Mind jumble: Understanding chemo brain

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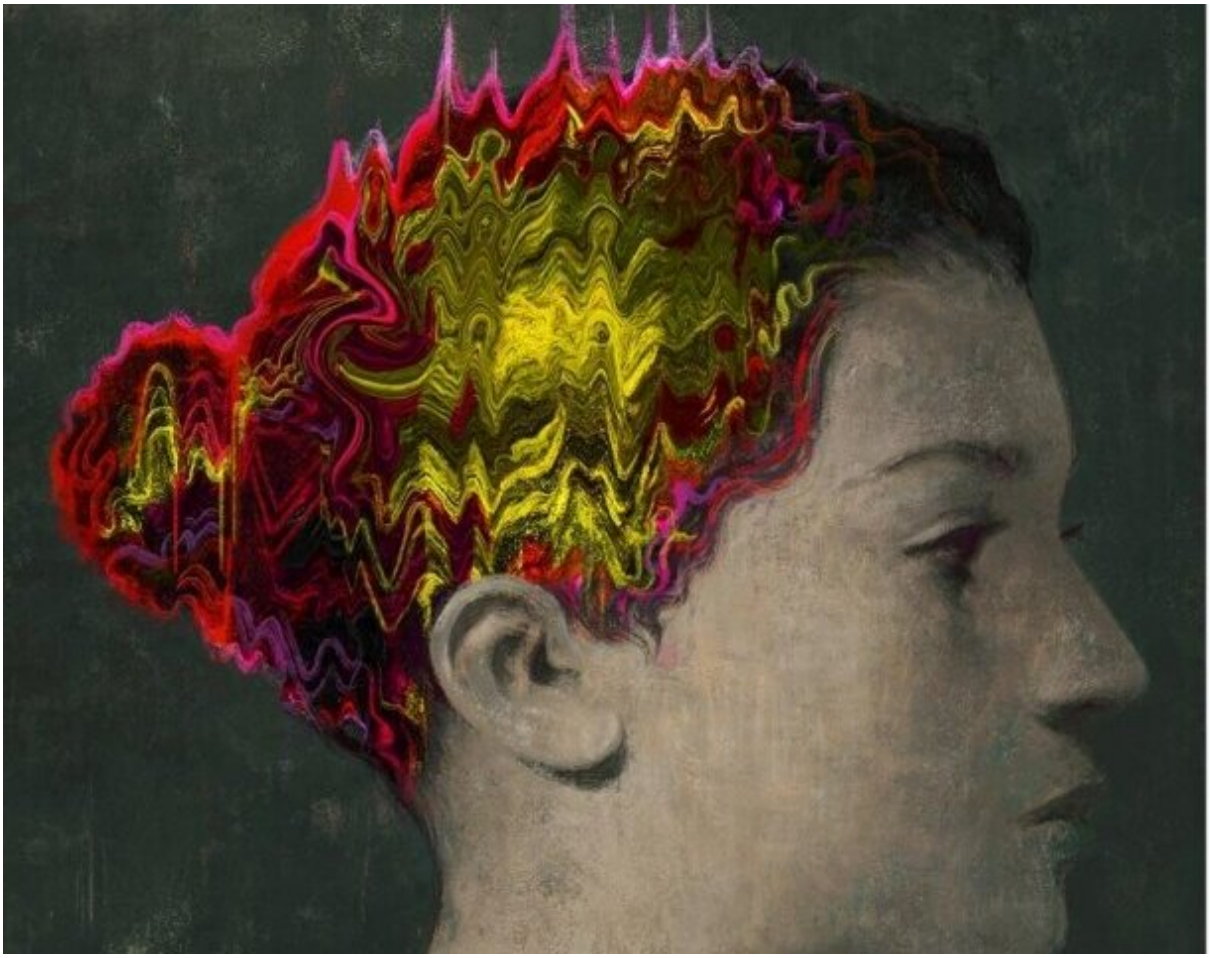

Illustration by Gérard DuBois

Sarah Liu was treated for leukemia as a teenager. She attended her high school graduation on a four-hour pass from Lucile Packard Children's

Hospital Stanford and was bald under her white graduation cap, her arm bandaged where she'd been receiving chemotherapy drugs.

Liu survived cancer and the ordeal of her treatment, and for many years she thrived. But today, at 53, she struggles to remember the names of all the Stanford oncologists who helped her, though she reveres them for saving her life. Many years later, her childhood cancer treatments—chemotherapy and radiation—have left her brain muddled.

She sometimes blanks out in the middle of a conversation or while reading a paragraph; her brain just shuts down, she said.

When her brain tires, she can't focus on the task at hand and is unable to follow a narrative, whether it's in a book or on a television show. And she frequently forgets things. Liu said she is grateful to have survived, but her survival has come at a great cost.

"I think it's a complete myth that you live past the five-year survival rate and that's it, you're clear. For pediatric cancers in particular, that's not true. These drugs and radiation all have a profound effect," said Liu, a Berkeley, California, resident. "You survive, but the price you pay to survive can be very traumatic."

She's among the legions of cancer survivors suffering from chemo brain, a neurological disorder formally known as chemotherapy-related cognitive impairment.

The majority of patients who overcome cancer experience the condition, which is marked by mental fogginess, slowed thinking, memory problems, inability to multitask and sometimes anxiety, said neuro-oncologist Michelle Monje, MD, Ph.D., an associate professor of neurology and neurological sciences at Stanford.

There is no cure, though some medications may help minimize symptoms, said Monje, who advises patients to consult with a neurologist familiar with the condition. She said there is also some evidence that aerobic exercise improves cognitive abilities after cancer therapy.

"Cancer is not done when the cancer is gone," Monje said. "We need to follow up on the pretty serious consequences of these life-saving therapies and hopefully promote regeneration and healing of the damage done by these very powerful treatments."

For the past two decades, Monje has studied cancer therapy-related cognitive impairment along with a small community of neuroscientists across the country who are excavating the biology that underlies the disorder.

Two of the major cancer treatments, radiation and chemotherapy, can lead to cognitive difficulties, though the impacts of cranial radiation tend to be more severe and to progress more rapidly. Scientists have recognized the effects of radiation on the brain for decades, but they have only recently begun to appreciate the true impact of chemotherapy on the brain.

Monje's latest studies, published in 2018 in *Cell* and last year in *Neuron*, have uncovered a cascade of cellular events caused by the common chemotherapy drug methotrexate that can disrupt brain function and cognitive abilities. Moreover, she and her colleagues have identified two molecules that can forestall the damage and restore normal brain processing, at least in mice.

"You never know what happens going from mouse to humans. However, we are encouraged that these drugs have worked in a number of entirely different mouse diseases," said Frank Longo, MD, Ph.D., professor and

chair of neurology at Stanford who has collaborated with Monje.

"We think we are really targeting a fundamental mechanism. It gives us a little more hope that the effects we're seeing in mice might also occur in humans."

Monje said she thinks of chemo brain as "plasticity interrupted," a glitch in the brain's ability to change and adapt.

"I think it can be reversed," she said. "I'm very hopeful that we'll be able to truly treat and repair the damage caused by our necessary but toxic cancer therapies."

Some 15.5 million Americans have survived cancer, and the number is expected to grow to 20 million by 2026, according to the National Cancer Institute. It's estimated that at least half of these individuals may suffer long-term effects from treatment that can hinder their ability to work, succeed in school and perform daily tasks, Monje said.

Symptoms 'rob' patients' soul

Stanford pediatric oncologist Paul Fisher, MD, recalled one patient who became distraught because she was having trouble finding her way in her neighborhood seven years after being treated for brain cancer. He was empathetic, but couldn't offer a remedy.

"She was driving her child to school and got lost. She was just beside herself," said Fisher, the Beirne Family Professor of Pediatric Neuro-Oncology.

"What's most gripping is when people are cognizant enough, like she was, to know they aren't the person they were—they are aware that they have deficits.

"Thinking, talking, memory—that's who you are," he said. "That's the very part of your soul. That's the thing that is devastating to people. It robs their soul."

Some studies of women with breast cancer show that, even 20 years later, some have such serious cognitive problems that they are unable to return to their jobs and regain the level of function they had before therapy, Monje said.

In children with cancer, the long-term effects are even more profound because the drugs assault the brain during a key time in development, she said. These children may not be able to finish college or live independently, particularly if they've had radiation therapy to the brain, she said.

"They may never drive a car. They may never get married. This really alters lives," said Monje, whose clinic is focused on treating children with brain tumors. "Of course, it's a spectrum, as some do better than others. I certainly know MD and Ph.D. students who were treated for cancer in childhood. There are many variables. But it's a big problem."

Monje's interest in the condition was sparked in 2000, when she was a Stanford medical student. In treating cancer patients, she was disturbed to see so many suffering from negative long-term neurologic consequences, particularly those who'd had radiation therapy.

She went on to complete her Ph.D. in neuroscience at Stanford, where she teamed up with Theo Palmer, Ph.D., a professor of neurosurgery, to examine how radiation therapy affects the hippocampus, an area of the brain central to forming memories and one of the few areas in which new neurons are formed throughout life.

To their surprise, the researchers found that radiation to the brain in

laboratory mice caused harm by revving up the microglia—immune cells in the brain that surround neurons. The microglia were causing inflammation, which prevented new neurons from forming.

When the mice were given the common anti-inflammatory drug indomethacin, it reversed the harm and restored normal brain function, the scientists reported in 2003 in the journal *Science*. As a consequence of these findings, clinicians now shield the patient's hippocampus during radiation therapy.

"Now it's very well established that microglia play fascinating and diverse roles in nervous system development and disease," Monje said. "But at the time, the idea of microglia influencing the development of neurons—wow, that was unexpected." It was also a hint of things to come.

Confirming chemo brain's validity

One of Monje's colleagues during her residency at the Harvard-affiliated Massachusetts General Hospital, Jorg Dietrich, MD, PhD, conducted early studies of chemo brain. In one published in 2006, his team tested three common chemotherapy drugs and analyzed their effects side by side on human cancer cells in the lab and normal brain cells, and found the drugs were more lethal to brain cells than to the cancer cells.

Their work also showed that the immature cells of the brain, progenitor cells, which are crucial for maintaining brain plasticity throughout life, were particularly vulnerable to chemotherapy.

The finding ran counter to what clinicians had long maintained—that the mental fog following cancer treatment was just a sign that patients were depressed about their disease, Dietrich said.

"We really had to work against this dogma in the field for about 20 years," said Dietrich, a professor of neurology at Harvard who directs a clinic focused on the neurologic effects of chemotherapy and radiation. Because no one wanted to believe that drugs targeting cancers outside the central nervous system could penetrate the blood-brain barrier and harm brain cells, the oncology community continually pushed back on this body of research.

"I think there was just enormous anxiety in the field of oncologists and providers that there was the risk for damage to the brain, but they didn't want to acknowledge this because there really wasn't any alternative," he said.

He said the ground began to shift around 10 years ago when evidence piled up confirming that cancer drugs could in fact target the brain and harm the brain's support system—the glial cells, which nourish and protect neurons and make up about half of the cells in the brain and spinal cord.

Glial cells include not only the microglia but also astrocytes—star-shaped cells that help neurons get nutrients and maintain their connections to other cells—and oligodendrocytes, which help build myelin, the protective sheath that insulates brain cells and allows for fast transmission of signals between them. Without myelin, signals become slowed or confused.

Recently, Monje's lab completed research in laboratory mice that shows how the cancer drug methotrexate disrupts these three types of glial cells. In one study, her team found the drug first activated the microglia to cause inflammation. That provoked a reaction from astrocytes. That, in turn, disrupted the formation of oligodendrocytes.

The mice in the study reacted by moving slowly and showing signs of

anxiety, impaired attention and memory problems. These changes persisted for at least six months after the animals were given methotrexate, a long time in the life of a mouse.

Most importantly, the researchers found that when they gave the animals a compound that depleted the microglia, an experimental drug called Plexxikon 5622, it corrected the cascade of damage and the mice behaved normally, said Erin Gibson, PhD, the study's leader and a former postdoctoral fellow in Monje's lab.

It was the first time scientists showed that disruptions in interactions between multiple cell types in the environment around the neurons were the source of their aberrant behavior after chemotherapy, said Gibson, now an assistant professor of psychiatry and behavioral sciences.

In retrospect, the result seems logical, Monje said: "How can neurons function when there's all this dysfunction around them?"

After the paper describing this research was published in December 2018 in the journal *Cell*, Monje heard from cancer survivors from around the country who were relieved to find an explanation for the problems that had plagued them after treatment, she said.

"Many people wrote to me and said, 'Thank you. I didn't understand why I couldn't go back to work. Everyone thought I was just crazy or depressed. It's not that. This is real,'" she said.

"There needs to be increased awareness about cancer treatment-related cognitive impairment," she added. "People need to be counseled about this. They need to know there are scientists and physicians working to make this better, though we don't have the cure for it just yet."

Finding solutions

When Liu read the article in Cell, she said, she practically cried with joy, knowing help might be on the way. "This was the first hope I'd ever had since my cancer," she said. "Because until then, all I'd heard was 'irreparable damage.' This was the first time I felt there might be something that isn't just relieving the pain, but actually making things better."

Monje said she'd like to test the impact on chemo brain of a compound that temporarily depletes microglia, such as Plexxikon 5622, as these cells are the trigger for the cascade of negative effects and require a reset to a more helpful, less harmful state. Her plan is to do more testing in animals with an eye to a clinical trial in a few years.

Meanwhile, scientists in her lab have pinpointed another possible treatment. Led by postdoctoral fellow Anna Geraghty, PhD, they focused on a protein called brain-derived neurotrophic factor, or BDNF. Normally, neurons release BDNF, which does many things, including prodding oligodendrocytes to build myelin.

But the researchers found that when the brain is exposed to methotrexate, the resulting microglial inflammation decreases BDNF made by neurons, and the oligodendrocytes lose their ability to form myelin in response to neuronal activity—a process, called myelin plasticity, that contributes to learning and memory. In the study, published in July 2019 in Neuron, the mice exposed to methotrexate had compromised brain function as a result.

In searching for a solution, Monje turned to Longo, forming a partnership that shows how scientific interests sometimes can converge in unexpected ways. Earlier work had indicated that BDNF latches on to the oligodendrocytes through a receptor called TrkB. It so happened that Longo had developed a small molecule, a kind of TrkB booster, that he was testing in the lab as a possible therapy for Alzheimer's, Parkinson's

and Huntington's diseases.

The researchers tested the TrkB booster in the chemo-compromised mice and, remarkably, the animals' myelin normalized and their brain function was restored. Both Monje and Longo agree that the molecule, LM22A-4, could be a great prospect for treating chemo brain.

"This is a major step—when you discover an entirely new mechanism that is amenable to therapeutics," said Longo, the George E. and Lucy Becker Professor in Medicine.

Though Longo has had dramatic results using LM22A-4 to treat degenerative diseases in laboratory mice, he has not yet tested it in people. So it's not known how humans might respond to the compound, he said.

But there are many questions to be answered first, said Monje, such as when patients should receive drug treatment to counter chemo brain. In both studies, the treatment immediately followed methotrexate exposure. She's now studying the use of LM22A-4 at different points in time after cancer therapy.

"What if someone is still suffering from cognitive impairment 10 years later? Might this be a viable therapeutic strategy for them? Or is this something we have to do right after therapy?" Monje asked. "We don't know that yet."

Even the time of day treatment takes place could make a difference, said Gibson, who is a circadian biologist. She said studies have shown that the time of day patients receive chemotherapy drugs can dramatically influence the drugs' effectiveness. The same may be the case with drugs used to combat the effects of chemo and radiation.

"Are there times in the day when glial cells might be less susceptible to disruption by a chemotherapeutic agent? We have some early indications that may be true," said Gibson, who is pursuing this research in her lab at Stanford. "So there might be a therapeutic strategy in which just changing the temporal component of administration could mitigate some of these neurological deficits."

Looking for the holy grail

Monje said scientists also need to figure out why the changes in microglia after chemotherapy are so persistent. The cells remain activated long after exposure to methotrexate, meaning they are undergoing some fundamental change, she said. This persistence helps explain why patients continue to have cognitive problems years after treatment.

"Imagine you fell down and bruised your knee but your knee was inflamed forever," Fisher said. "Some of the drugs and radiation cause this permanent activation of inflammation. It's like you have a bruised knee forever. And that's a big problem."

Dietrich said the key to countering the damage is to create a nurturing environment for neurons.

"I think of that as the holy grail," he said. "Take the case of the tree that does not have enough water. It's not so much the tree that is the problem. It's the microenvironment that doesn't give enough to the leaves, and it falls apart."

Monje said it's not known whether other cancer drugs might have the same impact on the brain as methotrexate, which is a particularly bad actor when it comes to cognitive impairment. However, some research suggests a similar pattern among other cancer-fighting agents.

"There are other drugs for which direct activation of microglia has been described, but we should do a more comprehensive study of that," she said. "It may be different cancer drugs work through a different mechanism. Then we would need a different strategy."

Cancer survivor Liu said she functioned well for years after her treatment, completing her PhD at UC-Berkeley in English and becoming fluent in Mandarin and French. But one day in 2006, while teaching a class at Berkeley, she had a warning sign of things to come.

"I blanked out in front of the class I was teaching," she said. "I had to fake it and let the class out early."

She began to have increasingly frequent memory gaps.

"When it first started, it really frightened me," she said. "I thought, 'Am I losing my mind?' The only thing I can do is rest my brain. I just lie down and focus on breathing, without distraction. It helps."

She runs most days but lacks the stamina to do any more marathons. She's been studying biochemistry online in very short spurts—she wants to be able to understand the science behind her condition. And she's writing a book about her experiences, cobbling together previous publications and years of notes, but she has limited mental energy for writing now.

Monje says Liu has done extremely well over time, particularly considering that she was exposed to intensive chemotherapy and cranial radiation.

"She is remarkable in how much she has accomplished despite these major challenges," Monje said. "It is so frustrating for me to see my patients like Sarah struggle with these daily burdens and not be able to

offer more restorative therapy yet."

Liu said she feels immense value in the doctor-patient relationship, as she and Monje "have a shared understanding of the cost of chemo, grief as we watch the decline, knowing that we are doing the best we can at both ends, for ourselves and untold others."

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