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Review

Chemobrain: A systematic review of structural and functional neuroimaging studies

Marta Simó[a,b], Xavier Rifà-Ros[a,c], Antoni Rodriguez-Fornells[a,c,d], Jordi Bruna[b,*]

[a] Cognition and Brain Plasticity Group, Bellvitge Biomedical Research Institute-IDIBELL, L'Hospitalet de Llobregat, Barcelona 08097, Spain
[b] Neuro-Oncology Unit, Hospital Universitari de Bellvitge (HUB)-Hospital Duran i Reynals (Institut Català d'Oncologia), L'Hospitalet del Llobregat, Barcelona 08097, Spain
[c] Department of Basic Psychology, Campus Bellvitge, University of Barcelona, L'Hospitalet de Llobregat, Barcelona 08097, Spain
[d] Catalan Institution for Research and Advanced Studies, ICREA, Barcelona, Spain

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ABSTRACT

Nowadays, chemotherapy-induced cognitive impairment or 'chemobrain' is a well-established clinical syndrome, consisting of moderate to subtle cognitive changes across various domains, especially working memory, executive function and episodic verbal memory that persist only in a subgroup of long-term cancer survivors. In recent years, several studies using neuroimaging techniques have reported structural and functional neural changes associated with chemotherapy. This review provides an overview of the relevant advances that neuroimaging techniques have added to the understanding of the underlying mechanisms of chemotherapy-induced cognitive impairment. In summary, our review showed: (i) a pre-treatment (prior to chemotherapy) widespread decrease in white matter (WM) volume as well as an increased level of activation of the frontoparietal attentional network of cancer patients compared to controls; (ii) an early diffuse decrease of gray matter (GM) and WM volume together with a decrease of the overactivation in frontal regions in chemotherapy-treated patients compared to controls and (iii) a long-term persisting decrease in GM and WM volumes together with a predominantly frontal cortex hypoactivation in only a subgroup of chemotherapy-treated patients.

Contents

* Corresponding author at: Neuro-Oncology Unit, Hospital Universitari de Bellvitge and ICO Duran i Reynals, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), C/ Feixa Llarga s/n, Hospitalet del Llobregat, Barcelona 08907, Spain. Tel.: +34 932607711; fax: +34 932607882.
E-mail addresses: 35078jbe@comb.cat, jordibruna09@gmail.com (J. Bruna).

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1. Introduction

1.1. Chemotherapy

Chemotherapy refers to the drugs used to treat cancer patients. These drugs are used to prevent cancer cells from multiplying, invading or spreading to other tissues. Most traditional chemotherapeutic agents appear to concentrate their effect on cell proliferation. Because cell proliferation is a characteristic of many normal cells, these agents also have toxic effects on normal cells (Skeel and Khleuf, 2007). Although the blood–brain barrier (BBB) provides some protection from systemic treatments, it is increasingly recognized that many agents gain access to this environment, via direct or indirect mechanisms, potentially contributing to central nervous system (CNS) toxicity. Some chemotherapeutic agents, for example antimetabolits (as metotrexate or fluorouracil), platinum-based agents or nitrosureas, have been associated with CNS neurological toxicity (Meyers and Perry, 2008). Moreover, several risk factors on developing neurotoxicity associated with chemotherapy have been identified, including exposure to high-dose regimens (Shah, 2005), additive effects of concurrent radiotherapy administration (Sheline et al., 1980; Sul and DeAngelis, 2006), intraarterial administration with BBB disruption or intrathecal administration (Delattre and Posner, 1995). Thus, the type, dose and administration route of chemotherapy are all variables of substantial importance in understanding the effect of chemotherapy on cognitive functions.

1.2. Chemobrain: general considerations

'Chemobrain' is the term used to describe the alterations in cognitive functioning reflecting the CNS toxic effects of systemic chemotherapy. Chemotherapy-related cognitive dysfunction has become a growing matter of interest in the last ten years (Meyers and Perry, 2008). This is due to the increasing population of cancer survivors in recent years as a result of the relevant advances in cancer therapy. Although acute cognitive changes during chemotherapy are common (Ahles and Saykin, 2002; Ferguson and Ahles, 2003), long-term post-treatment cognitive changes seem to persist in only a subgroup (17–34%) of cancer survivors (Ahles and Saykin, 2007).

Reported chemotherapy-induced cognitive effects are generally modest, remaining within normal limits but with a clear impact on everyday functioning (Tannock et al., 2004). Nevertheless, the affected domains have been remarkably consistent, with the greatest differences noted in processing speed, executive functions, working memory and certain aspects of episodic memory (Jansen et al., 2005).

Mechanisms underlying this cognitive and neurobehavioral toxicity have not yet been clearly elucidated. Nevertheless, multiple candidate mechanisms for chemobrain have been proposed, including individual or cancer-related variables as well as chemotherapy-induced damage or hormonal changes (Ahles and Saykin, 2007). Unfortunately, data directly supporting the proposed mechanisms are limited (Savitz et al., 2006; Seigers and Fardell, 2011).

Concerning individual susceptibility, genetic variability in genes that regulate neural repair and/or plasticity, such as apolipoprotein E (E4) and brain-derived neurothropic factor (BDNF), genetic variability in genes that regulate neurotransmission, such as catechol-O-methyltransferase (COMT), or genetic variability in BBB transporters, as protein P-glycoprotein, might increase the vulnerability of an individual to chemotherapy-induced cognitive changes (Savitz et al., 2006; Hoffmeyer et al., 2000; Nathoo et al., 2003). Recent data from animal studies suggest that very small doses of chemotherapy can cause cell death and reduce cell division in brain structures crucial for cognition, even at doses that do not effectively kill tumor cells (Dietrich et al., 2006). Other individual variables such as age and pretreatment cognitive reserve[1] have been associated with post-chemotherapy cognitive decline, as evaluated using processing speed measures (Ahles et al., 2010). Common risk factors for the development of both cancer and neurodegenerative disorders have been also suggested, for example, poor deoxyribonucleic acid (DNA) repair mechanisms (Goode et al., 2002).

Cancer-related variables such as cytokine levels have been also related with cognitive function (Meyers et al., 2005; Seruga et al., 2008; Reichenberg et al., 2001). Cytokine are small proteins secreted by the immune system which have a described negative effect on the hippocampus (Maier and Watkins, 2003).

In addition, chemotherapy treatment can induce changes through DNA damage directly or through increases in oxidative stress, lead to the shortening of telomeres thereby accelerating cell aging, contribute to cytokine deregulation, inhibit hippocampal neurogenesis or reduce brain vascularization and blood flow (Von Zglinicki and Martin-Ruiz, 2005; de Visser et al., 2006; Seigers and Fardell, 2011). All these biological pathways may influence the extent and the recovery of the effect of chemotherapy on cognitive function. Furthermore, chemotherapy agents can be given alone or with other more specific therapies. For example, women with hormone receptor-positive breast cancer are treated with the combination of chemotherapy and hormonal therapy. Changes in levels of hormones, such as estrogen and testosterone associated with menopause or induced by hormonal therapy, have been associated with cognitive decline (Zec and Trivedi, 2002; Castellon et al., 2004). Indeed, chemotherapy might influence hormonal levels or even interact with hormones through a reduction of antioxidant capacity or the ability to maintain telomere length (Lee et al., 2005; Seigers and Fardell, 2011).

1.3. Neuroimaging studies

Structural and functional neuroimaging has been applied to examine the neural substrate of these cognitive changes in cancer patients. Voxel-based morphometry (VBM) and diffusion-tensor imaging (DTI) are structural neuroimaging techniques that are capable of detecting alterations in gray matter (GM) and white matter (WM) tissue, respectively. Moreover, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies are functional neuroimaging techniques that may contribute to detect differences in brain functioning even when there is no clear structural damage. Hence, neuroimaging studies provide a fine-grained examination of neural changes associated with chemotherapy that are relevant for a better understanding of the

[1] *Cognitive reserve* refers to innate and developed cognitive capacity which is influenced by genetic and experience dependent factors, as for example, education, occupational attainment, and lifestyle (Stern, 2002).

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