Pharmacokinetic Investigation of Increased Efficacy Against Malignant Gliomas of Carboplatin Combined With Hyperbaric Oxygenation

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Abstract

The efficacy of intravenous administration of 400 mg carboplatin/m² body surface area over 60 minutes combined with hyperbaric oxygenation (HBO) therapy (0.2 MPa for 60 min) was investigated in 6 Japanese patients (aged 36–67 years) with malignant or brainstem gliomas. Plasma ultra-filtrate samples were analyzed by high-performance liquid chromatography to evaluate the relationship between efficacy and pharmacokinetics. Brain tumor response was evaluated by magnetic resonance imaging as a function of maximum plasma concentration, area under the curve, or mean residence time (MRT) for carboplatin. The MRT for carboplatin in the complete or partial response group (mean ± standard deviation 4.3 ± 1.7 hrs; 6 courses in 3 patients) was significantly longer (p º 0.05) than that in the progressive disease group (2.4 ± 0.1 hrs; 3 courses in 3 patients), but maximum plasma concentration and area under the curve showed no differences. These results suggest that HBO therapy prolongs the biological residence time of carboplatin. MRT for carboplatin may be useful for predicting continuation or modification of chemotherapy and/or clinical antitumor effects in patients with malignant gliomas.

Key words: brain stem glioma, magnetic resonance imaging, hyperbaric oxygenation, mean residence time, area under the curve

Introduction

Hyperbaric oxygenation (HBO) therapy has been used to treat decompression sickness, and various types of infections and ischemic damage.3,6–8) HBO pretreatment has been used to enhance the efficacy of radiotherapy6,9,10) although HBO may induce vasoconstriction in systemic organs including the brain.5) Recently, we observed that carboplatin, cis-diammine-1,1-cyclobutanedicarboxylatoplatnum (II) which is a second-generation platinum antineoplastic agent with modest activity against brain tumors,10 showed increased efficacy when combined with HBO therapy,13,14) in a similar way to that reported using cellular systems.5) However, the mechanism of action of HBO on the clinical efficacy of carboplatin is unknown.

The present study determined the pharmacokinetic parameters of carboplatin combined with HBO therapy in patients with malignant gliomas.

Materials and Methods

Six patients, 4 men and 2 women aged 36 to 67 years old (mean 55.0 years old), with recurrent malignant or brainstem gliomas were enrolled in this study between May 2006 and September 2007 in the Department of Neurosurgery of St. Marianna University School of Medicine Hospital (Table 1). Written informed consent was obtained from all participants. All patients, except for Case 2, underwent surgical resection and the histological diagnosis was established. Case 2 could not undergo surgery because of the tumor location, so the diagnosis was established based on the radiological findings. All the patients received chemotherapy with carboplatin in combination with HBO therapy because the previous chemotherapy and radiotherapy had resulted in incomplete response or tumor redevelopment. The
study protocol was approved by the Ethical Committee of St. Marianna University School of Medicine Hospital (petition No. 1057).

Patients received intravenous administration of 400 mg carboplatin/m² body surface area over 60 minutes. HBO treatment consisted of increase in pressure over 15 minutes to 0.2 MPa, maintenance of this pressure for 60 minutes, then decrease in pressure over 15 minutes to ambient pressure using a hyperbaric oxygen chamber (Model 2500B; Sechrist, Anaheim, Calif., U.S.A.). Additional HBO treatment was carried out 24 hours after the drug administration using the same method. The entire protocol was repeated every 6–8 weeks. Brain tumor reduction ratios were determined by magnetic resonance (MR) imaging (Gyroscan NT, Intera/Master 1.5T; Philips, Andorner, Mass., U.S.A.) regarding tumor volumes and evaluated using the following response evaluation criteria for solid tumors: complete response was defined as disappearance of all signs of tumor; partial response as $\geq 30\%$ reduction, and progressive disease as $\geq 20\%$ increase in the tumor.

Plasma ultra-filtrate samples (range 1–3 courses per patient) were taken before or 60, 90, 210, 240, and 270 minutes after the beginning of intravenous carboplatin infusion, and analyzed by high-performance liquid chromatography as described previously. Standard carboplatin (molecular weight 371.25) was obtained from Bristol-Myers (Tokyo). Maximum plasma concentration (Cmax), area under the curve (AUC), and mean residence time (MRT) were determined using WinNonlin Professional software (version 5.01) with the non-compartment model (Pharsight, Mountain View, Calif., U.S.A.). All statistical analyses were carried out with the InStat program (GraphPad Software, San Diego, Calif., U.S.A.).

### Results

Cases 1–3 showed complete or partial responses based on the MR imaging findings (Table 1). On the other hand, Cases 4–6 showed progressive disease. Serial MR imaging of Case 3 showed partial response after carboplatin treatment with HBO therapy compared with the image prior to surgical operation (Fig. 1A–C). Serial MR imaging of Case 4 showed tumors prior to treatment and indicated partial response after the first and second courses of carboplatin with HBO therapy, but progressive disease after the third course (Fig. 1D–F).

Pharmacokinetics of the carboplatin plasma concentrations could be analyzed for 9 courses in the 6 patients. Figure 2 shows representative elimination profiles following administration of 400 mg/m² carboplatin by intravenous infusion over 60 minutes. Carboplatin was detected in the plasma at 60 and 90 minutes after the start of intravenous infusion under normal atmospheric pressure (0.1 MPa). After HBO therapy at 0.2 MPa for 60 minutes, carboplatin was detected in the plasma at 210 minutes. However, no carboplatin was detected in the plasma after 24 hours in any patient (data not shown).

The pharmacokinetic parameters Cmax, AUC, and MRT are shown with the clinical responses for all patients (Fig. 3). The mean Cmax showed no difference between the complete or partial response group ($\text{mean } \pm \text{ standard deviation } 27 \pm 13 \mu g/ml$) and the progressive group ($24 \pm 15 \mu g/ml$). Likewise, the mean AUC showed no difference between the complete or partial response group ($92 \pm 47 h \cdot \mu g/ml$) and the progressive disease group $(70 \pm 41 h \cdot \mu g/ml)$.
Fig. 1 Representative T1-weighted magnetic resonance images with gadolinium-ethylene-diaminetetra-acetic acid in Case 3, (A) prior to the surgical operation, (B) before, and (C) after the hyperbaric oxygenation therapy showing good response, and Case 4, (D) prior to treatment, (E) after the first treatment showing partial response, and (F) after the third course showing progressive disease.

Fig. 2 Representative plasma concentration curves of carboplatin in Cases 2 (open triangle), 3 (open square), and 4 (closed circle). Hyperbaric oxygenation (HBO) therapy at 0.2 MPa for 60 minutes is indicated (increase or decrease of pressure took 15 min). iv: intravenous.

Fig. 3 Maximum plasma concentration (Cmax), area under the curve (AUC), and mean residence time (MRT) plasma values of carboplatin in Cases 1 (open circle), 2 (open triangle), and 3 (open square) who showed complete or partial responses, and Cases 4 (closed circle), 5 (closed triangle), and 6 (closed square) who showed progressive disease. Data points and bars represent individual parameters, and the mean ± standard deviation values in each group, respectively. Mean MRT is significantly longer in the complete or partial response group compared to the progressive disease group (p < 0.05).

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Carboplatin concentrations of 25-50 μg/ml. However, the mean MRT was significantly longer (p < 0.05) in the complete or partial response group (4.3 ± 1.7 hrs) compared to the progressive disease group (2.4 ± 0.1 hrs).

Discussion

The present study found that higher MRT was correlated with good response in Cases 1–3, and with initial partial response in Case 4, and lower MRT was correlated with later progressive disease in Case 4, and poor response in Cases 5 and 6. Carboplatin is generally excreted via the urine without extensive metabolism. In our preliminary study of carboplatin transport, carboplatin had low brain penetration potential in a cultured blood-brain barrier system. The half-life of carboplatin has been reported as 80 minutes. The present study measured concentrations of carboplatin at 210 minutes of approximately half of the concentrations at 90 minutes in Cases 2 and 3, indicating a half-life of 120 minutes. Therefore, HBO therapy at 0.2 MPa for 60 minutes resulted in apparently higher concentrations of carboplatin than expected.
The present findings of good clinical response may suggest that HBO therapy modified the pharmacokinetics of carboplatin. In our recent study with a rat model,[12,13] changes in the pharmacokinetics of carboplatin with HBO therapy were also suggested by the detection of carboplatin in the brain at 60 minutes (from the start of administration) after HBO treatment at 0.2 MPa for 20 minutes. The present and previous findings are apparently inconsistent with the reported review implying that a single exposure to hyperbaric or hyperoxic conditions would not affect the single-dose pharmacokinetics of drugs eliminated by the kidney (gentamycin) or the liver with capacity-limited clearance (pentobarbital, theophylline, caffeine) or with perfusion-limited clearance (pethidine, lidocaine).[11] On the contrary, oxygen-induced cerebral vasoconstriction could result in some modification of drug pharmacokinetics, presumably because of various biochemical changes in the brain such as inactivation of intracellular enzyme systems or changes in blood flow rates.[7] Any resultant prolonged biological half-life of carboplatin might explain the effect of combined cisplatin/HBO therapy for malignant gliomas. It should be mentioned that different administration protocol such as low-dose prolonged carboplatin infusion might result in the similar favorable therapeutic effects as the improved MRT with the hyperbaric oxygenation.

Recently, we reported that carboplatin had similar endothelial permeability compared with doxorubicin or verapamil, typical P-glycoprotein substrates, in an in vitro blood-brain barrier system.[15] Increased permeability of P-glycoprotein-dependent carboplatin by hyperbaric oxygenation (like by verapamil) may rapidly reach pharmacologically significant concentrations in the central nervous system. Moreover, we reported that increased distribution of carboplatin to rat brains with aid of hyperbaric oxygenation in vivo.[12] However, the mechanism(s) of HBO causing improvement in clinical efficacy of carboplatin combined with HBO, and the individual patient factor(s) resulting in different responses should be identified.

Prolonged biological residence time of carboplatin may be achieved by combination with HBO therapy, resulting in improved efficacy against malignant gliomas. The MRT may be important for predicting continuation or modification of chemotherapy and/or clinical antitumor effects on malignant gliomas.

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References

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Commentary

Various attempts have been made to use oxygenation either as an adjuvant or an independent treatment in tumor patients. The most frequent treatment forms are: inhalation of oxygen gas (hyperbaric oxygenation, HBO), and use of oxygen saturated water either in water or drinking cure. Recent international studies unanimously confirm the beneficial effect of oxygen intake on the sensitivity of chemo- and radiotherapy. However, the mechanism of action of HBO on the clinical efficacy is unknown. The authors found that HBO could prolong the biological residence time of the carboplatin, which may be useful for predicting continuation or modification of chemotherapy and/or clinical antitumor effects in patients with malignant gliomas. This study is valuable. The mechanism of the HBO affecting the biological residence time of the carboplatin is complicated. More animal experiments and clinical observations about the biological residence time of carboplatin in malignant gliomas are encouraged.

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