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REVIEW

CHEMOTHERAPY, COGNITIVE IMPAIRMENT AND HIPPOCAMPAL TOXICITY

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Abstract—Cancer therapies can be associated with significant central nervous system (CNS) toxicity. While radiation-induced brain damage has been long recognized both in pediatric and adult cancer patients, CNS toxicity from chemotherapy has only recently been acknowledged. Clinical studies suggest that the most frequent neurotoxic adverse effects associated with chemotherapy include memory and learning deficits, alterations of attention, concentration, processing speed and executive function. Preclinical studies have started to shed light on how chemotherapy targets the CNS both on cellular and molecular levels to disrupt neural function and brain plasticity. Potential mechanisms include direct cellular toxicity, alterations in cellular metabolism, oxidative stress, and induction of pro-inflammatory processes with subsequent disruption of normal cellular and neurological function. Damage to neural progenitor cell populations within germinal zones of the adult CNS has been identified as one of the key mechanisms by which chemotherapy might exert long-lasting and progressive neurotoxic effects. Based on the important role of the hippocampus for maintenance of brain plasticity throughout life, several experimental studies have focused on the study of chemotherapy effects on hippocampal neurogenesis and associated learning and memory. An increasing body of literature from both animal studies and neuroimaging studies in cancer patients suggests a possible relationship between chemotherapy induced hippocampal damage and the spectrum of neurocognitive deficits and mood alterations observed in cancer patients. This review aims to briefly summarize current preclinical and neuroimaging studies that are providing a potential link between the neurotoxic effects of chemotherapy and hippocampal dysfunction, highlighting challenges and future directions in this field of investigation.

This article is part of a Special Issue entitled: Hippocampus.

Key words: chemotherapy, neurotoxicity, hippocampus, neural progenitor cells, cognitive dysfunction.

Contents

INTRODUCTION

Chemotherapy can be associated with both *acute* and *delayed* toxic effects on the CNS. Among the most commonly reported neurotoxic adverse effects in adult and pediatric cancer patients treated with chemotherapy are mood alterations and neurocognitive symptoms, such as disruption of memory, impaired attention, concentration, processing speed, and executive function (Vardy et al., 2007; Dietrich et al., 2008a; Ahles et al., 2012; Wefel and Schagen, 2012). Notably, such symptoms can be progressive even after cessation of therapy and might significantly compromise the quality of life in affected patients who are unable to return to their prior social and academic level of performance (Collins et al., 2013).

Clinically, the impact of chemotherapy on cognition has been most extensively studied in breast cancer patients (Jenkins et al., 2006; Schagen et al., 2006; Kreukels et al., 2008; Ahles et al., 2010; de Ruiter et al., 2011). However, several recent studies suggest that chemotherapy-induced neurotoxicity is not restricted to breast cancer patients, but might represent a problem of a larger scale affecting patients treated for various types of cancer (Correa et al., 2007a,b, Janelsins et al., 2011;

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Abbreviations: fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; VEGF, Vascular Endothelial Growth Factor.

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Correa and Hess, 2012; Correa et al., 2012; Wu et al., 2013; Horky et al., 2014).

The identification of the exact mechanisms and risk factors associated with chemotherapy-induced neurotoxicity remains an important issue in oncology and in current clinical and basic research investigations (as reviewed in: (Simo et al., 2013; Kaiser et al., 2014)).

Notably, adverse neurological effects have been observed with virtually all categories of chemotherapeutic agents, including antimetabolites, DNA cross-linking agents, mitotic inhibitors and anti-hormonal agents.

Most patients will be exposed to multiple agents during their course of treatment, and different drugs might exert similar molecular and cellular effects, including mitochondrial damage and oxidative stress. Therefore, it usually remains challenging to attribute clinical adverse events to one single drug or mechanism.

Based on the spectrum of neurocognitive and behavioral symptoms encountered in cancer patients, and the well known function of the hippocampus in maintenance of memory and regulation of mood and anxiety, it has been hypothesized that many chemotherapeutic drugs might contribute to a disruption of hippocampal function and impairment of hippocampal neurogenesis (Monje et al., 2012; Nokia et al., 2012), which in turn could contribute to impairment of brain plasticity and accelerated aging (Ahles et al., 2010; Villeda et al., 2011).

We here briefly summarize the current field of investigation and focus on the preclinical and clinical studies that provide a potential link between the neurotoxic effects of chemotherapy and the disruption of hippocampal neurogenesis and hippocampal-dependent brain plasticity.

CHEMOTHERAPY EFFECTS ON HIPPOCAMPAL FUNCTION

The hippocampus plays a key role in memory formation, learning, spatial processing and pattern separation (Squire et al., 1992; Burgess et al., 2002; Ekstrom et al., 2003; Kempermann, 2008; Clelland et al., 2009; Deng et al., 2010; Knoth et al., 2010; Richard et al., 2013). Adult hippocampal neurogenesis, the process of generating new granule cell neurons in the hippocampus throughout life, has been identified as one of the major regulators of maintenance of brain plasticity, learning and memory (Deng et al., 2010; Castilla-Ortega et al., 2011; Kempermann, 2011; Burghardt et al., 2012; Lacefield et al., 2012; Spalding et al., 2013). Conversely, disruption of hippocampal function and neurogenesis has been linked to impaired cognitive function and mood alterations (e.g., (Lucassen et al., 2010; Eisch and Petrik, 2012).

Given the spectrum of neurocognitive deficits and depressive symptoms seen in cancer patients, it has been proposed that chemotherapy-induced hippocampal toxicity might be an important mediator of this clinical syndrome (Monje and Dietrich, 2012; Evenden, 2013; Wigmore, 2013; Pereira Dias et al., 2014).

Table 1. Chemotherapeutic drugs associated with impaired hippocampal neurogenesis and neurobehavioral abnormalities

Mechanism	Drug	References
DNA cross-linking and alkylating agents	• BCNU (Carmustine) • Cisplatin • Cyclophosphamide • Temozolomie • Thiotepa	Dietrich (2006) Mignone (2006) Reiriz (2006) ElBeltagy (2010, 2012) Janelsins (2010) Mondie (2010) Yang (2010) Briones (2011) Christie (2012) Nokia (2012)
Anti-metabolites	• Cytosine arabinoside (Ara-C) • 5-Fluorouracil (5-FU) • Methotrexate	Han (2008) Mustafa (2008) Seigers (2008, 2009, 2010) Lau (2009) Janelsins (2010) Lyons (2011, 2012) Methotrexate (2011, 2012) Wilson (2013)
Anthracyclines	Doxorubicine	Janelsins (2010)
Anti-hormonal agents	Tamoxifen	Walker (2011)

Preclinical studies in animals, including behavioral and histological studies, have helped to identify potential mechanisms of chemotherapy-induced neurotoxicity (Seigers and Fardell, 2011). The current body of literature suggests that exposure to multiple chemotherapeutic agents can cause impaired hippocampal neurogenesis along with behavioral and cognitive abnormalities in rodent models (Seigers et al., 2013b) (Table 1). Notably, the effects of chemotherapeutic drugs have mostly been studied in non-tumor bearing animals, and have therefore not been able to address the concern that the tumor itself might negatively influence neurocognitive function, as suggested by some clinical studies (Hermelink et al., 2007; Ahles et al., 2012).

Cognitive and behavioral abnormalities, usually comparing treated animals with matching controls, were seen in tasks that involve hippocampal dependent learning and fronto-temporal network systems, such as the Morris water maze, novel location recognition and non-matching to sample learning. Prospective longitudinal studies, that assessed memory function prior to and after chemotherapy, reported a negative impact of chemotherapy on memory retention, spatial memory and learning (Liedke et al., 2009; Seigers et al., 2009; Long et al., 2011; Winocur et al., 2012).

Chemotherapeutic agents implicated in impairment of *hippocampal neurogenesis* include DNA cross-linking agents (e.g., BCNU, Cisplatin, Cyclophosphamide, Ifosfamide, Thiotepa, Temozolomide), anti-metabolites (Methotrexate, 5-Fluorouracil, Cytosine arabinoside),

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