Research Stretches Survival for GIST Patients

BY BETSY BATES
Los Angeles Bureau

LAS VEGAS — Gastrointestinal stromal tumors, long an enigma, are revealing their secrets and their vulnerabilities in the face of revolutionary discoveries about their origins, speakers said at a multidisciplinary general session of the spring meeting of the American College of Surgeons.

Complete resection remains the initial treatment of choice for these often fatal tumors, but advances in their characterization and therapy are providing a more optimistic outlook for patients whose survival was once measured in months rather than years.

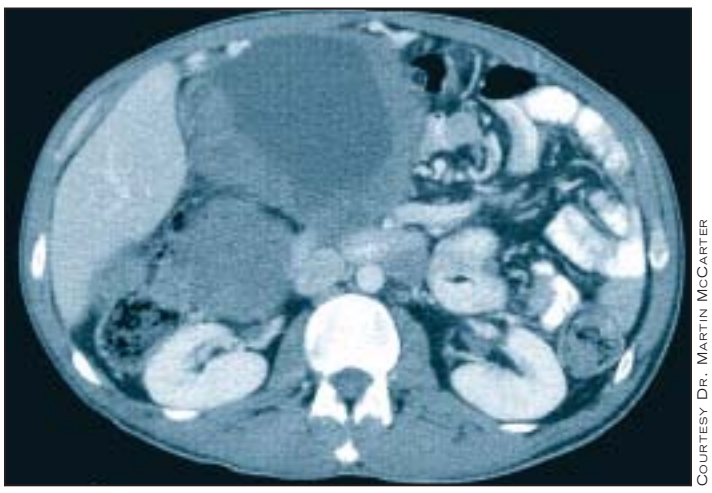
"These tumors were miscategorized for 20 years," said Dr. Stanley W. Ashley, vice chairman of surgery at Brigham and Women's Hospital and professor of surgery at Harvard Medical School, Boston.

In the late 1990s, Japanese researchers discovered that approximately 75%-80% of gastrointestinal stromal tumors (GISTs) have mutations in the c-kit gene.

This advance meant that tumors previously classified as leiomyomas, leiomyosarcomas, and leiomyoblastomas could be correctly recognized as GISTs. Further study revealed that 5%-10% of GISTs have a closely related mutation in the PDGFRA gene, while approximately 12%-15% are unrelated to these mutations and therefore characterized as "wild type" or "wild card" GISTs.

GISTs are now recognized as the most common sarcomas of the gastrointestinal tract and account for an official 0.2% of GI malignancies, "but that's changing" as the incidence increases, Dr. Ashley said.

Autopsy studies suggest that small GISTs exist in much of the population, with triggering genetic mechanisms likely responsible for turning these benign, incidental lesions into the "bad actors" they can become.



COURTESY DR. MARTIN MCCARTER

CT is the best preoperative planning tool for gastrointestinal stromal tumors, the most common sarcomas of the GI tract.

An important therapeutic turning point was the approval in 2002 of imatinib (Gleevec) for unresectable and/or metastatic GISTs, which drove median survival rates for these patients from "at best, 19 months" to about 58 months, said Dr. Martin McCarter, associate professor of surgery at the University of Colorado, Denver.

Adding nuance to basic understanding, Dr. Christopher Corless, chief of surgical pathology at Oregon Health and Science University, Portland, and others have begun to further characterize mutations according to exons within the c-kit and PDGFRA genes.

"We've come to think of GIST not as a single, unique entity, [but] rather as a family of tumors broken down by type of kit mutation or type of receptor alpha mutation," Dr. Corless said at the meeting.

Exon 11 mutations, for example, occur in GISTs seen throughout the GI tract and are quite sensitive to Gleevec, as are "wild type" tumors. Exon 9 mutations, however, occur only in tumors arising from the duodenum, jejunum, ileum, and right colon—"never in the stomach," he said. They respond to Gleevec in standard doses in only about 35%-40% of cases, which suggests to some the need to increase the dosage given to patients with this mutation.

And exon 18 mutations in the PDGFRA gene, seen in tumors arising in the stomach and omentum, appear to be 100% resistant to Gleevec—at least in vivo—which makes these patients potential candidates for sunitinib, which has been approved for salvage therapy and is marketed as Sutent.

Dr. McCarter recommends that advanced tumors be biopsied, then treated with one of the tyrosine kinase inhibitors for 3-6 months. Surgery should be performed while the tumor is still responding. Selective resection may be considered if focal resistance to the drug is detected.

For patients with suspected GISTs small enough to be resected, biopsy should be skipped, suggested Dr. Ashley. The best tool for preoperative planning is the CT scan, although endoscopic ultrasound–guided fine-needle aspiration has been used in the upper GI tract.

Once macroscopic disease has been resected (with negative microscopic margins, if possible), size (greater or less than 2 cm for intestinal tumors, and greater than or less than 5 cm for stomach tumors) and mitotic count determine prognosis and risk of recurrence.

Although tyrosine kinase inhibitors are approved only for advanced disease, neoadjuvant therapy is recommended by some.

"If it's less than 5 cm, proceed with surgery," opined Dr. Ashley, who added that although Gleevec has greatly improved survival for some patients, it is "no match for the response you get with surgery."

Dr. McCarter advised prudence in discussing prognosis with patients who have unresectable or metastatic GISTs, despite the advances made in understanding these lesions.

"It's important to point out that cure is still unlikely for those with metastatic GIST," he said. Significant differences in progression-free survival still mean that most patients can expect a "lifetime of chemotherapy."

Almost all patients with unresectable disease develop new mutations during the course of their treatment, he said. ■

Comorbidity, Warfarin Use Boost Colonoscopy Complications

BY ALICIA AULT
Associate Editor, Practice Trends

WASHINGTON — Patients who are sicker, who are taking warfarin, and whose polyps are removed by snare with cautery are at higher risk for complications following screening or surveillance colonoscopy, according to an analysis presented at the annual Digestive Disease Week.

Overall, the incidence of serious complications after screening was 2.2 of every 1,000 exams, and it was 1.7/1,000 for potential related events, according to Dr. Cynthia Ko of the University of Washington, Seattle.

There were no complications among the 40- to 49-year-olds, compared with 4.4/1,000 among patients aged 80 and older.

Dr. Ko and her colleagues prospectively assessed colonoscopies performed on 18,271 patients aged 40 years and older who were referred for average risk screening, surveillance of prior polyps or cancer, a family history of polyps or cancer, or follow-up after another diagnostic procedure, such as a positive result on a fecal occult blood test.

Patients were excluded if they had a history of recent gastrointestinal bleeding or of inflammatory bowel disease, or had an incomplete colonoscopy because of poor bowel preparation.

The researchers identified the study patients through the Clinical Outcomes Research Initiative, a database maintained by the Oregon Health and Science University, Portland. Participating practices include academic, Veterans Affairs, and community endoscopy practices that agree to generate electronic medical record reports for endoscopic procedures.

Currently, complication rates for surveillance and screening aren't well defined, Dr. Ko said. Perforation rates vary from 0.01% to 0.2%, and postpolypectomy syndrome incidence varies from 0.4% to 1%, she said.

In the Washington study, patients were queried at 7 and 30 days after colonoscopy about new symptoms, physician visits, hospitalizations, and unplanned surgeries.

Related events included colon perforation, GI bleeding, diverticulitis, and postpolypectomy syndrome. Potentially related complications included cardiac and neurologic events.

The 18,271 patients came from 19 sites and received colonoscopies from 89 endoscopists. The patients were referred because they were at risk (42%), they needed surveillance (27%), they had a family history (17%), or they had to have follow-up on a previous diagnostic test (14%).

Related complication rates were 1.3/1,000 for GI bleeding requiring hospitalization, 0.8/1,000 for GI bleeding requiring transfusion, 0.9/1,000 for diverticulitis, 0.3/1,000 for diverticulitis requiring hospitalization, 0.1/1,000 for postpolypectomy syndrome, and 0.2/1,000 for perforation.

The authors also calculated an overall complication rate of 2.2/1,000, which included GI bleeding with transfusion, diverticulitis with hospitalization, perforation, or postpolypectomy syndrome. The serious complication rate was 1.4/1,000; serious complications included GI bleeding with hospitalization, diverticulitis with hospitalization, perforation, or postpolypectomy syndrome.

Potentially related events included angina or myocardial infarction (0.6/1,000), stroke or transient ischemic attack (0.4/1,000), and other events, including hospitalization for intravenous catheter site infections, abdominal pain, arrythmia, gallstones, kidney stones, and drug reactions (0.7/1,000).

Complications were more common in patients undergoing a surveillance or follow-up exam, and for those who were older. There were no complications among the 40- to 49-year-olds, compared with 4.4/1,000 among patients aged 80 and older.

Using a multivariate analysis, the authors determined that there was a threefold increase in complications in patients who were American Society of Anesthesiologists class III, compared with class I or II patients; a fivefold increase in patients who took warfarin, compared with those who used aspirin or NSAIDs; and a fivefold increase for a polyp removed with cautery. If more than one polyp was removed, there was a 13-fold increase in complications, Dr. Ko said. There was no difference among the sites, and the endoscopist's case volume did not influence the findings, she said.

She cautioned against applying the results to all physicians because the study included only gastroenterologists.

The study was supported by the National Institutes of Health and the Centers for Disease Control and Prevention, said Dr. Ko, who had no disclosures. ■