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International Journal of Cancer, 2016; 139(12):2635-2645

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Conflicts of interest: None

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Abbreviations:

CIGT – chemotherapy-induced gut toxicity

BBB – blood brain barrier

VEGFR – vascular epidermal growth factor receptor

TKI – tyrosine kinase inhibitors

TNF – tumour necrosis factor

INFγ – interferon gamma

IL – interleukin

TLR – toll-like receptor

ZO – zonular occludens

5-FU – 5-fluorouracil

BMECs – brain microvascular endothelial cells

MTX – methotrexate

MMP – matrix metalloproteinase

Myd88 – myeloid differentiation factor

Key words: neurotoxicity, cognitive dysfunction, blood brain barrier, inflammation, chemotherapy-induced gut toxicity

Abstract

Neurotoxicity is a common side effect of chemotherapy treatment, with unclear molecular mechanisms. Clinical studies suggest that the most frequent neurotoxic adverse events affect memory and learning, attention, concentration, processing speeds and executive function. Emerging preclinical research points toward direct cellular toxicity and induction of neuroinflammation as key drivers of neurotoxicity and subsequent cognitive impairment. Emerging data now show detectable levels of some chemotherapeutic agents within the CNS, indicating potential disruption of blood brain barrier integrity or transport mechanisms. Blood brain barrier disruption is a key aspect of many neurocognitive disorders, particularly those characterised by a proinflammatory state. Importantly, many proinflammatory mediators able to modulate the blood brain barrier are generated by tissues and organs that are targets for chemotherapy-associated toxicities. This review therefore aims to explore the hypothesis that peripherally-derived inflammatory cytokines disrupt blood brain barrier permeability, thereby increasing direct access of chemotherapeutic agents into the CNS to facilitate neuroinflammation and central neurotoxicity.

1.0 Introduction

Neurotoxicity and its associated cognitive manifestations are poorly characterised, dose-limiting side effects of chemotherapy treatment [1]. Clinically, the impact of chemotherapy on cognition has been most extensively studied in breast cancer patients [2-4], however it is becoming increasingly recognised that cognitive symptoms affect a large portion of patients with varying malignancies and treatments [5-8]. Despite its prevalence, cognitive dysfunction, often referred to as *chemobrain*, remains an under-reported and ill-defined complication of anti-cancer treatment. Cognitive symptoms are vast, but are most commonly reported to affect memory and learning, attention, concentration, processing speeds and executive function [2, 4, 9, 10]. Importantly, unlike many acute chemotherapy-related toxicities, cognitive dysfunction presents both acutely and chronically, compromising quality of life for patients unable to return to prior levels of social and academic interaction [11].

Given its frequency, and its acute and chronic impact, the importance of better understanding chemotherapy-induced neurotoxicity has become a priority with an obvious goal of developing effective interventions. Like the overwhelming majority of regimen related toxicities, changes in neurological function occur in a subset of cancer patients and curiously these changes may or may not be associated with structural and functional alterations in the brain [12]. Compounding our ability to attribute cognitive changes directly to treatment has been the finding that impairment has been reported among cancer patients who are treatment naïve [13].

As yet, the molecular mechanism(s) involved in chemotherapy-induced neurotoxicity have not been clearly defined, however there is strong evidence implicating direct cytotoxicity and associated inflammatory mechanisms. Currently, the bulk of studies assessing the latter focus on neuroinflammatory pathways, however, it is important to consider the impact of cytokines derived from the tumor, as well as those elicited by the effect of chemotherapy on normal or tumour tissue. Most likely, direct cytotoxicity and neuroinflammation occur in concert with cytokine-mediated disruption of the blood brain barrier (BBB) serving to enhance drug penetration to augment local levels and result in amplification of cognitive symptoms.

The finding of detectable levels of systemically administered chemotherapeutic agents within the central nervous system (CNS) [14] supports this presumption and implies a level of BBB permeability that has not been previously appreciated. Increased levels of BBB permeability suggest that some chemotherapeutic agents are capable of disrupting its integrity, either directly or indirectly. Convincing evidence also exists linking BBB dysfunction with a proinflammatory state, with BBB dysfunction reported in patients with chronic inflammatory diseases as well as being a consequence of many forms of regimen-related peripheral toxicities. Among these, chemotherapy-induced mucosal injury, especially of the gastrointestinal tract, provides a compelling example of how focal chemotherapy-induced tissue damage can serve as a conduit for central neurotoxicity. Of interest, chemotherapy-induced gut toxicity (CIGT) has recently been shown to increase central markers of pain and neuroinflammation highlighting the ability of peripherally-derived inflammation to profoundly affect CNS function.

2.0 Structural and neuroimaging studies that define the scope of chemotherapy-associated changes in the brain

The neural basis for neurological deficiencies in cancer patients has been investigated with both structural and functional neuroimaging. Voxel-based morphometry (VBM) and diffusion-tensor imaging (DTI) are structural imaging techniques able to detect changes in both white and gray matter , whilst, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies enable assessment of functional deficiencies when structural changes are not evident. While these technologies have not been applied broadly, limited data suggest that chemotherapy is consistently associated with, changes in white matter (WM) structures. WM hyperintensities and hippocampal lesions have been identified using basic neuroimaging techniques in breast cancer patients treated with various chemotherapy regimens [17-19].

T1-VBM studies, an automated and quantitative method of neuroimaging which theoretically provides an unbiased, comprehensive, and highly reliable assessment sensitive to local changes [20, 21] have demonstrated diffuse cortical and subcortical WM and bilateral neocortical gray matter (GM) volume reductions or deficiencies in the superior frontal gyrus, parahippocampal gyrus, cingulate gyrus and the precuneus gyrus [22-24]. Based on the spectrum of neurocognitive symptoms seen in cancer patients and the well documented function of the hippocampus, a growing body of research now shows impaired neurogenesis and hippocampal function likely contribute to neurotoxicity [25, 26]. In support of this, hippocampal alterations have been identified in response to a spectrum of chemotherapeutic agents [5, 26-28] in a number of patient cohorts.

Structural changes, indicative of direct neurotoxicity, are often seen in conjunction with neurocognitive functional deficiencies detected through DTI and digital symbol testing (DST); a measure of processing speed. Although studies are limited in size and number, results have indicated associations between the integrity of the corpus collosum and processing speeds of patients receiving adjuvant chemotherapy for breast cancer [29]. Further associations have been identified between processing speeds and frontal WM integrity [30]. The largest study to investigate this association was conducted by Deprez and colleagues (2012) in premenopausal women with breast cancer. Patients receiving adjuvant chemotherapy exhibited worsening attention, psychomotor speed, verbal learning and memory, as well as decreased microstructural integrity in widespread regions of the corona radiata and the corpus collosum, compared to matched controls, reinforcing that WM changes may be the source of cognitive deficits seen in chemotherapy-treated patients [31].

Results of neuroimaging studies have been informative relative to describing observed structural and functional deficiency relationships associated with cancer- and chemotherapy-associated cognitive dysfunction. However, they are unable to mechanistically define the pathogenesis of chemotherapy-associated neurological toxicities. And at this early stage, their interpretation is limited by heterogeneity in experimental methodology, and confounded by neurological comorbidities commonly seen in cancer patients such as depression and anxiety, which can produce similar structural manifestations [1]. Furthermore, the inclusion of predominantly elderly patients, a lack pretreatment baseline controls and presence of structural deficits in treatment-naïve patients clouds the ability to make definitive conclusions regarding the mechanisms of chemotherapy-induced neurotoxcity.

3.0 Blood brain barrier dysfunction: an accelerant for neurotoxicity?

The presence of chemotherapeutic agents in the CNS after systemic administration indicates their ability to cross the BBB, either physiologically or pathologically [32]. Early research has demonstrated detectable levels of intravenously administered cisplatin, bis-chloroethylnitrosourea (BCNU) and paclitaxel in the brains of rodents using PET [32, 33]. This phenomenon has also been seen in higher order primates, with detectable levels of 5-fluorouracil in the cerebrospinal fluid after intravenous administration [14]. Although therapeutic drug levels effective for CNS malignancies were not seen, drug concentrations were sufficient to induce apoptosis and neuronal damage associated with neurological dysfunction [34]. In addition to these findings, it is well established that a number of proinflammatory cytokines have detrimental effects on tight junctions and thus the integrity of the BBB. This is critically important when considering BBB breakdown in cancer patients, as there are a number of sources of proinflammatory cytokines, derived from the tumour and the effects of chemotherapy on normal tissue.

3.3.1 Mediators of inflammation disrupt blood brain barrier integrity

The BBB (Figure 1) is highly plastic and can undergo significant modification in response to a raft of physiological and pathologies cues. Subsequently, impairment of the BBB has been implicated in a number of CNS pathologies, particularly those characterised by a proinflammatory state [35 36]. For example, traumatic brain injury (TBI) is often accompanied by a large inflammatory response resulting in grossly abnormal BBB permeability, the influx of inflammatory cells and subsequent oedema [37, 38]. A similar mechanism is now also hypothesised to play a role in the pathogenesis of stroke in which a weakening of the BBB, associated with a transient breakdown of tight junction proteins, is thought to contribute to the haemorrhagic transformation manifested by a heightened inflammatory state and worsened prognosis [39].

In light of these clinical associations between inflammation and BBB breakdown, there is now a wealth of *in vitro* and *in vivo* data demonstrating the ability of proinflammatory cytokines to disrupt the BBB (Table 1). From these observations, it is clear that some cytokines exclusively affect paracellular barriers (e.g. IL-1β), through breakdown and translocation of tight junction proteins, whilst others target transcellular processes mediated by caveolae (e.g. TNFα). A number of vasogenic agents (histamine, substance P) and proteases associated with inflammation, have also been identified to promote BBB remodeling. Of interest is the impact of matrix metalloproteinases (MMP) on tight junction integrity (Table 1) given the high levels of circulating MMPs observed after chemotherapy [40].

It is well documented that increased MMP activity correlates with elevated permeability of both endothelial and epithelial barriers (Table 1), strongly implying MMP-mediated tight junction disruption [41-44]. Particularly robust evidence supports a role for MMP-mediated tight junction disruption in the BBB as endothelial cells, astrocytes and pericytes are all potent sources of these signaling proteins [41]. Brain-derived microvascular endothelial cells (BMECs) exposed to oxidative stress expressed significantly elevated MMP-9 activity paralleled by downregulation and redistribution of occludin [45]. Numerous preclinical studies also support a role for MMP-mediated tight junction disruption [42, 43, 46]. For example, MMP-2/-9 levels have been shown to be significantly elevated following cerebral ischemia leading to tight junction protein degradation, increased BBB permeability and oedema [42, 47]. Furthermore, inhibition of MMP-2/-9 has been shown to reduce vascular permeability and attenuate tight junction disruption [42]. This is further supported by evidence showing that MMP-9 knockout mice have greater ZO-1 expression coupled with decreased BBB permeability and reduced oedema following stroke [48]. The impact of MMPs on caveolae-mediated transcytosis is now also being recognised for its potential role in CNS pathologies characterised by BBB disruption (Table 1).

4.0 Chemotherapy-induced cytokine production, blood brain barrier dysfunction and clinical implications for patients

Virtually every biological substance known to have the capacity to alter the integrity of the BBB has been shown to be generated by tissues and organs that are targets for chemotherapy-associated toxicities. Among these, chemotherapy-induced mucosal injury, especially of the gastrointestinal tract provides a compelling example of how focally-induced chemotherapy tissue damage can serve as a conduit for central neurotoxicity. While suggested by Seigers et al., (2011) [49], the potential impact peripheral inflammatory mediators as a driver of central toxicity has hardly been explored.

4.1 Chemotherapy-induced gut toxicity: a potential facilitator of CNS pathology

We have previously highlighted strong epidemiological data linking the development of neurotoxicity and gut toxicity following chemotherapy, and suggest that these off targets toxicities may in fact have common molecular roots [50, 51]. The development of CIGT is a dynamic process, characterised by overlapping and simultaneous biological events. Logan et al. (2008) demonstrated that the administration of irinotecan, 5-fluoruoracil and methotrexate induced significant elevations in TNFα, IL-1β and IL-6 in tumour-bearing rats. Importantly, these proinflammatory cytokines not only damage surrounding tissue through pro-apoptotic signals (e.g. caspases 3 activation), but they are also highly efficient activators of NFκB thus amplifying the mucotoxic cascade. Furthermore, TNFα and IL-1β induce MMP-1, MMP-2 and MMP-3 activation, which is thought to contribute to development of gut toxicity through inflammatory pathways, altered extracellular matrix composition, adhesion molecules and tight junction disruption. Toll like receptor (TLR)4-dependent mechanisms have also been linked to the development of gut toxicity, with increases in its expression seen following chemotherapy [52] as well as improvements in symptomatic parameters seen following genetic manipulation of its downstream signaling molecules (e.g. MyD88, MD-2) [53 54]. This aspect of CIGT has significant implications for BBB maintenance, as it is becoming increasingly clear that TLR4-dependent signaling pathways are critical for tight junction integrity [55].

TLR4-mediated barrier modulation has been shown in both endothelial and epithelial models. For example, Gao et al., (2015) recently showed that traumatic brain injury was not only associated with traditional proinflammatory markers, but also elevated TLR4 signalling and uncontrolled BBB transit. Importantly, administration of a vascular endothelial growth inhibitor (VEGI) up-regulated the tight junction proteins (claudin-5, ZO-1, occludin) and attenuated TLR4 activation, NF-κB signaling and the production of proinflammatory cytokines, as well as improving markers of brain injury. Alcohol-induced steatohepatitis is also well documented to present with acute intestinal barrier disruption, resulting from impaired tight junction protein expression [56]. In this study, administration of a TLR4 monoclonal antibody attenuated both functional and molecular markers of barrier function, emphasising the importance of TLR4-mediated tight junction disruption in an inflammatory setting.

TLR4-dependent tight junction disruption has also been shown to occur in response to irinotecan treatment in a TLR4 knockout (-/-) mouse model of gut toxicity {Wardill, 2016 #566}. Following irinotecan, increased permeability of both the intestinal barrier and BBB were detected, both seen at 24 h post-treatment. Although TLR4 knockout animals only showed improvements in intestinal barrier disruption, this study is the first to demonstrate central neurotoxic changes in a model of chemotherapy-induced gut toxicity and reinforces the bidirectional communication that exists between the gastrointestinal system and CNS. It is likely this communication that underpins the prevalent comorbidities affecting these organ systems.

4.2 Intestinal inflammation drives CNS changes

A number of intestinal pathologies are associated with an increased risk of behavioural comorbidities as indicated by increased rates of depression, mood disorders and cognitive dysfunction in patients with inflammatory bowel disease (IBD) [57]. For example, elevated circulating proinflammatory cytokines, increased in intestinal permeability and the number of circulating monocytes are commonly reported in acute phases of trinitrobenzene sulfonic acid

(TNBS)-induced colitis in mice. [58]. Importantly, these are accompanied by localised breaches in the BBB [59] leading to increased neuroinflammation [60, 61] and associated cognitive disturbance. These findings are consistent with those of Zonis et al., (2015) who, using a different murine IBD model (dextran sodium sulfate), found increased microglial and astrocytic reactivity in the hippocampus of treated mice.[62]. These results also compliment data indicating altered neuronal function and increased anxiety-like behaviour in models of parasitic gut inflammation [63, 64]. Other reports support the concept that patients with chronic inflammatory states initiated by autoimmune diseases, cancer or infections are at higher risk for central neurological pathology and that there is a high likelihood that such changes are mediated by proinflammatory cytokines directly impacting the brain [65].

5.0 Neuroinflammation and cognitive dysfunction

Increased systemic proinflammatory cytokine production has been previously suggested as a candidate mechanism for cognitive dysfunction in cancer patients [28]. It is therefore possible that proinflammatory cytokines may be involved in several aspects of neurotoxicity by; (1) increasing BBB transit, and (2) permitting neuroinflammation and associated tissue manifestations.

Substantial data, from a spectrum of clinical settings, highlight links between peripheral inflammation and cognitive symptoms. For example, peripheral activation of the immune system by a subseptic dose of lipopolysaccharide (LPS) has been shown to increase cytokine expression within the brain [67-69] at levels associated with learning and memory disruption in both models of disease and health [70-72]. In healthy volunteers, LPS lead to increased levels of IL-1, TNFα and IL-6 resulting in impaired working memory and cognitive dysfunction [73]. Similarly, increased peripheral inflammation has also been associated with gradual cognitive decline and the development of dementia in the elderly population [74].

Interestingly, the use of IFNα and IL-2 (proinflammatory cytokines) as anti-cancer agents is highly linked to the development of depression and other cognitive impairments [75, 76], however, there is only limited clinical data from cancer patients in which correlations between circulating cytokines and cognitive function have been evaluated. Meyers et al., (2009) reported an association between elevated levels of circulating IL-6 and worsened executive function in patients with acute myeloid leukemia [77]. In addition, elevated IL-6 and TNFα seen in chemotherapy-treated breast cancer survivors correlated with persistent hippocampal structural changes and reduced verbal memory performance [78, 79] well beyond the period during which patients received drug infusions.

When looking at other CNS pathologies characterised by neuroinflammation and cognitive impairment, Alzheimer's disease (AD) provides additional insight. Patients with AD often have elevated levels of TNFα in the cerebrospinal fluid and parenchyma [80], as well as expressing TNFα-related polymorphisms [81]. The pathological level of cytokines resulting in this chronic inflammatory state mimics that noted in cancer patients and perpetuates neuronal loss and cognitive decline [82]. Importantly, treatment with anti-TNFα agents in patients with AD has been shown to favorably impact the development of cognitive dysfunction [83, 84]. Of particular importance to our proposed hypothesis is that AD is often accompanied by increased BBB transit [85], leading to heightened inflammatory influx and worsened clinical outcomes.

5.1 Tumour-dependent cytokine production

Further confounding our understanding of how peripheral inflammation, BBB disruption and neuroinflammation contribute to cognitive dysfunction is the fact that results from clinical studies are neither uniform nor concrete. Cognitive dysfunction has been reported in patients with breast cancer or colorectal cancer after diagnosis, but before the administration of any anti-cancer treatment [87]. Similarly, in a recent study comparing patients with localised colorectal cancer (n=289) who received or did not receive chemotherapy, patients with metastatic or recurrent colorectal cancer (CRC) (n=73) and healthy controls, Vardy et al., (2015) reported significant differences in cognitive dysfunction prior to, and following, treatment between patients with CRC and healthy controls [13]. Surprisingly, there was no difference in the degree of cognitive dysfunction between patients who received chemotherapy and those who did not. In addition, the extent of disease (local vs. metastatic) did not effect neurological function clouding understanding of tumour-driven effects on cognition. While levels of proinflammatory cytokine levels were elevated in the CRC cohorts vs. controls, there was no statistically significant relationship between them and cognitive dysfunction. Patel et al's study of 174 newly diagnosed patients with breast cancer also reported baseline levels of cognitive dysfunction and elevations in proinflammatory cytokine levels (TNF) [87]. However, elevations in TNF were no higher in cancer patients compared to a non-cancer, demographically similar control group.

The findings of these, and similar studies, demonstrate the complexities of both the clinical and biological elements associated with cancer treatment-related cognitive dysfunction. First, the intrinsic and extrinsic biological activities associated with tumours have likely been underestimated. Tumours may actively produce inflammatory mediators as a consequence of local oxidative stress or stimulate inflammation in response to their presence [88]. These findings might account for baseline cognitive dysfunction. Nonetheless, the lack of significant differences in cytokine levels between recently diagnosed cancer patients and non-cancer controls clouds definitive conclusions.

6.0 The significance of symptom chronicity

Despite patient and study heterogeneity and methodological limitations, neurotoxicity is defined by the chronicity of symptoms which often persist long after treatment cessation [31]. It has been reported that patients treated with high dose chemotherapy and those that receive autologous haemopoietic stem cell transplantation have significant impairments in cognitive function up to 1 year after cessation of their treatment [89]. The longevity of cognitive symptoms has also been assessed in survivors of childhood acute lymphoblastic leukaemia 6-18 years after remission [90]. Deficits in figural memory as well as reduced hippocampal volume were also noted. Similarly, in breast cancer patients, chemotherapy treatment resulted in reduced gray matter volume in the right parahippocampal gyrus compared to untreated cancer patients, which correlated with reduced memory performance at 1 but not 3 years post-treatment [23]. These studies are somewhat complimented by two prospective studies that show hippocampal volume reductions at 1 month following chemotherapy treatment, which was lost at further time points (1 year) [91]. More persistent changes were observed in a recent investigation of 19 breast cancer patients [92], who showed right hippocampal gray matter volume reductions at both 1 month and 1 year after treatment completion.

Although variations exist in the time-course of these symptoms, chronicity is almost always reported and is a defining characteristic of neurotoxicity. Given the relatively short half-life of many chemotherapeutic agents, the chronicity of symptoms is biologically significant, and suggests that the impact of direct cytotoxicity would presumably be minimal; with chronic, reactive inflammatory processes, a more likely candidate. However, it is important to consider that neurotoxicity is unlikely to be attributable to a single mechanism, rather, various mechanisms may converge additively or synergistically to result in the heterogeneous symptoms seen in patients (Figure 2). This is well described by Dietrich et al., (2015) who highlights key mechanistic drivers such as oxidative stress, direct cellular toxicity and inflammation that contribute to altered cellular kinetics in the hippocampus as well as neurovascular/BBB disruption [5]. If a prolonged period of inflammation is present, either systemically or centrally, altered BBB transit could parallel the chronic, long-term changes in seen in patients and may provide a better biological understanding.

7.0 Conclusion

Regimen-related toxicities are poorly characterised and often have significant effects on patient quality of life. We have previously highlighted the importance of symptom clusters, emphasising the possibility of common underlying mechanisms, which could perhaps be simultaneously targeted [93]. Cognitive impairment is particularly devastating to patients, and currently has no universally accepted mechanism. This review has proposed that, contrary to traditional beliefs, chemotherapeutic agents can in fact gain access to the CNS. Importantly, we suggest that this is likely due to upregulated and uncontrolled BBB transit. The BBB, like many interfaces within the body, is subject to intense modification highlighting the plasticity of tight junctions and transcytotic mediators. Based on symptom clustering and potential linkages between the gut and CNS, we suggest that peripherally-derived inflammatory mediators are responsible for inducing BBB dysfunction, thus permitting central neurotoxicity. Importantly, neurotoxic changes may occur through the direct actions of the chemotherapeutic drug itself, or present as the behavioural manifestation of neuroinflammation. BBB disruption may therefore be the missing link in our understanding of how gut/CNS communication is involved in the development of two critically important regimen-related toxicities. Furthermore, it presents as an exciting opportunity to target peripheral inflammation and achieve wider reaching clinical outcomes.

8.0 Acknowledgements

Ms Hannah Wardill is the recipient of the Florey Medical Research Foundation Doctor Chun Chung Wong and Madam So Sau Lam Memorial Postgraduate Cancer Research Top Up Scholarship 2015. Ms Hannah Wardill, Ms Ysabella Van Sebille and Ms Kimberly Mander are recipients of an Australian Postgraduate Award.

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10.0 Figure legends

Figure 1 Blood brain barrier transport mechanisms. Cerebral endothelial cells of the blood brain barrier (Panel A) have specialised circumferential tight junctions and intracellular caveolae, which regulate blood brain barrier transit (Panel B). Tight junctions are highly plastic, multi-protein structures traversing the intercellular junction (Panel C). Each tight junction comprises the cytoplasmic protein family zonular occludens (-1, -.2, -3) and the transmembraneous protein families claudin, JAMs and occludin. Caveolae, comprised of Cav-1, Cav-2 and Cav-3, control transcellular permeability within the blood brain barrier (Panel D).

Figure 2 **Schematic highlighting multifactorial pathobiology of cognitive dysfunction.** Many cognitive disorders are characterised by blood brain barrier disruption and neuroinflammation. The impact of peripheral inflammation on central neurovascular integrity and the subsequent development of neuroinflammation is now considered a key driver in many neurological disease characterised by systemic inflammation. Blood brain barrier disruption may therefore compliment what is currently understood about neurotoxicity, by enhancing exposure of the CNS to chemotherapeutic agents (direct neurotoxicity) and permitting neuroinflammation (indirect).