Advances in Neuroimaging Help Unveil the Mechanisms of Chemobrain

By Jill Delsigne

Chemobrain, a catchall term for the cognitive dysfunction and neurophysiological changes produced by chemotherapy toxicity, is an important quality-of-life issue for cancer survivors.

“Cognitive dysfunction associated with cancer and cancer therapy directly impacts our patients and their families,” said Jeffrey Wefel, Ph.D., an associate professor in the Department of Neuro-Oncology at The University of Texas MD Anderson Cancer Center.

Because the symptoms of chemobrain reported by patients resemble those of other disorders, such as depression, patients may be misdiagnosed with a mood disorder. Chemobrain, however, is not a psychological but a physiological disorder. Using state-of-the-art neuroimaging technology, researchers are exploring the underlying mechanisms of chemotherapy-related cognitive dysfunction, and understanding these mechanisms could lead to screening techniques or treatments for chemobrain.

Researchers led by Dr. Wefel reported in 2004 the first prospective, longitudi-
nal study of chemobrain. Before then, chemobrain had been reported only in case reports and retrospective studies. The results of Dr. Wefel’s study demonstrated that chemobrain impairs memory, executive function, attention, and information processing speed. Having uncovered the functions affected by chemobrain, Dr. Wefel has since focused his research on finding the physiological causes of chemobrain.

Visualizing brain activity

Using structural and functional neuroimaging technology, researchers are beginning to understand the mechanisms of chemobrain and to detect chemotherapy-related cognitive dysfunction, which tends to be subtle. Functional magnetic resonance imaging (fMRI), which measures neural activity in the brain, can provide insight into how the brains of patients treated with chemotherapy function differently than those of cancer patients receiving other treatments.

According to Dr. Wefel, the emphasis in this area of research has expanded beyond merely characterizing the nature and prevalence of chemotherapy-related neurotoxicity. He and other researchers are using fMRI to find correlations between cognitive function and changes in brain morphology, brain functional activity patterns, and inflammatory cytokines as well as examining genetic risk factors that predispose patients to this neurotoxicity.

Structural imaging

Dr. Wefel’s research builds on knowledge gained from studies that employed other modalities, including standard MRI, which provides high-resolution snapshots of the brain that can be used to determine the volumes of white and gray matter. As of 2012, only 12 structural imaging studies in patients with chemobrain had been published. These studies showed volume reductions in both white and gray matter up to 10 years following the completion of chemotherapy and suggested that white matter may be particularly sensitive to damage. One study found permanent, long-term (after an average 21-year follow-up) reductions in total brain volume and gray matter in breast cancer patients who had received standard dosages of adjuvant chemotherapy.

Changes in brain structure associated with chemotherapy correspond to the cognitive changes found on neuropsychological testing. For example, in one study, worse performance on cognitive tests of attention and verbal memory correlated with lower fractional anisotropy (a sign of brain injury) in frontal, parietal, and occipital white matter tracts on diffusion tensor MRI, a modality that enables visualization of the microstructure of the white matter.

Functional imaging

Studies employing fMRI—which analyzes the dynamic patterns of neural activity while a patient engages in specific mental tasks—to assess the effects of chemobrain have shown physiological evidence of the condition’s cognitive symptoms. One study found decreased activity in the prefrontal cortex during a memory-encoding task in breast cancer survivors 3 years after they completed chemotherapy. Another study found that breast cancer survivors who had finished chemotherapy 5 years earlier (on average) had decreased left caudal lateral prefrontal activity, which corresponded to the decreased executive function experienced by these survivors.

fMRI studies have also shown how the brain compensates for the dysfunction produced by chemotherapy. “In patients with chemobrain, it takes more brain to do the same amount of work,” said Charles Cleeland, Ph.D., a professor in and chair of the Department of Symptom Research. In one study of a pair of monozygotic twins—a healthy twin and one who had breast cancer and received chemotherapy—fMRI showed that the chemotherapy-treated twin had increased task activation in the bilateral frontal and bilateral parietal brain regions when performing the easiest tasks. In other words, to accomplish even a simple task, the chemotherapy-treated twin’s brain had to engage more working memory circuitry. This compensation may help explain why some patients report symptoms of chemobrain but still perform within normal limits on cognitive tests. At some point, however, as the tasks in-

“We need to recognize the magnitude of these issues, the frequency of cognitive dysfunction across many cancer patient groups, and the profound effects of cognitive dysfunction on our patients’ lives.”

— Dr. Jeffrey Wefel
crease in difficulty, these compensatory strategies might be inadequate.

**Assessing functional neural networks**

fMRI also reveals the ways in which chemotherapy changes neural networks during resting states, when the brain is not engaged in a specific mental task. Dr. Wefel recently collaborated with a research group at Stanford University in a functional neuroimaging study that showed disruptions in the default mode network (DMN) connectivity of breast cancer patients after chemotherapy. The DMN, one of the most studied resting state networks, is believed to function in implicit learning, autobiographical memory retrieval, prospection, and other internally focused processes.

The DMN normally deactivates during task performance, but in patients with chemobrain, the DMN does not deactivate as much as it should; this may be associated with slower response times and errors.

According to Dr. Wefel’s research, altered DMN connectivity could be a promising biomarker for cognitive dysfunction after chemotherapy. His research compared the DMN connectivity in breast cancer survivors who had undergone chemotherapy with that in survivors who were treated without chemotherapy and that in healthy controls. The patterns of DMN connectivity revealed by fMRI could distinguish survivors who had undergone chemotherapy from both other groups with 90%–91% accuracy. Disrupted DMN connectivity also is one of the more promising imaging biomarkers of mild cognitive impairment in aging.

**Functional near-infrared spectroscopy**

In addition to fMRI, functional near-infrared spectroscopy (fNIS) may hold promise in the study of chemobrain. Whereas fMRI measures the magnetic properties of hemoglobin to detect the variations in blood flow and in the distribution of oxygenated and deoxygenated hemoglobin that occur to meet the oxygen needs of active neurons, fNIS measures the light absorption by molecules at two or more wavelengths to estimate the changes in hemoglobin concentration. This imaging modality is less expensive and requires less restriction of movement than fMRI. And unlike fMRI, fNIS does not take place in a small chamber, an attribute that can lead some patients to experience claustrophobia during MRI examinations. The advantages of fNIS—especially its portability and affordability—may facilitate longitudinal study of chemobrain and its effects as patients age.

**Current research**

Dr. Wefel is in the midst of conducting a longitudinal study of multimodal imaging, genetic profiling, and neuropsychological assessment approaches for chemobrain at MD Anderson. His group is also researching biomarkers that might identify women with breast cancer who are at increased risk for developing chemobrain. If a biomarker could identify high risk for chemobrain before a patient undergoes chemotherapy, the patient could be closely monitored or other treatment options might be considered. Also, identifying a high-risk population would allow physicians to study interventions aimed at preventing neurotoxicity.

Dr. Wefel’s study will include a comprehensive panel of neuropsychological tests and structural MRI and fMRI studies (including measures of both gray and white matter volume, white matter integrity, neural connectivity, resting state and task-based functional activity, and multivoxel spectroscopy to examine alterations in neurometabolites) both before and after women receive chemotherapy. Importantly, this research will focus on women 60 years and older, as most of the 53 studies of chemobrain in breast cancer patients to date have not assessed the cognitive effects of chemotherapy in older patients. Dr. Wefel hypothesizes that cancer and cancer therapy may accelerate the aging process and abnormal age-associated cognitive decline.

Of the 26 longitudinal studies of chemobrain, only four have included patients older than 60 years, despite the fact that more than half of women diagnosed with breast cancer are in this age group. Given the excellent survival rates for breast cancer patients, it is becoming increasingly important to research how chemotherapy affects cognitive ability as patients age.

In one study that used fMRI to

“**It is important to recognize that chemobrain has physiological causes; it is not a psychological disorder.**”

– Dr. Charles Cleeland

Charles Cleeland, Ph.D.
Opioids are a mainstay in the relief of pain—especially the chronic cancer-related pain often encountered in the palliative care setting. However, extended opioid use can result in tolerance, dependence, and opioid-induced neurotoxicity.

The symptoms of neurotoxicity—which include excessive sedation, confusion, hallucinations, and myoclonus—result from a buildup of the metabolites of opioids in the brain. Thus, when tolerance develops and pain is no longer controlled, simply increasing the opioid dose, as was commonly done in times past, may result in neurotoxicity.

In 1995, Eduardo Bruera, M.D., who was then a professor at the University of Alberta and is now a professor in and chair of the Department of Palliative Care and Rehabilitation Medicine at The University of Texas MD Anderson Cancer Center, proposed the notion of opioid rotation. In opioid rotation, the no-longer-effective opioid is replaced with a new one—but at a much lower dose, thereby minimizing the potential for toxicity. This is important because the most common indication for opioid rotation is opioid-induced neurotoxicity. “The cause of toxicity is the opioid, so that opioid needs to go,” said Akhila Reddy, M.D., an assistant professor in the Department of Palliative Care and Rehabilitation Medicine.

Opioid rotation is carried out using

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an equianalgesic table (these are published by numerous sources, including pharmaceutical companies) in which the morphine-equivalent daily dose of the original opioid is calculated and then decreased by 30%–50%.

Although opioid rotation was originally met with resistance by many clinicians—who were skeptical about cross-tolerance, which is common in patients treated with opioid analgesics—in the past decade, opioid rotation has become standard practice in the inpatient setting and is usually successful. For example, in a recent Italian study, 96 of 103 opioid substitutions were successful. This success is attributable to the daily monitoring of pain in inpatients, enabling rapid titration of drug doses.

Increasingly, opioid rotation is also being considered for use in the outpatient setting. Recently, Dr. Reddy and her colleagues reported a retrospective review of all outpatients seen in 1 year in MD Anderson’s Supportive Care Clinic. Of those who were receiving strong opioids (morphine, hydromorphone, oxycodone, methadone, or fentanyl), 31% underwent opioid rotation, and the rotation was successful in 65% of those cases. Of the patients who required opioid rotation, 83% did so for uncontrolled pain and 12% for opioid-induced neurotoxicity.

In the Supportive Care Clinic at MD Anderson, nurses and pharmacists follow up by phone with outpatients who have undergone opioid rotation to ensure the rotation went smoothly. In addition, physicians schedule all outpatients for follow-up within a week of the opioid rotation. The close monitoring via nurse calls and the short intervals to follow-up increase the likelihood that the opioid rotation will be successful and help prevent both overdosing and underdosing.

Dr. Reddy recommended that a patient’s support system and likelihood of compliance be considered in the decision whether to use opioid rotation in an outpatient clinic.

Indications for Opioid Rotation

Although uncontrolled pain and opioid-induced neurotoxicity are the most common indications for opioid rotation, the procedure can be valuable for addressing other situations, such as the need to change the route by which a particular medication is administered. For example, in patients with head and neck cancer who have radiation-induced dysphagia and thus trouble taking pills, solid medications can be switched to a long-lasting liquid form. Moreover, in patients who have renal failure, morphine can be switched to methadone. And in a non-medical but perhaps equally significant situation, opioid rotation can be implemented when a drug is not covered by a patient’s insurance.

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Researchers Identify Inhibitor of Cancer-Promoting Protein Skp2

Researchers have identified a new compound that inhibits the cancer-promoting enzyme Skp2 (or S-phase kinase–associated protein 2).

A team led by Hui-Kuan Lin, Ph.D., an associate professor in the Department of Molecular and Cellular Oncology at The University of Texas MD Anderson Cancer Center, had previously found that Skp2 promotes cancer by marking the cancer-inhibiting protein p27 for destruction and activating a signaling pathway that initiates glycolysis, a primary driver of cancer cell growth and survival.

In research based on these findings, Dr. Lin and Shuxing Zhang, Ph.D., an assistant professor in the Department of Experimental Therapeutics, and their colleagues discovered a compound (SLZ-P1-41) that suppresses the Skp2-related tagging and destruction of p27 and stifles the Skp2 signaling that activates the cancer-feeding glycolysis pathway. The inhibitor works by blocking critical protein binding sites to prevent Skp2 from forming a complex with Skp1; this binding is the initial step in both of Skp2’s cancer-promoting functions.

“Inhibitors often are discovered without an initial understanding of how they work,” Dr. Lin said. “The beauty of this study is that we identified an inhibitor and showed how it functions to block Skp2.”

Skp2 has a large area where it interfaces with other proteins, and finding one small molecule that completely blocks a surface of that size is difficult. To identify a compound capable of inhibiting the protein, the researchers used computer models and a database of 10 million compounds.

“To rationally design a drug, you must first understand the target’s biology and then look at its structure and fully comprehend its complex interactions and how disrupting those will help treat the disease,” Dr. Zhang said.

SLZ-P1-41 was first tested against prostate cancer cell lines and normal prostate epithelial cells. The compound selectively killed the cancer cells with minimal effects on the normal tissue. The drug’s effects were confirmed in lung cancer, hepatocellular carcinoma, and osteosarcoma cell lines and in mice bearing human tumor xenografts.

“This compound has a high degree of specificity,” Dr. Lin said. “Our tests in prostate and lung cancer show it preferentially targets the cancer cells but not the normal cells.”

The researchers also found that the inhibitor suppressed the self-renewal of cancer stem cells—which play a role in cancer initiation, progression, and resistance to chemotherapy—in a dose-dependent manner. The study was reported in the journal Cell in August.

“Change in CA-125 Level Over Time Shows Promise for Ovarian Cancer Screening

Repeated measurements over time of a woman’s levels of cancer antigen (CA)-125, the protein long recognized for predicting ovarian cancer recurrence, show promise as a screening tool for early-stage ovarian cancer, suggests an ongoing study led by researchers at The University of Texas MD Anderson Cancer Center.

The prospective, single-arm study enrolled more than 4,000 healthy, postmenopausal women with no strong family history of breast or ovarian cancer. The women received a baseline CA-125 blood test and annual tests thereafter. Women whose CA-125 levels demonstrated a sharp elevation at any time underwent transvaginal ultrasonography and were referred to a gynecologic oncologist. Women whose CA-125 levels demonstrated a slight elevation returned for a repeat test in 3 months.

The study’s primary endpoint was the specificity of an increase in CA-125 over time in revealing the presence of ovarian cancer; the researchers found that this specificity was 99.9%.

Only two patients had tumors that were not revealed by increases in CA-125 levels; both had borderline ovarian tumors (tumors of borderline malignancy). One hundred seventeen women were determined to be at high risk by sharp elevations in their CA-125 levels. Of those women, 10 underwent surgery: 4 had invasive ovarian cancer, 2 had borderline ovarian tumors, 1 had endometrial cancer, and 3 had benign ovarian tumors.

Principal investigator Karen Lu, M.D., a professor in and chair of the Department of Gynecologic Oncology and Reproductive Medicine, said that the four invasive ovarian cancers detected by changes in CA-125 were high-grade epithelial tumors, the most aggressive form of the disease. These were caught at early stages, when the disease is treatable and often curable.

Dr. Lu also noted that all four women who were found to have invasive disease had been monitored for at least 3 years before a rise in CA-125 level was seen.

These interim results were published online ahead of print in Cancer in August. Dr. Lu said that while encouraging, these findings were neither definitive nor immediately practice-changing. However, Dr. Lu said, “I’m cautiously optimistic that in the not-too-distant future, we may be able to...”
About 7 in 10 cancer patients experience pain at some point during cancer treatment, but some patients are hesitant to take medicine for their pain—often because they have been misinformed.

The following are common myths—and the facts that prove them wrong—about cancer pain and its treatment.

**MYTH:** All cancer patients live in pain.

**FACT:** Most cancer-related pain can be treated. Doctors can prescribe narcotics (such as morphine, fentanyl, or hydrocodone) and anti-inflammatory, antiepileptic, and antidepressant drugs to relieve pain. These medicines are available in many forms such as pills, liquids, and patches. If medicine alone does not work, nondrug treatments such as massage, hypnosis, and breathing and relaxation exercises can help. For patients with pain that cannot be treated with medicine, other treatments like radiation therapy, nerve blocks, and surgery are sometimes used to relieve pain.

**MYTH:** Pain means the cancer is getting worse.

**FACT:** Pain can occur for many reasons. Although more than half of cases of pain in cancer patients are tumor related, treatments like chemotherapy, radiation, and surgery can cause pain. In addition, pain can have a cause that is not related to the patient's cancer. Don't forget, people without cancer also have pain.

**MYTH:** Patients who tell their doctor they are in pain may not receive their desired cancer treatment.

**FACT:** Doctors need to know all of a patient's symptoms—including pain—to provide the best treatment. Pain that goes untreated can delay a patient's cancer treatment because a patient who has pain may need to visit the emergency room or be admitted to the hospital to control the pain.

Uncontrolled pain can also delay a patient's recovery. This delay happens because pain causes stress, and long-term stress causes the body to produce hormones that weaken the body. In addition, untreated pain causes unnecessary suffering. Patients should tell their doctor if they are in pain and describe their symptoms as specifically as possible to receive the best treatment.

**MYTH:** Pain medicines will erase all pain.

**FACT:** Although doctors hope to relieve all of a patient's pain, the patient should not expect a complete absence of pain. Doctors strive to relieve enough of the patient's pain so that the patient can go about daily activities and have the best quality of life possible. Managed pain allows patients to spend less time in the hospital and more time at home with loved ones.

**MYTH:** Pain medicines lose their effectiveness.

**FACT:** Over time, a patient's body will become used to, or tolerant of, a drug. Drug tolerance is a normal reaction, and doctors can easily increase the dose of many drugs to control a patient's pain. If a patient is already taking the highest safe dose of a drug, doctors may need to switch to a different drug.

**MYTH:** Pain medicines have uncontrollable side effects.

**FACT:** If patients have side effects from pain medicines, other medicines or therapies can be given to treat those side effects. For example, a common side effect of narcotics is constipation, which can be easily corrected by adding laxatives or stool softeners to the patient's medicine regimen.

Cancer patients can avoid living in unnecessary pain. Pain treatment options are available for patients with all types and stages of cancer.

“There is no cookie-cutter pain regimen. Each patient is an individual,” said Rob Yates, a physician assistant in the Department of Pain Medicine at The University of Texas MD Anderson Cancer Center. Patients should consult their doctor to learn how to manage their pain.

— C. Wilcox

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IN BRIEF
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offer a screening method that can detect ovarian cancer in its earliest, curable stages." ■

Preclinical Study Finds Origins of Kidney Fibrosis–Causing Cells

Four cell development pathways that lead to kidney fibrosis—uncontrolled, destructive scarring through collagen overproduction—have been pinpointed in mice, according to a study conducted in part at The University of Texas MD Anderson Cancer Center.

Because fibrosis can develop into cancer and enable cancer progression and resistance, preventing or treating fibrosis may be crucial to overcoming certain cancers.

In mouse models of kidney fibrosis, researchers used fate mapping to track which mesenchymal cells would become myofibroblasts, the dominant producers of collagen. In fate mapping, the promoter of a protein expresses a color inside a cell that remains with the cell until it dies, allowing researchers to determine the cell’s origin.

These experiments showed that half of the myofibroblasts came from preexisting resting fibroblasts, 35% came from mesenchymal stem cells originating in the bone marrow, 10% came from blood vessel cells that underwent endothelial-to-mesenchymal transition, and 5% came from kidney cells that underwent epithelial-to-mesenchymal transition.

Contrary to previous studies that implicated pericytes—connective, contractile cells surrounding blood vessels—in myofibroblast generation, this study found that pericytes did not transform into myofibroblasts and that destroying pericytes did not improve kidney fibrosis or alter the production of myofibroblasts. Instead, the differentiation of cells other than fibroblasts into myofibroblasts appeared to rely on transforming growth factor β1.

“Answering a fundamental question about the origin of myofibroblasts by identifying four separate pathways involved in their formation allows us to look at ways to block those pathways to treat fibrosis and potentially prevent future emergence of cancer in some organs,” said Raghu Kalluri, M.D., Ph.D., a professor in and chair of the Department of Cancer Biology and the senior author of the study’s report.

Although the study focused on kidney fibrosis, the researchers believe that their findings will apply to all types of fibrosis. “The sources are likely to be the same for lung or liver fibrosis, but the ratios may be different,” Dr. Kalluri said.

The study’s report was published in the August issue of Nature Medicine. ■

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