Misoprostol and Omeprazole in the Prevention of Chemotherapy-Induced Acute Gastroduodenal Mucosal Injury

A Randomized, Placebo-Controlled Pilot Study

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BACKGROUND. Chemotherapy (CT) may induce acute mucosal injury to the stomach and duodenum, but its prevention has been scarcely investigated.

METHODS. One hundred and eighty-two cancer patients with normal stomach and duodenum or having fewer than 3 erosions, selected to be treated with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) (77 breast carcinoma patients) or 5-fluorouracil (5-FU) (105 colon carcinoma patients), were randomly assigned to prophylactic treatment with misoprostol, 400 μg twice a day; omeprazole, 20 mg once a day; or placebo, 1 tablet twice a day. Seven days after the end of the second course of CT, all patients underwent control esophagogastroduodenoscopy. Endoscopic findings were quantified on the basis of an arbitrary score: 0 = normal; 1 = less than 3 erosions; 2 = 3–15 erosions; 3 = more than 15 erosions or ulcer; 4 = giant ulcer (greatest dimension of more than 2 cm) or multiple ulcers with cumulative greatest dimension exceeding 2 cm.

RESULTS. Mean score increased significantly in the placebo and misoprostol groups, either after CMF ($P < 0.001$ and $P < 0.05$, respectively) or after 5-FU ($P < 0.001$ for both), whereas it did not in the omeprazole group. Gastric and duodenal ulcers were significantly less frequent in patients receiving omeprazole than in those receiving placebo ($P < 0.05$ after both CMF and 5-FU). No significant difference was observed between placebo and misoprostol. Omeprazole was significantly more effective than placebo and misoprostol in reducing the frequency and degree of the endoscopic worsening, either after CMF or after 5-FU ($P < 0.05$ for both CT regimens). Epigastric pain and/or heartburn were significantly less frequent in patients receiving omeprazole than in those receiving placebo ($P < 0.01$) or misoprostol ($P < 0.001$).

CONCLUSIONS. The strong and prolonged inhibition of gastric acid production induced by omeprazole seems to be effective in preventing chemotherapy-induced gastroduodenal mucosal injury. Further trials are necessary to verify whether such a prevention of endoscopically observed injury can translate into prevention of clinically significant injury. ***Cancer* 1996; 78:1477–82.**

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Although clinically significant gastric or duodenal injury due to systemic chemotherapy (CT) is considered uncommon, life-threatening complications from ulcers induced by anticancer drugs can sometimes occur.[1–4] Recently, four gastroduodenal perforations with two deaths have been reported in four cases combining 5-fluo-

rouracil (5-FU) continuous infusion and cisplatin, with desamethaxone used as an antiemetic.[5]

It is known that antineoplastic drugs may cause severe damage to normal cells in organs with high cellular turnover. Because gastric, duodenal, and jejunal epithelium have a very high growth fraction,[6] the potential risk of CT-induced injury is high. Gastroduodenal damage ranging from changes in the gastric potential difference[7] to multiple mucosal erosions and/or ulcerations has been reported in patients undergoing various antineoplastic regimens.[8–13] 5-FU, cytosine arabinoside, actinomycin D, vinca alkaloids, and methotrexate are commonly considered to be the most injurious agents.[6,8,14] The evolutionary sequence of mucosal alterations generally follows three stages[8,14]: initial injury in the first 3 days, progressive injury over the next 7 days, and regeneration and repair starting a few days after the drug therapy is stopped.

Unlike the prevention of injury induced by nonsteroidal anti-inflammatory drugs (NSAIDs), the prophylaxis of CT-induced gastroduodenal injury has been scarcely investigated, with disappointing results. Two double-blind studies reported good efficacy of pirenzepine and ranitidine during various combination chemotherapies[15,16] but were not placebo controlled. A double-blind, placebo-controlled study performed on a very low number of patients reported that the prostaglandin (PG)-E1 analogue misoprostol is not effective in the prevention of gastroduodenal mucosal injury during hepatic arterial infusion of chemotherapeutic agents.[17] Another study showed good symptomatic relief of gastroduodenal symptoms in patients receiving cimetidine or sucralfate during hepatic arterial infusion CT, but it did not investigate the actual efficacy of the drugs in preventing mucosal injury.[18]

This randomized, placebo-controlled pilot study investigates the prophylactic efficacy of cytoprotection induced by misoprostol and inhibition of gastric acid secretion induced by omeprazole on the CT-induced acute gastroduodenal mucosal injury. Omeprazole was preferred to antacids and histamine$_2$ receptor blockers, as it is currently considered the most powerful inhibitor of gastric acid secretion.[19]

PATIENTS AND METHODS

Criteria for Entry

From January 1989 to June 1995, 300 patients with breast or colon carcinoma who were selected to be treated with chemotherapies consisting in cyclophosphamide, methotrexate, and 5-FU (CMF) (breast carcinoma patients) or 5-FU with or without folinic acid (colon carcinoma patients) were admitted to the study. All patients signed an informed consent form before participating in the study and fulfilled the following eligibility criteria.

1. No previous administration of other antineoplastic chemotherapeutic agents.
2. Absence of symptoms referable to upper gastrointestinal tract (epigastric pain, heartburn, vomiting).
3. Absence of symptoms or diseases requiring administration of steroids or NSAIDs.
4. Absence of brain metastases.
5. Absence of clinical, biochemical, and instrumental evidence of liver cirrhosis or other causes of portal hypertension.
6. A performance status of at least 2, according to the Eastern Cooperative Oncology Group World Health Organization classification.[20]
7. Absence of contraindications to esophagogastroduodenoscopy (EGDS).

Patients underwent EGDS 1 week before starting CT. Only those with normal endoscopic appearance or less than three *Helicobacter pylori*-negative gastric or duodenal erosions (assessed by histologic examination), and without endoscopic evidence of esophageal or gastric varices, were definitively admitted to the study. A total of 239 patients fulfilled such a definitive criterion of eligibility. Of these, 225 patients (86 men and 139 women, aged 37 to 66 years; 131 with colon carcinoma and 94 with breast carcinoma) agreed to continue the study.

Study Design

Patients were randomly assigned to treatment with omeprazole (20 mg once a day in the morning), misoprostol (400 μg twice a day), or placebo (1 tablet twice a day). Randomization regarded the two CT regimens separately and was performed using computer-generated randomization lists. The drugs were administered in their commercially available forms, and no effort was made to disguise the medication; however, the patients were not told which drugs they were receiving. If patients needed to take other drugs for concomitant diseases, they were enrolled into the study on the condition that these drugs were not gastrotoxic; thus, these patients could continue treatment. Randomization was performed, and medications were administered by a physician who was a member of our department but was not participating in the study. All investigators were unaware of which drug (placebo, misoprostol, or omeprazole) each patient had received and of the number of pills taken daily by each patient.

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 carcinoma patients. 5-FU (370 mg/m^2 bsa) preceded (72 patients) or not (59 patients) by folinic acid (200 mg/m^2 bsa) was given intravenously for 5 consecutive days every 28 days to colon carcinoma patients. Seven days after the end of the second course of CT, EGDS was performed again. Prior studies have showed that mucosal damage is quite evident, and erosions and ulcerations occur frequently at this time.[8,9,12]

Endoscopic findings were clustered into five categories and quantified according to an arbitrary score, obtained by modifying Lanza et al.'s combined endoscopic scoring system[21]: 0 = normal; 1 = less than 3 erosions; 2 = 3–15 erosions; 3 = more than 15 erosions or ulcer with a greatest dimension of less than 2 cm; 4 = giant ulcer (greatest dimension of more than 2 cm) or multiple ulcers with cumulative diameter exceeding 2 cm. Biopsies were performed only when gastric lesions were observed, to exclude the presence of epithelial atypias. Erosions and ulcers were defined as white-based mucosal breaks, the former being flat and the latter demonstrating unequivocal depth.[21] Either preliminary or control EGDS were performed by the same endoscopist, who was unaware of the prophylactic treatment given to patients.

The patients were asked weekly about NSAIDs use and were evaluated to assess the onset of upper gastrointestinal symptoms. Only epigastric pain and heartburn were taken into consideration; vomiting was not considered, as several different antiemetic drugs (with the exception of steroids) were given to the patients during CT administration. If some patients needed to take NSAIDs during the period of observation, they were excluded from the study.

Statistical Analysis

Pre- and post-CT findings, quantified on the basis of our arbitrary score, were compared in each treatment arm using Student's t test for paired data. Analysis of variance was done to compare the three treatment arms before and after CT.

The efficacy of the prophylactic treatments was then assessed on the basis of the frequency and degree of endoscopic worsening observed at control EGDS, either considering the two CT regimens separately or merging them into a global analysis. The patients were grouped into five categories from 0 (no worsening in the endoscopic score) to −4 (worsening of 4 points after CT). One-to-one comparisons were done for each active treatment against placebo, and for misoprostol against omeprazole, using chi-square test. Chi-square test was also used to compare the number of patients developing ulcers in the placebo group versus each active treatment, the frequency of post-CT epigastric pain and heartburn in relation to the prophylactic treatment administered, and in relation to the degree of gastroduodenal injury.

TABLE 1
Tumor Types and Composition of the Three Treatment Arms

Treatment arm	No. of patients	Breast carcinoma	Colon carcinoma
Placebo	63	27	36
Misoprostol	57	24	33
Omeprazole	62	26	36
Total	182	77	105

RESULTS

Forty-three patients dropped out of the study. Ten patients refused control EGDS. In eight patients, CT was stopped after the first course. In five patients (all in misoprostol treatment arm), intolerance to the prophylactic treatment (epigastric pain, diarrhea) occurred before CT administration, and the drug was withdrawn. Twenty patients needed to take NSAIDs during the period of observation. A total of 182 patients finished the study. Tumor types and patients assigned to each prophylactic treatment group are reported in Table 1.

Endoscopic score did not differ among the three treatment arms before CT administration, whereas a significant difference was observed either after CMF ($P < 0.01$) or after 5-FU ($P < 0.05$). Tables 2 and 3 show in detail the pre- and post-CT findings in each group of prophylactic treatment: mean score increased significantly in placebo and misoprostol groups, either after CMF ($P < 0.001$ and $P < 0.05$, respectively) or after 5-FU ($P < 0.001$ for both placebo and misoprostol), but not in omeprazole group. No significant differences in the score were observed in the three groups between patients treated with 5-FU alone and those treated with 5-FU plus folinic acid. The frequency of ulcers was significantly lower in patients receiving omeprazole (0 after CMF and one duodenal ulcer after 5-FU) than in those receiving placebo (four gastric and two duodenal ulcers after CMF, $P < 0.05$; four gastric and four duodenal ulcers after 5-FU, $P < 0.05$). No difference was observed between placebo and misoprostol patients (two gastric and two duodenal ulcers after CMF; three gastric and one duodenal ulcers after 5-FU). Three bleeding lesions developed in placebo group patients (one erosive-hemorrhagic gastritis, one gastric, and one duodenal ulcer) and two developed in misoprostol group patients (one erosive-hemorrhagic gastritis and one duodenal ul-

TABLE 2
Endoscopic Score, Mean Score, and Standard Deviation before and after Chemotherapy

	Pre-CMF endoscopic score			Post-CMF endoscopic score					
	0	1	Mean score (SD)	0	1	2	3	4	Mean score (SD)
Placebo	23	4	0.15 (0.35)	13	1	3	7	3	1.48[a] (1.58)
Misoprostol	18	6	0.25 (0.44)	15	0	2	5	2	1.13[b] (1.54)
Omeprazole	20	6	0.25 (0.43)	22	2	1	1	0	0.27 (0.72)
	Pre-5-FU endoscopic score			**Post-5-FU endoscopic score**					
	0	1	Mean score (SD)	0	1	2	3	4	Mean score (SD)
Placebo	30	6	0.17 (0.38)	18	3	4	7	4	1.33[a] (1.59)
Misoprostol	29	4	0.12 (0.33)	17	2	7	5	2	1.18[b] (1.38)
Omeprazole	29	7	0.19 (0.4)	27	4	2	2	1	0.5 (1.03)

CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; SD: standard deviation; 5-FU: 5-fluorouracil.
[a] $P < 0.001$ in comparison with prechemotherapy mean score.
[b] $P < 0.05$ in comparison with prechemotherapy mean score.

TABLE 3
Endoscopic Score

Grade	Description
0	No visible lesions
1	Less than 3 erosions
2	3–15 erosions
3	More than 15 erosions or ulcer with a greatest dimension of less than 2 cm
4	Giant ulcer (greatest dimension of more than 2 cm) or multiple ulcers with cumulative diameter exceeding 2 cm

cer). All these patients had mild melena; no therapeutic interventions or blood transfusions were necessary.

On the whole, post-CT endoscopic worsening was observed in 30, 25, and 12 patients in placebo, misoprostol, and omeprazole treatment arms, respectively. Omeprazole was significantly more effective than placebo in reducing the frequency and degree of the worsening, either after CMF or after 5-FU ($P < 0.05$ for both CT regimens). It was also more effective than misoprostol ($P < 0.05$ for both CT regimens). Merging the two CT regimens into a global analysis, the significance level was higher ($P < 0.001$ for omeprazole either vs. placebo or vs. misoprostol). No significant difference was observed between misoprostol and placebo patients. Table 4 reports these data in detail, grouping the patients into five classes of post-CT endoscopic worsening (from 0 [no worsening] to −4 [worsening of 4 points in the endoscopic score]).

Sixty-eight patients suffered from epigastric pain and/or heartburn. Forty-eight patients had post-CT endoscopic worsening, and 20 did not ($P < 0.001$). The symptoms were significantly less frequent in the omeprazole treatment arm (10 cases) than in the placebo (20 cases; $P < 0.01$) or misoprostol (32 cases; $P < 0.001$) arms. Thirty-two of 39 patients with mucosal injury scored as 3 or 4 had symptoms versus 16 of 31 with injury scored as 1 or 2 ($P < 0.05$).

DISCUSSION

These results confirm that antineoplastic drugs can cause mucosal damage to the stomach and duodenum and suggest that the frequency of upper gastrointestinal symptoms (epigastric pain or heartburn) may be related to the degree of damage. Although such an injury has been not shown by our study to be particularly important from a clinical point of view (five bleeding lesions with mild melena and no perforation), the percentage of acute lesions endoscopically observed in the placebo group is very high, similar to that reported in our recent work performed without any prophylactic treatment.[12] The choice of performing control EGDS 1 week after the second course of CT may have played a role in such findings, as gastroduodenal mucosa was examined during the stages of the initial and progressive injury, immediately after recovering from the toxic effect induced by the first course of CT.[8] Prior reports showed that mucosal damage is frequent at this time,[8,9,12] and it is likely that the percentage of lesions would be lower if

TABLE 4
Grades and Frequency of Postchemotherapy Worsening

	CMF					5-FU					Total				
	0	−1	−2	−3	−4	0	−1	−2	−3	−4	0	−1	−2	−3	−4
Placebo	13	2	3	8	1*	20	1	5	8	2	33	3	8	16	3
Misoprostol	15	0	4	4	1*	17	2	8	6	0	32	2	12	10	1
Omeprazole	22	3	0	1	0	28	4	1	3	0	50	7	1	4	0

CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; 5-FU: 5-fluorouracil; 0: no worsening; −1, −2, −3, −4: worsening of 1, 2, 3, 4 points in the endoscopic score.
Omeprazole vs. placebo: $P < 0.05$ for CMF and 5-FU; $P < 0.001$ for total. Omeprazole vs. misoprostol: $P < 0.05$ for CMF and 5-FU; $P < 0.001$ for total. Misoprostol vs. placebo: not significant.

the patients had undergone control EGDS earlier (when mucosal damage has not fully developed) or later (when repair mechanisms are already functioning).

To our knowledge, controlled trials concerning the prophylaxis of the acute gastroduodenal injury during systemic CT are lacking in the literature. The only two studies reporting good efficacy of ranitidine and pirenzepine were not placebo controlled. Moreover, in such studies, EGDS was performed on the day after the last administration of cytostatic drugs.[15,16] In our opinion, that is too early for observing the full CT-induced acute gastroduodenal injury.

Our findings suggest that Schwarz's dictum ("no acid, no ulcer") is valid concerning a peculiar field of peptic pathology, such as the acute mucosal injury caused by cytostatic drugs. Indeed, the strong and prolonged inhibition of gastric acid secretion induced by omeprazole was effective in preventing mucosal injury, significantly reducing the frequency and seriousness of mucosal lesions and related symptoms. However, cytoprotection exerted by misoprostol was not effective. Slavin et al,[8] examining patients who died 7 to 10 days after chemotherapeutic treatments including high doses of cytosine arabinoside, observed that cellular necrosis and epithelial depopulation involved the neck and foveolar epithelium of the body and fundus of the stomach, sparing the glandular compartment. In antral, duodenal, and jejunal mucosa, cellular necrosis and epithelial depopulation were present in both glands and surface lining. These findings suggest that the surface epithelium of the stomach and duodenum is damaged and the gastric mucosal barrier is impaired after CT, whereas acid production is spared, with imbalance between protective and aggressive factors. Indeed, we observed that 11 patients treated with cytostatic drugs without receiving antisecretory prophylaxis had gastric juice pH below 3 after stimulation with pentagastrin (unpublished data). If the damage induced by 5-FU and methotrexate has the same location as cytosine arabinoside, the different mechanisms of action of misoprostol and omeprazole can explain their different effectiveness. PG-E and their E1 analogue misoprostol have a weak, clinically unimportant inhibitory effect on acid production, whereas they exert several important protective effects on gastric mucosa.[22] According to their location with respect to the surface epithelial cells, the protective mechanisms of PG-E analogues can be described as preepithelial (mucus and bicarbonate secretion), epithelial (surface epithelial cell continuity and migration), and postepithelial (mucosal blood flow).[23] Since surface epithelial cells are killed and cellular renewal is blocked by antineoplastic drugs, it is likely that misoprostol cannot exert its protective preepithelial and epithelial effects: the aggressive action of hydrochloric acid is not counterbalanced and mucosal erosions and ulcers may develop. However, omeprazole strongly inhibits gastric acid secretion by altering the activity of the protonic pump (19): the imbalance between disruption of surface epithelium and integrity of glandular compartment is at least in part counterbalanced by the pharmacologic action of the drug, and mucosal erosions and ulcers develop less frequently.

It is known that most erosions and ulcers heal spontaneously 2 or 3 weeks after CT is stopped[8–10]; however, in some cases they may not heal, and complications may occur. Life-threatening bleeding and perforation have been reported by several authors.[1–5] In the current study, we observed symptomatic (although not life-threatening) bleeding in 4.7% and 3.5% of patients receiving placebo or misoprostol, respectively. Our pilot study suggests a good prophylactic effectiveness of omeprazole against the endoscopically documented gastroduodenal mucosal injury induced by CT. It also shows the efficacy of omeprazole in reducing the frequency of epigastric pain and heartburn, although it is not able to demonstrate a strong clinical usefulness of such a prevention. This could perhaps be due to the low number of patients enrolled or our choice of investigating the effects of CT regimens that are not particularly aggressive. However, we believe that our findings may jus-

tify the planning of wider, multicenter trials to verify whether the prevention of endoscopically observed injury can translate into prevention of clinically significant injury. Patients undergoing continuous infusion of anticancer drugs or dose-intensive chemotherapeutic treatments should be enrolled, as it is more likely that such regimens may cause clinically important gastroduodenal damage.

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