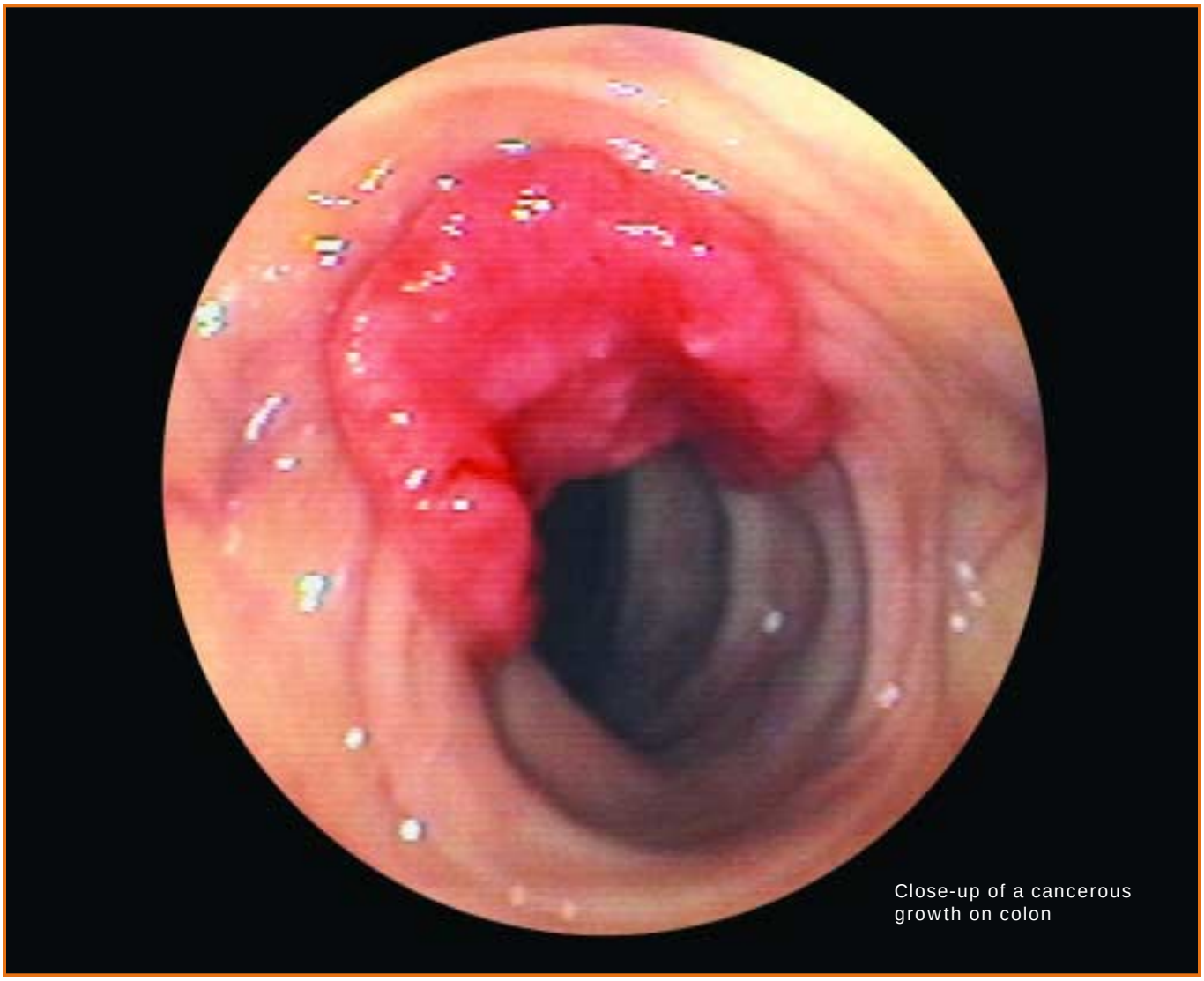
COLORECTAL CANCER:
NO LONGER AN UNSPEAKABLE SUBJECT

As two new drugs await FDA approval, R.Ph.s can urge patients to get screened for this common malignancy

Once an embarrassing subject, colorectal cancer is openly discussed these days. According to the American Cancer Society, colorectal cancer (CRC) is the No. 2 cancer killer in the United States. Last year, 147,500 people discovered that they had the disease, and 57,100 died of it.

Among the general U.S. population, CRC is the fourth most common type of cancer. It is the third most common type of cancer among American women, and also the third most common among American men. Fortunately, two drugs that will provide clinicians with additional tools to treat CRC—and offer hope for patients with the disease—are currently under review by the Food & Drug Administration. Approval of these new agents is expected by the second quarter of 2004.



Close-up of a cancerous growth on colon

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Erbitux: Efficacy against resistant tumors

Cetuximab (Erbitux, ImClone) is a monoclonal antibody that inhibits epidermal growth factor receptor-1 (EGFR-1), said Herbert Hurwitz, M.D., assistant professor of medicine at Duke University Medical Center in Durham, N.C. By doing so, it inhibits the transduction of a signal that generally leads to tumor cell proliferation and survival, he continued.

When ligands bind to and stimulate EGFR-1, messages are transmitted into the cell that tell it to grow and divide, explained Leonard Saltz, M.D., an associate attending physician at Memorial Sloan-Kettering Cancer Center in New York City. When deprived of that signal, tumor cells are likely to have their growth slowed or stopped completely, Hurwitz added. The malignant cells potentially may die, particularly when other antineoplastic agents, such as irinotecan (Camptosar, Pfizer), deliver additional signals for cell death.

Hurwitz pointed out that compared with most traditional chemotherapies, agents such as cetuximab have fewer adverse effects because the targets of these drugs are more characteristic of tumor cells and not healthy cells. He explained that tolerance for these drugs is largely related to the specificity of the target, in that the targets are found predominantly in a tumor environment. The most common adverse effect associated with cetuximab therapy in clinical trials was a skin rash.

According to Saltz, patients who failed prior treatment with irinotecan but continued treatment anyway achieved a 22% response rate when cetuximab was added to their therapeutic regimen. Patients from the same study population who received cetuximab alone achieved a 10% response rate.

"Although studies have shown a therapeutic response, they were not designed to assess survival, so no data exist to show that cetuximab confers a survival advantage," Saltz said. "That is not to say, however, that it does not confer a survival advantage, just that the question has not been asked in a scientific and systematic fashion. I expect that cetuximab will be approved for use in combination with irinotecan in those whose disease has progressed on irinotecan alone." He mentioned that the anticipated FDA action date for cetuximab is next month.

Avastin: Potential as first-line therapy

Bevacizumab (Avastin, Genentech) is also a monoclonal antibody, but one that inhibits a ligand called vascular endothelial growth factor (VEGF) and not a receptor, said Saltz. VEGF is somewhat specific for the abnormal vasculature that develops as part of tumor growth and progression, Hurwitz said. He pointed out that normal host blood cells tend not to have significant overexpression of VEGF.

The tumor-related blood vessels cannot grow if they are deprived of VEGF, Hurwitz explained. In fact, they may shrink, which could lead to tumor control and potentially tumor shrinkage as well.

A complex and dynamic interaction exists between tumor vasculature and the tumor cells themselves, but the exact biology of that interaction is still being evaluated, said Hurwitz.

VEGF is one of multiple tumor angiogenesis factors, but it is clearly clinically relevant because of the positive phase III data that were presented at the annual meeting of the American Society of Clinical Oncology this past year, Hurwitz said. These data are currently under review by the FDA.

Investigators randomized 800 patients with metastatic colorectal cancer to receive either irinotecan/5-fluorouracil/leucovorin (IFL) + placebo or IFL + bevacizumab as first-line chemotherapy, said Saltz. The researchers found that the bevacizumab group had a 4.7-month survival advan-

Other drugs in development

Drug	Company	Development status	Clinical benefit/study findings
PTK787/ZK222584	Novartis AG/Schering AG	Phase III	Shrank or halted the growth of tumors in early trials
Gefitinib	AstraZeneca	Phase II	Approved for the treatment of non-small cell lung cancer
ABX-EGF	Abgenix/Amgen	Phase II	Interim phase II results indicated ability to shrink tumors in 10% of patients
Tezacitabine	Chiron	Phase II	Preliminary phase II results expected this year
Erlotinib	Genentech/Hoffmann-La Roche/OSI Pharmaceuticals	Phase I/II	Preliminary phase I/II results indicated ability to shrink tumors when given in combination with other drugs

Source: Compiled from manufacturers and other sources

Does aspirin lower the risk of colorectal cancer?

The results of two clinical trials published in the *New England Journal of Medicine* last year suggest that daily aspirin therapy can help prevent the development of precancerous adenomas. Investigators in the first study randomized 635 persons with previous colorectal cancer (CRC) to receive either 325 mg of aspirin daily or placebo. The researchers found that 36% fewer of those in the aspirin group developed new adenomas compared with those in the placebo group. They also found that adenomas took longer to develop in those randomized to receive aspirin compared with those randomized to placebo. In addition, the mean number of new adenomas was fewer in patients receiving aspirin compared with those receiving placebo.

In the second study, investigators randomized 1,121 patients with a recent history of adenomas to receive either 325 mg of aspirin daily, 81 mg of aspirin daily, or placebo. After about three years of follow-up, the researchers found advanced lesions in 10.7% of those assigned to 325 mg of aspirin daily, 7.7% of those given 81 mg of aspirin daily, and 12.9% of those who received a placebo.

Although both sets of investigators concluded that aspirin had a beneficial effect against CRC, they concurred that further investigation regarding the risks and benefits of aspirin is necessary and that recommendations for its use as a chemopreventive agent against the disease are premature. The researchers also agreed that aspirin should not be viewed as a substitute for screening methods for CRC such as flexible sigmoidoscopy and colonoscopy.

tage compared with the placebo group.

According to Saltz, this is the largest survival advantage ever shown in a randomized study of CRC patients. It is also the first large-scale trial in which an angiogenesis inhibitor demonstrated significant efficacy in slowing the progression of a solid tumor. "What is important to understand is that the data for bevacizumab support its use with first-line chemotherapy," he said. "No data that I am aware of exist to support its use in the salvage setting. Cetuximab, however, is the exact opposite. No data exist to justify its use as a first-line agent. The current data support only its use as salvage therapy."

Last June, Genentech received fast-track designation from the FDA for bevacizumab. Saltz mentioned that the anticipated action date by the agency is in April. "It is very likely that by the second quarter of 2004, both cetuximab and bevacizumab will be in clinical use, which is very exciting," he said.

Matching patients with therapies

As they await the approval of these new drugs, clinicians are using genetic analysis to ensure that those with CRC receive the most appropriate treatment from among the therapies currently available. "One of the problems with treatment for almost all diseases, including CRC, is that we have multiple drugs with activity in the patient population, but we do not really know which patients are deriving optimal benefit from these therapies," explained Howard McLeod, Pharm.D., an associate professor of medicine in the division of oncology at Washington University School of Medicine in St. Louis.

When multiple drugs and drug combinations are used to treat a disease, the best drug to use for each patient must be chosen, and almost no information is available to help clinicians make that choice, according to McLeod. They try to look at people's DNA and the inherited variations in their genetic material and use that information to determine which drug or combination a patient will respond to best.

"We take large clinical trials and add a very simple test to them," McLeod continued. "Approximately 5 ml of blood is drawn into a purple-top tube. This is a sample that any place can obtain, from a small private practice to a large medical center. The blood sample is shipped to our lab, we extract the DNA, and then perform a genetic analysis to determine which variant of a particular gene a person has."

Initially, McLeod said, they looked at genes that have a known role relevant to a particular drug, such as genes encoding the proteins that metabolize the drug, like the cytochrome p450 enzymes. "We now also look at genes encoding the proteins that transport drugs across membranes and genes that are targets for therapy," he said. If it is known that a particular drug targets a particular gene, they look at genetic variation in that gene as a method of predicting who will respond to treatment.

"Although the problem of therapeutic nonresponse has been around forever, this is a relatively new field," McLeod said. "A few research centers are now starting to do genetic analysis, but we are the main group applying this technique to CRC. The technology is such that this type of analysis can now be done on a large scale. Oncology is one area where the human genome will start having

an impact. Lots of drugs are available, and lots more are coming to market, but we do not know how to use them."

One thing pharmacists may see in their practice is genetic information guiding the choice of therapy or at least being a part of the equation, said McLeod. "The members of my group are all pharmacists by training, so pharmacy has a real input into this developing field. This is an example of pharmacists making drug use better."

The role of the pharmacist

"CRC is an almost completely preventable disease if people are screened appropriately," said Saltz. Standard recommendations are that all people at average risk should get regular colonoscopy screening starting at age 50, and younger if they have familial or individual risk factors, he said. "This is a big public awareness issue. Everyone in the healthcare field, including pharmacists, should try to make patients cognizant of the importance of CRC screening."

In the background are the Medicare reform issues. "Medicare reform is very likely to change reimbursement for chemotherapy, which in turn will change the way these new drugs are used, because these agents will be very expensive," said McLeod. "Even if evidence exists of their effectiveness as first- or second-line therapy, clinicians may wait until the second- or third-line, and only give the drugs to those who have failed everything else," particularly if reimbursement for these expensive agents is very low.

Access to these new, more expensive drugs will be out of the pharmacist's hands, agreed Saltz. "It will be a real public policy issue, because both drugs will be very expensive," he said. "A significant factor in terms of making these agents available to people will be which third-party payers will cover their cost and in what context."

Current standards of care for colorectal cancer patients

Grim statistics regarding the morbidity and mortality associated with colorectal cancer reinforce the need for new and effective treatment options. In March 2003, the National Comprehensive Cancer Network (NCCN) published updated guidelines regarding the treatment of colorectal cancer. The updated guidelines contain treatment recommendations for the antineoplastic agent oxaliplatin (Eloxatin, Sanofi-Synthelabo), as well as updated guidelines regarding the use of radiation therapy in stages II, III, and IV disease.

The guidelines recommend combination therapy with 5-fluorouracil/leucovorin/oxaliplatin as a potential palliative option for patients with colorectal cancer who have distant, unresectable, or multiple metastatic lesions. Additionally, the combination therapy is included as one of several palliative therapies for patients with unresectable or multiple metastatic colon cancer lesions, and as both neoadjuvant (prior to surgery) therapy or adjuvant therapy following surgery in those with resectable liver metastases stemming from stage IV colon cancer.

The Food & Drug Administration recently approved oxaliplatin for the first-line treatment of metastatic colorectal cancer. The drug is now indicated for the treatment of advanced carcinoma of the colon or rectum in combination with infusional 5-fluorouracil and leucovorin. Oxaliplatin was previously approved only for the second-line treatment of metastatic colorectal cancer.

In addition to the incorporation of recommendations for oxaliplatin use, other updates to the guidelines include the following: radiation therapy to the pelvic area should be considered as an adjuvant therapeutic option after combination chemotherapy and resection of metastases/lesions in patients with stage IV colorectal cancer; irinotecan (Camptosar, Pharmacia), oxaliplatin, and capecitabine (Xeloda, Roche) cannot be considered standard adjuvant therapy for patients with stage II or III colorectal cancer at the present time, but may be considered in the context of a clinical trial; radiation is recommended as part of an adjuvant regimen for patients with stage II or III colorectal cancer who have localized perforation or with close, indeterminate, or positive margins.

The 2003 NCCN Clinical Practice Guidelines in Oncology: *Colon and Rectal Cancer Treatment* can be viewed in their entirety in the February 2003 issue of the *Journal of the National Comprehensive Cancer Network*, or by visiting NCCN's Web site at **www.nccn.org**.

Sources of hope, not magic bullets

McLeod, Saltz, and Hurwitz stressed that cetuximab and bevacizumab are not "miracle drugs." Rather, these agents should be considered additional tools that clinicians can use to help those with CRC, Saltz said.

"We have much to do before we fully understand all of the toxicities associated with their use and all of their potential clinical uses," cautioned Hurwitz. "More studies are necessary to further define the role of these therapies in treating CRC, and their value in treating other types of tumors."

Charlotte LoBuono