



# Neurocognitive effects of chemotherapy in adults

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## Summary

**A subset of patients complain that their memory and concentration is not as sharp after receiving treatment for solid tumours. This problem persists in some patients, but there is no correlation between self-reported impairment and cognitive impairment detected on formal neuropsychological testing. Self-reported cognitive impairment is strongly associated with fatigue, anxiety and depression, but these symptoms are not correlated with objective impairment. Cross-sectional studies found that 15–50% of oncology patients have impairment after chemotherapy, with prospective studies reporting that up to 30% of patients have cognitive impairment before chemotherapy. Apart from the treatment of anxiety and depression, there is no proven intervention to prevent long-term impairment or to treat it once it has occurred.**

Key words: cancer, cognitive impairment.

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## Introduction

There is growing evidence that a subset of people who survive cancer suffer cognitive impairment after chemotherapy.<sup>1,2,3,4,5,6</sup> Survivors have coined the terms 'chemobrain' and 'chemofog' to describe this symptom, although recent studies have found that some patients' cognitive impairment may predate the chemotherapy<sup>7</sup>, and hormonal treatment for cancer may also impact on cognitive function.<sup>6,8</sup> Fortunately, the problem is generally subtle and often improves after ceasing chemotherapy. However, for some survivors the symptoms are sustained and can impact significantly on their quality of life and ability to function in their everyday activities.<sup>5</sup>

## Overview of the literature

Most of the cognitive research has been in breast cancer survivors although there are currently ongoing studies investigating cognitive function in patients with colorectal, testicular and prostate cancer. Studies have reported a 15–50% incidence of cognitive impairment in patients who received chemotherapy for solid tumours.<sup>1,2,3,4,5</sup> The studies were mainly cross-sectional in design with no evaluation of cognitive

function before treatment and no longitudinal data. Comparison between studies is hampered by lack of clear definition of cognitive impairment and standardisation of neuropsychological tests used. Despite methodological problems and small sample size, the studies consistently showed a sub-group of people who suffered subtle cognitive impairment, with diffuse yet patchy deficits after chemotherapy. The cognitive domains most consistently impaired were attention, concentration, verbal and visual memory and processing speed.<sup>1,2,3</sup>

A lack of assessment before chemotherapy means that patients who have been functioning at a very high level may have a substantial decline in cognitive function but still formally test within normal limits, so that the true degree of their cognitive decline is not realised. Conversely, cognitive impairment that may have been present before treatment may be incorrectly attributed to chemotherapy.

Longitudinal studies with baseline cognitive assessments have been published in the last few years. These have reported that up to 30% of patients with solid tumours may have cognitive impairment before receiving chemotherapy.<sup>9,10,11</sup>

## Self-reported impairment

Multiple studies have reported no significant association between cognitive impairment after chemotherapy on formal cognitive testing and patients' self-report of their cognitive function. The patient's perception of cognitive impairment is generally worse than that detected by objective assessment.<sup>1,2,3,5,6</sup> The literature indicates consistently that there is a strong association between self-reported cognitive impairment and fatigue, anxiety and depression.<sup>2,6,11</sup> However, no association has been found between these symptoms and objective cognitive impairment.<sup>1,2,3,4,6,9,11</sup> Regardless of the reason for the dissociation between self-reported cognitive impairment and cognitive impairment detected on formal neuropsychological tests, any impairment can cause substantial distress.<sup>5</sup>

## Potential mechanisms

The cause of cognitive impairment in cancer patients after chemotherapy is unknown, but is likely to be multifactorial. Possible mechanisms by which chemotherapy might lead to cognitive dysfunction include:

- direct neurotoxic effects
- oxidative damage

- induced hormonal changes
- immune deregulation with release of cytokines
- blood clotting in small vessels of the central nervous system.

Some patients may have a genetic predisposition to developing cognitive impairment (for example, due to problems with DNA or neuronal repair, changes in neurotransmitter activity or apolipoprotein ε4 genotype).<sup>12</sup> Preliminary results of two studies suggest that elevated cytokines may be associated with increased cognitive dysfunction and fatigue.

### **Chemotherapy regimen and dose-related toxicity**

It is likely that the regimen, the dose and the duration of chemotherapy influence the incidence and severity of cognitive impairment.<sup>12</sup> The different regimens may account for the varying rates of incidence reported in the published studies. In particular, objective rates of impairment have been higher following treatment with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) than after anthracycline-containing regimens in which methotrexate is generally replaced by doxorubicin or epirubicin.

Studies comparing high-dose chemotherapy for breast cancer with standard-dose chemotherapy or no chemotherapy have generally found higher rates of cognitive dysfunction in patients who received high doses. One breast cancer study reported cognitive impairment in 32% of patients after high-dose chemotherapy, 17% after standard doses and in 9% of those who did not have chemotherapy. The odds ratio of cognitive impairment was 8.2 for high-dose chemotherapy when compared with local cancer treatment alone and 3.5 when compared with standard-dose chemotherapy.<sup>2</sup> However, another study found no significant difference between high-dose and standard-dose chemotherapy.<sup>13</sup>

### **Duration of impairment**

The duration of cognitive impairment after anticancer treatment is uncertain. One study of breast cancer and lymphoma found more cognitive dysfunction in patients up to 10 years after chemotherapy, compared to patients who had surgery or radiotherapy without chemotherapy.<sup>1</sup> A Dutch study reported impairment in breast cancer patients at a median of 1.9 years after chemotherapy<sup>3</sup>, but no difference between groups four years after treatment.<sup>14</sup> Longer-term follow-up of longitudinal studies is required to determine the duration of impairment.

### **Treatment of cognitive impairment after chemotherapy**

There are no proven interventions to prevent chemotherapy-associated cognitive impairment or to treat it once it has developed. Randomised controlled trials have investigated the use of prophylactic erythropoietin and methylphenidate,

however all trials were essentially negative. Other small intervention studies are ongoing, but it is difficult to design an intervention until we have a better understanding of mechanisms. At present the mainstay of treatment for patients with self-reported cognitive impairment is to treat any existing depression and anxiety.

Although there is no published research of cognitive rehabilitation programs in cancer survivors, cognitive rehabilitation has been shown to be effective in treating other patient groups with cognitive impairment.<sup>15,16</sup> Different interventions have been developed, but the majority of methods focus on either restoration of a specific cognitive function (for example, attention training) or compensatory training to help patients adapt to the presence of deficits, rather than trying to treat the underlying deficit.<sup>16</sup> A small interim analysis of a behaviour therapy program has shown some potential benefit, however further results are awaited.

### **Conclusion**

Approximately a third of cancer patients have cognitive impairment before receiving chemotherapy and possibly 20–30% have cognitive impairment after chemotherapy. The underlying mechanism of the impairment is currently unknown. Once we have insight into the mechanisms that might cause cognitive impairment, strategies for preventing or minimising chemotherapy-induced cognitive impairment can be devised.

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### Further reading

Vardy J, Rourke S, Tannock IF. Evaluation of cognitive function associated with chemotherapy: a review of published studies and recommendations for future research. *J Clin Oncol* 2007;25:2455-63.

*Conflict of interest: none declared*

### Self-test questions

*The following statements are either true or false (answers on page 27)*

7. The cognitive impairment reported by some patients after chemotherapy may be caused by depression.
8. Erythropoietin prevents the cognitive impairment associated with chemotherapy.

## New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

### Nitric oxide

INOmax (Delpharm)

2 and 10 litre gas cylinders containing 800 parts per million

Approved indication: neonatal respiratory failure

Australian Medicines Handbook Appendix A

Nitric oxide has a physiological role in several systems of the body. One of its actions is to cause vasodilation. When it is administered as a gas it dilates the vessels in the lung. There is little effect on the systemic circulation as nitric oxide is inactivated when it binds to oxyhaemoglobin. This has led to the study of inhaled nitric oxide in conditions where there is pulmonary vasoconstriction.

Pulmonary hypertension can cause hypoxic respiratory failure in neonates. The pulmonary vascular resistance causes

deoxygenated blood to be shunted from the right to the left heart through the foramen ovale. In severe cases extracorporeal membrane oxygenation is needed, but this procedure is very specialised and mortality remains high. If nitric oxide can reduce the pulmonary hypertension it could reduce the need for extracorporeal membrane oxygenation.

The Neonatal Inhaled Nitric Oxide Study (NINOS) involved 235 babies, of at least 34 weeks gestation, who needed ventilation for hypoxic respiratory failure. In about half the cases this resulted from meconium aspiration while 16–18% of the babies had persistent pulmonary hypertension of the newborn. There was a significantly greater improvement in the oxygenation of the babies randomised to receive nitric oxide. Extracorporeal membrane oxygenation was needed by 39% compared with 55% of a control group who received 100% oxygen.<sup>1</sup>