The toxicity of intrathecal bevacizumab in a rabbit model of leptomeningeal carcinomatosis.


Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, Smith 353, Boston, MA 02115, USA. pbrastianos@partners.org

Abstract

Leptomeningeal carcinomatosis (LC) is a devastating complication of cancer. Intrathecal administration of cytotoxic chemotherapy adds little to survival which is measured in weeks. The potential toxicities and efficacy of intrathecally administered anti-angiogenic agents in this setting have not previously been explored. A well-characterized animal model was used to evaluate the neurotoxicity of intraventricularly administered bevacizumab (BCM). Thirty-three New Zealand White Rabbits were studied. Subcutaneous reservoirs and ventricular catheters (SRVC) were placed in eight rabbits, which were randomized to receive weekly intraventricular saline with or without BCM for four weeks. These rabbits were euthanized on day 36 and the brains were examined by a blinded neuropathologist. Twenty-five additional rabbits underwent cisternal injection of VX2 carcinoma cells with or without a single dose of BCM and were followed for survival. No clinical manifestations of neurotoxicity were noted in rabbits treated with intraventricular BCM. Similarly, no evidence of BCM neurotoxicity was identified in autopsied animals. The median survival of evaluable rabbits with LC treated with intraventricular saline (N = 13) was 15 days compared to 18 days for the animals receiving VX2 and one dose of BCM (N = 12). Conclusion: Intraventricular BCM can be administered to rabbits without clinical or pathologic neurotoxicity. Survival following one dose of BCM in rabbits with LC should be cautiously interpreted given uncertainties regarding the dose, schedule, and limited expected benefit of this non-rabbit antibody. This neurotoxicity study provides safety data to allow phase I/II studies in humans with treatment refractory LC.

PMID: 21789699 [PubMed - indexed for MEDLINE]