OncoLog
MD ANDERSON'S REPORT TO PHYSICIANS ■ May 2014 Vol. 59, No. 5

New Treatments May Improve Outcomes for AL Amyloidosis Patients

By Bryan Tutt

AL amyloidosis—a rare, potentially fatal disease—has no approved treatments. The "standard" treatments are prescribed off-label, and few clinical trials have compared their effectiveness.

Recently, however, researchers at The University of Texas MD Anderson Cancer Center opened clinical trials of new drug combinations and even a new agent to treat this disease. If successful, this new agent would be the first drug approved by the U.S. Food and Drug Administration (FDA) specifically for the treatment of AL amyloidosis.

Cause and symptoms

AL amyloidosis occurs when clonal plasma cells in the bone marrow produce abnormal κ or λ light chains. These light chain proteins form amyloid fibrils, which accumulate in one or more organs and cause damage. The organs most often affected are the kidneys and the heart, but amyloid fibrils have been known to accumulate in all types of tissue except brain tissue.

A common cause of death for patients with AL amyloidosis is heart disease. "The amyloid deposits can cause thickening of the walls of the heart," said Robert Orlowski, M.D., Ph.D., a professor in the Department of Lymphoma and Myeloma. "This thickening impairs heart function and causes an irregular heart rhythm."

Unfortunately, symptoms of heart failure may be the first signs of AL amyloidosis. Indications of kidney damage such as fluid retention, anemia, increased serum creatinine levels, or proteinuria also may be the first signs of AL amyloidosis.

Fluorescence microscopy with Congo red stain reveals amyloid fibrils, which appear bright green, in a pancreatic tissue specimen. Image courtesy of Dr. Gregg Staerkel.

"It's important to recognize AL amyloidosis early in the disease process—before organ damage has occurred, which makes the disease more difficult to treat," said Jatin Shah, M.D., an assistant professor in the Department of Lymphoma and Myeloma. Suggestive of AL amyloidosis are indications of organ damage on routine physical examination, such as

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fluid retention because of kidney or heart failure, or laboratory findings such as increased serum creatinine levels or proteinuria.

AL amyloidosis should also be suspected in patients with multiple myeloma. Although most patients with AL amyloidosis do not have myeloma, AL amyloidosis occurs in 10%–15% of myeloma patients. For this reason, Dr. Shah recommends that all patients with multiple myeloma and symptoms of potential organ damage be screened for AL amyloidosis.

AL amyloidosis is typically diagnosed by the presence of clonal plasma in bone marrow aspirate and amyloid fibrils in a tissue biopsy. The tissue can be obtained by needle aspiration of the abdominal fat pad or of an organ suspected to be involved.

Standard treatments

Because AL amyloidosis and myeloma both arise from abnormal plasma cells in the bone marrow, treatments that are effective against myeloma are also used to treat AL amyloidosis. These treatments include stem cell transplantation, the proteasome inhibitor bortezomib, the corticosteroid dexamethasone, immunomodulatory drugs like thalidomide and its analogues lenalidomide and pomalidomide, and alkylating agents like melphalan or cyclophosphamide.

The standard treatments for newly diagnosed AL amyloidosis are melphalan plus dexamethasone and/or autologous stem cell transplantation. However, Dr. Orlowski said, "It's not known whether stem cell transplantation or a nontransplant approach is more effective, because AL amyloidosis is not common."

Because of the small number of patients with the disease, few randomized clinical studies have been done in patients with AL amyloidosis. However, a randomized study in France comparing stem cell transplantation with low-dose melphalan and dexamethasone found that transplantation did not offer an advantage in survival or response rates. Nevertheless, Dr. Orlowski said,

Dr. Robert Orlowski

Dr. Jatin Shah

patients with certain disease characteristics, such as kidney involvement, seem to benefit from stem cell transplantation. "In general, the approach is to consider using stem cell transplantation with or without preceding chemotherapy to reduce the disease burden," he said.

The main goal of AL amyloidosis treatment is to kill the abnormal plasma cells in the bone marrow that produce the amyloid proteins. Once these proteins are no longer being produced, the body can absorb some of the amyloid fibrils that have accumulated in the affected organ(s).

Complete remission is defined as the absence of amyloid proteins in the serum, also called a complete hematologic response. This occurs in about 60% of patients who receive standard treatment. However, Dr. Orlowski said, "Although the disease will stay in remission for prolonged periods of time, standard treatments don't cure the majority of patients with AL amyloidosis."

Another important measure of a treatment's effectiveness is organ function. Although organ function improves in 30%–40% of patients who receive standard treatment for AL amyloidosis, organ recovery is slow and depends on which organs are affected and how long the damage has been occurring. Dr. Shah said it can take as long as 2 years for the affected organs to heal.

> **"[S]tandard treatments don't cure the majority of patients with AL amyloidosis."**
>
> **– Dr. Robert Orlowski**

Multidisciplinary care

"Patients with AL amyloidosis are often very sick and can be difficult to treat," Dr. Shah said. "Many do not tolerate chemotherapy well and encounter many complications." He added that because of the various organs that can be damaged, the care of amyloidosis patients requires a multidisciplinary approach.

Dr. Orlowski agreed, suggesting that patients with AL amyloidosis be referred to a large center where the myeloma specialists who treat amyloidosis work closely with nephrologists, cardiologists, and other specialists who may be required to treat the affected organs. He said, "Input from all these people is important to ensure our patients get the best care."

Clinical trials

New treatments for AL amyloidosis are being investigated in two clinical trials at MD Anderson.

In the first trial, a phase I/II study available only at MD Anderson, patients with newly diagnosed AL amyloidosis receive melphalan and dexamethasone on days 1–4 and pomalidomide on days 1–21 of a 28-day cycle. Dr. Orlowski, the trial's principal investigator, said, "Pomalidomide with dexamethasone has been shown to work for people with relapsed amyloidosis, so combining pomalidomide with the standard of care for newly diagnosed patients, melphalan and dexamethasone, is likely to be effective in people with newly diagnosed disease."

The study's drug combination does not interfere with stem cell transplantation. Patients who are eligible for transplantation receive two cycles of the drug combination and then undergo a transplant; patients who are not eligible for transplantation but for whom the drugs are effective and well tolerated receive prolonged therapy and eventu-

ally move to a maintenance dose.

In the second trial, an international phase III study, patients are randomly assigned to receive the experimental oral proteasome inhibitor ixazomib (also called MLN9708) plus dexamethasone or the physician's choice of dexamethasone alone or dexamethasone plus melphalan, cyclophosphamide, thalidomide, or lenalidomide. Dr. Shah, MD Anderson's principal investigator for the trial, said that the study could lead to the FDA's approval of ixazomib for AL amyloidosis.

"AL amyloidosis affects a small number of patients, so it takes a major effort and commitment by multiple academic centers to complete a trial," Dr. Shah said. The difficulty of organizing large trials for a small patient population is a major reason why no drugs have yet been approved for the treatment of AL amyloidosis.

In both studies, it is hoped that the experimental drug combinations will prolong patients' remissions. Another potential benefit for patients is the convenience of taking oral medications. "Both these studies offer all-oral regimens," Dr. Orlowski said, "so patients don't have to schlep back and forth to the clinic for intravenous or subcutaneous injections." ■

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To learn more about the ongoing clinical trials at MD Anderson for patients with AL amyloidosis, visit www.clinicaltrials.org and select study No. 2012-0215 or 2012-1142.

DiaLog

Screening Mammography Reduces Breast Cancer–Related Deaths

By Therese Bevers, M.D., Professor, Department of Clinical Cancer Prevention

In a controversial report, the 25-year follow-up of the Canadian National Breast Screening Study (CNBSS) showed no reduction in mortality rate from annual mammography screening for breast cancer compared with physical examination or usual care for women 40–59 years old. The study investigators concluded, "The rationale for screening by mammography should be urgently reassessed by policy makers." This conclusion contests numerous studies that have shown screening mammography to reduce breast cancer–related mortality rates.

The findings of the CNBSS contradict not only findings from other mammography trials but also a meta-analysis conducted by the U.S. Preventive Services Task Force, which reported that mammographic screening significantly reduced the relative risk for breast cancer–related mortality for women 39–69 years old.

The CNBSS has been plagued by criticisms dating back to the early 1990s. Among the most important criticisms is that patients were randomly assigned to the intervention (mammography) or control (no mammography) arm after the performance of a physical examination rather than at study entry. The knowledge of the clinical breast exam findings prior to patients' assignment to the intervention or control arms had the potential to influence the randomization process. Indeed, in the CNBSS, the number of women 40–49 years old in the mammography arm who had breast cancers with four or more lymph node metastases exceeded that of the control group by 380%. Such a skewed allocation is unlikely to have occurred by chance and would minimize or eliminate any impact of mammographic screening on breast cancer–related mortality.

Additionally, concerns have been raised regarding the acquisition and interpretation of images for the CNBSS. According to an external review, more than half of the mammograms obtained in the first 4 years of the trial were judged as poor or unacceptable, but the image quality improved in the trial's final 2 years. Also, technologists in the trial were not taught to position patients properly, and the radiologists were not experienced in the interpretation of mammographic images.

Concerns about the CNBSS negate its strengths and render its recommendations regarding the use of mammography for breast cancer screening unhelpful. At this time, our greatest tool for the early detection of breast cancer remains screening mammography. ■

References

American College of Radiology and Society of Breast Imaging. BMJ article on breast cancer screening effectiveness: incredibly flawed and misleading. Society of Breast Imaging Web site. http://www.sbi-online.org/Portals/0/Position%20Statements/ACR%20SBI%20Response%20to%20BMJ%20Article%202-11-13.pdf. Posted February 11, 2014. Accessed April 16, 2014.

Miller AB, Wall C, Baines CJ, et al. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *Br Med J*. 2014;348:g366.

Nelson HD, Tyne K, Naik A, et al. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151:727–737.

"Sleeping Beauty" Technique Modifies T Cells to Treat B Cell Malignancies

By Zach Bohannan

A novel technique that helps the patient's own immune system find and destroy cancer cells could extend remission times for patients with B cell lymphomas and leukemias.

This technique uses a gene transfer approach known as Sleeping Beauty to create chimeric antigen receptors (CARs) for use in adoptive T cell transfer and is being used in clinical trials at The University of Texas MD Anderson Cancer Center.

Adoptive T cell transfer

Adoptive T cell transfer is a powerful innovation for the treatment of lymphoma and leukemia. The theory behind the treatment is that T cells harvested from the patient or a donor can be specifically targeted to cancer cells by altering the T cells' antigen receptors, which recognize pathogens and cells as foreign or dysfunctional. The modified T cells could effectively eliminate the cancer with minimal risk of side effects.

Unmodified native T cells generally do not attack cancer cells, which is one reason cancer cells can survive in a patient. Therefore, to make adoptive T cell transfer successful, doctors must somehow alter the T cells' antigen receptors to ensure that the cells actively target and kill the patient's cancer cells. For B cell malignancies, these CARs usually target CD19, a B cell–specific protein.

The traditional method of making CARs is to use viral transfection to modify the T cells' antigen receptors. After the antigen receptors are modified, the chimeric T cells are cultured with antigen-presenting cells that express CD19. These antigen-presenting cells stimulate the transformed T cells and cause them to proliferate. Unfortunately, the traditional viral method of creating CAR T cells is often expensive.

The Sleeping Beauty method

Recently, however, researchers led by Laurence Cooper, M.D., Ph.D., a professor in the Division of Pediatrics, developed a less expensive, nonviral method of creating CARs for patients. The method is called Sleeping Beauty because it relies on a reconstructed version of a transposon (a DNA sequence that can change its location within the genome) that was present millions of years ago in the last common vertebrate ancestor. The reconstructed transposon system can integrate DNA into the host genome without a viral vector.

In this new system, the doctors identify a tumor-specific antigen or marker, such as CD19, which they use to manufacture a CAR-containing DNA construct specific to a patient's cancer. The doctors insert that sequence into a Sleeping Beauty–specific DNA plasmid. Then, instead of using viruses to introduce the DNA to the T cells, the doctors use electroporation, which disrupts the T cells' membranes long enough for the Sleeping Beauty DNA to be taken up by the T cells.

Clinical applications

Adoptive T cell transfer therapy typically is done after standard treatment for lymphoma or leukemia. The patient's T cells are usually harvested before lymphoma or leukemia treatment begins. Depending on the nature of the patient's disease, such treatment may include chemotherapy, immunotherapy, and/or targeted drugs and may be followed by a hematopoietic stem cell transplant to help control residual disease.

While these therapies are occurring, the CAR construct is engineered and inserted into the patient's previously harvested T cells. When the patient's condition has stabilized after therapy, the patient receives CAR-bearing T cells. Partow Kebriaei, M.D., an associate professor in the Department of Stem Cell Transplantation, said, "Delivering CAR T cells after transplantation targets minimal residual disease in hopes of maintaining remission for people with high-risk B cell malignancies."

Dr. Kebriaei is the principal investigator for two of the three first-in-human clinical studies at MD Anderson in which patients with B cell malignancies receive Sleeping Beauty–derived CAR T cells after stem cell or umbilical cord blood transplantation. She and her col-

"Delivering CAR T cells after transplantation targets minimal residual disease in hopes of maintaining remission for people with high-risk B cell malignancies."

– Dr. Partow Kebriaei

leagues reported in December at the American Society of Hematology Annual Meeting that CAR T cells had been manufactured for 25 patients and administered to 9 patients: 5 who had acute lymphocytic leukemia and 4 who had non-Hodgkin lymphoma. Although it was too soon to tell whether the CAR T cells would extend remissions, the researchers reported that the treatment was well tolerated.

"Many drug companies are not in a financial position to pay attention to pediatric needs.... But we may be able to use CAR T cells as drugs in this group of vulnerable patients."

– Dr. Laurence Cooper

Looking ahead

Dr. Cooper said MD Anderson researchers and clinicians have started a clinical study in which patients with B cell malignancies receive CAR T cell treatment immediately after chemotherapy. This trial is led by Chitra Hosing, M.D., a professor in the Department of Stem Cell Transplantation and Cellular Therapy.

In all of the current studies of CAR T cells, researchers are observing how long the modified T cells remain in the body. Dr. Kebriaei said that future improvements in the persistence of the CAR T cells may someday allow adoptive T cell transfer to replace stem cell transplantation, which can be associated with significant side effects and cost.

MD Anderson researchers are also hoping to use CAR T cells as another treatment option for pediatric lymphoma patients, who generally have fewer treatment options than adult patients. Dr. Cooper said, "Many drug companies are not in a financial position to pay attention to pediatric needs simply because there's no return on investment for them. But we may be able to use CAR T cells as drugs in this group of vulnerable patients." ■

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CLINICAL TRIALS: Adoptive T Cell Transfer

CD19-specific T cell infusion in patients with B-lineage lymphoid malignancies after allogeneic hematopoietic stem cell transplantation (2009-0525). Principal investigator (PI): Partow Kebriaei, M.D. The main goal of this study is to learn whether infusion with allogeneic, genetically modified T cells is safe for patients with advanced B cell lymphoma or leukemia who have received an allogeneic stem cell transplant. Researchers want to find the highest dose of these T cells that can be given safely, how long the altered T cells remain in the body, and if they improve patients' responses to treatment.

Autologous CD19-specific T cell infusion in patients with B cell chronic lymphocytic leukemia (2011-1169). PI: Chitra M. Hosing, M.D. The goal of this study is to find the highest tolerable dose of genetically modified T cells that can be given in combination with standard chemotherapy to patients with chronic lymphocytic leukemia. The safety of this combination will also be studied.

CD19-specific T cell infusion in patients with B-lineage lymphoid malignancies (2007-0635). PI: Dr. Kebriaei. The main goal of this study is to learn whether infusion with autologous, genetically modified T cells is safe for patients with advanced B cell lymphoma or leukemia who have received an autologous stem cell transplant. Recently, the study protocol was modified to allow patients to receive a T cell infusion even if a transplant is contraindicated. Researchers want to find the highest dose of these T cells that can be given safely, how long the altered T cells remain in the body, and if they improve patients' responses to treatment. Researchers also want to learn whether interleukin-2 can help the modified T cells last longer in the body.

Donor-derived, CD19-specific T cell infusion in patients with B-lineage lymphoid malignancies after umbilical cord blood transplantation (2010-0835). PI: Elizabeth Shpall, M.D. The main goal of this study is to learn whether infusion with genetically modified T cells is safe for patients with B cell lymphoma or leukemia who have received umbilical cord blood transplants. Researchers also want to learn how long the modified T cells remain in the body and whether they improve patients' responses to standard treatment. ■

FOR MORE INFORMATION

Visit www.clinicaltrials.org.

Analysis Suggests Need to Revise Low-Grade Glioma Classification, Treatment

A comprehensive genomic and molecular analysis has shown that some low-grade gliomas have the molecular hallmarks of glioblastoma multiforme, the deadliest of brain tumors.

"The immediate clinical implication is that a group of patients with tumors previously categorized as low-grade should actually be treated as glioblastoma patients and receive that standard of care—temozolomide chemotherapy and radiation," said Roeland Verhaak, Ph.D., an assistant professor in the Department of Bioinformatics and Computational Biology at The University of Texas MD Anderson Cancer Center and the lead author of the study's report.

Using advanced platforms from The Cancer Genome Atlas, the researchers first analyzed 293 low-grade gliomas to group them by their gene expression, protein expression, microRNA expression, DNA methylation, and gene copy profiles. They then performed a second analysis to identify superclusters of tumors with similar combined profiles.

"The results overwhelmingly point to a natural grouping of low-grade gliomas into three superclusters based on the mutational status of the *IDH1* and *IDH2* genes and co-deletion of chromosome arms 1p and 19q," Dr. Verhaak said.

The researchers defined the three groups as tumors with 1) wild-type *IDH1* and *IDH2* (a glioblastoma-like phenotype), 2) *IDH1* or *IDH2* mutations and intact 1p and 19q chromosome arms, or 3) *IDH1* or *IDH2* mutations and co-deletion of chromosome arms 1p and 19q. The median patient survival durations for the groups were 18 months, 7 years, and 8 years, respectively.

"Classifying low-grade tumors in these three molecular clusters more accurately characterizes them than current methods used to group and grade tumors," Dr. Verhaak said.

Because the molecular markers that define the three tumor clusters are already assessed as part of patients' workup, the new categories can be implemented relatively quickly.

The researchers reported their findings at the American Association for Cancer Research Annual Meeting in April. ■

Combination of Antiangiogenic Drugs Shows Activity Against Solid Tumors

The combination of two antiangiogenic agents, bevacizumab and cediranib, has demonstrated activity against several types of solid tumors.

Bevacizumab, which targets vascular endothelial growth factor (VEGF), is active against several types of cancer but typically does not produce lasting responses because drug resistance develops. Combinations of drugs that target the VEGF pathway in different places might produce more robust or more durable responses.

The combination of bevacizumab and cediranib, an investigational VEGF receptor tyrosine kinase inhibitor, was tested in a phase I clinical trial led by David Hong, M.D., an associate professor in the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center.

The study enrolled patients who had advanced-stage solid tumors that were refractory to treatment or had no standard treatment. The patients received intravenous bevacizumab on days 1 and 15 and oral cediranib on days 1–21 of each 28-day cycle. The bevacizumab doses escalated from 3 mg/kg to 5 mg/kg and 10 mg/kg as more patients entered the trial; the cediranib doses escalated from 15 mg to 20 mg, 30 mg, and 45 mg.

The goals of the study were to determine the safety of the drug combination and to determine the doses that should be used in future studies. Treatment response was also evaluated.

Fifty-one patients were enrolled in the study: 17 with soft tissue sarcomas, 7 with renal cell cancers, 6 with colorectal cancers, and 21 with other cancers.

Nineteen patients, including 9 with soft tissue sarcoma, had stable disease and were still receiving therapy at 16 weeks. In addition, tumor regression exceeding 30% occurred in 4 patients (1 each with triple-negative breast cancer, basal cell carcinoma, alveolar soft part sarcoma, and synovial sarcoma), and tumor regression between 20% and 30% was seen in 4 patients (2 with renal cell cancer and 1 each with prostate cancer and alveolar soft part sarcoma).

The dose-limiting toxic effects (adverse events of grade 3 or higher) observed were chest pain in 1 patient, fatigue in 1 patient, thrombocytopenia in 2 patients, hypertension in 3 patients (including 1 with intracranial hemorrhage), and hemoptysis in 1 patient.

The recommended doses for future studies were 20 mg of cediranib daily and 5 mg/kg of bevacizumab; only one dose-limiting toxic effect occurred at this dose level.

The study's report was published in April (online ahead of print) in the journal *Cancer*. Dr. Hong and his coauthors recommended that future studies of the drug combination focus on patients with sarcoma. ■

Computed Tomography Predicts Chemotherapy Response in Pancreatic Cancer

Routine computed tomography (CT) scans of pancreatic tumors may not only guide treatment but also predict how well chemotherapy will penetrate the tumor.

The first clinical study to investigate the penetration of chemotherapy into pancreatic tumors was recently conducted at The University of Texas MD Anderson Cancer Center. Pancreatic tumors contain disorganized or nonfunctional blood vessels, high propor-

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Screening Mammography for Breast Cancer Saves Lives

MD Anderson recommends most women begin screening mammography at age 40

You may have seen conflicting reports about breast cancer screening over the past few months. Even among doctors, opinions vary about what the benefits of screening with breast mammography (x-rays) are and which women should be screened. Experts at The University of Texas MD Anderson Cancer Center continue to recommend screening mammography because it prevents cancer-related deaths.

Benefits of mammography screening

Mammography has been used in breast cancer screening for decades and evaluated in numerous clinical studies in various groups of patients. An overall analysis by the U.S. Preventive Services Task Force of multiple studies found that screening mammography reduced the risk of breast cancer–related death by 15%–20%.

"Screening mammography is the most studied cancer screening test available," said Therese Bevers, M.D., a professor in the Department of Clinical Cancer Prevention, "and it's clear that fewer women will die from breast cancer if more women are screened."

Risks from mammography

A common misconception about mammography is that the radiation dose poses a threat. Dr. Bevers said that although a person's lifetime radiation dose from all imaging is a concern, the radiation received during screening mammography is equivalent to that received during a round-trip transatlantic flight.

"It's important to keep concerns about the radiation dose in perspective," Dr. Bevers said. "Screening mammography uses the lowest radiation dose of any kind of x-ray examination."

Another major concern is that mammography can produce false-positive results, that is, the mammogram may show a lesion that looks like cancer but isn't. False-positive results can cause anxiety and lead to unnecessary testing.

When mammography reveals a suspicious-looking lesion, the patient may have to return to the clinic for further testing, which could include additional mammography, ultrasonography, or even a needle biopsy to rule out breast cancer. While these tests pose very little threat to the patient's health, they can be uncomfortable, inconvenient, and expensive.

Another concern is overtreatment, which occurs when patients receive treatment that was unnecessary. For example, it is possible for a false-positive finding to result in treatment for a precancerous lesion that might never develop into cancer or harm the patient if left alone. However, Dr. Bevers said that overtreatment is much less common in breast cancer than in some other cancers, such as prostate cancer.

The 2009 analysis by the U.S. Preventive Services Task Force found that although screening mammography reduced the risk of breast cancer–related death among women 40–49 years old, the rate of false-positive findings was higher for this group of women than for other age groups. However, Dr. Bevers said, "Forty percent of the years of life lost to breast cancer death are from women in their 40s. While we have to consider the possible harms, most women understand that a reduced chance of dying from breast cancer outweighs the risk of a follow-up test for a false-positive finding."

Who should be screened?

Dr. Bevers said that a risk assessment is the first step in breast cancer screening. Women can determine their risk level for breast cancer by having a discussion with their health care providers. Among the risk factors for breast cancer are age, family history of breast cancer, genetic mutations such as those to the *BRCA1* or *BRCA2* genes, and personal history of precancerous lesions.

MD Anderson recommends that women 20–39 years old at average risk for breast cancer undergo clinical breast examinations without mammography every 1–3 years. Women 40 years or older at average risk for breast cancer should undergo annual clinical breast examinations and mammography.

Women with a higher risk for breast cancer may begin screening mammography at a younger age, undergo more frequent screening, or be screened with additional tests such as magnetic resonance imaging (MRI).

"While we may add tests such as MRI, at this time nothing replaces screening mammography," Dr. Bevers said. "Mammography is the only test that has been shown to reduce a woman's chance of dying from breast cancer." ■

– B. Tutt

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- *Ask your physician*
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IN BRIEF

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tions of fibrotic tissue, and molecular variations that impede the transport of chemotherapy drugs from the blood vessels into tumor cells.

"We found that the distribution of intravenous dye used in CT scans is a surrogate for chemotherapy delivery in the tumor," said Jason Fleming, M.D., a professor in the Department of Surgical Oncology and the corresponding author of the study's report.

The researchers first enrolled 12 patients with primary pancreatic cancer who would undergo a surgical resection. During surgery, each patient received an infusion of the chemotherapy drug gemcitabine. After surgery, DNA from throughout the tumor was analyzed for gemcitabine incorporation.

Dr. Fleming and his colleagues found that gemcitabine penetrated the tumors to varying degrees and that tumors whose DNA had higher levels of gemcitabine incorporation also had higher levels of human equilibrative nucleoside transporter (hENT1) and lower levels of collagen. High hENT1 levels and low collagen levels both are known to correlate with good outcomes from gemcitabine treatment in patients with pancreatic cancer.

Dr. Fleming and his colleagues also noticed differences in the absorption of the CT contrast agent among the tumors and hypothesized that the uptake of contrast material could predict the path and absorption of gemcitabine. To test this hypothesis, the researchers analyzed pretreatment CT scans from 11 patients in the clinical study, 110 pancreatic cancer patients who had received gemcitabine before surgical resection, and 55 patients who had not received chemotherapy before their pancreatic tumors were resected.

"We found that the distribution of intravenous dye used in CT scans is a surrogate for chemotherapy delivery in the tumor."

– Dr. Jason Fleming

By employing mathematical models to measure transport factors in resected tumors, the researchers found that the pattern of CT contrast agent uptake was associated with gemcitabine incorporation, tumor response to therapy, and overall survival.

"The implication is that molecular information from a biopsy of the tumor can be combined with data from a standard CT study to place patients into categories that predict the way an individual tumor will respond to therapy," Dr. Fleming said.

The study's report was published in the *Journal of Clinical Investigation* in April. Dr. Fleming said future studies will focus on the application of this new knowledge to patient care and improving the delivery of chemotherapy to pancreatic tumors. ■

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