

**Chemotherapy-induced cognitive impairments.**

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Adjuvant chemotherapy has increased the survival of patients with numerous cancers with more than 60% of cancer patients surviving more than five years after diagnosis [1]. As improvements in cancer treatments lead to longer survival times for many cancers, researchers have moved towards investigating and improving quality of life for survivors. It is estimated that there are 22 million cancer survivors worldwide [2], and ~650,000 in Australia or 3.3% of the population [1]. This rate increases to 9% of the population for persons over 50, and 14% of the population of persons over 65 [1].

However there is substantial evidence that chemotherapy can cause side effects that last well beyond the treatment period (see our recent reviews [3, 4]). Many cancer survivors self-report problems with their memory and concentration during and after chemotherapy. Although the status of the cognitive impairments has been debated, these self-reports have been verified by objective neuropsychological testing, which reveal mild to moderate impairments in processing speed, attention/concentration, executive function, and verbal and visual memory in 17-50% of survivors persisting for years post-treatment [5]. Cognitive dysfunction has been identified in patients treated with all classes of anti-neoplastic drugs [4, 6].

Concerns of cognitive impairment occasionally lead patients to refuse chemotherapy treatment, with the potential to negatively affect treatment outcomes for cancer. More frequently it affects the quality of life in cancer survivors for many years after treatment. Survivors report that the impact on daily function is the

most troublesome survivorship issue they face [7], and focus group research of breast cancer survivors have found that many women do not feel confident enough to return to work due to a perceived loss of competency [8]. Unfortunately, oncology service providers may not consider themselves sufficiently knowledgeable or well equipped to deal with the cognitive changes that patients may experience [8]. Clearly, the cognitive problems following chemotherapy are a large untreated syndrome that leads to significant decline in quality of life in cancer survivors.

However, despite the severity of this problem, very little is known about how chemotherapy causes these deficits. Although it is commonly thought that the brain is protected from chemotherapy drugs, there is considerable evidence that chemotherapy induces widespread functional changes in the central nervous system (CNS). Neuroimaging studies of cancer survivors have correlated impaired performance in cognitive tasks with alterations in brain structure and activity in areas important for these tasks, such as the hippocampus and pre-frontal cortices [9, 10], and these abnormalities persist for up to 10 years post-treatment [4, 11]. Tests on laboratory rodents have demonstrated clear changes to the structure and functions of regions of the CNS important for memory and cognition. Chemotherapy causes the widespread death of cells throughout the CNS, including neurons and the vital non-neuronal glial cells that support neural function [12]. In the hippocampus, a region crucial for memory, chemotherapy halts the development of new neurons (neurogenesis), and reduces levels of important neuronal growth and support hormones [13]. Chemotherapy also has cytotoxic effects on the non-neuronal glial cells of the CNS. Human imaging studies show white matter degeneration and leukoencephalopathy in the CNS of chemotherapy-treated cancer survivors [9, 14], and animal studies have also revealed reduced myelin (white matter) [15], and death of the cells that make myelin [16]. Another side effect of chemotherapy is increased inflammation in the CNS. Neuroinflammation is a hallmark of many neurodegenerative disorders, disrupting normal neuronal function and contributing to learning and memory impairments in these diseases [17]. As in these other diseases, chemotherapy causes abnormal activity in the immune cells of the CNS, and increases the expression of

pro-inflammatory substances within the CNS [18-20]. Finally, chemotherapy causes energy balance problems for the CNS. In the CNS, chemotherapy has been shown to reduce hippocampal blood vessel density and decrease cerebral blood flow [18], and chemotherapy causes oxidative stress [21].

In view of this problem, the International Cognition and Cancer Taskforce has identified a need for well-validated treatments and interventions [11]. Emerging results suggest both pharmacological and behavioural approaches may offer patients some hope (see our recent review for more information [3]). Pre-clinical and clinical research has identified potential pharmacological treatments for chemotherapy-induced cognitive impairments. For instance, treatment with anti-oxidants [22, 23], anti-depressants (especially the serotonin specific reuptake inhibitor fluoxetine) [24, 25], or cholinesterase inhibitors (Donepezil) [26] reduced the cognitive effects of chemotherapy in laboratory rats and mice. Clinical random control trials suggest a positive effect of the psychostimulant modafinil on human cognition [27, 28]. In addition, low-risk psychological treatments that emphasize functional improvements in both cognition and quality of life, such as cognitive-behavioural interventions and cognitive rehabilitation, may also provide benefits for patients with cognitive impairment after cancer treatment [29, 30].

Finally, our own research has identified a positive role for increased physical activity in chemotherapy. We have observed accelerated recovery in cognitive function in chemotherapy treated laboratory rats if they were given voluntary access to running wheels one month after treatment [31]. There is a growing body of evidence that exercise improves cognitive function and quality of life [32, 33]. Moreover, while exercise has a mild effect on cognitive function in healthy people, exercise seems to be particularly beneficial for people suffering from disease or ageing [32]. Epidemiological data shows participation in exercise reduces the risk of neurodegenerative diseases [33], improves cognition for patients with Alzheimer's disease, Huntington's disease or depression, and facilitates post stroke recovery [34]. Importantly, several large observational studies have reported a benefit to physical activity in reducing the risk of disease recurrence, death from cancer, and death from all causes [35-37]. Moreover, in a case series,

Galantino *et al.* [38] found that an 8-week yoga intervention improved performance on measures of cognition and perceived cognitive function in three breast cancer survivors who had completed chemotherapy less than 6 months earlier. Thus, treatments that increase physical activity may serve as a low-risk, non-toxic intervention that may not only accelerate cognitive recovery, but may also serve other protective functions for the survivor as well.

In summary, emerging pharmacological and behavioral therapies offer some hope for cancer survivors who are experiencing chemotherapy-induced cognitive impairments. However, although progress is being made, more research is clearly required. Therapies that have broad neurobiological and psychological effects, and that have been shown to be beneficial in other populations with cognitive impairments similar to those reported after chemotherapy, may offer the best hope for cancer survivors in this regard.

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