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Role of memantine to mitigate radiation-induced cognitive dysfunction in brain metastasis patient receiving whole brain radiotherapy: a systematic review

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Purpose: Identifying comprehensively the evidence of neuroprotective effects of memantine for preserving cognitive function in brain metastasis patients receiving whole brain radiotherapy (WBRT).
Methods: We searched randomized clinical trials (RCTs) analyzing the effects of memantine to preserve cognitive function in patients with brain metastasis treated with WBRT, performed in some databases, including PubMed, Embase, and Cochrane Library. The protocol was registered at PROSPERO (CRD42023476632). We reported the selection process according to the Preferred Reporting Items for Systematic Review and Meta-Analysis guideline. The studies were appraised by using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2.0).
Results: We included three RCTs that met the eligibility criteria. No high risk of bias was found. Two articles compared WBRT + memantine to WBRT + placebo, and the other one compared hippocampal avoidance (HA)-WBRT + memantine to WBRT + memantine. There was no significant difference in characteristics among groups of treatment arms. The differences in cognitive function deterioration between treatment arms began to appear four months after initiated the treatment. The risk of cognitive failure was lower in patients receiving memantine compared to placebo. Moreover, combining HA-WBRT + memantine lowered the cognitive failure compared to standard WBRT + memantine. No article stated significant difference in quality of life (QoL) and survival outcomes in patients receiving memantine.
Conclusion: Although the evidence was still limited, memantine was reported to have the potential to mitigate radiation-induced cognitive dysfunction in patients with brain metastasis receiving WBRT. However, there was no evidence revealing the benefit of memantine for enhancing QoL and prolonging survival.

Keywords: Brain neoplasm, Cognition, Memantine, Radiotherapy

Introduction

Brain metastasis is one of the most frequent metastasis sites of primary solid tumors. The incidence reached 9%–17%, still increased by the improved availability of diagnostic imaging to detect earlier [1]. Lamba et al. [2] showed that 10%–40% of patients with solid tumors were susceptible to developing brain metastasis during the disease progression. The primary sites of brain metastasis commonly originate from lung and breast cancer [1]. Unfortunately, most patients with brain metastasis would survive for only less than 6 months [3]. In the advanced stage of cancer, systemic therapy is the essential backbone part of multimodal treatment [4,5]. However, some systemic therapies could not pass the blood-brain barrier, specifically the blood-tumor barrier [4,5]. Therefore, radiation therapy still becomes the most considered modality to treat brain metastasis [6,7].

Although the evolution of brain metastasis treatment favored the utilization of more advanced stereotactic techniques of radiotherapy, whole brain radiotherapy (WBRT) is still widely used to treat patients with brain metastasis, especially for multiple brain metastasis lesions [6-9]. Delivering WBRT prolonged the survival of patients with brain metastasis [10,11]. However, there were some toxicities affecting brain tissue leading to the deterioration of cognitive function, called radiation-induced cognitive decline (RICD). [12-14]. Brain irradiation induced the alteration of neurotransmitter levels and receptors, including glutamate, impairing neuronal plasticity, which was involved in the memory and learning process [12,15]. Some approaches to mitigate the risk of RICD have been explored, both pharmacologic and non-pharmacologic treatments [13].

Memantine, a low-affinity N-methyl-D-aspartate (NMDA) receptor antagonist widely used for dementia patients, has the potential to prevent RICD by inhibiting calcium ion influx, inflammation, and oxidative damage [13,16,17]. Moreover, memantine was reported as an effective, safe, yet relatively affordable drug [16]. It was also proven to improve the quality of life (QoL) in patients with dementia [18]. This rationale led memantine to be used as one of the alternatives for mitigating cognitive dysfunction caused by brain irradiation [12,13]. Nevertheless, some radiation oncologists were still skeptical about memantine effects [19]. Only a few of them recommended memantine in clinical practice.

This systematic review was conducted to investigate the potential effects of memantine for mitigating the risk of cognitive dysfunction and QoL impairment in brain metastasis patients induced by WBRT, with or without hippocampal avoidance (HA). This review also presents a comprehensive rationale for the administration of memantine and the practical utilization of memantine.

Materials and Methods

1.Strategy of literature searching

According to the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) guidelines, was performed a systematic review. The protocol of this systematic review was recorded at PROSPERO (CRD42023476632). The following information was the "PICO" that we used for this literature searching:

- Population: brain metastasis patients receiving WBRT, with or without HA.
- Intervention: patients receiving memantine.
- Control: patients receiving placebo.
- Outcome: cognitive functions.

Article searching was performed in some online databases, including PubMed, Embase, and Cochrane Library, on September 16, 2023. We used advanced search and Boolean operators combining the keywords consisting of all synonyms of PICO (Supplementary Table S1).

2. Eligibility criteria

We included randomized-control trials and observational studies analyzing the benefit of memantine to protect cognitive function for brain metastasis patients receiving WBRT, with or without HA. Literature review, case report, clinical trial protocol, and conference proceeding; non-human studies; and the study was not in English were excluded.

3. Study selection

The title and abstract of the studies were screened by two independent reviewers based on inclusion criteria to be assessed in full-text. Full-text articles were assessed by two independent reviewers for eligibility. We assessed whether it evaluates the cognitive function and/or QoL in brain metastasis patients receiving WBRT, either with or without memantine. Disagreement between authors was resolved with discussion until a consensus was reached. Fig. 1 shows the PRISMA flowchart of literature searching.

4. Data extraction

Data were extracted by reviewers. By using Microsoft Excel, the data was extracted by study citation (author and title) and characteristics of the study (location, period, study design, sample size, demographic, and clinical characteristics of population). The primary outcomes were cognitive function and QoL, assessed by using

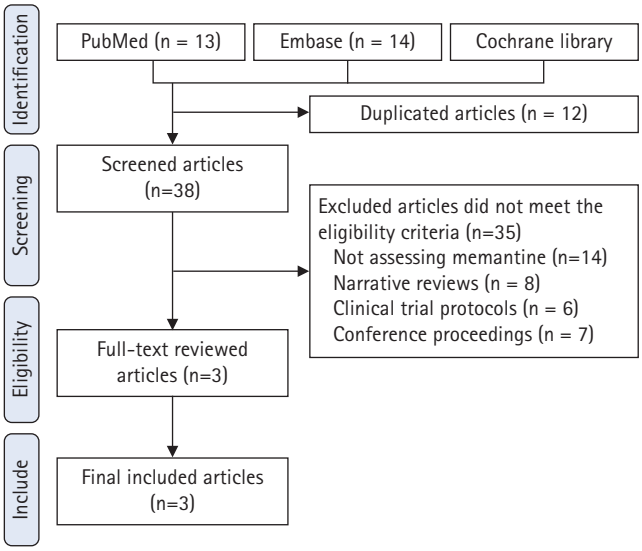

Fig. 1. The preferred reporting items for systematic reviews and meta-analyses flowchart of literature searching.

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some neuro-cognitive assessment tools and health-related QoL assessment tools. We also evaluated the overall survival as well as progression-free survival (PFS) of patients based on the groups of treatment arms.

5. Risk of Bias assessment

By using the revised Cochrane Risk of Bias for randomized trials (RoB 2.0) tool for randomized-control trials, we critically appraised the included articles. Study qualities were classified as low risk of bias, some concerns, and high risk of bias.

Results

After the literature search was completed, we deleted duplicate studies (n = 12), as well as studies that did not meet the eligibility criteria (n = 35). A total of three studies were included (Table 1). We used the RoB 2.0 tool to critically appraised the included articles (Supplementary Tables S2–4). There was no high risk of bias was found (Table 2).

1. Characteristics of the study participants

From the included studies, there were no significant differences between treatment groups regarding the demographic data of participants (Table 3). The median age ranged from 59 to 62 years old, with more than half of the participants being female. Most of them were educated in grades 0–12, followed by college degrees and bachelor's degrees [20-22].

In addition, Table 3 also showed that the clinical characteristics of participants were not significantly different. The participants included in the studies were in the same condition, with Karnofsky

Table 1. Characteristics of the included articles

Study, year	Study design	Country	Intervention	Control	Outcome
Brown et al. [20], 2020	Prospective multi-institutional RCT	USA and Canada	HA-WBRT 30 Gy in 10 fx + memantine[a]	Standard WBRT 30 Gy in 10 fx + memantine[a]	Primary: cognitive failure which was defined as cognitive decline in at least one of the cognitive tests (HVLT-R, COWA, TMT-A, and TMT-B) Secondary: PFS, OS, toxicity, patient-reported symptoms, and HRQoL
Laack et al. [21], 2019	RCT	USA and Canada	WBRT 37.5 Gy in 15 fx + memantine[a]	WBRT 37.5 Gy in 15 fx + placebo	HRQoL was measured by FACT-Br and MOS-C, related to cognitive changes, measured by HVLT-R, TMT, COWA, and self-report
Brown et al. [22], 2013	Double-blind, RCT	USA and Canada	WBRT 37.5 Gy in 15 fx + memantine[a]	WBRT 37.5 Gy in 15 fx + placebo	Primary: cognitive function, including memory measured by HVLT-R delay recall Secondary: time to cognitive failure, OS, PFS, and adverse events

USA, United States of America; HA, hippocampal avoidance; WBRT, whole brain radiotherapy; HVLT-R, Hopkins Verbal Learning Test - Revised; COWA, Controlled Oral Word Association; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; PFS, progression-free survival; OS, overall survival; HRQoL, health related quality of life; FACT-Br, Functional Assessment of Cancer Therapy - brain module; MOS-C, medical outcomes study – cognitive functioning scale; RCT, randomized controlled trial; fx, fractions.
[a]Memantine was given orally for 24 weeks with escalating doses during the initial 4 weeks: Week 1, 5 mg morning dose; Week 2, 5 mg morning and evening doses; Week 3, 10 mg morning dose + 5 mg evening dose; Week 4–24, 10 mg morning and evening doses.

Table 2. The risk of bias for each included study

Brown et al. [20], 2020	Laack et al. [21], 2019	Brown et al. [22], 2013	
+	+	+	Randomization process
+	+	!	Deviations from the intended interventions
+	+	+	Missing outcome data
+	!	+	Measurement of the outcome
+	+	+	Selection of the reported result
+	!	!	Overall

+ Low risk
! Some concerns
High risk

Table 3. Comparing characteristics of subjects in each study based on treatment arms

Characteristic	Brown et al. [20]		Laack et al. [21] & Brown et al. [22] (under RTOG 0614 trial)	
	HA-WBRT + memantine (n = 261)	WBRT + memantine (n = 257)	WBRT + memantine (n = 256)	WBRT only (n = 252)
Age (yr)	62 (27–91)	61 (20–88)	60 (31–84)	59 (29–86)
Sex, male	111 (42.5)	108 (42.0)	115 (44.9)	107 (42.5)
Education				
No formal education	1 (0.4)	1 (0.4)	NI	NI
Grade 0–12	112 (42.9)	110 (42.8)	164 (64.1)	165 (65.5)
College or associate degree	71 (27.2)	68 (26.5)	49 (19.1)	44 (17.5)
Bachelor's degree	38 (14.6)	43 (16.7)	43 (16.8)	43 (17.1)
Higher than a bachelor's degree	30 (11.5)	22 (8.5)	NI	NI
Not reported	9 (3.4)	13 (5.1)	NI	NI
Recursive partitioning analysis class				
1	33 (12.6)	38 (14.8)	114 (44.5)	112 (44.4)
2	228 (87.4)	219 (85.2)	142 (55.5)	140 (55.6)
Karnofsky performance score			> 70	> 70
70	48 (18.4)	53 (20.6)	NI	NI
80	81 (31.0)	75 (29.2)	NI	NI
90	85 (32.6)	95 (37.0)	NI	NI
100	47 (18.0)	34 (13.2)	NI	NI
Neurologic function status				
No symptoms	113 (43.3)	119 (46.3)	101 (39.5)	105 (41.7)
Minor symptoms	92 (35.2)	86 (33.5)	115 (44.9)	98 (38.9)
Moderate symptoms, fully active	24 (9.2)	27 (10.5)	26 (10.1)	29 (11.5)
Moderate symptoms, not active	18 (6.9)	15 (5.8)	14 (5.5)	19 (7.5)
Severe symptoms	NI	NI	0 (0)	1 (0.4)
Unknown	14 (5.4)	10 (3.9)	NI	NI
Primary disease site				
Breast	51 (19.5)	45 (17.5)	32 (12.5)	43 (17.1)
Colorectal	5 (1.9)	8 (3.1)	3 (1.2)	2 (0.8)
Lung	156 (59.8)	151 (58.8)	181 (70.7)	174 (69.0)
Other	49 (18.8)	53 (20.6)	40 (15.6)	33 (13.1)

Values are presented as median (range) or number (%).
HA, hippocampal avoidance; WBRT, whole brain radiotherapy; RTOG, Radiation Therapy Oncology Group; NI, no information.

performance scale not below 70 and recursive partitioning analysis (RPA) class minimal 2. Most participants had no or minor symptoms of neurologic function. Lung and breast cancer were the most common primary site of the brain metastasis.

Besides, Table 4 showed the baseline distribution of outcome measures in each study. The outcome from Brown et al. [20] and Brown et al. [22] was neurocognitive functions, while the outcome from Laack et al. [21] was health-related QoL (HRQoL).

2. Neurocognitive outcomes between treatment arms

The comparison of the neurocognitive test results is shown in Table 5. Two months after the treatment was initiated, there was no significant difference in all neurocognitive test results between treatment groups. The difference in test results began to be identified at four months. Brown et al. [22] showed that the declining score of Controlled Oral Word Association (COWA) assessing verbal fluency was significantly lower in the WBRT and memantine arm, compared to WBRT and placebo arm. Moreover, Brown et al. [20] showed the deterioration rate in Trial Making Test (TMT) Part B score, which assessed executive function was significantly lower in HA-WBRT plus memantine compared to standard WBRT plus memantine.

The difference in neurocognitive test results was mostly identified 6 months after the treatment started. The study by Brown et al. [22] showed significant differences in median decline for Hopkins Verbal Learning Test-Revised (HVLT-R) delayed recognition, TMT Part A, and Clinical Trial Battery (CTB) composite, favoring WBRT plus memantine arm. Besides, Brown et al. [20] showed a significant difference in the deterioration rate of HVLT-R total recall and HVLTR-delayed recognition, favoring HA-WBRT plus memantine rather than standard WBRT plus memantine. There were no significant differences in other test results.

Nevertheless, Laack et al. [21] showed that the HRQoL associated with cognitive function was not significantly different between

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Table 4. Baseline distribution on outcome measures in each study based on treatment arms

Outcome	WBRT only		WBRT + memantine		HA-WBRT + memantine	
	Brown et al. [22] (n = 252; median)	Laack et al. [21] (n = 199; median)	Brown et al. [22] (n = 256; median)	Laack et al. [21] (n = 203; median)	Brown et al. [20] (n = 257; mean)	Brown et al. [20] (n = 261; mean)
HVLT-R total recall	-1.7	NI	-1.5	NI	-1.29 (1.28)	-1.31 (1.26)
HVLT-R delayed recognition	-0.6	NI	-0.6	NI	-0.72 (1.55)	-0.64 (1.39)
HVLT-R delayed recall	-1.6	NI	-1.5	NI	-1.29 (1.60)	-1.17 (1.35)
COWA	-1.0	NI	-1.0	NI	-0.82 (1.20)	-0.82 (1.16)
TMT-A (s)	-1.1	NI	-1.3	NI	-1.21 (2.49)	-1.29 (2.47)
TMT-B (s)	-1.5	NI	-2.0	NI	-3.49 (8.82)	-3.18 (5.69)
CTB composite	-1.4	NI	-1.5	NI	-1.46 (2.08)	-1.40 (1.62)
FACT-Br total	NI	135.0 (69.0–184.0)	NI	134.0 (65.8–187.0)	NI	NI
FACT-Br brain cancer subscale	NI	61.0 (31.0–85.0)	NI	61.0 (21.8–88.4)	NI	NI
FACT-Br physical wellbeing	NI	21.0 (1.0–28.0)	NI	22.0 (0–28.0)	NI	NI
FACT-Br emotional wellbeing	NI	16.0 (0–24.0)	NI	16.0 (0–24.0)	NI	NI
FACT-Br functional wellbeing	NI	16.0 (0–28.0)	NI	16.0 (0–28.0)	NI	NI
FACT-Br social/family wellbeing	NI	24.0 (5.8–28.0)	NI	24.5 (0–28.0)	NI	NI
MOS-C	NI	80.0 (10.0–100.0)	NI	83.3 (0–100.0)	NI	NI

WBRT, whole brain radiotherapy; HA, hippocampal avoidance; HVLT-R, Hopkins Verbal Learning Test - Revised; COWA, Controlled Oral Word Association; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; CTB, Clinical Trial Battery; FACT-Br, functional Assessment of Cancer Therapy - brain module; MOS-C, Medical Outcomes Study - cognitive functioning scale; NI, no information.

Table 5. Comparing neurocognitive test results between treatment arms based on time interval

Outcome	WBRT only	WBRT + memantine		HA-WBRT + memantine
	Brown et al. [22] (median decline)	Brown et al. [22] (median decline)	Brown et al. [20], (deterioration rate, %)	Brown et al. [20], (deterioration rate, %)
2 months				
HVLT-R total recall	-0.62	-0.47	34.2	34.9
HVLT-R delayed recognition	-0.71	0	37.2	36.5
HVLT-R delayed recall	-0.72	-0.36	34.5	32.8
COWA	-0.31	-0.11	16.8	16.4
TMT-A (s)	-0.10	0	31.8	31.5
TMT-B (s)	-0.35	0	37.7	39.2
CTB composite	-0.48	-0.29	56.1	50.4
4 months				
HVLT-R total recall	-0.62	-0.62	34.9	29.0
HVLT-R delayed recognition	0	0	25.0	14.0
HVLT-R delayed recall	-0.71	-0.92	32.4	24.7
COWA	-0.42*	-0.05*	12.1	10.5
TMT-A (s)	-0.29	-0.20	24.1	20.4
TMT-B (s)	-0.59	-0.39	40.4*	23.3*
CTB composite	-0.45	-0.34	42.5	31.5
6 months				
HVLT-R total recall	-0.42	-0.23	24.7*	11.5*
HVLT-R delayed recognition	-0.72*	0*	33.3*	16.4*
HVLT-R delayed recall	-0.89	0	29.3	21.3
COWA	-0.16	-0.10	5.3	11.5
TMT-A (s)	-0.37*	0.08*	27.3	16.4
TMT-B (s)	-0.49	-0.45	35.6	21.7
CTB composite	-0.41*	-0.03*	41.3	29.5

WBRT, whole brain radiotherapy; HA, hippocampal avoidance; HVLT-R, Hopkins Verbal Learning Test - Revised; COWA, Controlled Oral Word Association; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; CTB, Clinical Trial Battery.
*$p < 0.05$, statistically different between two groups.

WBRT plus memantine and WBRT plus placebo. The study showed that cognitive function evaluated by CTB composite was significantly correlated to the change of the Functional Assessment of Cancer Therapy-brain module (FACT-Br) at all time periods and the change of the Medical Outcomes Study - cognitive functioning scale (MOS-C) at 2 months and a year [21] (Table 6).

The first cognitive failure on any of the tests defined the interval time to cognitive function failure. Fig. 2 shows the interval time trends of cognitive function failure based on the study by Brown et al. [22] and Brown et al. [22]. Brown et al. [22] significantly favored the memantine arm in terms of the estimation interval time to cognitive failure (hazard ratio [HR] = 0.78: 95% confidence interval [CI], 0.62–0.99; p = 0.01). Besides, Brown et al. [20] showed that the group of HA-WBRT and memantine had significantly lower cognitive function failure risk than the standard WBRT and memantine (HR = 0.76: 95% CI, 0.60–0.98; p = 0.03).

3. Survival outcomes between treatment arms

Table 7 compared the survival outcome between patients receiving WBRT only, WBRT plus memantine, and HA-WBRT plus memantine.

Table 6. Correlations between health-related quality of life and cognitive function [21]

	Correlation between CTB composite score with:			
	FACT-Br brain cancer subscale	ΔFACT-Br brain cancer subscale	MOS-C	ΔMOS-C
2 months	0.35 (p < 0.001)	0.20 (p = 0.003)	0.25 (p < 0.001)	0.21 (p = 0.003)
4 months	0.47 (p < 0.001)	0.31 (p < 0.001)	0.23 (p = 0.004)	0.10 (p = 0.261)
6 months	0.38 (p < 0.001)	0.32 (p < 0.001)	0.18 (p = 0.043)	0.16 (p = 0.078)
12 months	0.39 (p < 0.001)	0.27 (p = 0.027)	0.20 (p = 0.093)	0.36 (p = 0.003)

CTB, Clinical Trial Battery; FACT-Br, Functional Assessment of Cancer Therapy - brain module; MOS-C, Medical Outcomes Study - cognitive functioning scale; Δ, changes.

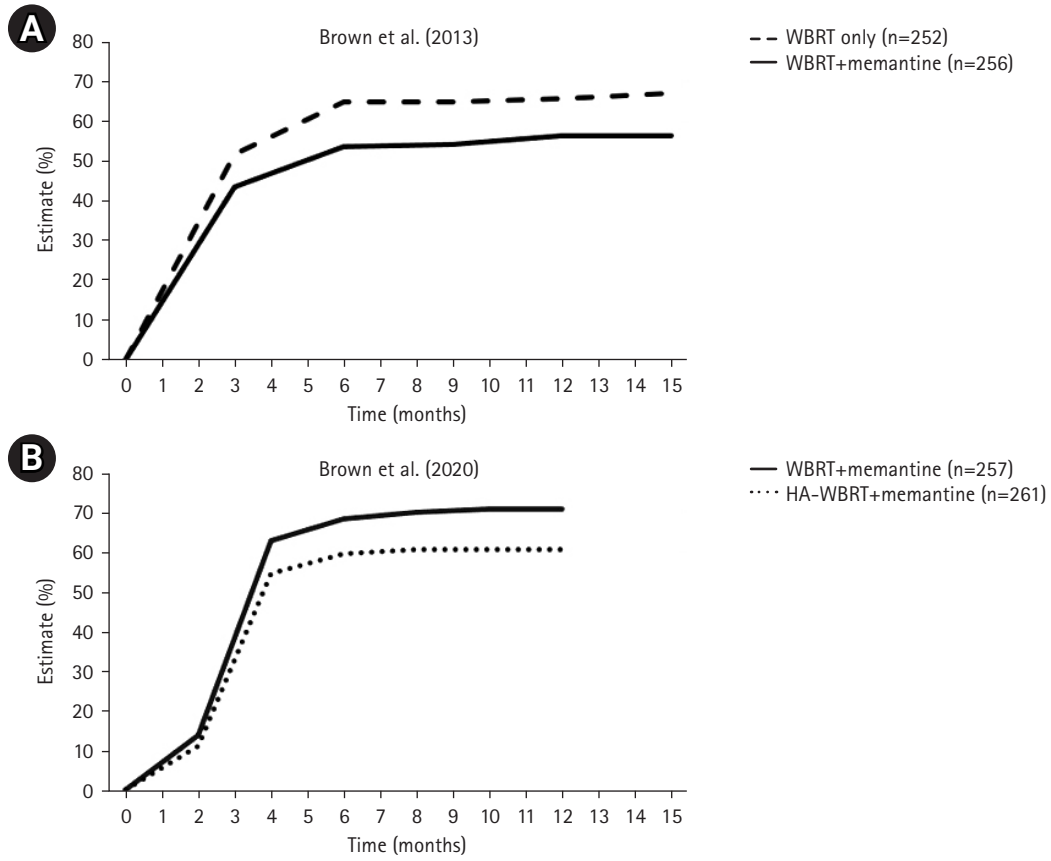

Fig. 2. Estimation of cognitive function failure by treatment arms between two studies: (A) Brown et al. [22] and (B) Brown et al. [20]. Adapted from: Brown et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 2013;15:1429-37 [22]. Brown et al. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG oncology CC001. J Clin Oncol 2020;38:1019-29 [20]. WBRT, whole brain radiotherapy; HA, hippocampal avoidance.

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Table 7. Overall survival and progression-free survival according to the treatment arms

Outcome	WBRT only	WBRT + memantine	HA-WBRT + memantine	HR (95% CI)	p-value
Median overall survival (month)					
Brown et al. [22]	7.8	6.7	NA	1.06 (0.86–1.31)	0.28
Brown et al. [20]	NA	7.6	6.3	1.13 (0.90–1.41)	0.31
Median progression-free survival (month)					
Brown et al. [22]	5.5	4.7	NA	1.06 (0.87–1.30)	0.27
Brown et al. [20]	NA	5.3	5.0	1.14 (0.93–1.41)	0.21

WBRT, whole brain radiotherapy; HA, hippocampal avoidance; HR, hazard ratio; CI, confident interval; NA, not applicable.

Based on the study by Brown et al. [22], there were no significant differences in overall survival and PFS between patients receiving memantine and patients receiving placebo. Moreover, Brown et al. [20] also showed that both of overall survival and PFS of the group receiving HA-WBRT plus memantine was not significantly different from standard WBRT plus memantine.

Discussion and Conclusion

WBRT is still widely applied as a standard of care for multiple brain metastasis patients [6,7,9]. Although the current evolution of brain metastasis management was favoring the advanced radiotherapy techniques, such as stereotactic radiosurgery (SRS) [6,7,9] a meta-analysis by Khan et al. [8] revealed that WBRT plus SRS had significantly better brain tumor control compared to WBRT only or SRS only. However, there was no significant difference in overall survival and toxicities between WBRT plus SRS, WBRT only, and SRS only.

The deterioration of cognitive abilities is one of the late effects of radiotherapy on the brain, commonly called RICD [13,14,23]. RICD occurred in more than 30% of patients who were alive at 4 months after brain irradiation, rising to 50%–90% of patients surviving more than 6 months after irradiation [13,14]. The impairment of cognitive functions included the deficit in memory, attention, and executive functions.

Recent studies have elaborated on the effects of irradiation in brain tissues up to the molecular and cellular levels. Balentova et al. [14] stated that irradiation initiated direct and indirect effects in brain tissues, including the activation of transcription factors signal transduction, as well as the impairment of vascular, glial cells, neurogenesis, and neural functions. Moreover, Cramer et al. [13] stated that RICD was related to the components of radiation-induced brain injury (RIBI), including microvascular alterations, demyelination, neuron and brain parenchymal cell damage, stem-cell attenuation, and microenvironment changes in the brain [13,23,24]. Oxidative stress and inflammation also played a crucial role in RIBI [13,14,23]. By the time after WBRT, vascular permeability of tumors and normal-appearing white matter in the brain tended to increase, detected by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), suggesting that WBRT induced vascular injury [25]. Neuroanatomical theory believes that different regions of the brain are also related to the different clinical presentations of cognitive dysfunction, and each structure has different constraints of radiation dose [14,23,24].

Based on the clinical presentation onset, RIBI was divided into three categories, including acute, subacute, and late symptoms [12,14]. Acute symptoms occurred during radiation until days after irradiation, characterized by headache, nausea, and vomiting due to the rise of intracranial pressure. Subacute symptoms occurred 12 weeks after irradiation, usually related to encephalopathy leading to somnolence and declining pre-existing deficits. Radio-necrosis, leukoencephalopathy, vascular abnormalities, calcification, and brain tissue abnormalities might be progressive and irreversible [14,23]. Six months to years after irradiation, late symptoms usually appeared to be mild to severe neurocognitive dysfunctions [12,14]. Some treatment strategies to prevent the risk of cognitive deficit included SRS, HA, and pharmacologic treatments, such as memantine [13,24]. Therefore, serial neurocognitive function evaluations were recommended for patients to identify the deterioration of cognitive functions and decide the management approach for patients.

The neurocognitive evaluations were ideally performed at the time of diagnosis and before the initiation of treatments to be baseline data [13,24]. It is suggested to be followed by serial evaluations to identify the progress of the disease and the benefit of therapies. Neurocognitive evaluation should be performed comprehensively to assess all contributing factors related to cognitive function.

Recent clinical trials used neuropsychological tests to assess cognitive domains, such as executive function, memory, learning, attention, and verbal fluency [24]. Some neurocognitive tests were performed to assess the trend of cognitive failure in patients receiving WBRT, including the HVLT-R, COWA, TMT Part A, as well as TMT Part B. The mean of a standardized score of HVLT-R, COWA, and TMT was used to measure the CTB, which was currently in use for clinical trials of brain tumor patients [26].

HVLT-R was used to evaluate multiple aspects of verbal learning and memory, containing 12 words, which included three semantic categories [13,27]. It consisted of total recall, delayed recall, and delayed recognition, with six alternate forms that relatively had more brief list length, word composition, and test length [27,28]. HVLT-R consisted of a list of word memorization to evaluate immediate recall after memorization and after 20 minutes delay abilities [29].

The TMT primarily assesses motor speed and visual attention and is divided into Part A and Part B [30]. TMT-A, referred to as an attention test, gave a task to quickly draw lines connecting 25 connective numbers [13,30]. The performance time of TMT-A was related to the bilateral superior parietal lobules [31]. Meanwhile, TMT-B measured executive function by drawing the lines alternating between numbers and letters. TMT-B had more difficult cognitive tasks requiring increased demands of motor speech and visual search.

COWA is commonly used to measure semantic and phonemic verbal fluency [13]. Moreover, the score was correlated to executive function, verbal learning, working memory, and vocabulary [32,33]. The participants were required to make verbal associations to different letters of the alphabet by giving as many words as possible, beginning with a given letter in a specified timeframe, typically 60 seconds [34].

Besides, cognitive dysfunction also affects the QoL of patients. For cancer patients, the FACT was a good psychometric instrument used to assess HRQoL [35]. FACT-Br was one of the most used questionnaires established for brain tumor patients, containing 50 items evaluating five scales of QoL, including physical wellbeing, emotional wellbeing, social wellbeing, functional wellbeing, and disease-specific concerns [36,37]. Thavarajah et al. [37] revealed that combining FACT-G and FACT-Br in brain metastasis patients had successfully undergone psychometric validation to assess their QoL. In addition, the MOS-C was a valid 6-item score representing cognitive dysfunctions, including in memory, confusion, reasoning, and attention/concentration aspects, over the previous four weeks, which was useful in the general population [38,39].

Besides, one of the effects induced by brain radiation is the microenvironment changes in the brain, including altered neurotransmitter levels and receptors [15,40,41]. Franco-Perez et al. [15] found that WBRT reduced inhibitory neurotransmitters in the hypothalamus but excess excitatory neurotransmitters in the prefrontal cortex. Neurochemical imbalance also happened after irradiation, indicated by increasing the ratio of glutamate/gamma-aminobutyric acid in the hypothalamus as well as the ratio of glutamine/glutamate in the prefrontal cortex. Increased serum glutamate levels leading to glutamate excitotoxicity in brain metastasis patients receiving irradiation was also identified by the study by Gagliardi et al. [41]. Moreover, Sanchez et al. [40] also reported that brain irradiation increased glutamate uptake as the response of neurons. Not only caused by irradiation, but tumor cells also release glutamate, triggering excitotoxic death to surrounding neurons, giving spaces for tumor growth [42].

The over-expression of glutamate, one of the main neurotransmitters in the central nervous system, plays a key role in neuronal degeneration [12]. Glutamate activates neuronal receptors and initiates excitatory intracellular signals, whose receptors were divided into metabotropic (G-protein coupled) and ionotropic (ligand-gated ion channels) receptors [12,43]. Glutamate plays an essential role in neuronal plasticity involved in memory and learning processes [12,13]. Exaggerate level of glutamate inflects the NMDA receptors activation [12]. The NMDA receptors are voltage-gated glutamate receptors, allowing calcium and sodium influx into brain cells, both of neuronal and glial cells, in synaptic plasticity [13]. Therefore, the excessive level of glutamate leads to the disequilibrium of intracellular calcium levels, triggering excitotoxicity and apoptotic death [12,16]. Neuro-inflammatory process triggered by the glutamatergic excitotoxicity was identified in neurodegenerative disease.

This pathogenesis basis led to the fundamental rationale for the use of NMDA receptor antagonists to mitigate cognitive dysfunction. Memantine, a low-affinity voltage-dependent NMDA receptor antagonist, was first found in the late 1960s as an antidiabetic drug but was reported inadequate for the initial purpose. Currently, memantine has been widely used as one of the standard treatments for dementia since the approval from the United States (US) Food and Drug Administration [12,13,44]. NMDA receptor antagonists stimulate dopaminergic transmission, showing neuroprotective effects. Memantine would bind to NMDA receptors, inhibiting calcium ion influx, which altered synaptic plasticity. Memantine also repairs brain inflammation and oxidative damage [45].

Memantine, a drug with a low plasma binding fraction (45%), has an onset of action occurring after 3 to 7 hours with a half-life of 60 to 80 hours [16,17]. Memantine is absorbed orally and metabolized in the liver. It would be excreted in unchanged form via the urinary system. Food ingestion does not affect the absorption. The pharmacokinetic pattern of memantine would be linearly reached in around three weeks.

Patients with brain metastasis commonly received WBRT with the range dose of 30–40 Gy in 15–20 fractions [46,47]. The trials included in this study administered memantine no later than the third fraction of WBRT [20-22]. The dose of memantine was escalated gradually over the first four weeks, administered orally for 24 weeks [13,20-22,48]. In the first week, the patients received a single morning dose of 5 mg, followed by an evening dose of 5 mg

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during the second week. In the third week, the morning dose increased to 10 mg, followed by the increase of the evening dose to 10 mg in the fourth week until the administration stopped after 24 weeks. Meanwhile, if the prescribed memantine was the extended-release drug, the dose became the multiplication of 7 mg. The patients would receive the total dose of 28 mg daily since the fourth week of administration.

Nevertheless, there are some considerations for some special populations, including patients with renal dysfunction, hepatic failure, and pediatric [48]. The trial by Brown et al. [22] lowered the total dose of 20 mg to 10 mg daily for patients with declined creatinine clearance under 30 mL/min and stopped if the creatinine clearance level was less than 5 mL/min. Weekly recheck of laboratory results was recommended for the patients. For patients with hepatic mild to moderate impairment, the dosage adjustment was not necessary because the hepatic cytochrome P450 system was not related to memantine metabolism [17,48]. However, there was a caution if the hepatic function was impaired severely. For pediatric, the efficacy and safety of memantine have not been established yet.

This review explained about the differences in cognitive function status and QoL between patients receiving standard WBRT only, standard WBRT with memantine, and HA-WBRT with memantine. The results of included studies reported that the effects of memantine in preventing neurocognitive dysfunction were observed in some neurocognitive assessment tools four months after the treatment was conducted [22]. Some studies reported that memantine commonly took up to three months to work fully, but it varied individually [49]. Orgogozo et al. [50] showed that memantine improved cognitive function in patients with mild–moderate dementia after 28 weeks; meanwhile, no significant difference was found at 12 weeks between memantine and placebo. Fukui et al. [51] also reported that the Apathy Scale in patients with Alzheimer's disease was identified at 3 and 9 months. Bakchine et al. [52] also stated that memantine significantly improved the condition of Alzheimer's disease at Week 12. In addition, neurocognitive dysfunction usually occurred as a late symptom of RICD, which appeared after more than 6 months subsequent to brain irradiation [12,14]. A pilot study by Wong et al. [25], under the Radiation Therapy Oncology Group 0614 trial, reported that memantine reduced the changes of normal-appearing white matter after WBRT which was assessed by using DCE-MRI. It suggested that memantine prevent brain vasculature injuries following WBRT.

Some articles reported that the utilization of memantine delayed cognitive failure, and adding HA in WBRT led to better outcomes in cognitive function [20,22]. Brown et al. [22] reported that the radiation dose in the bilateral hippocampi was constrained to achieve Dmax less than 16 Gy and D100% less than 9 Gy. The hippocampus played an essential role in bridging the external stimuli and producing perception in the spatial and temporal domains [53]. Neuronal atrophy in the hippocampus was also related to the development of dementia, both in neurodegenerative and cerebrovascular diseases [54]. Therefore, Gondi et al. [55] showed that the equivalent dose in 2-Gy fractions to 40% of hippocampus more than 7.3 Gy was related to long-term impairment of cognitive function, especially the delayed recall domain.

However, there was no evidence that stated memantine improved the HRQoL of the patients receiving WBRT [21]. Although HRQoL was correlated with cognitive function, it could not reflected in the measurable decline in HRQoL. It was supported by the study by Corn et al. [56], showing the decline of neurocognitive function in brain metastasis patients receiving WBRT, but their QoL remained stable during treatment and follow-up. Bitterlich et al. [57] and Fernandez et al. [58] also indicated that brain irradiation affected the decline of the QoL status of the patients relatively constant, while there was a significant decline in cognitive function. Laack et al. [21] stated that the HRQoL decline possibly occurred at a delayed event in the lives of the patients. However, it was the study by Larsson et al. [18], which reported the effects of memantine in improving QoL in Lewy body dementias. Thus, it was possible that memantine did not affect HRQoL because its deterioration caused by WBRT was relatively low.

In addition, this review also identified the differences in survival outcome between patients receiving standard WBRT only, standard WBRT with memantine, and HA-WBRT with memantine. The survival of patients with brain metastasis was mostly less than 6 months [3]. Suteu et al. [59] reported that the median survival of brain metastasis patients was 4.43 months. A study by Trikhirhisthit et al. [10] reported that the median survival time of brain metastatic non-small cell lung cancer patients was 4.4 months, including 5.1 months for patients receiving optimal supportive care (OSC) plus WBRT and 2.3 months for patients treated by OSC only. Renz et al. [11] also reported the median survival in small cell lung cancer patients with brain metastasis was improved with WBRT.

In addition, there were some contributing factors of WBRT effects on the survival of brain metastasis patients that needed to be explored. Some prognostic indices were established to predict the survival rate of patients, sometimes used to determine the treatment approaches for the patients [3]. Most of the indices basically consisted of performance status, age, other metastasis, primary tumor control, and brain metastasis characteristics. Some prognostic indices commonly used included RPA, scoring index for radiosurgery, Rotterdam score, Graded Prognostic Assessment, modified-Rades index, Basic Score for Brain Metastases, and nomogram

tool. Li et al. [60] revealed that tumor shrinkage response after WBRT was correlated with better survival. The median survival of good responders was ten months, while poor responders were eight months. Suteu et al. [59] also reported the number of brain metastatic lesions related to the 1-year overall survival.

The included studies revealed that no significant difference was found in survival outcome between patients receiving WBRT only, WBRT with memantine, and HA-WBRT with memantine [20,22]. Some studies reported that most radiation oncologists did not recommend the use of memantine in patients with poor performance status and worse life expectancy [13,19] Nevertheless, the main purpose of giving memantine was not to prolong the life expectancy of the patients but to mitigate cognitive dysfunction induced by WBRT.

Despite the benefit of memantine and HA, in patients receiving WBRT was reported, the utilization of memantine as well as HA was still limited. Chilukuri et al. [16] stated that memantine was a simple, beneficial, safe, and relatively inexpensive treatment mitigating neurocognitive dysfunction related to WBRT. However, the survey by Slade et al. [19] showed that only 17% of radiation oncologists recommended memantine for more than half of their WBRT patients, whereas 64% of them did not suggest memantine for their patients. Moreover, most of them did not recommend it because the patients had poor performance status and limited life expectancy (43%), followed by the unimpressive results of the trial (21%) and the cost of medication (13%). Cramer et al. [13] stated that they did not routinely offer memantine for patients with poor performance status or who had a relatively worse prognosis.

In addition, Slade et al. [19] also reported that more than half of radiation oncologists considered not using HA among WBRT patients because of the results of the phase II trial. The most common reasons were increased cost and limited insurance coverage, followed by the necessity of MRI and thin-slice CT scans, higher support of dosimetry and medical physics, and longer time consumption. Nevertheless, most radiation oncologists encouraged further exploration regarding the benefit of memantine and the validation of HA in patients receiving WBRT purposing into a phase III trial.

Since the trials of memantine and HA had been more explored, these approaches became more widely used in clinical practice. A survey by Jairam et al. [61] showed that most radiation oncologists in the US recommended the use of memantine (79.6%), HA-WBRT (72.7%), and both (63.1%) in patients receiving WBRT. Limited evidence concerning the adverse effects was the most common reason for not recommending memantine. Meanwhile, the most common reason for not using HA-WBRT was the necessity of higher treatment planning support and treatment delay. Jairam et al. [61] also stated that radiation oncologists with fewer years of practice were more likely to give memantine; meanwhile, HA-WBRT was more likely utilized by the central nervous system sub-specialists and radiation oncologists working in academic hospitals.

Nevertheless, there are some concerns regarding the adverse effects and contraindications of memantine. Common adverse effects of memantine included headaches, dizziness, drowsiness, confusion, irritability, and constipation [13,48]. In Alzheimer's disease, the discontinuation of memantine due to adverse effects was not significantly different compared to placebo [44,62]. The most common adverse effects in patients receiving WBRT and memantine were alopecia, fatigue, nausea, and headache [22]. Brown et al. [22] reported that no significant difference in grade 3–4 toxicities was found between the memantine arm and placebo arm. There were 14% of patients who had grade 3–4 toxicities associated to treatment, whereas there were no grade 5 toxicities reported in the study. In addition, Brown et al. [20] also reported that there was no significant difference in grade more than three toxicities between patients receiving standard WBRT with memantine and HA-WBRT with memantine arms, either related to treatment or not.

Patients with hypersensitivity to memantine were contraindicated [48]. Moreover, there were some precautions before giving memantine to the patients, including genitourinary conditions, cardiovascular disease, and hepatic dysfunction.

Currently, we identified six clinical trials that assessed the role of memantine in mitigating cognitive functions for patients with brain metastasis receiving radiotherapy, presented in Table 8. Of these six trials, five trials were phase III, and one trial was phase II. Five trials were conducted in the US, while others were conducted in Asia. The initiation of trials ranged from 2007 to 2022.

This study might have some limitations. A limited number of clinical trials was the major limitation of this study. A wide variation of variables to assess cognitive function restricted us from continuing our study into a meta-analysis. Some trials also had some concerns regarding the risk of bias. Moreover, there were some confounding factors related to cognitive function that should be explored, such as the number, size, and location of brain metastasis lesions, as well as the dosimetry of WBRT. Therefore, more trials should explore the benefit of memantine for patients with brain metastasis receiving WBRT in the future.

In conclusion, this review revealed that memantine had a potential effect of preserving cognitive function in patients with brain metastasis receiving WBRT. The neuroprotective effects commonly appeared four months after the treatment was initiated. The utilization of memantine also delayed the cognitive failure caused by brain irradiation. Furthermore, adding memantine with HA could provide more optimal preservation of cognitive functions. However, the benefit of memantine for improving both of QoL and survival

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Table 8. Registered clinical trials evaluating the role of memantine to preserve neurocognitive functions among brain metastasis patients

Trial Registry Number	Phase	Country	Year	Title	Intervention	Control	Objectives
NCT00566852	Phase III	USA and Canada	2007	Memantine in preventing side effects in patients undergoing whole-brain radiation therapy for brain metastases from solid tumors	WBRT 37.5 Gy + memantine	WBRT 37.5 Gy + placebo	Cognitive function, especially memory: HVLT-delayed recall Time to neurocognitive failure measured by CTB (HVLT-R, COWA, TMT-A, TMT-B, MOS, MMSE); quality of life measured by FACT-Br; PFS; OS; adverse events Time frame: 12 months
NCT02360215	Phase III	USA and Canada	2015	Memantine hydrochloride and whole-brain radiotherapy with or without hippocampal avoidance in reducing neurocognitive decline in patients with brain metastases	HA-WBRT 30 Gy + memantine	Standard WBRT 30 Gy + memantine	Time to neurocognitive failure: HVLT-R, COWA, TMT-A, and TMT-B Symptom burden measured by MDASI-BT; survival and cost analysis measured by EQ-5D-5L; PFS; OS; adverse events Time frame: 12 months
NCT04588246	Phase III	USA	2020	Testing the addition of whole brain radiotherapy using a technique that avoids the hippocampus to stereotactic radiosurgery in people with cancer that has spread to the brain and come back in other areas of the brain after earlier stereotactic radiosurgery	HA-WBRT 30 Gy + salvage SRS + memantine	Salvage SRS	Neurologic death interval time, evaluated by Gray's test OS; intracranial PFS; brain metastasis velocity; cognitive abilities by PROMIS; symptom burden by MDASI-BT; health status by EQ-5D-5L; adverse events Time frame: up to 3 years
NCT04801342	Phase II	Taiwan	2021	Neurocognitive outcome of bilateral or unilateral hippocampal avoidance WBRT with memantine for brain metastases	Unilateral HA-WBRT 30 Gy + memantine	Bilateral HA-WBRT 30 Gy + memantine	Neurocognitive function: HVLT-R, TMT-A, TMT-B, COWA, CTB Quality of life Cognitive functioning: FACT Acute and late toxicities Time frame: 6 months
NCT04804644	Phase III	USA and Canada	2021	Testing if dose radiation only to the sites of brain cancer compared to whole brain radiation that avoids the hippocampus is better at preventing loss of memory and thinking ability	SRS	HA-WBRT 30 Gy + memantine	Time to neurocognitive failure: RCI on HVLT-R, COWA, TMT-A, and TMT-B Preservation of neurocognitive function; perceived difficulties in cognition measured by PROMIS; symptom burden by MDASI-BT; OS; time to neurologic death by Gray's test; salvage procedures; adverse events Time frame: 12 months
CTRI/2022/01/039599	Phase III	India	2022	Randomized study on memantine for prevention of cognitive impairment in brain metastasis patients	WBRT + memantine	WBRT + placebo	Cognitive function Quality of life, safety, and tolerability Time frame: 6 months

WBRT, whole brain radiotherapy; USA, United States of America; HA, hippocampal avoidance; CTB, Clinical Trial Battery; HVLT-R, Hopkins Verbal Learning Test - Revised; COWA, Controlled Oral Word Association; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; MOS-C, Medical Outcomes Study - cognitive functioning scale; MMSE, Mini-Mental State Examination; FACT-Br, Functional Assessment of Cancer Therapy – brain module; OS, overall survival; PFS, progression-free survival; PROMIS, patient-reported outcomes measurement information system; MDASI-BT, MD Anderson Symptom Inventory - brain tumor; EQ-5D-5L, EuroQol-5 dimension 5-level; RCI, Reliable Change Index; SRS, stereotactic radiosurgery.

outcomes has not been proven.

Since the evidence of better cognitive preservation in WBRT patients receiving memantine had been proven, the application of memantine was more widely utilized in clinical practices since it was a simple, safe, and relatively affordable drug. Nonetheless, the trials about the efficacy and safety of memantine were still limited, both in numbers and population diversity. Thus, further controlled trials in diverse populations were necessary to strengthen the evidence, providing recommendations for a standardized guideline for brain metastasis patient's treatment approach. Combining meman-

tine with other approaches to preserve neurocognitive function in patients receiving brain irradiation was a promising idea for further research.

Statement of Ethics

This review does not involve subjects.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Materials

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