

Missouri Cancer Care Perspectives

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Gastrointestinal Tumor Study Group Being Formed

Will foster collaborative treatment approaches among area physicians

Missouri Cancer Care medical oncologist John Wilkes is organizing a gastrointestinal tumor study group for interested area physicians.

The purpose of the group is to foster collaborative treatment approaches among specialists involved in the diagnosis and management of gastrointestinal malignancies, to identify individuals at risk for hereditary disease and, ultimately, to reduce local mortality rates.

The group will focus on all tumors of the gastrointestinal system including cancers of the esophagus, stomach, small intestine, colon, rectum, anus, pancreas, liver, bile ducts and gall bladder. Less frequent carcinoid and GI stromal tumors will also be included.

“Although surgery is the initial treatment for many of these patients, some will present with unresectable disease or will experience a recurrence,” said Dr. Wilkes. “A coordinated multidisciplinary approach combining surgery, radiation and medicine (often) provides the best outcome.”

The study group will provide local physicians interested in gastrointestinal malignancies with a forum for discussion. “It will be an open, collaborative think-tank of sorts and a means to raise the collective abilities of all interested parties,” said Dr. Wilkes, who specializes in gastrointestinal malignancies at Missouri Cancer Care.

“I am hopeful that we may eventually have regular meetings as either tumor board or case presentations, lectures by national and international experts, and develop innovative funded research protocols.” An initial goal of establishing a formal genetic testing program for individuals believed to be at risk for hereditary non-polyposis colorectal cancer (HNPCC) is already underway.

MCC initiative to include lectures, clinical trials, genetic testing & counseling

a positive or negative test result that requires the development of a formal genetic testing program.”

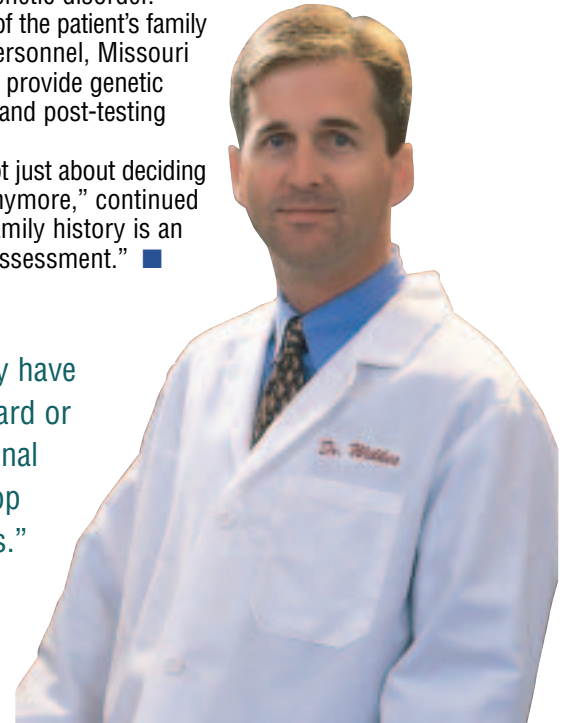
If individuals do harbor one of the mutant HNPCC genes, earlier and more frequent screenings, such as colonoscopies, should be performed. Persons who fit a high-risk profile but who test negative for HNPCC are not out of the proverbial woods, however.

They still need careful monitoring. The current test detects only two of the five genetic mutations known to cause 95 percent of cases of the hereditary condition.

Continued Dr. Wilkes, “The actual blood test is a relatively minor aspect of patient care. The more complex issue is the counseling of other family members and their understanding of the potential implications of being diagnosed with a genetic disorder.”

After a detailed screening of the patient’s family history by trained nursing personnel, Missouri Cancer Care oncologists will provide genetic counseling, testing services, and post-testing recommendations.

“Colorectal screening is not just about deciding what type of scope to use anymore,” continued Dr. Wilkes. “Now, taking a family history is an integral part of patient risk assessment.” ■



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John Wilkes, M.D., regarding a GI tumor study group for physicians

According to the Centers for Disease Control, there were approximately 413 cancer deaths attributable to gastrointestinal malignancies per a population of 100,000 during 1994-1998 in St. Charles County.

Source: National Center for Health Statistics, Centers for Disease Control, 1994-1998.

Genetic testing & counseling for HNPCC

Although HNPCC accounts only for five percent of all colorectal cancer, persons with the condition have a 50 percent chance of passing the genetic mutation to their children.

“The (HNPCC) test is initially meant for the person with a high-risk pedigree who has already been diagnosed with HNPCC-related cancer,” said Dr. Wilkes. “The affected individual becomes the point person, the first member of that family who should be tested. It is the potential complex ramifications of either

From Our Point Of View

Colorectal screenings are underutilized

According to recent data, less than 40 percent of American adults age 50 or older have undergone one of the colorectal cancer screening tests at the recommended intervals. Researchers further estimate that at least one-third of cancer deaths would be prevented if such screenings were employed at the suggested timetable. This would translate into nearly 20,000 lives saved annually in this country alone. These are sobering statistics, and one of the reasons why we have included screening guidelines in this edition of *Perspectives*.

Collectively, cancers of the digestive system are the most common group of malignancies accounting for over 250,000 cases in this country each year.* They are also the focus of this issue.

Although surgery is often the initial treatment approach for many of these patients, a multidisciplinary approach often provides the best potential outcome. And that leads to our article about a new GI tumor study group for local physicians being organized by Dr. Wilkes, a medical oncologist who specializes in gastrointestinal malignancies. We also detail, in time-line fashion, new chemotherapeutic approaches doubling the median survival rate for persons with metastatic colorectal cancer. The importance of palliative care for those with pancreatic malignancies is also reviewed, as well as information about a newly-discovered mutant protein responsible for some gastrointestinal stromal tumors.

And that is the news, as we perceive it. ■

*Source: American Cancer Society

Colorectal Screening Guidelines

For Asymptomatic People

Beginning at age 50, men and women should follow one of the following examination schedules:

- A colonoscopy every ten years
- A double-contrast barium enema every five years
- Annual fecal occult blood test and flexible sigmoidoscopy every five years
- A flexible sigmoidoscopy (FSIG) every five years
- A fecal occult blood (FOBT) test every year

Combined testing is preferred over either annual FOBT, or FSIG every five years, alone.

Source: American Cancer Society Cancer Facts & Figures 2003

Hereditary Colorectal Cancer Risk Factors

- HNPCC
 - Accounts for 5 percent of all CRC
 - Diagnosis suspected by family history
- “3-2-1-1” Rule — Amsterdam Criteria
 - Three or more family members affected (1st or 2nd degree relatives)
 - Two or more successive generations affected
 - One must be a 1st degree relative
 - One must be diagnosed before age 50

Guidelines For Patients At High Risk (i.e., HNPCC)

Colonoscopy

- Every one-two years
- Beginning at age 20

Genetic counseling

50-70 percent of mutations can be found in families meeting Amsterdam Criteria ■

2nd Defective Protein Linked With Rare & Deadly GI Cancer

May serve as "target" for new molecular treatments

Researchers at Oregon Health & Science University have discovered a mutant protein that triggers some cases of a rare and deadly cancer known as gastrointestinal stromal tumors (GISTs). The defective protein is a mutated form of the enzyme platelet-derived growth factor receptor alpha (PDGFRA).

Researchers theorize that identification of this enzyme's pathway may lead to the development of other targeted or "smart" bomb" therapies, besides Gleevec, for treating GISTs.

Now the treatment of choice, Gleevec specifically targets an abnormal form of the enzyme KIT which is believed to be responsible for 85 percent of the rare stromal tumors.

Initially, however, Gleevec was approved for the treatment of chronic myeloid leukemia (CML).

"Independent research groups from Europe and the United States recognized that a similar enzyme pathway existed in both CML and gastrointestinal stromal

tumors," said John Wilkes, M.D., a medical oncologist at MCC. "These investigators hypothesized that Gleevec would also be effective in GISTs based on the strong tumor expression of tyrosine kinase, KIT."

According to the first-ever study of Gleevec in solid tumors i.e. GISTs, 89 percent of the patients experienced a marked reduction in symptoms. In phase II clinical trials of 139 patients, 68 percent experienced a partial response while 54 patients had stable disease. Results of both studies were presented during the plenary session of the annual meeting of the American Society of Clinical Oncology.

"The response of GISTs to Gleevec was exciting as these tumors were historically unresponsive to all treatments," continued Dr. Wilkes. "Solid tumors are traditionally more difficult to treat than CML. These results provide proof-in-principal that targeted therapies can work in solid tumors as well and may indeed be the future of medical oncology." ■

Each year 5000 to 10,000 Americans are stricken with GISTs which invade the organs or linings of the gastrointestinal tract. Once the tumors metastasize, they often prove unresponsive to conventional treatment — prior to Gleevec.

Source: Oregon Health & Science University

New Treatments For Advanced Colorectal Cancer Boost Survival

Irinotecan, oxaliplatin and capecitabine responsible for gains; decades of clinical research finally pay off

New chemotherapy drugs and combination therapies have helped double the median life expectancy for persons with advanced colorectal cancer (CRC) from nine to 18.6 months. "Current clinical studies suggest that the average survival may reach two years once we become more experienced in sequencing these regimens," said John Wilkes, M.D., a medical oncologist who specializes in gastrointestinal malignancies at Missouri Cancer Care.

Advances have been recent. For decades prior to 1996, the standard treatment for metastatic colorectal cancer was a combination of 5-fluorouracil (5-FU) and leucovorin. Responses were infrequent and usually of short duration. The median survival was a mere nine months.

"I remember almost being astonished when a patient's tumor would respond to treatment with 5-FU and leucovorin," said Dr. Wilkes. "With today's regimens, I'm surprised if they don't respond."

Three new chemotherapy agents, irinotecan, oxaliplatin and capecitabine are largely responsible for the improved response rates.

Irinotecan was studied in randomized clinical trial conducted by Leonard B. Saltz, M.D, of Memorial Sloan Kettering Cancer Center. The three arm trial compared 5-FU/leucovorin, irinotecan alone, and a combination of all three drugs, IFL. By itself, irinotecan showed no benefit over 5-FU/leucovorin. However, the three drug combination doubled tumor response rates, demonstrated longer time to disease progression and increased median survival to 14.8 mos. Consequently IFL became the standard chemotherapeutic approach.

"The next major advance in CRC therapy came with the publication of an Intergroup trial comparing

IFL to regimens containing a new drug called oxaliplatin which previously had been available only in Europe," continued Dr. Wilkes. The trial compared IFL with an experimental regimen called FOLFOX-4 (5-fluorouracil, leucovorin and oxaliplatin) and another experimental regimen combining oxaliplatin and irinotecan.

Patients receiving the FOLFOX-4 regimen fared significantly better than those receiving IFL, or the oxaliplatin and irinotecan combination. These patients with metastatic disease lived four months longer with median survival now at 18.6 months.

The Intergroup trial results were reported at the 2002 annual meeting of the American Society for Clinical Oncology during which new data about a tumor-activated chemotherapy drug called capecitabine was also presented.

Capecitabine is an oral 5-FU precursor," explained Dr. Wilkes. It is 5-FU — in pill form. A targeted therapy of sorts, capecitabine is activated by an enzyme highly expressed by the tumor. As a result, the cancer killing agent is delivered directly to the tumor site. Consequently side effects are minimized. "This unique agent has offered a new level of convenience with a very acceptable toxicity profile. It is currently being studied in combinations with irinotecan and oxaliplatin," continued Dr. Wilkes. Other studies suggest that capecitabine has the potential to replace intravenous 5-FU in many, if not all, gastrointestinal malignancies.

But efforts to identify new and effective regimens continue. "I expect that future advances will involved the sequencing of regimens incorporating capecitabine," continued Dr. Wilkes. "The combinations of capecitabine with oxaliplatin (XELOX) and irinotecan (XELIRI) appear to be extremely promising approaches." ■

According to the most recent data available from the American Cancer Society, colorectal malignancies account for 10 percent of new cancers diagnosed in St. Charles County annually.

"In the early 90's, I had the opportunity to work with oxaliplatin in the lab as a research fellow. No one had any idea at the time that it would be a major advance in the care of patients with CRC. It is very exciting to see a drug that I worked with in the lab now available to treat my patients a decade later."

John Wilkes, M.D.,
medical oncologist

Caring For Patients With Advanced Pancreas Cancer

Symptom management & pain relief are often main goals of therapy

Pancreatic cancer is the second-most common malignancy of the gastrointestinal tract, and fourth leading cause of cancer deaths in the United States. With vague symptoms and no screening tests, early diagnosis is infrequent.

Surgical resection provides the best chance of cure, but only in specific patients whose disease is confined to the pancreas. Radiation may shrink or slow tumor growth. Chemotherapy has had a modest impact as a result of new drugs such as gemcitabine* and irinotecan. With little convincing evidence indicating that systemic chemotherapy provides survival benefits, the goals of therapy are often palliative.

Pain is reported in 80 percent of patients with advanced pancreas cancer and may be refractory to traditional analgesics. Celiac blocks may be effective interventions although they are underutilized. Radiation therapy may provide the best palliation for these patients.

"Radiation is effective in palliating pain from pancreatic cancer," concurred John Bedwinek, M.D., radiation oncologist at Missouri Cancer Care. "Pain relief occurs in 60 to 70 percent of these patients."

A combination of chemotherapy (specifically 5-fluorouracil) and concurrent radiation can also offer both symptom relief and increase the number of one-year survivors. According to results in an older randomized trial, this approach increased the proportion of one-year survivors from 10 percent (with radiation therapy alone) to 40 percent. Similarly, the median survival for the combination was 35 weeks versus 18 weeks in the radiation therapy alone arm. This combined approach has been used by Missouri Cancer Care oncologists.

Nutritional variables may also complicate the treatment of patients with metastatic pancreatic cancer. Weight loss, cachexia and pancreatic insufficiency are nearly universal symptoms of advanced disease. Although an experienced clinical dietitian can provide assistance, various pharmaceutical interventions including prokinetics, corticosteroids, medroxyprogesterone, dronabinol and



Above is a 3D image of a metastasized pancreatic tumor

pancreatic enzyme replacements may also be required.

Depression and fatigue are other common symptoms and may be managed with SSRI's, psychostimulants and erythropoietin.

The inherent resistance of pancreatic cancer cells to chemotherapy remains an ongoing challenge. Future treatments will most probably include targeted therapies and molecular approaches. Inhibitors of the epidermal growth factor receptors are currently in advanced clinical trials. Missouri Cancer Care is currently involved in the clinical evaluation of these agents. Within the next few months, MCC hopes to have a phase III multi-institution study available to its patients with advanced pancreas cancer. This study will evaluate a new agent designed to overcome resistance to 5-fluorouracil. ■

*Approved for the treatment of advanced pancreas cancer in 1996, gemcitabine improved one-year survival rates to 18 percent, from two percent with 5-FU. Burris et al. *Journal of Clinical Oncology* 1997.

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