INTRODUCTION

• More than 1.68 million new cases of cancer expected to be diagnosed in 2016. About 60% of patients survive >20 years. 1/3rd of the 1.68 million diagnosed will develop brain mets.

• For many of these metastatic lesions, along with primary tumors (25,000 new cases/yr), radiotherapy remains a primary treatment modality involving 200,000 patients/yr that receive partial or whole brain irradiation (IRR).

• Cranial IRR is shown to be associated with progressive dementia and hippocampal-dependent cognitive dysfunction, especially in pediatric cases. Persistent cognitive decrements adversely affect quality of life with little or no clinical recourse.

• Anti-oxidant and anti-inflammatory strategies have shown marginal benefit for improving cognition after irradiation.

• NSI-189 is novel BBB permeable small molecule shown to increase neurogenesis and hippocampal volume.

• Importantly, NSI-189 has shown behavioral benefits in a mouse model of depression and considerable promise in a Phase 1B clinical trial for the treatment of major depressive disorder (MDD, Fava et al., Mol. Psych., 2016).

• Using clinically-relevant fractionated whole brain IRR, we show beneficial neurocognitive effects of orally administered NSI-189 on hippocampal- and frontal cortex-dependent behavior tasks 1 month post-irradiation in rats.

RESULTS

NSI-189 treatment preserved hippocampal proliferation

Cognitive function

NSI-189 treatment ameliorates radiation (27 Gy)-induced cognitive deficits

CONCLUSIONS

• Oral administration of NSI-189 mitigated radiation-induced behavior impairments.

• NSI-189 treatment ameliorated radiation-induced impairments in hippocampal- and frontal cortex-dependent episodic and spatial memory function as assessed by 4 spontaneous exploration tasks.

• Cranial irradiation showed a trend toward impaired contextual fear conditioning.

• Measurements of hippocampal volume did not show significant effects of cranial irradiation.

• NSI-189 treatment also preserved the number of proliferating cells within the hippocampal subgranular zone.

• In summary, the BBB permeable, small molecule compound NSI-189 shows promise as a potential translational intervention against radiation-induced cognitive dysfunction.

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