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NEW FINDINGS ON
Aspirin and Heart Attacks

A surprising new study suggests that physicians should consider using aspirin therapy in cancer patients having heart attacks, despite the presence of thrombocytopenia. The benefits appear to outweigh the risks of severe bleeding.

by Dianne Witter

A long-standing conundrum for emergency room physicians, oncologists, and other clinicians may now be solved. The question: whether to administer potentially life-saving aspirin to cancer patients with thrombocytopenia who are having heart attacks—or to withhold aspirin out of concern that it may further lower platelet counts and cause lethal bleeding.

No guidelines currently exist for treatment of heart attacks in patients with cancer, so there is a great variation in the way such patients are treated. Physicians have been especially perplexed about what to do for cancer patients who develop blood clots, which can be caused by the cancer itself or by the chemotherapy.

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THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Aspirin and Heart Attacks

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New findings by researchers at The University of Texas M. D. Anderson Cancer Center shed much more light on the issue and may soon simplify such decisions for doctors. With her colleagues, Dr. Mona G. Sarkiss, an assistant professor in the Department of Anesthesiology and Pain Medicine, published an article on this topic in the February 1, 2007, issue of *Cancer*. Their study suggested that aspirin *should* be given to cancer patients having heart attacks, and that—in fact—without it, many of them will die.

The findings of the retrospective study defy conventional logic but make a compelling case for the benefits of aspirin in such situations. Researchers found that fully 9 of 10 cancer patients with thrombocytopenia who were experiencing a heart attack and who did not receive aspirin died, while only one cancer patient out of a group of 17 who *did* receive aspirin died.

"From this analysis, we have found that the single most important predictor of survival in these patients is whether or not they received aspirin," said the study's senior investigator, Jean-Bernard Durand, M.D., an assistant professor in the Department of Cardiology at M. D. Anderson. "Why that is, we're not sure. There appears to be a 'platelet paradox' suggesting that cancer may affect the mechanism of the way blood clots."

According to Dr. Durand, more research is needed to better understand this contradiction, but in the meantime, the decision on the use of aspirin should be made by both the cardiologist and oncologist on the treatment team.

At higher risk

According to the World Health Organization, of the approximately 10 million cancer patients worldwide, about 1.5 million may develop blood clots during their treatment. As such, they are at a much higher risk of dying from heart disease. "Now that we have this study, it would be a travesty if someone who survived treatment for cancer died of a heart attack soon after because they didn't receive treatment with aspirin," Dr. Durand said.

After making the empirical observation that M. D. Anderson patients who were being treated for heart attacks often seemed to have very good clinical outcomes when given aspirin and/or beta-blockers, Dr. Durand and a multi-institutional team of researchers conducted a retrospective analysis of cancer patients treated for heart attacks at M. D. Anderson over a one-year period. The 70 patients were divided into two groups based on their platelet counts, and data were collected on the use of aspirin, bleeding complications, and survival.

The team found that heart attack patients with low platelet counts who did not receive aspirin had a seven-day survival rate of only 6%, while those who received aspirin had a 90% survival rate. In addition, the patients who used aspirin had no severe bleeding complications, but patients with low platelet counts who developed a blood clot and were not given aspirin died.

The beneficial effect of aspirin also was seen in cancer patients with normal platelet counts. Seven-day survival was 88% in aspirin-treated patients and 45% in patients who did not receive aspirin, the researchers found.

Dr. Durand observed that these death rates are still abnormally high compared with those of patients without cancer. "For someone with acute coronary syndrome anywhere in the United States, an expected seven-day mortality is less than one percent," he said.

The findings in patients in either group who were treated with beta-blockers paralleled those of the aspirin-only treatment groups. The protective effect was not as strong as was seen with aspirin but was still life-saving.

The researchers noted that their report may be the first to describe the risk-benefit profile of aspirin therapy in patients with thrombocytopenia. ●

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Anti-Allergy Drug Slows Pancreatic Tumor Growth

Cromolyn, an anti-allergy drug in use for more than 40 years, may be the key to a much-needed treatment advance for pancreatic cancer, considered the most lethal of all cancers.

Researchers at M. D. Anderson found that combining cromolyn with the chemotherapy agent gemcitabine was markedly more effective at retarding the growth of pancreatic tumors in mice than gemcitabine alone. These findings were reported in the December 20 issue of the *Journal of the National Cancer Institute*.

"Our goal is to offer longer life to these patients, and the combination of these two agents may well do that," said the study's lead author, Craig Logsdon, Ph.D., a professor in the Department of Cancer Biology. To date, cromolyn has been used only as a topical agent, so the research team is determining ways to deliver the drug internally.

"Cromolyn, however, seems to reduce survival mechanisms in pancreatic cancer cells enough to make chemotherapy significantly more effective."

– Dr. Logsdon

"Pancreatic cancer is usually refractory to chemotherapy, and the vast majority of patients die from the disease, half of them within six months of diagnosis," Dr. Logsdon said. "Cromolyn, however, seems to reduce survival mechanisms in pancreatic cancer cells enough to make chemotherapy significantly more effective."

In this study, pancreatic cancer with the cromolyn-gemcitabine combination grew 85% less than the study's controls, Dr. Logsdon said. The relationship between how the drug controls allergies and its antitumor effect in pancreatic cancer remains unclear. "It may be possible that cromolyn has more than one target that influences cancer," he said.

Dr. Logsdon suspects that cromolyn may have antitumor effects in other types of cancer, a theory he is currently testing. "For a basic scientist, this is pretty thrilling," he said. "In a relatively short time, we have gone from discovering a molecule all the way to preparing for a clinical trial."

Dual Gene Therapy Suppresses Lung Cancer

Combination gene therapy delivered in lipid-based nanoparticles drastically reduces the number and size of human non-small cell lung cancer tumors in mice, researchers at M. D. Anderson Cancer Center and U.T. Southwestern Medical Center reported in the January 15 edition of *Cancer Research*.

Given separately, two genes suppressed tumor cell growth, but they had an even more powerful effect when administered together, cutting the average number of tumors per mouse by 75% and the average weight of tumors by 80%.

Combining treatments for a synergistic effect isn't new in cancer treatment, but combined gene therapy is. "In cancer treatment we have combination chemotherapy, and we also combine different modes of therapy—surgery, radiation, and chemotherapy. Now we've got the possibility of combined targeted gene therapy," said Jack Roth, M.D., a professor in M. D. Anderson's Department of Thoracic and Cardiovascular Surgery and a senior researcher on the project.

The genes wrapped in the nanoparticles were p53, a well-known tumor-suppressor gene that causes the apoptosis of defective cells and is often shut down or defective in cancer cells, and FUS1, a novel candidate tumor-suppressor gene identified in human lung cancer chromosome.

The investigators report that FUS1 works with p53 to force the apoptosis of lung cancer cells because FUS1 suppresses a gene that expresses a protein known to rapidly degrade p53, said senior author Lin Ji, Ph.D., an associate professor in the Department of Thoracic and Cardiovascular Surgery.

Lab experiments first showed that 48 hours after treatment, the gene combination cut the number of viable cells in four lines of human non-small cell lung cancer by 70% to 80% while leaving a control group of normal cells unaffected. In cancer cell lines treated with the gene combination, two to three times more cells underwent apoptosis than in those treated by either gene individually. The research team then confirmed these findings in mouse studies.

Together, p53 and FUS1 cut the average number of tumors per mouse by 75% and the average weight of tumors by 80%. The two tumor-suppressing genes were not so effective separately.

"We certainly hope this approach will be more effective than current treatment, but we also think it's likely to be much less toxic, with fewer side effects, than other types of combined cancer therapy," Dr. Roth said.

In the first phase of investigations, the FUS1 nanoparticles are being tested alone in a phase I clinical trial at M. D. Anderson for patients with metastatic non-small cell lung cancer.

In the coming years, Dr. Roth expects the research team to explore combination therapies in clinical trials of combinations of genes, or of genes and other biologic or chemotherapeutic agents.

Kicking Off a Trend:
Cancer-Related Deaths Decline

It's the news physicians and researchers have been steadily working toward for years—new data show a significant drop in deaths from cancer. According to the American Cancer Society, 3014 fewer people died from cancer in 2004 than 2003, following a decline of 369 deaths in 2003 from 2002.

"This shows everything we're doing—prevention, detection, improved drugs, better diets, and more exercise—is working. There's a real curve at work—the trend is unmistakable," said Maurie Markman, M.D., vice president for clinical research at M. D. Anderson Cancer Center.

Experts believe the improvements in survival were an effect of smoking cessation and the improved detection and treatment of these cancers.

Areas of improvement

Experts believe the improvements in survival—colorectal, breast, and prostate cancers caused fewer deaths in general, and deaths from lung cancer declined among men—were an effect of smoking cessation and the improved detection and treatment of these cancers. According to Gabriel N. Hortobagyi, M.D., a professor and chair of the Department of Breast Medical Oncology, these declines are especially encouraging because they occurred during a period of population growth.

The greatest decline was in deaths from colorectal cancer: 1110 fewer men and 1094 fewer women died from it, partly because more people have undergone screenings, including colonoscopy and sigmoidoscopy. Some doctors have called this "the Katie Couric effect," because colonoscopy rates increased more than 20% in the months after Ms. Couric underwent a colonoscopy on national television in 2000.

Still, more people should be screened for colorectal cancer. Bernard Levin, M.D., vice president for cancer prevention and population science, said, "Perhaps not even half of the population who should be screened is actually getting screened. If screening were more widely implemented, I think we could drive down the number of colorectal cancer cases and subsequent deaths possibly by as much as 50%."

After colorectal cancer, the next largest drop was in deaths due to breast cancer—666 fewer women died from it. "This reduction is likely due to increased mammographic screening having led to earlier diagnosis and more effective treatments," said Dr. Hortobagyi.

As for men, the 2004 data held good news—prostate cancer caused 552 fewer deaths—but many believe that the aging of the U.S. population in the coming decades will lead to an increase in the number of prostate cancer deaths. Researchers at M. D. Anderson are searching for new markers that correlate to tumors rather than prostate tissue. They hope to develop more accurate prostate cancer screening tools, ones that will help keep the number of deaths from rising. Other M. D. Anderson investigators are conducting a study on the role of selenium and vitamin E in prostate cancer prevention.

Areas of ongoing concern

Even though 333 fewer men died from lung cancer, this improvement was offset by the deaths of 347 *more* women from the disease, although researchers expect that the decline in deaths that benefited men will reach women in the next few years. Many efforts to reduce the number of deaths from lung cancer in the future are based on the fact that smoking accounts for 30% of all cancer deaths and 87% of deaths from lung cancer. As part of its efforts, M. D. Anderson started a Tobacco Treatment Program, which offers free counseling and pharmacological treatment to patients who smoke or are recent quitters.

Other areas in which death rates rose somewhat include esophageal cancer in men and liver cancer in both men and women.

Racial and social disparities

Although death rates declined overall, physicians and researchers noted significant racial disparities in the rates of decline. For almost every kind of cancer, African-Americans had a much higher death rate than whites: African-American men and women had death rates 38% and 17% higher than those of white men and women, respectively. And while Hispanics had lower incidence rates than whites for the most common cancer sites, they had higher rates of the cancers associated with infection, including liver, uterine cervix, and stomach cancers.

M. D. Anderson researchers are conducting numerous studies to address these differences, as well as disparities evident across categories other than race. ●

HOUSE•CALL

Working Out How to Lower Your Risk of Cancer

Now you have yet another reason to start working out. Recent research shows that regular exercise plays an important part in preventing cancer.

The latest American Cancer Society (ACS) Nutrition and Physical Activity Guidelines recommend a physically active lifestyle to help prevent cancer. For adults, "active" means completing at least 30 minutes of moderate to vigorous physical activity **beyond your normal daily activities**, on five or more days of the week. If you already get in a half-hour daily, ramping up to 45- to 60-minute sessions could increase the benefits. For children and adolescents, the ACS recommends engaging in a minimum of 60 minutes of moderate to vigorous physical activity at least five days every week.

Get moving for your own good

What constitutes moderate physical activity? You've got a wide range of choices. It could be walking, dancing, mowing the lawn, gardening, or practicing yoga; playing volleyball, baseball, golf, or doubles tennis; bicycling leisurely; going ice-skating or roller-skating; riding horses; canoeing or downhill skiing.

Vigorous activities include running or jogging; fast bicycling; taking aerobic dance or martial arts classes; circuit weight training; jumping rope; swimming; playing soccer, basketball, field or ice hockey, singles tennis, or racquetball; cross-country skiing; and doing carpentry or heavy manual labor. Vigorous activities generally use large muscle groups and cause a noticeable increase in heart rate, breathing, and sweating.

Your physical activity need not be in one long session to be beneficial. Two separate sessions of 20 to 30 minutes are just as helpful as one 45- to 60-minute session, said Sally Scroggs, senior health education specialist in M. D. Anderson Cancer Center's Prevention Center.

How activity helps prevent cancer

Updated every five years to reflect the latest research findings, the most recent ACS guidelines put more emphasis on the importance of physical activity in preventing cancer than they did before, Ms. Scroggs said. Research studies have shown that people who exercise regularly can reduce their risk of colon and breast cancer. Physical activity also may reduce the risk of cancers of the prostate and uterus as well as the risk of heart disease, high blood pressure, diabetes, and osteoporosis.

MAXIMIZE YOUR BENEFIT

Beyond your normal daily activities, complete more than half an hour of vigorous physical activity every day.

Exercise seems to protect against cancer in a variety of ways. According to M. D. Anderson Cancer Center experts, physical activity may reduce the risk for breast and prostate cancer by regulating hormone levels in the body, and it may reduce colon cancer risk by aiding bowel movement, thus limiting the time the bowel lining is exposed to harmful substances.

"Evidence is accumulating that 45 to 60 minutes of moderate to vigorous physical activity on five or more days of the week is optimal for reducing cancers of the colon and breast," Ms. Scroggs said. More vigorous activity may even further reduce the risk of colon cancer.

Exercise also helps people maintain a healthy weight. Being overweight or obese increases the risk of cancers of the colon, breast, uterus, esophagus, and kidney.

Tips for making your own 'activation' plan

Becoming more active takes a little planning, but activity can easily become a part of your regular routine. Walk or bicycle to your destination, or get off the bus one stop early. Exercise at lunch with coworkers, play with your children after dinner, or use a stationary bicycle or treadmill while watching television. Mow your lawn or work in the garden. Join a sports team. Go dancing. Plan active vacations rather than driving trips.

Particularly for people who haven't been exercising, it's important to start slowly and then gradually increase the minutes per session and the number of days you exercise. Trying to instantly change from a couch potato to a dedicated athlete can lead to injuries and decrease your resolve to stick with your exercise program. Remember that you're building a consistent habit that can extend your life and increase your sense of well-being. ●

For more information, talk to your physician, or:

- *call askMDAnderson at (877) MDA-6789*
- *visit www.mdanderson.org.*

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