Faithful Companions: A Proposal for Neurooncology Trials in Pet Dogs

Jonathan Kimmelman\textsuperscript{1} and Josephine Nalbantoglu\textsuperscript{2}

\textsuperscript{1}Biomedical Ethics Unit, Department of Social Studies of Medicine, and \textsuperscript{2}Department of Neurology and Neurosurgery, Montreal Neurological Institute, Faculty of Medicine, McGill University, Montreal, Quebec, Canada

Abstract

Although relatively rare, malignant glioma (MG) is frequently used for testing novel cancer treatments. However, human MG trials have often been initiated on the basis of preclinical models that involve numerous discontinuities with the human disease. Below, we discuss various limitations of the mainstay model used in MG preclinical research, the murine orthotopic xenograft. After discussing alternative model systems like transgenic mouse models and canine xenografts, we argue that companion animals with spontaneous brain cancers offer a scientifically and ethically attractive system for preclinical testing of novel MG interventions. Ethical advantages and practical challenges of companion animal brain cancer trials are briefly discussed. [Cancer Res 2007;67(10):4541–4]

Background

Malignant glioma (MG) represents one of the grimmest medical diagnoses. As the disease progresses, patients often experience cognitive impairment, personality changes, and seizures; median survival for the most malignant form is under a year. Although relatively rare, MG is an attractive system for validating novel cancer treatments. First, of course, is the clear demand for new interventions: few major treatment advances have emerged over the last several decades, and major progress against MG seems unlikely to be achieved through modifications of existing therapies. Second, MG offers advantages to clinical investigators wanting to test novel treatment strategies. Because MG tumors do not metastasize, interventions can be delivered to the tumor with diminished risk of inducing systemic toxicity. As well, some data suggest that patients with MG are more amenable to trial participation than other cancer patients (1). Perhaps as a result, the volume of phase I glioblastoma trials is disproportionate with disease incidence when compared with common cancers (Table 1).

Translational trials have sometimes been presented to patients as last ditch therapies; in one incident in 1993, a gene transfer researcher sought exemption from standard regulatory review because he wanted "to give his patient the best available therapy." Lurking in the background when investigators portray novel MG trials as care is the implication that the disease’s morbidity in and of itself justifies enrollment in a study. Such thinking, although understandable, can subconsciously justify the initiation of human trials that rest on a thin evidentiary basis. Below, we review the translational models that have typically provided evidence to support translational trials against MG and defend an ethically and scientifically attractive (although logistically challenging) alternative: the spontaneous canine brain tumor model (SCBT).

Translational Models, Companion Animals, and Brain Cancer

Numerous novel approaches are presently being developed and tested for treatment of MG. These include various gene transfer strategies, RNA interference, immunostimulatory approaches, and nanoparticles for drug delivery, thermotherapy, or tumor imaging. One of the most significant scientific and ethical hurdles in advancing such novel approaches is deciding when preclinical evidence is sufficiently compelling to warrant human testing. A major component of this decision is an assessment of how well data collected in model systems predicts an investigational agent's behavior in the clinical setting. In oncology, and particularly, for MG, such projections often seem to stretch across a large "translational distance," and MG trials have often been justified on the basis of models that involve numerous discontinuities with the human disease.

Consider, for instance, one mainstay model used in preclinical brain cancer studies: the murine orthotopic xenograft of human tumor tissue. First, mouse xenograft tumors are less likely to emulate conditions found in larger, MG tumors, including hypoxia or clonal variation. Second, tumor grafts also show different architectural and physiologic properties than spontaneous tumors: the latter, for example, tend to be much more invasive. Third, tissues are passaged through many generations before grafting and may not reflect the tumor in its original state. A fourth discontinuity relates to the properties of the tumor host. Although an intact immune system can critically alter the behavior of tumor tissue and study drugs, xenograft experiments involve immunodeficient mice. Last, the genetic homogeneity of xenograft hosts also does not recapitulate the genetic diversity seen in the clinical testing.

One disheartening result has been the failure to reproduce in human beings the occasionally stunning results observed in preclinical studies. According to one study, xenograft activity within a particular tissue type poorly predicts clinical activity in the same tissue (3). What are the ethical consequences of
this preclinical, type 2 error bias? First, the brain is the seat of human consciousness. Conducting human studies on the basis of evidence from dissimilar models can expose this sensitive organ to possibly unnecessary risk. Second, substantial evidence suggests that patients with refractory cancer who participate in clinical trials are motivated by the remote prospect of cure (4). Owing to their desperation and sometimes, disease state, persons with MG may be uniquely susceptible to the false hope offered by trials that may be premature or ill conceived. Last, premature trials frequently waste resources, the clinical-investigator’s energies, as well as the time of patients and their caregivers. That a person faces almost certain death from their brain tumor is insufficient justification, by itself, for inviting them into a trial.

Several approaches have been proposed that address deficiencies in preclinical MG models. Various groups, for example, have pursued transgenic strategies for inducing rodent gliomas that reflect many of the structural and histologic features of human tumors (5). Although these show promise in overcoming limitations of the xenograft approach, other discontinuities persist (6). For instance, murine tumors may respond to cancer treatments differently than human cancers. As well, first-line treatments of human brain tumors typically involve surgical resection, which is not feasible in mice. Small animal models therefore cannot replicate the medical conditions under which a new MG intervention will be tested.

Another alternative is the canine allogeneic graft brain tumor model. Berens et al. (7) have pursued a method of inducing in fetal beagles immune tolerance to tissues derived from a spontaneous canine astrocytoma; the tumor tissues are later implanted into the dog’s brain. The approach offers several advantages over xenografts: the animals retain a functional immune system, and tumors have sufficient volume to reproduce critical features of human tumors. In addition, dogs may be a better predictor of human toxicity than rodents or even nonhuman primates, especially when it comes to neurologic toxicity (8). However, the method has a high failure rate: many beagle pups die during prenatal surgery, and the procedures inflict significant suffering on those that survive. Not surprisingly, the implantation of brain cancers in beagle puppies has drawn the ire of antivivisection activists, who in April 2006 were cleared by an appeals court to pursue legal action against Berens (9).

An alternative model that retains some of the strengths of the dog model without its ethical baggage would be the use of SCBTs in pets. The use of companion animals with spontaneous cancers has been profitably applied in numerous other instances of translational research (10). A plausible case can be made that SCBTs recapitulate important features of human disease and would thus provide a superior system for testing MG interventions. With respect to pathologic features, canine astrocytic tumors show the same pathologic subtypes as their human counterparts. On neuroimaging, SCBTs frequently present peritumoral edema with a ring of contrast enhancement (11). Like with humans, microvascular proliferation is prevalent, as are focal areas of necrosis and hemorrhage (11, 12). Molecular abnormalities also have important similarities. For example, canine glioblastomas show immunoreactivity for glial fibrillary acidic protein (11–13), and epidermal growth factor receptor and vascular endothelial growth factor overexpression has been observed in canine astrocytic tumors, as has p53 deregulation (11, 13). Finally, microarray analysis indicates similar patterns of differentially expressed genes in canine and human brain tumors (14). Chemo- and radiosensitivity similarities are less well documented. However, SCBT treatment, which involves conventional or hypofractionated radiotherapy (15–17), does not prolong survival beyond a few months (as is the case for humans), and canine glioma cells respond to a variety of treatments that are effective against human glioma cell lines (18, 19). Meantime, dogs, like human patients, are genetically outbred, and their immune systems intact. Unlike humans, dogs tend to be less heavily pretreated than the types of patients enrolled in translational studies; however, this actually improves the likelihood that benefits will be observed and reduces sources of confounding. To the best of our knowledge, no study has investigated SCBT in a translational setting, although at least one group conducted a nontranslational SCBT trial (16).

### Table 1. Cancer incidence and volume of phase I trials

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Incidence (per 100,000)*</th>
<th>Phase I trials †</th>
<th>Trials/Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>180</td>
<td>67</td>
<td>0.4</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>132</td>
<td>103</td>
<td>0.8</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>66</td>
<td>100</td>
<td>1.5</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>55</td>
<td>61</td>
<td>1.1</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>36</td>
<td>18</td>
<td>0.5</td>
</tr>
<tr>
<td>Uterine cancer</td>
<td>24</td>
<td>32</td>
<td>1.3</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>19.5</td>
<td>104</td>
<td>5.3</td>
</tr>
<tr>
<td>Brain and other nervous system cancer*</td>
<td>7</td>
<td>47</td>
<td>6.7</td>
</tr>
</tbody>
</table>

*Figures derived from values provided in ref. 26.
† Based on a search of http://www.clinicaltrials.gov on July 12, 2006.
‡Phase I trial volume based on search of “glioblastoma” only.

Meaning and Implication: Problems and Challenges of SCBT Studies

Despite such advantages, the use of SCBT presents logistical obstacles. The most obvious is accrual. According to one recent estimate from the United Kingdom, brain cancers occur at a rate of 20 per 100,000 dogs/year (20). Assuming dog ownership of 60 million in the United States, this would theoretically provide 12,000 “recruitable” dogs annually for study. Most spontaneous canine oncology trials conducted thus far have involved sarcomas, which occur at an approximately 10-fold higher rate. However, the low incidence of brain tumors may not, in itself, represent an insuperable barrier to trials. Investigators have in the past conducted studies against spontaneous osteosarcoma (ref. 21; incidence: 57/100,000) and hemangiosarcoma (ref. 22; incidence: 24/100,000). One urban veterinary hospital reported 173 intracranial primary neoplasia over a 16-year period (23). A sophisticated referral network, multicity...
design, and an incentive structure for recruiting dog owners could conceivably produce larger numbers of eligible dogs for study.

A second major concern is expense. Companion animal trials are significantly more expensive than mouse preclinical studies, although they are still less costly than human trials. A major cost driver in such trials is reagents (which are less readily available for dogs) and the scale-up for producing investigational agents (10). The establishment of the Canine Comparative Oncology and Genomics Consortium, which plans a large, accessible tissue repository, might diminish these challenges (24).

Another limitation of SCBT trials would be time. According to one estimate, a randomized controlled trial in dogs can take 1 to 3 years, which may be a long time for small biotechnology companies running on precarious venture capital. Again, however, such disadvantages are diminished when one considers that the same trial in humans can run 5 to 15 years (10).

A fourth challenge concerns the ethics and oversight of such trials. Typical preclinical studies require compliance with animal welfare regulations. However exacting these may seem to scientists, investigators who use companion animals also incur ethical obligations to their client (the animal owner), in accord with the American Veterinary Medicine Association code of ethics (arguably, they incur obligations to the animal as well). As such, investigators in companion animal trials have competing obligations to maximize the scientific utility of such trials and advance the interests of their clients. As in human trials, these interests can conflict. Various ethical and social complications flow from such conflicts. For one, companion animal trials require an informed consent process, which may be complicated by the distressed emotional state of pet owners. Second, clients may be more inclined to withdraw their pets from such trials or refuse invasive testing, although pet owners are reportedly more compliant with study protocols than human subjects (for example, autopsy compliance approaches 85%; ref. 25). Third, pet owners can demand time and resources from the investigator team. There is insufficient space here for a full explication of the ethical and social issues surrounding companion animal studies. However, such difficulties are clearly offset by ethical advantages. SCBT trials would strengthen the evidentiary base on which human studies are designed. From an animal welfare standpoint, the advantages are multiple: spontaneous tumor trials avoid the induction of painful disease states in animals, and they endow preclinical studies with a beneficent orientation. Last, because clients represent the interests of their pets, such experiments are less amenable to abuses of animal subjects.

Although SCBT trials promise to reduce the distance separating preclinical and clinical testing, they clearly have important limitations and are not a replacement for murine models. The expense, time, and scarcity of eligible subjects for SCBT studies would warrant judicious use of such a resource. Nevertheless, the SCBT should be considered as a promising model for testing novel MG interventions. Doing so will require policy makers, investigators, academic centers, and the private sector to evolve incentives and coordination mechanisms, the details of which await further elaboration.

Those who might dismiss this proposal as impractical should consider the achievements in research made possible through creative organizational strategies. Major advances in high-energy physics, astronomy, genomics, and oncology have been accomplished through consortia that coordinate dispersed scientific activities. Applying this approach in the preclinical trial context has already received some institutional support through the National Cancer Institute Comparative Oncology Program.

Dogs have long helped the visually impaired to find their way. With some basic institutional commitments, they may also help in navigating the complex and ethically challenging landscape of translational oncology.

Acknowledgments

Received 1/13/2006; revised 1/10/2007; accepted 2/12/2007.

Grant support: Canadian Institutes of Health Research, MOP 77670, Therapeutic Hopes and ethical concerns: Clinical research in the neurosciences.

References

18. Saltman M, Ebert PS. In vitro response of human glioblastoma and canine glioma cells to hyperthermia,
Faithful Companions: A Proposal for Neurooncology Trials in Pet Dogs

Jonathan Kimmelman and Josephine Nalbantoglu


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/67/10/4541

Cited articles
This article cites 24 articles, 2 of which you can access for free at:
http://cancerres.aacrjournals.org/content/67/10/4541.full.html#ref-list-1

Citing articles
This article has been cited by 7 HighWire-hosted articles. Access the articles at:
/content/67/10/4541.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.