Cancer Treatment and Cognitive Function: Chemotherapy Is Not the Only Culprit

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With the growing number of cancer survivors, there is increased interest in understanding and preventing post-treatment sequelae that may limit full recovery to prediagnosis health.

As discussed by Moore,[2] the major challenge in evaluation of cognitive complaints following cancer treatment has been the lack of a strong association of the subjective experience of increased cognitive difficulties with standardized neuropsychological (NP) tests, which are considered objective and the gold standard for identifying deficits in cognitive function. However, it should be noted that NP tests were designed for the assessment of patients with major head trauma, vascular insults, psychiatric conditions, and dementias; thus, their sensitivity for the detection of more subtle changes in performance is limited. In addition, the difficulty of simply and efficiently performing objective assessments (NP testing or imaging) concurrently with chemotherapy treatments has made it difficult to monitor the potential toxic impact of chemotherapy on cognitive function. More recent use of neuro-imaging together with subjective reports and NP testing has demonstrated that subjective complaints are, in fact, associated with changes in brain activity.[3-5] These studies are costly and complex, limiting their use to research settings; nevertheless, they provide observational support for the validity of self-reported complaints.

The cognitive complaints implicating chemotherapy exposure that were the subject of early investigations were often reported in women receiving CMF (cyclophosphamide, methotrexate, fluorouracil [5-FU]) adjuvant chemotherapy.[6,7] Both methotrexate and 5-FU cross the blood-brain barrier, so their effect on the CNS was a possible mechanism for the development of cognitive difficulties. Subsequent animal model studies probed these two agents, examining behavioral and pathologic changes in rodents.[8] However, changes in adjuvant chemotherapy regimens for breast cancer, as well as in common treatment regimens for other cancers, resulted in the omission of these two agents, yet patient reports of cognitive difficulties persisted. Thus, other mechanisms have been entertained, including genetic predisposition, changes in the blood-brain barrier, DNA damage with telomere shortening, inflammation, and changes in testosterone and estrogen levels.[9,10]

In our research, we have found significant elevations of the soluble proinflammatory cytokine tumor necrosis factor receptor 2 in association with adjuvant chemotherapy and radiation exposure in a contemporary sample of breast cancer patients.[11] These levels fall during the 12 months after the end of adjuvant chemotherapy, and as systemic levels normalize, there is also normalization of cerebral metabolism on brain imaging.[11] Animal models examining systemic administration of doxorubicin implicate doxorubicin’s generation of reactive oxygen species that then cross the blood-brain barrier and stimulate local production of inflammatory cytokines in the brain, potentially affecting cerebral function—so this can be a secondary mechanism associated with inflammation.[12] Recent work from our laboratory also finds an association of cognitive complaints, specifically those involving deficits in verbal fluency, after initiation of endocrine therapy, independent of recent chemotherapy and radiation exposure.[13] To explain post-treatment cognitive difficulties, it is important to account for the multiple potential exposures that a patient receives while undergoing cancer treatment, and not just chemotherapy.

As noted by Moore, there have been many challenges surrounding the design and conduct of studies to evaluate cognitive function, with those studies that have included testing prior to chemotherapy...
showing pre-existing NP test deficits in some patients. These evaluations are helpful in that they establish the pre-chemotherapy baseline for individuals; however, they rarely are conducted prior to the surgery and general anesthesia that may precede chemotherapy. Only a few studies have evaluated cognitive function prior to surgery.\[14,15\] It is likely that patients have variable cognitive reserves at the time of diagnosis,\[9\] and that the insults of multiple cancer treatments (surgery, chemotherapy, radiation therapy, immunotherapy) can affect subsequent outcomes. Host factors and personal vulnerability may be just as important as the treatment exposures. It is well recognized with other treatments (eg, taxanes) that there is tremendous variability in who develops a specific toxicity and how persistent it will be. In the case of cognitive dysfunction after breast cancer treatments, patients with certain specific single nucleotide polymorphisms in the promoter region of proinflammatory cytokines appear to be at greater risk for cognitive complaints.\[16\]

In reviewing potential intervention strategies, Moore overlooked a number of more recent reports that have examined other strategies, including some that have used computerized tools,\[17,18\] and cognitive rehabilitation strategies that have been evaluated.\[19-21\] We have recently reported on the results of a randomized trial of a 5-week group-based cognitive rehabilitation intervention study in breast cancer survivors that showed improvement in self-reported cognitive complaints, improved NP test performance, and normalization of electroencephalography (EEG) patterns in women in the intervention group as compared with the control group, and these improvements were sustained in the 2 months post-intervention. \[22-24\] The EEG findings in this study suggest that this may be a useful biomarker of cognitive changes in cancer patients, and as noted by Moore et al,\[25\] might be integrated into the prospective evaluation of patients receiving chemotherapy. An intervention in older adults that involved computerized training has suggested that EEG findings may reflect brain plasticity\[26\]—and suggests that such computerized training might be used for the mitigation of cognitive deficits that can occur with cancer treatments. All of these efforts at rehabilitation and “brain training” are in their infancy, but clearly reflect the need and potential opportunities to address this toxicity of cancer treatment.

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