

Arambawattage N.S.A.

CLINICAL BURDEN OF POST CHEMOTHERAPY MORBIDITY: LONG TERM COGNITIVE IMPAIRMENT IN CANCER SURVIVORS

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The increasing population of cancer survivors has shifted the oncological approach, moving past a singular focus on tumor eradication towards a comprehensive analysis of long term physiological health. Chemotherapy and other systemic therapies induce long term alterations in cellular, vascular, metabolic, and neuro-immune pathways that extend far beyond the period of active treatment. Clinically, these disruptions present as a collection of chronic, multi-systemic morbidities—most notably cardiovascular dysfunction, persistent neuropathy, and metabolic instability. Understanding these late effects through the lens of pathological physiology is essential for advancing survivorship care and eliminating long term disability. While chemotherapeutic agents effectively target malignancies, they inadvertently trigger a cascade of mitochondrial damage and sustained oxidative stress. This cellular injury releases damage-associated molecular patterns (DAMPs), fueling a state of chronic, low grade systemic inflammation. Ultimately, this persistent inflammatory and oxidative signaling serves as the primary biological driver for long term complications, ranging from cardiovascular dysfunction to premature frailty. Among the most consequential late effects is cancer-related cognitive impairment, commonly referred to as “chemobrain” or “brain fog.”

This phenomenon emerges from a destructive interaction between systemic vascular decay and chronic neuro-inflammation. At the foundation of this decline is a profound disruption of the neurovascular unit; chemotherapy accelerates microvascular aging by impairing endothelial nitric oxide signaling and increasing capillary permeability. This vascular senescence or premature aging, compromises the blood-brain barrier, allowing a tide of systemic pro-inflammatory cytokines—specifically IL-1 β , IL-6, and TNF- α to infiltrate the central nervous system. Such infiltration triggers chronic microglial activation and astrogliosis, creating a neurotoxic environment that suppresses hippocampal neurogenesis and disrupts neurotransmitter homeostasis. Simultaneously, chemotherapy-driven oxidative stress causes mitochondrial dysfunction, further compromising the energetic demands of neural transmission. These combined mechanisms ultimately end in measurable structural alterations, including diminished white matter integrity and disrupted connectivity within prefrontal and hippocampal networks, manifesting clinically as persistent deficits in executive function, memory, and processing speed that may endure for years post-treatment. Other side effects such as chemotherapy-induced ovarian failure, thyroid dysfunction, and insulin resistance also affect hippocampal plasticity, cerebral perfusion, and neurochemical balance. These physiological changes interact with psychological factors such as sleep disturbance, anxiety, and depression, creating a complex, self reinforcing cycle of cognitive dysfunction.

Clinically, CRCI has significant implications for daily functioning transforming high-functioning individuals into patients who struggle with the basic executive load of modern life. This shift represents a fundamental reduction in neurocognitive efficiency; while survivors may perform within normal ranges on static neuropsychological tests, they often find it challenging when faced with real world complexity. Due to damaged white matter integrity and impaired neurovascular coupling, the brain must exert a disproportionate amount of metabolic effort, leading to difficulty in multitasking, slowed information processing, reduced occupational performance, and challenges managing complex responsibilities. For many survivors, the burden of cognitive and physical late effects can rival the functional impact of the original malignancy, stressing the need for comprehensive survivorship care.