Effects of convection-enhanced delivery of bevacizumab on survival of glioma-bearing animals.


Abstract

OBJECT Bevacizumab (Avastin), an antibody to vascular endothelial growth factor (VEGF), alone or in combination with irinotecan (Camptosar [CPT-11]), is a promising treatment for recurrent glioblastoma. However, the intravenous (IV) administration of bevacizumab produces a number of systemic side effects, and the increase in survival it provides for patients with recurrent glioblastoma is still only a few months. Because bevacizumab is an antibody against VEGF, which is secreted into the extracellular milieu by glioma cells, the authors hypothesized that direct chronic intratumoral delivery techniques (i.e., convection-enhanced delivery [CED]) can be more effective than IV administration. To test this hypothesis, the authors compared outcomes for these routes of bevacizumab application with respect to animal survival, microvessel density (MVD), and inflammatory cell distribution.

METHODS Two human glioma cell lines, U87 and U251, were used as sources of intracranial tumor cells. The glioma cell lines were implanted into the brains of mice in an orthotopic xenograft mouse tumor model. After 7 days, the mice were treated with one of the following: 1) vehicle, 2) CED bevacizumab, 3) IV bevacizumab, 4) intraperitoneal (IP) irinotecan, 5) CED bevacizumab plus IP irinotecan, or 6) IV bevacizumab plus IP irinotecan. Alzet micro-osmotic pumps were used to introduce bevacizumab directly into the tumor. Survival was monitored. Excised tumor tissue samples were immunostained to measure MVD and inflammatory cell and growth factor levels.

RESULTS The results demonstrate that mice treated with CED of bevacizumab alone or in combination with irinotecan survived longer than those treated systemically; CED-treated animals survived 30% longer than IV-treated animals. In combination studies, CED bevacizumab plus CPT-11 increased survival by more than 90%, whereas IV bevacizumab plus CPT-11 increased survival by 40%. Furthermore, CED bevacizumab-treated tissues exhibited decreased MVD compared with that of IV-treated tissues. In additional studies, the infiltration of macrophages and dendritic cells into CED-treated animals were increased compared with those in IV-treated animals, suggesting a highly active inflammatory response taking place in CED-treated mice.

CONCLUSIONS The administration of bevacizumab via CED increases survival over that of treatment with IV bevacizumab. Thus, CED of bevacizumab alone or in combination with chemotherapy can be an effective protocol for treating gliomas.

KEYWORDS: CED = convection-enhanced delivery; IP = intraperitoneal; IT = intratumoral; IV = intravenous; MVD = microvessel density; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor; bevacizumab; combination therapy; convection-enhanced delivery; glioma; monotherapy

PMID: 25727230 [PubMed - in process]