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Pathways in Cancer

Clinical insight and analysis
in advanced cancer care

Colon and Rectal Cancer Prevention and Treatment

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Colon and rectal cancer is one of the most common cancers in the industrialized nations of the world. There will be an estimated 143,460 new cases diagnosed in the United States alone in 2012. 51,690 will die of the disease. Almost 50% of those diagnosed will die of the disease. Although in the last decade there has been a decrease in incidence and mortality of the disease, it remains a major public health problem. The following guidelines for screening can decrease the disease by as much as 75–80%.

Screening and Prevention

The biggest risk factor for colon and rectal cancer is an age of over fifty years—this group contains 90% of those diagnosed. Of those with colon and rectal cancer, only 5% have a clear genetic predisposition (familial polyposis, hereditary nonpolyposis coli). Only about 25% of those diagnosed will be in the "high risk" category (first-degree family history of adenomas or colon cancer, personal history of ovarian, endometrial or breast cancer). Therefore, a screening program must evaluate the whole population for prevention and detection. Most, if not all, colon cancers are preceded by non-cancerous polyps. Data today would suggest that removing precancerous polyps decreases (but does not eliminate) colon and cancer incidence by 80% and colonoscopy decreases mortality from the disease by 50%. Colonoscopy remains the most effective modality for prevention of colon and rectal cancer, and is recommended every 10 years for average-risk persons over age fifty and every five years for people of increased risk. Alternatively, flexible sigmoidoscopy every five years, double contrast enema or CT colonography every five years may be offered, with their limitations. For detection of colon and rectal cancer, three-card fecal occult blood testing (or preferably the more accurate fecal immunochemical test) should be performed. Screening is recommended for average-risk persons up to ages 75–80.

Treatment

The treatment of colon cancer is dependent on stage. Stage is defined by the World Health Organization's TNM Staging system. One looks at tumor characteristics (depth of penetration through the bowel wall), lymph node involvement (attention to number of nodes collected and involved with tumor) and distant cancer spread. Based on clinical staging—determined by patient history, physical exam, laboratory studies, imaging studies and patient co-morbidities—a treatment plan is offered. Generally speaking, initial treatment for all but the most advanced colon cancers is surgery. This affords definitive pathologic staging and the best chance of cure or, if not, palliation. Based on pathological staging, those with stage III and IV cancer are offered chemotherapy. This commonly is comprised of FOLFOX (5FU, Leukovorin and Oxaliplatin) for up to six months. The use of chemotherapy for stage II disease is controversial and is generally reserved for those with poor prognostic findings.

Rectal cancer treatment is slightly different. Though the cell type is the same, the confines of the bony pelvis prevent wide local excision in those tumors that penetrate the bowel wall. Therefore, those localized tumors that show penetration through the bowel wall (stage II) or lymph node involvement (stage III) on specialized imaging studies are often treated with preoperative radiation and chemotherapy, followed by surgery and completion of postoperative chemotherapy.

Following these treatment strategies, disease-free intervals and cure rates are increased. Local recurrence rates are decreased in rectal cancer.

The Future

Colon and rectal cancer remains a major public health issue with respect to healthcare cost and population morbidity and mortality. More cost-effective and patient-acceptable screening for prevention and early detection of colon and rectal cancer would have major impact. DNA fecal studies, to date, have not proved reliable, but promise to be less expensive and

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Colon Cancer Prevention

Kuldip Sandhu, MD, FACG

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths. Each year there are 150,000 new cases of colon cancer diagnosed in the United States, and 56,000 patients die from this cancer annually. A person at age 50 has about a 5% lifetime risk of developing this cancer and a 2.5% risk of dying from it.

The extent of spread at diagnosis of CRC (stage I–IV) determines the chance of survival. Hence, early detection and prevention of CRC are of critical importance.

The risk factors for CRC include age, race (especially African Americans), a personal history of colon polyps, inflammatory bowel disease (ulcerative colitis/Crohn's disease) or other cancers (e.g., uterine cancer) and a family history of colorectal neoplasia. There is also an increased awareness of the relationship between diet, obesity and smoking with CRC. Red meat, animal fat and processed meats increase the risk of CRC while fiber, fruits, vegetables, calcium, fish oils, antioxidants, folic acid and selenium decrease the risk. Intake of aspirin and NSAIDs is also associated with decreased risk.

Individuals with a 20-pack-year history of smoking have a 30% increased risk of CRC. A one-unit increase in BMI above normal increases CRC risk by 3%.

Screening and surveillance are cornerstones in the prevention of CRC. Recommended strategies for CRC screening fall into two broad categories: stool tests and structural examinations. Stool tests need to be done annually. Stool tests include guaiac fecal occult blood test (gFOBT), fecal immunochemical test (FIT) and fecal DNA test. Comparative studies have shown that the semi-quantitative FIT is more accurate than the gFOBT for the detection of CRC and advanced adenomas. FIT is now recommended as the first choice fecal occult blood test in CRC screening. However, population-based studies showing a decrease in CRC mortality (by 15%–20%) are based on gFOBT.

The fecal DNA test detects more CRC and advanced adenomas; however, it is still not the first choice in view of the high cost.

According to the US Multisociety Task Force on CRC[1], the structural examinations should be offered first as these examinations not only detect cancer but are also CRC prevention tests. The preferred structural examination is colonoscopy every 10 years beginning at age 50 and age 45 in African Americans. In other high-risk groups, such as persons with a family history of HNPCC (Hereditary Nonpolyposis Colon Cancer/Lynch Syndrome) or FAP (Familial Adenomatosis Polyposis Syndrome), the timing and frequency of screening needs to be individualized.

> "Individuals with a 20-pack-year history of smoking have a 30% increased risk of CRC. A one-unit increase in BMI above normal increases CRC risk by 3%."

The alternative examinations are flexible sigmoidoscopy, CT colonography (CTC), or double contrast barium enema (DCBE) every five years. The US Multisociety Task Force, along with the American Cancer Society and the US Preventive Services Task Force, all declined to endorse CTC, also known as "virtual" colonoscopy, for CRC screening. The Center for Medicare and Medicaid Services (CMS) declined to include CTC as an option for CRC screening for Medicare beneficiaries. The Multisociety Task Force does not recommend DCBE due to low sensitivity and decreasing experience of newly trained radiologists.

Recent evidence suggests that patients with no abnormalities on a previous colonoscopy have a markedly reduced risk of CRC.[2,3] Studies involving patients with adenomas have suggested that polypectomy can prevent approximately 80% of CRC and decrease mortality from CRC by 53%.[4] In various studies, the flexible sigmoidoscopy has been shown to decrease mortality from CRC by

1 *American Journal of Gastroenterology*, 2009; Volume 104; page 741.
2 *Gastroenterology*, 2010; Volume 138; pages 870–876.
3 *New England Journal of Medicine*, 2008; Volume 359; pages 1218–1224. *N Engl J Med*, 2009; 361; 2004.
4 *N Engl J Med*, 2012; 366; 687–696.

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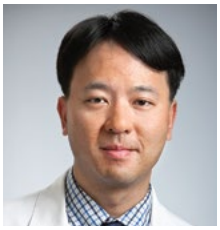
Chemotherapeutic Agents

Christian Kim, MD, MO



Medical oncology relies on the arsenal of chemotherapeutic agents to treat colorectal cancer. The basic general staging, surgical treatment and epidemiology have been presented by other authors. This brief article will attempt to cover chemotherapeutic agents with both a historic and pharmacologic perspective in treating colon cancer.

The Past

5-Fluorouracil (5FU), synthesized in 1957 by Charles Heidelberger, MD, has served as the backbone for colorectal cancer chemotherapy for many years. It has been used in conjunction with leucovorin and levamisole with differing dose and infusion (bolus vs. infusion) schedules. These drugs were the cornerstone of treatment for about 40 years.

The Present

Irinotecan (approved by the FDA in 1999) and oxaliplatin (approved in 2002) opened the door for additional treatment options and would prove to be effective agents and lead to FOLFOX and FOLFIRI regimens. Novel drugs such as capecitabine (approved by the FDA in 2001) was a 3rd generation oral fluoropyrimidine pro-drug offering an alternative and convenient form of 5FU.

Soon afterwards began the introduction of biologic agents in 2004 with drugs such as cetuximab, bevacizumab and panitumumab. Cetuximab, an IgG1 chimeric antibody directed against the external cell surface domain of EFGR when combined with irinotecan, showed improvements in time to progression although survival was similar in patients with metastatic progressive disease. Panitumumab is a recombinant human IgG2 kappa monoclonal antibody that binds specifically to the human Epidermal Growth Factor Receptor (EGFR), similar to cetuximab.

Bevacizumab, a recombinant humanized monoclonal antibody directed against VEGF (overexpressed in colorectal cancer), showed improved overall response rates, improved progression-free survival and overall survival versus IFL alone, as noted by Dr. Hurwitz et al. in a pivotal phase III trial.

More recently, the FDA approved regorafenib, an oral agent that inhibits a wide variety of tyrosine kinases including antiangiogenic kinase (e.g., VEGFR1-3), as well as stromal kinases (PDGFR-beta), FGFR1 and oncogenic kinases (KIT, PDGFR,RET). CORRECT, a large phase III randomized trial, evaluated regorafenib versus best supportive care. This study demonstrated a modest improvement in progression-free survival and a statistically significant improvement in overall survival. It also suggested that a subset of patients may experience a longer durable benefit but there was no way to identify those patients.

In August 2012, ziv-aflibercept ("iv" standing for "intravenous," distinguishing this product from the same molecule that is used to intraocularly treat wet macular degeneration) was FDA-approved. Approval was based on the data from the VELOUR trial which demonstrated a survival advantage in patients that progressed on FOLFOX when given in conjunction with FOLFIRI in the second-line setting.

The Future

The future of colorectal cancer treatment will focus on tailoring therapeutic agents based on the patient's individual cancer profile. For example, patients with codon 12 mutation of KRAS correlates to resistance to anti-EGFR monoclonal antibodies such as cetuximab and panitumumab. Another issue is predicting a response to VEGF therapy. Some data may suggest that low levels of VEGF-A splice form or VEGF(165)b may be a predictive marker for bevacizumab in metastatic colorectal cancer while individuals with high relative levels may not benefit.

Currently there are other agents such as ramucivumab, ganitumab and brivanib—all with varying success in phase II studies. The question remains on how to incorporate these drugs and select patients that could benefit the most from these newer agents. We shall see what the future has in store.

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more accurate than present strategies in disease screening and prevention as development moves forward.

Colon and rectal cancer treatment for the last half century has been primarily surgery with adjuvant cytotoxic chemotherapy. Advances in immunology, tumor-specific chemotherapy, genetics and biotherapy are promising to revolutionize the effective treatment of this cancer.

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up to 30%. There are no studies involving CTC or DCBE showing a decrease in mortality from CRC.

The post-polypectomy surveillance guidelines were updated and published in the September 2012 issue of *Gastroenterology*. These include a 10-year interval for individuals with no polyps or hyperplastic polyps in the rectum and sigmoid colon, and a 5–10 year interval for those with one or two tubular adenomas less than 10mm in size. A 3-year interval is recommended for patients with 3–10 small tubular adenomas and patients with advanced adenomas (tubular adenoma 10mm or larger, adenoma with high grade dysplasia and a villous adenoma). In addition, individuals with one or more sessile, serrated polyps (SSPs) less than 10mm in size and no dysplasia should be screened after five years. Those with one or more SSPs 10mm or larger or any SSP with dysplasia or serrated adenoma should be screened after three years. Individuals with serrated polyposis syndrome (SPS) should be screened after one year. The surveillance and screening should be discontinued when the risks outweigh the benefits based on advanced age and co-morbidities.

After curative colon cancer surgery, the surveillance colonoscopy should be done at intervals of one, three and five years after a clearing colonoscopy before or after surgery.

Patients with ulcerative and Crohn's colitis should start surveillance colonoscopy after eight years of pancolitis or 15 years of left-sided colitis.

The role of different modalities for CRC screening continues to evolve. The current focus is on quality indicators before (prep quality) and during colonoscopy including cecal intubation rate, adenoma detection rate and withdrawal times. Moreover, the role of FIT versus fecal DNA will be clarified in the future.

Colon cancer is one of the most preventable cancers. We should focus our energy in recommending lifestyle changes and screening to our patients.