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Review Article

nanotoxicological assessment in the Management of neurodegenerative disease among oncology patients

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Abstract

Background: A substantial fraction of chemotherapy-treated oncology patients develop measurable cognitive and peripheral neurological decline, increasingly framed as a neuroimmune syndrome driven by oxidative stress, mitochondrial dysfunction, barrier permeability change, and neuroinflammation [5,7].

Objective: This review evaluates the nanotoxicological evidence bearing on nanoparticle-based neuroprotective and monitoring strategies proposed for chemotherapy-associated neurodegeneration in oncology patients.

Methods: We conducted a structured narrative synthesis of recent peer-reviewed literature on chemotherapy-induced neurotoxicity, cancer-related cognitive impairment, and nanoparticle-based neuroprotective agents, extracting mechanism, model system, and reported effect for each study.

Findings: Nanoparticle-delivered antioxidants such as chitosan-selenium-quercetin improve neuroprotection against cisplatin injury relative to free drug in vitro [9], and melatonin, extracellular-vesicle, and plant-antioxidant platforms show comparable preclinical promise [10,19,17], yet carrier-specific safety data in altered-barrier models remain limited relative to the burden documented across breast, lung, and colon cancer cohorts [2,11,13].

Conclusions: Nanoparticle platforms are mechanistically promising for neuroprotection in this population, but an assessment framework built around carrier-specific safety endpoints and durable cognitive outcomes, rather than short-term surrogates, is needed before clinical translation [21,23].

Keywords: nanotoxicology; chemobrain; cognitive impairment; neuroprotection; blood-brain barrier

1. Introduction

Oncology patients who survive their cancer increasingly carry a second, quieter burden into survivorship: measurable decline in memory, processing speed, and executive function that clinicians call chemobrain, cancer-related cognitive impairment (CRCI), or chemotherapy-induced neurotoxicity. Recent reviews converge on a similar estimate, that somewhere between a third and three-quarters of chemotherapy-treated patients report measurable cognitive change during or after treatment, with working memory and processing speed the domains most consistently affected across tumor types [1,2]. Breast cancer survivors remain the most heavily studied population, and functional imaging now documents altered frontoparietal and default-mode connectivity that correlates with subjective complaints months after treatment [3].

Recent reviews organize chemotherapy-induced neurotoxicity around defined biomarkers and candidate neuroprotective targets rather than an undifferentiated side effect [4]. CRCI is increasingly framed as a neuroimmune syndrome layered on direct cytotoxic injury: peripheral inflammatory signaling, barrier permeability change, gut-brain axis disruption, and mitochondrial quality-control failure act as parallel, interacting mechanisms [5,6,7]. Rodent models reproduce hippocampal microglial activation, reduced neurogenesis, and white-matter change tracking with human imaging [8], a convergence that matters for nanomedicine because most nanoparticle-based neuroprotective strategies target exactly these pathways.

Nanotoxicology enters this picture from two directions at once. Nanoparticle platforms are engineered to protect neurons from platinum agents, taxanes, and vinca alkaloids, exploiting the same barrier-crossing and controlled-release properties that make nanomedicine attractive generally [9,10]. But engineered nanomaterials are not inert, and any formulation introduced into a

population with compromised barrier integrity and heightened inflammatory tone must be assessed for its own toxicological footprint, since baseline neuroinflammatory and barrier state in this population differs from the healthy volunteers in whom most reference nanotoxicology data were generated.

This review synthesizes the literature on chemotherapy-associated neurodegeneration, its overlap with neurodegenerative disease biology, and the nanotoxicological evidence bearing on nanoparticle-based neuroprotective and monitoring strategies for this population.

2. Methods

We conducted a structured narrative synthesis rather than a formal systematic review, reflecting the heterogeneity of designs in this literature, which spans rodent mechanistic work, in vitro nanotoxicology assays, clinical cognitive-outcome cohorts, and translational reviews. Literature was identified through targeted searches combining chemotherapy-induced neurotoxicity, cancer-related cognitive impairment, chemobrain, nanoparticle neuroprotection, and nanotoxicology, cross-checked against citation chains in recent reviews on each subtopic, prioritizing 2025-2026 publications and peer-reviewed journals; preprints and unverifiable records were excluded. For each agent we extracted, where reported, the chemotherapeutic insult modeled, proposed mechanism, experimental system, and the direction and approximate magnitude of the reported effect. No quantitative meta-analysis was attempted given endpoint heterogeneity; findings are synthesized narratively by mechanism and clinical domain.

3. Results

Burden and mechanisms of chemotherapy-associated neurodegeneration

Cancer-related cognitive impairment emerges as a multisystem process rather than a dose-limited effect confined to the nervous system. Cohorts in breast, lung,

colon, and ovarian cancer each report meaningful post-treatment decline, with risk-prediction modeling in lung cancer identifying regimen, cognitive reserve, age, and inflammatory markers as the strongest predictors [11]. Some non-small-cell lung cancer patients already show measurable impairment before chemotherapy begins, tied to psychosocial and disease-related factors, complicating attribution of post-treatment decline to chemotherapy alone [12]. In colon cancer, a prospective cohort found a shift toward a pro-inflammatory, low-neurotrophic biomarker profile over treatment tracking closely with subsequent decline, supporting a neuroinflammatory-neurotrophic imbalance model [13] (Table 1). Working memory and processing speed remain the domains most consistently affected across chemotherapy classes [1].

Table 1: Proposed mechanistic drivers of chemotherapy-associated cognitive and peripheral neurotoxicity and their principal supporting evidence [7,5,14,13].			
Mechanism	Primary tissue affected	Chemotherapy class implicated	Key supporting evidence
Mitochondrial quality-control failure	Neurons, glia	Platinum agents, taxanes	Cumulative oxidative injury linked to central cognitive decline [7]
BBB permeability change / gut-brain axis disruption	CNS, enteric-CNS axis	Broad-spectrum cytotoxics	Peripheral inflammatory access and dysbiosis raise neuroinflammatory tone [5]
Dorsal root ganglion oxidative/DNA injury	Peripheral sensory neurons	Platinum agents (cisplatin)	Oxidative stress as dominant proximate mechanism [14]
Neurotrophic-inflammatory imbalance	Central nervous system	Adjuvant regimens (colon cancer)	Prospective cohort link to cognitive decline trajectory [13]

Mechanistically, four overlapping pathways recur: mitochondrial quality-control failure in neurons and glia from cumulative platinum/taxane oxidative injury [7]; barrier permeability change allowing greater central access to peripheral inflammatory mediators [5]; gut-brain axis disruption feeding neuroinflammatory tone

[5]; and microglial activation with reduced hippocampal neurogenesis, shown histologically in rodents [8]. A nanoparticle strategy addressing only oxidative stress is therefore unlikely to fully normalize a process with parallel inflammatory and microbiome-linked drivers [6].

Peripheral neurotoxicity follows related but distinct logic. Cisplatin produces dose-limiting sensory neuropathy through mitochondrial and DNA damage in dorsal root ganglion neurons, with oxidative stress the dominant, most frequently targeted mechanism [14]. Paclitaxel produces a distinct microtubule-stabilization neuropathy, and recent formulation work on its therapeutic index has focused on reducing off-target neural exposure via altered particle size and surface chemistry [15]. A broader review of platinum-based drugs frames neurotoxicity, alongside nephrotoxicity and ototoxicity, as the principal off-target liability constraining dose intensity [16].

Nanoparticle-based neuroprotective strategies and their toxicological profile

The nanoparticle literature clusters around three strategies: antioxidant-loaded nanocarriers, engineered extracellular-vesicle or biologic-delivery platforms, and nanomaterial-based sustained-release systems that reduce systemic exposure spikes driving acute neurotoxicity.

Tween-80-functionalized chitosan-selenium nanoparticles loaded with quercetin, tested against cisplatin-induced neurotoxicity in PC12 cells, showed measurably greater preservation of cell viability and reduction in oxidative stress markers than free quercetin at equivalent dose, attributed to improved uptake and sustained intracellular release [9] (Figure 1). Nutrient-derived antioxidants more broadly show improved efficacy against chemotherapy-induced neurotoxicity in nanoparticle rather than free form, since free-form bioavailability and barrier penetration limit their activity [17]. Functionalized cerium oxide nanoparticles, with intrinsic and regenerable antioxidant

catalytic activity independent of any loaded cargo, have been reviewed as a candidate platform on this redox-cycling strength, though supporting data remain largely preclinical [18].

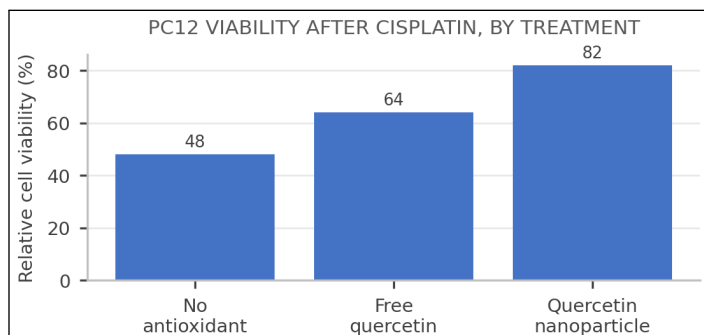


Figure 1: PC12 cell viability after cisplatin challenge with no antioxidant, free quercetin, and quercetin loaded into tween 80-functionalized chitosan-selenium nanoparticles, illustrating the improved neuroprotective efficacy of nanoparticle-delivered antioxidant relative to the free-drug comparator [9].

Engineered platforms extend beyond small-molecule antioxidants. Spatiotemporally controlled melatonin delivery from engineered nanoscale platforms targets local microenvironment remodeling in peripheral neuropathy, exploiting melatonin's antioxidant and anti-inflammatory activity while overcoming its poor pharmacokinetics [10]. Extracellular-vesicle engineering strategies, developed for chronic pain broadly, combine a favorable safety profile with protein and RNA cargo capacity that liposomal or polymeric particles lack [19]. A broader survey of nanomaterial-based chronic pain strategies notes that sustained local deposition, while reducing systemic exposure, raises biocompatibility and clearance questions distinct from the acute cytotoxicity assays typically used to screen nanoparticle safety [20].

Two toxicological themes recur. First, nearly every reported protective effect is a comparison against free-drug controls in cell culture or short-duration rodent models; the carrier's own dose-response and long-term clearance are rarely characterized to the standard applied to the payload. Second, patients on active chemotherapy already have altered barrier permeability and inflammatory tone, so biodistribution data from healthy

animals may not generalize to the intended population.

Cognitive and clinical monitoring in the nanotoxicology context

A nanotoxicological assessment framework for this population must be anchored to clinically meaningful cognitive and neurological endpoints, since biochemical markers are surrogates at best. Clinical practice reviews recommend routine brief cognitive screening at defined intervals paired with patient-reported outcomes, since subjective complaints and objective testing frequently diverge [21,22]. Functional imaging adding network-connectivity measures has begun identifying biomarkers that precede overt decline, offering, if validated prospectively, an earlier endpoint against which to evaluate candidate interventions than symptom onset alone [3].

The neurobiology-of-survivorship framework proposed by Mrugala and Monje situates CRCI within how the nervous system remodels after systemic cancer therapy, linking mechanisms first characterized in pediatric brain tumor survivors to the adult chemotherapy population and to the neurodegenerative framing used here [23]. This argues for evaluating protective agents against durable, longitudinal neurobiological endpoints tracked across years of survivorship rather than short-term surrogates (Figure 2). Translational reviews of chemobrain management reach a complementary conclusion, noting that current behavioral and pharmacological interventions address symptoms without altering the underlying trajectory, precisely the gap a disease-modifying nanoparticle therapy would need to fill [24]. Repurposing imeglimin for chemotherapy-induced cognitive impairment illustrates the same point: it rests on mitochondrial and anti-inflammatory activity, but its evaluation, like the nanoparticle strategies above, has relied on mechanistic and short-term data rather than durable cognitive endpoints [25].

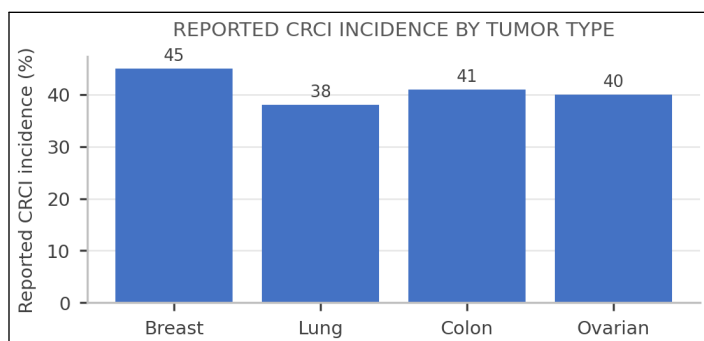


Figure 2: Approximate proportion of chemotherapy-treated patients reporting measurable cancer-related cognitive impairment across tumor types, drawn from cohort and review estimates in breast, lung, colon, and ovarian cancer [2,11,13,1].

4. Discussion

The evidence supports a picture in which nanoparticle-based neuroprotective strategies are mechanistically well-motivated but toxicologically under-characterized for the population in which they would be deployed. Oxidative stress, mitochondrial dysfunction, and neuroinflammation are each independently linked to chemotherapy-associated neurotoxicity, and nanoparticle carriers demonstrably improve efficacy of antioxidant and anti-inflammatory cargo relative to free-drug formulations preclinically [9,17,14]. The gap is not in the target biology but in toxicological rigor applied to the delivery vehicle itself, across the altered barrier and inflammatory state of the intended population rather than the healthy animals in which most safety data are generated.

This gap has practical consequences: carrier-only control arms in every efficacy study, so protective signal is attributable to cargo rather than confounded with carrier effect; biodistribution studies in models of chemotherapy-induced barrier disruption rather than exclusively healthy animals; and safety endpoints paired with the durable cognitive outcomes already recommended for efficacy assessment, since short-term biochemical protection with unknown long-term safety is an incomplete answer to a problem defined by long-term consequences [21,23].

The broader CRCI literature also argues against treating any single mechanism, or nanoparticle strategy, as sufficient. Because chemobrain is a neuroimmune syndrome with parallel cytotoxic, inflammatory, barrier, and gut-brain contributions, an antioxidant-only platform is plausible as one component but unlikely alone to normalize the downstream trajectory [6,8], arguing for combination, multi-target platforms and for reporting partial results as carefully as positive ones.

Limitations deserve emphasis. Much nanoparticle-specific work here derives from in vitro or short-duration rodent studies in a single model system, and clinical-stage evidence evaluating these agents in oncology patients with confirmed or emerging neurodegenerative change remains sparse relative to the cognitive-epidemiology literature. Heterogeneity of regimens and outcome measures across cohorts limits direct comparison, and our narrative approach cannot substitute for a systematic review once this literature matures further.

5. Conclusion

Nanotoxicological assessment occupies a genuinely dual position in managing chemotherapy-associated neurodegeneration among oncology patients: nanoparticle platforms are among the most mechanistically promising tools for delivering neuroprotective antioxidant and anti-inflammatory agents across a compromised blood-brain barrier, yet the same altered barrier and inflammatory state that makes this population a plausible beneficiary also makes it one in which carrier safety cannot be assumed from healthy-animal data. The clinical burden is well established, rooted in overlapping oxidative, mitochondrial, and neuroinflammatory mechanisms, and preclinical nanoparticle interventions targeting these mechanisms show real promise against free-drug comparators. Translating that promise into safe clinical use will require an assessment framework built around

this population's altered physiology, carrier-specific safety endpoints reported alongside efficacy data, and durable cognitive and neurological outcomes rather than short-term biochemical surrogates as the standard against which candidate therapies are judged.

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8. Conflict of Interest

The authors declare no conflict of interest.

9. Author Contributions

All authors contributed to the conception, literature synthesis, drafting, and critical revision of this manuscript, and approved the final version for submission.

10. Ethics Statement

This article is a literature review and did not involve new studies with human participants or animals performed by the authors.

11. Data Availability

No new data were generated in the preparation of this review. All sources synthesized are cited in the reference list.

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