Neither marimastat nor Bayer's compound appear to affect wound healing. Because angiogenesis is vital to cell growth and wound healing, researchers have been concerned about possible side effects. So far, neither drug affected patients who required surgery while they were on the drug.

Perhaps reacting to the over-promise of the May New York Times article, several company spokespersons were extremely reluctant to convey any optimism about their products. But, in theory, there may be several beneficial by-products that result from the fact that angiogenesis inhibitors target normal dividing endothelial cells, and not tumor cells. One is that they are not likely to cause bone marrow suppression, gastrointestinal symptoms, or hair loss, characteristic of standard chemotherapy. Also, drug resistance may not develop because endothelial cells are not genetically unstable. Most cancer cells have a propensity for mutation and genetic diversity, and are therefore likely to produce drug-resistant cells. None of the trials have lasted long enough to evaluate resistance.

Also, because anti-angiogenic drugs are designed to prevent the further growth of tumors, but do not necessarily kill tumors, anti-angiogenic therapy may prove useful in combination with therapy aimed at tumor cells. Early trials using marimastat and another angiogenesis inhibitor, TNP-470, in combination with standard cytotoxic drugs have begun.

For some researchers, however, not even cautious optimism seems appropriate. "All the information we have is that the drug is working," said Rasmussen. "We have treated 2,500 patients and we haven't seen any problems yet. I would be stunned if the drug doesn't work."

— Nancy J. Nelson

Colon Cancer: New Drug Options Improve on 5-FU

For years, 5-fluorouracil — with or without either oral leucovorin or levamisole — has been about the only chemotherapy option for colorectal cancer patients. But recent insights into the biology of this cancer have spurred development of new drugs that researchers hope will not only work better but carry less toxicity.

The prospect of these new experimental treatments, which are now available or expected to be so shortly, created jam-packed sessions at two cancer meetings earlier this year — the American Society of Clinical Oncology in Los Angeles and the International Congress on Anti-Cancer Treatment in Paris.

"People are clearly looking for a new drug for a disease that is difficult to treat," noted Yousef Rustum, Ph.D., a senior vice president for scientific affairs at Roswell Park Cancer Institute in Buffalo, N.Y., who chaired an ASCO educational session on new drugs for colon cancer.

Added Richard Pazdur, M.D., professor of medicine at the University of Texas M. D. Anderson Cancer Center, Houston, "In essence [with 5-FU], we have a marginally active drug that has significant toxicities when used in optimal fashion." Pazdur, who spoke both in Paris and Los Angeles, said that although 5-FU has been used in a variety of ways, "fewer than a third of the patients achieve an objective response rate with 5-FU and approximately 20% of patients in large clinical trials are hospitalized for treatment-related toxicity."

A Full Menu

Among the three classes of drugs under study, some of which are already approved for use in the United States or in other countries, are the folate-based thymidylate synthase (TS) inhibitors, such as raltitrexed (Tomudex); the oral fluorinated pyrimidines, such as the recently approved (for a breast cancer indication) capcitabine; and the topoisomerase I inhibitors, such as topotecan or CPT-11 (irinotecan), which was recently approved by the Food and Drug Administration for refractory breast cancer and has now shown promise in the treatment of colorectal cancer. In addition, researchers are evaluating a platinum compound, oxaliplatin.

The folate-based TS inhibitors were developed to overcome one of the problems inherent in the use of 5-FU, which is that the inhibition of TS could be limited if folate levels are low. 5-FU is believed to work by conversion within the cell to 5-fluorodeoxyuridine, which forms a covalent complex when bound to TS with the folate substrate. TS plays a rate-limiting role in DNA synthesis.

The oral fluorinated pyrimidines are essentially modifications of 5-FU, aimed at improving efficacy and toxicity. Tegafur, for example, is a prodrug which is converted to 5-FU by hepatic microosomal

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enzymes, thus leading to a slower and more sustained release of 5-FU within the tumor.

Oxaliplatin has a mechanism of action similar to that of cisplatin, in which the platinum complex binds to DNA, changes its structure, and inhibits nucleic acid synthesis.

The topoisomerase I inhibitors act on nuclear enzymes that control the topology of DNA during its transcription and replication. Inhibition of this enzyme results in the breaking of DNA strands, leading to cell death.

At the ASCO plenary session in Los Angeles, David Cunningham, M.D., consultant at the Royal Marsden Hospital in London, described his trial results with CPT-11 in 279 patients with refractory colorectal cancer. The benefits of the drug compared to the gold standard of best supportive care were “so overwhelming that we are recommending it as standard treatment after 5-FU has failed.”

**Better Than Palliative Care**

Cunningham reported that patients randomly assigned to CPT-11 started to show a survival advantage over patients receiving the best supportive care within 2 months of receiving treatment. The current best supportive care includes antibiotics, analgesics, transfusions, corticosteroids, and psychotherapy. Those on CPT-11 had a 2.6 times increased chance of 1-year survival over those on the supportive care regimen.

Even though median survival was only prolonged by 2.7 months, he said, “This research shows for the first time that there is a second-line chemotherapy treatment with a demonstrable survival benefit for colorectal cancer patients.” Measurement of quality of life also showed an advantage for CPT-11 over best supportive care.

Also impressed with CPT-11 was Michael O’Connell, M.D., of the Mayo Clinic in Rochester, Minn., who suggested that the drug be used in the control arm in future clinical trials of other drugs being investigated for colorectal cancer treatment.

Studies are under way, Cunningham added, to look at this drug in the adjuvant setting and in combination with other agents.

The major toxicity problem with CPT-11 is moderate to severe diarrhea, noted Mark Ratain, M.D., of the University of Chicago, who discussed the use of topoisomerase I inhibitors at the ASCO meeting. Ratain said that another drug in this class, topotecan, may offer an advantage over CPT-11 in causing less diarrhea, but trials so far indicate that topotecan may be somewhat less active.

In another approach, oral formulations of a class of compounds known as fluorinated pyrimidines, such as UFT (uracil and tegafur), and a sec-

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**Stat Bite**

**Kidney and Renal Pelvis Cancer Rates**

The incidence rate for kidney and renal pelvis cancer increased more than 45% in the United States from 1973 to 1995. Males are diagnosed with the disease twice as often as females, and it is somewhat more common among African American men than among white men. In addition to tobacco smoking (smokers are twice as likely as nonsmokers to develop kidney and renal pelvis cancer), obesity is the most well-established risk factor.

<table>
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<th>Year of diagnosis</th>
<th>Age-adjusted incidence rate per 100,000, all races*</th>
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<tr>
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*Age-adjusted to the 1970 U.S. standard population.

Congress Cools to Medical Privacy, but Tobacco Legislation Heats Up

The momentum that seemed to be building on Capitol Hill toward enacting legislation related to medical confidentiality has fizzled; thus, issues such as ensuring patients have access to their own data, limiting access to patient records by other parties, and allowing the use of certain data in research settings will probably not be tackled by the 105th Congress as was previously thought. However, the tobacco settlement bill continues to move forward, with legislation introduced by Sen. John McCain (R-Ariz.) as the vehicle.

The tobacco bill would address the authority of the Food and Drug Administration to regulate tobacco and establish penalties for vendors that sell tobacco products to minors, among other provisions. It would also increase the cost of cigarettes per pack, thus providing funds for states for smoking cessation and tobacco use prevention programs, as well as funds for federal programs, including research on tobacco and smoking. Other provisions are likely to be added and dropped as the bill moves through the Senate and the House.

Congressional interest in programs at the National Institutes of Health and at the National Cancer Institute remains high. Recent hearings and briefings have addressed tamoxifen, virtual colonoscopy, minority issues (access to care, burden of disease), efforts to develop a melanoma vaccine, research on a cervical (HPV) vaccine, and advances in cancer treatment.

Awards, Appointments, Announcements

The Fred Hutchinson Cancer Research Center, Seattle, recently honored E. Donnell Thomas, M.D., by dedicating its clinical research building to him. Thomas, director emeritus of the center's Clinical Research Division, was awarded the Nobel Prize for medicine and physiology in 1990.

The E. Donnell Thomas Clinical Research Laboratory Building will house the clinical research laboratories and offices of Thomas's colleagues. The announcement said that the opening of the building moves the Hutchinson center one step closer to bringing more than 2,000 scientists and staff together on one campus. The building is on the South Lake Union campus of the center.

Kleihues Re-elected at IARC

The International Agency for Research on Cancer, Lyon, France, announced that its Board of Governors re-elected Paul Kleihues, M.D., to a second 5-year term as director of the agency, beginning next Jan. 1.