Chemoprevention Researchers Look for Ways to Halt the Process of Carcinogenesis

by Mariann Crapanzano

Years before the disease develops, genetic alterations are present in the cells that will become cancer. The body is unable to repair the damage, and the altered cells elude the immune system. Further genetic changes occur, perhaps caused by exposure to carcinogens. The cells divide, and over time, a malignancy develops.

The discovery of that malignancy has always marked the beginning of treatment. But understanding the multiple steps to cancer development has inspired investigation of chemoprevention—the use of natural or synthetic agents to interrupt or reverse the process of carcinogenesis—and is changing the way some researchers think about cancer.

"Think of it as you do a chronic disease, like hypertension or diabetes," said Waun Ki Hong, M.D., professor, chairman of the Department of Thoracic/Head and Neck Medical Oncology, and head of the Division of Cancer Medicine at The University of Texas (Continued on next page)
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M. D. Anderson Cancer Center. “The treatment controls the disease. You may not entirely eliminate the precancerous cells, but you can undermine their growth, so it will take a longer time for the cancer to develop.”

Retinoid studies
Multistep carcinogenesis, the stepwise development of cancer, was recognized years ago in epithelial cancers and provided the framework for Dr. Hong’s early studies of retinoids, synthetic and natural derivatives of vitamin A, to interrupt the progression of oral premalignant lesions. In 1986, Dr. Hong and other investigators at M. D. Anderson reported in the New England Journal of Medicine that high-dose 13-cis-retinoic acid substantially reduced the size of the lesions in 67% of the patients who had them and produced histologic responses in more than half of the patients treated. This study provided proof that pharmacologic agents could alter the progression of premalignant lesions to cancer.

Dr. Hong, together with Scott M. Lippman, M.D., professor and chairman of the Department of Clinical Cancer Prevention, and others at M. D. Anderson, later demonstrated that 13-cis-retinoic acid was effective in preventing second primary tumors in patients who had previously been successfully treated for primary cancers of the head and neck. Patients with these cancers have an increased risk of developing second primary tumors, in part because of a phenomenon known as field carcinogenesis: exposure to a single carcinogen, such as tobacco, causes different genetic alterations in epithelial tissues throughout an entire field, such as the aerodigestive tract.

“For head and neck cancers, retinoids are quite promising agents in controlling precancerous cells,” said Dr. Hong.

Retinoids have toxic side effects, however, and the inhibitory effects shown in the 1986 study as well as in other studies did not continue after the treatment was stopped. According to Dr. Lippman, this suggests that although 13-cis-retinoic acid blocks the progression from genotypic to phenotypic changes, the molecular genetic changes in the tissue remain, leading to recurrence in the absence of the drug. Nonetheless, the benefits seen thus far are substantial, and research on retinoids forges ahead. A current study led by Dr. Hong will determine whether low-dose 13-cis-retinoic acid—which should have fewer and less severe side

## PROTOCOLS

### Chemoprevention Clinical Trials

Clinical trials of chemopreventive agents in progress at The University of Texas M. D. Anderson Cancer Center include the following.

- **Randomized chemoprevention trial with fenretinide (4-HPR) in superficial bladder cancer (ID95-236).** **Physician:** H. Barton Grossman, M.D.
  
  Patients in this phase III trial must have solitary or multifocal superficial transitional cell carcinoma of the bladder that is either newly diagnosed or secondary in patients who have been primary tumor-free for more than a year. Newly diagnosed bladder tumors must have been resected less than four weeks prior to study entry. Women must not be pregnant at the time of enrollment and must use a contraceptive during the trial and for one year afterwards.

- **Phase II study of efomithine (DFMO) in patients with Barrett’s esophagus with dysplasia (DM98-204).** **Physician:** Frank A. Sinicrope, M.D.
  
  Patients 18 years of age and older with histologically confirmed or suspected Barrett’s esophagus with any degree of mucosal dysplasia are eligible for treatment on an outpatient basis in this study. Participants with any prior malignancy must have no evidence of disease by clinical assessment and imaging studies at study entry and cannot have received chemotherapy or radiation therapy for six months prior to study entry. All patients must consent to four esophagogastroduodenal exams and esophageal biopsies for histologic evaluation.

- **Induction of biochemoprevention followed by fenretinide versus placebo maintenance for advanced laryngeal dysplasia (ID98-017).** **Physician:** Waun Ki Hong, M.D.
  
  Participants must have measurable laryngeal premalignant lesions that can be biopsied and histologic proof of moderate or severe dysplasia or carcinoma in situ. Patients may have received prior retinoid therapy but must have discontinued therapy at least three months prior to study entry. Patients receiving treatment with concurrent chemotherapy, immunotherapy, radiotherapy, or megadose vitamins will not be eligible. Those using tetracycline or its derivatives or oral anticoagulants may not enroll in this study.

- **Study of tamoxifen and raloxifene (STAR) for the prevention of breast cancer (NSABP99-2).** **Physician:** Therese B. Bever, M.D.
  
  Postmenopausal women who are 35 years old or older and are at increased risk for developing breast cancer are eligible for this randomized study. Women are considered to be at increased risk if they have a personal history of lobular carcinoma in situ or an estimated five-year risk of developing invasive breast cancer of at least 1.7% as established by the modified Gail model. A general physical examination, including a breast exam showing no evidence of malignancy, is required within 180 days prior to randomization. Women using estrogen, progesterone, oral contraceptives, androgens, or similar drugs are not eligible unless they discontinue use three months prior to randomization. Women who have had prior invasive breast cancer of any type or intraductal carcinoma in situ are not eligible.

- **A phase II study of adenovirus ONYX-015 administered by mouthwash as a chemopreventive agent and for the treatment of oral dysplastic lesions (HNS99-140).** **Physician:** Vassiliki Papadimitrakopoulou, M.D.
  
  Patients 18 years or older with a
effects—given over three years is effective in preventing second primary tumors in patients cured of an initial, early-stage head and neck cancer.

Retinoic acid is also a key component in a biochemoprevention regimen that Drs. Hong and Lippman and others at M. D. Anderson developed and are currently investigating. The combination of 13-cis-retinoic acid, alphatocopherol (vitamin E), and interferon reversed the progression of advanced premalignant laryngeal lesions in one study and has shown promise against recurrent squamous cell cancers of the skin, said Dr. Lippman.

Retinoids alone number in the thousands and make up just one class of the many potential chemopreventive agents that are still under investigation. Some other agents are nonsteroidal anti-inflammatory drugs (NSAIDs), carotenoids, alpha-difluoromethylornithine (DFMO), vitamins D and E, and selenium. These and other compounds are being evaluated through M. D. Anderson’s multidisciplinary chemoprevention program, which was largely developed by Dr. Hong in the field of head and neck cancer and has expanded to include thoracic, breast, colorectal, prostate, bladder, and skin cancers.

Chemoprevention in breast and colon cancers

Although chemoprevention is still in its infancy, it has already commanded considerable attention. Tamoxifen, a selective estrogen-receptor modulator, took center stage as a chemopreventive agent in late 1998 when it became the first drug to be approved by the U.S. Food and Drug Administration (FDA) for use in reducing the occurrence of breast cancer in women at high risk for the disease. In the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial, the incidence of invasive breast cancer in women who took tamoxifen was reduced by 49%, and other studies of the drug have shown impressively consistent results. This success and subsequent FDA approval of tamoxifen signaled a shift in the approach to breast cancer.

Another more recent milestone in the field of chemoprevention was the FDA approval of the NSAID celecoxib (as a supplement to routine management) to reduce the number and size of colorectal polyps in patients with familial adenomatous polyposis (FAP). Patients with FAP, who have a germline (Continued on page 4)

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**PROTOCOLS**

clinical diagnosis of oral dysplasia but no evidence of malignancy or open ulceration of the oral mucosa are eligible for this study. Return visits will be daily for five days every four weeks with the four-week cycle repeated up to 12 times. Women who are pregnant or lactating are not eligible, and study participants must use a contraceptive.

- A two-arm, phase II chemoprevention study of celecoxib (Celebrex) with or without DFMO in patients with familial adenomatous polyposis (ID00-109). **Physician: Frank A. Sinicrope, M.D.**
  Eligible subjects must be between the ages of 18 and 65 and have a confirmed diagnosis of familial adenomatous polyposis. Endoscopic evaluation of the colon or rectum must be possible, and patients must have at least five polyps at baseline. Individuals with hypersensitivity to aspirin or aspirin-related drugs, cyclooxygenase (COX)-2 inhibitors, or sulfonamides, a prior history of pelvic radiation, or significant hearing loss are not eligible. Participants must consent to colonoscopies, one esophagogastroduodenoscopy (a second one would be required only if duodenal disease was present at baseline), and three audio-grams during the six-month study period and must agree to refrain from using aspirin or aspirin-related drugs while on the study.

- A phase II double-blind, placebo-controlled, randomized study of celecoxib (SC-58635) in oral premalignant lesions (ID00-131). **Physician: Vassiliki Papadimitrakopoulou, M.D.**
  Participants must be older than 18 years and have a histologically confirmed early or advanced oral premalignant lesion that is at least 8 mm in diameter and has not been biopsied in the six weeks prior to study entry. Study participants must be willing to abstain from chronic use of all nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors, excluding low-dose aspirin (≤ 100 mg per day) and must not be taking ≥ 60 mg/day of beta-carotene alone or in a supplement within two weeks prior to study entry and for the duration of the study. Patients who have received chemotherapy, immunotherapy, hormonal therapy (other than hormone replacement therapy for menopause), or radiation therapy within three weeks of study entry or who need concurrent treatment with any of these therapies will not be eligible.

- A phase II study of colorectal aberrant crypt foci screening, regression, and prevention in high-risk patients (ID01-454). **Physician: Frank A. Sinicrope, M.D.**
  Men and women between the ages of 40 and 80 with prior or current colorectal adenomas or prior colorectal cancer will be recruited to this study. At baseline, all eligible participants must have at least five colorectal aberrant crypt foci documented by chromoendoscopy. Patients with a history of gastroduodenal ulcers, prior pelvic radiation, a known diagnosis of hereditary colon cancer, or inflammatory bowel disease will be excluded. Hypersensitivity to aspirin or aspirin-related drugs, COX-2 inhibitors, or sulfonamides renders patients ineligible. Patients must agree to refrain from using all nonsteroidal anti-inflammatory drugs (NSAIDs) while on study and must consent to two colonoscopies.

**FOR MORE INFORMATION** about these clinical trials, physicians or patients may call the M. D. Anderson Information Line. Those within the United States should call (800) 392-1611; those in Houston or outside the United States should call (713) 792-6161. Visit the M. D. Anderson Center clinical trials Web site at http://www.clinicaltrials.org for a broader listing of treatment research protocols.
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"One of the goals is to find an agent or combination that will control the polyp growth and progression so that we can delay surgery (colectomy) to allow the patient to reach physical and psychological maturity."

Frank A. Sinicrope, M.D., associate professor and chairman ad interim, Department of Gastrointestinal Medicine and Nutrition

mutation in the adenomatous polyposis coli gene, develop innumerable adenomatous polyps in the colon and have a nearly 100% risk of developing colon cancer by their fifth decade of life. Celecoxib selectively inhibits the cyclooxygenase (COX)-2 enzyme, whereas conventional NSAIDs inhibit both COX-1 and COX-2 isoforms. Inhibition of COX-1 is believed to account for gastrointestinal and other side effects of NSAIDs.

The FDA approval of celecoxib as a pharmacologic adjunct in the management of FAP was based largely on the results of a multi-institutional, placebo-controlled study headed by Gideon Steinbach, M.D., Ph.D. (now at the University of Washington), Patrick M. Lynch, M.D., J.D., an associate professor in the Department of Gastrointestinal Medicine and Nutrition, and Bernard Levin, M.D., vice president for Cancer Prevention at M. D. Anderson. This study showed a mean 28% decrease in the number of colorectal polyps in patients who took 400 mg of celecoxib twice daily for six months.

"This important study demonstrated the chemopreventive efficacy of a selective COX-2 inhibitor and has led to the development of subsequent studies in FAP as well as in patients with sporadic adenoma," said Frank A. Sinicrope, M.D., associate professor and chairman ad interim of the Department of Gastrointestinal Medicine and Nutrition.

The ongoing quest for even more effective agents or combinations of agents to help clinically manage colonic polyps is especially significant in patients with FAP because in addition to the cancer risk, they face grave quality-of-life issues, with many under-going a prophylactic colectomy at an early age. Dr. Sinicrope and others at M. D. Anderson, together with researchers from the Cleveland Clinic and St. Mark's Hospital in London, England, hope to build on the data from the celecoxib study. In a National Cancer Institute (NCI)-sponsored trial, they are comparing the effects of combined celecoxib and DFMO with celecoxib alone in patients with FAP. Animal studies have shown that the combination of an NSAID and DFMO is more effective than either drug alone.

"One of the goals," said Dr. Sinicrope, "is to find an agent or combination that will control the polyp growth and progression so that we can delay surgery (colectomy) to allow the patient to reach physical and psychological maturity." The other goal, he added, is to control the polyps in the rectum after a colectomy is performed and to prevent subsequent cancer.

Dr. Sinicrope is the principal investigator in another NCI-sponsored study to determine whether sulindac or aspirin (both NSAIDs) or ursodeoxycholic acid, a drug sometimes used to treat gallstones, can reduce the number of aberrant crypt foci in the colorectums of patients with a history of colonic polyps or colon cancer. Aberrant crypt foci are mucosal lesions in the colorectum that may be precursors to precancerous polyps and can be visualized during a colonoscopy using a dye to spray the mucosa.

Mechanisms of action

The exact mechanisms by which chemopreventive agents work are not fully understood and are the subject of extensive investigation. Reuben Lotan, Ph.D., professor and deputy division head for research, Division of Cancer Medicine, has played a key role in many studies by leading the laboratory analyses.

Multistep carcinogenesis begins with initiation, said Dr. Lotan, a genetic change that occurs in the cell that, if not repaired, persists in the cell's progeny. The body's complex DNA repair mechanism frequently does repair the damage, and most initiated cells do not develop into cancer.

"Many cells are initiated every day through inadvertent exposure to environmental physical and chemical carcinogens," Dr. Lotan said, "and our bodies are constantly repairing the damage."

But if the DNA repair is incomplete—or new genetic errors are introduced during the repair process—and the genetically altered cell escapes the immune system, said Dr. Lotan, the abnormal cells proliferate, a process often promoted by repeated exposure to carcinogens. This promotion stage may last 20 years or longer before the cells become malignant. Thus, multistep carcinogenesis provides both time and multiple opportunities to intervene in the progression of the disease.

Some agents are studied for their ability to prevent initiation, but the two principal modes of action by many agents are growth inhibition and programmed cell death, or apoptosis. A single type of agent may have more than one mechanism. For example, NSAIDs are known to induce apoptosis by inhibiting the COX enzyme, which is highly expressed in many colorectal lesions. But recent research at M. D. Anderson has shown that some NSAIDs trigger apoptosis in cells that do not express the COX enzyme by increasing the expression levels of 15-lipoxygenase, indicating that the chemopreventive effect of these agents can be COX-independent.

Retinoids affect the expression of genes that regulate cell growth and differentiation or cell death, generally acting through retinoid receptors in the cell's nucleus that are abnormally expressed in various cancer types, Dr. Lotan said. Laboratory analyses in the
Finding a way to prevent lung cancer from developing after healthy lung tissue has been exposed to carcinogens and genetic changes have occurred is the challenge faced by researchers designing chemoprevention trials for former smokers. In an ongoing clinical trial at The University of Texas M.D. Anderson Cancer Center, doctors and researchers in the Department of Thoracic/Head and Neck Medical Oncology are studying the effects of retinoic acid on precancerous cells in both current and former smokers to try and reverse or delay the cellular processes that may lead to the development of lung cancer.

"Once lung tissue is exposed to carcinogens, an initiation phase occurs, which means that some genetic changes occur and then progress into multiple phases of premalignant lesions that then become cancer," said Waun Ki Hong, M.D., chairman of the Department of Thoracic/Head and Neck Medical Oncology and head of the Division of Cancer Medicine at M.D. Anderson. Targeting precancer cells for treatment may delay the onset of cancer in particular people. "If you can eliminate the precancer cells, that's wonderful; if not, then you may undermine the precancer cells and even kill some of these cells," Dr. Hong explained.

Retinoic acid, which act by binding to a specific set of receptors and inducing differentiation in cells that have lost normal regulatory mechanisms, have shown the ability to suppress lung carcinogenesis in animal models, and clinical trials are being conducted to discover the effects of retinoids on human lung tissue.

In one such trial, current and former smokers are randomly assigned to receive 13-cis-retinoic acid, alone or in combination with alpha-tocopherol, or a placebo for three months. Although former smokers are the subjects in this study, current smokers are enrolled because patients who quit smoking sometimes start smoking again, and it is important to know the risks to these patients. "Carcinogens and chemopreventive agents can become in effective collaborative," said Dr. Hong. "They can actually work together and induce adverse reactions."

Also, chemopreventive agents may not be very effective for people who continue to smoke. "We think that former smokers are a great target for chemoprevention because we don't have to really worry about countering the tobacco carcinogens' effects on the chemopreventive agent," said Dr. Hong. About 240 patients are currently enrolled in the chemoprevention trial. A bronchoscopy is performed before patients are accepted into the study to identify any precancerous or cancerous cells developing in the lungs. A chest x-ray is also performed to see if any mass is visible.

"Patients enrolled in the study will be those who have some cellular changes that indicate that they are at high risk but who do not have cancer," said Michele Glover, a research nurse in the Department of Thoracic/Head and Neck Medical Oncology.

After three months, the study is unblinded to see which patients received the drug, if the results of bronchoscopy have changed, and if the change was significant. Patients who received the placebo are given the opportunity to take 13-cis-retinoic acid for three months, and then a final bronchoscopic examination is performed, and the results are compared with those of the first and second examinations for any changes. "Patients will receive some benefit from the study one way or another," said Glover. "They may not get the luck of the draw at the beginning, but eventually all patients will be treated."

According to Dr. Hong, the study is important because it will demonstrate whether chemoprevention with 13-cis-retinoic acid is capable of eliminating genetic or phenotypic changes in the airway, which could in turn delay or prevent the development of lung cancer.

Dr. Hong's group is also conducting molecular, molecular, marker, and epidemiological studies to establish a model to identify individuals at high risk for lung cancer development who could benefit the most from chemopreventive therapy.

"We are working very hard at developing a risk model," Dr. Hong said. "Once we establish the model and get a profile of patient characteristics, a computer could tell a patient's risk of getting lung cancer in 5 or 10 years. That is something we are struggling with."

FOR MORE INFORMATION, contact Dr. Hong at (713) 792-6363.
We Want to Hear from You

Your opinions are important to us. Please take a few moments to complete the survey below if you haven't before. Return it to OncoLog Survey, Department of Scientific Publications--Box 234, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030. Or simply fax your answers to (713) 794-1370. Your responses will help us ensure that OncoLog continues to meet your cancer information needs. Thank you!

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III. Indicate your level of interest in the following topics.

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The news hits a woman hard—the results of her Pap test are abnormal, and the diagnosis is cancer of the cervix. What she hears next may surprise her. The agent that caused the disease is a sexually transmitted infection known as human papillomavirus (or HPV). For women and men alike, this virus and its effects can have far-reaching implications.

More than 30 types of HPV—more than 100 have been identified—are transmitted through sexual contact, and approximately half of these have been linked to cancer. For years recognized as the major cause of cancer of the cervix (the opening to the uterus), HPV has also been associated with some cancers of the vulva, vagina, anus, penis, and oropharynx (the middle throat, including the base of the tongue and the tonsils).

HPV infections cause symptoms in some but not all patients. Some types of sexually transmitted HPV, including HPV types 6 and 11, cause wart-like lesions in the genital tract or anus of both men and women but rarely lead to cancer. The warts may appear within weeks of sexual contact with an HPV-infected person or may appear years later, if at all. Other types of the virus, including HPV types 16, 18, 31, 33, and 35, can cause growths that are usually flat and difficult to see and can lead to the development of cancer. A test for the viral DNA in the affected tissue can reveal the type of HPV that is present.

In women, HPV infection can cause abnormal changes in the outermost layer of cells (the epithelium) covering the cervix. These abnormal cells, known as squamous intraepithelial lesions (SILs) (or sometimes dysplasia or cervical intraepithelial neoplasia), are not cancerous, but they are precursors to cancer. SILs can be detected by a Pap test performed during a gynecologic examination.

Many low-grade dysplasias regress and become normal over a period of months or years. In these patients, the Pap test may become normal, and the HPV is considered to be latent or possibly to have been eliminated by the patient’s immune system. It is believed that a latent infection can be reactivated years after the patient’s initial exposure to HPV. In patients who develop cervical cancer, the HPV persists or is reactivated, and the SILs progress over many years, becoming increasingly abnormal and invading deeper and deeper levels of the epithelium. High-grade SILs include abnormal cells that extend through the full thickness of the epithelium, also known as carcinoma in situ, an early form of cervical cancer.

Risk factors for HPV infection

1. Commencing sexual intercourse at a young age (16 years or younger)
2. Having many sexual partners
3. Smoking
4. Oral contraceptives
5. Infection with other sexually transmitted diseases or with HIV
6. Giving birth to many children

Possible cofactors with HPV

The following may act as cofactors with HPV and thus play a role in the development of cancer.

1. Smoking
2. Oral contraceptives
3. Infected with other sexually transmitted diseases and with HIV
4. Giving birth to many children

For more information, contact your physician or contact the M. D. Anderson Information Line:

(800) 392-1611 within the United States, or
(713) 792-6161 in Houston and outside the United States.

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Serving International Clients

Wendeline Jongenburger, M.B.A.
Director, International Programs

M. D. Anderson Cancer Center serves patients from countries around the globe who seek the best hope for survival. But these international patients and their families also receive care that extends beyond treatment to meeting their communication, cultural, and social needs.

Eight percent of M. D. Anderson's patient population comes from abroad. Of these, half are from Latin America, while the rest come from all corners of the world. Many arrive in Houston unable to speak English, uncomfortable, and isolated. Some patients come from cultures where the word "cancer" is so taboo that it is not openly discussed. Others bear the stigma that they are somehow being punished by "catching" cancer. Many have philosophical and religious beliefs that can set the stage for ethical conflicts with Western medical practices, especially in regard to treatment and end-of-life choices.

Understanding the needs of M. D. Anderson's international patients and helping them feel at home is the responsibility of International Programs, which includes the International Patient Center (IPC) and the Department of Language Assistance. Before the patients arrive, the IPC staff verifies that they meet the medical clearance and financial requirements for treatment at M. D. Anderson and helps them arrange travel to the United States and locate a place to stay while in Houston.

Communication between patients and faculty and staff is a critical component of successful cancer treatment. The Department of Language Assistance has a staff of 28 interpreters who speak 13 languages and act as cultural liaisons, helping the faculty and staff understand the cultural differences among their patients so that they can provide the most sensitive care. The staff of International Programs also provides valuable insights into the beliefs and traditions of international patients to those involved in patient treatment and to the institution's Ethics Committee.

In some cultures, the family is the sole support structure, and many patients are pleasantly surprised by the availability of supportive care within the institution. International patients are encouraged to use services such as the chaplaincy and bilingual support groups to overcome feelings of isolation and help them feel connected to others facing similar challenges.

International Programs also participates in M. D. Anderson's educational mission by organizing educational conferences around the world and hosting political and medical leaders, such as Ministers of Health, who come to Houston to see our cancer center. By promoting education, communication, and understanding, the International Programs staff helps our international patients and their families find care, comfort, and hope thousands of miles from home.

For more information, contact International Programs at (713) 745-0450.