A link between vascular damage and cognitive deficits after whole-brain radiation therapy for cancer: A clue to other types of dementia?

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1. Introduction

Whole brain radiation therapy (WBRT) is commonly used for the treatment of brain tumors and cancers with brain metastasis. Since growing cells such as tumor cells are more sensitive to irradiation than normal cells, irradiation can be used to kill the malignant cells and improve the survival rate in patients with tumors. However, cognitive impairment is a well-documented consequence of WBRT (1-4). In addition to acute encephalopathy (5,6), memory deficits have been noted in up to 50% of patients undergoing WBRT over a short period of several months. In addition, WBRT is reported to increase the rate of dementia three-fold in younger patients (< 65 years old, up to around 0.2% of irradiated persons) (7) and to lower the intelligence quotient (IQ) of children (8) over the longer term, i.e. years.

A deficit in neurogenesis has been postulated to be the main cause of cognitive decline (9-11), but recent data on irradiation therapy (RT) for various parts of the brain appear to indicate the complex causes of cognitive deficits. Analysis indicated that different regions are of varying importance when performing certain cognitive tasks, suggesting that hippocampal neurogenesis alone may be an oversimplification of the brain injury processes occurring after RT (12).

Irradiation can directly damage various types of cells other than neuronal stem cells (13), but the current paper will focus on injury to brain vasculature leading to cognitive decline since vessels represent a better therapeutic target for drug development than other cells in the brain because of the blood-brain barrier.

2. Small blood vessels in the brain

The brain has an elaborate vascular system. Arteries and veins are joined by a fine network of capillaries that are intertwined with the surrounding neuronal architecture (14,15). A brain capillary has an endothelial cell layer tightly surrounded by thin pericytes and the diameter is often smaller than 10 micrometers (16). Since red blood cells are around 13 micrometers in diameter and monocytes are 22 (17), cells shiny through the dilated thin tubules in a physiological state. The mean distance

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Summary

Whole brain radiation therapy for the treatment of tumors can sometimes cause cognitive impairment. Memory deficits were noted in up to 50% of treated patients over a short period of several months. In addition, an increased rate of dementia in young patients has been noted over the longer term, i.e. years. A deficit in neurogenesis after irradiation has been postulated to be the main cause of cognitive decline in patients, but recent data on irradiation therapy for limited parts of the brain appear to indicate other possibilities. Irradiation can directly damage various types of cells other than neuronal stem cells. However, this paper will focus on injury to brain vasculature leading to cognitive decline since vessels represent a better therapeutic target for drug development than other cells in the brain because of the blood-brain barrier.

Keywords: Irradiation, angiogenesis, memory, learning, cognitive deficits, Alzheimer disease

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from the center of the neuronal somata to the closest microvessel is 15 microns (14). Neurons need a supply of nutrients and oxygen from vessels and would be affected by any defect in the immediate vasculature.

3. Radiation sensitivity of vascular cells

The endothelial cells of brain capillaries and their surrounding pericytes are known to display certain characteristics. Although these characteristics are not fully understood, studies have described their relationship to radiation.

3.1. Cell viability

AA study compared rat primary cerebrovascular endothelial cells in culture to neurons, microglia, and astrocytes in terms of their sensitivity to radiation. The endothelial cells had marked sensitivity to radiation (a ~2-fold larger number of dead cells) (18).

3.2. Angiogenesis

Angiogenesis, i.e., the making of new blood vessels, could play an important role in natural cognition. Physical exercise is known to have beneficial effects on mental health (19) to have anti-depressant action (20), and on learning ability (21). In these instances, angiogenesis seems to be indispensable because injection of angiogenesis inhibitors canceled out the effects of exercise (20).

After irradiation, angiogenesis, i.e. CD31-positive capillary density, decreases substantially in laboratory mice (22) and is accompanied by learning deficits (23). Thus, a deficit in angiogenesis may cause cognitive decline. However, this decline might be inevitable for patients who have a tumor since the target for RT is not merely tumor cells but also angiogenesis inside the tumor. Limiting irradiation sites to areas around tumors seems to be the most ideal way to resolve this problem. Bevacizumab (Avastin) and other recent anti-cancer drugs inhibits angiogenesis, so this type of drugs should be used with caution in combination with RT (6).

3.3. Transcriptome profiles

A study reported on the transcriptome profiles of mouse brain tissue after whole-body irradiation. The study noted that the most altered genes involved ion channels, long-term potentiation, depression, and vascular damage (22).

4. Similarity and relationship to forms of senile dementia including Alzheimer’s disease

Many possible remedies of irradiation-induced cognitive decline and precautions to limit that decline have been proposed and used (24,25) in patients and animals. Two effective remedies were memantine (26,27) and donepezil (28,29). Both are drugs to treat Alzheimer’s disease and both have different targets of action (30).

Some recent studies of Alzheimer’s disease have suggested that vascular defects in small capillaries may play a central role (31-34). In addition, cognitive decline as a result of radiation and cognitive decline as a result of senile dementia (25,35) seem to have common features. Animal models using radiation (1,5,10) would be of great benefit if they can serve as a general model of dementia because they can be produced in young animals in a short period of time.

5. Conclusion

Cognitive deficits after whole-brain radiation therapy for cancer should be studied in light of vascular damage along with forms of dementia, including Alzheimer’s disease.

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