PEER REVIEWED

Targeted Therapy for Cancer in Veterinary Medicine

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According to the National Cancer Institute (NCI), "Targeted therapy is a type of cancer treatment that targets proteins that control how cancer cells grow, divide, and spread. It is the foundation of precision medicine. As researchers learn more about the DNA changes and proteins that drive cancer, they are better able to design treatments that target these proteins."

It wasn't until late 1990s that the types of chemotherapy used to treat cancer started to expand. Until that time, almost all drugs used worked through one mechanism – they killed rapidly dividing cells. That means rapidly dividing normal cells as well as cancer cells. Virtually all of the drugs that veterinarians use to treat cancer are in this class–vincristine, doxorubicin, cyclophosphamide, carboplatin–to name a few.

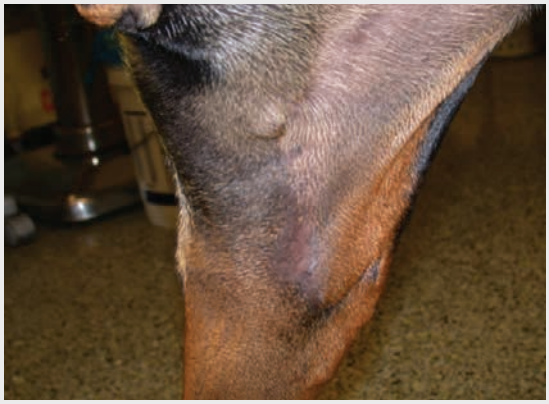
It was during the 1980's that cancer researchers found that many of the growth factors responsible for the growth and progression of cancer were the proteins produced by oncogenes (a mutated gene that has the potential to cause cancer). Scientists then started looking for drugs, targeted therapies, that were able to block these growth signals. One of the first targeted therapies to enter the market was Gleevec® (Imatinib), a drug that had phenomenal success in the treatment of chronic myelogenous leukemia in people. The target for this therapy was a protein produced by mutated genes, BCR and ABL and this mutation occurs in all cases of CML. This revolutionary drug was approved by the FDA in 2001, only 21 years ago!

The human genome was decoded in 2003 and since that time, the number of targeted therapies that the FDA has approved for use in people has skyrocketed, with over 200 drugs being approved for more than 15 types of cancer. As researchers learn more about the genomic and epigenomic (the chemical tags that modify the genome) landscape of the multitude of cancers, the development of more and better targeted therapies is highly likely.

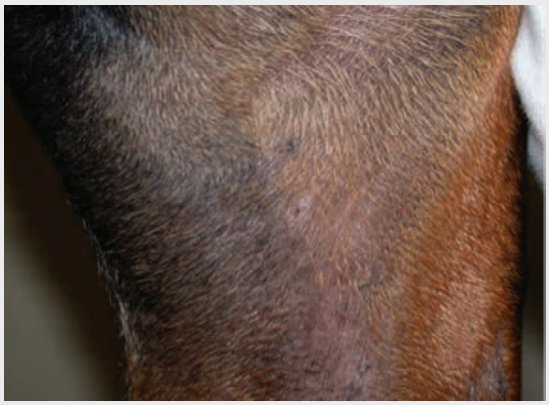
In people, the use of targeted therapies has dramatically changed the treatment for a variety of cancer types. The outlook for chronic myeloid leukemia, gastrointestinal stromal tumor (GIST), and even renal cell carcinoma, for instance, has been completely transformed by the use of targeted therapies. Targeted therapy has also revolutionized the treatment of breast cancer, colorectal cancer, lung cancer, and head and neck cancer. Not all cancers will respond as dramatically to a single targeted therapy as CML, but with increasing knowledge about the genetic and epigenetic underpinnings of cancer, rational combination therapies can be designed to help maximize effectiveness while minimizing toxicity.

The use of targeted therapies in veterinary medicine is 20 years behind human medicine. It wasn't until June 2009 that Palladia® (toceranib) was approved by the FDA and became the first targeted therapy approved for veterinary use. The pace of targeted therapy development approval in veterinary medicine, unfortunately, has not followed the trajectory seen in human medicine. Likely this is because the genomic characterization of dogs, cats and their various tumors has significantly lagged behind humans. As of now, Palladia® is still the only fully FDA approved targeted therapy for veterinarians; with Laverdia TM -CA1 (verdinexor), another targeted therapy, having conditional approval by the FDA for the treatment of lymphoma in dogs. Now that more and more universities, veterinary schools, and a few commercial entities are genetically sequencing canine tumors, the knowledge needed to use targeted therapies in dogs is now available for some cancers.

Day 0 of Therapy



Day 21 of Therapy



Dog with recurrent Grade III Mast cell tumor that was treated with toceranib phosphate tablets (2.4mg/kg) every other day for several months and then switched to a MWF schedule for a year. Tumor did not recur following treatment although there was mild weakness in the hind limb and some mild appetite decrease during treatment. Case and images courtesy of Cheryl London, DVM, PhD, DACVIM.

Palladia® and Laverdia TM -CA1, along with most targeted therapies, are orally administered; this is becoming increasingly important. Due to the large number of pets that were adopted during the COVID-19 pandemic, pet parents are now facing a crisis in access to veterinary care, with wait times to see oncologists sometimes exceeding 6-8 weeks. Dogs on oral therapy typically require fewer and shorter duration visits to the veterinarian, therefore addressing this important issue. In addition, these targeted therapies, which by their very nature are selective in their targets, have a lower toxicity profile than traditional chemotherapy. This is based upon their mechanism of action, killing all rapidly dividing cells, which harms both normal and cancerous cells.

Palladia® was approved for the treatment of cutaneous mast cell tumors and multiple studies have shown this therapy effective [1, 2]. Since the original approval by the FDA, numerous other studies have shown that Palladia® (toceranib) has activity in a variety of tumor types, ranging from insulinomas [3], thyroid carcinomas [4], apocrine gland anal sac adenocarcinomas [5], gastrointestinal stromal tumors (GIST) [6] and to nasal adenocarcinomas [7].

The mechanism of action of Palladia® is through its inhibition of various tyrosine kinases, VEGFR, PDGFR, Kit, CSF-1, and Flt-3 [4]. These proteins are often important signals for the growth and spread of many types of cancer. It has been subsequently shown that Palladia® also decreases regulatory T cells (Treg) which are cells that are involved in both tumor development and proliferation by inhibiting antitumor immunity [8]. Thus, Palladia® can improve the effectiveness of the immune system as it relates to its anticancer functions.

There is very new and promising research showing that Palladia®, when combined with a drug that affects immune function, Losartan, can have substantial clinical benefits in dogs with metastatic osteosarcoma [9].

Because of AMDUCA (Animal Medicinal Drug Use Clarification Act), veterinarians can access targeted therapies that are approved for people. Despite the current paucity of targeted therapies approved for veterinary medicine, there are a number of targeted therapies borrowed from human medicine that are in clinical use. For example, the use of lapatinib in dogs with invasive transitional cell carcinoma (TCC) was recently demonstrated to significantly improve overall survival without the need for injectable chemotherapy [10].

Full disclosure, I am the Chief Medical Officer of FidoCure®, a company that offers next generation sequencing of canine tumors and then recommends available targeted therapies based upon the genomic landscape of those tumors to veterinarians. FidoCure®, by tracking the outcomes, advances outcomes research in canine cancer by leveraging genomics, targeted therapies and real world evidence, is quickly learning which targeted therapies work best in dogs and in what context. I therefore have a biased view of the value of these targeted therapies. Regardless, I truly believe that the future use of targeted therapy in veterinary medicine looks quite bright. My reasons for this belief are multifold. Firstly, the genomic characterization of canine tumors is progressing at a more rapid rate now than ever before [11]. Secondly, there are a number of abstracts that have recently been presented with promising results as it relates to the use of targeted therapy in dogs with hemangiosarcoma [12] and pulmonary carcinoma [13]. Lastly, there is overwhelming evidence that the use of targeted therapy has been successful in a variety of human cancers and there is growing evidence that the genomic profile- the targets of these therapies- of many canine cancers are quite similar to human cancers [11].

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