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SYMPOSIUM-INTRODUCTION

Cognitive Dysfunction after Chemotherapy For Breast Cancer

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Approximately 13 million adult cancer survivors live in the United States; about 2 million of them were diagnosed over 20 years ago (National Cancer Institute, 2012). Current 5-year survival rates are close to 70% and rising, so the number of people living with the physical and mental health consequences of cancer and cancer treatment will increase. One of these consequences is cognitive decline, popularly known as chemo-brain. The papers in this symposium reflect some of the approaches used to understand the nature and course of cognitive decline in women with breast cancer.

Oncology research has long recognized that cognition may be affected by cancer. This was attributed to distress until 1978, when cognitive symptoms in breast cancer patients were attributed to "organic brain syndrome" (Levine, Silverfarb, & Lipowski, 1978). The first reports documenting greater cognitive deficits in cancer patients treated with chemotherapy than in patients who did not receive chemotherapy were published in the early 1980s (Greer and Silberfarb, 1982; Oxman and Silberfarb, 1980; Silberfarb, 1983). Following a lull, Wieneke and Dienst (1995) showed that breast cancer survivors treated with chemotherapy performed more than two standard deviations below test norms on tests of memory, mental flexibility, processing speed, attention, visuospatial ability, and/or motor function. Performance was correlated with length of treatment but not depression or time since treatment. Since then, studies examining cancer, chemotherapy, and cognition have increased exponentially.

However, the field is relatively new and there is a great deal we do not understand. Although many studies using self-reported concerns distinguish people who received chemotherapy from those who have not (Pullens, De Vries, & Roukema, 2010), cohort studies using standardized neuropsychological measures often reveal "average" abilities relative to population norms (Anderson-Hanley, Sherman, Riggs, Agocha, Compas, 2003; Correa & Ahles, 2008; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006; Wefel & Schagen, 2012). Discrepancies between patients' complaints and objective test performance (Bender et al., 2008; Castellon et al., 2004; Cimprich, So, Ronis, & Trask, 2005; Hermelink et al., 2007) are frustrating for cancer survivors who express concerns about concentration, memory, processing speed, word-finding, decision making, and problem solving (Pullens et al., 2010). These changes hinder people from returning to work, school, or household obligations (Oberst, Bradley, Gardiner, Schenk, & Given, 2010), and affect psychological well-being (Boykoff, Moieni, & Subramanian, 2009) as well as relationships with the medical team, family and friends (Munir, Burrows, Yarker, Kalawsky, & Bains, 2010). In young adults with cancer, 27% fail to return to school or work 15–35 months after diagnosis and 30% report memory, attention and processing speed problems (Parsons et al., 2012). Although cognitive decline may be one factor contributing to these outcomes, other reasons may underlie the discrepancy between subjective concerns and performance. Wefel and Schagen (this issue) provide compelling evidence that quiets suspicions about motivation or secondary gain (e.g., perhaps due to return to work, disability support, or other issues). Their analysis of large samples of breast cancer patients showed no evidence of non-credible performance on performance validity testing.

Another challenge is making sense of variable results across studies. The divergence between subjective and objective deficits indicates that they are not identical constructs; direct measurement of performance is important to characterize abilities rather than only relying on patient report. Yet across cross-sectional and longitudinal studies that use neuropsychological tools, either no impairment is found, or there is variability in which cognitive domains are impaired and the magnitude of impairment (see Vardy & Tannock, 2007 for review).

These discrepancies may result from methodological differences, including but not limited to:

1. Different tests evaluating the same domain. Some tests are more sensitive to practice than others, masking subtle

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changes in cognition in longitudinal designs (Jansen, Miaskowski, Dodd, & Dowling, 2007).
2. Different criteria and statistical methods determining impairment or reliable change. Discrepant findings may be related to data categorization (e.g., grouping domains to capture "global" scores) or analysis (e.g., impairment cutoff scores, such as one or two standard deviations below comparison). There are also differences in how reliable change is best defined (Bläsi et al., 2009; Chelune, Naugle, Lüders, Sedlak, & Awad, 1993; Iverson, 2001; Jacobson & Truax, 1991; McSweeny, Naugle, Chelune, & Lüders, 1993).
3. Choice of comparison groups. Results may vary based on whether patients are compared to norms, healthy non-cancer controls, or cancer patients who do not receive chemotherapy (Castellon et al., 2004; Collins, Mackenzie, & Kyeremanteng, 2013; Collins, this issue; Schagen et al., 2002; Vardy et al., 2006).
4. The timing of assessments. Cancer without chemotherapy can affect cognition and brain function (e.g., Ahles et al., 2008; Cimprich et al., 2010; Hermelink et al., 2007; Wefel et al., 2010). Therefore, pre-post treatment comparisons may differentiate chemotherapy effects from those of the disease. Also, variable intervals between diagnosis, treatment, and testing make it difficult to compare results across studies (Rugo & Ahles, 2003), because of the time course of cognitive changes after treatment (e.g., see Collins, this issue).

In addition to differences in methodology, participant characteristics within and across studies should be taken into account because of potential effects on cognition. These characteristics include age, education, previous head injury, genetics, medical comorbidities, anxiety, depression, and fatigue (Wefel, Vardy, Ahles, & Schagen, 2011). Hormonal status can also be affected by chemotherapy or non-chemotherapy treatment (e.g., cytotoxic chemotherapy agents, estrogen receptor antagonists) and may independently affect cognition (Bender et al., 2007; Paganini-Hill & Clark, 2000; Schilder et al., 2010). Cancer-specific variables that contribute to the variance within and across studies include disease staging, surgery, anesthesia, chemotherapy regimens (i.e., drug type, dose, and number of cycles), and newer targeted therapies such as human epidermal growth factor receptor 2 antagonist, trastuzumab (Herceptin), or vascular endothelial growth factor receptor inhibitor, bevacizumab (Avastin). These factors increase the between-subject variance, making it hard to detect differences between people who do and do not receive chemotherapy, or to interpret such differences when they emerge.

Notwithstanding these differences, longitudinal studies demonstrate lower cognitive performance following chemotherapy compared with healthy or with cancer no-chemotherapy cohorts (e.g., Collins et al., 2013; Deprez et al., 2012). Although the time course and domains impacted are being actively studied, there is evidence that immediate and delayed recall, attention, working memory, executive function, and processing speed can be affected (e.g., Ahles et al., 2010; Collins et al., 2009; Deprez et al., 2012; Wefel et al., 2010), with small to moderate effect sizes (Jansen et al., 2007; Jim et al., 2012; Stewart et al., 2006). These effects are dose dependent: more chemotherapy is associated with worse cognitive performance (Collins et al., 2012; Collins et al., this issue; van Dam, Schagen, & Muller, 1998). Cognitive symptoms tend to improve following chemotherapy, but the speed of improvement is variable across individuals, and objective dysfunction persists in a subset of survivors for months or even many years after treatment has ended (Ahles & Saykin, 2001; Ahles et al., 2010; Coates et al., 1983; de Ruiter et al., 2011; Deprez et al., 2012; Jenkins et al., 2006; Koppelmans et al., 2012; Schagen et al., 2006; Silverman et al., 2007; Tannock et al., 2004; Wefel et al., 2010).

Why do some patients decline while others remain stable or improve? Perhaps some patients learn to cope with cognitive changes and develop compensation strategies. In others, the problem may be variability in performance, which may not be evident in one standard neuropsychological assessment or when using traditional neuropsychological measures (Bernstein, Catton, & Tannock, this issue).

Possible physiological underpinnings of cognitive decline after chemotherapy have been outlined in several reviews, and the causes are certainly multi-factorial. Symptoms appear to be associated with damage in white matter microstructure and cerebral vasculature (Ahles & Saykin, 2007). Proposed mechanisms include altered integrity of the blood brain barrier, increased oxidative stress, and release of inflammatory cytokines (Ahles & Saykin, 2007; Seruga, Zhang, Bernstein, & Tannock, 2008). Reductions in structural integrity of cortical white matter tracts, smaller gray matter volumes, axonal injury, and changes in neural activation in response to cognitive demands are consistent with this idea (de Ruiter et al., 2011; Deprez et al., 2012; Ferguson, McDonald, Saykin, & Ahles, 2007; Inagaki et al., 2007; Kesler et al., 2013; Koppelmans et al., 2012; McDonald, Conroy, Ahles, West, & Saykin, 2012). This body of work suggests that cancer and/or its treatment affect the brain, even when treatments are not targeting the brain.

New approaches lay the groundwork for better understanding this issue. The International Cancer and Cognition Task Force, a multidisciplinary group of experts in neuropsychology, clinical health psychology, and medical oncology issued recommendations to address study design discrepancies that should facilitate comparisons across clinical trials (Wefel, Vardy, Ahles, & Schagen, 2011). Recommendations included: longitudinal studies that incorporate pre-chemotherapy assessments; appropriate comparison groups; a brief standardized test battery shown to be sensitive to cognitive changes after chemotherapy (i.e., Controlled Oral Word Association Test, Trailmaking Test, Hopkins Verbal Learning Test-Revised); control variables that account for physical and psychosocial factors; and analyses that address reliable change. Collins et al.'s elegant study design (this issue) incorporates these recommendations along with state of the art statistical techniques. They show that the chemotherapy dose-dependent cognitive decline largely remits 1 year

after treatment due to improved working memory, although deficits persist in a subset of survivors.

New statistical approaches to test development may provide stronger links between subjective complaints and cognitive performance following cancer treatment. For example, revision of the Neurocognitive Questionnaire using item response theory, a technique that provides discrimination and difficulty parameters for test items, resulted in a self-report measure that is significantly correlated with memory and executive function performance in childhood cancer survivors with moderate effect sizes (Kenzik et al., 2012). In the future, application of these approaches to questionnaires examining cognitive dysfunction in adult cancer patients may result in screening tools that can identify those at risk for cognitive impairment.

Neuroimaging techniques reveal relationships between chemotherapy and cognition that are undetected by behavioral measures. In one of the most frequently cited functional magnetic resonance imaging (fMRI) studies, Ferguson et al. (2007) evaluated performance on an n-back task in identical twins, one of whom had previously received chemotherapy for breast cancer. The twins performed equally well and showed comparable effects of working memory load on task performance. However, the twin who had cancer showed greater bilateral prefrontal and posterior parietal activation during the task, and had substantially more white matter hyperintensities bilaterally on structural MRI, than her unaffected sister. Those results suggest that chemotherapy for breast cancer can affect brain structure and function.

More recent longitudinal imaging studies using fMRI or DTI add knowledge about brain changes during and after chemotherapy (for reviews, see Saykin, de Ruiter, McDonald, Deprez, & Silverman, 2013; Simó, Rifà-Ros, Rodriguez-Fornells, & Bruna, 2013). These approaches lead toward developing diagnostic and predictive biomarkers of cognitive decline after chemotherapy. For example, Kesler et al. (2013) applied multivariate pattern analysis (MVPA) to fMRI, and accurately differentiated default-mode network connectivity in breast cancer survivors who received chemotherapy from those who did not receive chemotherapy and healthy controls. Hosseini & Kesler (this issue) applied this technique to examine prefrontal cortex connectivity during an executive function task (go-nogo) and found a similar pattern of results with discrimination between women who were treated with chemotherapy and those who were not, despite equivalent task performance. This approach provides evidence of changes in neural circuitry "at rest" and when executive functions are challenged. The authors note that MVPA is concerned with *reliability* of a difference between groups rather than the existence of a difference between groups. This is consistent with the suggestion that variability underlies cognitive difficulties experienced after chemotherapy (Bernstein et al., this issue).

Finally, in addition to implementation of rigorous approaches to study design and novel methodologies, theoretically driven studies are critical for advances in this field. Recent suggestions that cancer treatments place survivors at risk for premature aging (Ahles, Root, & Ryan, 2012; MacCormick 2006), provides another framework for future studies.

CLINICAL IMPLICATIONS

Cancer and/or its treatment are associated with long-lasting cognitive disturbance in a subset of survivors. Factors that contribute to cognitive decline can be grouped into those related to the disease (e.g., diagnosis, stage, treatment intensity) or individual (e.g., cognitive reserve, age, genetics). Cognitive reserve, a theoretical construct associated with education, occupational attainment, and lifestyle, is thought to buffer brain injury effects (Dennis, Yeates, Taylor, & Fletcher, 2007; Scarmeas & Stern, 2003; Stern, 2006). In terms of age, older age is a risk for poorer cognitive outcomes in cancer studies with adults (Hurria et al., 2006; Nguyen et al., 2013). Conversely, younger age is a risk for poorer outcomes in pediatric cancer studies, including adult survivors of childhood cancer (Brouwers, Riccardi, Fedio, & Poplack, 1985; Edelstein et al., 2011; Kadan-Lottick et al., 2010; Krull et al., 2012). The findings that both immature and aging brains are vulnerable to cancer-related injury may seem counterintuitive. However, the developing brain is more susceptible to cancer treatment's effects on white matter growth (Brouwers et al., 1985; Krull et al., 2012), whereas older adults may face more risk than they already do, if cancer treatments accelerate cognitive aging (Ahles et al., 2012; MacCormick, 2006). Because development does not stop at age 18, and aging does not begin at age 65, it may be helpful to apply lifespan-developmental approaches used in pediatric neuro-psycho-oncology (Children's Oncology Group, 2008) to adult cancer populations. Specifically, baseline and follow-up cognitive assessments at treatment transitions (i.e., before, during and after treatment) and life transitions (i.e., return to work or school) should be implemented to monitor change over time and provide early intervention.

Persistent cognitive decline has a detrimental impact on quality of life and daily functioning (Boykoff et al., 2009). Although there are no diagnostic criteria for cancer-related cognitive dysfunction in individual survivors yet, the advances described above are helping move the field toward this goal. On an individual basis, as with other patient populations, a thorough evaluation should include an interview documenting change in functional status, self-report and family rating measures, and tests of performance that emphasize attention, memory, processing speed, and executive functions. Tests used should have good sensitivity because effects may be subtle. Ultimately, identifying factors that contribute to risk for cognitive decline, and identifying groups that may require closer attention and follow-up during and after treatment is critical. Although most research on chemotherapy and cognitive dysfunction has been conducted in 50- to 70-year-old women with breast cancer, recent studies in hematological, testicular, colorectal, and head and neck cancers have also documented cognitive dysfunction post-treatment (Gan et al., 2011; Vardy et al., 2012; Wefel,

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Vidrine, et al., 2011). Converging lines of research in long-term pediatric cancer survivors (Krull et al., 2012) and in those with older adult-onset cancers (Ahles et al., 2012) suggest that chemotherapy and radiation treatments, even when not directed to the central nervous system, place survivors at risk for premature physical and cognitive aging. Long-term follow-up studies on the impact of cancer treatments on cognitive functions and clinical neuropsychological assessments are warranted to monitor changes in individuals living with the chronic effects of the disease and its treatment.

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