

EFFICACY OF INTRACEREBRAL CONVECTION-ENHANCED DELIVERY OF HERCEPTIN IN AN ATHYMIC RAT MODEL OF INTRACEREBRAL BREAST CANCER METASTASES

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Introduction

Metastatic breast cancer is the second most frequent cause of intracranial tumors.¹ In 1993, approximately 46,000 people died of breast cancer, of which 20% to 30% of patients were found to have brain metastases at the time of autopsy.² Brain metastases indicate a poor prognosis and are frequently the cause of death in breast cancer patients. Even with aggressive treatment, including radiation, chemotherapy, and surgery, the average patient diagnosed with intracranial metastatic breast cancer survives only 14 months.³

Herceptin has been shown to be efficacious against primary and extracranial metastatic breast cancers that overexpress HER2. Systemic therapy of intracranial tumors with relatively large therapeutic agents, such as monoclonal antibodies like Herceptin, is less efficacious because the blood-brain barrier restricts the entry of these large molecules into the brain.⁴ For example, our human imaging studies using anti-tenascin monoclonal antibody 81C6, a monoclonal antibody specific for malignant gliomas, demonstrated that after systemic intravenous administration, only 0.0006% to 0.0043% of the total injected dose localized to the intracranial tumor.⁵ As expected from these data, it has been noted that patients in trials of Herceptin for metastatic breast cancer may have systemic metastases that respond to Herceptin, but they still succumb to intracranial metastatic disease.⁶ This is a relatively common cause of treatment failure.

Regional intracerebral drug delivery can bypass the capillary barrier of the cerebral vasculature, deliver high concentrations of therapeutic agent directly into the tumor, and reduce systemic exposure to drug-induced toxicity. However, existing techniques of regional drug delivery, such as impregnated polymer discs or bolus injection, depend on physical diffusion to distribute the therapeutic agent. Distribution of monoclonal antibodies into the brain using such approaches is severely limited because the rate of diffusion is inversely related to the size of the agent and is slow relative to tissue clearance.^{7,8} This limits the distribution of regionally delivered monoclonal antibodies using these techniques to within a few millimeters of the injected area. Thus, lethal tumor cell populations that exist a few millimeters beyond the site of drug delivery escape exposure to the therapeutic agent because of the inhomogeneous distribution obtained after diffusion and the steep concentration gradient that develops between the point of delivery and the advancing tumor border.

In contrast to diffusion, a pressure gradient-dependent convection-enhanced delivery (CED) of therapeutic agents has been predicted to produce a bulk flow current that has the potential to homogeneously distribute even large molecules much greater distances throughout the brain. CED is an innovative technique of delivering therapeutic agents directly into brain parenchyma, thus circumventing the blood-brain barrier and minimizing systemic toxicity. CED is capable of achieving concentrations of therapeutic agents within the brain that are several orders of magnitude greater than those obtainable after systemic

delivery.⁹ CED also provides a more homogeneous distribution of the therapeutic agent than can be obtained after placement of drug-impregnated polymer implants or bolus injection. Such enhancement of drug distribution has already been demonstrated in experimental animal models⁹ (Figure 1), and we are currently confirming these results in preliminary human trials (Figure 2). Thus, CED should allow homogeneous delivery of therapeutic monoclonal antibodies such as Herceptin to a greater portion of the tumor and should enable such agents to saturate invasive neoplastic cells far from the site of infusion.

This study examines the safety and efficacy of intracerebral regional delivery of Herceptin using CED in an athymic rat model of intracranial metastatic breast cancer.

Methods

The therapeutic efficacy of Herceptin was determined in an intracranial athymic rodent model. MCF-7, a human breast cancer cell line stably transfected to overexpress HER2, was implanted intracranially into 200- to 250-g female athymic rats in a volume of 10 μ L. All rats were primed with 1.6-mg controlled-release β -estradiol subcutaneous pellets. Treatment consisted of CED of Herceptin at a concentration of 2 mg/mL. Treatment was compared with control groups of saline or Campath-1H, a humanized IgG_κ monoclonal antibody, administered in equivalent manner and concentration as an isotype control. All rats were monitored daily and were subjected to complete postmortem pathologic examination. Kaplan-Meier survival plots and log-rank survival analysis were used to examine the survival benefit of treatment.

Results

All control rats succumbed to intracranial tumor. Saline treatment led to a median survival of 16 days (95% CI, 14.54–17.46 days; Figure 3). Treatment with Campath-1H resulted in a median survival of

21 days (95% CI, 16.62–25.38 days) and did not differ significantly from saline treatment ($P=0.42$). Treatment with Herceptin led to a median survival of 45 days (95% CI, 27.96–62.04 days), and 3 of 10 rats were still alive >60 days after tumor implantation. This represents a 181% increase in median survival compared with saline and a 114% increase compared with the Campath control ($P<0.001$). No significant toxicity was associated with treatment.

Discussion

Herceptin has proven to be an effective treatment for systemic HER2-overexpressing metastatic breast cancer; however, systemic delivery of therapeutic agents to brain tumors, especially high-molecular-weight agents such as intact monoclonal antibodies, is severely limited by the blood-brain barrier and other physiologic barriers such as increased interstitial pressure within the tumor. Systemic delivery of Herceptin for intracranial metastases would require extremely high concentrations of drug over prolonged intervals only to attain relatively ineffective drug concentrations within the tumor. Similarly, it has also been shown that intravenous infusion of Herceptin in human patients results in a 300-fold lower concentration in cerebrospinal fluid compared with serum concentration.¹⁰ Direct intracerebral CED of therapeutic agents bypasses these physiologic barriers to drug delivery to brain tumors and provides high concentrations of the therapeutic agent directly at the tumor site while minimizing systemic exposure. So-called regional therapy is particularly attractive as a modality for the treatment of metastatic brain cancers for several reasons. First, these tumors have proven to be resistant to systemic chemotherapeutic agents. Second, intracranial metastases are often fatal despite aggressive treatment. Finally, patients with brain metastases are more likely to die as a result of complications from their intracerebral disease than as a result of progression of systemic disease.¹¹

The dismal prognosis for patients with intracranial metastatic breast cancer prompts the search for novel therapeutic strategies. We have demonstrated that intratumoral infusion of Herceptin directly into intracranial HER2-overexpressing neoplasms results in a significant survival advantage in an athymic rat model. Moreover, this survival benefit does not appear to be associated with any intracerebral or systemic toxicity. Additionally, we have confirmed the efficacy of intratumoral Herceptin against intracranial breast neoplasms in other rodent models and with other HER2-overexpressing cell lines. Furthermore, previous studies performed in our laboratory have demonstrated the clinical feasibility and efficacy of intratumoral infusion of monoclonal antibodies into intracranial lesions in both animal and human clinical trials.

The data presented here suggest that direct intracerebral CED of Herceptin may prove to be an efficacious and safe treatment in human clinical trials. Future studies that further define the pharmacokinetics and distribution of monoclonal antibodies such as Herceptin into brain neoplasms will help optimize drug delivery. This therapeutic efficacy may be maximized by conjugating the antibody to cytotoxic drugs and radioisotopes, thereby using the monoclonal antibody as a specific, targeted drug-delivery device.

Conclusion

Intratumoral infusion of Herceptin is a safe and efficacious treatment for HER2-overexpressing intracranial neoplasms in an athymic rat model of metastatic human intracranial breast cancer.

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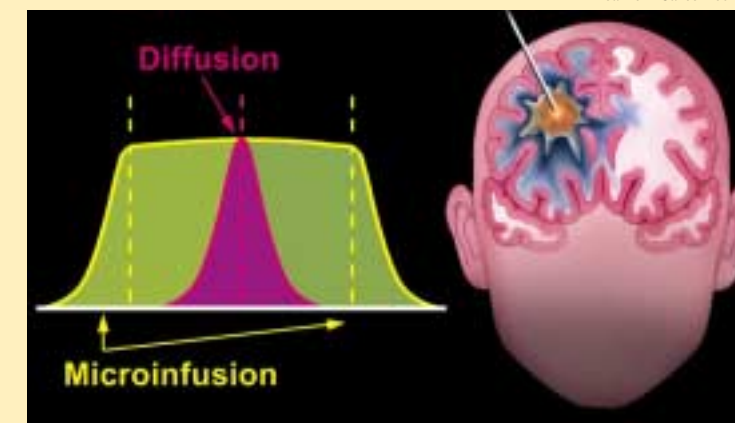


Figure 2. Preliminary human trials are confirming results demonstrated in experimental animal models.

Figure 1. Infusion cannulas were implanted in the caudate nuclei of athymic rat brains, and Evan's blue dye (0.5%) was infused by CED. At the level of the cannula (A), the majority of the infusion surrounds the cannula within the caudate nucleus. The infusion also crosses to the contralateral hemisphere via the corpus callosum, tracks along white matter tracts (B), and was identified along the cerebral convexities within the lateral third and fourth ventricles and subarachnoid space (C).

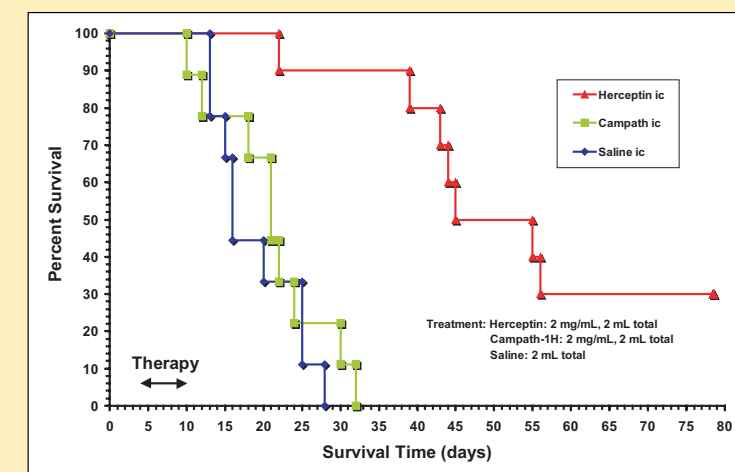
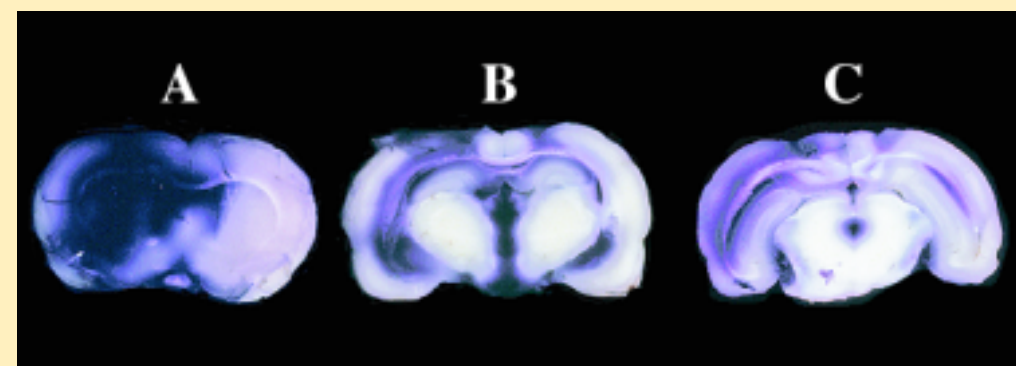


Figure 3. Significantly increased survival was provided by intratumoral Herceptin therapy for intracranial MCF-7/HER2 tumors in athymic rats. ic = intracranial.