Cognitive Deficits Are Usually Mild in Patients With Breast Cancer After Chemotherapy

Results of a recent meta-analysis suggest that the long-term cognitive deficits after chemotherapy in patients with breast cancer are, for the most part, small in magnitude (J Clin Oncol. 2012;30:3578-3587).

“On average, cognitive impairments after chemotherapy appear to be slight and to be limited to the domains of verbal ability, such as difficulty finding words, and visuospatial ability, such as getting lost more easily in an unfamiliar location,” says Heather Jim, PhD, lead author and researcher in the Health Outcomes and Behavior Program at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida.

The authors state that current data suggest that cognitive deficits during treatment are pronounced, but there are conflicting data regarding the long-term persistence of symptoms. The goal of this study was to focus on the postchemotherapy period. The population was limited to patients with breast cancer, as most of the studies examining the cognitive effects of chemotherapy have been performed in women with breast cancer.

Dr. Jim and her colleagues identified 17 studies comprising 807 patients with breast cancer who received chemotherapy, 391 patients with breast cancer who received local or endocrine therapy, and 291 participants without cancer. Four of the studies included longitudinal comparisons of patients who received chemotherapy, 6 studies compared patients who received chemotherapy with those who received only local therapy, 3 studies compared patients receiving chemotherapy with noncancer participants, and the remaining studies contained multiple types of comparisons.

To help with the interpretation of neuropsychological testing, researchers categorized the study participants according to the main type of cognitive function that was tested. The measured domains included attention, executive functioning (planning and carrying out activities), information processing, motor speed, verbal ability, verbal memory, visuospatial ability, and visual memory.

Researchers found that the patients with breast cancer who received chemotherapy had significantly worse cognitive functioning with regard to verbal ability and visuospatial ability ($P < .01$ for both) than those who did not. A nonsignificant trend toward worse performance was seen for executive functioning. There were no differences in cognitive functioning noted in the remaining measured domains.

Further analysis of the verbal ability outcomes showed that patients who were treated with chemotherapy did worse than noncancer control participants, but not when compared with their own prechemotherapy baseline or when compared with patients treated without chemotherapy. Study design was also found to have a statistically significant effect on visuospatial ability outcomes. In this domain, patients with breast cancer who were treated with chemotherapy fared significantly worse than patients treated without chemotherapy, but no differently when compared with their own prechemotherapy baseline or with noncancer controls. Furthermore, neither verbal ability nor visuospatial ability outcomes were affected by age, education, time since the end of chemotherapy treatment, or the use of endocrine therapy.

“The magnitudes of the effect were $-0.210$ and $-0.291$ standard deviations, respectively, for verbal ability and visuospatial ability,” Dr. Jim says. “We consider these deficits to be small in magnitude based on an established rule of thumb that $<0.3$ standard deviations is small,
0.5 is medium, and >0.7 is large. Clinically, it means that the average breast cancer patient treated with chemotherapy performed worse than 58% of women without cancer on verbal ability and 61% of women with breast cancer not treated with chemotherapy on visuospatial ability.”

Potential for Underestimation

Dr. Jim believes that the strengths of this study are its large sample size, its focus on the postchemotherapy period, the inclusion of recent studies that had stronger methodology than earlier studies (such as the use of a longitudinal design and well-validated measures of cognitive function), and the inclusion of many studies not previously included in a meta-analysis.

However, the current study findings contrast with data from 4 previous meta-analyses showing larger and more diffuse cognitive impairments in patients with breast and other cancers. The authors believe this suggests that cognitive impairments after chemotherapy for breast cancer are relatively mild compared with other types of cancer treatment (and with the active treatment period) as the current meta-analysis focused only on the postchemotherapy time period.

“The main weakness is that meta-analysis gives information about patients on average, and there can be much heterogeneity in cognitive function after chemotherapy,” says Dr. Jim. Furthermore, the findings of the current study are from patients with breast cancer, and may not apply to those with other cancer types. “Looking at all the studies together may give a perception that the cognitive effects are smaller than [they appear] in the separate studies because looking at an aggregate of trials does not allow you to assess an individual's risk factors,” says Tim Ahles, PhD, director of the Neurocognitive Research Laboratory at Memorial Sloan-Kettering Cancer Center in New York City.

“Having a more defined study population may be the key to more easily understood and clinically useful answers.” However, Dr. Ahles believes the study gives good news in that the overall population tends to do well in the longer term.

Clinical Implications

An accompanying editorial coauthored by Dr. Ahles points out that many investigators believe certain subgroups of patients may be at higher risk for significant cognitive deficits (J Clin Oncol. 2012;30:3568-3569). Previous studies have shown that older age and lower cognitive reserve (measured by such factors as education, occupation, and cognitive stimulation) are risk factors for significant cognitive impairment. The results of the current study did not demonstrate this, but the authors admit that most participants were young to middle-aged with high levels of education. Furthermore, the editorial states that recent studies indicate genetic factors may play a role in increasing susceptibility to cognitive dysfunction such as associations with apolipoprotein E and catechol-O-methyltransferase. “We have an active program of research examining genetic predictors of side effects of cancer treatment,” says Dr. Jim. “Our goal is to be able to determine ahead of time which patients are at the greatest risk of developing cognitive problems so that we can provide early intervention and management.”

The authors state that, in general, patients can be told to expect any cognitive changes to be small 6 months after chemotherapy. Changes may be variable, with some patients reporting much more than others. Patients reporting large changes should be referred to a neuropsychologist for evaluation and management strategies.

“People are anxious to get better quickly,” says Dr. Ahles. “It is important to educate patients that it may take at least 6 to 12 months to recover from the cognitive deficits that occur during chemotherapy. If they do persist, treatments are emerging (both pharmacologic and behavioral) and should be tailored to the individual’s needs.” Dr. Ahles also believes that patients need to think about the cognitive side effects within the larger context of care. “I often get patients calling me who have a great fear of cognitive side effects,” he adds. “I encourage them not to let that fear stop them from getting the treatment they should. Avoiding recurrence is a larger issue.”

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