Genotypes Guide Treatment for Rectal Carcinoma

BY BETSY BATES

Los Angeles Bureau

SAN FRANCISCO — Physicians are using patients' genotypes to determine the type of treatment they receive for rectal carcinoma in a Washington University study, with a more aggressive regimen reserved for patients with "bad-risk" genetic profiles.

The strategy appears to have paid off so far, with significantly improved outcomes

for a subgroup of patients predicted to do poorly on the basis of polymorphisms of a pivotal gene, reported Dr. Benjamin R. Tan, a medical oncologist at Washington University in St. Louis.

A total of 86 patients had been enrolled in the study, out of an expected total of 108, prior to Dr. Tan's release of preliminary results at a symposium that was sponsored by the American Society of Clinical Oncology.

Patients were stratified by polymor-

phisms in the thymidine synthase (TYMS) gene, which encodes for an enzyme that serves as a prime target for 5-fluorouracil

The more triple-repeat patterns identified in a certain region of the gene, the more likely a patient is to be resistant to 5-FU and to face a poor prognosis, Dr. Tan

'If you can identify patients that will have a poor response to 5-FU-only chemoradiation, then the addition of another active agent may improve outcomes," he said.

A prospective study was therefore designed to selectively add the drug irinotecan to a neoadjuvant chemoradiation protocol in patients with a bad-risk TYMS genetic profile, also known as a tripletriple polymorphism.

All patients in the study also received the standard regimen used to treat Washington University patients with T3 and T4 adenocarcinoma of the rectum: 5-FUbased chemotherapy plus radiation, followed by restaging and resection 6-10 weeks following therapy.

Of the 86 patients, 63 were found to have good-risk genetic profiles. Previous research suggested that 60% of the goodrisk patients would be expected to respond so well to the regimen that they could be downstaged at surgery.

Downstaging is associated not only with a better prognosis, but also with a better chance at sphincter preservation during surgery, Dr. Tan noted.

The predicted outlook was less opti-

Of the bad-risk patients, 12 of 17 (71%) were downstaged at surgery, far more than expected; 8 had a complete pathologic response to chemoradiation.

mistic for the remaining 23 patients.

Previous research suggested just 22% of patients with a bad-risk genetic profile could be downstaged at surgery. Not all of the patients underwent surgery following

chemoradiation, but of those who did, 30 of 52 patients (58%) with a good-risk genetic profile were downstaged, just as predicted.

Moreover, 12 of 17 (71%) of the bad-risk patients were downstaged at surgery, far more than expected. Eight of the patients showed a complete pathologic response to chemoradiation.

Among the five bad-risk patients who were not downstaged, four had surgical pathology specimens that showed only microscopic disease.

Of 17 bad-risk patients who were treated with irinotecan, 5-FU, and radiation, 16 "had a very good response to this strategy," Dr. Tan said at the symposium.

In addition to the American Society of Clinical Oncology, the symposium was co-sponsored by the American Gastroenterological Association, the American Society for Therapeutic Radiology and Oncology, and the Society of Surgical

Oncology. Grades 3 and 4 diarrhea were more prevalent among patients in the bad-risk group who were receiving irinotecan in addition to the standard chemoradiation regimen, he added.

One death occurred in both the bad- and good-risk groups.

Dr. Tan and his associates concluded that "genotype-directed therapies" are feasible for rectal cancer, and may offer significant advantages for patients with badrisk genetic profiles.

Brief Summary of Prescribing Information (Nos. 1541, 1543, 1544, 3046, 7309, 7311) 03-5366-B24-Brf, Rev. July. 2004

PREVACID® (lansoprazole) Delayed-Release Capsules

PREVACID® (lansoprazole) For Delayed-Release Oral Suspension

PREVACID® SoluTabTM (lansoprazole) Delayed-Release Orally

PREVACID Delayed-Release Capsules, PREVACID Solution
Disintegrating Tablets and PREVACID For Delayed-Release Oral Suspension are indicated for:
Short-Term Treatment (4 weeks) of Active Duodenal Ulcer
H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
Triple Therapy: PREVACID/amoxicillin/clarithromycin
Dual Therapy: PREVACID/amoxicillin/clarithromycin or in whom resistance to clarithromycin is known or suspected.
Who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.
Maintenance of Healed Duodenal Ulcers
Controlled studies do not extend beyond 12 months.
Short-Term Treatment (up to 8 weeks) of Active Benign Gastric Ulcer
In patients who continue NSAID use. Controlled studies did not extend beyond 8 weeks.

Plet Reduction of NSAID-Associated Gastric Ulcer VACID Delayed-Release Capsules, PREVACID SoluTab Delayed-Release Orally ntegrating Tablets and PREVACID For Delayed-Release Oral Suspension are indicated

Risk Reduction of NSAID-Associated Gastric Ulcer
In patients with a history of a documented gastric ulcer who require the use of an NSAID.
Controlled studies did not extend beyond 12 weeks.

Gastroesophageal Reflux Disease (GERD)

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Short-Term Treatment (0) symptomatic GEND
Short-Term Treatment (up to 8 weeks) of Erosive Esophagitis
For patients who do not heal with PREVACID for 8 weeks (5-10%), it may be helpful to give
an additional 8 weeks of treatment. If there is a recurrence of erosive esophagitis an
additional 8-week course of PREVACID may be considered.

Maintenance of Healing of Erosive Esophagitis
Controlled studies did not extend beyond 12 months.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

the formulation of PREVACID.

Amoxicialisi is contraindicated in patients with a known hypersensitivity to any penicillin. Charithromycin is contraindicated in patients with a known hypersensitivity to alry penicillin. Clarithromycin, erythromycin, and any of the macrolide antibiotics.

Concomilant administration of Carithromycin with cisapride, primozide, astemizole, or terfenadine is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are of administrated with cisapride, primozide, astemizole, or terfenadine resulting in cardiac arrhythmias (OT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

tyrease refer to full prescribing information for amoxicilin and clarithromycin before prescribing.)

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCLIMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN.)

PROCECURS WHILE TAKING CLARITHROMYCIN.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of ambitacterial agents. Treatment with antibacterial agents afters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be invited. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be invited. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be invited. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be invented that the presentivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin thypersensitivity and/or a history of penicillinin, careful inquiry reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions have penicillins, exphalosporins, and other

PRECAUTIONS
General
Symptomatic response to therapy with lansoprazole does not preclude the presence of

gastric malignancy.

Information for Patients
PREVACID is available as a capsule, orally disintegrating tablet and oral suspension, and is available in any available in a wailable in the route and available in the route and available in the sound or administration for each of these dosage forms is presented below. PREVACID should be taken before eating. PREVACID products SHOULD NOT BE CRUSHED OR CHEWED.

Phenylketonurics: Contains Phenylalanine 2.5 mg per 15 mg Tablet and 5.1 mg per 30 mg Tablet.

so my Tablet. Administration Options 1. *PREVACID Delayed-Release Capsules* PREVACID Delayed-Release Capsules should be swallowed whole

Alternatively, for patients who have difficulty swallowing capsules, PREVACID Delayed-Release Capsules can be opened and administered as follows:

Open capsule.
 Sprinkle intact granules on one tablespoon of either applesauce, ENSURE[®] pudding, cottage cheese, yogurt or strained pears.
 Swallow immediately.
 PREVACID Delayde-Release Capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows:

Sprinkle intact granules into a small volume of either apple juice, orange juice or tomato juice (60 mL – approximately 2 ounces).

volumes of juice and the contents swallowed immediately.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

lease Orally Disintegrating Tablet 2. PPEVACID Solutab elayed-release orany Dismegrating labers PREVACID Solutab should not be chewed. Place the tablet on the tongue and allow it to disintegrate, with or without water, until the particles can be swallowed. The tablet typically disintegrates in less than 1 minute.

disintegrates in less than 1 minute.

Alternatively, for children or other patients who have difficulty swallowing tablets,
PREVACID Solurab can be delivered in two different ways.

PREVACID Solurab – Oral Syringe

PREVACID Solurab – Oral Syringe, PREVACID Solurab can be administered as follows:

Place a 15 mg tablet in oral syringe and draw up approximately 4 mL of water, or place a 30 mg tablet in oral syringe and draw up approximately 4 mL of water.

Shake gently to allow for a quick dispersal.

After the tablet has dispersed, administer the contents within 15 minutes.

Helli the syringe with approximately 2 mL (5 mL for the 30 mg tablet) of water, shake gently, and administer any remaining contents.

PREVACID SoluTab – Nasogastric Tube Administration (≥ 8 French)
For administration via a nasogastric tube, PREVACID SoluTab can be administered as

tollows:
Place a 15 mg tablet in a syringe and draw up 4 mL of water, or place a 30 mg tablet in a
syringe and draw up 10 mL of water.

syringe and draw up 10 mL of water.

• Shake gently to allow for a quick dispersal.

• After the table has dispersed, inject through the nasogastric tube into the stomach within

15 minutes.

Refill the syringe with approximately 5 mL of water, shake gently, and flush the nasogastric

upen packet. To prepare a dose, empty the packet contents into a container containing 2 tablespoons of **WATER** DO NOT USE OTHER LIQUIDS OR FOODS.

• This product should not be given introugn enteral autimistration in users.

Trul plareactions in metabolized through the cytochrome P₄₅₀ system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P₄₅₀ system, such as warfarin, antipyrine, indomethacin, ibupyroten, phenytoin, propraodio, prednisone, diazepam, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P₄₅₀ isozymes including CYP1A2, CYP3A, a minor increase (10%) in the clearance of theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional tiration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

In a study of healthy subjects neither the pharmacokietics of warfarin enantioners nor

started or stopped to ensure clinically effective blood levels.

In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including lansoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin. In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucrafiate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucrafiate. In clinical trials, antacids were administered accominantly with sucrafiate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucrafiate. In clinical trials, antacids were administered concominantly with PREVACID Delayed-Release Capsules is, sit in oil interfere with its effect.

majoritime states in the an impuriant oterminant of bioavailability (e.g., ketoconazole, ampicillim esters, iron salts, digoxin).

Carcinogenesis, Mutagenesis, Impairment of Fertility
In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/dga, about 1 to 40 times the exposure on a body surface (mg/m²) basis, of a 50-kg person of average height (1.46 m² body surface area) given the recommended human dose of 30 mg/dga (222 mg/m²). Lansoprazole produced doserelated gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestiant metaplasis of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of the situation mass in rats receiving doses of 15 to 150 mg/kg/dga (4 to 40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/dga (13 times the recommended human dose based on body surface area) in a 1-year toxicity study.

50 mg/kg/day (13 times the recommended human dose based on body surface area) in a 1-year faxicity studiey, entire the activation of the commended human dose based on body surface area. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia, It also produced a dose-related increased incidence of gastric ECL cell hyperplasia, It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based no hody surface area) and female intect treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on body surface area) exceeded the ranges of background incidences in historical controls or this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on body surface area).

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (1005) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. It was positive in *in vitro* human lymphocyte chromosomal aberration sessor.

arithromycin e **WARNINGS** (above) and full prescribing information for clarithromycin before using in

egnant women.

Insting Mothers
Insoprazole or its metabolites are excreted in the milk of rats. It is not known whether
isoprazole is excreted in human milk. Because many forgs are excreted in human milk. Because and progress are excreted in human milk. Because of the potential for serious adverse reactions in unusing infants from lansoprazole,
id because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity
udies, a decision should be made whether to discontinue nursing or to discontinue the
ug, taking into account the importance of the drug to the mother.

incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in younger patients. For elderly patients, dosage and administration of lansoprazole need not be altered for a particular indication. seen in younge, paramen, need not be altered for a particular indication.

ADVERSE REACTIONS
Clinical
Worldwide, over 10,000 patients have been treated with lansoprazole in Phase 2-3 clinical trials involving various dosages and durations of treatment. The adverse reaction profiles for PREVACID Delayed-Release Crisquises and PREVACID for Delayed-Release Crisquises and PREVACID for Telayed-Release Crisquises and Service of the Crisquise of the C

Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Studies		
	PREVACID	Placebo
	(N= 2768)	(N= 1023)
Body System/Adverse Event	%	%
Body as a Whole		
Abdominal Pain	2.1	1.2
Digestive System	4.0	0.4
Constipation	1.0	0.4
Diarrhea	3.8	2.3
Nausea	1.3	1.2
Jandacha was also open at greater than 19/ incidence but was more common on place		

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received lansoprazole 60 mg (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhae. In the risk reduction study of PREVA/CID for NSAID-associated gastric ulcers, the incidence of diarrhae for patients treated with PREVA/CID was 5%, misoprostol 22%, and placebo 3%. Additional adverse experiences occurring in <1% of patients or subjects in domestic trials are shown below. Refer to Postmarketing for adverse reactions occurring since the drug was marketed.

Additional adverse experiences occurring in <1% of patients or subjects in domestic trials are shown below. Refer to Postmarketing for adverse reactions occurring since the drug was marketed.

Body as a Whole — abdomen enlarged, altergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain; Cardiovascular System — angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation; Digestive System — abnormal stools, anorexia, bezoar, cardiospasm, choleithiasis, colitis, dry mouth, dyspensia, dysphagia, enteritis, erucutation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastrior noduels/mulic gland polysy, gastritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal anomany, gastrointestinal disorder, gastrointestinal anomany, gastrointestinal disorder, gastrointestinal anomany, gastrointestinal disorder, gastrointestinal memorhage, glossitis, june hemorrhage, hematemesis, increased appetite, increased aslaviation, melena, mouth ulceration, nausea and vomitting, nausea and vomitting and diarrhea, oral moniliasis, rectal and lymphatic System - ambanis, hemolysis, hymphadenopathyr, Metabolic and Mutritional Disorders — gout, dehydration, hyperdycemia/hypogycemia, peripheral edema, weight jainloss, Musculoskeletal System - arthralia, arthritis, bone disorder, joint disorder, long rainloss, Musculospallar sha, anxiety, apathy, contision, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility agarvated, hyperkinesia, hypertonia, hypesthesia, insomnia, libiloi decreased, dyspnea, epistaxis,

Operator enesses* speech unisorde, originanal ossessin* unitially retenuors. Combination Therapy with Amoxicillin and Clarithromycia In clinical trials using combination therapy with PREVACID plus amoxicilin na clarithromycin, and PREVACID plus amoxicilin, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with PREVACID, amoxicilin, or clarithromycin.

Dual Therapy: PREVACID/amoxicillin
The most frequently reported adverse events for patients who received PREVACID Li.d. plus
amoxicillin Li.d. dual therapy were diarrhea (8%) and headache (7%). No treatmentemergent adverse events were observed at significantly higher rates with PREVACID Li.d.
plus amoxicillin Li.d. dual therapy whan with PREVACID alone.
For more information on adverse reactions with amoxicillin or clarithromycin, refer to their
package inserts, ADVERSE REACTIONS sections.
Laboratory Values
The following changes in laboratory parameters for lansoprazole were reported as adverse
events:

events:
Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal ABC, billrubinemia, eosinophilla, hyperfipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased/abnormal patients, and increased/abnormal patients, and increased gather livels. Unire abnormalities such as abuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were recorded.

and lielaturia were also reported. Accordance in Societies accordance in the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (41/2677) lansoprazole patients had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these lansoprazole patients reported jaundice at any time during the study. In clinical trials using combination therapy with PREVACID plus amoxicillin activities and PREVACID plus amoxicillin, no increased laboratory abnormalities particular to these drug combinations were observed. For more information on laboratory value changes with amoxicillin or clarithromycin, refer to their package inserts, ADVERSE REACTIONS section.

For more detailed information, see full prescribing information or contact TAP Medical Information at 1-800-622-2011. MR030-0134

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