Memantine and Exercise for Cancer-Related Cognitive Impairment During Chemotherapy for Breast Cancer

Submitter Zev Nakamura

Affiliation University of North Carolina at Chapel Hill

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Methodological Issue Being Addressed This three-arm randomized controlled trial (RCT) tests the combination of the NMDA receptor antagonist memantine and a cancer exercise program (MEM+EX) for cancer-related cognitive impairment (CRCI) among patients receiving chemotherapy for breast cancer.

Multicomponent, Mechanistically-Focused Intervention in a Complex Clinical Context. CRCI likely results from dysregulation across systemic pathways, including neuroinflammation and neurotrophin depletion. Prior trials have focused on monotherapeutic, untargeted interventions with limited benefits. Our trial integrates inflammatory biomarkers and neurotrophin signaling and intervenes during chemotherapy, before irreversible changes occur.

Rich Cognitive Profiling. CRCI typically presents with subtle deficits on neuropsychological testing and discrepancies between performance-based and patient-reported cognition. To capture functioning comprehensively, we include multimodal assessments: neuropsychological testing, patient-report, and cognitive neuroscience tasks.

Data Reduction Techniques. To address heterogeneity, minimize Type I error, and enhance power in a modest sample, cognitive and biomarker outcomes will be aggregated into composite domain indices using validated gatekeeper approaches [1].

Introduction CRCI affects up to 75% of breast cancer patients and remains one of the most distressing treatment-related complications. CRCI thought leaders have identified interventions integrating mechanistic biomarkers have as a critical gap and essential to advance the field [2].

Advantages and Disadvantages of the Novel Design.
Our three-arm RCT is an efficient design and well suited for CRCI, which is heterogeneous in mechanism and phenotype. However, our multiple active components may complicate interpretation of individual component effects. While composite study endpoints are less directly translatable to clinical practice, they are ideal to reduce the influence of isolated positive findings and improve sensitivity to domain-level effects.

Methods Ninety patients with stage I–III breast cancer will be randomized 1:1:1 to MEM+EX,

memantine, or placebo before chemotherapy cycle 3. Cognition, frailty, and biomarkers will be assessed at baseline, week 4, post-intervention (1-month post-chemotherapy), and 6-month follow-up.
We will determine feasibility and acceptability (Aim 1); evaluate preliminary efficacy of MEM+EX and memantine on cognition (Aim 2) and biomarkers (Aim 3); and explore frailty as a treatment moderator (Aim 4).

We will use general linear models, adjusting for key covariates. Cognitive composites (attention/executive, learning/memory) will be derived from the sum of z-scores of individual subtests assigned to domains through factor analysis; effects on BDNF and an inflammatory composite of TNF-α, IL-6, and CRP will be evaluated in parallel models.

Results Enrollment began in May 2025. We will present baseline clinical, cognitive, frailty, and neurobehavioral data at the meeting (20 participants anticipated). Given the preliminary nature of this study, effect size calculations will be performed using the Omnibus F-test to detect any difference between study arms. We are powered to detect an overall Cohen's d of 0.77. We anticipate that the MEM+EX and memantine arms will demonstrate less cognitive decline and more favorable biomarker profiles compared to placebo with stronger effects in the MEM+EX arm.

Conclusion Our multicomponent intervention with multimodal cognitive profiling and gatekeeper-based analyses, addresses key methodological challenges in CRCI trials. This approach offers a scalable model for testing complex interventions where multidomain outcomes and limited samples constrain interpretability

Co-Authors

Zev Nakamura[1], Patrick Smith[1], Hyman Muss[1], Tim Ahles[2], Bradley Gaynes[1]

[1] University of North Carolina at Chapel Hill

[2] Memorial Sloan Kettering Cancer Center

Keywords

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Guidelines I have read and understand the Poster Guidelines

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