretion and plasma gastrin. J Gastroenterol Hepatol 4:19-25, 1989 (suppl 2)

29. Chiverton SG, Hunt RH: Relationship between inhibition of acid secretion and healing of peptic ulcers. Scand J Gastroenterol 166:43-47, 1989 (suppl 1)

30. Savarino V, Mela GS, Zentilin P, et al: Duration of acid suppression in H2-antagonist nonresponders. Digestion 51:185-192, 1992