Abstract. HIV protease inhibitors are antiretroviral drugs able to prevent production of infectious particles. It has been shown that these protease inhibitors are able to inhibit cancer-promoted angiogenesis in patients affected by Kaposi’s sarcoma. A preliminary phase I study on dogs with stage III splenic hemangiosarcoma was designed in order to evaluate the efficacy and toxicity of the protease inhibitor Indinavir to delay the progression of this advanced neoplasm. The results suggest that Indinavir is potentially beneficial in dogs affected by microscopic residual disease.

To critically evaluate the results obtained from cell cultures and rodents and to better assess the degree of angiogenesis inhibition, a modified preclinical phase I/II trial in dogs with spontaneously occurring splenic hemangiosarcoma (HAS) was undertaken. HA5 of the spleen is an aggressive soft tissue neoplasm that originates from cancer endothelial cells and leads to the death of most affected dogs within 6 months from diagnosis (10, 11). The adoption of Indinavir for the treatment of canine splenic HA5 is based on the fact that the tumor strongly produces angiogenic factors such as VEGF and bFGF (12).

Materials and Methods

Phase I study on dogs with stage III splenic hemangiosarcoma. Cohorts of 3 dogs were enrolled in an escalation study of oral Indinavir. Eligible dogs were required to have histologically confirmed stage III splenic HAS according to the World Health Organization (WHO) staging system (Table I) and an owner-signed informed consent form detailing the risks, benefits and responsibilities associated with participation in this trial. The staging process involved complete blood cell count, serum biochemistry, coagulation profile, urinalysis, thoracic radiographs (3 projections), abdominal ultrasonography and cardiac echography. Enrollment had to be performed within 3 weeks after surgical splenectomy, at which time the dogs, average weight 30 kg, were scheduled to receive 400 mg of Indinavir per os on an every-other-day basis for a month (15 doses), as extrapolated from human and murine studies. If the protocol was well tolerated and the recheck imaging studies evidenced tumor responses or stable disease, the dogs would receive the treatment with the same schedule for another month. The following cohort was planned to be treated on an every-day basis and, if the treatment was not associated with toxicities, the daily schedule was to be increased by a 10% factor. Tumor
On the basis of the cell culture investigations and the preclinical studies conducted in vitro on cell lines and in vivo on ectopic murine tumor xenografts (2-5), a pilot study for the evaluation of efficacy and toxicity of Indinavir in a canine HA5 model was set up. Stage III HA5 is extremely metastatic and its usual outcome after splenectomy is the death of the animal. The addition of a doxorubicin-based protocol, albeit efficacious, failed to significantly extend the survival; the average survival of stage III dogs receiving antiblastic drugs was 87 to 107 days (15, 16). The massive and fatal bleeding of the first cohort of 3 dogs has led to the termination of this study in consideration of the limited efficacy of Indinavir in dogs with stage III splenic HA5. This could be ascribed to the advanced stage of the neoplasm in our subjects, making them less responsive to PI therapy due to reduced angiogenic activity or to excessive tumor mass. The role of Indinavir in the bleeding observed in the dogs cannot be completely ruled out, however, this phenomenon is less frequently encountered since the adoption of new and safer PIs (1). Further studies are warranted to identify new antiangiogenic molecules to control this aggressive canine neoplasm; a promising strategy could be the association of such compounds with conventional anthracycline therapy to increase the action of the two drugs.

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References


Table I. Modified WHO staging system for canine splenic HA5.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Tumor confined to the spleen</td>
</tr>
<tr>
<td>II</td>
<td>Splenic tumor with ruptured capsule or spread to regional lymph node</td>
</tr>
<tr>
<td>III</td>
<td>Splenic tumor with measurable metastases or multicentric disease</td>
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progression or the occurrence of unacceptable hematological or gasto-intestinal toxicities were considered end-points.


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