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Letter to the editor

Reply to Madewell and Kraegel

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Drs Madewell and Kraegel raise a number of important issues in their letter concerning a recent report on our toxicological evaluation of free and liposomal vincristine that we wish to address.

The primary goals of preclinical toxicologic evaluation of cytotoxic agents prior to phase I clinical trial in man are to (i) exclude those agents with unacceptable toxicity, (ii) to provide a safe starting dose in man, (iii) to gain information about the organ-specific toxicities of the agent and (iv) evaluate the dose–response relationship to toxicity, which is information needed to provide a safe dose-escalation scheme in phase I clinical trial. These studies are a legal (and ethical) requirement prior to introduction of the agent into man. Our goals in safely bringing potentially lethal agents into human clinical trial are clearly different than setting minimally toxic doses of drugs for treatment of dogs with tumors and treating the toxicities at such doses.

Unlike other classes of agents, considerable toxicity is expected from the use of antineoplastic agents. Due to the general lack of specificity of these agents, they are routinely used at maximally tolerated dosage in man. We therefore feel it absolutely necessary to study these agents at overt toxicity levels in our animal models. Our Institute Review Board (IRB) would have difficulty approving a human clinical protocol, where our patients are literally at risk of an early and painful death from a new cytotoxic agent, unless the toxicities of the agent were well defined at doses that may induce death in animal models.

Drs Madewell and Kraegel appear profoundly disturbed by our choice of dosage in excess of what they consider appropriate regarding their clinical experiences and what is contained within the veterinary literature. Their goals are palliation of animals with disseminated disease, or euthanasia of the patient if the owner declines therapy or cannot afford therapy. Our toxicology goals and requirements in connection with human clinical trials of anticancer drugs are different, where risk of death from aggressive chemotherapy can approach 30%.[1]

The choice of species for this study was problematic, as there is no accepted animal model for the dose limiting neurologic toxicity of the vinca alkaloids in man. Cats and chickens have been proposed as models,[2] but considerable mortality (seven of eight chickens and four of fourteen cats) was reported at neurotoxic doses after chronic administration (e.g. twice weekly for 3 months). Further, consultation with scientists at Eli Lilly suggested that such models are not reliably predictive of the neurological toxicity of vinca alkaloids in humans. Nevertheless, because of the requirement for evaluation in two species (one non-rodent), we chose the dog and mouse. We felt that we could at least do reasonable neurologic exams in the dogs. Our concern was that the liposomal preparation, because of its prolonged circulation time, may accumulate in higher levels in the nervous system than free drug and produce functional if not morphologic disturbances. Increased CNS accumulation of liposomal agent is suggested by the pharmacokinetic studies we carried out in rats.

Drs Madewell and Kraegel have confirmed their criticisms to our study of vincristine, without reference to the nature of the formulation. It should be made clear that our primary goal and our study design were based upon the evaluation of liposomal vincristine, a new agent with unknown toxicities, with no prior toxicology studies reported in the literature. While neurotoxicity was a concern, it was certainly not our only concern.

It is difficult/impossible to reconcile the concerns of the disparate groups who oversee toxicologic evaluations of anticancer drugs, e.g. the granting agencies, the Food and Drug Administration (FDA), the Institute Animal Care and Use Committee (IACUC), the IRB, state and federal departments of Agriculture, etc. We are currently rerunning a study (conducted by another laboratory) that was turned

down by the FDA because of a lack of lethal dosage. However, if we proposed to our IACUC doses for this study known to induce lethality (and in a statistically significant number of animals, as Madewell and Kraegel insist is necessary) we would certainly be turned down by our own board. Our approach is to slowly escalate drug dosage to overt toxicity and if possible avoid lethality. We also employ the time consuming step of sequential dose escalation, using one or two animals per dose, rather than concurrent treatment of all proposed doses, to avoid excessive animal suffering/lethality.

Drs Madewell and Kraegel are quite right in their comment that statistically significant numbers of dogs were not used in our studies. They rarely are. We rely on the dog model to define the spectrum of toxicities a drug may produce, in a bare minimum number of dogs. We are not concerned with defining the incidence of each toxicity in a statistically significant manner. We actually violated our protocol in only using two dogs in the groups where deaths were seen, rather than four, to keep animal pain and suffering to a minimum. It should also be noted that fewer dogs for each drug and schedule are placed on test than humans are in phase I clinical trial.

As pointed out by Madewell and Kraegel, we demonstrated little difference between the drug formulations (free and liposomal vincristine). That finding permitted us to design a human clinical protocol based upon the extensive experience we have with free vincristine, employing a minimal number of patients at a minimal number of dose escalations. Our data and conclusions were thoroughly reviewed and approved by the regulatory authorities responsible for approval of human clinical trials. The liposomal vincristine trial has gone smoothly and safely to date, and we successfully avoided the use of a large number of homeopathic doses prior to reaching doses of agent expected to have therapeutic potential.

We appreciate the concerns of Drs Madewell and Kraegel. As veterinarians (PK and JK) we share exactly those same concerns, and design and execute our studies with this difficult class of agents in the most humane way we can, while still attempting to fulfill our obligations of complete study of potentially lethal agents prior to their administration to our human patients.

References

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