Cognitive Dysfunction Following Adjuvant Treatment of Breast Cancer: a New Dose-Limiting Toxic Effect?

Patricia A. Ganz*

In recognition of the growing number of cancer survivors, the National Cancer Institute (NCI) established the Office of Cancer Survivorship (OCS) in 1996. Research on the late effects of cancer treatment is high on the scientific agenda of the OCS. Somewhat more information is available on the late effects of cancer treatment in children than in adults (1–6). Research with children has been facilitated by their frequent participation in clinical treatment trials, the high cure rates for many childhood cancers, and the long-term commitment of pediatric oncologists to the follow-up of survivors. Study of the neurocognitive effects of therapy for childhood leukemia has been particularly important because of the targeting of treatment to the central nervous system of patients with this disease (7,8). In contrast, studies of neurocognitive late effects in adults are sparse and have focused primarily on patients receiving cranial irradiation, especially those with small-cell lung cancer (9–11).

In this issue of the Journal, van Dam et al. (12) take an important first step in assessing the prevalence of cognitive dysfunction in women who received adjuvant treatment for high-risk breast cancer. Clinical reports of cognitive changes after high-dose adjuvant therapy for breast cancer prompted this systematic evaluation. The design of the study is important, for it is probably the first to examine comprehensively cognitive functioning in patients with breast cancer within the context of a randomized trial. A further strength is the inclusion of a stage I breast cancer comparison control group that had not received any adjuvant treatment. The use of a disease-specific comparison group permits control for the impact of the diagnosis of breast cancer on psychologic distress and quality of life (QOL), both of which might affect cognitive functioning. Finally, the use of a battery of standardized neuropsychologic tests with healthy population normative reference data provides another important comparison.

The key findings from the study include the following: 1) any adjuvant therapy increases the likelihood of women reporting cognitive problems in daily life in comparison with breast cancer patients who have not had adjuvant therapy [Table 2 (12)]; 2) emotional well-being, as determined by a standardized measure of QOL, does not differ in breast cancer survivors according to receipt of adjuvant chemotherapy; 3) there is a strong correlation between depression and anxiety and self-reported daily difficulties with concentration, memory, and thinking; 4) breast cancer patients who have received adjuvant therapy are significantly more likely to be classified as cognitively impaired on standardized tests (32% for the high-dose chemotherapy group versus 17% for the standard-dose chemotherapy group versus 9% for the control group [two-sided P = .043]); and 5) logistic regression analysis demonstrates that the risk of cognitive impairment is substantially increased for patients who receive high-dose chemotherapy when compared with patients in the control group (odds ratio = 8.2; 95% confidence interval = 1.8–37.7) and when compared with the patients in the standard-dose chemotherapy group (odds ratio = 3.5; 95% confidence interval = 1.0–12.8).

Although this study was very carefully performed, there are several limitations, including the small sample sizes of the treatment and control groups, the multiplicity of statistical comparisons, the cross-sectional design, and the limited information about the potential mechanisms for the cognitive abnormalities. Furthermore, we are not told whether the measured differences in cognitive functioning in these survivors were associated with clinical disability or an inability to work. Therefore, this research should be seen as an important hypothesis-generating study rather than as a definitive investigation.

Nevertheless, the study suggests a credible dose–effect relationship between adjuvant therapy and cognitive impairment. The finding of increased central nervous system toxicity with higher doses of chemotherapy is very salient, since standard adjuvant chemotherapy regimens have increased in dose intensity substantially during the past 5 years (13–15). Large numbers of women are being treated with these more intensive adjuvant therapies (including drug doses that are close to those requiring autologous bone marrow transplantation or stem cell rescue), with the result that many women are surviving disease free for long periods of time and are at potential risk for cognitive impairment. Therefore, it is imperative that more studies of this type be conducted. In addition, newer regimens often include the taxanes—a class of drugs for which there is limited information on late effects, especially central nervous system toxicity.

How should future studies of cognitive functioning be planned? In North America, there are several ongoing NCI-
sponsored high-dose adjuvant chemotherapy trials for breast cancer with comparison standard-dose groups. These trials have already enrolled several hundred patients in each treatment arm, and an ancillary study to examine cognitive functioning in these women could easily be considered. This could include both a cross-sectional evaluation (several years beyond therapy, as in the study by van Dam et al.) and a longitudinal assessment (a smaller sample might be used) to examine the prevalence of cognitive dysfunction shortly before and after treatment, as well as the longitudinal pattern of dysfunction. Equally important might be further evaluation of the relationship between depression and cognitive dysfunction that was noted by van Dam et al. (12) in their patient population. Testing of treatments with pharmacologic agents for depression might prove to be an effective intervention for this troubling late effect of treatment. Additional work should be done to elucidate the mechanisms of cognitive dysfunction. Special attention should be given to the chemotherapeutic agents used, their doses, and potential drug interactions. Other issues of importance in middle-aged women include the interaction of hormonal status and cognitive functioning as well as the potential effects of antiestrogen treatments (16). The large sample sizes available in the ongoing randomized trials of high-dose chemotherapy should allow better evaluation of patient subgroups, a task that was not feasible in the current study (12).

Why are these late effects important? Women with a history of breast cancer constitute the largest disease group in the cancer survivor community (17). We have an obligation to obtain information on the late effects of therapy for these women from a descriptive and preventive standpoint. Many of these women want to return to employment or other activities that are affected by cognitive functioning. Although the extent of the disability associated with cognitive dysfunction from adjuvant therapy is not well characterized as yet, treatment modifications or preventive/therapeutic interventions could be important in the future. As the dose intensity of adjuvant therapy increases for women with even more favorable prognoses, central nervous system toxicity has the potential to affect even larger numbers of survivors. More research is necessary to have a better understanding of this late effect.

The study by van Dam et al. (12) is important for another reason. It emphasizes the value of listening to our patients. We must become more aware of the importance of nondisease outcomes in our patients, and we must listen when patients report persistent functional problems or symptoms. Such exchanges can provide the stimulus for new research that can identify important late effects of treatment. While most individuals with cancer put survival highest on their list of priorities, they are also concerned about the quality of their survival. Often, it is enough to explain to patients that these types of problems (e.g., cognitive dysfunction) have been described and that clinicians and researchers are working to understand ways to treat and prevent them. We must continue to listen to these clues from our patients and to push for systematic research on the late effects of cancer treatment.

References