Catching Cancer by the Tail: New Perspectives on the Use of Kinase Inhibitors

Commentary on London et al., p. 3856

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In this issue of Clinical Cancer Research, London and colleagues evaluate a small molecule multiple-targeted tyrosine kinase inhibitor in dogs with c-kit driven skin cancer. The study represents another example of opportunities to include pet dogs in studies that improve our understanding of human cancer biology and therapy.

In this issue of Clinical Cancer Research, London and colleagues report on the evaluation of a small molecule multiple-targeted tyrosine kinase inhibitor in pet dogs with a cancer of the skin (cutaneous mast cell tumor, MCT), which often possesses an activating mutation in c-kit (1). The study represents another example of the opportunity to include pet animals with cancer in studies that improve our understanding of human cancer drugs and cancer biology (Fig. 1). As exemplified in this study, these goals may be met in parallel with clinical trial designs that seek regulatory approval for a new veterinary drug intended to treat the canine cancer patient.

MCT are the most common skin tumor in dogs; these can behave in an aggressive manner resulting in local and distant metastasis. Although MCT are rare in human patients, the fact that canine MCT biology is linked to dysregulation of the c-kit oncogene has made them an important disease model to evaluate the functional consequences of c-KIT abnormalities in cancer and more recently the role of KIT inhibitors as therapeutic agents (2–4). Furthermore, the c-kit mutations found in canine MCTs are similar to those found in gastrointestinal stromal tumors (GIST) in humans as both occur in the juxtamembrane domain of c-kit. In MCT, these mutations are most commonly insertions, whereas in human GIST they are typically deletions. Both mutations disrupt the negative regulatory function of the juxtamembrane domain, leading to ligand independent activation of KIT. Approximately 75% of GIST and 25% to 50% of canine MCTs possess c-kit mutations (1, 5). The dependence of GISTs on aberrant KIT signaling for survival explains the dramatic response rates seen in GIST patients who receive therapeutic agents that target KIT, with more than 80% responding to the small molecule inhibitor imatinib (6). However, more than half of GIST patients develop drug resistance and many questions remain about optimal management strategies for GIST at diagnosis and at relapse.

A recognized problem in the development path of novel human cancer therapeutics is the translation of safety and efficacy data from preclinical models to the human clinic. With respect to targeted therapies, early human clinical trials often do not answer critical questions important for the optimal design of later phase studies. These problems are particularly important when dealing with relatively rare diseases such as GIST. On the basis of the shared biology of aberrant and ligand independent activation of KIT, comparative studies in canine MCT provide translational opportunities to answer questions both before these agents enter the human clinic and, as exemplified by London and colleagues, following the approval of similar human therapeutics.

The canine MCT clinical trial reported in this issue of Clinical Cancer Research involved toceranib, a small molecule inhibitor of KIT, PDGFR, and VEGFR with strong similarities to other multitargeted inhibitors available for human patients (i.e., imatinib, sorafenib, sunitinib). Toceranib emerged from the development portfolio of Sugen (SU11654) and was initially used as a test agent to investigate the biologic activity of split-kinase inhibitors in spontaneous canine cancers prior to the testing of a similar agent in humans. Toceranib was evaluated in canine MCT to define the pharmacokinetic (PK) and pharmacodynamic (PD) relationship of KIT inhibition in vivo. Indeed, these studies were the first, in any species, to show the relationship between drug exposure, target modulation in tumor, and antitumor activity with a tyrosine kinase inhibitor (7). Moreover, these studies provided a unique opportunity to assess therapeutic index (i.e., safety and efficacy) in a single species during chronic exposures to a new drug. Such data are not currently provided by conventional preclinical modeling strategies and are not available before first-in-human studies. Interestingly the spectrum and nature of adverse events noted in dogs treated with toceranib were very similar to other multitargeted tyrosine kinase inhibitors in human patients (8–10). These initial data showed the value of a comparative approach that includes the assessment of novel cancer therapeutics in pet dogs with naturally occurring cancer early in the development path of a new cancer drug.

Despite the fact that several multitargeted tyrosine kinase inhibitors are now commercially available for many human
cancers, the current report including a large population of dogs with MCT ($n = 153$ dogs) has been informative for the future use of this class of agents (Fig. 1). First, this study shows the opportunity to evaluate and validate alternative treatment regimens/schedules for novel therapeutics. Currently, similar small molecule inhibitors are often administered to human patients using discontinuous treatment schedules meant to reduce toxicities associated with their long-term use. There is concern that such discontinuous schedules may result in more rapid drug resistance. The current toceranib study showed that continuous dosing at exposures sufficient to modulate the target were effective and yielded durable treatment responses. Future canine studies could compare distinct treatment schedules and prioritize schedules based on tolerability, response, and recurrence patterns, thereby providing a rationale to consider alternative treatment schedules with similar agents in humans.

A second finding was that response to toceranib was linked to disease burden; the response rate was lower and time to progression was shorter in dogs with more extensive disease. The current toceranib study showed that continuous dosing at exposures sufficient to modulate the target were effective and yielded durable treatment responses. Future canine studies could compare distinct treatment schedules and prioritize schedules based on tolerability, response, and recurrence patterns, thereby providing a rationale to consider alternative treatment schedules with similar agents in humans.

Fig. 1. Parallel opportunities: Comparative evaluation of multitargeted tyrosine kinase inhibitors in pet dogs with spontaneous arising oncogene (c-KIT) driven cancers. The past evaluation of SU11564 in canine mast cell tumors, a c-KIT driven cancer, has yielded important new information on the use of tyrosine kinase inhibitors before and during their approval as human cancer therapeutics. This includes safety after chronic exposures, resulting pharmacokinetics, target modulation in tumor, and antitumor activity. Comparative opportunities to inform the now postmarket use of these human cancer agents may be equally informative. Canine comparative studies may assist in prioritizing alternative treatment schedules and regimens for the chronic use of multitargeted tyrosine kinase inhibitors, the selection of therapeutic agents that may be used in combination therapy protocols both at initial diagnosis and at relapse, and in the timely assessment of drug activity in the setting of minimal residual disease.

Finally from the standpoint of cancer biology, an important value of the pet dog cancer model was also highlighted by this study. The underlying heterogeneity of human cancers is similarly observed in dogs with cancer. It is reasonable that this heterogeneity contributes to differences in response rates, development of resistance to therapy, disease recurrence, and development and progression of metastatic disease. This complex heterogeneity of cancer in pet dogs provided an informative context to evaluate the role of c-kit mutation as a function of treatment response. Specifically, dogs with tumors possessing a mutation had an objective response rate of 69% versus 37% when no such driver mutation was noted. These data are concordant with results in human cancer and are recently reported canine MCT study using a distinct tyrosine kinase inhibitor (AB1010) in which the presence of driver mutations predicts response to target inhibition (11). Important future such MRD studies is increasingly feasible through the development of comparative oncology centers at academic programs in the United States and abroad, and their participation in a national cooperative group managed through the Comparative Oncology Program within the National Cancer Institute Center for Cancer Research. These studies could prioritize the clinical development of agents with unique or specific activity against microscopic or dormant disease. It is interesting to note that the approval of imatinib for use in the setting of MRD was only recently announced, despite knowledge of its profound activity in chronic myelogenous leukemia and GIST for over 8 years.

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opportunities exist to study the biology and genetics of resistance and recurrence in dogs that are initially responsive to a targeted therapy but later develop resistance, presumably related to this initial cancer heterogeneity.

In summary, the recent trial by London and colleagues shows the potential value across species of a comparative approach to the study of oncology. The series of work from identification of the target in a spontaneously occurring disease in an animal, followed by demonstration of the ability to modify that target with accompanying PK/PD correlations, leading to a large scale trial in a nonhuman model species can be integrated within and inform the development path of human cancer drugs in ways not possible using conventional strategies alone.

Disclosure of Potential Conflicts of Interest

The authors are employed by Animal Clinical Investigation, LLC.

References

1. London C, Malpas PB, Michels GM, et al. Multi-center, placebo-controlled, double-blind, randomized study of oral toceranib phosphate (SU11654), a receptor tyrosine kinase inhibitor, for the treatment of dogs with recurrent (either local or distant) mast cell tumor following surgical excision. Clin Cancer Res 2009;15:3856–65.
2. Webster JD, Yuzbasiyan-Gurkan V, Kaneene JB, Miller R, Resau JH, Kupel M. The role of c-KIT in tumorigenesis: evaluation in canine cutaneous mast cell tumors. Neoplasia 2006;8:104–11. PubMed doi:10.1593/neo.05622.
3. Downing S, Chien MB, Kass PH, Moore PE, London CA. Prevalence and importance of internal tandem duplications in exons 11 and 12 of c-kit in mast cell tumors of dogs. Am J Vet Res 2002;63:1718–23. PubMed doi:10.2460/ajvr.2002.63.1718.
4. London CA, Galli SJ, Yuuki T, Hu ZQ, Helfand SC, Geissler EN. Spontaneous canine mast cell tumors express tandem duplications in the proto-oncogene c-kit. Exp Hematol 1999;27:689–97. PubMed doi:10.1016/S0301-472X(98)00078–7.
5. Du CY, Shi YQ, Zhou Y, Fu H, Zhao G. The analysis of status and clinical implication of KIT and PDGFRα mutations in gastrointestinal stromal tumor (GIST). J Surg Oncol 2006;98:175–8. PubMed doi:10.1002/jso.21104.
6. Bracci C, Bracci R, Cellerino R. Molecular targets in Gastrointestinal Stromal Tumors (GIST) therapy. Curr Cancer Drug Targets 2008;8:359–66. PubMed doi:10.2174/156800908785133169.
7. Liao AT, McMahon M, London CA. Characterization, expression and function of c-Met in canine spontaneous cancers. Vet Comp Oncol 2005;3:61–72. doi:10.1111/j.1476-5875.2005.00067.x.
8. Pryer NK, Lee LB, Zadovoskaya R, et al. Proof of target for SU11654: inhibition of KIT phosphorylation in canine mast cell tumors. Clin Cancer Res 2003;9:5729–34. PubMed.
9. London CA, Hannah AL, Zadovoskaya R, et al. Phase I dose-escalating study of SU11654, a small molecule receptor tyrosine kinase inhibitor, in dogs with spontaneous malignancies. Clin Cancer Res 2003;9:2755–68. PubMed.
10. Fedler W, Serve H, Dohner H, et al. A phase I study of SU11248 in the treatment of patients with refractory or resistant acute myeloid leukemia (AML) or not amenable to conventional therapy for the disease. Blood 2005;105:986–93. PubMed doi:10.1182/blood-2004-05–1846.
11. Hahn KA, Ogilvie G, Rusk T, et al. Masitinib is safe and effective for the treatment of canine mast cell tumors. J Vet Intern Med 2008;22:1301–9. PubMed doi:10.1111/j.1939–1676.2008.0190.x.