

# A new era in management of gastrointestinal cancers

Key studies presented at the 2011 Oncology Congress focus on treatments, prevention, and early diagnosis of GI tract cancers.



Adenocarcinoma of the stomach

© GASTROLAB / PHOTO RESEARCHERS, INC.

BY JOHN SCHIESZER

**N**ew and emerging treatment regimens for gastrointestinal (GI) cancers were presented at the Seventh Annual Oncology Congress, held in San Francisco, California, October 13-15, 2011. Researchers presented studies on the efficacy of preoperative and postoperative chemotherapy with surgical resection for gastric cancer, combination radiotherapy-chemotherapy for locally advanced pancreatic cancer, the effects of genetics on treatment response, the association between *Helicobacter pylori* infection and gastric cancer, and a new approach to early diagnosis of GI cancers. This article reviews the study results presented at the 2011 Oncology Congress.

## PREOPERATIVE/ POSTOPERATIVE CHEMOTHERAPY AND RESECTION

Management of gastrointestinal tract cancer is much different today than it was just a few years ago. Studies are demonstrating that adjuvant and neoadjuvant therapies are increasingly effective for gastric cancer, gastroesophageal junction tumors, and esophageal cancer, according to David Ilson, MD, PhD, of the Memorial Sloan-Kettering Cancer Center in New York, New York.

Ilson, who presented *Prevention, Screening, and Management: New Frontiers in Managing Gastric Cancer* at the 2011 Oncology Congress, said preoperative regimens of carboplatin, paclitaxel (Abraxane, generics), and radiotherapy are becoming the new standard of care. “For esophageal and gastroesophageal (GE) junction

cancers, the addition of chemotherapy to radiation therapy seems to offer survival and local control benefits,” Ilson said. Many new agents for treating this disease are in clinical trials, including phase III evaluation of adding cetuximab and bevacizumab to preoperative and postoperative therapy. Positron emission tomography (PET) is being used to direct therapy in esophageal and gastroesophageal junction cancers in the preoperative setting.

Studies suggest survival rates are poor (20%–30%) for patients with locally invasive gastric cancer when treated with surgery alone. However, preoperative chemotherapy and chemotherapy plus radiation may improve overall survival rates. In addition, the latest data suggest that chemotherapy plus radiation may have advantages over chemotherapy alone.

## Increasing evidence supports the use of neoadjuvant therapy before surgical resection. However, there are potential disadvantages.

“Nurses will need to understand management of patients with preoperative chemotherapy and chemotherapy/radiation, in particular chemotherapy/radiation because it is more toxic. Attention to treatment of toxicities including esophagitis from radiation therapy, nutritional needs, and assessment preoperatively are key nursing issues,” Ilson said.

A large, phase III trial, by the US GI Intergroup Study led by the Southwest Oncology Group (INT 0116), previously demonstrated improved survival when treatment consisted of a combination of postoperative radiation therapy and chemotherapy with fluorouracil and leucovorin.<sup>1</sup> The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial also demonstrated that perioperative chemotherapy can provide a significant survival benefit.<sup>2</sup> This trial showed a significant downstaging or downsizing of tumors.

The MAGIC trial included patients with adenocarcinoma of the stomach, the lower third of the esophagus, and the esophagogastric junction.<sup>2</sup> All the subjects were recruited through medical centers in Europe, South America, Asia, and New Zealand. The patients were randomly assigned to receive surgery alone (250 patients) or surgery and perioperative chemotherapy (250 patients) with epirubicin (Ellence, generics), cisplatin, and infused 5-fluorouracil (ECF). Perioperative chemotherapy in this trial consisted of three preoperative cycles and three postoperative cycles. Patients were given epirubicin and cisplatin intravenously

on the first day of each cycle, and fluorouracil was given daily for 21 days as a continuous IV infusion.<sup>2</sup>

The researchers found significantly smaller tumors in the chemotherapy group.<sup>2</sup> In addition, patients receiving perioperative chemotherapy had a significantly higher likelihood of both progression-free and overall survival. The 5-year survival rate was higher in the chemotherapy group compared with the surgery-only group (36.3% versus 23.0%, respectively). Postoperative complication rates were similar in both groups (46% in the chemotherapy group versus 45% in the surgery-only group). The MAGIC trial researchers concluded that administering chemotherapy before and after surgery resulted in improved survival. “But we don’t know if that is better than chemotherapy and radiation,” said Andrew Ko, MD, an associate professor in the division of Hematology/Oncology at the University of California, San Francisco.

Ko, also a speaker at the 2011 Oncology Congress, said increasing evidence supports the use of neoadjuvant therapy before surgical resection when treating GI tract cancers. However, there are also some potential disadvantages including delay of a potentially curative surgical resection, treatment-related side effects may weaken the patient before surgery, and obscured surgical pathology may result in inaccurate staging.

The changing treatment paradigm for gastrointestinal tract cancers requires yet another set of new nursing skills. “I think the oncology nurse plays a very important role,” Ko said. Nurses need to be aware of the various side effects of the new agents and counsel their patients on the toxicities. Many new agents have their own unique set of side effects.

### **COMBINATION RADIOTHERAPY CHEMOTHERAPY**

Phase I/II trials currently underway are investigating stereotactic body radiotherapy (SBRT) and stereotactic ablative radiotherapy (SABR) combined with chemotherapy for treating locally advanced pancreatic cancer. Albert Koong, MD, an associate professor of radiation/oncology at Stanford University, Stanford, California, said preliminary findings suggest these approaches may have advantages over conventional radiation therapy. Koong said SBRT and SABR avoid some toxicities associated with conventional radiation therapy. In addition, these types of radiotherapy reduce the treatment time from 5 to 7 weeks to just 1 week. “We treated about 30 plus patients. So it is relatively early,” Koong said. However, these patients are doing better than patients who underwent conventional therapy.

Koong, who presented *Novel Radiation Techniques in the Management of GI Tract Cancers* at the 2011 Oncology Congress, said there is an overall general shift toward combining

---

different therapies to manage pancreatic, as well as other GI tract, cancers. Up until just 5 years ago, surgeons removed the tumor and then postoperative treatment was managed by a multidisciplinary team. The new standard of care involves discussing different modalities and in what sequence they should be tried. “Sometimes chemotherapy and radiation are better before surgery than after surgery,” explained Koong. This is true for rectal cancer, and studies are now indicating this is true for some GI cancers, too.

### EFFECTS OF GENETICS ON TREATMENT RESPONSE

Stomach cancer has two distinct disease variations based on its genetic makeup, and each responds differently to chemotherapy, according to a new study.<sup>3</sup> This study is the first large-scale genomic analysis of gastric cancer to confirm the two discrete tumor types. In addition, these researchers found that a specific chemotherapy regimen is more effective on one tumor type, while a different drug works best on the other.<sup>3</sup> “Our study is the first to show that a proposed molecular classification of gastric cancer can identify genomic subtypes that respond differently to therapies, which is crucial in efforts to customize treatments for patients,” explained study investigator Patrick Tan, MD, PhD, associate professor in the Cancer and Stem Cell Biology Program at Duke University, Durham, North Carolina.

The National Cancer Institute (NCI) estimates 21,520 new cases of stomach cancer will be diagnosed in the United States and 10,340 persons will die of the disease in 2011.<sup>4</sup> Gastric cancer patients have long had markedly different responses to treatments, suggesting that tumors have underlying differences. Hinting at those differences, a microscopic pathology test developed in the 1960s broadly described how well the tumor cells clumped together, typing them as either “intestinal” or “diffuse.” However, the Lauren classification, an analysis named for the doctor who first described the distinctions, fell short as a reliable prognostic tool.<sup>5</sup>

“Most gastric cancer patients today are still being treated with a common, ‘one-size-fits-all’ regimen,” said Tan. “One reason for this is that the Lauren classification requires significant gastric cancer experience and there is considerable variation in classifying gastric cancers, even among qualified pathologists.”

But the new genetic findings add greater specificity to the microscopic classifications and, for the first time, provide some guidance with which clinicians can prescribe effective treatments. By establishing a highly accurate definition of tumor subtypes, Tan’s team was able to observe the different responses to chemotherapy. Intestinal-type tumors showed significantly better response to 5-fluorouracil (5-FU) and

oxaliplatin (Eloxatin, generics) and were more resistant to cisplatin than diffuse tumors. “The exact mechanistic reasons for this difference are currently unclear, and this is an area that we are actively working on,” said Tan. He and his colleagues have launched a prospective clinical trial where gastric cancer tumors will be genomically profiled, and treatments will be allocated on the basis of the tumor type.

### PREVENTION STRATEGIES

The stomach bacterium *Helicobacter pylori* has a significant role in the development of gastric cancer. Recently, molecular biologists from the University of Zurich identified a mechanism of *H pylori* that damages the DNA of cells in the gastric mucosa and sets them up for malignant transformation.<sup>6</sup> Chronic infection of the gastric mucosa with *H pylori* is a primary risk factor for developing gastric cancer. The study demonstrated infection of host cells leads to breaks in both strands of the DNA double helix.<sup>6</sup>

The researchers found the frequency of the double-strand breaks depends on the intensity and duration of the infection. DNA breaks induced by *H pylori* trigger the cell’s natural DNA damage signaling and repair mechanisms. If the bacterium is eradicated with antibiotics within a few hours of infection, most of the DNA breaks are successfully repaired. Prolonged infections that imitate the conditions of a chronically infected host, however, exhaust the cell’s repair response,

**Currently, only approximately 10% of patients with cancers of the upper GI tract are still alive 5 years after diagnosis.**

and the dangerous double-strand breaks can no longer be repaired, causing genetic mutations or cell death.

New research also suggests alcohol use may play a role in the development of gastric cancers. Heavy beer drinkers who have a specific genetic variant in the cluster of three genes that metabolize alcohol, known as rs1230025, are at significantly greater risk of developing noncardia gastric cancer.<sup>7</sup> Heavy beer drinkers who do not have the variant and nondrinkers who have rs1230025 or rs283411 have the same risk; however, it is not as significantly elevated.

“This is a classic gene-environment interaction,” said Eric Duell, PhD, senior epidemiologist in the Cancer Epidemiology Research Program at the Catalan Institute of Oncology in Barcelona, Spain. “Having both of these risks, heavy beer

consumption and rs1230025, appears to be worse in terms of gastric cancer risk than having just one or neither.”

Gastric cancer is the second leading cause of cancer death worldwide, but because some countries, including the United States, have much lower rates of gastric cancer than others, Duell believes this disease has a stronger environmental component than a genetic component.<sup>8</sup> Alcohol use has been suspected to contribute to gastric cancer, but numerous studies have shown mixed results. Duell and colleagues conducted a comprehensive analysis of alcohol consumption and gastric cancer risk in more than 521,000 people aged 35 to 70 years who participated in the European Prospective Investigation into Cancer and Nutrition (EPIC) study from 1992 through 1998.<sup>8</sup>

The researchers evaluated the type of alcohol consumed (wine, beer, or liquor) and the location and grade of cancer.<sup>8</sup> Total consumption of 60 g of pure ethanol/alcohol from all beverage types combined carried a 65% increased risk. One 12-ounce beer contains about 13 g of pure alcohol/ethanol. However, this association was confined to beer. Duell’s results linked drinking 30 g or more a day of pure ethanol/alcohol as beer to a 75% increased risk of developing gastric cancer. Wine and liquor were not associated with gastric cancer risk.<sup>8</sup>

In a further analysis, using the EurGast study nested within EPIC, which included 365 gastric cancer cases and 1,284 controls, the researchers analyzed the effects of known single nucleotide polymorphisms (SNPs) in the gene cluster (ADH1) that produces an enzyme that breaks down alcohol.<sup>8</sup> Two variants in the ADH1 locus were statistically significantly associated with gastric cancer risk, and only one variant, rs1230025, interacted with beer consumption to increase the risk.

### A NEW APPROACH TO EARLY DIAGNOSIS

Diagnosing GI cancers earlier in the course of the disease can dramatically lower morbidity and mortality. New research suggests that a simple urine test may detect cancers of the gut, stomach, and pancreas much sooner. Researchers at the University of Edinburgh, United Kingdom, have identified key proteins in the urine of patients with advanced cancers.<sup>9</sup> The findings may help detect these cancers in people who are asymptomatic, and earlier diagnosis may lead to improved survival rates. Currently, only approximately 10% of patients with these cancers, categorized as cancers of the upper GI tract, are still alive 5 years after diagnosis.

The researchers compared urine samples from patients with upper GI cancers with urine samples from people who were cancer-free. Scientists analyzed the samples and identified thousands of proteins. Then, they identified six proteins that were present in 98% of the samples from patients with

cancer but absent in almost 90% of the samples from patients without cancer.<sup>9</sup>

The researchers then narrowed the field down to two proteins, S100A6 and S1009, most likely to appear in samples from patients with cancer but not in samples from people who are cancer-free. The scientists intend to see whether people with early stage cancers, such as those not yet diagnosed, have the same levels of proteins present. They plan to analyze samples from at least 1,000 volunteers and track the participants for a number of years to identify those who develop upper GI cancers.

“The aim of this work is to enable these cancers to be diagnosed much earlier. This would help us to treat the cancer before it has a chance to spread. The majority of these cancers are currently diagnosed late, where no surgery is possible due to its advanced stage. Earlier diagnosis would mean that curative surgery or chemotherapy would be possible for more patients,” said study investigator Holger Husi, MD, of the University of Edinburgh Tissue Injury and Repair Group. ■

**John Schieszer** is an international medical journalist and radio broadcaster of *The Medical Minute*.

### REFERENCES

1. Leong CN, Chung HT, Lee KM, et al. Outcomes of adjuvant chemoradiotherapy after a radical gastrectomy and a D2 node dissection for gastric adenocarcinoma. *Cancer J*. 2008;14(4):269-275.
2. Cunningham D, Allum WH, Stenning SP, et al; MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355(1):11-20.
3. Tan IB, Ivanova T, Lim KH, et al. Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy. *Gastroenterology*. 2011;141(2):476-485, 485.e1-485.e11.
4. Stomach (gastric) cancer. National Cancer Institute Web site. <http://www.cancer.gov/cancertopics/types/stomach>. Accessed November 14, 2011.
5. Lee WS, Song HS, Kim IH, et al. Prognostic significance of lauren classification in curatively resected gastric cancer. *Proc Am Soc Clin Oncol*. 2003;22:Abstract 1453.
6. Toller IM, Neelsen KJ, Steger M. Carcinogenic bacterial pathogen *Helicobacter pylori* triggers DNA double-strand breaks and a DNA damage response in its host cells. *Proc Natl Acad Sci U S A*. 2011;108(36):14944-14949.
7. Bad mix: heavy beer drinking and a gene variant increases gastric cancer risk. Paper presented at: 102nd Annual Meeting of the American Association for Cancer Research; April 4, 2011; Orlando, Florida.
8. Slimani N, Kraaks R, Ferrari P, et al. European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: rationale, design and population characteristics. *Public Health Nutr*. 2002;5(6B):1125-1145.
9. Husi H, Stephens N, Cronshaw A, et al. Proteomic analysis of urinary upper gastrointestinal cancer markers. *Proteomics Clin Appl*. 2011;5(5-6):289-299.

SL9366

Stomach cancer. Endoscopic view of stomach (gastric) cancer of the intestinal type. Intestinal type cancers are so-called as they show a marked resemblance to cancers of the colon (large intestine). The tumors (right) are adenocarcinomas, a type of cancer arising from glandular epithelial tissue. Stomach cancer is the fourth most common cancer worldwide. Several risk factors are thought to be involved including poor diet, smoking, and *Helicobacter pylori* (bacterial) infection.

Credit: Gastrolab / Photo Researchers, Inc.