Studying cancer in dogs as a path towards a world where we no longer fear cancer

A new strategy raises hope for treating hemangiosarcoma

(HSA Part II)

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In part one of this series, we reviewed the characteristics of canine hemangiosarcoma. For this installment, we will describe how a promising new therapy might overcome some of the major challenges faced when treating this disease.

The current standard of care for hemangiosarcoma

Hemangiosarcoma in dogs develops insidiously without any obvious signs of pain or discomfort, and it is generally diagnosed late in the course of the disease. Furthermore, the cells that give rise to hemangiosarcoma seem to disseminate to different organs in the body early during the development of the disease, and they are resistant to conventional cancer therapies. Together, these characteristics make the treatment of hemangiosarcoma extremely challenging.

The major goals of treatment for hemangiosarcoma are to slow down or delay the spread of the disease and to prevent life-threatening bleeding episodes. The only approach currently known to be effective in managing hemangiosarcoma combines surgery to remove accessible tumors with chemotherapy to kill or disable any tumor cells that are inaccessible, or that are not eliminated by surgery. This practice for hemangiosarcoma treatment has not significantly changed for about 40 years. No other therapy introduced since then has been shown to be effective in more than a few anecdotal cases.

eBAT: A new type of cancer drug

Through our efforts to develop more effective treatments for hemangiosarcoma, we discovered hemangiosarcoma tumor cells display two proteins on their surface that could serve as targets for therapy. These two proteins are the epidermal growth factor receptor (EGFR), which is normally present on cells of the skin and internal organs such as liver, kidney, and gut, and the urokinase-type plasminogen activator receptor (uPAR), which is normally present on certain white blood cells, cells of the female reproductive tract, and cells that line blood vessels. EGFR and uPAR are not expressed at the same time by normal cells. The observation that both of these proteins were present on hemangiosarcoma cells led us to test the hypothesis that these tumors would be sensitive to a targeted therapy that attacked both simultaneously (Figure 1).

Our approach was to use the proteins as baits to deliver a lethal toxin. EGF-bispecific angiotoxin (eBAT), is a drug invented by Dr. Daniel Vallera at the University of Minnesota, and developed by members of the Animal Cancer Care and Research Program of the University of Minnesota, including the authors of this article. This drug consists of two proteins which simultaneously target EGFR and uPAR linked to a lethal bacterial toxin. The design of eBAT is responsible for its high specificity because the toxin component is only delivered to cells that display EGFR and uPAR on their surface. But eBAT has another unique property — it also disrupts the environment surrounding the tumor, making the tumor inhospitable for the cancer cells.

eBAT is exceptionally safe and improves survival rates of dogs with hemangiosarcoma

We initially verified that eBAT was able to kill cells responsible for the formation and growth of hemangiosarcoma tumors. Next, we demonstrated that eBAT was effective in treating laboratory animals with cancer, but these experiments produced an even more remarkable result: while other drugs targeting EGFR have life-threatening toxicities, eBAT did not appear to cause any severe side effects. These experiments cleared the way for us to evaluate the safety and efficacy of eBAT in dogs with hemangiosarcoma.

In SRCBST-1 (sarcoma bispecific toxin trial-1), the first clinical trial using eBAT, we added eBAT to the standard of care for dogs with hemangiosarcoma of the spleen. In order to participate, dogs had to undergo surgery to remove the

spleen and there could not be any evidence of metastasis. Ten days after their surgery the dogs received three doses of eBAT over the course of one week. Two weeks after the last dose of eBAT the dogs were given a standard course of doxorubicin chemotherapy, consisting of five treatments spaced three weeks apart.

The dogs were monitored for side effects from the beginning of treatment until their death. Dogs whose tumors returned either during the course of treatment or after treatment ended were allowed to receive other therapies. To establish if eBAT improved patient outcomes, we compared the duration of remission and the overall survival time of dogs receiving eBAT with that of dogs treated with surgery and chemotherapy, but without eBAT.

The study was designed to treat 30 dogs; the comparison group included 28 dogs. After the 23rd dog completed treatment, we determined that adding more dogs to the trial would not affect the results in a meaningful way. The study results showed that eBAT had predictable and manageable side effects: four dogs had a drop-in blood pressure during eBAT treatment that required medical attention. Two dogs had changes in liver blood tests, although these returned to normal within a few days without treatment. We concluded that eBAT could be administered safely to dogs with hemangiosarcoma, although its use requires precautions to prevent or manage a potential drop in blood pressure. It is especially worth noting that, as we saw in the laboratory experiments, eBAT did not cause any of the severe side effects typically associated with other drugs that target EGFR, suggesting that its simultaneous targeting of uPAR greatly reduces the risk for toxicity.

The most encouraging result was that 16 of the dogs receiving eBAT in addition to surgery and chemotherapy were alive six months after their diagnosis. This represents more than 70% of the dogs in the experimental group, compared with only 38% of the dogs in the control group. Even more striking, six of the 23 dogs treated with eBAT were alive 15 months after their diagnosis, compared with only two of the 28 dogs in the control group.

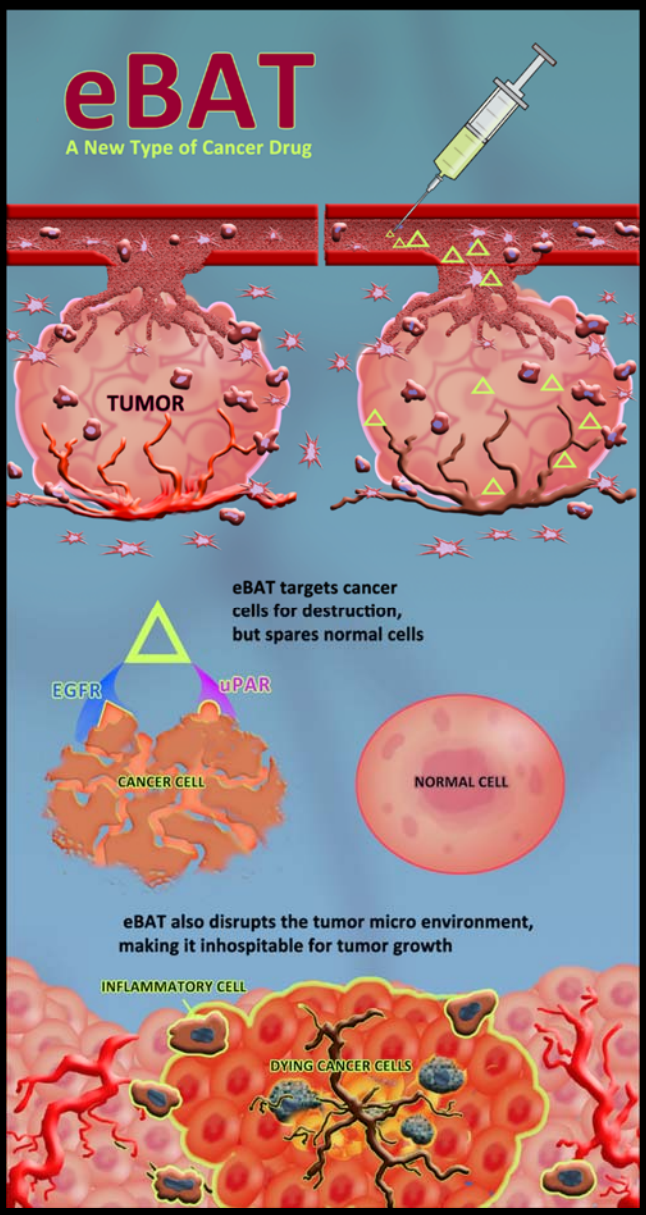

Figure 1. How eBAT Works to Eliminate Tumors.

eBAT, or EGF-bispecific angiotoxin, consists of a lethal bacterial toxin linked to proteins which simultaneously target the epidermal growth factor receptor (EGFR) and the urokinase receptor (uPAR). After it is injected into a vein, eBAT can reach and enter tumors where it specifically kills malignant cancer cells that display EGFR and uPAR on their surface. Another unique property of eBAT is its capability to kill inflammatory cells and blood vessels in and near the tumor, making the environment inhospitable for the cancer cells.

eBAT availability and next steps

The success of eBAT is extremely encouraging, but much work remains to be done. A second trial in which 26 more dogs were treated using eBAT was completed, which helped us to define effective dose and timing for drug administration. A new compassionate care clinical trial has recently opened at the University of Minnesota. Information about the eBAT compassionate care study and eligibility criteria for participation are available at z.umn.edu/ebatcc while the trial remains open.

The potential to use eBAT to prevent hemangiosarcoma in dogs at risk is an important aspect of the ongoing Shine On study being conducted at the University of Minnesota with support from the Golden Retriever Foundation, the Portuguese Water Dog Foundation, and the American Boxer Club Charitable Foundation. Information about the Shine On study and eligibility criteria for participation are available at z.umn.edu/Shine while the trial remains open. Future trials are also planned to identify other tumor types where eBAT can improve quality of life and survival for affected dogs.

Our results give us hope and inspiration. The efforts to optimize eBAT are guided by our relentless focus on improving survival and reducing the impact of hemangiosarcoma and other terminal malignancies on our patients' quality of life, helping us to achieve a world where we no longer fear cancer.

eBAT and Its Potential as a New Treatment for Hemangiosarcoma

* eBAT is a new type of drug designed to attack specific molecules present exclusively or at high levels in tumors.
* eBAT is still an experimental drug but it has been shown to be safe and appears to have potential to improve the treatment outcome for dogs with hemangiosarcoma when it is added to the standard of care of surgery and chemotherapy.
* Ongoing research will allow us to determine whether eBAT might also benefit dogs and people with other incurable cancers.

About the authors

Dr. Borgatti is Associate Professor of Oncology at the University of Minnesota Veterinary Medical Center. She graduated cum laude from the University of Torino, Italy (1996). After three years in general practice, she received a scholarship to pursue specialized training in oncology at North Carolina State University where she subsequently remained as a Research Associate, Oncology Intern, and Clinical Instructor in Oncology. She completed a Residency in Comparative Oncology at Purdue University where she also received a Master of Sciences Degree in 2006. Dr. Borgatti became a Diplomate of the American College of Veterinary Internal Medicine (Oncology) in 2006 and a Diplomate of the European College of Veterinary Internal Medicine in 2007. She worked at a specialty referral hospital in North Carolina for two years before joining the faculty at the University of Minnesota in 2008. She is also a Member of the Masonic Cancer Center at the University of Minnesota and Director of the Oncology residency program.

Ms. Fahrenkrug is the former Associate Director of the Comparative Oncology Program and Senior Development Officer at the University of Minnesota College of Veterinary Medicine. She is a graduate of Saint Cloud State University and completed her master's degree at Hamline University in 2005. Ms. Fahrenkrug worked in the medical device industry before joining the University of Minnesota in 2008. She currently serves as Chief Strategy Officer for Half Moon Bay Biotechnology, a company focused on diminishing the impact of cancer on our society.

Dr. Modiano graduated from the Veterinary Medical Scientist Training Program (VMD/PhD) at the University of Pennsylvania in 1991. He completed a residency in Veterinary Clinical Pathology at Colorado State University in 1993 and postdoctoral research at the National Jewish Medical Center in 1995. He was on the faculties of Texas A&M University and the University of Colorado before joining the College of Veterinary Medicine and the Masonic Cancer Center of the University of Minnesota in 2007 as the Alvin and June Perlman Endowed Chair of Animal Oncology and Director of the Animal Cancer Care and Research Program.

Last updated May 2019