DOI:10.31557/RRO.2025.11.1.1

EDITORIAL

Beyond "Chemo Brain": Advancing Precision Prevention and Personalized Survivorship Care for Chemotherapy-Related Cognitive Impairment

Mostafa Robatjazi[1], Reza Chaman[1], Saeideh Sadat Shobeiri[2]

[1]Non-Communicable Diseases Research Center, Sabzevar University of Medical Sciences, Sabzevar, Iran. [2]Clinical Research Development Unit Vasei Hospital, Sabzevar University of Medical Sciences, Sabzevar, Iran.

Rep Radiother Oncol, **11 (1)**, 1-3

Submission Date: 02/25/2025 Acceptance Date: 03/14/2025

Dear Editor

The remarkable improvement in cancer survival over the past two decades has transformed the focus of oncology from merely prolonging survival to preserving long-term health and quality of life. Among the chronic toxicities affecting cancer survivors, chemotherapy-related cognitive impairment (CRCI), commonly known as "chemo brain," has emerged as one of the most clinically significant yet under-recognized complications. Although CRCI has long been recognized, it continues to receive considerably less clinical attention than cardiotoxicity, peripheral neuropathy, or hematologic toxicities, despite its substantial impact on occupational performance, treatment adherence, social functioning, and overall quality of life [1, 2–7].

Our understanding of CRCI has evolved substantially. Once regarded largely as a subjective complaint, CRCI is now increasingly recognized as a biologically mediated syndrome supported by converging evidence from neuroimaging, molecular, and translational research. These studies demonstrate persistent structural and functional brain alterations associated with neuroinflammation, oxidative stress, mitochondrial dysfunction, impaired neurogenesis, disrupted neurotransmission, and abnormalities in neural connectivity [3, 8, 9].

Importantly, CRCI does not arise from a single pathological process but rather from the complex interaction of multiple interconnected biological mechanisms. Oxidative stress amplifies inflammatory signaling, inflammatory cytokines compromise blood–brain barrier integrity, while neuroglial dysfunction further impairs neuronal repair, synaptic plasticity, and myelin maintenance. This intricate biological network provides a plausible explanation for why therapeutic approaches targeting a single molecular pathway have generally yielded only modest and inconsistent clinical benefits.

This biological heterogeneity also exposes a fundamental limitation of current clinical research. Most intervention trials continue to evaluate individual pharmacological agents in clinically and biologically diverse patient populations, an approach that may partly explain the inconsistent efficacy observed with psychostimulants, cholinesterase inhibitors, antidepressants, NMDA receptor antagonists, and anti-inflammatory therapies. Rather than continuing a "one-size-fits-all" strategy, future research should adopt biologically informed patient stratification and mechanism-based intervention, thereby advancing CRCI management toward the principles of precision survivorship care.

Precision oncology has transformed cancer treatment through molecular characterization of tumors; survivorship care should now adopt an equally individualized approach based on the principles of precision supportive care. Growing evidence indicates that genetic polymorphisms involving APOE, COMT, BDNF, and oxidative stress–related genes, together with demographic characteristics, cognitive reserve, menopausal status, and cumulative treatment exposure, substantially influence individual susceptibility to CRCI [9-29]. Integrating these variables into clinically applicable risk prediction models could enable identification of vulnerable patients before chemotherapy is initiated.

Such an approach would shift CRCI management from reactive treatment to proactive prevention. Patients identified as being at high risk could undergo baseline neurocognitive assessment followed by individualized surveillance and early implementation of preventive strategies, including cognitive rehabilitation, structured exercise, nutritional optimization, sleep management, and psychosocial support throughout the treatment trajectory. Given that established CRCI is often difficult

Corresponding Author:
Dr. Mostafa Robatjazi
Non-Communicable Diseases Research Center, Sabzevar University of Medical Sciences, Sabzevar, Iran.
Email: robatjazi1361@gmail.com

to reverse completely, early identification of susceptible individuals may offer substantially greater clinical benefit than attempting to treat cognitive dysfunction after neural injury has already occurred.

Another emerging concept deserving greater attention is the striking overlap between CRCI and biological aging. Neuroimaging studies have identified similarities between chemotherapy-associated cerebral alterations and accelerated brain aging, including reductions in gray matter volume, white matter disruption, hippocampal dysfunction, and impaired functional connectivity [10-15]. Although it remains uncertain whether chemotherapy directly accelerates biological aging, this hypothesis provides a promising framework for future biomarker discovery and the development of mechanism-based preventive strategies.

Equally encouraging is the growing body of evidence supporting multimodal non-pharmacological interventions. Exercise, mindfulness-based interventions, cognitive rehabilitation, dietary optimization, and acupuncture have demonstrated the potential to improve cognitive function while simultaneously modulating neuroplasticity, neurogenesis, inflammatory signaling, oxidative stress, and mitochondrial function. Rather than being viewed as complementary therapies, these interventions should increasingly be incorporated into comprehensive survivorship care for appropriately selected patients.

Despite substantial advances, several important challenges remain. Standardized diagnostic criteria for CRCI are still lacking, neuropsychological assessment methods remain heterogeneous, and large prospective longitudinal studies integrating neuroimaging, molecular biomarkers, and clinical outcomes are limited. Furthermore, much of the current evidence has been generated in breast cancer populations, whereas survivors of gastrointestinal, gynecologic, hematologic, and other malignancies remain considerably underrepresented.

Emerging technologies including advanced neuroimaging, multi-omics profiling, circulating biomarkers, wearable digital monitoring, and predictive analytics powered by artificial intelligence offer unprecedented opportunities to improve objective risk assessment, facilitate earlier diagnosis, and support individualized intervention strategies.

Ultimately, CRCI should no longer be regarded as an unavoidable consequence of effective chemotherapy but as a potentially preventable and modifiable survivorship outcome. Future survivorship care should therefore shift from reactive management of cognitive symptoms toward proactive risk prediction, early prevention, and personalized intervention. Such a transition would align supportive oncology with the broader principles of precision medicine and may ultimately improve both cognitive outcomes and long-term quality of life for cancer survivors.

References

1. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. Journal of the National Cancer Institute. 2002 01 02;94(1):39-49. https://doi.org/10.1093/jnci/94.1.39
2. Alhowail AH, Aldubayan M. Recent progress in the elucidation of the mechanisms of chemotherapy-induced cognitive impairment. European Review for Medical and Pharmacological Sciences. 2021 09;25(18):5807-5817. https://doi.org/10.26355/eurrev_202109_26799
3. Kim H, Jung S, Kim H, Abraham I. Systematic review of longitudinal studies on chemotherapy-associated subjective cognitive impairment in cancer patients. Psycho-Oncology. 2020 04;29(4):617-631. https://doi.org/10.1002/pon.5339
4. American Cancer Society. Cancer Facts & Figures 2014. Atlanta: American Cancer Society; 2014.
5. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang X, Bannon F, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 2015 03 14;385(9972):977-1010. https://doi.org/10.1016/S0140-6736(14)62038-9
6. Beckjord EB, Reynolds KA, Londen GJ, Burns R, Singh R, Arvey SR, Nutt SA, Rechis R. Population-level trends in posttreatment cancer survivors' concerns and associated receipt of care: results from the 2006 and 2010 LIVESTRONG surveys. Journal of Psychosocial Oncology. 2014;32(2):125-151. https://doi.org/10.1080/07347332.2013.874004 PMID 24364920
7. Mandelblatt JS, Stern RA, Luta G, McGuckin M, Clapp JD, Hurria A, Jacobsen PB, et al. Cognitive impairment in older patients with breast cancer before systemic therapy: is there an interaction between cancer and comorbidity?. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2014 06 20;32(18):1909-1918. https://doi.org/10.1200/JCO.2013.54.2050
8. Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. Cancer. 2004 06 01;100(11):2292-2299. https://doi.org/10.1002/cncr.20272
9. Dos Santos M, Hardy-Léger I, Rigal O, Licaj I, Dauchy S, Levy C, Noal S, et al. Cognitive rehabilitation program to improve cognition of cancer patients treated with chemotherapy: A 3-arm randomized trial. Cancer. 2020 Dec 15;126(24):5328-5336. https://doi.org/10.1002/cncr.33186
10. Davies MR, Greenberg Z, Vuurden DG, Cross CB, Zannettino ACW, Bardy C, Wardill HR. More than a small adult brain: Lessons from chemotherapy-induced cognitive impairment for modelling paediatric brain disorders. Brain, Behavior, and Immunity. 2024 01;115:229-247. https://doi.org/10.1016/j.bbi.2023.10.013
11. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. Nature Reviews. Cancer. 2007 03;7(3):192-201. https://doi.org/10.1038/nrc2073
12. Rummel NG, Chaiswing L, Bondada S, St Clair DK, Butterfield DA. Chemotherapy-induced cognitive impairment: focus on the intersection of oxidative stress and TNFα. Cellular and molecular life sciences: CMLS. 2021 Oct;78(19-20):6533-6540. https://doi.org/10.1007/s00018-021-03925-4
13. Bagnall-Moreau C, Chaudhry S, Salas-Ramirez K, Ahles T, Hubbard K. Chemotherapy-Induced Cognitive Impairment Is Associated with Increased Inflammation and Oxidative Damage in the Hippocampus. Molecular Neurobiology. 2019 Oct;56(10):7159-7172. https://doi.org/10.1007/s12035-019-1589-z
14. Shi D, Huang Y, Lai CSW, Dong CM, Ho LC, Wu EX, Li

Q, et al. Chemotherapy-Induced Cognitive Impairment Is Associated with Cytokine Dysregulation and Disruptions in Neuroplasticity. Molecular Neurobiology. 2019 03;56(3):2234-2243. https://doi.org/10.1007/s12035-018-1224-4
15. McDonald BC, Saykin AJ. Alterations in brain structure related to breast cancer and its treatment: chemotherapy and other considerations. Brain Imaging and Behavior. 2013 Dec;7(4):374-387. https://doi.org/10.1007/s11682-013-9256-x
16. Wardill HR, Mander KA, Van Sebille YZA, Gibson RJ, Logan RM, Bowen JM, Sonis ST. Cytokine-mediated blood brain barrier disruption as a conduit for cancer/chemotherapy-associated neurotoxicity and cognitive dysfunction. International Journal of Cancer. 2016 Dec 15;139(12):2635-2645. https://doi.org/10.1002/ijc.30252
17. Simó M, Rifà-Ros X, Rodriguez-Fornells A, Bruna J. Chemobrain: a systematic review of structural and functional neuroimaging studies. Neuroscience and Biobehavioral Reviews. 2013 09;37(8):1311-1321. https://doi.org/10.1016/j.neubiorev.2013.04.015
18. Chen Y, Jungsuwadee P, Vore M, Butterfield DA, St Clair DK. Collateral damage in cancer chemotherapy: oxidative stress in nontargeted tissues. Molecular Interventions. 2007 06;7(3):147-156. https://doi.org/10.1124/mi.7.3.6
19. Dietrich J, Han R, Yang Y, Mayer-Pröschel M, Noble M. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. Journal of Biology. 2006;5(7):22. https://doi.org/10.1186/jbiol50
20. Gibson EM, Nagaraja S, Ocampo A, Tam LT, Wood LS, Pallegar PN, Greene JJ, et al. Methotrexate Chemotherapy Induces Persistent Tri-glial Dysregulation that Underlies Chemotherapy-Related Cognitive Impairment. Cell. 2019 01 10;176(1-2):43-55.e13. https://doi.org/10.1016/j.cell.2018.10.049
21. Geraghty AC, Gibson EM, Ghanem RA, Greene JJ, Ocampo A, Goldstein AK, Ni L, et al. Loss of Adaptive Myelination Contributes to Methotrexate Chemotherapy-Related Cognitive Impairment. Neuron. 2019 07 17;103(2):250-265.e8. https://doi.org/10.1016/j.neuron.2019.04.032
22. Park H, Kim C, Kwak H, No M, Heo J, Kim T. Physical exercise prevents cognitive impairment by enhancing hippocampal neuroplasticity and mitochondrial function in doxorubicin-induced chemobrain. Neuropharmacology. 2018 05 01;133:451-461. https://doi.org/10.1016/j.neuropharm.2018.02.013
23. Shi D, Dong CM, Ho LC, Lam CTW, Zhou X, Wu EX, Zhou Z, Wang X, Zhang Z. Resveratrol, a natural polyphenol, prevents chemotherapy-induced cognitive impairment: Involvement of cytokine modulation and neuroprotection. Neurobiology of Disease. 2018 06;114:164-173. https://doi.org/10.1016/j.nbd.2018.03.006
24. Zuniga KE, Moran NE. Low Serum Carotenoids Are Associated with Self-Reported Cognitive Dysfunction and Inflammatory Markers in Breast Cancer Survivors. Nutrients. 2018 08 17;10(8):1111. https://doi.org/10.3390/nu10081111
25. Orchard TS, Gaudier-Diaz MM, Weinhold KR, Courtney DeVries A. Clearing the fog: a review of the effects of dietary omega-3 fatty acids and added sugars on chemotherapy-induced cognitive deficits. Breast Cancer Research and Treatment. 2017 02;161(3):391-398. https://doi.org/10.1007/s10549-016-4073-8
26. Derry HM, Jaremka LM, Bennett JM, Peng J, Andridge R, Shapiro C, Malarkey WB, et al. Yoga and self-reported cognitive problems in breast cancer survivors: a randomized controlled trial. Psycho-Oncology. 2015 08;24(8):958-966. https://doi.org/10.1002/pon.3707
27. Reid-Arndt SA, Matsuda S, Cox CR. Tai Chi effects on neuropsychological, emotional, and physical functioning following cancer treatment: a pilot study. Complementary Therapies in Clinical Practice. 2012 02;18(1):26-30. https://doi.org/10.1016/j.ctcp.2011.02.005
28. Zeng Q, Li C, Yu T, Zhang H. Comparative Effects of Exercise Interventions and Mindfulness-Based Interventions for Cognitive Impairment and Quality of Life in Breast Cancer Survivors During or After Cancer Treatment: A Systematic Review and Bayesian Network Meta-analysis. American Journal of Physical Medicine & Rehabilitation. 2024 09 01;103(9):777-788. https://doi.org/10.1097/PHM.0000000000002531
29. Alwi SMS, Narayanan V, Din NC,Taib NAM. Cognitive Rehabilitation Programs for Survivors of Breast Cancer Treated With Chemotherapy: A Systematic Review. Rehabil Oncol. 2021;39:155-67. 2026 06 15;. https://doi.org/10.1097/01.REO.0000000000000268