Special Article

New Approaches to Understand Cognitive Changes Associated With Chemotherapy for Non-Central Nervous System Tumors

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Abstract

Context. Researchers have described a constellation of cognitive deficits (e.g., impairments in executive functions, working memory, attention, and information-processing speed) associated with cancer treatment, and specifically chemotherapy, for non-central nervous system tumors. However, findings have been inconsistent, largely because of measurement and study design issues.

Objectives. To propose ways for researchers to more clearly delineate and characterize the mild cognitive deficits and related outcomes that appear to affect a subset of cancer patients and suggest methods to make more effective use of the existing data to understand risk factors for impaired neuropsychological functioning.

Methods. We examined the literature on the relationship between chemotherapy and cognitive impairment, as well as related literature on neuropsychological measurement, structural and functional neuroimaging, alternative measures of health outcomes, and integrative data analysis.

Results. A more comprehensive picture of cognitive functioning might be obtained by incorporating nontraditional ecological measures, self-reports, computational modeling, new neuroimaging methods, and markers of occupational functioning. Case-control and integrative data analytic techniques potentially could leverage existing data to identify risk factors for cognitive dysfunction and test hypotheses about the etiology of these effects.

Conclusions. There is a need to apply new research approaches to understand the real-world functional implications of the cognitive side effects of chemotherapy to develop and implement strategies to minimize and remediate these effects before, during, and after cancer treatment. J Pain Symptom Manage 2013;■:■−■. © *2013 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

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Cancer, chemotherapy, cognitive impairment, neuropsychological testing, computational modeling

Is it permanent? I had chemo 11 years ago and I'm still in a fog.

– Cancer survivor posting on Facebook

Introduction

When the neurotoxic effects of antineoplastic drugs were first recognized nearly 40 years ago, it was assumed that neurotoxicity was secondary to central nervous system metastasis as it was generally believed that most cytotoxic drugs did not cross the blood-brain barrier.[1,2] However, in 1980, doctors at Dartmouth Medical School found that cancer chemotherapy patients who did not have metastases to the central nervous system were experiencing cognitive impairment that was independent of affective disorders or other psychiatric conditions.[3] Since then, the neurotoxicity of many commonly used chemotherapeutic agents has been widely recognized,[4] although the underlying mechanism has not been elucidated. The survivor community, however, has been acutely aware of these cognitive effects for some time, and it is widely believed that they coined the term "chemo brain" to describe the diffuse mental slowing and fogginess that often accompanies cancer treatment, and specifically chemotherapy, often for months or years.

Numerous researchers have described a constellation of cognitive deficits associated with chemotherapy for non-central nervous system tumors. These include decrements in executive functions, working memory, information-processing speed, attention, concentration, reaction time, psychomotor speed, and visuospatial ability[2] (Table 1). Although impairment in these domains can range from subtle to profound, particularly for patients receiving high-dose chemotherapy,[2,5] most studies, including five meta-analytic reviews,[6–10] report deficits in the mild-to-moderate range. However, severe neurotoxicity has been documented in case reports of toxic leukoencephalopathy and progressive multifocal leukoencephalopathy occurring in patients receiving oral and intravenous chemotherapy.[11,12]

Findings from clinical studies have been inconsistent, largely because of wide variations in study design, methodology, and definitions of cognitive impairment.[13] Because researchers have operationalized cognitive impairment in different ways, it is often difficult to make cross-study comparisons. To illustrate the extent of this problem, Shilling et al.[14] analyzed their breast cancer patient data using seven different methods of calculating cognitive impairment reported in the literature: impairment ranged from 12% to 68%, depending on the analytical method used. Measurement of cognitive impairment across studies is further hampered by differences in inclusion criteria, comparison groups (e.g., published normative data, healthy matched controls, non-chemotherapy-exposed cancer patients, and medical patients without cancer), clinical regimens, neuropsychological test protocols and cutoff scores, timing of cognitive assessments, and self-report instruments. Within patient samples, patients often differ with respect to stage of disease, concomitant treatments (e.g., pain medication and hormone therapy), and concomitant illnesses.

Although most of the literature supports an association between chemotherapy and cognitive decline for a subset of cancer patients,[15–17] a few studies involving breast cancer and testicular cancer patients have failed to find one.[18–20] Some have suggested that changes in cognition subsequent to chemotherapy are overdetermined and may represent normal variation in cognitive functioning, low levels of pretreatment cognitive functioning, effects of treatment-induced menopause, classification error, or artifacts of study design.[19–21] Genetic variation in blood-brain transporters, DNA-repair genes, and neural repair genes (e.g., apolipoprotein E) also may be contributory factors.[2] Others have proposed that chemotherapy actually may be associated with improvement in cognitive functioning for certain patients.[21,22] It is important to remember that when considering improvement