Journal of Neuroimmunology 301 (2016) 74–82

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Relationship of systemic cytokine concentrations to cognitive function over two years in women with early stage breast cancer

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ARTICLE INFO

Article history:
Received 29 June 2016
Received in revised form 4 November 2016
Accepted 11 November 2016

Keywords:
Cytokine
Breast cancer
Cognition
Chemotherapy
Hormonal therapy

ABSTRACT

Cancer and its treatment are frequently associated with cancer-related cognitive impairment (CRCI). While CRCI has been associated with linked to chemotherapy, there is increasing evidence that the condition may start prior to treatment and for some, remain unresolved after active treatment and into survivorship. Although the pathophysiology of the condition is complex, alterations in systemic cytokines, signaling molecules activated in response to infection or injury that trigger inflammation, are a possible mechanism linked to cognitive dysfunction in breast cancer and other conditions. Given the conflicting results in the literature, the lack of focus on domain specific cognitive testing, and the need for a longer time period given the multiple modalities of standard treatments for early-stage breast cancer, this longitudinal study was conducted to address these gaps.

Methods: We assessed 75 women with early-stage breast cancer at five points over two years, starting prior to the initial chemotherapy through 24 months after chemotherapy initiation. Measures included a validated computerized evaluation of domain-specific cognitive functioning and a 17-plex panel of plasma cytokines. Linear mixed-effects models were applied to test the relationships of clinical variables and cytokine concentrations to each cognitive domain.

Results: Levels and patterns of cytokine concentrations varied over time: six of the 17 cytokines (IL-6, IL-12, IL-17, G-CSF, MIPS-1β, and MCP-1) had the most variability. Some cytokine levels (e.g., IL-6) increased during chemotherapy but then decreased subsequently, while others (e.g., IL-17) consistently declined from baseline over time. There were multiple relationships among cytokines and cognition, which varied over time. At baseline, elevated concentrations of G-CSF and reduced concentrations of IL-17 were associated with faster psychomotor speed. At the second time-point (prior to the mid-chemotherapy), multiple cytokines had significant associations with psychomotor speed, complex attention, executive function, verbal memory, cognitive flexibility, composite memory and visual memory. Six months after chemotherapy initiation and at the one-year point, there were multiple, significant relationships among cytokines and multiple cognitive. At two years, fewer significant relationships were noted; however, lower concentrations of IL-7, a hematopoietic cytokine, were associated with better psychomotor speed, complex attention, and memory (composite, verbal and visual). MCP-1 was inversely associated with psychomotor speed and complex attention and higher levels of MIP-1β were related to better complex attention.

Conclusion: Levels and patterns of cytokines changed over time and demonstrated associations with domain-specific cognitive functioning that varied over time. The observed associations between cytokines and cognitive

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http://dx.doi.org/10.1016/j.jneuroim.2016.11.002

performance provides evidence that not only prototypical cytokines (i.e., IL-6, TNF-α, and IL1-β) but also cytokines from multiple classes may contribute to the inflammatory environment that is associated with cognitive dysfunction. Future studies to better delineate the cytokine changes, both individually and in networks, are needed to precisely assess a mechanistic link between cytokines and cognitive function in women receiving treatments for breast cancer.

1. Background

Cancer-related cognitive impairment (CRCI) has been the subject of considerable research inquiry, with most research focused on post-chemotherapy CRCI in women with breast cancer. The pathophysiology of CRC, although still unclear, is thought to involve the activation of cytokines, signaling molecules that mediate and regulate immunity, inflammation, and hematopoiesis. The link between inflammation and the development and progression of cancer is well-documented (Balkwill et al., 2005). Higher levels of circulating proinflammatory cytokines and their receptors have been found in individuals with cancer prior to treatment, during chemotherapy, and in survivorship. In addition to chemotherapy, cytokine interactions may be affected by other cancer treatments, including radiation therapy (Bentzen, 2006) and hormonal therapies (Collins et al., 2009; Lee et al., 2016), as well as multiple host factors including older age (Hurria et al., 2006; Mandelblatt et al., 2016), menopausal status and symptoms (Miura et al., 2016), and adiposity (Hartman et al., 2015). Although cytokines have been implicated in breast cancer development and progression for many years (Dethlefsen et al., 2013), the understanding of the multiple roles of cytokines in the central nervous system has been appreciated only in the more recent past (Maier and Watkins, 1998; Wilson et al., 2002). It is now well-accepted that cytokines can cross the blood brain barrier by active transport mechanisms in the choroid plexus and circumventricular organs, and have effects on neural processing (Dantzer et al., 2008), dopamine and serotonin metabolism, neural repair and neuronal/glial cell modulation (Aluise et al., 2010). Given these mechanistic linkages, there is mounting evidence that cytokines may influence neuroinflammation and contribute to cognitive and brain dysfunction in the context of breast cancer and its treatments (Janelsins et al., 2014).

The relationships among cytokine perturbations and cognitive outcomes are emerging across many fields (Wilson et al., 2002). Distinctive cytokine signatures have been identified in multiple immune-mediated medical conditions (e.g., heart failure (Pasic et al., 2003), Alzheimer's disease (Swardfager et al., 2010), multiple sclerosis (Heesen et al., 2010), and Parkinson's (Dursun et al., 2015)). In our studies, we have shown that (Cohen et al., 2011) serum cytokine concentrations are associated with attention, executive function, and learning-memory performance among adults with HIV infection. Although a relationship between systemic cytokine concentrations and CRCI has been confirmed in animal models of cancer (Janelsins et al., 2011) and in some studies of women with breast cancer undergoing chemotherapy (Briones and Woods, 2014; Galimberti et al., 2006), past studies have tended to focus on "prototypical" cytokines or have been short-term studies that have not represented the potential cytokine changes in the context of multiple cancer treatments over time. A recent study using a multiplex panel of cytokines demonstrated multiple relationships with subjective cognitive impairment and cytokine networks, but the study was truncated to the first twelve weeks of the chemotherapy phase of treatment (Cheung et al., 2015). In addition, the investigation of cytokines as a possible biological mechanism of cognitive dysfunction has been limited by the use of multiple measures of cognition (including subjective memory complaints) and cross-sectional or short-term longitudinal measures that focus on a single aspect of treatment, such as chemotherapy, radiation, hormonal therapy or survivorship. Further, most studies have measured prototypical cytokines which (delete that) that limits our understanding of pro- and anti-inflammatory interactive networks. To date, there have been very few studies that have investigated cognition over time, using objective neuropsychological batteries that have started prior to the initial chemotherapy and cytokine panels that permit the measure of multiple cytokines. Given the gaps in the literature, the lack of focus on domain-specific cognitive testing, and the need for a longer time period given the multi-modalities of standard treatments for early-stage breast cancer, we addressed these gaps by examining the association between plasma cytokine levels and cognitive performance across multiple domains in women with early-stage breast cancer over two years using validated, computerized cognitive testing.

2. Methods

As described in previous papers (Aboalela et al., 2015; Lyon et al., 2016), women between the ages of 21–65 with stage I to IIIA breast cancer were recruited through from a National Cancer Center designated Cancer Center affiliated with an urban research University in the mid-Atlantic region and multiple collaborative sites across the state. A total of 77 women with early stage (I to IIIA) breast cancer, who ranged from 23 to 71 years of age, were recruited through 5 regional cancer centers in Central Virginia. Two women withdrew from the study prior to the initial data collection yielding an $N = 75$. To identify potential study participants, each site had a study coordinator who screened patients for eligibility. The eligibility criteria were: (1) an age of 21 years or older; (2) a diagnosis of early stage breast cancer with a scheduled clinic appointment to receive chemotherapy; and (3) female gender (males were excluded since too few male participants were available for study). Exclusion criteria were a history of: (1) a previous cancer, or chemotherapy; (2) a diagnosis of dementia; (3) active psychosis; or (4) immune-related diagnoses (e.g., multiple sclerosis; systemic lupus erythematosus). After providing informed consent (VCU IRB #HM 13194), participants were enrolled and the first study visit was scheduled prior to the initiation of chemotherapy. The five time points for evaluation in this study were: prior to the start of chemotherapy (T1), at the midpoint of chemotherapy (T2), 6 months after the initial chemotherapy (T3), one year after the initial chemotherapy (T4) and two years after the initial chemotherapy (T5). The initial assessment (T1) was conducted after surgery but prior to commencing chemotherapy in women receiving adjuvant therapy. Women receiving neoadjuvant therapy had chemotherapy prior to surgical resection. After obtaining informed consent, participants were asked to complete questionnaires and performance-based cognitive testing via a computerized system. Participants were given incentives (a $25 gift card to a local store that has both food and personal items for sale) at each data collection point over the two-year study.

2.1. Measures

2.1.1. Cytokines

Whole blood was collected at each study visit. Plasma was separated by centrifugation, and all specimens were aliquoted immediately, frozen, and stored in a − 80 °C freezer. A standard capture sandwich assay was used to determine the levels of different cytokines. Each