Survival, tumor response, and tolerability with a combinatorial antiangiogenic regimen (OLCAT-007) in a canine model of spontaneous cancer

William W. Li, Vincent W. Li, Nina Vasan, Erwin Kruger, Marion Haber and Christopher J. Bonar
The Angiogenesis Foundation, Cambridge, MA

Background: Antiangiogenesis is a validated strategy for targeting cancer. Monotherapy directed against VEGF improves survival in colorectal cancer, but a combinatorial approach may suppress additional targets with greater efficacy. We report a novel combinatorial regimen (OLCAT-007) of 3 oral agents with antiangiogenic properties: celecoxib (C), tamoxifen (T), and doxycycline (D). We performed an open-label, prospective study of OLCAT-007 in spontaneous cancers employing pet canines with advanced tumors. **Methods:** Antiangiogenic activity of C, T and D was confirmed in the modified rat aortic ring and zebrafish assays. Doses for canines were metabolically scaled for varying sizes/weights (C = 25-100 mg; T = 1-5 mg; D = 50-300 mg; all BID). Canines diagnosed with cancer (n = 51; 28 breeds; 26 tumor types) were treated using C + T + D mixed into dog food, with owner consent and under veterinarian supervision at 50 sites. Study criteria included: verified tumor histopathology, predicted survival defined at entry, oral intake ability, blood laboratory testing, owner compliance, and veterinarian documentation of tumor response and survival. Quality of life (QoL) was determined using an owner-reported index normalized to objective measures. A subset of cases (n=30; 18 breeds) with sarcoma (osteosarcoma=16; soft tissue sarcoma=12; both=2) treated for > 8 weeks were analyzed: 70% were treated for progressive disease; 30% were treated in a neoadjuvant setting. Data were obtained via veterinary records, clinical evaluations, pathology reports, and study forms. **Results:** OLCAT-007 was well tolerated in 93% of canines treated. In 29/30 dogs, 76% maintained or gained weight (average 1.8% increase) after 8 weeks of treatment. 77% of canines maintained or exhibited improved QoL, resulting in delayed/averted euthanasia. In 26 dogs, disease stabilization (n=3), tumor regression (n=5; 25-100% shrinkage), no recurrence (n=9), and tumor progression (n=9) were observed on treatment. Tumor was not measurable in 4 dogs. Survival time increased, compared to prediction at diagnosis, in 86% of treated dogs. Predicted average survival was 4.5 months compared to actual average survival of 10.3 months (228% increase).
Conclusion: Pet canines with spontaneous cancers offer a novel and relevant model for studies of antiangiogenesis. OLCAT-007 was well tolerated for treating sarcoma in many breeds with tumor response, disease stabilization, and increased survival observed. QoL, a key determinant for mortality in this model, was preserved with treatment. OLCAT-007 may be useful for treating canine sarcoma with or without standard therapy. Evaluation in other canine tumors is underway. Based on these results, OLCAT-007 merits evaluation in human cancer patients.