Memantine for Prevention of Brain Irradiation–Induced Cognitive Toxicity: A Tale of an Underappreciated and Underused Intervention

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There is now a strong emphasis on limiting the use of whole-brain radiation therapy (WBRT) in patients with brain metastases because of the well-known spectrum of acute, subacute, and late toxicities. The most significant and irreversible of these is neurocognitive (NC) decline. Multiple mechanisms have been proposed to explain radiation-induced effects on normal brain tissue at a cellular level.[1] The primary mechanism that has been proposed is the ischemia-hypoxia cascade induced by RT leading to increased glutamate levels which, in turn, lead to excessive activation of N-methyl-D-aspartate (NMDA) receptors (NMDARs). NMDARs, which are ion channel proteins, play a critical role in maintaining synaptic plasticity (critical mechanism for memory and learning). The overactivation of NMDARs leads to influx of calcium ions, which leads to cellular disequilibrium or excitotoxicity and cell death. This glutamate-induced overactivation of NMDARs has also been the proposed mechanism of damage in other neurodegenerative disorders.

Multiple nonpharmacologic interventions have been proposed to prevent, limit, and reverse the damage induced by brain irradiation. Control of comorbidities such as hypertension and diabetes, limiting exposure to alcohol, and smoking cessation are some of the common interventions that must be practiced. Limiting the dose of radiation to certain areas of the brain such as the hippocampus[2] and the supratentorial brain, along with de-escalation of the total dose and limiting dose per fraction are also practiced because they have been shown to limit the NC decline. Multiple pharmacologic interventions have been evaluated in the randomized controlled trial (RCT) setting, and a few have been shown to improve radiation-induced effects on normal healthy brain tissue[7]; however, none of these drugs have been shown to prevent radiation-induced NC decline except memantine (Table 1).

Memantine was one of the earliest drugs to show promise in this setting. It was initially developed and patented as an antidiabetic drug in the late 1960s but was found to be ineffective for this purpose. Subsequently, it was determined that memantine is a low-affinity voltage-dependent noncompetitive glutamatergic NMDAR antagonist. Memantine preferentially binds to NMDARs and prevents the influx of calcium ions, thereby preventing the disruption of synaptic plasticity. The onset of action is after 3 to 7 hours with a half-life of 60 to 80 hours; it is metabolized in the liver and excreted through the kidneys. The most common toxicities associated with memantine (seen in more than 2% of patients) are headache, dizziness, hypertension, fatigue, pain, and constipation. Memantine is currently approved for the treatment of moderate to severe Alzheimer's disease, especially for those who do not tolerate or have a contraindication to the use of acetylcholinesterase inhibitors such as donepezil. It has been shown to provide modest improvement in cognition, behavior, mood, and physical functioning in patients with moderate to severe Alzheimer's disease.[8] It is also being used as an off-label medication for treating vascular dementia and other psychiatric conditions such as depression and schizophrenia, along with posttraumatic stress, obsessive compulsive, general anxiety, and bipolar disorders.

One of the earliest studies[9] that evaluated the role of memantine as a neuro-protector demonstrated, through a series of experiments, that it allows near normal physiologic NMDA activity despite high levels of glutamate. In fact, the authors showed that its effectiveness increases with escalating levels of glutamate, which could be seen after WBRT. Subsequently, its neuro-protective effect in patients receiving WBRT was evaluated in a relatively large placebo-controlled phase III RCT.[10] Memantine was started within 3 days of initiation of WBRT and was continued for 24 weeks with gradual dose escalation from 5 mg to 20 mg per day. The primary end point of this study was the score on the Hopkins Verbal Learning Test-revised (HVLT-R) at 24 weeks. The study was powered to detect a difference between the two arms of 0.87 in HVLT-R score at 24 weeks. Although the study showed that there was a small decline in delayed recall in the memantine arm at 24 weeks ($P = 0.059$), it was not statistically significant. The authors argued that because only approximately 30% (of the original number) of evaluable patients remained at the end of 24 weeks, statistical power to detect a significant difference was considerably reduced. Among the secondary end points,

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TABLE 1. Summary of the Pharmacologic Interventions Useful for Reducing the Burden of Neurocognitive Deficits

Drug Name and Reference	Mechanism of Action	Best Clinical Evidence	Patient Type	Toxicities
Modafanil[3]	Eugeroic or wakefulness promoting agent, otherwise used for patients with narcolepsy	Phase II RCT showed that patients with greater baseline fatigue benefitted by having reduced fatigue, improved mood, and improved speed and quality of memory.	Patients with primary or metastatic brain tumor receiving focal RT and WBRT	20% had insomnia, headaches, nausea, and anxiety
Donepezil[4]	Centrally acting reversible acetylcholinesterase inhibitor, approved for Alzheimer's disease	Phase III RCT did not improve composite cognitive score (primary end point), but modestly improved cognitive domains such as memory, motor speed, and dexterity. Patients with higher baseline deficits benefited more.	Patients with primary or metastatic brain tumors receiving focal RT or WBRT	25% had diarrhea
Methylphenidate[5,6]	CNS stimulant with dopamine and norepinephrine reuptake inhibition and dopaminergic and noradrenergic activity in prefrontal cortex	Phase III RCT; no benefit before WBRT, based on Mini Mental State Examination (MMSE). A previous phase III trial showed benefit with respect to psychomotor speed, memory, visual-motor function, and other executive functions.	Patients with primary or metastatic brain tumors receiving focal RT or WBRT	Prone to substance abuse, psychosis, insomnia, cardiac toxicities, and prolonged erections
Memantine[10]	Blocks the effects of glutamate by binding to NMDA receptors and prevents the influx of calcium ions	Phase III RCT; memantine delayed time to cognitive decline and reduced rate of decline in memory, executive function, and processing speed in patients receiving WBRT.	Patients with primary or metastatic brain tumors receiving WBRT	Most common adverse effects were fatigue, alopecia, nausea, and headache

Abbreviations: NMDA, N-methyl-D-aspartate; RCT, randomized controlled trial; RT, radiation therapy; WBRT, whole-brain radiation therapy.

memantine resulted in significantly longer time to cognitive decline (hazard ratio [HR], 0.78; 95% CI, 0.67 to 0.99), lower probability of cognitive function failure at 24 weeks (53.8% *v* 64.9%), superior executive function at 8 and 16 weeks, and delayed recognition at 24 weeks. Memantine was well tolerated with no additional toxicities compared with placebo. The conclusion of this study is a classic example of having an intervention that results in a clinically meaningful yet not statistically significant outcome. Despite the negative results of this study, memantine continued to be evaluated in clinical trials mainly in combination with other interventions.

Another publication that evaluated the effect of memantine on preventing vascular changes induced by WBRT using dynamic contrast enhanced magnetic resonance imaging (MRI),[11] noted increased vascular permeability of tumors and normal-appearing white matter (NAWM), which was demonstrated by area under the curve (AUC) changes after WBRT. Memantine significantly reduced the AUC changes noted in NAWM after WBRT. A recently published phase III trial (NRG-CC001; ClinicalTrials.gov identifier: NCT02360215) that randomly assigned patients to WBRT with or without hippocampal avoidance (HA-WBRT) used memantine in both the arms.[12] This RCT demonstrated that HA-WBRT and memantine resulted in a relative reduction of 26% in NC decline and led to a significantly better patient symptom profile without altering disease outcomes. Although this study did not evaluate the impact of memantine, the trial has established this combination as the new standard of care in the setting of WBRT. This combination of memantine and HA-WBRT is being compared with stereotactic radiosurgery (SRS) for patients with 5 to 15 brain metastases (ClinicalTrials.gov identifier: NCT04277403).

The above-mentioned studies prove that this drug is at least modestly effective in limiting the decline in global cognition and leads to better preservation of certain cognitive domains such as processing speed and executive function for patients receiving WBRT. Memantine has also been shown to delay the time to cognitive decline. Because the NC decline during the early follow-up period is predominantly a result of intracranial progression, the benefit of memantine would be more important in patients who survive longer with good intracranial control (Radiation Therapy Oncology Group [RTOG] Recursive Partitioning Analysis [RPA] class 1 and 2 with responsive systemic therapy options). The benefits come without significant toxicity concerns, despite the fact that these patients are likely to be receiving several concurrent medications such as antiseizure medications, steroids, antidepressants, hormonal therapy, and chemotherapeutic drugs.

Despite this, the story of memantine use so far is underscored by the unfortunate fact that this drug is not widely accepted. A SEER database noted that overall, only 5.14% (2% of patients who survived beyond 12 months) of patients undergoing nonstereotactic treatment of brain metastases received memantine, which increased to 9.36% in 2016.[13] There could be many reasons for this drug being underused. The international guidelines for recommending memantine are divided. Although National Comprehensive Cancer Network guidelines recommend considering memantine in patients with good prognosis, the National Institute for Health and Care Excellence guidelines recommend against its use. This problem of underuse could also be partially because of a traditional sense of nihilism when managing patients with brain metastases. Fortunately, there is now a renewed optimism with better understanding of the molecular milieu of the brain metastases and discovery of corresponding targeted agents with good CNS penetration. With increased adoption of aggressive MRI screening of the brain, there is a higher probability of detecting asymptomatic brain metastases,[14] and a good proportion of these patients may receive WBRT with a longer expected survival and possibly with higher burden of NC decline. Despite the clear emphasis on avoiding or delaying WBRT, nearly one fourth of patients with brain metastases in the United States continue to receive it.[15] This percentage is likely to be significantly higher in parts of the world where cost and labor-intensive advanced radiation techniques such as SRS or hippocampal avoidance intensity-modulated RT to the whole brain are either not available or are infrequently performed. In these situations, memantine remains the only intervention that is accessible, relatively inexpensive (less than 1 [US] dollar per day in most countries), safe, and effective. Indirect comparison of NRG-CC001[12] and RTOG 0614 (ClinicalTrials.gov identifier: NCT00566852),[10] reveals a similar magnitude of benefit of the experimental intervention over the control arm with respect to the end point of cognitive toxicity at 24 weeks (HR, 0.74 for NRG-CC001; HR, 0.78 for RTOG-0614), suggesting an impact of memantine comparable to that of now established HA-WBRT.

Unfortunately, memantine has almost exclusively been evaluated in patients receiving WBRT for brain metastases, and it has not been evaluated in patients receiving WBRT as part of prophylactic cranial irradiation and as part of craniospinal irradiation in patients with medulloblastoma and other pediatric brain tumors. In addition, there are limited data regarding memantine in patients treated with focal brain irradiation. With RTOG-9802 (ClinicalTrials.gov identifier: NCT00003375) and RTOG-9402 (ClinicalTrials.gov identifier: NCT00002569) studies[16,17] showing long-term survivorship in patients with low-grade gliomas treated with chemoradiotherapy and the fact that these patients receive irradiation to large portions of brain, there are valid concerns regarding NC decline, especially in younger patients. The effect on the vasculature and glutamate-mediated effects on neurons is likely to remain relevant in these patients as well. The MEMCRT (ClinicalTrials.gov identifier: NCT03194906) trial is evaluating the role of memantine in limiting NC decline induced by focal brain irradiation in children older than age 6 years and

young adults diagnosed with low-grade tumors, including gliomas, craniopharyngiomas, ependymomas, and germ cell tumors. A quadruple blind RCT (ClinicalTrials.gov identifier: NCT03342443) is evaluating the role of memantine in patients receiving radiation to the head and neck region. And memantine is also being evaluated as a neuroprotector in patients with breast cancer who are receiving systemic chemotherapy in a single-arm phase II study (ClinicalTrials.gov identifier: NCT04033419). There is growing enthusiasm for memantine and memantine-like substances that show putative antiproliferative and autophagic effects on several glioma and medulloblastoma cell lines through NMDAR1.[18,19] In a phase I trial,[20] memantine was found to be safe when combined with temozolomide, mefloquine, and metformin in patients with glioblastoma.

In summary, memantine is a simple, safe, modestly effective, and relatively inexpensive intervention that can prevent WBRT-associated NC decline. There is a need for robust prospective studies to establish its role in patients with brain metastases and define its benefit in more diverse indications. As the role of memantine continues to evolve, on the basis of the available literature, it must be considered for all patients who receive WBRT or HA-WBRT who are likely to survive beyond 6 months.

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