

New Advances Extend Survival in 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 about 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, and about 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, said Dr. Ashley.

Data from 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.

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, rather as a family of tumors broken down by type of *kit* mutation or type of receptor alpha mutation," said Dr. Corless at the meeting.

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.



A bulky abdominal metastatic gastrointestinal stromal tumor is shown here on a computed tomography scan.

COURTESY DR. MARTIN MCCARTER

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, adding 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.

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

Panel Passes on Biologics as a First-Line Therapy for Inflammatory Bowel Disease

BY DIANA MAHONEY

New England Bureau

Biologic agents should not be used as first-line therapy for inflammatory bowel disease (IBD), according to the recommendations of a consensus development conference convened by the AGA Institute.

While certain biologic therapies have demonstrated efficacy in some patients with Crohn's disease and ulcerative colitis, especially patients with refractory or fistulizing disease, there is also evidence of serious, potentially fatal side effects, wrote Dr. Paul Rutgeerts and Dr. Steven Hanauer, co-chairs of the consensus conference, as well as the other members of the AGA Institute IBD Biologics Conference panel.

Thus, despite emerging evidence that the early use of biologics may modify the course of IBD, there is insufficient data so far to support their routine use as first-line agents, according to the group's findings, which are reported the July 2007 issue of *Gastroenterology*.

Biologic therapy can be considered prior to steroid use in some patients with IBD, including those for whom other therapies have failed or in whom steroids are contraindicated,

the panel wrote. Additionally, use of biologic agents may be warranted in specific subgroups of patients with IBD, such as those with complex fistulas for whom conventional therapies are relatively ineffective.

The majority of available data regarding the use of biologic agents in IBD relates to anti-tumor necrosis factor (anti-TNF) drugs. In comparing the results of clinical trials of currently available anti-TNF agents approved for Crohn's disease (in-



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DR. HANAUER

fliximab and adalimumab) and for ulcerative colitis (infliximab), as well as certolizumab pegol, for which approval is pending for Crohn's disease, the panel determined that the drugs, "when optimally dosed, are similarly effective in their ability to induce response and remission."

In terms of other biologic agents, the drug etanercept, in doses that are effective in rheumatoid arthritis, "is not effective in Crohn's disease,"

while the human monoclonal antibody natalizumab appears to have similar maintenance benefits to those of the anti-TNFs, "although there [are fewer] high-quality data to evaluate pertaining to induction of remission," the authors wrote.

The degree and duration of therapeutic response to biologic agents can be affected by the development of antibodies to the drugs, which is a common occurrence, the panel stated. High-dose induction accompanied by scheduled maintenance regimens can reduce this immune response, as can immune suppression that has been initiated in advance of the biologic therapy in order to assure adequate immunomodulatory effects, they said.

The use of immune suppression with anti-TNF agents and natalizumab, however, appears to increase the risk of serious infections and neoplasia. For example, natalizumab use with concomitant immune suppression has been associated with progressive multifocal leukoencephalopathy (PML), while infliximab combined with azathioprine has been associated with neoplasia, such as hepatosplenic T-cell lymphomas. "These uncommon but serious risks require additional risk-benefit evaluations for individual patients," the authors stated. ■

Obesity Does Not Alter Colon Cancer Screening

WASHINGTON — People who are overweight or obese appear to take advantage of colorectal cancer screening opportunities at the same rate as normal-weight Americans.

Several studies have indicated that people with a higher body mass index (BMI) do not seek out screening for breast and colon cancer. But Dr. Deborah A. Fisher, of Duke University, Durham, N.C., and Durham Veterans Affairs Medical Center, and her colleagues determined that overweight and obese residents of North Carolina access fecal occult blood tests, flexible sigmoidoscopy, and colonoscopy at the same rate as those who are normal weight.

At the annual Digestive Disease Week, she presented an analysis of the North Carolina Colon Cancer Study, a case-control population-based study. The study used height and weight measurements to calculate BMI, but information about colon cancer screening was self-reported by patients.

The primary outcome was whether the patient was current for any colon cancer screening test, which included a fecal occult blood test in the past year, a colonoscopy within the past 10 years, a flexible sigmoidoscopy within the past 5 years, or a barium enema within the past 5 years.

Among the 928 patients, the average age was 67 years; half were male, 59% were white, and 41% were African American. Of these patients, 29% were normal weight (BMI of 18-24.9 kg/m²), 39% were overweight (BMI of 25-29.9), 19% were obese category I (BMI of 30-34.9), 9% were obese category II (BMI of 35-39.9), and 4% were obese category III (BMI of 40 and over). There were no patients with a BMI of less than 18 in this study, Dr. Fisher said.

Across all the BMI categories, the percentage of those who had undergone screening ranged from 54% to 67%. There was no difference in screening behavior in any of the overweight or obese patients, compared with normal-weight patients. Gender also had no impact on screening behavior. Dr. Fisher reported no disclosures. The study was supported by a National Institutes of Health grant.

—Alicia Ault