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Chemobrain: Causes & Remedies Remain a Subject of Scrutiny

BY MICHELLE PERRON

National cancer data show that U.S. deaths from cancer overall are declining, leading to more survivors. That's great news. But for a large percentage of these survivors, life after cancer produces new challenges that can alter daily life. Challenges that occur in areas of cognitive functioning are collectively known as chemobrain.

CME Article

Cognitive deficits related to cancer or its treatments are wide-ranging. They may be subtle or dramatic, temporary or permanent. They may stay the same for years or get worse with time. The estimated incidence and effects of chemobrain have been reported by multiple sources over the years:

- As much as 75 percent of cancer patients experience cognitive impairment during or after treatment for cancer.

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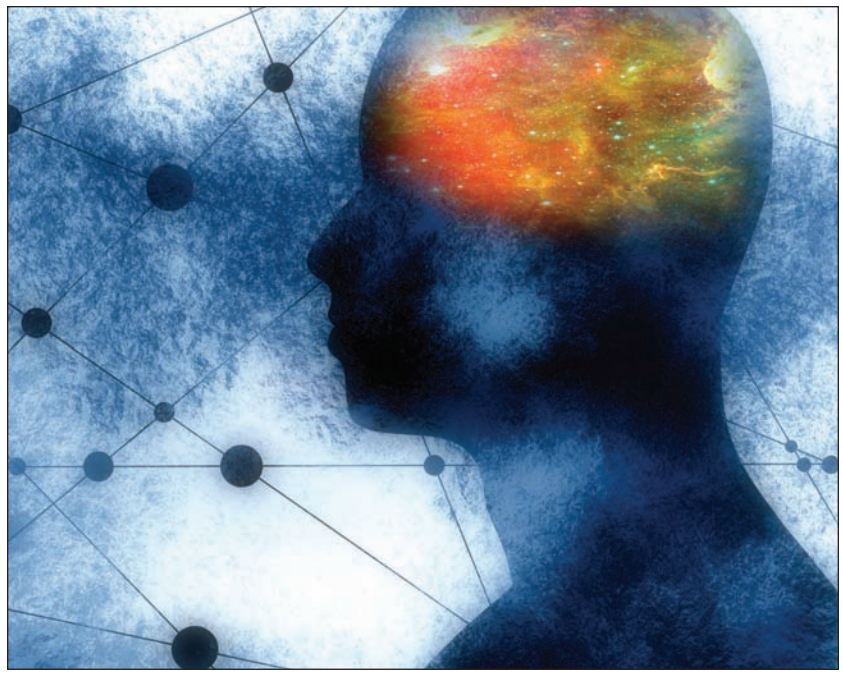

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The Ibrutinib-Venetoclax Combination in Mantle Cell Lymphoma

BY RICHARD SIMONEAUX

Mantle cell lymphoma is a somewhat rare B-cell hematologic malignancy that comprises approximately 6 percent of non-Hodgkin lymphoma cases. Each year, there are roughly 4,000 new cases in the U.S., while the 5-year survival rates range from 70 percent for those with limited stage disease to 50 percent for those having advanced disease. The average age at diagnosis tends to be in the mid-60s. Typical treatment for those younger patients with few comorbidities often includes systemic chemotherapy that is often followed by autologous stem cell transplantation; however, for older patients with preexisting comorbidities, standard treatment consists of systemic chemotherapy followed by maintenance rituximab.

Recently, therapies have emerged that target B-cell malignancies, such as the Bruton's tyrosine kinase (BTK) inhibitor

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Helping Patients Overcome Enrollment Barriers in Blood Cancer Trials

BY SCOTT KERWIN, MN, RN, CCRC, CCRN

The goal of increasing clinical trial enrollment in cancer trials has been around for many years, yet there has been little success. Patient and system barriers have been widely studied, yet fewer than 10 percent of cancer patients participate in clinical trials, and less than 20 percent of patients say their physician discussed clinical trials with them (*Community Oncol* 2009;6(5):207-288).

Because of the complex nature of the problem, no single solution exists for all cancer centers or for all patients. It is important, however, to use innovative approaches to remove these barriers, especially since it has been shown that overall survival rates in some cancer populations are significantly higher for patients who participate in clinical trials versus those who do not (*J Clin Oncol* 2016;34[suppl 4S; abstr 216]).

Hematologic malignancies are the most common type of cancer that affect young patients, making up nearly 40 percent of childhood cancers. The good news is that children are well-represented in clinical trials, with over half of pediatric cancer patients participating in a clinical trial, according to the American Cancer Society Cancer Action Network 2018 report. The same is not true for adults, however, and efforts need to be made to reduce barriers for patients, as well as for health care professionals.

Finding a Clinical Trial

In July 2017, a new program was launched by the National Marrow

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• For up to 35 percent of them, this impairment persists for months or years following treatment.

• Commonly reported symptoms are problems with memory, executive functioning, and attention.

Given that more than 15.5 million Americans now survive cancer, more than 5 million people could be living with long-lasting cognitive difficulties resulting from cancer and its treatments.

"One of my first patients with cognitive deficits after cancer treatment was a high-level accountant who couldn't go back to work," said Patricia A. Ganz, MD, Director of Cancer Prevention and Control Research at Jonsson Comprehensive Cancer Center in Los Angeles and Distinguished Professor of Health Policy & Management and Medicine at UCLA Fielding School of Public Health and the David Geffen School of Medicine. "I've seen lawyers, physicians, and others who simply couldn't go back to what they were doing before. When you see that, you believe that this problem is real."

A Little History

The first reports of chemobrain began to appear in the literature in the 1990s and reflected complaints by patients with breast cancer, especially those who received high-dose chemotherapy with stem cell transplantation. Women were some of the first patients to speak up about cognitive symptoms and are informally credited with coining the term chemobrain.

"Some researchers would say anecdotally that women patients may be more likely to come forward about cognitive symptoms," explained Jerry Suls, PhD, a health psychologist who is a senior scientist in the Behavioral Research Program at the NCI. "They are therefore more willing to participate in research about it. We have also seen these effects in lymphomas and other types of cancers. It's not exclusive to women, but the majority of studies about cognitive impairment involve women."

Initially, oncologists met these complaints with a degree of skepticism. This was based on the understanding that chemotherapy agents administered to patients with non-central nervous system malignancies did not cross the blood-brain barrier. Toxic effects on the brain didn't make sense. At first.

"Part of the original 'resistance' was due to this fact. Oncologists thought there must be something else going on," Suls said. "Over the last few decades, many studies have looked at the extent to which chemotherapy drugs cross the blood-brain barrier. We now know that some agents do, and therefore could potentially produce inflammation or be toxic to the brain's gray or white matter.

"We now know a lot more about what chemotherapy agents do to the immune system," he continued. "Even if a chemotherapy agent doesn't cross the blood-brain barrier, its action in other parts of the body can in fact result in inflammation or other potential processes that can influence the brain."

Research Focus

Roughly 120-150 researchers throughout the world are focusing on unraveling the mystery of chemobrain, Ganz said. "It's hard work to do. It's problematic because accessing the patients before treatment is difficult. If you don't have a baseline, it's challenging." Many of these researchers participate in the work of the International Cognition and Cancer Task Force.

The panel's most recent gathering was in April 2018 in Sydney, Australia, where members explored topics such as cognitive and neuroimaging outcomes, the use of technology to assess cognition, and the influence of cancer on cognition in preclinical models. Suls attended the meeting and said the task force is now encouraging scientists to examine the cognitive effects of all types of cancer therapy. Although chemotherapy may have brought attention to the problem, evidence is showing that other forms of cancer treatment may also lead to cognitive deficits.

"One speaker talked about very long-term follow-up of pediatric cancer; he followed patients decades later to assess cognitive processes," Suls said. "They had received lots of anesthesia due to multiple procedures. Independent of any chemotherapy agents they received, cognitive deficits occurred. These survivors showed deficits possibly related to cumulative amounts of anesthesia exposure. Now we have a new thing to look at."

The expanding use of immunotherapy to treat cancer also warrants attention. "There's a lot of promise in immunotherapy," Suls said, "but there has been little attention so far to its effects on cognitive processes. In animal model findings, one of the researchers found evidence that immunotherapies influence executive function. This needs follow-up. Given the fact that immunotherapy has become an option, it's important to know whether it has cognitive impacts."

Overall, research efforts in this area need a longitudinal approach. Suls added. "We have some but need more longitudinal studies of patients to get more answers. We need to recruit patients to study them right after diagnosis—before they start any treatment. That is the best way to determine the relative effect of each cause."

Root Causes

The attention paid to chemobrain has produced several theories about the mechanisms of causation. What is it about chemotherapy that causes dysfunction and decline? The hypotheses tend to center around inflammation, aging, and pre-existing inclination toward executive functioning problems. The effects of endocrine therapy, such as hormonal treatments for breast cancer, and the influence of genetics are newer areas of exploration.

"Cancer treatment itself causes systemic inflammation," Ganz explained. "The most intensively treated patients develop an increase in pro-inflammatory cytokines as a direct result of treatment; that's what it does. In most people, the inflammation quiets down and they get better over 6 months to a year later. But some have persistent inflammation. It can be subtle, but it crosses the blood-brain barrier and activates cells in the brain."

The cognitive changes of chemobrain can be similar to those seen in accelerated aging, Ganz pointed out. "We all age at different rates. There are people who are aged at 55 and people who are not aged until they are 95. Some people treated for cancer may not have good cognitive reserve, may have limited education, may not have exercised much, and they may have cognitive decline at a more rapid rate," she said. "If you develop a lot of inflammation and toxicity from treatment, you may experience more significant effects."

Ganz, who frequently provides survivorship consults to patients experiencing chemobrain, said she considers "host factors" important for consideration. "A lot of my work has been looking at host factors.

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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to identify possible causes of chemobrain and evaluate strategies to manage the symptoms.

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By that I mean what the person brings to the diagnosis. Patients who have fibromyalgia, are inactive, are depressed, had childhood trauma, or who have abnormal functioning of the hypothalamo-pituitary axis may not be able to control or suppress the increased inflammatory response that occurs with cancer treatment."

Clinical Response

As efforts to unravel the mysteries of cognitive deficits associated with cancer treatment continue, patients continue to ask for help. What can oncologists offer them?

"Right now, we have no standard of care for these impairments," Suls said. "Various things have been tried sporadically, but there is no universal recommendation to use them. So what do we have as an available route? Some cognitive behavioral modification strategies, such as teaching patients skills like anticipating problems in order to compensate for deficits, may be useful. Another strategy is to come to grips with the fact that you have some cognitive deficits. This will enable you to think about things ahead of time that you might need assistance with."

In her survivorship clinic at the Jonsson Comprehensive Cancer Center, Ganz often takes patients through a process of elimination to determine which treatments or interventions might be helpful. "We look at their sleep quality and any depression or anxiety as individual elements," she explained. "This helps to identify individual problems that may benefit from intervention. If we don't find any of these, it might be worth a neuropsychology evaluation to determine whether there are objective cognitive deficits in specific domains, such as memory, attention, or executive function. Interventions such as cognitive behavioral strategies to manage anxiety and stress associated with chemobrain can be useful."

She describes depression as "very undetected and untreated" in patients with cancer. "There is very little screening going on in spite of a call for it," she noted.

In commentary published last year in the *Journal of Oncology Practice*, psychiatrist Wendy Baer, MD, offered oncologists this advice: "Thinking of the cancer survivorship care plan recommendations as opportunities to enhance patient wellness may feel more manageable for the practicing oncologist than 'fixing' chemobrain" (2017;13(12):794-796).

Indeed, it is unlikely that anyone will fix—or prevent—chemobrain. But attention to how it develops, why it develops, and the many ways patients can navigate the alterations it creates will continue to add to the good news of increasing cancer survivorship. OT

Michelle Perron is a contributing writer.

Selected Strategies for Management of Chemobrain Symptoms

- Cognitive behavioral therapy
- Cognitive rehabilitation
- Regular exercise
- Management of anxiety
- Management of depression
- Improved sleep hygiene; adequate rest
- Treatment of sleep apnea, if present
- Mindfulness meditation
- Yoga modified for cancer survivors
- Relaxation breathing techniques
- Stress-reduction techniques

*None of these therapies has been universally recommended, and some are based on evolving research

Source: Dana-Farber Cancer Institute: http://www.dana-farber.org/health-library/articles/tips-for-managing-chemobrain/