

STUDY PROTOCOL

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Memantine to preserve memory and neurocognition following craniospinal irradiation (MEMENTO): a phase 3 randomized controlled trial

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Abstract

Introduction Craniospinal irradiation (CSI) forms an integral role in the management of primary brain tumors like embryonal tumors (medulloblastoma), non-seminomatous germ cell tumors, metastatic ependymoma, etc. The cranial component with radiation of whole brain and boost can lead to decline in neurocognitive function. Memantine is an NMDA receptor antagonist with an established role in reducing radiation-induced neurocognitive decline in patients treated with whole brain radiotherapy, but the benefit in pediatric and adults treated with CSI remains unclear.

Methods This is a phase 3 open-label, randomized controlled trial. Pediatric and young adults (5 to 39 years) treated with CSI will be eligible for the study. Patients will be randomized in 1:1 accounting for stratification factors such as age, CSI dose, location of tumor boost, and use of chemotherapy. Patients in the experimental arm will receive memantine 5 mg once daily for 1 week, 5 mg twice daily for 1 week, and finally escalated to 10 mg twice daily for 6 months. The primary endpoint will be cognitive deterioration-free survival (CDFS) at 2 years, with secondary endpoints being safety and compliance of memantine, slope of decline of neurocognitive scores, and survival. To demonstrate the improvement of 2-year CDFS of 75% in memantine arm compared to 50% in standard arm, 84 patients need to be evaluated (alpha 0.05 and power 80%). Considering an attrition of 20%, a total of 101 patients will be randomized.

Discussion If trial results are positive memantine will be established as a new standard of care to be used with CSI.

Trial registration The trial is registered on ClinicalTrials.gov (study identifier NCT06275035) and Clinical Trial Registry India (CTRI/2024/02/062273).

Keywords Craniospinal irradiation, Medulloblastoma, Memantine, Memory, Neurocognition

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Introduction

Craniospinal irradiation (CSI) involving radiation (RT) of the entire neuraxis (brain and spine), along with tumor-bed boost with or without adjuvant systemic chemotherapy, is the contemporary standard of care in the management of medulloblastoma and other primitive embryonal tumors of the central nervous system (CNS) [1, 2]. Also, CSI forms an integral role in the management of certain germ cell tumors, metastatic ependymomas, and other metastatic CNS tumors. With high rates of cure witnessed in many tumor subgroups, the cranial component of CSI can lead to neurocognitive decline. Radiation-induced dementia in survivors of brain tumors impacts the quality of life significantly, leading to the search for appropriate strategies to improve memory and neurocognitive function using advanced radiation techniques (e.g., proton beam therapy) or medical therapy (e.g., memantine, metformin) [3–5].

Memantine is an uncompetitive N-methyl D-Aspartate receptor antagonist and reduces glutamate excitotoxicity [6, 7]. Memantine has been proven to effectively mitigate cognitive decline induced by cranial RT in patients with brain metastasis [4]. However, the role of memantine in preventing or reducing neurocognitive decline in patients with primary brain tumors treated with CSI (including the pediatric age group) remains to be established. The current study aims to investigate the role of memantine in the protection of neurocognitive function in patients to be treated with CSI.

Study methodology

Study design/population

This phase 3 open-label randomized controlled trial is being conducted in a single institute (Tata Memorial Centre, Mumbai). Pediatric patients >5 years and young adults with a diagnosis of primary brain tumor planned for CSI as standard of care will be considered eligible for the study. The study protocol has been duly reviewed and approved by the institutional ethics committee (vide IEC Project No 4235), and periodic monitoring is to be undertaken by the data safety and monitoring committee. The trial is registered on ClinicalTrials.gov (study identifier NCT06275035) and Clinical Trial Registry India (CTRI/2024/02/062273). The study eligibility criteria are as follows:

Inclusion criteria

1. Age at irradiation: 5 to 39 years.
2. Planned for CSI (with or without boost dose) with or without systemic chemotherapy.
3. Informed consent or assent taken.
4. Karnofsky Performance Status/Lansky Performance Status ≥ 60 .

Exclusion criteria

1. Patients undergoing re-irradiation.
2. Prior exposure to memantine.
3. Inability to undergo neurocognitive test.

Study intervention

After meeting study eligibility, written consent forms and assent will be obtained from all the patients and their caregivers as applicable. Patients will be randomized to 1:1 to the experimental arm (memantine) and control arm via computerized software using a permuted block design. The stratification factors are as follows:

1. Age during irradiation: (5 to ≤ 12 vs. $> 12 < 18$ vs. ≥ 18) years
2. CSI dose (≤ 30 vs. > 30) Gy
3. Boost location (supratentorial boost vs. no supratentorial boost)
4. Chemotherapy (yes vs. no)

Randomization will be done before starting radiotherapy. Once randomization is done, patients in the experimental arm (memantine) will start the medication on the day of radiation starting. The starting dose of memantine will be 5 mg once daily at bedtime for 1 week, followed by 5 mg twice daily for 1 week, and finally increased to the full dose of 10 mg twice daily for 6 months. Patients will continue on radiation and chemotherapy (when indicated) as per schedule without any influence of memantine in the experimental arm. All patients in the study will undergo neurocognitive evaluation using age-appropriate tests by psychologists, including the Wechsler Adult Intelligence Scale (WAIS), and Wechsler Intelligence Scale for Children (WISC). The Verbal Intelligence Quotient (VQ), Performance Intelligence Quotient (PQ), and Full-Scale Intelligence Quotient (FSIQ) will be calculated. Clinically meaningful neurocognitive decline will be considered as a decline of 5 points in any of FSIQ, VQ, or PQ, from the baseline (pre-radiation). The time points for neurocognitive evaluation will be pre-radiation (baseline), 6 months post-radiation, 1-year post-radiation, and annually after that for 5 years from radiation. The study endpoints are summarized in Table 1.

All the patients will be treated with radiation (CSI and boost) as per standard institutional practice based on tumor histology and risk stratification without any influence of the current study on radiation protocols. Baseline workup investigations for diagnosis and treatment plan will be undertaken as per standard practice, which will include histopathological evaluation along with molecular evaluation, blood and cerebrospinal fluid analysis, imaging with magnetic resonance imaging (MRI) brain tumor protocol, spine screening, and functional

Table 1 Different endpoints for the study

Primary endpoint	Cognitive-deterioration-free survival at 2 years; defined by a drop of 5 points in any of FSIQ, VQ, or PQ compared to baseline (pre-radiation) on WAIS/WISC.
Secondary endpoints	1. The slope of decline of FSIQ and other domains with time. 2. Overall survival (OS) and progression-free survival (PFS). 3. Safety and compliance of memantine.
Exploratory endpoints	1. To assess the impact of memantine on the preservation of cognition in each stratum. 2. To assess radiological features of radiotherapy-induced cognitive decline. 3. Neuro-inflammatory markers in CSF and blood and correlation with neurocognition and survival.

sequences. For CSI, patients will be simulated in the supine position and dual immobilization using head-neck and abdominal-pelvic thermoplastic masks. Radiation planning computed tomography (CT) scan (non-contrast) will be acquired from the top of the vertex till mid-thigh. Separate CT scans will be acquired for boost (tumor bed/metastatic sites). Planning MRI of the brain (or spine when indicated) will be done as per institutional practice. The contouring of target volumes and organs at risk will be done by the responsible radiation oncologists and dose prescriptions as per standard practice. All patients will be treated with photon-based techniques using 3-D conformal techniques (3DCRT), volumetric modulated arc therapy (VMAT), or helical tomotherapy using image guidance. Chemotherapy (pre-radiation, concurrent, or maintenance) will be given as indicated without any influence of the current study. During radiation, patients will be reviewed twice weekly by the radiation oncologist along with routine blood investigations as per standard practice.

Patients will undergo imaging with an MRI of the brain and spine 4 weeks post-treatment completion. Adjuvant chemotherapy will be given as per institutional practice. After completion of treatment, standard follow-up protocols will include a clinical examination 3 monthly for the first 2 years, followed by 6 monthly visits till 5 years post-RT. Imaging will be undertaken using MRI brain and spine screening along with functional sequences every 6–12 months or sooner if indicated clinically. The compliance of memantine will be done by providing drug diary to patient or their caregivers and periodic telephonic consultations. The biological tissues (CSF pre-radiation and serial blood samples before, during RT, and follow-up) undertaken during standard investigations for clinical management (no additional tests will be conducted) will be archived for exploratory analysis of neuroinflammatory markers. The study workflow has been represented in Fig. 1.

Sample size calculation

Sample size estimation was done based on the assumption of improvement of 2-year cognitive deterioration-free survival from 50% (control arm) to 75% (experimental arm) with memantine. Cognitive deterioration is defined by a drop of 5 points in any of FSIQ, VQ, or PQ compared to baseline (pre-radiation) on WAIS/WISC. With 84 eligible patients, 42 events (27 in the standard arm and 15 in the interventional arm) will be required to detect the desired difference with an alpha of 0.05 and a power of 80%. Expecting an attrition of 20%, the total sample size will be 101. No interim analysis is planned for the study. The total duration of the study is 7 years (2 years for accrual and 5 years for long-term follow-up).

Statistical analysis

Primary endpoint

Cognitive deterioration-free survival will be tested using the Kaplan-Meier method, and differences between the treatment arms will be compared using the log-rank test. The date of randomization will be considered as the baseline for survival analysis, and a p-value of 0.05 (two-sided) will be considered for statistical analysis. Patients lost to follow-up or dead (in either arm) will be censored for the assessment of cognitive deterioration-free survival.

Secondary endpoints

The slope of FSIQ and other domains between the two study arms at different time points will be compared using linear mixed-effect regression models. Survival analysis of overall survival (OS) and progression-free survival (PFS) will be tested using the Kaplan-Meier method, and differences between the treatment arms will be compared using the log-rank test. The date of randomization will be considered the baseline, with the date of death considered an event for overall survival. The date of radiological progression or death will be regarded as an event for PFS. Patients who are lost to follow-up will be censored. Patients who withdraw from the study will not be analyzed. Toxicity will be documented using Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 and compared between the groups using the Chi-square test or Fischer exact test as appropriate.

For other exploratory analysis, a comparison of factors for continuous variables (e.g., scores) between the two arms or different strata will be analyzed using the independent-t test or Mann-Whitney test as appropriate (depending upon normality). Categorical variables will be analyzed using the Chi-square test or Fischer exact test as appropriate. All data collection and analysis will be done using International Business Machine, Statistical Package for the Social Sciences (IBM SPSS) version 29.

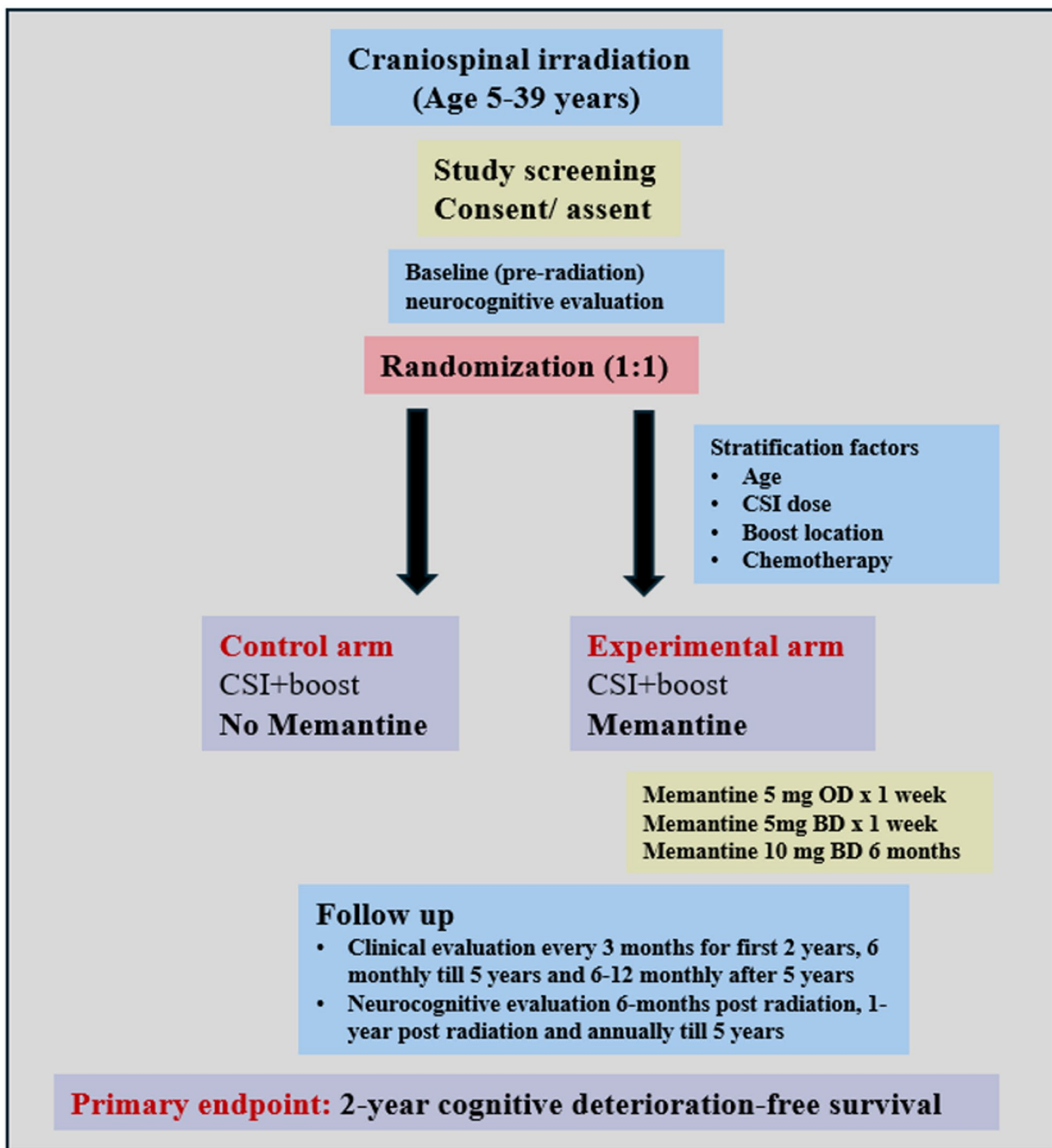


Fig. 1 Schematic workflow of the study

Discussion

The pathophysiology of RT-induced dementia is hypothesized to be primarily driven by vascular effects mimicking the pathophysiology of vascular dementia. The impact of RT on endothelial cells in brain vasculature leads to the activation of apoptosis of these cells along with the release of acid sphingomyelinase and ceramide, which are the activators of apoptosis [8–11]. This leads

to fibrinoid necrosis of vessels, eventually leading to ischemia and coagulative necrosis of the brain parenchyma. The demyelination of cells accompanies the coagulative necrosis. Impairment of the integrity of white matter has a significant impact on memory and intelligence. Besides this indirect effect, radiation induces an inflammatory response characterized by increased activated microglia and cytokine releases, such as tumor necrosis

factor-alpha and interleukin-1beta. These cytokines are responsible for causing immune-mediated damage to the nervous system tissue. The coping mechanism of brain parenchyma to this global stress includes an excess release of the stimulatory neurotransmitter like glutamate. This leads to glutamate excitotoxicity, which is triggered by excessive glutamate release from neurons and glial cells and leads to cell death [12].

Memantine is an uncompetitive N-methyl D-Aspartate receptor antagonist and reduces glutamate excitotoxicity [6, 7]. Memantine is FDA-approved for moderate to severe dementia of Alzheimer's disease and is used in the pediatric population for several developmental disorders, including attention-deficit hyperactivity disorder (ADHD), autism, and autism spectrum disorders [13–16]. Hardan et al. reported the efficacy and safety of memantine use in children from three phase 2 multicentric trials, and no safety concerns were raised [17]. A recent study reported the safety of memantine in 18 pediatric patients treated with cranial RT, with one patient discontinuing the medication after one dose because of nausea, while in other 16 assessable patients, 100% completion rate was achieved [18]. A recent Cochrane review has also reported no undue adverse effects of memantine compared to placebo [15]. The minor and uncommon adverse effects reported are dizziness, headache, and confusion.

Factors affecting the degree and severity of neurocognitive decline include age at the time of RT, the dose of CSI, location and volume of RT, and the addition of systemic chemotherapy [19]. Memory decline is primarily affected by the dose of RT to the whole brain (including patients treated with CSI, where the whole brain is included in the target volume). The hippocampal doses have been largely correlated with memory function following radiation [20, 21]. A phase 3 randomized controlled trial using conformal techniques like stereotactic conformal radiotherapy to reduce radiation dose spillage to the surrounding brain demonstrated improved neuropsychological outcomes in patients treated with partial brain RT [22]. For patients with medulloblastoma treated with CSI, the use of proton beam therapy (PBT) demonstrated better memory outcomes, primarily attributed to a lesser dose to surrounding structures with PBT for tumor bed boost [3]. Proton therapy has potential in improving neurocognitive function post radiotherapy. With the proton therapy centre currently operational at our centre, we are developing a phase 3 randomized controlled trial comparing photon and proton-based CSI. Also, data have shown that using a hyperfractionated regimen for CSI leads to better preservation of neurocognition, although routine use can be challenging due to the burden on available resources [23]. The use of metformin has shown better cognitive recovery in survivors of pediatric brain tumors [5].

Memantine has been proven to effectively mitigate cognitive decline induced by cranial RT [4]. A double-blind, placebo-controlled, randomized controlled trial investigated the role of memantine in 508 patients with brain metastasis treated with WBRT. The time to cognitive decline was significantly longer with the use of memantine compared to placebo, and particularly executive function, processing speed, and delayed recognition were better preserved compared to placebo. The NRG Oncology CC001 trial compared memantine with standard WBRT to hippocampal avoidance-WBRT with memantine for the preservation of memory in patients with brain metastases; usage of the drug in either arm validates the use of memantine in memory preservation, with no undue events attributed to memantine [24]. A recent meta-analysis by the Cochrane Library suggested that memantine is a safe agent to be given in the early radiotherapy treatment phase and may help prevent cognitive decline in patients with brain metastasis treated with cranial RT [25]. Currently, two randomized controlled trials (RCT) are underway to investigate the role of memantine in the pediatric age group treated with cranial RT. A phase 2 RCT (MEMCRT) is being conducted at St Jude Children's Research Hospital (sample size 50) using memantine in patients with diverse histology (low-grade glioma, craniopharyngioma, ependymoma, or germ cell tumor) undergoing RT (clinicaltrials.gov identifier NCT03194906). Another multicentric phase 3 RCT (ACCL 2031) is being conducted by the Children's Oncology Group (COG) (sample size 192) in pediatric patients treated with cranial RT (clinicaltrials.gov identifier NCT04939597). The initial results from the MEMCRT study involving 30 patients demonstrated better processing speed, academic fluency, and fatigue at 12 weeks with the use of memantine [26]. In our study, to avoid any potential bias, using a placebo for a double-blind study would have been ideal for study conduct. However, due to logistics, this was not feasible when the study was initiated.

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Authors' contributions

Study concept and design: ** Tejal Gupta, Archya DasguptaStudy conduct and data collection: ** All authors**Statistical analysis: ** Sadhana Kannan, Tejal Gupta, Archya Dasgupta**Writing manuscript and approval: ** All authors**Funding acquisition: ** Tejal Gupta**Study administration: ** Tejal Gupta.

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Data availability

Data will be provided upon reasonable request to the principal investigator, following the guidelines by the institutional ethics committee.

Declarations

Ethics approval and consent to participate

The study is being conducted in accordance with ICMR (2017) "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, Good Clinical Practice and the principles of the Declaration of Helsinki.

The study, including all the study-related documents, has obtained approval from the Ethics Committee prior to the enrollment of participants. The trial is registered on ClinicalTrials.gov: NCT06275035 and Clinical Trial Registry India (CTRI): CTRI/2024/02/062273).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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