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doi: 10.48095/cccsnn2023322

Radiation-induced cognitive toxicity in era of precision oncology – from pathophysiology to strategies for limiting toxicities

Kognitivní toxicita indukovaná radioterapií v éře precizní onkologie – od patofyziologie ke strategiím omezení toxicity

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Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

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Accepted for review: 27. 12. 2022
Accepted for print: 3. 10. 2023

Abstract
Radiotherapy is one of the cornerstones for treatment of patients with intracranial metastases. Whole brain radiotherapy (WBRT) as well as stereotactic radiosurgery are part of the non-surgical treatment for brain metastases. The toxicities associated with the treatment, among which we cannot neglect cognitive impairment, represent a current topic in an era marked by advances in oncological treatments with implications for the long-term survival of these patients. The mechanisms that involve the onset of cognitive decline are multiple and are still the subject of research. We propose to highlight the pathophysiological elements involved in cognitive impairment as well as strategies including hippocampal avoidance (HA) WBRT for different histological cancer type candidates for target therapies that cross the blood-brain barrier. Even if the implementation of HA-WBRT plus memantine as standard is still a subject for debate, for cases with multiple brain metastases or metastases unsuitable for targeted radiotherapy and a life expectancy > 4 months, it is necessary to apply a preventive strategy for the impairment of cognitive function. New studies to evaluate cognitive function for long term survivals, but also an evaluation of other factors including the number and volume of brain metastases, their intracranial and extracranial localization and the effect of modern oncological therapies must be included in future analyzes and studies.

Key words
whole brain radiotherapy – hippocampal avoidance – brain metastases – memantine – cognitive impairment – dementia

Souhrn
Radioterapie je jedným ze základních složek léčby pacientů s intrakraniálními metastázami. Součástí nechirurgické léčby mozkových metastáz jsou celomozkové ozáření (whole brain radiotherapy – WBRT) a také stereotaktická radiochirurgie. V éře pokroku onkologické léčby s implikacemi pro dlouhodobé přežití pacientů je diskutovaným tématem toxicita těchto léčebných postupů, u které nemůžeme přehlédnout kognitivní poruchy. Mechanizmů, na jejichž základě kognitivní poruchy vznikají, je několik a jsou stále předmětem výzkumu. Zaměřujeme se na patofyziologické elementy, které se podílí na kognitivních poruchách, a na strategie, jakými jsou hipokampus šetřící (hippocampal avoidance; HA) WBRT pro kandidáty na cílenou léčbu s různými histologickými typy nádorů, která přechází hematoencefalickou bariéru. I když je léčba HA-WBRT plus memantinem jakožto standard stále předmětem diskuzí, v případech mnohočetných mozkových metastáz nebo metastáz, u kterých není vhodná cílená radioterapie, a u pacientů s očekávaným přežitím > 4 měsíce je nutné aplikovat strategii pro prevence poruch kognitivních funkcí. V budoucnu musí být do analýz a studií zařazeny nové studie, které zhodnotí kognitivní funkce u pacientů s dlouhodobým přežitím, ale také další faktory, jako je počet a objem mozkových metastáz, jejich intrakraniální a extrakraniální lokalizace a efekt moderních onkologických terapií.

Klíčová slova
celomozkové ozáření – šetření hippokampu – mozkové metastázy – memantin – kognitivní porucha – demence

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Introduction

The percentage of patients diagnosed with cancer who develop cerebral metastases during the evolution of the disease is about 30%, a proportion with potential for growth in the context of improving the prognosis with the tendency to transform cancer, even at an advanced stage, into a chronic disease. Half of these patients with intracranial metastases will be treated with whole brain radiotherapy (WBRT). The increased interest in the quality of life (QoL) and the use of neurocognitive tests have brought to the fore the neuro-cognitive decline associated with irradiation, a toxicity historically considered late and rare. Even if the DeAngelis study mentions the use for brain metastases irradiation radiation doses higher than the current standard and the association of systemic therapy, an 11% rate of severe dementia is worrying and considered related to an aggressive treatment. The authors of the Radiation Therapy Oncology Group Study (RTOG) 93-10 propose a radiation dose of 45 Gy and the addition of high-dose cytarabine for all patients. This neurocognitive toxicity must be considered for metastatic lesions that benefit from targetable mutations, with the old statistical data mentioning overall survival (OS) of 3–4 months for cases that did not benefit from surgical intervention being no longer current and valid [1,2].

Autopsy reports mention an underreporting of brain metastases cases and high-resolution MRI techniques have contributed to enhanced detection of subclinical disease. At the same time, cancer types that historically were not associated with brain metastases, such as digestive cancers, could be related with a less aggressive intracranial evolution [2–4].

The reduction of neurogenesis is one of the most plausible hypotheses, with this phenomenon being assumed to take place in the sub-granular zone (SGZ) of the hippocampus and in the sub-ventricular zone (SVZ) of the lateral ventricles. A prevailing hypothesis for a mechanism responsible for cognitive impairment, particularly memory impairment following cranial radiation therapy, is reduced neurogenesis after exposure of neuronal precursors to ionizing radiation. Neurogenesis is thought to occur predominantly in two critical regions of the developing brain: the SGZ of the hippocampus and the SVZ of the lateral ventricles. In these areas, there are the stem cells that will later differentiate into neurons and glial cells. However, animal model studies that evaluated the response of these neuronal progenitors to irradiation demonstrated that, although an ablative dose of 10 Gy can lead to a quasi-total reduction of neuron production, there is still a progenitor reserve identical to that of non-irradiated tissues one month after treatment [2,5]. Rola et al. highlight a proportional reduction with the dose of proliferating SGZ cells and of immature neurons in young mice. In this case, the mechanisms that affected neurogenesis were associated with chronic inflammation, while the effect of irradiation on glial cells was minimal. Using the Morris water maze, the authors highlight a cognitive deficit 3 months after irradiation, impairment starting from the hippocampus region. The effect of the reduction of neuronal progenitors after irradiation appears both in the SGZ and in the SVZ. In the case of the SVZ there is a phenomenon of delayed neurogenesis and in the hippocampus neurogenesis is inhibited. The involvement of the microenvironment, the effect of resident microglia and resident immune cells in the brain are also mentioned in radiation-induced cognitive toxicity [2,6].

It is possible that the microenvironment modulation effect is more important than the destruction by mitotic catastrophe of neuronal precursors. The differences between the effects of irradiation *in vitro* and *in vivo* and the promotion of differentiation on astrocytic lines in vivo are proof of microenvironment involvement in toxicity via the inflammatory response. Fike et al. also mention oxidative stress along with chronic inflammation as a mechanism involved in the inhibition of neurogenesis induced by radiation. Markers of inflammation such as tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β detected at long intervals after irradiation in the hippocampus explain the effect of cognitive decline mediated by oxidative stress in this region. IL-10 and histamine are also released in the hippocampus after irradiation as mentioned by Tőkés et al. [7].

Not only inflammation and oxidative stress are incriminated in neurocognitive degradation due to irradiation of the hippocampus region. An impaired microvascular network is observed after partial brain irradiation on an animal model monitored ex vivo at intervals of 3, 5 days and 10 weeks in the hippocampal cornu ammonis. The microvasculature was affected in the experiment only in the irradiated region, thus explaining another mechanism that inhibits the development of neural precursors, with these cells being located around small vessels [1,2]. Changes in dendritic spines associated with synaptic plasticity were identified by Ding et al. 1 month (40.58%) and 3 months (28.92%) after mice irradiation. It is worth noting the reduction of basal dendrites and the lack of changes in the apical region of cornu ammonis [8].

Target therapy and brain metastases – implications in prognosis

Until the emergence of new innovations in oncology including target therapy and immunotherapy, the benefit of chemotherapy on brain metastases was limited by the inability of available agents to penetrate the blood-brain barrier (BBB) [2–4,9]. Bai et al. report a modest activity of erlotinib, a specific inhibitor of epidermal growth factor receptor (EGFR) in brain metastases of non-small cell lung carcinoma (NSCLC). However, the authors mention the significant benefit of erlotinib in cases of NSCLC with EGFR mutation [10]. Osimertinib, a third generation EGFR inhibitor demonstrated the ability to generate a rapid intracranial response in NSCLC cases with EGFR T790M mutation. Similar results were published for gefitinib, another EGFR inhibitor in NSCLC by Hotta et al. [11]. Lapatinib, an agent that crosses the BBB, demonstrated the ability to prevent brain metastasis of HER2+ breast cancer. Lapatinib is also effective in the regimen that associates capecitabine for the treatment of brain metastases having HER2+ breast cancer profile. Trastuzumab emtansine (T-DM1), an antibody drug conjugate, has demonstrated intracranial activity for the subtype of breast cancer mentioned previously, with a median reduction of 30% being associated with the administration of transtuzumab, a monoclonal antibody that binds to emtansine, a microtubule inhibitor. However, in the studies associated with radiation therapy, T-DM1 did not highlight the potential for radiosensitisation [12–14]. In BRAF V600-mutant brain metastatic malignant melanoma, dabrafenib plus trametinib induced a favorable, but short-term response [15–17]. Some of the target molecular agents routinely used in modern oncology practice, known for BBB permeability and cognitive effects reported in preclinical and clinical studies, are summarized in Tab. 1 [18–27].

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Tab. 1. Molecular target agents for the blood-brain barrier permeability – preclinical and clinical data regarding the effect on cognitive impairments.

Target agent used in brain metastases treatment	Mechanism of action	Cancer type	Results
Lorlatinib	3rd generation ALK/ROS1 TKI	ALK-positive NSCLC	1% cognitive disorder [18]
Erlotinib	1st generation TKI	EGFR positive NSCLC	a 74-year-old patient out of 40 included in study was diagnosed with dementia 2 years after treatment [19]
Erlotinib		EGFR positive NSCLC	improve quality of life including cognition [20]
Gefitinib	1st generation TKI	EGFR positive NSCLC	cognitive functions improved during treatment [21]
Dacomitinib	1st generation TKI	EGFR positive NSCLC	trouble concentrating and remembering things comparing with patients treated with Gefitinib [22]
Osimertinib	3th generation TKI designed to overcome resistance from T790M mutations	EGFR positive NSCLC	used to avoid radiation induced cognitive impairment [23]
Trametinib	MEK1/2 inhibitor	melanoma (in this preclinical study evaluated in Alzheimer's disease)	mitigates cognitive impairment in a mice model due reduces synapse loss [24]
Trametinib		melanoma	cognitive function better for combination Dabrafenib-Trametinib [25]
Trametinib		evaluated in preclinical mice model with traumatic brain injury	attenuates neuroinflammation and cognitive deficits [26]
Trastuzumab deruxtecan	antibody-drug conjugate active in HER2 positive tumors	breast	preservation of cognitive functions [27]

ALK – anaplastic lymphoma kinase; EGFR – epidermal growth factor receptor; HER2 – human epidermal growth factor receptor 2; MEK1/2 – mitogen-activated protein kinase 1/2; NSCLC – non-small cell lung cancer; ROS1 – ROS proto-oncogene 1, receptor tyrosine kinase; TKI – tyrosine kinase inhibitors

Pharmacological strategies to reduce and limit the cognitive deficit post-WBRT

Memantine, a non-competitive agonist of N-methyl-D-aspartate receptor, is intensively studied for its potential to reduce dementia associated with cerebral irradiation and the mechanism of action involves limiting the binding of glutamate when it is released at high levels in pathological ischemic states. The double mechanism involving neurocognitive toxicity related to both vascular dementia and radiation-induced vasculopathy makes memantine an agent of major interest in clinical trials. The effect of memantine was studied in The Radiation Therapy Oncology Group (RTOG) 0614 trial concurrent with WBRT and the evaluation by Hopkins Verbal Learning Test–Revised Delayed Recall (HVLT-R DR) 24 weeks after treatment showed a reduction in memory functions, but not a cognitive impairment in patients, who received memantine compared to the control group. The trial highlighted a probability of cognitive decline of 53.8% in the memantine study arm and 64.9% in the control arm, evaluating the results at 24 weeks. Even if less decline in delayed recall was observed in the memantine arm at 24 weeks, the possibility of analyzing only data from 149 patients out of the 508 eligible to be included in the study led to a statistical power of only 35%. Thus, the high rate of patient loss was associated with a lack of statistical significance, but the authors still note the benefit of memantine both in the delay of cognitive decline and in the reduction of memory decline rates and the improvement of executive functions and processing speed. Donepezil, but even low dose insulin for intranasal metabolic stimulation have also been tested as preventive strategies for neurocognitive decline after WBRT [28,29].

Hippocampal sparing WBRT

Hippocampal sparing was proposed as a radiotherapy planning method by Gupta et al. more than 10 years ago. In the context created by the progress of oncological therapies and the possibility of obtaining prolonged survival due to active agents that cross the BBB, the concept of hippocampal sparing associated with pharmacological therapy to reduce cognitive impairment was proposed. The study by Gupta et al. proposed the contouring of the hippocampus on 5 cases previously treated with WBRT using a 5-mm expansion around the hippocampus. The treatment plans were designed with helical tomotherapy and LINAC based intensity modulated radiotherapy (IMRT) using a total dose of 30 Gy in 10 fractions. The study identified a median hippocampal volume of 3.3 cm, representing 2.1% of the target volume. Using a normalization to 2 Gy according to the linear quad-

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ratic (LQ) formalism, the results revealed an 87% reduction of the dose per hippocampus per each radiotherapy fraction, with both treatment planning modalities being considered feasible [2,28–30]. Gondi et al. identified a dose ≤ 30 Gy as the tolerance limit of the left hippocampus in order to preserve neurocognitive function. It should be mentioned that the dose proposed by the authors as a constraint was derived from the irradiation of primary brain tumors with standard 2 Gy/fraction regimen. Consequently, it is necessary to normalize the prescription radiation doses to 2 Gy according to LQ in order to make an objective comparison in the case of WBRT [31–33].

The German phase II prospective randomized HIPPORAD trial proposed the evaluation of cognitive functions if patients receive a WBRT regimen with a total dose of 30 Gy in 12 daily fractions to which simultaneous integrated boost (SIB) is added up to a dose of 51 Gy/42 Gy in 12 daily fractions on the macroscopic volume of cerebral metastases/resection cavities. The study included cases with solid tumors with at least 4 metastases, not more than 10 metastases, and not with sizes ≥ 5 mm. In the experimental group, it was proposed to limit the dose to the hippocampus to 9 Gy in 98% of the volume and 17 Gy in 2% of the volume. It should also be mentioned that patients initially diagnosed with dementia, but also with meningeal disease, cerebral lymphomas, germ cell tumors, and small cell carcinomas were excluded from the study. As a primary endpoint, the study evaluated the cognitive status 3 months, 9 months and 18 months after treatment, and annually thereafter [34].

The increased biological equivalent dose received by the brain with implications on the long-term vasculature used in NRG Oncology Trial CC001 trial was also mentioned as an underestimated factor for possible late toxic effects. The phase III trial enrolled adult patients with brain metastases treated with hippocampal avoidance radiotherapy (HA-WBRT) plus memantine or WBRT plus memantine aimed to evaluate the deterioration of cognitive functions assessed with specific tests, but also to assess overall survival (OS), intracranial progression-free survival (PFS), toxicity and patient-reported subjective symptoms as secondary objectives. The study included 518 patients and revealed a lower rate of cognitive impairment in cases treated with HA-WBRT plus memantine for a median follow-up of 7.9 months. The difference was generated by a reduction in the impairment of executive functions at 4 months in the group that benefited from hippocampal sparing technique by 17.1% and a reduction in memory deterioration by 13.2% in favor of the previously mentioned hippocampal sparing treatment regimen. The other secondary objectives did not differ significantly in the two groups, with the exception of fatigue, speaking difficulty and difficulty remembering certain things, with these effects being reduced in the HA-WBRT plus memantine group. The authors consider the combination of HA-WBRT plus memantine as a new standard that must be offered to patients with an indication for WBRT. However, Levy et al. mentioned several confounding factors that were ignored in clinical studies including histological type, metastatic burden and intracranial and extracranial location of metastases. The authors mentioned the possibility that these factors underestimated in clinical trials influenced the final results [35]. However, mentioning five possible pitfalls of Brown et al.'s trial, Andratschke et al. recommended waiting for long-term follow-up results before implementing HA-WBRT plus memantine as a new standard, mentioning the lack of benefit of this new approach for hippocampal prophylactic cranial irradiation, from the point of view of cognitive impairment, in 2 trials including cases of lung cancer [36–41].

Current SRT role in brain metastases – focus on cognitive functions

WBRT administered after SRT has demonstrated benefit in tumor control, but due to cognitive decline, the association of the two methods is controversial. Brown et al. aimed to analyze if 3 months after SRT as the only treatment, there was an association with less cognitive deterioration compared to SRT followed by WBRT. The study included cases with 1–3 brain metastases and randomized the cases into 2 groups. The dose of SRT as a single treatment was 20–24 Gy and 18–22 Gy in the case of associated WBRT. The WBRT treatment was delivered in a total dose of 30 Gy in 12 daily fractions. The rate of cognitive deterioration was significantly higher when SRT was followed by WBRT (91.7%) compared to SRT administered as a single treatment (63.5%). The time to intracranial failure was shorter and the quality of life at 3 months was better when only SRT was administered. The OS in this case was 10.7 months and 7.4 months, respectively, being higher in the case when only SRS was administered. The incidence of cognitive deterioration was higher both at 3 months and at 12 months in the group that received WBRT. The results argue for the use of SRT as the only method for 1–3 metastases, and the arguments include the absence of a benefit in OS but also a lower cognitive decline [29].

Repeated SRT may be an option to reduce cognitive decline, considering the findings of Kuntz et al. who noted that 20–40% of patients would need rescue treatment after initial SRT. However, depending on the location and number of metastases, the choice of treatment may vary between repeating SRT, surgery, targeted therapy, WBRT or supportive care. A retrospective monocentric study including 184 cases demonstrated that the repetition of the SRT sequence without the intercalation or association of WBRT was associated with maintaining the quality of life including the cognitive status, with more than 95% of the cases maintaining a Karnofsky Performance Status (KPS) score > 70 during the SRS sequences. Upfront WBRT and higher metastatic burden were associated with the decline of quality of life (QoL) after SRS [30,31].

Conclusions

Even if the implementation of HA-WBRT plus memantine as a standard for cases with multiple brain metastases or metastases unsuitable for targeted radiotherapy is still the subject of a debate, for cases with brain metastases with a life expectancy > 4 months, it is necessary to apply a preventive strategy for the impairment of cognitive functions. New studies to evaluate the cognitive functions for long term survivals, but also an evaluation of other factors including the number and volume of brain metastases, intracranial and extracranial localization and the effect of modern oncological therapies must be included in future analyzes and studies.

Conflict of interest

The authors declare that there are no conflicts of interest related to this article.

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