A Systematic Assessment of Blood and Neuroimaging Indicators for Cognitive Side Effects During Chemotherapy in Breast Cancer Patients

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Abstract

Blood- and neuroimaging-based indicators can change as a result of breast cancer treatment. For breast cancer survivors, a summary of the prognostic usefulness of these markers for cognition is missing. Following PRISMA guidelines, this systematic review summarised studies from the previous ten years that used the PubMed database to assess blood markers and the relationship between blood- or structural neuroimaging markers and cognition throughout the chemotherapy trajectory for primary breast cancer. There were 44 studies total. All blood marker categories showed variations from the start of chemotherapy to years after the end of the treatment. White and grey matter measurements in frontal, temporal, and parietal brain areas were linked to cognitive functioning, as were blood indicators (mostly inflammation-related) during, shortly after, or years post-chemotherapy. There is preliminary evidence that epigenetic and metabolic changes only occur after chemotherapy and are related to cognition. This review showed temporally dependent relationships between particular blood-based and structural neuroimaging indicators and cognitive impairment in breast cancer patients. Further research on predicting the long-term cognitive consequences of chemotherapy is recommended to use both neuroimaging- and blood markers (such as those of neural integrity, epigenetics, and metabolism.

Keywords: Neuroimaging • Chemotherapy • Cognitive impairment • Biological markers • Breast cancer

Introduction

Female breast cancer will have 2.3 million new cases worldwide in 2020, making it the most prevalent cancer form overall. The number of cancer survivors has increased significantly as a result of advancements in treatment, and study has extended to include negative effects of such therapies. Cancer-related cognitive impairment (CRCI) is widely reported, affecting a wide spectrum of patients (17–78%), primarily in the executive functioning, memory, attention, and psychomotor speed domains. At the start of therapy, during therapy, and even years following treatment, CRCI might develop. CRCI is thought to be a complex combination of susceptibility (i.e. processes involved in DNA damage/repair or immune modulation), ageing, cancer biology, and both direct and indirect hazardous treatment effects, despite the fact that underlying mechanisms are still largely unknown. The Blood Brain Barrier (BBB) is known to be permeable to several chemotherapy drugs, which can directly harm brain tissue in regions necessary for cognitive function. It is unlikely that CRCI can be fully explained by the direct processes of chemotherapy, though, considering the intricacy and length of CRCI. Hence, in order to fully understand CRCI, it is also necessary to take into account indirect harmful mechanisms of chemotherapy, such as cytokine-induced neuroinflammation and increased allostatic burden in a person. Allostatic load, which can be measured, for example, using epigenetics and metabolomics, refers to the cumulative weight of chronic stress and living events that may lead to a state in which stress response systems are continually triggered. Neuroimaging studies have made an effort to more directly understand the underlying neurobiology of CRCI using MRI and PET sequences in order to examine the ongoing neurobiological effects of chemotherapy. Cancer patients' brains exhibit widespread anatomical and functional (like metabolic) alterations. The reader is directed to recent literature for reviews that provide summaries of MRI investigations. These studies also demonstrate relationships between brain measurements, such as white matter markers or brain volume, and cognitive functioning. There is currently a lack of a thorough assessment of markers discovered using various imaging modalities and their correlation with (i.e., potential predictive value of) cognitive impairment following breast cancer treatment. Blood-based biomarkers offer an alternative to neuroimaging that is less expensive and more accessible for detecting cancer patients who may be more prone to cognitive impairment over time. During chemotherapy treatment, it has been noted that there is an increase in peripheral inflammation, hormone dysregulation, anaemia, alterations in epigenetic markers, or changes in telomeric length. Castel and colleagues gave a summary of associations/correlations between cognitive deficits and particular circulating variables, cerebral spinal fluid components, and genetic polymorphisms in various cancer groups. Nonetheless, the body of research on this subject has grown significantly in recent years, particularly for individuals with breast cancer. Furthermore, it is not known to what extent neuroimaging can be augmented by blood-based markers to understand and prevent cognitive side effects from chemotherapy. To be able to recognise and classify patient subgroups that are at risk for CRCI in a non-invasive and cost-effective manner, it is imperative to have a better understanding of the biomarkers and processes of CRCI. This systematic review's goal is to create a thorough summary of research from the last ten years that looked at cognitive consequences of these and neuroimaging biomarkers along with fluid-based biomarkers over the course of chemotherapy treatment for breast cancer. More precisely, based on our systematic search, we seek to understand the relationships between fluid-based and markers generated from structural neuroimaging and (objective and self-report) cognition over the course of chemotherapy treatment, as well as how these correlations change over time. 19 studies used a cross-sectional design, 25 used a prospective longitudinal design, and 1 study combined the two designs. Assessments were made prior to surgery or treatment and up to 20 years later. Among the C+, C-, and HC subjects, respectively, sociodemographic characterisation indicated an average age at assessment of 52.93 (SD=8.26), 52.07 (SD=6.17) and 56.28 (SD= 10.23) years. Although using varying definitions or categories, seventeen papers described the race or ethnicity of their subjects. The majority of studies (n=12) classified participants' ethnicity as either white/ Caucasian or non-white/African-American, resulting in 82% of them being white and 14% being non-white. Three studies asked participants if they

belonged to a minority group (no more details provided), and 32% of participants in those studies were identified as such. Eighty-one percent of participants in two studies that indicated ethnicity also identified themselves as Chinese or non-Chinese. The majority of studies (n=27) mentioned the participants' menopausal state at the time of the evaluation. Among those, 51% of the C+ patients, 43% of the C- patients, and 37% of the HC participants were postmenopausal, however only 16% of this last group's menopausal status was documented. Clinical characterisation showed that the majority of C+ patients received standard-dose multi-agent chemotherapy regimens that included radiation and/or anti-hormone treatment along with docetaxel, epirubicin, doxorubicin, 5-fluorouracil, carboplatin, cyclophosphamide, methotrexate, or paclitaxel. The breast cancer stage was reported in 20 papers; of the total C+ patients, 0.12% were in stage 0, 22% in stage 1, 56% in stage II, 21% in stage III, and 1% in stage IV. Six research out of the 20 papers reported breast cancer patients with stage C- disease: 19% were in stage 0, 66% were in stage I, and 15% were in stage II. Breast cancer stage in C- patients was often lower than in C+ patients, as expected. The ratings of the listed studies' bias risk are displayed in Appendix B. 41% of the included studies revealed no evidence of bias, 30% had a risk that was unclear in one category, and 30% had risks in two or more categoriesThe domain of patient selection (n=18), followed by the reference standard (n=7),had highest prevalence of high risk of bias. The majority of studies demonstrating a high risk of bias in the reference standard either used screening tools [e.g., Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MOCA)] that do not evaluate multiple cognitive domain scores, enabling domain-specific comparison to norm data, or did not interpret the cognitive results blinded for the results of the biomarker tests. Studies that showed a high risk of bias in patient selection either used an age restriction (for example, only including women who were 70 years or older) or included subjects based on cognitive cut-off scores (e.g., positive answer on at least a subset of questions), In studies examining relationships between blood markers (inflammatory, metabolic, epigenetic, hormones, blood cells/ proteins, and neuronal integrity markers) and cognition in chemotherapy-treated patients, 76% (16 studies) discovered significant relationships, both of which decreasing the representativeness of adult women. All but two studies looked into associations that were evaluated simultaneously. The blood markers that were linked to both objective and self-reported cognitive functioning will be described in the following sections in accordance with the time point at which the association was seen, i.e., baseline, pre-treatment (during chemotherapy), immediately (one week to five months), or more distantly (six months to 20 years) after chemotherapy.

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