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Mind Games

BY LAURA BEIL

Addressing and correcting cognitive problems in older cancer patients.

In 2003, Don Leatherman considered himself a healthy man of 60 on the cusp of retirement. Though he spent his days as a desk-bound computer programmer, weekends would find him working his 38 acres of Texas prairie land, or running a five-mile stint, “as easily as you could walk across the room.” He did not know, until the day his urine turned crimson, he was carrying a grapefruit-sized kidney tumor. By the time doctors discovered the malignancy, cancer had worked its way into his lungs and the bones of his legs.

He began chemotherapy just after diagnosis, starting what has become a six-year marathon with his cancer. Tumors come and go with treatment, leaving Leatherman unable to wean himself from “the juice”—as he refers to it—even as he returned to work in Arlington, Texas, and reclaimed much of his old life.

But as his body began to recover, Leatherman noticed his mind had gotten sluggish. He would stare at his computer, his brain struggling to summon software coding that should have come to him automatically. “Picking up new things is really difficult,” he says. When he raised these concerns with his oncologist, Leatherman says the doctor shrugged and replied, “Well, Don, you’re not getting any younger.”

Yet research suggests that Leatherman may not be suffering from a sudden attack of senior moments. Even though the science in this area remains imprecise, doctors are finding that age, cancer, and chemotherapy often conspire to create greater mental consequences than any could cause alone. It is a phenomenon far more complex than “chemobrain,” a reference to the general mental fog many with cancer experience during treatment.

Don Leatherman, with his son Glen, at their family's ranch in Texas.
Photo by Wes Wolfe.

Patients in their 60s and older generally seem more haunted by cognitive declines after treatment, perhaps because an aging brain has lost some of its mental agility, or because complications from other medical conditions (such as cardiovascular disease) also affect cognition, or because of a host of factors not yet understood. Cognitive problems may be more pronounced in older patients because they are more likely to experience malignancies that spread to the brain, or that call for aggressive, longer treatment.

“There are more questions than answers at this point,” says Tim Ahles, PhD, director of the Neurocognitive Research Laboratory at Memorial Sloan-Kettering Cancer Center in New York. He says most studies concerning the cognitive aspects of cancer started less than a decade ago, and usually focused on young breast cancer patients. Until very recently, he says, providers remained skeptical that patient complaints were because of their treatment.

“Most of the chemotherapy agents typically used don’t cross the blood-brain barrier very well,” Ahles says. “There was always this assumption that if they don’t cross the blood-brain barrier they can’t be affecting cognitive functioning.”

That assumption appears to be wrong. Most of the time, Ahles says, the mental effects from cancer treatment are subtle—struggles with concentration, working memory, or multitasking. Older people with cancer are not getting lost in the supermarket, but they may have more moments when they find themselves idling in the frozen food aisle, wondering what on earth they went there for.

A Lasting Change?

Basic questions remain: Do cognitive problems occur in some cancers more than others? Who is at risk of long-term impairment? Do certain chemotherapy agents carry a greater risk of cognitive side effects? How much are the effects accelerated by other medical conditions, such as diabetes or depression, or medications? “It gets very complicated very fast,” Ahles says.

Older cancer patients and their families are often forced to use two of the most dreaded words in one’s vocabulary—dementia and delirium—and realize that

cancer might raise the risk of both. Delirium usually comes on quickly and causes a patient to experience wildly fluctuating degrees of alertness throughout the day, says Terry Rabinowitz, MD, of Fletcher Allen Health Care in Burlington, Vermont.

Delirium most often results from a definite cause, such as medication or infection. Dementia has a more gradual progression, and a person's alertness is steadier throughout the day. And while delirium is usually treatable and reversible, other forms of impairment are more difficult to treat, or even define.

The search for answers has been difficult because cancer affects a diverse group of patients who experience different diseases with different treatments, and clinical studies are of little help. Cognitive side effects usually escape detection since older patients are often excluded from studies because of pre-existing illnesses.

"One of the biggest issues is, is the change permanent?" says Andrea Bial, MD, a geriatric specialist at the University of Chicago Medical Center. "Does it cause cognitive deficits, and if so, how long does it last? Does this cancer and its treatment affect cognition, and at what point will the baseline return?"

View Chart: Dementia Versus Delirium

In 2006, Bial and her colleagues reviewed studies on cognition in cancer patients in *Critical Reviews of Oncology/Hematology,* finding that the selection of published studies so far can't offer firm conclusions. Only 17 percent of research studies on cognition in cancer have included patients age 65 and over. Reports have combined types of cancer and involved more than 60 different tests to assess mental ability. "None of the data is even robust enough to say, 'I'm not treating you with that because it's going to affect your brain,' " she says.

Nonetheless, Sloan-Kettering's Ahles offers a general framework. Patients undergoing cancer treatment will typically experience cognitive changes, not just from chemotherapy but from the combination of treatment, fatigue, depression, symptom-control medications, and even the physiology of the cancer itself. Once chemotherapy ends, most people gradually regain their mental capacity within a year. A few—around 20 percent, Ahles says—"will hit a plateau, and it just stays."

It is the prospect of long-term cognitive problems that has physicians most concerned. In 2005, researchers from the University of Southern California described a study of 702 older cancer survivors, comparing their cognitive function with that of a twin who had not had cancer. The study, published in the *Journal of the National Cancer Institute*, found that five years or more after treatment, the twin with cancer was about twice as likely to have been diagnosed with cognitive deficits severe enough to affect daily life.

But researcher Beth Meyerowitz, PhD, professor of psychology and preventive medicine at USC, says scientists still can't say whether the combination of cancer and treatment itself caused a permanent problem, or whether the experience simply accelerated a decline that was coming anyway. She explains it this way: We all have a certain amount of "cognitive reserve," a buffer that keeps us from crossing the threshold into dementia. Perhaps chemotherapy doesn't cause

dementia, she says, “but it decreases that reserve.”

Looking for Explanations

Until researchers find some explanation for cancer’s cognitive side effects, the cognitive reserve hypothesis remains.

“What we don’t know enough about is the general mechanism of how these conditions occur,” says Rabinowitz. Animal studies suggest that common chemotherapy agents can increase cell death in the central nervous system. Imaging studies have also found structural changes in the brain that appear to be associated with chemotherapy.

The search for answers doesn’t stop with chemotherapy. Cancers themselves could be triggering the release of substances that are toxic to the brain, or affecting hormones, such as estrogen, already under investigation for their role in brain function.

Until more answers emerge, doctors stress that regular exercise for the brain becomes particularly important for older cancer patients. Studies are also under way to see if certain medications, such as low doses of stimulants, can boost mental function.

For his part, Don Leatherman has taken a philosophical view, wondering if a person contemplating his or her own mortality simply finds grasping the finer points of JavaScript, or today’s grocery list, less important by comparison.

“I find myself wondering if the cognitive problems I experience might not be in part related to a new attitude about life,” he says. A life, he hopes, that will provide him with many more memories to come.