Phase I Trial of Sulindac plus 5-Fluorouracil and Levamisole: Potential Adjuvant Therapy for Colon Carcinoma

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ABSTRACT

Epidemiological studies indicate that nonsteroidal anti-inflammatory agents may reduce colorectal cancer incidence and mortality. Moreover, sulindac has been shown to attenuate the growth and progression of colonic neoplasms in an experimental model of colon carcinoma and in patients with familial adenomatous polyposis. To determine whether sulindac (300 mg/day) would increase toxicity associated with 5-fluorouracil (5-FU) and levamisole, 15 patients with advanced colorectal cancer were treated. Median treatment duration was 3 (range, 0.6–6.0) months, and median age was 56 years (33% $\geq$ 60 years). All patients had failed prior 5-FU-based therapy, had measurable disease, and were evaluable for toxicity. Grade III/IV granulocytopenia occurred in four patients; three patients had received prior pelvic irradiation resulting in a predisposition to myelosuppression. Two patients developed grade III anemia, and occult gastrointestinal bleeding was suspected in one. No other grade II or greater gastrointestinal or other nonhematological toxicity occurred. One patient had a partial response, 3 patients had disease stabilization, and 10 patients progressed on study. Our results indicate that sulindac does not significantly increase short-term toxicity associated with 5-FU and levamisole. To determine whether sulindac increases the efficacy of adjuvant chemotherapy, we propose a phase III randomized trial in patients with lymph node-positive colon cancer.

INTRODUCTION

Adjuvant chemotherapy with 5-FU[2] and levamisole was shown to significantly improve survival rates in patients with resected lymph node-positive (stage III) colon carcinomas (1). Attempts to improve on these results are being actively pursued. Epidemiological (2–7), clinical (8–12), and laboratory (13–19) studies indicate that NSAIDs, including sulindac, may reduce colorectal cancer incidence and mortality. Furthermore, an in-

verse association between aspirin intake and metastatic colorectal cancer has been reported, suggesting that aspirin may inhibit progression of established cancer (7). In patients with metastatic solid tumors including colon cancers, indomethacin was shown to significantly prolong mean survival compared to placebo (20). In support of these observations are several recent studies demonstrating that sulindac can significantly inhibit growth and attenuate progression of colorectal adenomas, precursor lesions of carcinomas, in patients with familial adenomatous polyposis (8–12). Additionally, in an experimental model of colon cancer, administration of sulindac during the postinitiation/progression phase of colon carcinogenesis significantly suppressed the incidence, size, and multiplicity of invasive and noninvasive colon adenocarcinomas (19). NSAIDs also inhibit growth of transplanted colon carcinomas in rodents (21–23) and decrease the growth and metastasis of murine mammary and lung carcinomas (24, 25). Moreover, in tumor-bearing mice given NSAIDs, increased survival following tumor excision was observed, especially when administered concurrently with cytotoxic drugs (26).

Neoplastic growth and metastatic potential are mediated by complex interactions between cytokines, growth factors, and potentially by prostaglandins as well. NSAIDs inhibit the cyclooxygenase pathway of arachidonic acid metabolism and thereby block PG production (27). Colon tumors contain and/or produce large quantities of PGs (27), and PG inhibition by sulindac and other NSAIDs is associated with an inhibition of colon tumorigenesis in rodents (19). NSAIDs also reverse PGE_2-mediated immune suppression of mitogenesis which is abnormally increased in colon cancer patients (28). Additionally, NSAIDs block natural killer cell-mediated cytotoxicity which limit vascular dissemination of cancer cells (24, 25, 27, 29, 30). Also inhibited by NSAIDs is the lipoxygenase metabolite 12-hydroxyeicosatetraenoic acid which promotes tumor cell adhesion and augments tumor metastasis (19, 31). NSAIDs inhibit platelet aggregation which has been shown to activate tumors cells for attachment to vascular endothelium, assist in the arrest of tumor cells in capillary beds, or provide an immunological shield for tumor cells (27). E series PGs are also angiogenic and tumor growth and metastases are angiogenesis dependent (32). Inhibition of cyclooxygenase and lipoxygenase metabolism in colon tumors may, therefore, have significant effects on cancer progression and clinical outcome.

Although the antitumor mechanism(s) of NSAIDs remain to be elucidated further, the aforementioned studies suggest that sulindac may enhance the effectiveness of adjuvant chemotherapy in eradicating micrometastatic disease. However, use of NSAIDs is associated with significant gastrointestinal side effects including an increased frequency of peptic ulcers and ulcer complications (33–36). Risk factors predisposing patients to NSAID-induced gastrointestinal toxicity include patient age, steroid use, previous peptic ulcer disease, and severe underlying illness or disability (34, 36). Additionally, a linear relationship

Table 1   Characteristics of study patients (*n* = 15)

Variable	Frequency (No. of patients)	%
Patient age (yr)		
30 or under	1	7
40–50	4	27
51–60	5	33
61–70	5	33
Site of primary		
Colon	7	47
Rectum	8	53
Disease stage (TNM)		
IV	15	100
Previous treatment (5-FU)	15	100

Table 3   Major toxic effects in patients who received sulindac plus 5-FU and levamisole for advanced colorectal cancer (*n* = 15)

Toxic effect	Grade[a, b]			
	I	II	III	IV
Granulocytopenia	3	0	1	3
Anemia	7	2	2	0
Thrombocytopenia	1	0	0	0
Indigestion	1	0	0	0
Nausea	4	0	0	0
Stomatitis	2	0	0	0
Diarrhea	1	0	0	0

[a] According to National Cancer Institute common toxicity criteria.
[b] Number of patients per grade.

Table 2   Schema for regimen of 5-FU + levamisole + sulindac

Agent	Dose	Route	Schedule
5-FU	450 mg/m^2	i.v. Push	Days 1–5, then once weekly beginning on day 29
Levamisole	50 mg three times daily (total daily dose 150 mg)	p.o.	Days 1–3 during first cycle of 5-FU, then repeated for 3 days on alternate weeks beginning on day 15
Sulindac	150 mg twice daily (Total daily dose 300 mg)	p.o.	Daily, to begin on day 1

has been found between the NSAID dose and gastrointestinal complications (34). Given that toxic reactions observed during treatment with fluoropyrimidines are predominantly due to their effects on rapidly dividing cells, including the gastrointestinal mucosa (36), our study was designed to determine whether sulindac increases the frequency of toxic effects associated with 5-FU and levamisole.

PATIENTS AND METHODS

Fifteen patients with measurable, advanced colorectal carcinoma were enrolled in a pilot study of sulindac plus 5-FU and levamisole; characteristics of these patients are listed in Table 1. All patients had failed at least one 5-FU-based regimen and had not received chemotherapy for at least 4 weeks prior to study entry. Our aim was to treat all patients for a minimum of 2 months. Systemic 5-FU (450 mg/m^2) and p.o. levamisole (Janssen Pharmaceutica, Titusville, NJ) were given in the same doses and schedules as used in the Intergroup (National Cancer Institute Cooperative Group Consortium) adjuvant trial (Ref. 1; Table 2). Sulindac (Schein Pharmaceuticals, Florham Park, NJ), 150 mg, was administered p.o. twice daily beginning on the first day of treatment. This dosage of sulindac was selected based on its demonstrated efficacy in inhibiting colorectal neoplastic growth in familial adenomatous polyposis patients (12). Patients received pretreatment and weekly serum chemistry tests, com-

plete blood counts with differential and platelet counts, as well as chest radiographs and computed tomographic scans which were obtained at study entry and again after 2 months of therapy. Patients were seen monthly in the outpatient clinic and pill counts were performed to assess compliance. Toxicity was graded according to the National Cancer Institute common toxicity criteria. Responding patients continued therapy until disease progression occurred. None of the patients received H2 receptor antagonists, sucralfate, or misoprostol. This study was approved by the MD Anderson Cancer Center Institutional Review Board.

RESULTS

Fourteen patients were evaluable for response, and toxicity data were available on all 15 patients (Table 3). The primary tumor site was the rectum in eight patients and the colon in seven patients (Table 1). There were 10 men and 5 women; median age of the patients was 56 (range, 35–70) years, and 33% of the patients were over 60 years old. All patients had a Zubrod performance status of 0 or 1 and had a serum creatinine and serum bilirubin <1.5 mg/dl. Furthermore, all patients had a negative stool guaiac at study entry, had not had a peptic ulcer in the previous year, and were not currently taking aspirin or other NSAIDs. Median number of months on study was 3 (range, 0.6–6.0) months.

Leukopenia was the principal toxic reaction that led to dose limitation or patient removal from the study. In this regard, severe (grade III/IV) granulocytopenia occurred in 4 (27%) of 15 patients, 2 of whom required hospitalization for neutropenic fever and were taken out of the study (Table 3). Leukopenia generally followed induction chemotherapy and was fully reversible in all cases. Three of these four patients had received prior pelvic irradiation, and this factor, particularly pelvic irradiation in addition to prior therapy, appears to have resulted in a predisposition to myelosuppression. Two patients developed grade III anemia, and one was taken off therapy due to suspected occult gastrointestinal bleeding. This patient complained of nausea without vomiting or abdominal pain, and denied that any gross gastrointestinal bleeding had occurred. The rapidity of the fall in this patient's hemoglobin suggested that if a gastrointestinal source was responsible, melena or hematochezia should manifest but none was observed.

Nonhematological toxicities were mild (grade I), and no grade II or greater toxic effects occurred. Mild nausea and/or vomiting were the most frequent gastrointestinal toxic effects and were experienced by 4 (27%) of 15 patients, followed by stomatitis in 2 patients, and diarrhea and indigestion in one patient each (Table 3). No significant perturbation of hepatic, renal, or electrolyte function was noted. Compliance was assessed by pill counts at the time of monthly clinic visits and was excellent. All toxic effects were reversible, and there were no chemotherapy-related deaths. A partial response was seen in 1 patient, 3 patients had disease stabilization, and 10 patients progressed while in the study. The one objective clinical response was maintained following 5 months of treatment, as indicated by a sustained reduction in the number and size of pulmonary metastases. This patient, however, elected to discontinue further treatment given that her disease was no longer measurable.

DISCUSSION

Evidence indicates that sulindac can prevent tumor progression in an experimental colon cancer model (18, 19) and in patients with familial polyposis (8–12). These results and studies demonstrating inhibition of tumor metastasis by NSAIDs provide the rationale for a study to evaluate sulindac to eradicate micrometastatic disease. Before examining sulindac as postoperative adjuvant therapy for colon cancer, we sought to determine whether the concurrent administration of sulindac with 5-FU and levamisole would increase the incidence or severity of toxic effects, particularly those involving the gastrointestinal tract. Given that fluoropyrimidines inhibit gastrointestinal mucosal proliferation (37) and as a consequence impair mucosal repair, we were concerned that 5-FU may potentiate the sulindac-related mucosal injury. Our results indicate that toxic effects involving the gastrointestinal tract were always mild in severity. Moreover, the frequency of gastrointestinal toxic effects observed in this study was decreased compared with that produced by 5-FU and levamisole in the Intergroup adjuvant colon cancer trial (1). One cannot exclude the possibility that our patients may have been more tolerant of gastrointestinal side effects given their advanced tumor stage and prior exposure to 5-FU-based chemotherapy. Nevertheless, the relatively low incidence of adverse gastrointestinal side effects indicates that sulindac (300 mg/day) does not significantly increase short-term gastrointestinal toxicity associated with 5-FU and levamisole. The duration of treatment in this study was limited by the rapid disease progression observed in many of the patients. However, extensive evaluation of sulindac in patients with arthritic conditions has shown that the incidence of adverse effects was most frequent within the first 42 days of treatment and did not increase with extended use of sulindac.[3] Therefore, we believe that our median treatment duration of 3 months was sufficient to assess the toxicity of this regimen.

Sulindac is a prodrug that is converted in the colon by bacterial microflora to its sulfone and sulfide metabolites (27).

Consistent with the fact that sulindac itself is not a cyclooxygenase inhibitor, endoscopic studies have shown that sulindac (300 mg/day) produces less gastric mucosal injury than several other NSAIDs, including aspirin, and is associated with fewer gastrointestinal symptoms than with aspirin (38, 39). However, the use of any NSAID is associated with an increased frequency of peptic ulcers and ulcer complications, including gastrointestinal bleeding (33–36). In a study of patients 65 years of age or older hospitalized for peptic ulcer disease, the relative risk of developing a peptic ulcer among users of sulindac (300 mg/day) was 4.2 (95% confidence interval, 2.8–6.3; Ref. 34). In our study, 33% of the patients were over the age of 60 years, which approximates the population receiving adjuvant chemotherapy for colon cancer.

Although none of our patients took H2 receptor antagonists or sucralfate, studies have failed to demonstrate a protective effect of these agents in the prevention of NSAID-related gastric ulcers. However, ranitidine can prevent NSAID-related duodenal ulcers (40–42). Controlled studies have shown that misoprostol produces a significant reduction in both gastric and duodenal ulcers in osteoarthritic patients taking NSAIDs on a continuous basis (43, 44). Given that misoprostol is a synthetic PGE_1 analogue, it has the potential, in theory, to interfere with the antitumor properties of NSAIDs. Furthermore, this agent produces diarrhea in a significant number of patients and may thereby exacerbate diarrhea seen in patients receiving 5-FU (43). Compared with ranitidine (300 mg/day), omeprazole (40 mg/day) has been shown to produce significantly better healing of gastric ulcers despite continued use of NSAIDs (45). However, the efficacy of omeprazole in preventing NSAID-induced ulcers awaits further study.

In this study, we observed an increased frequency of severe leukopenia (27%). Three patients received prior pelvic irradiation for rectal cancer, which may explain their predisposition to leukopenia. With the exception of these three cases, leukopenia was no more frequent in our study than in patients receiving 5-FU and levamisole in the Intergroup adjuvant trial (1). Anecdotal cases of agranulocytosis and aplastic anemia attributed to sulindac have been reported (46–48). In our study, however, cases of severe leukopenia generally followed induction chemotherapy. Moreover, two of the four patients experienced recovery of their leukocyte counts despite continuous sulindac therapy which excludes sulindac as the etiological agent of their leukopenia.

Our results suggest that the addition of sulindac to 5-FU plus levamisole does not result in a significant increase in short-term toxicity and that this regimen should be well tolerated. Sufficient data regarding the antitumor properties of sulindac exist to warrant its evaluation in combination with postoperative adjuvant chemotherapy for colon cancer. Furthermore, these data appear to be more compelling than that which existed for levamisole before its incorporation into the Intergroup trial (1). We believe that the addition of sulindac to 5-FU and levamisole represents a novel approach to the adjuvant therapy of colon cancer. Therefore, we propose a phase III randomized trial to determine whether this three-drug regimen can improve survival rates in patients with resected lymph node-positive colon cancer.

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[3] Merck & Co., Inc., manufacturer communication.

NOTE ADDED IN PROOF

Recent evidence indicates that sulindac sulfone and sulfide can induce apoptotic cell death in cultured colon carcinoma cells, suggesting that induction of apoptosis contributes to the antitumor effects of these compounds (49). Apoptosis is a genetically regulated mechanism of cell death characterized by specific morphological and biochemical features (50, 51). Essentially all anticancer drugs, as well as radiation, kill tumor cells primarily by inducing apoptosis (50). Therefore, sulindac may induce apoptosis by utilizing a common biochemical pathway of cell death shared by conventional anticancer treatments.

REFERENCES

1. Moertel, C. G., Fleming, T. R., Macdonald, J. S., Haller, D. G., Laurie, J. A., Goodman, P. J., Ungerleider, J. S., Emerson, W. A., Tormey, D. C., Glick, J. H., Veeder, M. H., and Maillard, J. A. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N. Engl. J. Med., *322:* 352–358, 1990.

2. Thun, M. J., Namboodiri, M. M., and Heath, C. W., Jr. Aspirin use and reduced risk of fatal colon cancer. N. Engl. J. Med., *325:* 1593–1596, 1991.

3. Rosenberg, L., Palmer, J. R., Zauber, A. G., Warshauer, M. E., Stolley, P. D., and Shapiro, S. A. A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large bowel cancer. J. Natl. Cancer Inst., *83:* 355–358, 1991.

4. Kune, G. A., Kune, S., and Watson, L. F. Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer Study. Cancer (Phila.), *48:* 4399–4404, 1988.

5. Peleg, G., Melbach, H. T., Brown, S. H., and Wilcox, C. M. Aspirin and nonsteroidal anti-inflammatory drug use and the risk of subsequent colorectal cancer. Arch. Intern. Med., *154:* 394–399, 1994.

6. Schreinemachers, D. M., and Everson, R. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology, *5:* 138–146, 1994.

7. Giovannucci, E., Rimm, E. R., Stampfer, M. J., Colditz, G. A., Ascherio, A., and Willett, W. C. Aspirin use and the risk of colorectal cancer and adenoma in male health professionals. Ann. Intern. Med., *121:* 241–246, 1994.

8. Waddell, W. R., Ganser, G. F., Cerise, E. J., and Loughry, R. W. Sulindac for polyposis of the colon. Am. J. Surg., *157:* 175–179, 1989.

9. Waddell, W. R., and Loughry, R. W. Sulindac for polyposis of the colon. J. Surg. Oncol., *24:* 83–87, 1983.

10. Labayle, D., Fischer, D., Vielh, P., Drouhin, F., Pariente, A., Bories, C., Duhamel, O., Trousset, M., and Attali, P. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. Gastroenterology, *101:* 635–639, 1992.

11. Rigau, J., Piquè, J. M., Rubio, E., Planas, R., Tarrech, J. M., and Bordas, J. M. Effects of long-term sulindac therapy on colonic polyposis. Ann. Intern. Med., *115:* 952–954, 1991.

12. Giardiello, F. M., Hamilton, S. R., Krush, A. J., Piantadosi, S., Hylind, L. M., Celano, P., Booker, S. V., Robinson, C. R., and Offerhaus, G. J. A. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N. Engl. J. Med., *18:* 1313–1316, 1993.

13. Moorghen, M., Ince, P., Finney, R. J., Sunter, J. P., Appleton, D. R., and Watson, A. J. A protective effect of sulindac against chemically-induced primary colonic tumors in mice. J. Pathol., *156:* 341–347, 1988.

14. Pollard, M., and Luchert, P. H. Prolonged antitumor effect of indomethacin on autochthonous intestinal tumors in rats. J. Natl. Cancer Inst., *70:* 1103–95, 1983.

15. Narisawa, T., Sato, M., Tani, M., Kudo, T., Takahashi, T., and Goto, A. Inhibition of development of methylnitrosurea-induced rat colon tumors by indomethacin treatment. Cancer Res., *41:* 1954–1957, 1981.

16. Reddy, B. S., Maruyama, H., and Kelloff, G. Dose-related inhibition of colon carcinogenesis by dietary piroxicam, a nonsteroidal anti-inflammatory drug, during different stages of rat colon tumor development. Cancer Res., *47:* 5340–5346, 1987.

17. Kudo, T., Narisawa, T., and Abo, S. Antitumor activity of indomethacin or methylazoxymethanol-induced large bowel tumors in rats. Gann, *71:* 260–264, 1980.

18. Skinner, S. A., Penney, A. G., and O'Brien, P. E. Sulindac inhibits the rate of growth and appearance of colon tumors in the rat. Arch. Surg., *126:* 1094–1096, 1991.

19. Rao, C. V., Rivenson, A., Simi, B., Zang, E., Kelloff, G., Steele, V., and Reddy, B. S. Chemoprevention of colon carcinogenesis by sulindac, a nonsteroidal anti-inflammatory agent. Cancer Res., *55:* 1464–1472, 1995.

20. Lundholm, K., Gellin, J., Hyltander, A., Lonnroth, C., Sandstrom, R., Svaninger, G., Korner, M., Gulich, M., Karrefors, I., Norli, B., Hafstrom, L. O., Kewenter, J., Olbe, L., and Lundell, L. Anti-inflammatory treatment may prolong survival in undernourished patients with metastatic solid tumors. Cancer Res., *54:* 5602–5606, 1994.

21. Ross, D. S., Bitzer, D., Roy, T., and Murphey, J. E. Piroxicam inhibits the growth of an adenocarcinoma isograft in Fisher rats. J. Surg. Res., *45:* 249–253, 1988.

22. Tanaka, Y., Tanaka, T., and Ishitsuka, H. Antitumor activity of indomethacin in mice bearing advanced colon 26 carcinoma compared with those with early transplants. Cancer Res., *49:* 5935–5939, 1989.

23. Gelin, J., Andersson, C., and Lundholm, K. Effects of indomethacin, cytokines, and cyclosporin A on tumor growth and the subsequent development of cancer cachexia. Cancer Res., *51:* 880–885, 1991.

24. Fulton, A. M. Interaction of natural effector cells and prostaglandins in the control of metastasis. J. Natl. Cancer Inst., *78:* 735–741, 1987.

25. Fulton, A. M. Inhibition of experimental metastasis with indomethacin. Role of macrophages and natural killer cells. Prostaglandins, *35:* 413–425, 1988.

26. Bennett, A., Berstock, D. A., and Carrol, M. A. Increased survival of cancer-bearing mice treated with inhibitors of prostaglandin synthesis alone or with chemotherapy. Br. J. Cancer, *45:* 762–768, 1982.

27. Marnett, L. J. Aspirin and the potential role of prostaglandins in colon cancer. Cancer Res., *52:* 5575–5589, 1992.

28. Balch, C. M., Dougherty, P. A., Cloud, G. A., and Tilden, A. B. Prostaglandin E_2-mediated suppression of cellular immunity in colon cancer patients. Surgery, *95:* 71–77, 1984.

29. Braun, D. P., Bonomi, P. D., Taylor, S. G., and Harris, J. E. Modification of the effects of cytotoxic chemotherapy on the immune responses of cancer patients with a nonsteroidal anti-inflammatory drug, piroxicam. A pilot study of the Eastern Cooperative Oncology Group. J. Biol. Response Modif., *6:* 331–345, 1987.

30. Wiltrout, R. H., Herberman, R. B., Zhang, S-R., Chirigos, M. A., Ortaldo, J. R., Green, K. M., Jr., and Talmadge, J. E. Role of organ-associated NK cells in decreased formation of experimental metastases in lung and liver. J. Immunol., *134:* 4267–4275, 1985.

31. Timer, J., Chen, Y. Q., Liu, B., Bazar, R., Taylor, J. D., and Honn, R. V. The lipoxygenase metabolite 12(5)-HETE promotes αIIβ3 integrin-mediated tumor-cell spreading on fibronectin. Int. J. Cancer, *52:* 594–603, 1992.

32. Ziche, M., Jones, J., and Gullino, P. M. Role of prostaglandin E_1 and copper in angiogenesis. J. Natl. Cancer Inst., *69:* 475–482, 1982.

33. Carson, J. L., Strom, B. L., Soper, K. A., West, S. L., and Morse, M. L. The association of nonsteroidal anti-inflammatory drugs with upper gastrointestinal tract bleeding. Arch. Intern. Med., *147:* 85–88, 1987.

34. Griffin, M. R., Piper, J. M., Daugherty, J. R., Snowden, M., and Ray, W. A. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann. Intern. Med., *114:* 257–263, 1991.

35. Duggan, J. M., Dobson, A. J., Johnson, H., and Fahey, P. Peptic ulcer and nonsteroidal anti-inflammatory agents. Gut, *27:* 929–933, 1986.

36. Soll, A. H., Weinstein, W. M., Kurata, J., and McCarthy, D. Nonsteroidal anti-inflammatory drugs and peptic ulcer disease. Ann. Intern. Med., *114:* 307–319, 1991.

37. Chu, E., and Takimoto, C. H. Antimetabolites. *In:* V. T. DeVita, Jr., S. Hellman, and S. A. Rosenberg (eds.), Cancer: Principles and Practice of Oncology, pp. 362–365. Philadelphia: J. B. Lippincott Co., 1993.

38. Lanza, F. L., Nelson, R. S., and Rack, M. F. A controlled endoscopic study comparing the toxic effects of sulindac, naproxen, aspirin, and placebo on the gastric mucosa of healthy volunteers. J. Clin. Pharmacol., *24:* 89–95, 1984.

39. Caruso, I., and Bianchi Porro, G. Gastroscopic evaluation of anti-inflammatory agents. Br. Med. J., *280:* 75–78, 1980.

40. Agrawal, N. M., Roth, S., Graham, D. Y., White, R. H., Germain, B., Brown, J. A., and Stromatt, S. C. Misoprostol compared with sucralfate in the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcer: a randomized, controlled trial. Ann. Intern. Med., *115:* 195–200, 1991.

41. Ehsanullah, R. S., Page, M. C., Tildesley, G., and Wood, J. R. Prevention of gastroduodenal damage induced by non-steroidal anti-inflammatory drugs: controlled trial of ranitidine. Br. Med. J., *297:* 1017–21, 1988.

42. Robinson, M. G., Griffin, J. W., Jr., Bowers, J., Kogan, F. J., Kogut, D. G., Lanza, F. L., and Warner, C. W. Effect of ranitidine on gastroduodenal mucosal damage induced by nonsteroidal anti-inflammatory drugs. Dig. Dis. Sci., *34:* 424–8, 1989.

43. Graham, D. Y., Agrawal, N. M., and Roth, S. H. Prevention of NSAID-induced gastric ulcer with misoprostol: multicenter, double-blind, placebo-controlled trial. Lancet, *2:* 1277–1280, 1988.

44. Graham, D. Y., White, R. H., Moreland, L. W., Schubert, T. T., Katz, R., Jaszewshi, R., Tindall, E., Triadafilopoulos, G., Stromatt, S. C., Teoh, L. S., and the Misoprostol Study Group. Duodenal and gastric ulcer prevention with misoprostol in arthritis patients taking NSAIDs. Ann. Intern. Med., *119:* 257–262, 1993.

45. Walan, A., Bader, J. P., Classen, M., Lamers, C. B., Piper, D. W., Rutgersson K., and Eriksson, S. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. N. Engl. J. Med., *320:* 69–75, 1989.

46. Miller, J. L. Marrow aplasia and sulindac. Ann. Intern. Med., *92:* 129, 1980.

47. Sanz, M. A., Martinez, J., Gomis, F., and Garcia-Borras, J. J. Sulindac-induced bone marrow toxicity. Lancet, *2:* 802, 1980.

48. Andrews, R., and Russel, N. Aplastic anemia associated with non-steroidal anti-inflammatory drug: relapse after exposure to another such drug. Br. Med. J., *301:* 38, 1990.

49. Piazza, G. A., Kulchak Rahm, K. L., Krutzsch, M., Sperl, G., Shipp Paranka, N., Gross, P. H., Brendel, K., Burt, R. W., Alberts, D. S., Pamukcu, R., and Ahnen, D. J. Antineoplastic drugs sulindac sulfide and sulfone inhibit cell growth by inducing apoptosis. Cancer Res., *55:* 3110–3116, 1995.

50. Stewart, B. W. Mechanisms of apoptosis: integration of genetic, biochemical, and cellular indicators. J. Natl. Cancer Inst., *86:* 1286–1296, 1994.

51. Sinicrope, F. A., Ruan, S., Clearly, K. R., Lee, J. J., and Levin, B. bcl-2 and p53 oncoprotein expression during colorectal tumorigenesis. Cancer Res., *55:* 237–241, 1995.

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