“Doctor, Will the Treatment You Are Recommending Cause Chemobrain?”

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For more than a decade, patients and their oncologists have been sharing conversations about cognitive complaints after chemotherapy treatment. Early on, only occasional patients complained of trouble with concentration and memory during treatment, with a minority noting persistence beyond the end of treatment. The oncologist, who rarely heard this complaint, could be dismissive, saying that the drugs the patient received did not cross the blood-brain barrier, and therefore, it was unlikely that the difficulties were related to the cancer treatment. Post-treatment cognitive complaints became much more evident during the late 1990s and early 21st century as adjuvant treatment regimens intensified and autologous bone marrow transplantation became more common in adults. Often, cognitive complaints were associated with persistent fatigue and depressive symptoms, making it challenging to sort out whether or not the complaints of poor memory, attention, and difficulties with multitasking were related to brain dysfunction or were merely a manifestation of an uncontrolled mood disorder. Many who complained were younger patients with breast cancer who became menopausal prematurely with chemotherapy, and their experiences of vasomotor symptoms, nighttime awakening, and poor sleep might have explained some of their cognitive complaints.

With continued improvements in disease-free survival after cancer treatment, there are increasing numbers of survivors of cancer who wish to return to work and to their pre-illness activities. The costs of care for these patients include the need to endure cancer treatments that are toxic and usually multimodal and prolonged (surgery, radiation, chemotherapy, biotherapy) with frequent post-treatment fatigue, debilitation, and cognitive complaints that take months to years to resolve. During this same time period, the research portfolio on cognitive changes after cancer treatment has expanded rapidly, benefiting from research advances in the cognitive sciences and neuropsychology. Concomitantly, an increased understanding of immunology and mind-body interactions (psychoneuroimmunology) has made us more aware that events in the body (tissue trauma and inflammation from surgery, radiation, chemotherapy, and biologic and targeted therapies) can trigger systemic inflammation with secondary effects on the CNS. In parallel, stress and cognitive threats can have direct effects on the hypothalamic pituitary adrenal axis and the sympathetic nervous system, leading to systemic responses that can affect the immune system. In addition, immune cells, responding to inflammation can traverse the blood-brain barrier and increase local inflammation in the brain, affecting emotional and cognitive function without the need for direct diffusion of chemotherapy into the brain substance.

So what does this all have to do with the patient in your office asking about her risk for chemobrain? An emerging literature examines the exposure to cancer treatments and subsequent cognitive functioning including the relationship between self-reported cognitive complaints, formal neuropsychologic (NP) test abnormalities, and changes in brain activity/function by using multiple and diverse strategies. In the article that accompanies this editorial, Deprez et al evaluate the effects of chemotherapy exposure on structural changes in cerebral white matter and correlate these findings with impaired cognitive functioning. In this well-designed, observational cohort study of younger premenopausal women with breast cancer, the authors examined pre- and postchemotherapy self-reported cognitive complaints, NP test performance, and brain function with magnetic resonance imaging diffusion tensor imaging (DTI). The investigators used two separate control groups: one of age-matched patients with breast cancer who were not initiating adjuvant chemotherapy and one of healthy controls. As might be expected, the patients with breast cancer reported more depressive symptoms at the baseline pretreatment assessment compared with the noncancer controls. Across the three groups, there were no baseline pretreatment assessment differences in NP test results or in brain imaging, except for the inadvertent diagnosis of subclinical multiple sclerosis in one of the participants who was then excluded from the study.

What happened at the post-treatment assessment 3 to 4 months after chemotherapy ended? The two control groups improved their performance significantly in all three domains of NP testing (attention and concentration, memory, processing speed), likely as a result of expected practice effects. In contrast, as a group, the patients treated with chemotherapy experienced declines in NP testing in all three domains. This paralleled significantly increased self-reported cognitive complaints (controlled for depressive symptoms) in the subscales representing executive function (distraction) and memory (names and words), occurring only in those women treated with chemotherapy. Finally, the DTI detected decreased white matter integrity in tracts involved in cognition in the women treated with chemotherapy with no changes observed in the two control groups; this suggests a causal relationship between the chemotherapy exposure, cognitive complaints, NP test abnormalities, and white matter changes. Areas of change on brain imaging in this study are consistent with those noted in the brain imaging and cognitive test results of the patients treated with chemotherapy. Further studies are needed to determine whether these changes are temporary or permanent.
in other studies that use different imaging technologies, with growing evidence for frontoparietal and occipital regional changes in this setting in studies of survivors of breast cancer. It is important to note that these are group data and not all women in the chemotherapy-treated group may have suffered a change in white matter integrity. In an earlier article by this research group that used an identical methodology, the investigators examined patients only at the postchemotherapy time point and noted that DTI white matter changes were only present in those chemotherapy-treated women who were impaired on NP testing.

The specific domains of NP test abnormality and self-reported cognitive complaints identified in this study are highly consistent with the findings of other studies and are also representative of the types of complaints voiced by patients after cancer treatment. These include being easily distracted, having difficulty concentrating and staying on task, and having difficulty recalling recent events or something that was just said to them. The reliability of self-reported cognitive complaints mapping onto NP test abnormalities in the general NP literature, as well as in the cancer cognitive functioning literature, is mixed. There are a variety of self-reporting tools that have been used, and often a global or summary scale has been examined as a correlate rather than a specific domain of cognitive complaints. Thus the ability to map the specific cognitive complaints onto NP test performance might have had limited predictive validity in earlier studies, which was not the case in the current report. In addition, uncontrolled depressive symptoms are well-known to impair NP test performance, and many studies have shown greater association of NP performance with depression than with cognitive complaints.

In this study, Deprez et al have used an established self-reporting instrument—the Cognitive Failures Questionnaire—and have focused on only two subscales and their relationship to NP test performance. Indeed, by using this more specific strategy to associate self-reported complaints with decrease in NP test performance, they found significant relationships. In a cross-sectional sample of 190 patients with breast cancer who were evaluated postadjuvant chemotherapy and radiation treatment, we have also identified a significant relationship between self-reported memory and executive function complaints by using the self-reporting Patient’s Assessment of Own Functioning Inventory and relevant NP domains (unpublished data) as have Bender et al. What are the limitations of the Deprez et al study and what are the implications for clinical practice? First, the sample examined in this longitudinal study was quite small (chemotherapy: n = 34; no chemotherapy: n = 16; healthy control group: n = 19), and each of the patient groups had more than 50% who were on tamoxifen at the time of the post-treatment assessment. Thus, the post-treatment effects seen in the chemotherapy group may be a result of multiple exposures (including radiation and tamoxifen). In addition, although the two breast cancer groups have similar demographic characteristics, the decision to use adjuvant chemotherapy was not random, and unknown biases might have influenced the observed outcomes. Second, the patients were only observed for a short time after treatment, and it is possible that the self-reported cognitive complaints, NP test findings, and brain imaging changes could resolve over time as has been reported by others. Finally, all of the patients in this study received an anthracycline-based chemotherapy regimen, which has been associated in animal models with the generation of reactive oxygen species and intracerebral increased levels of tumor necrosis factor-α. At this point in time, limited data are available about whether or not cognitive changes after cancer treatments are specific to regimen or result from a more generalized systemic effect of chemotherapy and radiation such as has been observed for post-treatment fatigue in association with increased soluble tumor necrosis factor receptor type II (sTNF-RII). Whether or not these findings are specific to the regimen needs additional study, and if so, regimens that may be more strongly associated with increased cognitive changes could be avoided.

In summary, patient complaints of persistent cognitive difficulties after cancer treatment ends must not be dismissed, given that there is mounting evidence for the biologic effects of cancer treatments on behavioral symptoms, and cognitive complaints are one of the most troublesome of these manifestations. Susceptibility to cognitive complaints may reflect host genetic factors, such as single nucleotide polymorphism variants in genes involved in brain function or inflammation. To the extent that ongoing and future research elucidates the underlying mechanisms related to post-treatment cognitive complaints (ie, delineation of specific causative treatments and vulnerable patients), ultimately we may be able to personalize treatment and avoid this important toxicity. At this point in time, there is limited evidence to suggest that all patients will develop cognitive difficulties after chemotherapy, and in general, the magnitude of impairment in cognitive functioning post-treatment is modest, with many longitudinal studies describing recovery over a longer period of observation. Thus, fears of developing cognitive difficulties should not deter the use of potentially beneficial chemotherapy, particularly in settings in which chemotherapy treatment is lifesaving and not discretionary. However, for those survivors of cancer who currently are unable to resume their pre-illness professional and personal activities that require attention and concentration, we must work to find effective rehabilitation and treatment strategies that will improve their outcomes. We can no longer deny the existence of this long-term effect of cancer treatment; we must work to tailor future treatments to minimize this adverse outcome.

REFERENCES

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