Mortality rates were similar at urban and rural hospitals and, in the multivariate analysis, teaching hospitals held no mortality advantage over nonteaching facilities.

Hospital volume was initially highly significantly associated with mortality, but that association disappeared when surgeon volume was factored into the analysis.

Surgeons who performed the most procedures had significantly lower patient mortality rates than did surgeons with lower volume; that difference remained significant even after overall hospital volume was factored in to the analysis.

However, the authors noted, the difference in mortality rates between surgeon groups was not great: Average inpatient mortality was 9.25% for high-volume surgeons (six or more cases per year), 7.5% for medium-volume surgeons (two to six cases per year), and 12.75% for low-volume surgeons (fewer than two cases per year).

Because of the wide scatter in each category, picking the best surgeon or hospital based on volume wouldn't work, the authors said.

"This is highlighted by the fact that one hospital with a caseload of more than 13 per year had a mortality rate of 25%, and one surgeon with caseload of more than 6 per year had a mortality rate of 40%. Choosing those particular providers on the basis of volume might well be a mistake," they noted.

A better alternative, they suggested, would be a national system of outcome benchmarks. "A benchmark-based system simply sets clear guidelines and allows institutions and surgeons to find their own means to achieve them," the investigators wrote. "In the medium term, it would also reassure patients that the institution they were going to had satisfactory and verified outcomes for that procedure." ■

Western Diet Linked to Colon Cancer Return

BY MARY ANN MOON
Contributing Writer

Colon cancer patients who eat a typical Western diet appear to have triple the risk of recurrence, compared with those who do not follow a Western diet.

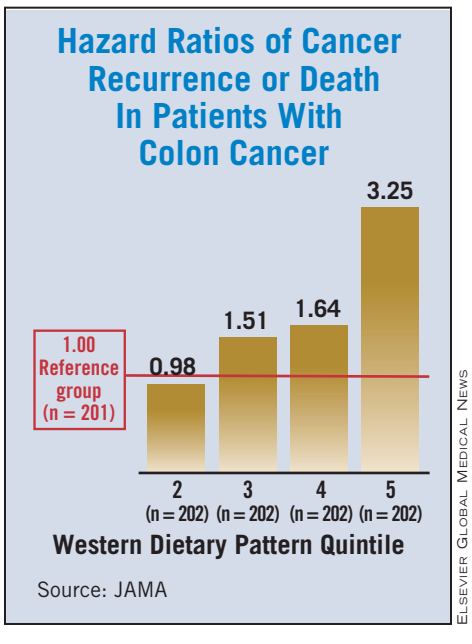
After a potentially curative resection of stage III colon cancer and adjuvant chemotherapy, a diet replete with sweets, french fries, refined grains, and red and processed meats "may facilitate a milieu that allows residual microscopic disease to proliferate and spread," Dr. Jeffrey A. Meyerhardt of the Dana-Farber Cancer Institute, Boston, and his associates said.

Numerous studies have examined the influence of diet and other lifestyle factors on the development of colon cancer, but few have addressed diet's influence in patients with established colon cancer. Dr. Meyerhardt and his associates assessed the effect of two distinct dietary patterns—a typical Western diet versus what the investigators termed a "prudent" diet that included greater intakes of fruits, vegetables, legumes, fish, poultry, and whole grains—in 1,009 adult subjects who were already participating in a National Cancer Institute trial comparing different chemotherapy regimens.

The subjects had undergone complete surgical resection of the primary tumor in 1999-2001, and were found to have regional lymph node metastases but no distant metastases. Their diets were assessed midway through the course of adjuvant chemotherapy. The patients were followed for a median of 5 years; a total of 324 developed a recurrence during follow-up.

Greater intake of a Western diet was associated with recurrence and with cancer mortality. Patients in the highest quintile of the Western dietary pattern were three times more likely to develop recurrence and to die from cancer than were those in the lowest quintile of the Western dietary pattern, Dr. Meyerhardt and his associates said (JAMA 2007;298:754-64).

In contrast, there was no association between the prudent diet and risk of cancer recurrence or cancer mortality. ■



6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Amitiza. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Voluntary reports of adverse reactions occurring with the use of Amitiza include the following: syncope, malaise, increased heart rate, muscle cramps or muscle spasms, rash, and asthenia.

7 DRUG INTERACTIONS

Based upon the results of *in vitro* human microsome studies, there is low likelihood of drug–drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to the metabolite M3 (See *Pharmacokinetics, Metabolism* [12.3].). Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies of primary cultures of human hepatocytes show no induction of cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4 by lubiprostone. No additional drug–drug interaction studies have been performed. Based on the available information, no protein binding–mediated drug interactions of clinical significance are anticipated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C. [See *Warnings and Precautions* (5.1).]

Teratology studies with lubiprostone have been conducted in rats at oral doses up to 2000 mcg/kg/day (approximately 332 times the recommended human dose, based on body surface area), and in rabbits at oral doses of up to 100 mcg/kg/day (approximately 33 times the recommended human dose, based on body surface area). Lubiprostone was not teratogenic in rats or rabbits. In guinea pigs, lubiprostone caused fetal loss at repeated doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the recommended human dose, respectively, based on body surface area) administered on days 40 to 53 of gestation.

There are no adequate and well-controlled studies in pregnant women. However, during clinical testing of Amitiza at 24 mcg twice daily, four women became pregnant. Per protocol, Amitiza was discontinued upon pregnancy detection. Three of the four women delivered healthy babies. The fourth woman was monitored for 1 month following discontinuation of study drug, at which time the pregnancy was progressing as expected; the patient was subsequently lost to follow-up.

Amitiza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman is or becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

8.3 Nursing Mothers

It is not known whether lubiprostone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lubiprostone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been studied.

8.5 Geriatric Use

The efficacy of Amitiza in the elderly (≥ 65 years of age) subpopulation was consistent with the efficacy in the overall study population. Of the total number of constipated patients treated in the dose-finding, efficacy, and long-term studies of Amitiza, 15.5% were ≥ 65 years of age, and 4.2% were ≥ 75 years of age. Elderly patients taking Amitiza (any dosage) experienced a lower incidence rate of associated nausea compared to the overall study population taking Amitiza (18% vs. 29%, respectively).

8.6 Renal Impairment

Amitiza has not been studied in patients who have renal impairment.

8.7 Hepatic Impairment

Amitiza has not been studied in patients who have hepatic impairment.

10 OVERDOSAGE

There have been two confirmed reports of overdosage with Amitiza. The first report involved a 3-year-old child who accidentally ingested 7 or 8 capsules of 24 mcg of Amitiza and fully recovered. The second report was a study patient who self-administered a total of 96 mcg of Amitiza per day for 8 days. The patient experienced no adverse reactions during this time. Additionally, in a Phase 1 cardiac repolarization study, 38 of 51 patients given a single oral dose of 144 mcg of Amitiza (6 times the recommended dose) experienced an adverse event that was at least possibly related to the study drug. Adverse reactions that occurred in at least 1% of these patients included the following: nausea (45%), diarrhea (35%), vomiting (27%), dizziness (14%), headache (12%), abdominal pain (8%), flushing/hot flash (8%), retching (8%), dyspnea (4%), pallor (4%), stomach discomfort (4%), anorexia (2%), asthenia (2%), chest discomfort (2%), dry mouth (2%), hyperhidrosis (2%), and syncope (2%).

16 HOW SUPPLIED/STORAGE AND HANDLING

Amitiza is available as an oval, orange, soft gelatin capsule with "SPI" printed on one side. Each capsule contains 24 mcg of lubiprostone. Amitiza is available as follows:

- Bottles of 100 (NDC 64764-240-10)
- Bottles of 60 (NDC 64764-240-60)

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F).
PROTECT FROM EXTREME TEMPERATURES.

17 PATIENT COUNSELING INFORMATION

17.1 Dosing Instructions

Patients should take a single 24 mcg capsule of Amitiza twice daily with food or a meal. The capsule should be taken once in the morning and once in the evening daily as prescribed. Physicians and patients should periodically assess the need for continued treatment with Amitiza.

17.2 Nausea and Diarrhea

Patients should take Amitiza with food or a meal to reduce symptoms of nausea. Patients on treatment who experience severe nausea or diarrhea should inform their physician.

Marketed by:
Sucampo Pharmaceuticals, Inc., Bethesda, MD 20814
and
Takeda Pharmaceuticals America, Inc., Deerfield, IL 60015

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750-03568-1 06/07
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