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The novel HSP90 inhibitor STA-9090 exhibits activity against Kit dependent and independent malignant mast cell tumors.

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Mutations that induce ligand-independent activation of the receptor tyrosine kinase Kit are found in several human and canine cancers including gastrointestinal stromal tumors, malignant mast cell disease, and acute myelogenous leukemia. Small molecule Kit inhibitors have been exhibited significant activity in the clinical setting, but they possess variable efficacy against particular forms of mutant Kit, and drug resistance often develops over time. Recently, inhibitors of HSP90, a chaperone for which Kit is a client protein, have demonstrated biologic activity in human cancers and evidence suggests they can efficiently down-regulate several mutated and imatinib-resistant forms of Kit. The purpose of this study was to evaluate a novel HSP90 inhibitor, STA-9090, against wild-type (WT) and mutant Kit in normal canine bone marrow derived cultured mast cells (BMCMCs), malignant canine mast cell lines and fresh malignant canine mast cells cultured *ex vivo*. Cells were treated with STA-9090, 17-AAG (a geldanamycin analogue), and SU11654 (a small molecule Kit inhibitor) and evaluated for loss of cell viability, cell death, alterations in HSP90 and Kit expression/signaling, and evidence of Kit mutation. STA-9090 activity was also tested in a mastocytoma xenograft model. HSP90 expression levels were found to be similar among the BMCMCs, cell lines and fresh malignant mast cells. Treatment of BMCMCs, cell lines, and fresh malignant cells with STA-9090 induced growth inhibition and apoptosis that was caspase-3 dependent at low nM concentration. STA-9090 down-regulated phospho/total Kit and phospho/total Akt, but not ERK or PI-3 kinase. Loss of Kit cell-surface expression was also observed within 24 hrs of STA-9090 treatment. Furthermore, STA-9090 exhibited superior activity against malignant mast cells compared to 17-AAG or SU11654, and was effective against malignant mast cells expressing either WT or mutant Kit, while SU11654 was effective only against cells expressing mutant Kit. Lastly, STA-9090 inhibited tumor growth in a mastocytoma xenograft model. In summary, STA-9090 exhibits broad activity against mast cells expressing WT or mutant Kit suggesting it may be an effective agent in the clinical setting against Kit-associated malignancies.