

A Randomized Placebo-Controlled Clinical Trial Of ABT-526 Antiangiogenic Therapy Plus Lomustine Chemotherapy Versus Lomustine Chemotherapy Alone In Dogs With Relapsed Lymphoma.

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Thrombospondin-1 (TSP-1), a natural angiogenesis inhibitor, has been found to act broadly against a wide variety of proangiogenic growth factors. Its large molecular size and multifunctional nature has precluded its use as a therapeutic agent. Modified peptide segments of the antiangiogenic domain of TSP-1 containing D-amino acids have been shown to mimic the antiangiogenic action of TSP-1. Recently, a modified nonapeptide, ABT-526 (DI-TSPa) has been found to show significant antiangiogenic activity in vitro and in vivo. As a single agent ABT-526 treatment has resulted in objective tumor responses in histologically confirmed measurable tumors in pet dogs. Surprisingly, chemotherapy resistant lymphoma was found to be a responsive histology. Since the mechanism of action and targets for antiangiogenic agents and conventional cytotoxic agents are distinct, it is rationale to study combinations of these agents in the treatment of cancer.

Ninety-three dogs experiencing their first relapse of histologically confirmed lymphoma were randomized for study to a prospective, randomized, placebo-controlled, and double-blinded multicenter clinical trial to assess the safety and efficacy of ABT-526 when given in combination with Lomustine (CCNU) chemotherapy. Treatments assignments included ABT-526 + CCNU versus placebo + CCNU. Response rate, duration of response, time to progression, and prevalence of toxicoses, particularly number of episodes of dose-limiting neutropenia, thrombocytopenia, and both gastrointestinal and hepatic toxicoses were compared between groups.

No difference in response rate was seen between treatment groups. Median response duration and time to progression for responding cases was significantly greater in patients receiving ABT-526 plus CCNU compared to placebo plus CCNU (Median time to progression 41 vs 21 days; P=0.047). No differences in the incidence of dose-limiting episodes of neutropenia and gastrointestinal or hepatic toxicoses were seen between treatment groups.

The results of this study confirm significant biological activity for ABT-526 in dogs with relapsed lymphoma. The activity of ABT-526 demonstrated in this trial appears to be associated with the maintenance of CCNU induced treatment responses. The clinical value of ABT-526 in this treatment setting is of questionable significance due to the short CCNU induced response duration. Further studies to define the clinical utility of ABT-526 in combination with chemotherapy protocols that are able to induce more durable response durations and/or in the treatment of more responsive populations, i.e., dogs with newly diagnosed lymphoma, are warranted.