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# Chemotherapy and Cognitive Function in Breast Cancer Patients: The So-Called Chemo Brain

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## Abstract

Self-perceived problems of cognitive functioning after treatment for early-stage breast cancer have the potential to substantially affect the lives of patients. In the past two decades, neuropsychological studies have accumulated evidence of corresponding cognitive deficits that have mostly been attributed to neurotoxic effects of chemotherapy. Nevertheless, observations of impaired cognitive functioning already before the start of adjuvant or neoadjuvant chemotherapy question the singular role of chemotherapy for the causation of these deficits. The divergence between mostly subtle neuropsychological deficits and often dramatic subjective cognitive complaints as well as the lack of association between both in the majority of studies present an unsolved puzzle. Recent investigations that include brain imaging have begun to yield tentative answers in this regard. The present review aims at briefly summarizing and integrating the current evidence from clinical studies for purposes of patient counseling.

After treatment for breast cancer, many patients complain of impaired memory, attention, speed of processing, word finding, and other basic cognitive functions (1), which they and researchers alike have generally assumed reflected the neurotoxicity of chemotherapy. Starting in the mid-1990s, a series of neuropsychological studies assessed cognitive function in breast cancer patients who had received chemotherapy. These studies consistently found that a subgroup of patients showed lower than expected cognitive performance on the neuropsychological tests (2). Thus, after about 10 years of research, the detrimental effects of chemotherapy on cognitive functioning seemed to be confirmed beyond any reasonable doubt. However, all first-generation studies were of cross-sectional design, so results of ongoing prospective, longitudinal studies were eagerly awaited, with the expectation they would clarify important details and further corroborate the growing body of evidence. As of 2004, when prospective data finally began to emerge, something quite surprising happened instead—the concept of "chemo brain" was rattled.

First of all, many of the prospective studies found cognitive deficits already before the initiation of adjuvant chemotherapy. Because baseline assessments typically were done postsurgically, these deficits may have been transient, induced by surgery and general anesthesia. However, in two studies where baseline status was assessed before neoadjuvant chemotherapy, cognitive deficits were seen in 21% (3) and 30% (4) of patients with as yet untreated breast cancer. Such strong evidence of pretreatment cognitive deficits rendered most findings from the first-round cross-sectional studies obsolete. Presumably, preexisting cognitive deficits had been misattributed to chemotherapy effects in past investigations (5).

Secondly, several prospective studies, including methodologically sound large-scale studies (6,7), found no evidence of cognitive deterioration in chemotherapy patients. In the majority of prospective studies, nevertheless, some rather subtle cognitive change has indeed been observed, usually in a limited subset of cognitive domains. Generally, a minority of 15%–25% of patients seemed to be affected (8), with much higher rates (up to 61%) (9) sporadically reported. A recent meta-analysis of the neuropsychological studies concluded that at least 6 months after cessation of a standard chemotherapy regimen for breast cancer, cognitive deficits are on average "small in magnitude and limited to the domains of verbal ability and visuospatial ability" (10).

The prospective second-generation neuropsychological studies thus challenge the concept of "chemo brain" in a twofold way. They raise the question whether chemotherapy is truly the principal cause of cognitive deficits in this setting. Other

factors, aside from chemotherapy, clearly induce such deficits before breast cancer treatment and may continue to influence cognition in later stages of the cancer trajectory. Furthermore, the mild changes observed in only few cognitive domains raise doubt as to whether the often dramatic complaints of patients represent objective functional impairment at all.

The latter issue is closely linked to a problem haunting the investigation of cognitive deficits in cancer patients from its very inception, namely that subjective complaints and objective neuropsychological parameters for the most part do not correlate (11). This is also true if only cognitive change is considered; the patients with increased complaints after chemotherapy are not those who show deteriorated cognitive performance (12). Subjective cognitive complaints instead have consistently correlated with depressive symptoms, anxiety, and other measures of psychological distress (11). A recent study (13) did identify domain-specific associations between complaints and cognitive test performance; even in this study, though, complaints were more strongly related to depressive symptoms than to their domain-specific neuropsychological counterparts.

A number of reasons have been offered to explain observed discrepancies between subjective cognitive complaints and neuropsychological test performance. The tests may lack sensitivity and ecological validity, or the specific deficits from which cancer patients suffer may not arise in structured test situations that help patients focus on a cognitive task. For a variety of other reasons, neuropsychological studies may fail to capture the impairments claimed. The neuropsychological investigation of cognitive deficits in cancer patients presents many demands, from selecting patient and control groups to the choice of analytical methods and establishment of criteria for cognitive change/impairment. Slight variations of methodology may distort results considerably (14). Furthermore, if the overall picture drawn by the prospective studies is correct and cognitive deficits are indeed mild after cancer therapy, it is still possible that even subtle compromise may have very serious consequences for a subgroup of affected patients, especially at high-level performance. Finally, severe deficits in some patients may possibly be masked by a preponderance of normal or near-normal performance when data are aggregated across groups.

Given these uncertainties, another generation of studies have begun to weigh in on recent discussions. These studies rely on neuroimaging techniques (mostly magnetic resonance imaging) to examine the brain for correlates of cognitive deficits and complaints. Both structural and functional brain differences between breast cancer patients treated with chemotherapy and control groups have been found. Structural differences include reduced regional gray matter volumes and decreased white matter integrity (8). Recently published prospective studies have linked a decline in white matter integrity with deterioration of attention and memory performance at 5 months following chemotherapy (15) and a reduction in gray matter density of frontal areas with increased subjective difficulties in executive function shortly after chemotherapy (16). Studies targeting brain activity patterns have observed regional hypoactivation (17) as well as more widespread brain activation (18) in chemotherapy patients during cognitive tasks. These altered activation patterns may indicate that affected patients compensate dysfunction in areas relevant to the task by activation of additional brain areas. This interpretation offers an explanation of the puzzling discrepancy of unimpaired test performance and cognitive complaints in many patients. Conceivably, in spite of damaged brain functioning, these patients reach normal performance level by compensatory activation of further brain areas, which is subjectively perceived as greater effort (19).

To date, most of the studies using brain imaging are cross-sectional in design and typically are exploratory rather than hypothesis-driven in nature, with small sample sizes. Although still in an early stage, the findings are compelling, indicating that there are neurological correlates to the cognitive complaints of breast cancer patients. Nevertheless, this does not imply that these investigations support the simplistic chemo brain concept established 10 years ago. Like neuropsychological assessments, brain imaging, too, has demonstrated that cognitive functioning in breast cancer patients is affected by other causes than just chemotherapy: Abnormalities of brain activation patterns have been observed in patients before chemotherapy (18,20) and, to a lesser extent than postchemotherapy, in patients managed without chemotherapy (17,18,21).

The role of chemotherapy neurotoxicity in the causation of cognitive deficits in cancer patients is therefore still unclear. Many other factors potentially leave traces in the brains of breast cancer patients and potentially affect on their cognitive functioning, among them surgery, radiotherapy, endocrine therapy, the psychological burden of having cancer, treatment-related life disruption, and disease-related biological factors such as elevated cytokine levels; furthermore, shared vulnerability for cancer and cognitive deficits is being discussed (22). Patients who receive chemotherapy are clearly at an elevated risk of cognitive deficits, but not necessarily due to neurotoxic effects. These patients also have a more advanced cancer stage, with a worse prognosis and a greater psychological burden. In addition, undergoing chemotherapy is a frightening experience that in itself aggravates psychological burden and further disrupts life. Cognitive deficits in breast cancer patients may be caused by an accumulation of many of these factors.

Informing patients facing neoadjuvant or adjuvant chemotherapy presents a dilemma. Information about “chemo brain” has been found to act as a nocebo: Chemotherapy patients randomized to receive information about cognitive consequences of chemotherapy subsequently reported more cognitive problems and performed worse on a learning task than patients who had not received this information (23). Nevertheless, patients obviously need to be informed about a potentially serious side effect of treatment. As assessments in advance of neoadjuvant treatment have shown, even having breast cancer alone may threaten cognitive functioning, and the risk increases with treatment, particularly with chemotherapy. However, there is some at least mildly reassuring information, too. Cognitive changes are generally subtle and even nondetectable in most breast cancer patients. They seem to become palpable for patients mainly in the context of psychological distress. Recently, it has been found that cognitive deficits are not responsible for delayed return to work after treatment (24). Although cognitive changes in breast cancer patients are potentially long-lasting, epidemiological studies have demonstrated that chemotherapy has no bearing on long-term risk of dementia in patients without a diagnosis of cognitive impairment before breast cancer treatment (25).

Cognitive change associated with breast cancer and its treatment is still far from being fully understood. Further investigations are necessary to deepen the knowledge about this clinically relevant topic.

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