Proof of Target for SU11654: Inhibition of KIT Phosphorylation in Canine Mast Cell Tumors


ABSTRACT

Purpose: The purpose of this study was to evaluate the effect of the receptor tyrosine kinase inhibitor SU11654 on the activity of its molecular target KIT in canine mast cell tumors (MCT) and correlate target inhibition with mutational status of the c-kit juxtamembrane domain and SU11654 plasma concentration.

Experimental Design: Tumor biopsies were obtained from dogs with advanced MCTs before and 8 h after administration of single oral dose of SU11654, previously shown to be active in dogs with MCTs. Blood samples were taken to determine the plasma concentration of SU11654. Levels of phosphorylated KIT and ERK1/2 were assessed in tumor biopsies by Western blot. Tumors were analyzed by PCR for the presence or absence of an internal tandem duplication (ITD) in the juxtamembrane domain of c-kit.

Results: Fourteen dogs with advanced MCTs were enrolled in the study; 11 of these were evaluable for KIT target modulation (the remaining tumor specimens had inevaluable amounts of total KIT protein). Of these, eight MCTs showed reduced levels of phosphorylated KIT relative to total KIT after treatment with SU11654, compared with pretreatment biopsies. All four evaluable MCTs expressing ITD mutant c-kit showed modulation of KIT phosphorylation, as did four of seven tumors expressing non-ITD c-kit. Phosphorylated ERK1/2 was modulated in seven tumors; this did not correlate with inhibition of KIT phosphorylation.

Conclusion: SU11654 treatment at the efficacious dose results in inhibition of KIT phosphorylation in canine MCTs.

INTRODUCTION

The development of targeted therapies for cancer offers the opportunity to directly evaluate drug effects on the molecular target and correlate these effects with tumor biology and drug pharmacokinetics. This can be instrumental in oncology drug development because it establishes a pharmacodynamic/pharmacokinetic relationship and provides critical information regarding the therapeutic impact of a targeted agent. Although such data can be derived from preclinical studies using tumor xenograft models in rodents, more informative data are obtained in a clinical setting. Clinical proof of concept studies have been reported recently for several targeted therapeutics (1–8). However, most of these studies were performed after initial clinical studies were either underway or completed. Obtaining early proof of concept in a clinical setting before initiating human studies can significantly impact the design of subsequent studies, including protocol objectives and dose regimen selection. Spontaneous tumors in dogs represent a unique opportunity for accelerated entry into clinical oncology studies (9). Canine and human tumors have a similar biology in that they both arise spontaneously over a number of years as a result of multiple genetic alterations and frequently present with microscopic metastatic spread at the time of diagnosis. Additionally, several of the molecular defects known to contribute to human tumorigenesis also occur in canine tumors (e.g., p53 mutations and c-kit mutations; Refs. 10–15).

RTKs are excellent candidates for molecular targeted therapy, because they play key roles in controlling cell proliferation and survival and are frequently dysregulated in a variety of malignancies. The mechanisms of dysregulation include overexpression (Her2/neu in breast cancer, epidermal growth factor receptor in non-small cell lung cancer; Refs. 16–18), activating mutations (KIT in gastrointestinal stromal tumors, FLT3 in acute myelogenous leukemia; Refs. 19–21), and autocrine loops of activation (VEGF/VEGFR in melanoma, PDGF/PDGFR in sarcoma; Refs. 22–26). Aberrantly regulated RTKs have been described in comparable human and canine cancers. For example, aberrant expression of the Met oncogene occurs in both human and canine osteosarcoma (27–29). Interestingly, comparable activating mutations in the JM domain of c-kit are seen in 50–90% of human GISTs and in 30–50% of advanced canine MCTs (13–15, 30–33). Although the mutations in human GISTs consist of deletions in the JM domain and those in canine MCTs consist of ITDs in the JM domain, both lead to constitutive phosphorylation of KIT in the absence of ligand binding.

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3 The abbreviations used are: RTK, receptor tyrosine kinase; FLT3, fms-related tyrosine kinase 3/Flik2; MCT, mast cell tumor; ITD, internal tandem duplication; PDGF, platelet-derived growth factor; PDGFR, PDGFR receptor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; JM, juxtamembrane; GIST, gastrointestinal stromal tumor; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase.
SU11654 is a small molecule inhibitor of the RTKs PDGFR, VEGFR, KIT, and FLT3. SU11654 has been shown to inhibit KIT phosphorylation, arrest cell proliferation, and induce cell cycle arrest and apoptosis in malignant mast cell lines in vitro expressing various forms of mutant KIT (34). SU11654 and related molecules are effective in preclinical models against tumor xenografts arising from cell lines of diverse human tumor origin (35), and SU11654 was recently shown to be clinically effective against a number of spontaneous malignancies in dogs (36). In the latter study, 11 of 22 canine MCTs possessed ITDs in the JM domain of c-kit.

In the current correlative study, we used a similar population of canine patients with advanced MCTs to evaluate the effect of a single dose of SU11654 at the therapeutic level defined in a previous Phase I study, using KIT phosphorylation as a marker of direct target inhibition. We also monitored phosphorylation of ERK1/2 (a MAPK downstream of KIT signaling), SU11654 plasma concentration, and the mutational status of c-kit to determine how these parameters correlate with KIT phosphorylation status after SU11654 treatment.

MATERIALS AND METHODS

Eligibility. This study was sponsored by the Center for Companion Animal Health at the University of California–Davis School of Veterinary Medicine. SU11654 was administered to dogs with advanced MCTs accessible for repeat biopsy. Informed consent from the owner of each dog was obtained according to federal and institutional guidelines.

Drug Product. SU11654 drug product [5-(5-fluoro-2-oxo-1,2-dihydro-indol-3(3H)-ylidenemethyl)-2,4-dimethyl-1H-pyrrrole-3-carboxylic acid (2-pyrrolidin-1-ethyl)-amide] was available in 20-mg scored tablets.

Study Design. This study was a proof of target modulation study in dogs with recurrent or metastatic grade II/III MCTs. Patients received a single oral dose of SU11654 at 3.25 mg/kg; this was determined to be a well-tolerated and efficacious dose in a previous Phase I clinical study (36). Using a 6-mm punch biopsy instrument, samples were obtained from the tumor before SU11654 administration and 8 h after treatment. When possible, multiple biopsies were taken. Each sample was flash frozen in liquid nitrogen and stored at −70°C before analysis. Blood samples for analysis of plasma SU11654 levels were obtained at the same time as tumor biopsies (see below).

SU11654 Plasma Levels. Blood samples were drawn from the jugular vein and placed into a red-top serum collection vacuum glass tube. Specimens were kept at room temperature, allowed to clot, centrifuged at 1500 rpm at 4°C for 10 min, transferred to cryovials, and plasma frozen at −70°C pending analysis. Briefly, plasma samples (20 μL) or SU11654 standards in canine plasma were mixed with methanol (200 μL) containing DL-propranolol hydrochloride (internal standard) in a 96-well polypropylene plate (Orochem Technology, Westmont, IL). The plate was mixed by vortex for 1 min, and the samples were centrifuged for 10 min at 4000 rpm. Ten microliters of the supernatant were injected onto the LC/MS/MS system, in which separation occurred on a BataBasic C-18 (5 μm, 100 × 4.6 mm) reverse-phase high-performance liquid chromatography column (Keystone Scientific, Foster City, CA). The amount of SU11654 and the internal standard in each canine plasma sample were quantified based on standard curves generated using known amounts of compound ranging from 0.2 to 500 ng/ml.

c-kit Mutation Analysis. For the majority of the samples, RNA was extracted using TRIzol (Invitrogen, Carlsbad, CA) according to the manufacturer’s specifications. cDNA was then generated from the RNA using dNTPs, random primers, 5× First Strand Buffer, 0.1 m DTT, and Superscript Taq polymerase (all from Promega, Madison, WI). The cDNA was quantified for each sample. For the remaining samples, genomic DNA was prepared as described previously (13). The primers used for PCR amplification of the c-kit JM domain from cDNA and genomic DNA are shown in Fig. 1A. For both reactions, the PCR was run for 40 cycles consisting of 94°C (1 min), 59°C (1 min), and 72°C (1 min), with a 5 min 72°C extension at the end of the reaction. A c-kit cDNA generated from the canine C2 mast cell line and cDNA generated from normal canine cerebellum were used as controls.

The PCR products were separated by electrophoresis on a 4% agarose gel; the expected wild-type c-kit PCR product is 196 bp in size for PCR from cDNA and 190 bp in size for genomic DNA PCR. For those cases in which an ITD was not obvious (only a single band was present), the PCR products were gel purified using the Promega PCR Wizard Clean-Up kit (Promega) and sequenced using both P1 (forward) and P5 or P2 (reverse) primers at the core sequencing facility at the University of California–Davis, to rule out the presence of very small ITDs, deletions, or point mutations. Sequence alignment and comparison were performed using the DNASIS sequence analysis program.

Analysis of KIT and ERK Phosphorylation. Tumor biopsies were frozen in liquid nitrogen and later pulverized using a liquid nitrogen-cooled cryomortar and pestle, then stored at −70°C until used. For the analysis of KIT, pulverized tumors were homogenized, lysed, and immunoprecipitated from 1 mg of starting tumor lysate, as described (37), using an agarose-conjugated antibody to KIT (SC-1493AC; Santa Cruz Biotechnology, Santa Cruz, CA). When multiple biopsies were available, repeat immunoprecipitation/Western blot analysis was performed on separate biopsies. The amount of phosphorylated KIT in each sample was determined by Western blot using an antibody to phosphotyrosine 719 of murine KIT (3391; Cell Signaling Technology, Beverly, MA), which corresponds to tyrosine 721 of canine KIT and is an autophosphorylation site and, thus, a surrogate for KIT kinase activity. For the analysis of total KIT, the blots were stripped, reblocked, and reprobed with an antibody to KIT (A-4542; DAKO Corp., Carpinteria, CA). For analysis of p42/44 ERK, the same tumor lysates used for KIT analysis were probed by Western blot with an antibody to phospho-Thr Tyr 202/204 ERK1/2 (9101B; Cell Signaling Technology) and then stripped and reprobed with an antibody to total ERK (9102; Cell Signaling Technology). Evaluatable tumor biopsy pairs for both KIT and ERK1/2 were considered those for which detectable total protein was present in both biopsies of the pair. Target modulation was scored by eye by three observers blinded to the JM status and plasma concentration. Reduction of ≥50% in phospho-protein signal relative to total protein signal in the biopsy sample taken post-treatment compared with the pretreatment biopsy was scored as positive for target modulation, whereas a reduction of <50% was scored negative.
RESULTS

Fourteen dogs were enrolled in this clinical study with the primary objective to determine whether a reduction in KIT tyrosine phosphorylation occurred after oral administration of a single dose of SU11564. KIT tyrosine phosphorylation was assessed using a phospho-specific antibody directed against an autophosphorylation site in KIT, serving as a surrogate for KIT kinase activity. In addition, \textit{c-kit} JM mutational status (ITD\textsubscript{ITD} or ITD\textsubscript{H11001} or ITD\textsubscript{H11002}) was determined from the baseline tumor biopsy, and plasma concentrations of SU11654 were measured 8 h after dosing to correlate these parameters with inhibition of KIT phosphorylation. Eleven of the 14 dogs were evaluable for KIT target modulation. The three dogs deemed not evaluable had undetectable or greatly reduced total KIT protein in one or both biopsies and so could not be scored for target modulation. The data for all dogs enrolled in the study are summarized in Table 1.

Of the 14 dogs analyzed, 5 (36\%) had an ITD by PCR analysis (Fig. 1B). The PCR products from the remaining nine dogs that did not have evidence of an ITD were directly sequenced, and none demonstrated any type of mutation (insertion, deletion, or point mutation; data not shown).

The level of total and phosphorylated KIT expressed in the MCTs at baseline varied between animals. Higher KIT expression correlated with higher tumor grade, as reported previously (38). Four of eight grade III tumors had high KIT expression, compared to one of six grade II tumors (Fig. 2). For example, the total KIT expression in the tumor from patient 2 (grade III) was markedly higher than that in the tumor from patient 11 (grade II). Dogs with grade III tumors also had a higher incidence of high levels of phosphorylated KIT at baseline than those with grade II tumors, consistent with the increased frequency of \textit{c-kit} ITD mutations in advanced tumors and consequently elevated levels of ligand-independent phosphorylated KIT (13–15). Five of the evaluable seven dogs with grade III tumors had high levels of phosphorylated KIT at baseline; four of these were positive for the presence of an ITD in \textit{c-kit}. Only 1 grade II tumor had significant phosphorylated KIT; this animal also expressed ITD-mutated \textit{c-kit}.

Eight of the 11 evaluable dogs scored positive for target modulation using the criterion of a 50\% reduction in phosphorylated KIT relative to total KIT in the biopsy sample taken after SU11654 treatment when compared with the pretreatment sample. Examples of phosphorylated KIT and total KIT phosphorylation are shown in Fig. 2. Five tumors (Fig. 2, \textit{left}) were scored as positive for target modulation, whereas two tumors (Fig. 2, \textit{right}) were scored as negative. Biopsy pairs that were scored as negative for inhibition of KIT phosphorylation after SU11654 treatment all had markedly less phosphorylated KIT at baseline than those that scored positive (Fig. 2). This may be relevant biologically but may also have a technical explanation if the antiphospho-Y719 KIT antibody has some cross-reactivity to KIT on nonphosphorylated residues of the antibody epitope, and those samples with low levels of phosphorylated KIT approach the limits of antibody selectivity for phosphorylated residues.

To evaluate effects of SU11654 inhibition on downstream signaling pathways regulated by KIT phosphorylation, levels of the phosphorylated MAPK ERK1/2 were evaluated by Western blot analysis of the same biopsy pairs used for KIT analysis. Eleven of 14 tumors were evaluable for phosphorylated MAPK ERK1/2 target modulation (two of these were also nonevaluable for KIT target modulation, perhaps reflecting tumor heterogeneity between the regions sampled.)
pled before and after drug treatment). Of the 11 evaluable, 7 showed a reduction in the ratio of phospho-ERK1/2 to total ERK1/2 in tumors sampled after the administration of SU11654, compared with baseline tumor samples (see Fig. 2). ERK target modulation was more frequently detected in MCTs with relatively high baseline ERK expression and phosphorylation than in those with low ERK.

Based on preclinical work in rodent models, the therapeutic range of SU11654 for target inhibition was considered to be 50–100 ng/ml for 12 h of a 24-h dosing period (36). The plasma concentration of SU11654 at 8 h (Cmax) after a single dose at 3.25 mg/kg ranged from 33.2 to 186 ng/ml, with an average of 105 ± 9 ng/mL (Table 1). In one animal, the plasma concentration of SU11654 was outside the range of the other samples (0.3 ng/ml). Excluding this sample, the plasma concentrations of SU11654 observed in this study were within the same range of those observed previously in a preclinical pharmacokinetic study (data not shown). Twelve of 14 dogs had plasma levels considered to be in the therapeutic range established in a Phase I clinical study (36). The average plasma concentration for dogs with evidence of KIT target modulation (79.2 ± 41 ng/ml) and those that did not score for KIT target modulation 137 ± 36 ng/ml) was not significantly different (P = 0.08). The variation in the plasma concentration of drug may be related to differences in the size of dogs, creating a need to approximate the dose for different weights of dog by dividing presized drug tablets, and may be caused by differences in individual absorption profiles, as previously observed in a preclinical pharmacokinetic study.

**DISCUSSION**

As is the case with humans, cancer is a common and serious disease in dogs. More than half of dogs that live until the age of 10 will develop some form of cancer (39). Many aspects of canine cancer are similar to human cancer, presenting an opportunity to model human disease in an accessible clinical population with characteristics that more accurately represent the human disease than rodent xenograft models (9). Most relevant for translational studies with molecular-targeted therapeutics, human and canine cancers have a number of conserved molecular defects. Canine mammary tumors, similar to human breast cancers, overexpress the growth factor receptor erbB2, (40) and VEGF, an angiogenic factor (41). The c-Met oncogene is overexpressed in canine osteosarcoma, as in the human disease, and the tumor suppressors p53 and PTEN are also mutated in canine osteosarcomas (10–12, 29). Finally, activating mutations in c-kit have been described in both human and canine cancers.

MCTs are one of the most common malignancies in dogs, occurring with an incidence of 7–21% in the canine population (42,

![Table 1](#)

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<th>Patient no.</th>
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<th>c-kit ITD mutation present</th>
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<th>P-ERK1/2 reduction postdose</th>
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*NE, nonevaluable, P-KIT, Phospho-Tyr721 KIT, P-ERK1/2, Phospho-Thr202/Tyr204 ERK1/2.*
43). These tumors have been particularly well studied with regard to molecular alterations in the c-kit proto-oncogene. The protein product of c-kit, the receptor tyrosine kinase KIT, is expressed on mast cells and is critical for mast cell differentiation, proliferation, survival, and activation (44). Mutations in exon 11 of c-kit correlate with higher grade (malignant) MCTs and occur in those tumors more likely to recur after surgery and to eventually metastasize (13, 14). Exon 11 mutations, primarily consisting of ITDs, have been identified in 30–50% of MCTs (13, 14). Similar mutations in exon 11 have been identified in 50–90% of human GISTs (31, 33). Because exon 11 encodes a negative regulatory domain, these mutations render KIT active in the absence of ligand binding, leading to constitutive or amplified KIT signaling, which ultimately results in aberrant proliferation and survival of cells expressing this mutation (15, 34). The correlation in the molecular alteration between canine MCTs and human GISTs provides a rationale for translational studies with new oncology drugs for these human cancers in canine MCT patients.

A recent Phase I clinical study with the multitargeted indolinone kinase inhibitor SU11654 enrolled 22 canine patients with MCTs (36). Eleven of these patients had MCTs expressing KIT ITDs; 9 of these 11 canine patients had durable objective responses (complete response and partial response), with an additional patient experiencing stable disease for >10 weeks. In contrast, of the 11 patients with MCTs that did not express an ITD in KIT, only 2 had objective responses and 1 had stable disease. This difference in response also translated into a significantly increased time to progression for those dogs whose tumors expressed KIT-ITD, but not for those with MCTs expressing non-ITD KIT.

The current correlative study was designed to investigate target modulation in a comparable clinical population by studying the effects of a single clinically efficacious dose of SU11654 on the phosphorylation of KIT in canine MCTs and the subsequent impact on signaling through MAPKs. The plasma concentrations of SU11654 achieved in this study were measured near the expected C\textsubscript{max}, based on preclinical pharmacokinetic studies, and were consistent with drug levels measured in the Phase I clinical study investigating the efficacious dose and regimen (Table 1).

Eight of 11 (73%) evaluable MCT biopsy pairs had detectable inhibition of KIT activation as measured by a reduction in phosphorylated KIT after a single oral dose of SU11654. The three patients that did not show detectable KIT target modulation after treatment had MCTs that expressed low levels of KIT and phospho-KIT at baseline. The lack of significant target modulation in these patients may be attributable to technical limits in the detection method; the sensitivity of the phospho-specific antibody for phosphorylated KIT may be insufficient in samples with low baseline KIT expression. Inhibition of KIT activity correlated more closely with baseline KIT phosphorylation than with c-kit ITD genotype. Based on cellular assays, it would be predicted that both wild-type and ITD mutant KIT would be inhibited by SU11654 in vivo, because SU11654 in vitro blocked the phosphorylation of wild-type and ITD mutant KIT with comparable potency (34).

SU11654 also affected a signaling pathway downstream of KIT. Mutations in c-kit in GIST and hematopoietic malignancies have been reported to activate different signaling pathways from each other and from wild-type KIT. In canine MCTs, all but one tumor sample had detectable phosphorylated ERK1/2 at baseline, consistent with the observed frequency in human GISTs expressing exon 11 mutations in c-kit (33). In 7 of 11 evaluable tumor biopsy pairs, ERK1/2 was inhibited, as measured by a reduction in phosphorylated ERK1/2 after treatment. Not all of the tumors scoring positive for ERK1/2 inhibition were also positive for inhibition of KIT phosphorylation, most likely reflecting multiple signaling pathways impinging on ERK1/2, some of which are not initiated by SU11654 targets. ERK1/2 target modulation did not correlate with tumor grade or the presence or absence of c-kit ITD mutation. As for KIT target modulation, ERK1/2 target modulation was detected more frequently in tumors that expressed high levels of ERK1/2 and phosphorylated ERK1/2 at baseline.

The detection of inhibition of a molecular target of SU11654 after treatment of MCTs serves as proof of target modulation for SU11654 in this setting. The clinical relevance of this finding is supported by the correlation between inhibition of the molecular target and plasma drug concentrations in the therapeutic range, and the previously reported clinical objective responses in canine patients with MCTs expressing activating mutations in the target gene, providing proof of concept for SU11654 in this population of patients.

Because dogs with other malignancies (including mammary carcinoma, soft tissue sarcoma, and multiple myeloma) also experienced durable objective responses on treatment with SU11654 (36), KIT inhibition at this plasma concentration may be reasonably extrapolated to successful inhibition of the other closely related receptor tyrosine kinase targets of SU11654 expressed by these tumors, based on in vitro and in vivo potency of SU11654, providing a molecular rationale for objective responses in these tumors. For example, canine mammary tumors express VEGFR, which is inhibited at comparable concentrations to KIT in cellular in vitro assays (34). SU11654 inhibition of both wild-type and ITD mutant c-kit in MCTs can, thus, serve as a surrogate for inhibition of the related RTK targets of SU11654, VEGFR, and PDGFR, which are aberrantly expressed and/or regulated by a many different tumor types. Finally, molecular target inhibition, coupled with clinical objective responses in canine tumors, directs the development of related compounds in human cancer toward clinical populations expressing activated KIT, VEGFR, or PDGFR.

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