Evaluation of Potential Therapeutic Action of the SET/I2PP2A Inhibitor OP449 in Head and Neck Squamous Cell Carcinoma

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Introduction: The head and neck cancer has an occurrence of 500,000 cases annually worldwide; 90% of cases are head and neck squamous cell carcinoma (HNSCC) and only 40-50% of patients have an overall survival rate of five years. The study of molecular profile in cancer has allowed the development of several targeting agents, such as the OP449. OP449 is a synthetic peptide with antineoplastic action in chronic lymphocytic leukemia and non-Hodgkin lymphoma cells, probably through a direct binding to SET and release of SET-mediated PP2A inhibition. SET/I2PP2A, a 39 kDa phosphoprotein encoded by the *SET* gene, is a multifunctional protein up-regulated in HNSCC, and proposed to have a role as an oxidative stress sensor, promoting cell survival in association with increased phosphorylated-Akt levels and enhanced antioxidant defense. **Objectives:** To evaluate a potential application of OP449 in HNSCC, anti-tumoral effects were assessed by *in vitro* studies in HNSCC and fibroblasts cells, and by xenograft tumor growth model in nude mice (SCC9 cell line). **Material and Methods:** The cytotoxic effect of OP449 peptide was assessed in human cell lines by the Resazurin cell viability assay. The inhibition of SET protein was confirmed by Western blotting and Akt phosphorylation. SCC9 xenograft tumor growth (flank) was established in Balb/c nude mice eight days after a subcutaneous injection of cells. **Results and Discussion**: The OP449 at 5.11-8.14 µM was enough to decrease 50% of viability of HNSCC cells, while in fibroblasts the concentration was >10 µM. The SET protein inhibition showed reduction in the levels of $pAKT_{473}$, an important SET target. The mice bearing SCC9 subcutaneous xenograft tumors (n=5) treated with OP449 showed a significant reduction in tumor growth. **Conclusions:** OP449 treatment in mice bearing HNSCC xenograft tumors has an antineoplastic potential. These results open perspectives to either alternative or combined therapies, and reinforce the relevance of SET protein in HNSCC.

Keywords: Antitumor drug, oral cancer, SET.
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