Drug delivery

New portals for treating metastatic brain tumors

Among cancer patients, one of the most devastating complications is metastasis of the cancer to the brain. Metastasis accounts for the majority of newly diagnosed brain tumors and of the 170,000 cancer patients diagnosed with such tumors each year, 25–50% die from neurological complications. Surgery is sometimes an option but new brain metastases most often cause death within three to six months following recurrence. Chemotherapy has not been an effective treatment for metastatic brain tumors, even in conjunction with surgery. One reason for the ineffectiveness of chemotherapy is the existence of the blood–brain tumor barrier (BBTB), which inhibits diffusion of water-soluble compounds and large lipophilic compounds from the blood vessels to the tumor. Many studies have confirmed that the BTBB of metastatic brain tumors is more permeable compared with the normal blood–brain barrier (BBB) but the BTBB remains a significant obstacle to the delivery of chemotherapeutic drugs to brain tumors. Increasing the permeability of the BTBB during administration of chemotherapeutic drugs should allow many existing drugs to reach the tumor and perhaps increase survival rates of patients.

Recently, Emerich and colleagues reported that CEREPORT® (Alkermes, Cambridge, MA, USA), a bradykinin analog that increases the uptake of chemotherapeutics into gliomas in animal models, also increases the survival rate of rats with implanted metastatic brain tumors[1]. The mediator is a receptor agonist with selectivity for glioma tissue and has been shown to modify the permeability of the glioma vascular barrier. However, until the present study, it was not known whether it, or any other receptor-mediated method of increasing BTBB permeability, would increase the uptake of chemotherapeutic drugs into the brain. A series of experiments were conducted in a rat metastatic brain tumor model to investigate the following: (1) the ability of the mediator to enhance the uptake of several hydrophilic and hydrophobic chemotherapeutic drugs; (2) the nature of the uptake effects with carboplatin; and (3) whether the mediator increases survival rates when used in conjunction with the chemotherapeutic drugs carboplatin, carmustine, vinorelbine and gemcitabine. The remainder of this short article will focus on the increase in survival rate. With regard to the first two points, simultaneous administration of the mediator increases the level of carboplatin in the tumor by 87% and in the brain surrounding the tumor by 98%, based on autoradiography and scintillation studies. By contrast, the uptake of hydrophobic chemotherapeutic drugs, such as carmustine or paclitaxel, is not appreciably affected by the mediator.

For the survival rate studies, male Fischer rats were injected unilaterally into the striatum with a metastatic brain tumor cell line (MATB-III was used). The rats received intravenous infusions of the chemotherapeutic drugs carboplatin, vinorelbine, gemcitabine or carmustine alone or in combination with the mediator on days seven and nine after tumor implantation. Appropriate control experiments in which the animals were injected with either saline vehicle or saline containing the mediator were simultaneously conducted. Saline-treated animals survived for 22–32 days post-tumor implantation. Animals injected with the mediator alone also survived for 22–32 days post-tumor implantation. Intravenous infusions of all the chemotherapeutics tested modestly increased survival rates, with maximum survival rates of 36–43 days, depending on the drug. Little benefit was realized from combining CEREPORT® with the hydrophobic drug carmustine; the maximum survival rate without the mediator was 43 days and with the mediator–carmustine combination the maximum survival rate was 50 days.

Simultaneous intravenous administration, together with the hydrophilic drugs carboplatin, vinorelbine and gemcitabine, produced substantially longer survival rates. The combination of gemcitabine and the mediator produced a maximum survival rate of 70 days and the combination with vinorelbine produced a similar increase in survival rate of 70 days, compared with maximums of 37 and 36 days without the mediator, respectively. In this model, the greatest survival rate benefit was achieved by combining the mediator with carboplatin. Median survival rates were approximately four times longer with the mediator and maximum survival rates were approximately nine times longer compared with carboplatin alone. Two individuals in the CEREPORT®/carboplatin combination group were sacrificed at 98 days post-tumor implantation and necropsy revealed only a small necrotic area within the implanted striatum. This work offers the first empirical evidence that a receptor-mediated approach to increasing the permeability of the BTBB could be beneficial in combination with chemotherapeutic drugs for treatment of metastatic brain tumors.

1 Emerich, D.F. *et al.* (2000) Intravenous CEREPORT® (RMP-7) enhances delivery of hydrophilic chemotherapeutics and increases survival in rats with metastatic tumors in the brain. *Pharm. Res.* 17, 1212–1219

Oral delivery of new heparin derivatives

Heparin is the anticoagulant of choice in the treatment of patients with a high risk of deep vein thrombosis (DVT) and pulmonary embolism. Currently, it is available only by parenteral administration because it is highly hydrophilic and negatively charged; it has a range of molecular weights, which can be as much as ~12 KDa. Heparin is favored by

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physicians over anti-vitamin-K oral anticoagulants, such as warfarin, because it produces a rapid onset of anticoagulant activity and has a short physiological half-life. Heparin therapy also results in a significantly lower incidence of drug–drug interactions. Rather than receiving a daily injection, patients requiring daily heparin treatments would prefer oral administration of heparin. Several research groups have been in the process of developing oral dosage forms of heparin but none has yet been approved for clinical use.

Recently, Lee and colleagues[2] reported that a conjugate of heparin and deoxycholic acid (DOCA) is absorbed through the GI tract and exhibits anticoagulant activity. The conjugate of heparin and deoxycholic acid was synthesized by coupling the amino groups of heparin to the carboxylic acid group of DOCA. The resulting heparin–DOCA conjugate had an average of ten DOCAs incorporated into each molecule of heparin. The anticoagulant activity of heparin–DOCA was measured by an activated partial thromboplastin time (APTT) assay, which measures clotting time. Heparin–DOCA was dosed to male Sprague-Dawley rats by oral gavage in the range of 50–200 mg kg^{-1}, and compared with appropriate controls. When heparin alone was administered orally to rats, the observed clotting time one-hour after administration was 18 sec by APTT, which remained the average baseline APTT value. When heparin and DOCA were physically mixed, the observed APTT value was 20 sec, and this value did not change over time, which indicates that the mixture does not promote oral absorption of heparin. When heparin–DOCA was orally administered, clotting times increased, and the increase was dose dependent. Blood sampling was carried out at one-hour intervals and the maximum clotting time was observed at the first hour, thus the true maximum clotting time might not have been determined. However, the observed clotting times at one hour when heparin–DOCA was given at 50, 80, 100 and 200 mg kg^{-1} were 25.7 ± 2.6, 43.1 ± 4.0, 51.2 ± 9.3, and 136 ± 33 sec, respectively. Given that the therapeutic window of heparin is 1.5–2.5 times the baseline, the therapeutic effect can be seen at a dose of 80–100 mg kg^{-1}.

Additional experiments were conducted to measure the concentration of heparin–DOCA in the plasma using the Factor Xa assay. Again, for a 200 mg kg^{-1} dose of heparin–DOCA, the mean concentration at one hour was 9–10 times baseline, indicating absorption of heparin–DOCA in the GI tract. In further experiments to determine any adverse effects on the GI wall, animals were sacrificed at one, two and three hours after a 200 mg kg^{-1} dose of heparin–DOCA and the tissues of the GI tract were examined using staining techniques and transmission electron microscopy. There was no evidence of tissue damage, which indicates that the oral absorption of heparin–DOCA was not a result of a change in the structure of the GI tissue. Although further study is needed, in the future this heparin–DOCA derivative could prove useful as an orally available anticoagulant.

2 Lee, Y. *et al.* (2000) Oral delivery of new heparin derivatives in rats. *Pharm. Res.* 17, 1259–1264

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