NATIONAL CANCER INSTITUTE

NCI Cancer Bulletin

A Trusted Source for Cancer Research News

May 13, 2008
Volume 5 | Number 10

In this issue:

A Publication of the
National Cancer Institute
U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health
NIH Publication No. 05-5498
http://www.cancer.gov

Genome Scans Find Clues to Childhood Cancer

In the first genome-wide association study of a rare cancer, researchers have identified common genetic variants that may increase the risk of neuroblastoma, a childhood cancer of the nervous system.

Risk factors for the more aggressive forms of neuroblastoma may reside on a region of chromosome 6, according to a report published online last week in the *New England Journal of Medicine (NEJM)*. The region was not previously linked to the disease.

Little has been known about susceptibility to neuroblastoma. The disease often begins in early childhood (or before birth) and initially affects the nerve tissue of the adrenal glands. Many researchers have thought that mutations in several major genes would largely determine the inherited component of the disease.

The new results suggest that different types of genetic changes, including some common variations, contribute to susceptibility. The findings also suggest that it should be possible to identify the common risk factors using genome scans, according to the researchers.

"This study is an important proof of concept," said lead investigator Dr. John Maris of the Children's Hospital of Philadelphia. "There was a real possibility before we began that we might not find any common variants, but the results clearly show that common genetic variants contribute to the risk of neuroblastoma."

Neuroblastoma remains one of the most challenging childhood cancers. More than 90 percent of patients with localized neuroblastomas survive, even when regional lymph nodes are

(Genome Scans continued on page 5)

Cancer Research Highlights

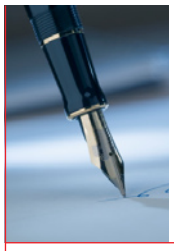
Mammography Plus Breast Ultrasound Yields Mixed Results

First-year screening data from a study comparing ultrasound with or in addition to mammography in women who have increased breast cancer risk indicate that combining the two tests has benefits and drawbacks.

Adding a screening ultrasound to routine mammography revealed 28 percent more cancers than mammography alone. However, the addition of ultrasound to mammography also resulted in a fourfold increase in false-positive findings—that is, screening results leading to a biopsy that revealed no cancer.

The results, published in the May 14 *Journal of the American Medical*

(continued on page 3)



Director's Update

The Future of Cancer Research: What's at Stake

When we speak about the future of cancer research, it's important to understand what's at stake, particularly given everything we have achieved over the past several decades.

When interacting with members of Congress, I often relay stories about individual cancer patients. One recent story is of a woman in her late 20s, with two young children, whose body and life had been dismantled by cutaneous T-cell lymphoma. Seemingly out of options, she came to NCI and the NIH Clinical Center. There she found "hope," in the form of the skill and dedication of NCI's Dr. Martin Gutierrez and an experimental drug being developed by NCI's Rapid Access to Intervention Development program, which has, for a year now, given her optimism for a longer, productive life.

That is what's at stake—individuals, sick patients, families.

As NCI's leadership continually assesses and attempts to manage a challenging budgetary scenario, we recognize that the extent of our progress is inextricably linked to our available resources. Yet we know that progress can and will continue. It will continue by supporting the young investigators who will build on today's remarkable discoveries; by ensuring that those discoveries can and do benefit all cancer patients, regardless of where they live or their socioeconomic status; by maintaining a vigorous intramural and extramural research program and helping to forge collaboration between academia, industry, government, and the nonprofit sector; and by driving the development of new technologies, tools, and resources that can hasten improvements while enhancing efficiency and cost effectiveness.

I always stress to legislators that, despite the challenges, our nation's investment in cancer research is paying great dividends—in lives saved, in a better quality of life, and in cancers prevented. I also emphasize the progress being made toward personalized therapy, and that a continued substantial investment in cancer research is necessary if we are going to realize our vision of therapies specifically designed to treat each individual's cancer in highly targeted ways. This investment—approximately $275 per person over the last 30 years—not only benefits cancer patients, but the advances cancer researchers are making in molecular biology, immunology, and genomics are impacting every disease.

And that's why we continue to push forward, despite the resource constraints we currently face. Because the cost of being content with the current state of affairs—as favorable as they have become for certain cancer types—is unacceptable.

And that cost extends beyond the many lives lost to cancer. According to the American Cancer Society's most recent estimate, the annual personal and financial cost of cancer in the United States is $206 billion. But our population is aging rapidly, and cancer is largely a disease of aging. As a result, NCI estimates that by 2017—less than a decade from now—the total economic burden of cancer in the United States will be *$1.82 trillion*.

That's why we are working so diligently to place more emphasis on carefully reviewing and more aggressively funding new applications from young investigators; pursuing genome-wide association studies to identify small genetic and environmental factors that contribute to cancer risk; investing in subcellular imaging, in finding markers of disease before the disease is even measurable; investigating through the NCI Community Cancer Centers Program how best to educate, screen, and prevent cancer to make our discoveries readily accessible to people where they live. It's why we have pioneered phase 0 clinical trials to help make smarter decisions about which experimental agents to move into phase I and II trials, and why we have developed a program to help small businesses with promising new cancer interventions traverse the so-called "valley of death" to get those interventions into advanced clinical studies and to market.

What's at stake is clear. We have made tremendous gains and we must sustain and build upon them. Our future success depends upon a sustained commitment to research, so we can deliver on the promise of a world where stories about successful battles against cancer are the only ones to tell. Like the case of our patient with T-cell lymphoma, we need to be able to deliver hope and successful outcomes. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

Cancer Research Highlights

(continued from page 1)

Association, come from a 3-year study of approximately 2,800 women led by the American College of Radiology Imaging Network (ACRIN). The study, ACRIN 6666, was co-funded by NCI and the Avon Foundation, and included participants from 21 different sites.

Of the 40 total cancers diagnosed within 12 months of initial screening, 8 were not detected by either modality alone or the combination of the two, but were discovered later during the 12-month period, for a rate of 3 cancers missed per 1,000 women screened. Overall, mammography alone showed 20 cancers (50 percent of all cancers detected) for a cancer detection rate of 7.6 per 1,000 women screened, while the combination of mammography and ultrasound revealed 31 cancers (78 percent of all cancers detected) for a cancer detection rate of 11.8 cancers per 1,000 women screened.

"Adding a single screening ultrasound to mammography will yield an additional 1.1 to 7.2 cancers per 1,000 high risk women, but will also substantially increase the number of false positives," wrote the study's principal investigator, Dr. Wendie Berg, and colleagues.

The results raise a number of issues, said Dr. Christiane K. Kuhl, from the University of Bonn in Germany, in an accompanying editorial. They include whether the high false-positive rate associated with adding ultrasound to mammography is worth the benefit of the additional cancers found, and whether MRI may end up being a superior option given the strong results seen with it in a recent study. "Individualized screening schemes tailored to the individual risk and to the personal preferences of a woman may be the way to consider how to screen for breast cancer," Dr. Kuhl concluded.

Follow-up continues in ACRIN 6666 and will include another screening round with mammography and ultrasound at 24 months from study entry, as well as an MRI within 8 weeks of that screening. Reporting of the final results is anticipated in 2009.

Sugar and Signals: EGFR's Dual Role in Cancer

The epidermal growth factor receptor (EGFR), a surface protein found on many cancer cells and an established drug target, is best known for relaying signals into cells that spur their growth. But researchers have now discovered another role for EGFR. The protein helps a cell maintain an adequate supply of the essential nutrient, glucose, according to research in the May 6 *Cancer Cell*.

Dr. Isaiah Fidler of the University of Texas M.D. Anderson Cancer Center and his colleagues found that EGFR stabilizes another protein on the cell surface, called sodium/glucose cotransporter 1 (SGLT1). This protein channels a constant supply of glucose to cancer cells. A prolonged period without the sugar can cause a cell to destroy itself through a process of self-cannibalization known as autophagy.

The discovery of a second important cellular function of EGFR could help explain why drugs such as erlotinib (Tarceva) and gefitinib (Iressa), which target EGFR signaling, are effective against only a small minority of cancers that express high levels of this protein, the researchers say.

By maintaining proper glucose levels and preventing starvation, EGFR may help tumor cells survive chemotherapy and drugs that inhibit cell signaling. To eradicate these tumor cells, it may be necessary to inhibit both EGFR's glucose-related activities and growth-promoting signals, the researchers conclude.

In an experiment, the researchers blocked the EGFR protein itself, rather than its signals, in prostate cancer cells, and the cells died through autophagy. An accompanying editorial predicts that "this exciting new study" will broaden efforts to target EGFR both as a growth promoter and "as a sweetener."

Two Proteins Interact to Turn Moles Cancerous

Researchers at the Pennsylvania State University College of Medicine have found that two proteins, B-Raf and Akt3, cooperate to change the cell-signal pathways that transform benign moles into melanomas. Their report appears in the May 1 issue of *Cancer Research*.

Moles (or nevi) are tight clusters of pigment-producing skin cells called melanocytes. These cells are normally distributed evenly between the top two layers of skin, the epidermis and the dermis. The average person has between 10 and 40 moles on their body, usually benign. However, with genetic changes that are still being discovered, nevi can transform into melanoma, which represents fewer than 10 percent of all skin cancers

(continued on page 4)

(Highlights continued from page 3)

but accounts for 75 percent of skin cancer deaths.

The study team examined a mutation that is found in about 90 percent of moles and approximately 60 percent of melanomas: a single nucleotide change in the *B-Raf* gene that causes expression of a mutated form of B-Raf protein. Previous research had shown that this mutation alone was insufficient to produce melanoma, so the team tested it in mice with modified levels of another protein, Akt3, that shows deregulated expression in the disease and is known to interact with B-Raf in cell signaling.

They found that the cell-signal pathways associated with Akt3 and normal B-Raf (PI3k and MAPK, respectively) do not inhibit one another in melanocytes, but in melanoma cells where B-Raf is mutated and Akt3 is active, cross-regulation is evident, resulting in decreased MAPK activity and significantly higher activity of PI3k—both signatures of melanoma. Together, the B-Raf mutation and normal Akt3 levels encouraged cells to grow without regard for attachments to surrounding tissues, marking the transformation of melanocytes into melanoma.

When the two proteins were inhibited in melanoma cells, tumor development slowed and apoptosis increased, prompting the researchers to suggest that "therapies for human patients should simultaneously target these signaling pathways for maximal clinical efficacy."

Nutlin-3a Induces Senescence through the p53

Although the tumor-suppressor gene *p53* is mutated or deleted in about half of all cancers, it remains functional in the other half and could potentially be harnessed to suppress cancer's growth. Recent studies showed that the small molecule nutlin-3a can induce apoptosis in cancer cells by inhibiting the protein MDM2 from binding to and breaking down the p53 protein, but the effects of nutlin-3a on normal cells were not completely understood.

Now, researchers from NCI's Center for Cancer Research (CCR) and their Japanese colleagues report in the May 1 *Cancer Research* that nutlin-3a induces cell senescence (the inability to grow or divide) in normal cells by the activation of *p53* and its associated cell-signaling pathways.

When the researchers treated normal human skin and lung fibroblast (connective tissue) cells with nutlin-3a, almost 100 percent of the cells underwent senescence, but in p53-deficient cell lines, nutlin-3a could neither increase *p53* activity nor cause senescence. The investigators confirmed that a set of microRNAs involved in cell senescence were upregulated after the treatment: mir-34a, mir-34b, and mir-34c. In addition, many genes involved in DNA replication, chromatin remodeling, and gene expression, including *ING2*, were downregulated.

"We need to note the difference in effects of [nutlin-3a] between normal and cancer cells," explained CCR co-author Dr. Izumi Horikawa. "We knew nutlin-3 induced apoptosis in cancer cells. In this research, in normal cells, the major response to nutlin-3a was senescence. Apoptosis is an irreversible death, but cells in senescence are still alive and can be functional." Further preclinical studies are needed to see if nutlin-3a's ability to induce apoptosis in cancer cells and senescence in normal cells is therapeutically relevant and applicable to cancer, he concluded.

Long-Term Smoking Cessation Cuts Cancer, Mortality Risk

New data from the Nurses' Health Study confirm the lethal effect of long-term smoking and indicate that starting smoking at an earlier age increases the risk of death from cancers caused by smoking. However, the study also confirms that the risk of death from diseases caused by smoking, including lung cancer, heart disease, stroke, and respiratory disease, drops dramatically after sustained periods of cessation.

Overall, the analysis, published in the May 7 *Journal of the American Medical Association*, found that nearly two-thirds of deaths among current smokers were caused by cigarette smoking, compared with only 28 percent among former smokers.

The new data come from more than 20 years of follow up on approximately 104,000 women participating in this long-running observational study. A similar report in 1993 was based on 12 years of follow up. The new report includes an expanded array of disease endpoints. Current smokers had a 63 percent increased risk of colorectal cancer compared with people who had never smoked, but no significant increased risk of ovarian cancer.

"Smoking cessation was beneficial for each cause-specific mortality outcome examined," wrote the study's lead author, Dr. Stacey A. Kenfield, and her colleagues from the Harvard School of Public Health. For example, within 5 years of quitting, the risk of death from lung cancer decreased by 21 percent, while the risk of death from coronary heart disease decreased by 50 percent when compared with people who continued smoking.

(continued on page 5)

(Highlights continued from page 4)

Breast Cancer Stem Cells May Resist Chemotherapy

Some breast tumors may contain a subset of cells that not only drive the disease but also resist conventional chemotherapy, new research suggests. These cells, often called cancer stem cells, are defined in part by their ability to self-renew. To eradicate them, it may be necessary to combine chemotherapy with drugs that target pathways involved in self-renewal, according to results in the May 7 *JNCI*.

One such drug is lapatinib (Tykerb). This drug targets the HER2 and epidermal growth factor receptor proteins, which may contribute to self-renewal. Dr. Jenny Chang of Baylor College of Medicine and her colleagues found that cancer stem cells in breast tumors were unaffected by chemotherapy but may be sensitive to lapatinib.

Previous studies have reported that some breast cancer stem cells express the surface protein CD44 (but little or no CD24 protein), so the researchers examined this population of cells in tumor biopsies before, during, and after treatment. The study included 31 women who received chemotherapy and 21 who received chemotherapy plus lapatinib.

In the chemotherapy group, the proportion of cancer stem cells to other cells in the tumor increased, suggesting that chemotherapy had eradicated the bulk of tumor cells without affecting cancer stem cells. By contrast, in the lapatinib group, the proportion of cancer stem cells to other cells in the tumor remained basically the same. This indicates that the different cell types may have been eradicated with roughly the same frequency.

"The results are encouraging and suggest that inhibition of key regulatory pathways responsible for self-renewal could augment the effects of conventional therapy and improve clinical outcome," the researchers concluded. ◆

(Genome Scans continued from page 1)

affected. But more than half of all patients have a more aggressive form of the disease that is often fatal.

There are approximately 700 cases in the United States each year, yet despite these small numbers, the study was large. DNA came from 1,700 neuroblastoma patients and twice as many children without the disease. The patient samples had been collected over a decade by the NCI-sponsored Children's Oncology Group.

The researchers plan to analyze up to 5,000 neuroblastoma patients in the coming years. They are also investigating other types of genetic variation, such as changes in the number of copies of genes. Preliminary results suggest that these also play a role.

"There clearly are other variants that we have not found yet," said Dr. Hakon Hakonarson of Children's Hospital of Philadelphia and the report's senior author. "This is an ongoing study, and our hope is to identify the bulk of the underlying genetic factors that predispose to neuroblastoma."

The chromosome 6 variants—which include three single nucleotide polymorphisms (SNPs), or single-letter changes in genetic code—occur in two overlapping genes. The researchers are "re-sequencing" the entire region to identify the precise source of the risk.

The absolute risk conferred by the chromosome 6 variants is extremely small, and therefore these SNPs, on their own, would be of little value in screening.

"This is a terrific study," said Dr. Stephen Chanock of NCI's Division of Cancer Epidemiology and Genetics, who was not an author. "Many have thought that the genetics of rare childhood diseases would be explained by a couple of rare mutations, but this study tells us that the genomic architecture is complex and that different types of genetic variation play a role."

Neuroblastoma could offer researchers a rare opportunity to study the interactions of genes and environmental factors in a complex disease, Dr. Chanock added, noting the relatively short time between conception and the development of the cancer. ◆

By Edward R. Winstead

National Women's Health Week: May 11-17, 2008

NCI supports research on women's health and cancers in women at all stages, from disease prevention through cancer survivorship. This includes both "women's cancers" (such as ovarian and uterine), as well as all cancers that affect women. In addition, studies to identify and understand the differences between cancers in women and men, down to the molecular and sub-cellular level, accelerate progress toward the goals of personalized medicine and improved health outcomes.

For information on women's health and cancer, go to:

http://women.cancer.gov

http://www.cancer.gov/cancertopics/types/womenscancers

http://orwh.od.nih.gov/

http://www.womenshealth.gov/whw/ ◆

Spotlight

New Treatment Bubbles Up from Old Imaging Technology

Reader suggested

Ultrasound has been a cancer-diagnosis workhorse for decades, bouncing high-frequency sound waves off of internal tissues and creating echoes that form pictures called sonograms. In the 1990s, researchers began studying the use of ultrasound for tumor ablation, harnessing the ability of sound waves to produce focused heat within the body. Now, they are combining advances in ultrasound technology with nanotechnology in a new category of experimental cancer therapies: microbubbles to facilitate drug delivery.

"What is promising about focused ultrasound is the potential spectrum of cancer therapies it enables, ranging from hyperthermia to minimally invasive surgery to drug delivery and activation," says Dr. Keyvan Farahani, acting chief of the Image-Guided Intervention Branch in NCI's Cancer Imaging Program, which has helped support this area of research through both academic and small business grants. "These processes can be guided and monitored through a variety of imaging techniques, most notably ultrasound and magnetic resonance imaging," explains Dr. Farahani.

Microbubble-mediated ultrasound therapies are based on ultrasound contrast agents, which were developed to make it easier to differentiate target structure from surrounding tissue during imaging. Ultrasound contrast agents consist of a gas enclosed in a nanoscale lipid coating, called a microbubble, which is about 10 times smaller than the average human vascular cell.

When microbubbles are exposed to doses of ultrasound slightly longer than those used in imaging, the bubbles oscillate in a state called stable cavitation, expanding and contracting and exerting small forces on the tissue around them. With longer exposures, the bubbles collapse (called inertial cavitation), generating high shear stress, temperature, pressure, and shock waves in adjacent cells.

The therapeutic potential of cavitation quickly caught the eye of researchers working on ways to bypass the blood-brain barrier so chemotherapy drugs and other treatments can reach primary and metastatic brain tumors. The blood-brain barrier, a collection of tightly packed epithelial cells within the blood vessels leading to the brain, prevents most larger molecules—including therapeutic drugs—from passing from the bloodstream into the brain.

Researchers had tried to use ultrasound to temporarily open small portions of the blood-brain barrier, but obtained inconsistent results. They realized that microbubbles could be used to concentrate focused ultrasound energy on a precise tissue volume, sparing the surrounding brain tissue from exposure and minimizing damage to healthy cells.

"When we started to use the microbubbles [with ultrasound], we were able to get a reliable window…a blood-brain barrier 'opening' that was large enough to allow drugs through, and could be opened repeatedly," says Dr. Nathan McDannold, research director of the Therapeutic Ultrasound Laboratory at Brigham and Women's Hospital.

Interestingly, it's not clear how microbubble-mediated ultrasound actually causes the blood-brain barrier to open. "We don't think it's just a physical modification of the microvessels—we're not just poking holes in the blood vessels or stretching out the tight junctions," explains Dr. McDannold.

"It's probably related to the stable cavitation of the microbubbles," he continues.

Using electron microscopy, researchers have observed an increase in active transport of drugs across the blood-brain barrier after microbubble-mediated ultrasound, as if in response to physical stimulation from the oscillation.

So far, in animal models, this strategy has successfully delivered chemotherapy and trastuzumab (Herceptin) through small, temporary disruptions in the blood-brain barrier. These disruptions are self-healing, closing most of the way in several hours and completely in less than a week.

In a related area, researchers are looking at the use of inertial cavitation for targeted drug delivery. By loading drugs into the microbubbles or attaching them to their surface, researchers create delivery vehicles that can be injected into the bloodstream and triggered to release their cargo when they are hit by focused ultrasound at precisely the right time

(continued on page 7)

(Spotlight continued from page 6)

and in the correct location.

"Some drugs might have positive effects in one location, and harmful effects in others. If you localize them precisely, you might be able to maximize the dose and avoid the harmful effects," says Dr. Kullervo Hynynen, director of imaging research at Sunnybrook Health Sciences Centre and professor of medical biophysics at the University of Toronto.

An added benefit of this technique, explains Dr. Chrit Moonen, director of the Laboratory for Molecular and Functional Imaging at the Université Victor Segalen Bordeaux 2, is that when the microbubbles collapse and release their payload, the adjacent blood vessels and cell membranes become more permeable from the forces of cavitation, enhancing absorption of the drug.

Before it can be tested in humans, microbubble-mediated ultrasound therapy requires additional safety data. Of particular concern are the consequences of multiple rounds of treatment, whether potential damage to local tissue could be prevented by real-time MRI monitoring, and the effects of high initial concentrations of drugs delivered to a small area of tissue. *In vivo* studies to address these concerns are currently underway at academic centers around the world. ◆

By Sharon Reynolds

These projects and other ultrasound research were presented at the first annual NIH-sponsored Image-Guided Interventions Workshop, held March 10 and 11 of 2008 in Rockville, Maryland.

Legislative Update

Senate Hearing Focuses on Cancer Research Challenges

On May 8, a panel of cancer survivors, advocates, and researchers testified before the U.S. Senate Committee on Health, Education, Labor, and Pensions at a hearing on cancer. The topics discussed included prevention, access to health care, insurance coverage, and cancer research.

Panel members included Lance Armstrong, Elizabeth Edwards (cancer survivor and wife of former Senator John Edwards, D-NC), AOL founder Steve Case, Dana-Farber Cancer Institute President Dr. Edward Benz, Greg Simon (president of FasterCures), and Hala Moddelmog (president and CEO of the Susan G. Komen for the Cure).

The legislators and panelists called for greater emphasis on prevention and early detection and increased access to health care. Mr. Case stressed the need for greater innovation in cancer research and more interagency and public-private collaborations. He also suggested that a computer industry-like approach may reinvigorate current biomedical research strategies that have stalled. Ms. Moddelmog and several other panelists urged the committee to mandate health insurance coverage for clinical trials to increase participation.

Committee Chairman Senator Edward Kennedy (D-MA) announced his intention to introduce legislation, co-sponsored by Senator Kay Bailey Hutchison (R-TX), encouraging a comprehensive approach to cancer research, rather than placing an emphasis on one or more types of cancer. Dr. Benz concurred, saying he favors studying molecular signatures and other biological identifiers of cancers rather than continuing to focus on cancers in specific organ sites.

An archived webcast of the hearing can be found at http://help.senate.gov/Hearings/2008_05_08/2008_05_08.html. ◆

Cancer.gov Update

NCI's State Cancer Legislative Database (SCLD) Web site has been updated. A fact sheet on tobacco products excise taxes and the winter 2008 issue of the *SCLD Update* have been added to the site. This special year-in-review issue of the *SCLD Update* includes a summary and matrix of all legislation enacted and resolutions adopted in 2007, as well as a table focusing on legislative activity related to state tobacco settlements.

For more information about state cancer-related legislation or to learn about the SCLD program, go to http://www.scld-nci.net. ◆

A Closer Look

Progression-free Survival: Patient Benefit or Lower Standard?

The U.S. Food and Drug Administration (FDA) recently granted bevacizumab (Avastin) accelerated approval for use in combination with paclitaxel (Taxol) to treat some patients with metastatic breast cancer. The decision cast a spotlight on a somewhat controversial clinical trial endpoint that the agency used to support its decision. Though the combined therapy improved progression-free survival (PFS) by 5 months compared with the control group, which received only paclitaxel, there was no significant improvement in patients' overall survival (OS).

The difference between PFS and OS is that PFS measures the time from a patient's random assignment to one treatment arm or another until the patient's cancer begins to grow again or the patient dies from their cancer; whereas OS measures the time from randomization until death from any cause.

Central to the controversy over the use of PFS as an endpoint in cancer clinical trials is whether delaying disease progression matters if a cancer treatment doesn't also lengthen patients' lives. Put another way, which matters more: longer life or better quality of life?

FDA considers OS the most reliable cancer endpoint. It is a universally accepted direct measure of the benefit of an experimental drug or other treatment, and it is unequivocal and easy to measure. Demonstrating in a clinical trial that a drug improves OS, however, is no easy feat. It often requires trials with hundreds of patients that take years to complete.

Furthermore, with multiple treatment options now available for many types of cancer, patients can switch to other therapies if the treatment they are receiving in a clinical trial stops working. That's good for patients, but it creates a conundrum for those who must interpret trial results: If a patient's OS improved, how much of that improvement was due to the study drug and how much was due to subsequent treatments?

In this respect, explains Dr. Daniel J. Sargent, a biostatistician with the North Central Cancer Treatment Group (an NCI-sponsored clinical trials cooperative group) who has authored numerous articles about endpoints in cancer clinical trials, PFS offers an advantage over OS because it requires patients to be followed only until their disease progresses. PFS, therefore, measures only the effect of the study drug and is not diluted by subsequent treatments patients receive, as OS may be.

"Most patients stop taking the study drug when their disease begins to progress," he says, "so the PFS clock stops at that point." This also means that trials using PFS as an endpoint can be completed more quickly than trials using OS, and they generally require fewer patients.

A key advantage of PFS as a clinical trial endpoint, says Dr. Sargent, is that "it captures both a tumor-shrinkage and a tumor-stabilization effect." This is important because, unlike conventional chemotherapeutic drugs that kill cancer cells, causing tumors to shrink, many new targeted drugs (including bevacizumab) work by other mechanisms, which may stop tumors from growing but don't always cause them to shrink.

A concern with using PFS as a trial endpoint, says Dr. Sargent, is that it's more subjective than OS and can be influenced by outside factors, including how disease progression is defined and measured, which may vary from one trial to another. For example, because progression is measured by X-rays or computerized tomography (CT) scans, measures of PFS can differ depending on how frequently those assessments are performed.

Other questions surrounding PFS include: What magnitude of improvement in PFS is clinically meaningful? And is an improvement in PFS beneficial to patients in and of itself, regardless of whether OS is also improved?

Dr. Jo Anne Zujewski, head of Breast Cancer Therapeutics in NCI's Division of Cancer Treatment and Diagnosis, is emphatic that, at least in advanced breast cancer, an improvement in PFS is beneficial to patients in and of itself. "In advanced breast cancer, disease progression is often symptomatic and uncomfortable, so if we can delay that, it's a benefit to the patient," she says.

However, Dr. Zujewski adds two caveats: "The magnitude of the benefit must be sufficient to be confident

(continued on page 9)

(Closer Look continued from page 8)

that it's not biased. An increase of a month or two would not provide that confidence and would probably not be clinically meaningful. Second, patients must not endure a lot of toxicity as a price for keeping their disease in control longer. If an oral agent had very few side effects and delayed progression for 4 months, most patients with advanced breast cancer would take it."

Dr. Richard Pazdur, director of the FDA Office of Oncology Drug Products, agrees. "I have no problem accepting that, in a lethal disease such as metastatic cancer, delaying progression is a clinical benefit in itself, provided that the magnitude of the benefit is sufficient and the side-effect profile acceptable."

FDA has recently approved several other new anticancer drugs based on an improvement in PFS, notes Dr. Pazdur, including sorafenib (Nexavar) for renal cell cancer, gemcitabine (Gemzar) for ovarian cancer, and ixabepilone (Ixempra) for breast cancer.

The agency still asks clinical trial sponsors to enroll a sufficient number of patients to detect an effect on OS, adds Dr. Pazdur. "We always want to be sure a drug isn't reducing OS," he explains. "But a dogmatic approach that we will accept only an improvement in OS for drug approval doesn't serve anyone well, certainly not patients. I know there are people who think granting approvals based on an improvement in PFS amounts to lowering the standard, but I view it as having greater flexibility." ◆

By Eleanor Mayfield

Featured Clinical Trial

Adjuvant Aromatase Inhibitor Therapy for Breast Cancer

Name of the Trial
Phase III Randomized Adjuvant Study of Exemestane Versus Anastrozole in Postmenopausal Women with Receptor-Positive Primary Breast Cancer (CAN-NCIC-MA27). See the protocol summary at http://cancer.gov/clinicaltrials/CAN-NCIC-MA27.

Principal Investigators
Dr. Paul Goss (Study Chair) and Dr. Kathleen Pritchard, NCIC-Clinical Trials Group; Dr. James Ingle, NCCTG; Dr. Matthew Ellis, CALGB; Dr. George Sledge, ECOG; Dr. George Budd, SWOG; and Dr. Manuela Rabaglio, IBCSG

Why This Trial Is Important
Aromatase inhibitors (AIs) have emerged as an important treatment option for postmenopausal women with hormone receptor-positive breast cancer. AIs interfere with the body's ability to make the hormone estrogen, which can fuel the growth of breast cancer cells that have estrogen receptors. AIs block the activity of an enzyme called aromatase, which is necessary to make estrogen.

Anastrozole (Arimidex) and exemestane (Aromasin) are two AIs approved by the FDA to treat early-stage, hormone receptor-positive breast cancer. Anastrozole is a reversible inhibitor that competes with estrogen precursor molecules for binding to aromatase; exemestane attaches permanently to aromatase, preventing estrogen precursors from binding to the enzyme at all (making it an irreversible "suicide" inhibitor). Exemestane also exerts androgenic (male hormone-like) effects in women, and this may contribute to its anticancer efficacy while possibly causing fewer side effects.

In this clinical trial, postmenopausal women with hormone receptor-positive breast cancer that has been surgically removed will be randomly assigned to receive either anastrozole or exemestane for 5 years. Doctors will monitor breast cancer recurrence and the side effects of these drugs. Separate companion studies will examine whether there is a difference in how the drugs affect bone mineral density and breast density in these patients; only those locations enrolling patients in the breast density companion study (NCCTG-N0434) are currently accepting patients for the AI study.

"While anastrozole and exemestane have not been compared previously in a clinical trial, evidence from preclinical studies and other clinical trials comparing each agent to tamoxifen support the idea that exemestane may be a more potent inhibitor of aromatase and have androgenic effects that may be important in enhancing efficacy and affording a better side effect profile," Dr. Goss said.

For More Information
See the lists of entry criteria and trial contact information at http://cancer.gov/clinicaltrials/CAN-NCIC-MA27 or call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). The toll-free call is confidential. ◆

Notes

Oberholtzer and Mackall Named CCR Chiefs

Dr. J. Carl Oberholtzer has been named chief of the Laboratory of Pathology in NCI's Center for Cancer Research (CCR). He is an internationally respected pathologist and is board certified in anatomic pathology with expertise in neuropathology. Dr. Oberholtzer came to NCI in 2006 as associate director for training.

Dr. Crystal Mackall has been appointed the chief of CCR's Pediatric Oncology Branch. She has served as acting chief since August 2005. Dr. Mackall is an international leader in pediatric oncology translational research, with a primary focus on development of effective immune response therapies for pediatric cancer and immune reconstitution.

NIH Seeks New Ideas for Roadmap Initiatives

NIH has issued a Request for Information (RFI) seeking input from the scientific community, health professionals, patient advocates, and the general public on innovative and cross-cutting initiatives to be supported through the Common Fund as part of the NIH Roadmap for Medical Research. Responses will be accepted through June 2, 2008.

The Common Fund/NIH Roadmap supports trans-NIH programs that address gaps in fundamental knowledge, develop transformative tools and technologies, and foster innovative approaches to complex problems. The Roadmap programs are expected to have exceptionally high impact and transform the way research is conducted. This collection of ideas is an initial step in the process of identifying a new cohort of NIH Roadmap programs for fiscal year 2011.

PLCO EEMS Seeks Applicants

The Etiologic and Early Marker Studies (EEMS) is a component of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. By collecting biologic materials and risk factor information from trial participants before the diagnosis of disease, EEMS provides a resource for cancer research, focused on cancer etiology and early markers. Etiologic studies investigate the environmental, biochemical, and genetic risk factors for cancer. Early detection studies aim to develop reproducible, diagnostics-ready biomarkers of early disease.

PLCO data and biospecimens are available to qualified researchers through a peer review process. The EEMS program accepts proposals for access to PLCO biospecimens twice a year in June and December. Proposals will be accepted for the EEMS summer review cycle starting June 1, 2008. Applications will be accepted until June 30, 2008, at 5:00 p.m. ET. Details of the review process and application materials are available at http://www.parplco.org. Questions may be directed to plco-eems@westat.com or 240-314-5896.

PHS Releases New Tobacco Cessation Guidelines

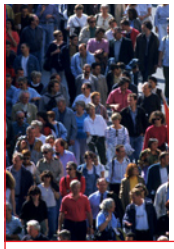
An updated clinical practice guideline was released last week by the U.S. Public Health Service to assist health care providers who are trying to help their patients quit or never start smoking. *Treating Tobacco Use and Dependence: 2008 Update* was developed by a 24-member panel of leading national tobacco treatment experts, who reviewed more than 8,700 research articles published between 1975 and 2007. The resource, co-authored by Dr. Glen Morgan of NCI's Tobacco Control Research Branch, includes information about new medications, advances in counseling methods, and treatments that are proven to be effective for adolescent smokers. Of particular note are findings that counseling significantly improves the effectiveness of tobacco cessation medications, that quitline counseling is effective and broad reaching, and that counseling increases abstinence from smoking among adolescents. The updated resource can be accessed online at http://www.surgeongeneral.gov/tobacco/default.htm and copies can be ordered through the national tobacco quitline, 1-800-QUIT-NOW (1-800-784-8669), which connects people with their local, state-based quitline service. ◆

NCI at ONS

Be sure to visit the NCI exhibit booth during the Oncology Nursing Society (ONS) 33rd Annual Congress May 15-18 in Philadelphia, PA. The NCI exhibit will be located in booth #349. ◆

Funding Opportunities

For a complete listing of current NCI funding opportunities, please go to the HTML version of today's *NCI Cancer Bulletin* at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_051308/page10. ◆



Community Update

CECCRs Share Results and Lessons

Every week, new information about cancer is published in scientific journals. But the impact of that research falls short without methods of sharing it in a way that actually changes behavior to reduce risk, improve screening, and create access to treatments.

This is why NCI funded the Centers of Excellence in Cancer Communications Research (CECCR) in 2003. The initiative provided four university-based research centers with $10 million each over 5 years to test effective strategies for cancer communications and translate them into tools for practice.

The key to the centers, explains Dr. Bradford Hesse, who oversees the initiative and is chief of the Health Communications and Informatics Research Branch in NCI's Division of Cancer Control and Population Sciences, has been a transdisciplinary approach.

"The CECCRs brought communication scientists, often for the first time, into direct contact with oncologists; they put computer scientists in touch with health educators; and they allowed statisticians to work in tandem with health behavior theorists," Dr. Hesse says. "The whole purpose was to create a synergistic environment for innovation."

At the end of last month, CECCR grantees came together in Atlanta to showcase their research results to stakeholders in cancer communications from within the government and the advocacy community.

Attendees learned about tools developed by the CECCR at the University of Michigan, led by Dr. Victor Strecher, which focused on three main research studies. One project, for example, analyzed Web-based smoking cessation programs.

The University of Pennsylvania CECCR, led by Dr. Robert Hornik, focused on ways to improve public information campaigns in three projects, including one that looked at ways in which people search for cancer information.

Under Dr. Matthew Kreuter, Saint Louis University's CECCR focused three projects on cancer communications for African Americans. One of these projects tested 80 videotaped "Living Proof" testimonies from African American breast cancer survivors as a way to encourage women to get mammograms.

And at the University of Wisconsin, Dr. David Gustafson has led a center that developed computer tools to help with all aspects of a cancer diagnosis. One of these three projects evaluated whether CHESS, an interactive communication system, improved palliative care and communication between patients and their clinicians.

The CECCR initiative has not only produced new tools and peer-reviewed literature; it has sparked institutional changes. At the University of Pennsylvania, for example, 34 graduate and 14 post-graduate scholars have trained or are being trained at the CECCR and 19 have already gone on to obtain positions in the fields of public health and communications research. The center has also stimulated a shift toward research on cancer among several leading scholars at the university's Annenberg School for Communication.

The University of Wisconsin's CECCR has created very exciting opportunities for cross-departmental collaboration, says Dr. Gustafson, pointing to partnerships between the School of Pharmacy and the departments of Radiology and Computer Science as examples. "We are working much more closely than ever before with the Transdisciplinary Tobacco Use Research Center here and the Department of Psychology in particular," he adds.

There have been similar changes at the University of Michigan, notes Dr. Strecher. "An important legacy of the initiative is our open-source Michigan Tailoring System software and the weeklong Michigan Tailoring Workshop, which provides tools and training that will prepare the next generation of health communications researchers," he says.

These are exactly the kind of changes that were hoped for when the CECCR initiative began, says Dr. Hesse. Even so, "We need to solve the 'last mile problem'—that is, getting our evidence-based communications applications out of the laboratory and into the public domain."

The recent meeting in Atlanta was one step toward this goal; the next will come later this year through a second round of CECCR funding, which will have greater emphasis on projects with clinical relevance for patients across the cancer care continuum. ◆

By Brittany Moya del Pino