B-7

Enhancing Efficacy of PRRT for Neuroendocrine Tumors by Combining with Everolimus and Histone Deacetylase Inhibitors

Dongyoul Lee[1]; Mengshi Li[1]; Dijie Liu[1]; Somya Kapoor[1]; Joshua Prindle[2]; Addelynn Smith[3]; Michael Schultz[1]

[1]University of Iowa; [2]Clarke University; [3]University of California, Berkeley

BACKGROUND: Therapeutic options available for the treatment of Neuroendocrine tumors (NETs) include inhibitors of mTOR; somatostatin analogs; and peptide receptor radionuclide therapy (PRRT) targeting the somatostatin subtype 2 receptor (SSTR2). While these approaches to NET treatment have improved outcomes for NET patients, efficacy is largely limited to disease stabilization and symptomatic relief – and complete responses are rare. Emerging biochemical evidence suggests that combinations of these drugs have the potential to improve outcomes for NET patients further. Within this context, we explored the potential for combining PRRT with everolimus, histone deacetylase inhibitors (HDACi), octreotide, and a MEK inhibitor (MEKi).

METHODS: The effects on cell growth and clonogenic survival of BON-1 cells when incubated with everolimus, 4-phenylbutyric acid (4-PBA; HDACi), octreotide, and PD0325901 (MEKi) were evaluated (alone and in combination). The effect of the drugs on SSTR2 expression was measured by qRT-PCR (mRNA) and flow cytometry (protein). The effect of each drug alone and in combination with [^{90}Y]DOTATOC PRRT was examined by clonogenic cell survival assay.

RESULTS: The effects of everolimus were cytostatic, while treatments with MEKi and HDACi decreased both cell proliferation and clonogenic survival. Incubation of BON-1 cells with everolimus and HDACi upregulated SSTR2 by mRNA and

protein. Combining everolimus with HDACi (as well as everolimus combined with MEKi) significantly decreased cell proliferation relative to these drugs alone as controls. Interestingly, the combination of everolimus and HDACi enhanced SSTR2 expression, while everolimus plus MEKi abrogated the upregulation of SSTR2 induced by treatment with everolimus alone. [^{203}Pb]DOTATOC SPECT/CT imaging confirmed the potential to enhance radiolabeled peptide uptake in BON-1 xenograft tumors by pretreatment with the combination of everolimus and HDACi.

CONCLUSION: This study suggests the co-treatment of everolimus and HDACi can be used to enhance the therapeutic efficacy of PRRT by upregulating SSTR2 and increasing anti-tumor effects for NETs.