Preclinical Study and Translational Application of Concurrent Radiotherapy and Valproic Acid for Intracranial Hemangioblastomas in Sporadic Hemangioblastomatosis.

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Introduction

Sporadic hemangioblastomatosis is characterized by multifocal, malignant progression of histologically-benign hemangioblastomas that commonly carry inactivating mutations of the von-Hippel Lindau (VHL) gene. Despite aggressive management with surgery and radiotherapy (RT), hemangioblastomatosis inevitably leads to dismal outcomes and death within 2 years of diagnosis. Histone deacetylase (HDAC) inhibition with concurrent high-dose valproic acid (VPA) has been used to potentiate RT in some patients with glioma. We postulated that a similar regimen may improve therapy for hemangioblastomatosis.

Methods

To test the effect of concurrent HDAC inhibition and RT in a VHL-deficient background, we exposed the human-derived, VHL -/-, 786-O tumor cell line to RT and the HDAC inhibitors VPA, suberanilohydoxamic acid (SAHA), and panobinostat. Cell viability analysis, quantitative gamma-H2AX expression (a measure of double-strand DNA breaks) and cell-cycle analysis were performed. Under a compassionate use protocol, one patient with sporadic hemangioblastomatosis and multiple, rapidly-enlarging tumors was offered this regimen of conrurrent VPA and RT. Clinical evaluation and craniospinal MRI were performed at 3-month intervals.

Results

In the preclinical setting, all 3 drugs potentiated RT response. VPA treatment prior to RT led to a decrease in cell viability relative to control (VPA alone: 65.87%, RT alone: 67.46%, VPA+RT: 38.79%) as well as increased gamma-H2AX foci/cell (VPA alone: 5.29, RT alone: 5.46, VPA+RT: 15.49). Cell-cycle analysis revealed progression to G2 phase and reduction in S-phase populations in all drug-RT combinations. The patient with hemangioblastomatosis, tolerated RT (45 Gy, 25 fractions) with concurrent high-dose VPA (25 mg/kg) for 16 days. At 6 months follow-up, the patient was recovering well and target lesions had stabilized.

Learning Objectives

By the conclusion of this session, participants should be able to:

1) Understand the morbidity of sporadic hemangioblastomatosis

2) Discuss the rationale for combinatorial radiotherapy and HDAC inhibition for these patients

3) Describe the results of such therapy in a pre-clinical setting

Conclusions

Concurrent RT and HDAC inhibition may have therapeutic benefit in patients with hemangioblastomatosis, for whom no effective therapies exist. This study provides rationale for further clinical study and extension of this combinatorial regimen to other benign intracranial neoplasms.