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Review

Mechanisms underlying select chemotherapeutic-agent-induced neuroinflammation and subsequent neurodegeneration

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ABSTRACT

This review demonstrates the importance of uncovering the mechanisms that underlie chemotherapy-induced neuroinflammation. It builds upon the well-established connection between chemotherapeutic-agents and neurotoxicity along with widespread peripheral toxicities. This article summarises the major studies which have linked chemotherapy-induced neurodegeneration with direct evidence of neuroinflammation. Cancer and chemotherapy-related adverse effects impact a large proportion of the population. A better understanding of the link between chemotherapy, neurotoxicity and specifically the mechanisms of neuroinflammation, will allow the development of strategies to improve the management of side effects, and overall to reduce the burden on cancer patients receiving chemotherapy. This review has developed a summary schematic of the relationship between different chemotherapeutic agents and inflammatory markers within the central nervous system and links this correlation with some major ailments associated with chemotherapy use.

1. Introduction

Cytotoxic chemotherapy is limited by significant toxicities which often lead to cessation of treatment or variation from the optimal treatment protocol to ensure compliance (Chabner and Longo, 2011). These include myelosuppression leading to blood cytopenia and immunosuppression, gastrointestinal distress such as vomiting and nausea, and alopecia (Corrie, 2008). High dose chemotherapeutic methotrexate given intravenously can induce a stroke-like syndrome that presents with transient neurological defects, for example alternating hemiparesis, aphasia, encephalopathy and seizures (Martino et al., 1984; Walker et al., 1986). These side effects are significant contributors to loss of quality-of-life in patients, and there has been mounting concern about mental side effects such as anxiety and depression and cognitive decline which has become a focus of research in recent years.

Side effects experienced by cancer survivors are backed up by experimental findings of structural changes in the brain and many observational studies. It is thought these structural changes could be occurring as a direct result of treatment. Both functional MRI and positron emission tomography scans of the brain display reductions in grey and white matter in those treated with chemotherapy and suffering cognitive side effects. Functional MRI testing has highlighted the cingulate region of the human brain to be active during working memory tasks in those who have received chemotherapy *versus* controls – in whom the cingulate remains dormant. In the study by Vardy and Tannock, patients were given adjuvant chemotherapy and underwent positron emission tomography scanning. Patients displayed metabolic brain activity in the inferior frontal gyrus of the frontal lobe and posterior part of the cerebellum during a memory task – compared to controls whose brain activity centred around the parietal lobes and contralateral primary visual cortex (Vardy and Tannock, 2007). Along with these findings of functional differences during chemotherapy use, another pathological finding has been asymmetrical brain alpha activity of ≥ 0.5 Hz detected by electroencephalograms and event related potential testing (van Dam et al., 1998). In other efforts an initial work-up was done to test the cognitive function of 184 participants receiving cyclophosphamide-thiotepa-carboplatin or fluorouracil-epirubicin-cyclophosphamide chemotherapy treatment regimes, no chemotherapy and a healthy control six months before, and after, treatment. No initial

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differences were observed between groups until after treatment, at which point cyclophosphamide-thiopeta-carboplatin regime patients deteriorated 25% and controls only 6.7% (confidence interval 95%) (Schagen et al., 2006).

1.1. Neuroinflammation

Neuroinflammation is the activation of the brain's innate immune system in response to an inflammatory challenge (Hein and O'Banion, 2009), including alterations in tissue homeostasis, abnormal protein aggregates, trauma, ischaemic damage, aging and certain disease states and toxins (Becher et al., 2017). Neuroinflammation can be acute and chronic, often existing for extended periods of time after the removal of the initial stimuli (Lyman et al., 2014).

Peripheral inflammation, once thought separate to the CNS, has also been shown to be a trigger for the neuroinflammatory response through modification of blood brain barrier (BBB) integrity. The BBB is composed of a highly specialised form of endothelium that separates the blood of the peripheral nervous system (PNS) from entering the CNS. This endothelial layer is made up of transmembrane proteins such as tight junctions which selectively accept compounds and prevent passive diffusion across the barrier from the blood (Luissint et al., 2012). Peripheral TNF-α, IL-6 and IL-1β are known to increase permeability of the BBB, *via* altering the resistance of tight junctions in endothelial cells in brain vasculature (Wong et al., 2004). This alteration occurs when electrical resistance across the junctions is lowered, which is seen alongside increased permeability (Wong et al., 2004). This enables peripheral cytokine entry to the CNS adding to the neuroinflammatory response (Laflamme et al., 1999; Terrando et al., 2011). Further, this defective BBB allows both innate immune cells such as monocytes and neutrophils, as well as adaptive immune cells, such as $CD8^+$ T cells, $CD4^+$ T cells and B cells, to enter and affect the CNS, causing release of inflammatory mediators, adding to the enhancement of neuroinflammation (Russo and McGavern, 2015). It is also interesting to note that after spinal cord injuries, it has been found that 'classical' monocytes with proinflammatory properties ($Ly6C^{hi,}$ $CX3CR1^{lo}$ and $CCR2^{hi}$) were immediately recruited to the CNS. It is believed this may also occur during other activation of the CNS, which would deem relevant here and would compile with the proinflammatory environment experienced in neuroinflammation.

1.1.1. Cell types and mediators in neuroinflammation

The immune response in the CNS involves the glial cells, with a focus on microglia and astrocytes as key mediators (Block and Hong, 2005). Microglia are the innate immune cells of the central nervous system, accounting for 10–15% of cells within the brain and spinal cord (Lawson et al., 1992). Microglia form a network of immunity for the CNS, capable of destroying invading micro-organisms, removing deleterious debris, promoting tissue repair *via* growth factor secretion, all facilitating a return to CNS homeostasis (Kreutzberg, 1996).

Upon activation from factors including nitric oxide (NO), lipopolysaccharides, IL-1β and reactive oxygen species, microglia transform from an inactive state to a highly active, phagocytic state (Lyman et al., 2014). This highly active state triggers a change to an active phenotype, resulting in a shift of cellular function causing a release of cytotoxic factors aimed at restoring homeostasis (Lull and Block, 2010). These include superoxide, nitric oxide, TNF-α and inflammatory prostaglandins and cytokines (Colton and Gilbert, 1987; Moss and Bates, 2001; Sawada et al., 1989; Wang et al., 2005). It is this release that is believed to contribute to the issues experienced with extended periods of neuroinflammation (Becher et al., 2017; Lyman et al., 2014; Vichaya et al., 2015).

Astrocytes are a multifaceted type of glial cell, found in numerous forms throughout the CNS including star-shaped, protoplasmic and fibroblastic (Becher et al., 2017). Astrocytes found in the CNS account for approximately one third of the total cell population (Rothhammer and Quintana, 2015). Astrocytes form a selective barrier for entry of immune cells into the CNS between brain parenchyma and blood vessels at the BBB, but are also an important source of cytokines in the circulating blood. This includes IL-1β, IL-6 and CCL2 (Rothhammer and Quintana, 2015), demonstrating the role of astrocytes in the neuroinflammation pathway. Although microglia show much greater inflammatory cytokine release, it is important to highlight astrocytes as a contributing factor (X. Liu et al., 2012).

1.2. Consequences of neuroinflammation

Release of inflammatory cytokines from microglia and astrocytes is necessary to perform normal physiological functions (Kempuraj et al., 2016). However, issues arise when the inflammation becomes excessive as this carries the potential to inhibit neuronal regeneration (Russo and McGavern, 2016), and is associated with increased neuronal death and reduced neuronal survival leading to alterations in structure and functions of the CNS (Ransohoff, 2016). This is believed to contribute to numerous CNS issues, including synaptic dysfunction, inhibition of neurogenesis, neuronal death and cognitive impairment (Lyman et al., 2014).

Further issues arise when this neuroinflammation becomes chronic, as this has been linked to neurodegeneration. This is demonstrated in numerous neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis (Kraft and Harry, 2011). This neurodegeneration is primarily due to increased pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6, IL-8, and also other inflammatory mediators and neurotoxic molecules including PGE_2 (Shabab et al., 2016; Skaper et al., 2014).

Furthermore, reactive oxygen species and NO have been shown to play a crucial role in neurodegeneration. Increased reactive oxygen species production has been shown to significantly increase arachidonic acid release, increasing eicosanoid biosynthesis which is crucial to the inflammation process (Martínez and Moreno, 2001), with evidence showing increased production of reactive oxygen species by astrocytes directly enhances inflammation and has neurotoxic effects (Abramov et al., 2005). NO, produced by iNOS in glial cells under inflammatory conditions, produces peroxynitrate, a highly toxic compound causing internal and external cellular damage. This evidence is significant to the topic at hand because increases in oxidative stress in Alzheimer's disease has been linked to a decline in mitochondrial function, inhibition of neurite outgrowth and microtubule organisation, and alteration of phospholipid asymmetry in synaptic membranes (Anoopkumar-Dukie et al., 2005; Sun et al., 2007). It has also been shown that metabolites of arachidonic acid have anti-proliferative and pro-apoptotic effects *in vitro* on PDGF-stimulated 3T6 fibroblasts. Therefore, the increase in arachidonic acid from reactive oxygen species production may result in increases in apoptotic cell death within the CNS due to neuroinflammation (Nieves and Moreno, 2007).

1.3. Chemotherapy-induced neuroinflammation

The literature has shown chemotherapy directly results in an upregulation of various well known pro-inflammatory mediators. These can be seen in Table 1 and Fig. 1. This upregulation is believed to contribute to symptoms including but not limited to fatigue, peripheral neuropathy and cognitive decline, commonly experienced by chemotherapy patients (Vichaya et al., 2015).

Besides neuroinflammation, other potential mechanisms do exist. Damage-associated molecular patterns, cellular metabolism and mitochondrial dysfunction associated with chemotherapy use have been proposed as potential mechanisms in neurotoxicity (Briones and Woods, 2014; Janelsins et al., 2011; Vichaya et al., 2015). Despite this, evidence linking neuroinflammation to CNS issues and neurodegenerative diseases makes chemotherapy-induced neuroinflammation the major-suspected toxicity and an area needing further study for

Table 1
Summary of current evidence regarding chemotherapy-induced neuroinflammation. The table summarises findings from 2010 onwards and highlights specific cytotoxic chemotherapy agents and their effect on pro-inflammatory mediators.

Author, year	Inflammatory marker (s)	Chemotherapeutic drug(s)	Study type/model	Original findings
Cheruku et al.	Nitrate	Doxorubicin	*In vitro* (IMR-32 cells) and *in vivo* (Wistar male rats)	Catechin hydrate, a tea polyphenol, increased viability and neurite length in undifferentiated and differentiated IMR-32 cells when combined with doxorubicin. *In vivo* studies also showed dose-dependent reversal of time-induced memory deficits due to doxorubicin exposure in Wistar rats. Furthermore, catechin treatment showed significant reductions in oxidative stress and neuroinflammation in the same model.
Chen et al. (2017)	CD68	Paclitaxel	*In vitro* (dorsal root ganglia from C57BL/6J mice, ND7/23 cells, MDA-MB-231 cells, SiHa cells), *in vivo* (C57BL/6J and NOD/SCID female mice)	In paclitaxel-treated mice, minoxidil protected against thermal sensitivity and alleviated mechanical allodynia, through suppressed neuroinflammation and remodelled dysregulation of intracellular calcium homeostasis.
Makker et al. (2017)	TNF-α, IFN-γ CCL11 CCL4 CCL3 IL-12p70 GM-CSF	Paclitaxel	*In vivo* (C57BL/6j male mice)	Paclitaxel caused significant mechanical allodynia, and increased circulating CD4+ and CD8+ T-cell populations. In the PNS, paclitaxel increased activating transcription factor-3 as well as CCL2 and CCL3 in lumbar dorsal root ganglion. In the CNS, paclitaxel significantly increased astrocyte activation in the spinal cord dorsal horn, with several inflammatory markers (see column 3) also being increased.
Cerles et al.	IL-6 TNF-α AOPP	Oxaliplatin	*In vitro* (CT26 cells, N2a cells, HUVEC cells, THP1 cells), *in vivo* (BALB/cJRj male mice)	In neuronal-like cells, niclosamide downregulated the production of oxaliplatin-induced H_2O_2, preventing cell death. In colon cancer cells, niclosamide enhanced oxaliplatin-mediated cell death through increased H_2O_2.
Feiock et al.	TNF-α	Methotrexate	*In vivo* (BALB/c female mice)	Methotrexate and non-brain directed radiation (NBDR) significantly increased TNF-α levels in female BALB/c mice. NBDR increased brain glucose metabolism, and also increased activated astrocytes and microglia.
Shen et al. (2015)	TNF-α MCP-1	Vincristine	*In vivo* (ICR male mice)	Vincristine induced activation of TNF-α and MCP-1 in the spinal cord. Heme-oxygenase 1 was exogenously induced and this proved to reduce TNF-α and MCP-1 suggesting HO-1 has potential to reduce spinal cord inflammation and related neuropathic pain.
Borniger et al.	IL-6	Cyclophosphamide + doxorubicin	*In vivo* (C57BL/6 female mice)	Cyclophosphamide + doxorubicin increased IL-6 mRNA expression in the hypothalamus. This correlated with low quality and fragmented sleep.
Janes et al. (2014)	TNF-α IL-1β	Oxaliplatin	*In vivo* (Sprague-Dawley male rats)	Oxaliplatin administration was associated with mechano-hypersensitivity (allodynia and hyperalgesia), hyperactivation of astrocytes (but no microglia), increased production of TNF and IL-1β and decreases in IL-10 and IL-4 in the dorsal horn of the spinal cord. A_3AR agonists were able to reverse all changes.
Briones et al.	IL-1β TNF-α COX-2	Cyclophosphamide + doxorubicin + 5-fluorouracil	*In vivo* (Sprague-Dawley female rats)	CMF increased IL-1β, TNF-α and COX-2 while levels of IL-10 were reduced. CMF-induced cognitive impairment which persisted for 4 weeks after the treatment had ended. Administration in conjunction with NS-398, a highly selective COX-2 inhibitor, attenuated CMF-induced neuroinflammation and effects on memory and cognitive impairment, suggesting possible benefits of concurrent anti-inflammatory use in preventing neuroinflammation.
Gao et al. (2013)	IL-1β	Paclitaxel	*In vivo* (Sprague Dawley male rats)	Paclitaxel increased IL-1β levels in the spinal dorsal horn 19 days after the first paclitaxel injection. Protein expression of GFAP, a marker for astrocyte activation, significantly increased in the paclitaxel group when compared to control.
Christie et al. (2012)	ED-1	Cyclophosphamide	*In vivo* (Athymic nude male rats)	Using ED-1 immunostaining as a marker for activated microglia, cyclophosphamide animals had significantly more ED-1 cells, when compared to saline control. Doxorubicin animals did not differ from control.
Doyle et al. (2012)	TNF-α IL-1β IL-10 IL-4	Paclitaxel	*In vivo* (Sprague Dawley male rats)	Paclitaxel increased in TNF-α, IL-1β, IL-10 and IL-4 in the spinal cord when compared to vehicle control.

(*continued on next page*)

Table 1 (*continued*)

Author, year	Inflammatory marker (s)	Chemotherapeutic drug(s)	Study type/model	Original findings
Burgos et al. (2012)	IL-1β TNF-α IL-6	Paclitaxel	*In vivo* (Wistar male rats)	Paclitaxel significantly increased IL-1β, TNF-α and IL-6 in the lumbar spinal cord of paclitaxel-treated rats on day 4 and day 8, compared to normal naïve animals. No significant differences were found between paclitaxel-treated rats and naïve rats at day 29.
Seigers et al.	All	Methotrexate	*In vivo* (Wistar male rats)	Methotrexate reduced all cytokine levels at 5 and 20 days post-sacrifice in plasma, but no effects on cytokine levels were found in hippocampal tissue.

confirmation. Though existing literature has widely sought to observe and validate the existence of post chemotherapy cognitive impairment, studies have shifted to seek out a mechanistic cause through a focus on *in vitro* and *in vivo* animal work. This has been conducted through examination of peripheral and central inflammatory markers to represent potential neuroinflammation and human cognitive tests. This work forms the basis of this review.

1.4. Use of NSAIDs in chemotherapy-induced-neuroinflammation

There is increasing evidence for anti-inflammatory medication having a neuroprotective role in neurodegenerative diseases such as Alzheimers disease, with NSAIDs having been shown to reduce its severity. One study found ibuprofen significantly reduced known neurotoxins quinolinic acid-induced peroxidation and cyanide-induced superoxide production in rat brain homogenate, suggesting a possible mechanism for its neuroprotection (Lambat et al., 2000). Another study found NSAID indomethacin was able to offer neuroprotection by reducing the ion-induced rise in lipid peroxidation by binding the Fe^{2+}/Fe^{3+} ion, preventing its use in free radical production and therefore being neuroprotective (Anoopkumar-Dukie et al., 2003).

Given the similarities in proposed mechanisms underlying these disease conditions and chemotherapy-induced neuroinflammation, the use of anti-inflammatories has been identified as a potential treatment option, with evidence emerging supporting its use. Briones et al. tested NS-398, a COX-2 inhibitor, to block CMF-induced-neuroinflammation in a rat model. NS-398 attenuated CMF-induced neuroinflammation, with reductions in IL-1β, TNF-α and COX-2 production. This reduction in inflammation correlated with improvements in cognitive impairment experienced in the CMF-control rats. Furthermore, NS-398 attenuated significant decreases in oligodendrocyte precursor cells and myelin basic protein in the corpus callosum, as well as significantly reduced chemotherapy-induced myelin loss (Briones and Woods, 2014). However, there is limited further evidence supporting the use of NSAIDs in chemotherapy-induced neuroinflammation. Studies looking at the benefit of NSAIDs in neurodegenerative diseases give hope to future studies. For example, one study showed long term use of NSAIDs correlated with a decreased risk of developing AD, delayed onset of clinical dementia, and reduced severity and slowed progression of cognitive symptoms (Etminan et al., 2003) with another study showing indomethacin slowed cognitive decline in patients with mild-to-moderate AD. Furthermore, studies *in vivo* and *in vitro* show the ability of NSAIDs to reduce neuroinflammation, with evidence showing NSAIDs inhibit the neuroinflammatory response in glial cells in culture (Du and Li, 1999; Minghetti et al., 1997), and also inhibit activation of glia in animal models (Netland et al., n.d.). Given this evidence, the use of anti-inflammatories in chemotherapy-induced neuroinflammation is a promising target, with further studies needed for confirmation.

2. Suspected chemotherapy-induced neuroinflammation toxicities

2.1. Peripheral neuropathy

Pain, numbness and temperature sensitivity is experienced by up to 70% of chemotherapy patients, and is a common cause for early cessation of treatment (Makker et al., 2017). Chemotherapy-induced peripheral neuropathy (CIPN) is most frequent in what is called a 'glove and stocking' distribution, meaning these symptoms are most common in hands and feet (Kim et al., 2015). The exact mechanism that induces CIPN is unknown, as it appears unique to each drug class. Platinum compounds are thought to induce neuronal damage and axonal degeneration, whereas paclitaxel is believed to result in distal axonal degeneration and secondary demyelination and nerve fibre loss (Quasthoff and Hartung, 2002).

Numerous studies have indicated that raised levels of pro-inflammatory cytokines sensitise peripheral sensory neurons leading to

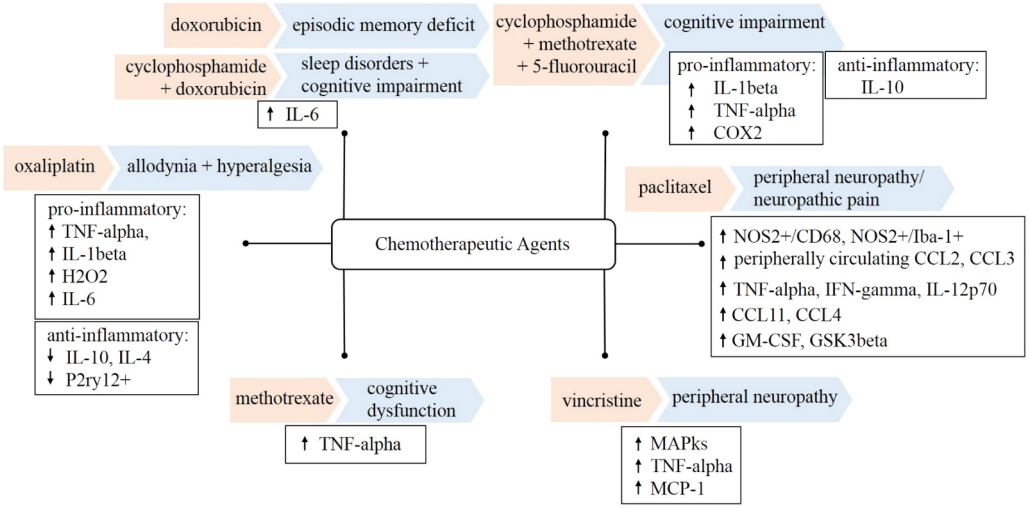

Fig. 1. The relationships between chemotherapeutic agents, inflammatory markers, and resultant side effects. Arrows depict changes (↑: increase; ↓: decrease) in level of listed marker.

CIPN, particularly when found in the dorsal root ganglia or spinal cord (Vichaya et al., 2015). One heavily implicated chemotherapy drug in CIPN is paclitaxel. This drug showed an increase in IL-1β, TNF-α and MCP-1 in the lumbar spinal cord of rats, which could be prevented by WIN 55-212-2, a mixed cannabinoid receptor agonist (CB_1 and CB_2), (Burgos et al., 2012). CB_2 receptor has been identified at having a functional role in the CNS, which is primarily mediated through microglia. Microglia express both CB_1 and CB_2 receptors, with CB_2 receptor being expressed in much higher levels and is modulated in relation to cell activation state (Pertwee, 2006). CB_2 receptor mRNA and proteins are not detected in 'resting' microglia, but are present in high levels in 'responsive' and 'primed' microglia, with levels diminishing in fully activated cells. This is in contrast to CB_1 receptor, which is present in microglia and low levels regardless of activation state. This suggests that CB_2 receptor is expressed when needed as they participate in the inflammatory response (Cabral et al., 2008) Furthermore, the increased expression during 'active' microglial states suggests there are periods of time where cells are more susceptible to cannabinoids, such as when activated by paclitaxel in the above study.

Paclitaxel dosing in rodents has been linked to peripheral neuropathy and causes significant mechanical allodynia with observed increases in circulating CD4+ and CD8+ T-cells. Mice dosed with paclitaxel experienced thermal sensitivity and mechanical allodynia which could be prevented with the alopecia drug minoxidil. This drug was found to act through suppression of neuroinflammation, relating to levels of CD68 linked to NOS2+, and aiding dysregulation of intracellular calcium homeostasis (Chen et al., 2017). In the peripheral regions where CIPN symptoms are felt, there was an increase in transcription factor-3 and CCL-2 and -3 in the lumbar dorsal root ganglion along with several inflammatory markers increased in the spinal cord dorsal horn (see Fig. 1). TNF-α, IFN-γ, CCL11, CCL4, CCL3, IL-12p70 and GM-CSF were all seen to be heightened in one study in 2017 which characterised the neuroinflammatory and neuroimmune variations linked with chemotherapy-induced peripheral neuropathy and pain (Makker et al., 2017). Prior to this work it was found that symptoms of CIPN could be reduced in rodents when anti-inflammatory cytokines IL-10 and IL-4 were administered (Janes et al., 2014). This same study by Janes et al. created a model for CIPN using oxaliplatin which is linked to problems with mechano-sensitivity, including allodynia and hyperalgesia, which could be attenuated by A_3 adenosine receptor agonists (Janes et al., 2015). Furthermore, the Janes et al. study found the oxaliplatin model for CIPN increased expression of TNF-α and IL-1β, but decreased IL-10 and IL-4 in the dorsal horn of the spinal cord. Both IL-10 and IL-4 are considered to be anti-inflammatory markers of neuroinflammation which builds upon the theory that neuroinflammation is a major mechanism occurring from chemotherapeutic agent administration and likely the cause of its many side effects. Other experimental work used the same model of oxaliplatin-induced neurotoxicity in mice and *in vitro* and found oxaliplatin treatments caused H_2O_2 production and observed an increase in neuroinflammatory markers IL-6, TNF-α and AOPP (Cerles et al., 2017). In addition to this, endogenous or exogenous increases in peripheral cytokine levels sensitise peripheral sensory neurons leading to peripheral neuropathy in non-chemotherapy cases, confirming a relationship does exist (Schäfers and Sorkin, 2008; Wieseler-Frank et al., 2005).

A significant part of peripheral neuropathy is the symptom of pain which rates high as having a deleterious effect on the quality of life of its sufferers. Several studies in rodents have looked at neuropathic pain specifically. Paclitaxel increased IL-1β levels in rat spinal dorsal horns 19 days post-administration, along with the activated-astrocyte marker GFAP. This study went on to establish the glycogen synthase kinase 3-beta activity of lithium could prevent and halt the paclitaxel-induced pain (Gao et al., 2013). Another study confirmed the increase of IL-1β in the spinal cords of rats, and additionally found an increase in TNF-α, IL-10 and IL-4 in this same region. This work reiterates the theory of neuroinflammation as it prevented and reversed neuropathic pain by targeting excess production of peroxynitrite in the rats (Doyle et al., 2012). Another chemotherapeutic agent vincristine was seen to cause neuropathic pain by increasing levels of TNF-α and MCP-1 in the spinal cord of male mice. This work then utilised heme-oxygenase 1, which can degrade to become a potent antioxidant, to alleviate the chemotherapy-induced symptom of peripheral neuropathy (Shen et al., 2015).

2.2. Cognitive dysfunction

Cognitive issues are experienced by up to 80% of chemotherapy patients, with issues mainly reported with executive function, memory and processing speeds (Cleeland et al., 2003; Janelsins et al., 2012). For up to 35% of patients, this dysfunction persists for months or years after the cessation of treatment (Janelsins et al., 2011), demonstrating the impact on patient overall wellbeing. Post chemotherapy cognitive impairment (PCCI) was first documented in women afflicted with breast cancer. One study found as many as 1 in 5 breast cancer patients present with this side effect, with other studies reporting significantly higher incidence with upwards of 20% of breast cancer survivors and 46% of testicular cancer patients (Ahles et al., 2008; Jansen et al., 2011; Porter, 2013). The duration of this symptom never fully goes away for

92% of patients with PCCI. 61% rate the severity some time after treatment to be the same as between doses and the remainder experience some symptomatic reductions. This means only 8% in this particular study found PCCI to ease once treatments had stopped (Hede, 2008). PCCI was found to be the most debilitating side effect post-treatment, indicating the need for further information regarding this toxicity development, -with most patients suffering severe decreases in quality of life, including simple tasks such as paying bills and preparing meals (Boykoff et al., 2009; Hislop, 2015).

Clinical studies have focused on the relationship between increased peripheral inflammatory markers and cognitive performance. Correlations between increased levels of soluble TNF receptor type II (sTNF-RII), a marker for TNF-α activity, IL-6, IL-1β and COX-2 and a decrease in cognitive performance has been observed with various chemotherapy agents – cyclophosphamide, doxorubicin and 5FU (Briones and Woods, 2014; Janelsins et al., 2011; Kempuraj et al., 2016; Lyman et al., 2014; Vichaya et al., 2015). Early studies indicate anti-inflammatory agents lead to a decrease in inflammation and an increase in cognitive performance (Briones and Woods, 2014). One study used ED-1 immunostaining as a marker for activated microglia and used this method to study neurogenesis. This work found rats treated with cyclophosphamide who displayed impaired cognitive function had significantly more ED-1 positive cells in the hippocampus than a saline treated control. The marker of activated microglia inferred neuroinflammation could be the mechanism occurring in chemotherapy induced cognitive decline (Christie et al., 2012).

A previously undervalued side effect of chemotherapy is transient memory loss which can occur during, afterward and in some cases, years' post-treatment (Hermelink, 2015; Phillips and Bernhard, 2003). This is commonly referred to as '*chemo brain*' or '*brain fog*' (Ganz et al., 2013; Schmidt et al., n.d.). This cognitive impairment presents as difficulty with overall thinking, decision- making and forming of memory – which can bear some resemblance to dementia symptomatically (Porter, 2013; Vigliani et al., 1999). These short term memory problems and general mental fogginess frequently occur in combination with a short attention span, difficulty learning new skills and multitasking, being less organised, having difficulty retrieving the correct word when speaking and experiencing verbal and visual memory problems specifically (Hislop, 2015; Prouse, 2010).

A major but underappreciated hypothesis behind PCCI is that it is caused by neuroinflammation resulting from chemotherapy used in the treatment of an initial cancer diagnosis (Briones and Woods, 2014; Vichaya et al., 2015). On a structural level rats have been found to lose white matter and neural precursor cells in the brain following chemotherapeutic treatment – a trend similarly observed in humans when studied with neural imaging (Kaiser et al., 2014). Wistar rats given doxorubicin exhibited a dose-dependent series of memory deficits. Rodents were given catechin hydrate, a tea polyphenol and an established antioxidant, and a reduction in oxidative stress was observed. This study insinuates a link between neuroinflammation and the episodic memory deficits seen in the animals (Cheruku et al., 2018)

Hormonal therapies exist for cancers of the reproductive organs, with patients also presenting with brain fog (Hislop, 2015). Patients given tamoxifen, a selective oestrogen reuptake modulator used to treat breast cancer, had decreased metabolism in the basal ganglia compared to those not receiving chemotherapy at all but also those getting chemotherapy in isolation (Silverman et al., 2007).

2.3. Fatigue

Although not specified in the literature search in Table 1, it is of note that fatigue is a common side effect of chemotherapy with up to 60% of patients experiencing fatigue symptoms. It is now considered one of the most debilitating side effects, with 30–60% of patients experiencing moderate to severe fatigue (Bower, 2014). However, the exact mechanism behind fatigue is not confirmed, but is traditionally associated with anaemia (Ryan et al., 2007). Fatigue generally occurs after each dose of chemotherapy, and has also been known to persist for weeks, months or years after the completion of treatment, suggesting chronic inflammation has a role in its development (Weymann et al., 2014). Further, large, well-controlled studies linking neuroinflammation to fatigue in breast cancer survivors are particularly strong, with changes in IL-6 levels being associated with changes in fatigue level over the course of treatment (L. Liu et al., 2012). Further support comes from the role of inflammatory cytokines in non-cancer contexts, including chronic fatigue syndrome, rheumatoid arthritis and multiple sclerosis, with TNF-α and IL-6 levels being highly correlated with fatigue levels (Chao et al., 1990; Patarca et al., 1994). In summary, fatigue appears multi-dimensional, with neuroinflammation being a contributing factor.

3. Conclusions

Increasing evidence suggests that chemotherapy triggers neuroinflammation in a large percentage of patients receiving treatment. Furthermore, this may contribute to cognitive impairment and other CNS toxicities observed with treatment. However, the mechanism by which this occurs is largely unknown. This review presents evidence linking chemotherapy use to neuroinflammation. The studies overviewed identify a clear increase in circulating and tissue-borne cytokines and other inflammatory mediators concurrent with chemotherapy use. Other evidence including the involvement of neuroinflammation in several neurodegenerative diseases, and the potential neuroprotective effects of NSAIDs, make neuroinflammation a suspected mechanism for the development of these CNS toxicities. However, further investigation is required to demonstrate a causal role for neuroinflammation with these toxicities, with minimal studies showing decreases in neuroinflammation correlating to improvements in cognitive performance and a reduction in toxicities. A greater understanding of the mechanisms by which these toxicities occur may potentially inform treatment strategies to deal with this debilitating side effect associated with chemotherapy use.

Author contributions

Shailendra Anoopkumar-Dukie, Fleur Mcleary, Arie Davis, Santosh Rudrawar and Anthony Perkins conceived and designed the study, carried out the review, and prepared and drafted the manuscript. Shailendra Anoopkumar-Dukie, Fleur McLeary and Arie Davis responded to reviewer feedback on made changes to the final manuscript. All authors agree to be considered authors on the manuscript.

Appendix A. Literature search selection criteria

See Table A1.

In addition to this database search, the following articles were retrieved from PubMed by searching for every chemotherapeutic agent listed in the 2018 Australian Medicines Handbook: Burgos et al., 2012; Doyle et al., 2012; Gao et al., 2013.

Exclusion criteria were used to remove papers that included the listed phrases in either the title or abstract, but lacked any relevance to chemotherapy-induced neuroinflammation.

Table A1
Inclusion/exclusion search terms/filters included in methodology.

Search term:
Chemotherapy AND neuroinflammation AND cancer
Filters Applied in **PubMed**
Text – full text journal article
Search Fields – Title/Abstract
Publication date – previous ten years
Language – English
Subjects – all
Exclusion terms: In Title/Abstract
Review, stem cell
Search results:
11

Search term:
Chemotherapy AND neuroinflammation AND cancer
Filters Applied in **Scopus**
Document type – article
Publication date – 2008–2018
Language – English
Exclusion terms: In Title/Abstract
curcumin, retinoic acid, DTI, MRI, review, alopecia areata, clinical trial, monoclonal antibodies, stem cell
Search results:
11

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