Response
In the last decade, neuropsychological research indicated occurrence of cognitive problems in patients with a variety of malignancies, including breast cancer, that were treated with systemic chemotherapy without the specific aim to target the central nervous system. The reported percentage of patients affected varies considerably (between 15% and 70%), and certain cytotoxic agents may be more likely to adversely affect cognitive function (1). Memory, processing speed, and executive function seem to be most vulnerable to the
effects of chemotherapy. Recent human imaging studies support a neuroanatomic basis for cognitive problems associated with noncentral nervous system-directed chemotherapy and indicate structural changes in the brain, including alterations in gray matter density and white matter (WM) integrity (2,3). Although human and animal research is in progress to elucidate the underlying neural mechanisms, at present there is still a paucity of information on what causes the changes in cognitive performance and brain structure and function.

Morelli et al. propose an interesting mechanism concerning the sensitivity of mitochondrial DNA in oligodendrocytes to the cytotoxic actions of chemotherapeutic agents. The authors hypothesize that the myelin-producing oligodendrocytes are particularly vulnerable to mitochondrial damage because of their increased mitochondrial turnover. In a previous study (4), it was shown that oligodendrocytes and their precursor cells are actually more vulnerable to the antimetabolite 5-fluorouracil than cancer cells. WM integrity is indeed negatively affected by systemic chemotherapy in breast cancer patients, with patients who exhibit more extensive WM injury performing worse than expected on neuropsychological tests. Direct neurotoxicity, causing toxic injury to brain parenchyma and producing WM demyelination, could be one of the factors associated with the observed cognitive impairment (3).

The hypothesized particular vulnerability of mitochondrial DNA in oligodendrocytes and the relevance of extramitochondrial oxidative production of ATP in myelin sheaths (5) in the deterioration of WM integrity following chemotherapy require further investigation. For example, the equal vulnerability of dividing precursor cells and nondividing differentiated oligodendrocytes to low doses of 5-fluorouracil (4) contradicts the relative insensitivity of mature oligodendrocytes to inhibition of the mitochondrial complex I (6). However, an increased focus on WM integrity in relation to cognitive deficits following chemotherapy does make sense. WM in the brain is not only sensitive to deterioration following treatment with cytostatics but also to decreases in blood supply to the brain, as observed in ischemia and hypoperfusion during the aging process (7). Because endothelial damage by antimetabolites (4) may reduce microvascularization of the brain (8), the vulnerability of WM to systemic chemotherapy may therefore be associated with both a direct sensitivity to chemotherapy-induced cytotoxic actions and an indirect effect because of a reduction in blood supply. Patients are increasingly becoming aware of the effects of chemotherapy on cognition. This awareness will in all likelihood increase patients’ requests for information on the risk factors for cognitive decline, diagnoses, and interventions. Studies into the mechanisms underlying decreases in cognitive function are an imperative step toward yielding the necessary advances in the research and treatment of cognitive dysfunction following chemotherapy.

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References

Notes
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DOI: 10.1093/jnci/djr033
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Advance Access publication on February 24, 2011.