



## Editorial

## Chemotherapy-related cognitive impairment: What we need to know and what we can do



Cognitive changes including chemotherapy-related cognitive impairment (CRCI), are a prevalent side effect of chemotherapy, often colloquially referred to as 'chemo brain' or 'chemo fog.' A prior study reported a CRCI incidence rate of 75% in noncentral nervous system cancer survivors.<sup>1</sup> CRCI has a detrimental impact on the quality of life (QOL) of cancer survivors. However, cognitive function is seldom discussed between cancer survivors and medical professionals, potentially due to a lack of awareness. Patients are less likely to notice CRCI since their primary focus is often on addressing more immediate side effects like nausea, while cognitive issues may go unnoticed.<sup>2</sup> Moreover, medical professionals may not routinely assess CRCI. It is essential for both medical professionals and cancer survivors to comprehend and address CRCI.

### Mechanisms

The principal mechanisms behind CRCI involve oxidative stress and inflammation,<sup>3</sup> which lead to cognitive decline by causing disruptions in the blood–brain barrier, neuroinflammation, neurotransmitter dysfunction, and decreased neurogenesis.<sup>4,5</sup> Cognitive impairment can result from chemotherapy, other cancer treatments, the cancer itself, and noncancer-related factors. For instance, hormonal therapy for breast cancer can suppress estrogen secretion, affecting cognitive function. Estrogen plays a crucial role in promoting the development of synapses in memory-related brain areas and inhibiting the secretion of estrogen that promotes growth and development. Physical and psychological symptoms, including fatigue, sleep disturbances, and depression, are closely linked to cognitive impairment.<sup>6–8</sup> Comorbidity factors such as cardiovascular and neurological diseases, patient-specific variables like age and education level, and genetic predispositions also contribute to cognitive function.

### Symptoms

CRCI symptoms are typically subtle and encompass memory impairments, learning difficulties, executive function deficits, reduced concentration, attention issues, and slower processing speed.<sup>9</sup> Common difficulties reported by cancer survivors include experiencing mental 'cloudiness' or 'fog,' difficulty recalling words and names, challenges in maintaining focus, reduced ability to learn new information, difficulties in managing daily activities, and impaired multitasking capabilities. Cancer survivors' perceptions of cognitive dysfunction can vary based on individual characteristics and circumstances. For example, employed breast cancer survivors under 65 years old may perceive poor workplace performance as cognitive dysfunction,<sup>10</sup> whereas older breast cancer

survivors may perceive their cognitive abilities differently, potentially influenced by their peers' cognitive decline.<sup>11</sup> Oncology nurses should be aware that cancer survivors may interpret their symptoms differently, even if they share similar cognitive issues. CRCI often appears alongside other comorbidities such as fatigue, sleep disorders, and mood disorders.<sup>7</sup> Oncology nurses must recognize CRCI as a symptom cluster within the context of other symptoms and comorbidities.

### Assessment

To assess cognitive function, neuropsychological evaluation, involving comprehensive clinical assessment and standardized cognitive tests, is conducted. A comprehensive clinical assessment considers the patient's complaints, cancer-specific risk factors, comorbidities, medications, relevant laboratory values, and social history.<sup>12</sup> The gold standard for standardized cognitive tests is the mini-mental state examination (MMSE); however, it primarily screens for dementia and is inadequate for detecting CRCI.<sup>13</sup> Neuropsychological tests are designed to assess specific cognitive domains, but they were initially developed to detect significant brain damage and may not be ideal for evaluating cognitive impairment associated with cancer treatment. Neuroimaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), and electroencephalogram (EEG) can be valuable, but their clinical use is hampered by cost and human resource limitations. Moreover, objective evaluations may not align with subjective reports.<sup>14</sup> Therefore, it is recommended to employ both objective assessments and self-report measures like Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) to evaluate cancer treatment-related cognitive concerns, especially in clinical practice where nurses should attentively listen to patients to understand their experiences, perceived symptoms, and daily life impacts.

### Prevention

Efforts to address chemotherapy-related adverse events should be taken proactively. Recommended prevention strategies include mental activities, adequate rest and sleep, regular exercise, and a balanced diet. While no established strategies exist for preventing cognitive dysfunction, recent research has suggested the potential benefits of medications like memantine and probiotic supplements.<sup>15,16</sup> A longitudinal study examining pre-chemotherapy diets proposed that consuming more monounsaturated fat and less saturated fat might protect against cognitive decline.<sup>17</sup> Additionally, a study protocol was published aiming to investigate the effects of exercise interventions.<sup>18</sup> However, it's crucial to consider that some cancer survivors may experience distressing symptoms like gastrointestinal issues and fatigue before and during chemotherapy. Therefore, the development

<https://doi.org/10.1016/j.apjon.2023.100334>

Received 30 October 2023; Accepted 2 November 2023

2347-5625/© 2023 The Author(s). Published by Elsevier Inc. on behalf of Asian Oncology Nursing Society. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

of cognitive decline prevention strategies should consider the diverse conditions of cancer survivors.

### Intervention

According to the Oncology Nursing Society guidelines, cognitive training is an effective intervention, holding a higher level of recommendation than other clinical practices.<sup>19</sup> Recent reviews suggest that cognitive behavioral therapy and brain training show more promise than other interventions, and exercise may also be effective. To enhance intervention effectiveness, understanding the mechanisms underlying their effects is beneficial. Exercise benefits cognitive function in cancer survivors and the general population through complex mechanisms such as promoting brain plasticity, cytokine release, improved mitochondrial health, enhanced brain metabolism, and regulation of gut microflora.<sup>20</sup> A meta-analysis revealed that exercise training reduced inflammatory cytokines like C-reactive protein (CRP) and tumor necrosis factor (TNF) in cancer survivors.<sup>21</sup> Additionally, cognitive training combining exercise and cognitive games increased insulin-like growth factor-1 (IGF-1), which may explain its effects.<sup>22</sup> The efficacy of pharmacological interventions remains uncertain, but as intervention mechanisms become clearer, they may contribute to the development of nonpharmacological and pharmacological approaches.

### Nursing care

Providing information to help cancer survivors comprehend CRCI is crucial. Oncology nurses play a vital role in explaining effective strategies for preventing and managing cognitive impairment and encouraging patients to address their cognitive issues. Oncology nurses also focus on minimizing the impact on daily life and motivate cancer survivors to employ problem-solving and emotion-focused coping strategies. Specific coping strategies include using reminders like memos and smartphones, establishing a consistent physical environment, adhering to a daily routine or schedule, avoiding multitasking, repeating information, seeking help when necessary, and accepting changes in cognitive function. Continuous information and support are key, as CRCI may improve over time.

### Directions for future research and practice

While progress has been made in researching CRCI, several unresolved issues persist. Future directions for research and practice include:

- Elucidating the mechanisms of CRCI
- Identifying predictive factors of CRCI
- Developing valid and reliable CRCI assessment methods
- Understanding CRCI symptoms as part of symptom clusters
- Developing interventions to prevent or alleviate CRCI
- Uncovering the mechanisms underlying intervention effects
- Promoting patient information provision
- Providing educational support to medical professionals
- Enhancing community knowledge and understanding of CRCI

In the future, with a deeper understanding of CRCI, nursing care is expected to be designed to maintain and enhance the QOL of cancer survivors.

### Declaration of competing interest

The author declares no conflict of interest related to study.

### Funding

This study received no external funding.

### Ethics statement

Not required.

### Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tool/services were used during the preparation of this work.

### References

- 1 Lange M, Licaj I, Clarisse B, et al. Cognitive complaints in cancer survivors and expectations for support: results from a web-based survey. *Cancer Med.* 2019;8(5):2654–2663. <https://doi.org/10.1002/cam4.2069>.
- 2 Von Ah D, Habermann B, Carpenter JS, Schneider BL. Impact of perceived cognitive impairment in breast cancer survivors. *Eur J Oncol Nurs.* 2013;17(2):236–241. <https://doi.org/10.1016/j.ejon.2012.06.002>.
- 3 Ren X, Keeney JTR, Miriyala S, et al. The triangle of death of neurons: oxidative damage, mitochondrial dysfunction, and loss of choline-containing biomolecules in brains of mice treated with doxorubicin. Advanced insights into mechanisms of chemotherapy induced cognitive impairment (“chemobrain”) involving TNF- $\alpha$ . *Free Radic Biol Med.* 2019;134:1–8. <https://doi.org/10.1016/j.freeradbiomed.2018.12.029>.
- 4 Murillo LC, Satachan JJ, Albarracín SL. An update on neurobiological mechanisms involved in the development of chemotherapy-induced cognitive impairment (CICI). *Toxicol Rep.* 2023 28;(10):544–553. <https://doi.org/10.1016/j.toxrep.2023.04.015>.
- 5 Fleming B, Edison P, Kenny L. Cognitive impairment after cancer treatment: mechanisms, clinical characterization, and management. *BMJ.* 2023;380:e071726. <https://doi.org/10.1136/bmj-2022-071726>, 15.
- 6 Vearncombe KJ, Rolfe M, Wright M, Pachana NA, Andrew B, Beadle G. Predictors of cognitive decline after chemotherapy in breast cancer patients. *J Int Neuropsychol Soc.* 2009;15(6):951–962. <https://doi.org/10.1017/S1355617709990567>.
- 7 Xu S, Thompson W, Ancoli-Israel S, Liu L, Palmer B, Natarajan L. Cognition, quality-of-life, and symptom clusters in breast cancer: using Bayesian networks to elucidate complex relationships. *Psycho Oncol.* 2018;27(3):802–809. <https://doi.org/10.1002/pon.4571>.
- 8 Oh PJ. Predictors of cognitive decline in people with cancer undergoing chemotherapy. *Eur J Oncol Nurs.* 2017;27:53–59. <https://doi.org/10.1016/j.ejon.2016.12.007>. doi: 10.1200/JCO.2006.07.8303.
- 9 Ahles TA, Saykin A. Cognitive effects of standard-dose chemotherapy in patients with cancer. *Cancer Invest.* 2001;19(8):812–820. <https://doi.org/10.1081/cnv-100107743>.
- 10 Myers JS. Chemotherapy-related cognitive impairment: the breast cancer experience. *Oncol Nurs Forum.* 2012;39(1):E31–E40. <https://doi.org/10.1188/12>.
- 11 Tenda Y, Miyashita M, Yamada A, et al. Older patients' experience of living with cognitive impairment related to hormone therapy for breast cancer: a qualitative study. *Eur J Oncol Nurs.* 2022;57:102115. <https://doi.org/10.1016/j.ejon.2022.102115>.
- 12 Jansen CE. Cognitive changes associated with cancer and cancer therapy: patient assessment and education. *Semin Oncol Nurs.* 2013;29(4):270–279. <https://doi.org/10.1016/j.soncn.2013.08.007>.
- 13 Le Rhun E, Delbeuck X, Lefevre-Plesse C, et al. A phase III randomized multicenter trial evaluating cognition in post-menopausal breast cancer patients receiving adjuvant hormone therapy, 2019 *Breast Cancer Res Treat.* 2015;152(3):569–580. <https://doi.org/10.1007/s10549-015-3493-1>.
- 14 Dhillon HM, Tannock IF, Pond GR, Renton C, Rourke SB, Vardy JL. Perceived cognitive impairment in people with colorectal cancer who do and do not receive chemotherapy. *J Cancer Surviv.* 2018;12(2):178–185. <https://doi.org/10.1007/s11764-017-0656-6>.
- 15 Nakamura ZM, Deal AM, Park EM, et al. A phase II single-arm trial of memantine for prevention of cognitive decline during chemotherapy in patients with early breast cancer: feasibility, tolerability, acceptability, and preliminary effects. *Cancer Med.* 2023;12(7):8172–8183. <https://doi.org/10.1002/cam4.5619>.
- 16 Juan Z, Chen J, Ding B, et al. Probiotic supplement attenuates chemotherapy-related cognitive impairment in patients with breast cancer: a randomised, double-blind, and placebo-controlled trial. *Eur J Cancer.* 2022;161:10–22. <https://doi.org/10.1016/j.ejca.2021.11.006>.
- 17 Crowder SL, Welniak TL, Hoogland AI, et al. Diet quality indices and changes in cognition during chemotherapy. *Support Care Cancer.* 2023;31:75. <https://doi.org/10.1007/s00520-022-07513-5>.
- 18 Kiesel D, Kuzdas-Sallaberger M, Fuchs D, et al. Protocol for the exercise, cancer and cognition - the ECCO-study: a randomized controlled trial of simultaneous exercise during neo/adjuvant chemotherapy in breast cancer patients and its effects on neurocognition. *Front Neurol.* 2022;13:777808. <https://doi.org/10.3389/fneur.2022.777808>.
- 19 Oncology Nursing Society. Symptom interventions and guide lines, Cognitive Impairment. <https://www.ons.org/pep/cognitive-impairment> Accessed 23 October 2023.
- 20 Lu Y, Bu FQ, Wang F, et al. Recent advances on the molecular mechanisms of exercise-induced improvements of cognitive dysfunction. *Transl Neurodegener.* 2023;12(1):9. <https://doi.org/10.1186/s40035-023-00341-5>.

- 21 Khosravi N, Stoner L, Farajivafa V, Hanson ED. Exercise training, circulating cytokine levels and immune function in cancer survivors: a meta-analysis. *Brain Behav Immun.* 2019;81:92–104. <https://doi.org/10.1016/j.bbi.2019.08.187>.
- 22 Myers JS, Pathak HB, He J, et al. Combined exercise and game-based cognitive training intervention: correlative pilot study of neurotrophic and inflammatory biomarkers for women with breast cancer. *Cancer Nurs.* 2022 Dec 1. <https://doi.org/10.1097/NCC.0000000000001175>. Online ahead of print.

Mika Miyashita  
Department of Palliative Care Nursing, Human Health Sciences, Graduate  
School of Medicine, Kyoto University, Kyoto, Japan  
E-mail address: [miyashita.mika.3w@kyoto-u.ac.jp](mailto:miyashita.mika.3w@kyoto-u.ac.jp).