Laboratory Investigation

Relationship between drug delivery and the intra-arterial infusion rate of SarCNU in C6 rat brain tumor model

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Summary

The influences of the flow rate on the concentration and distribution of drug in the rat brains and brain tumors after intra-arterial (intra-carotid) administration of [³H]SarCNU (sarcosinamide chloroethyl-1-nitrosourea) were examined. Results obtained at three flow rates via intra-carotid route were compared to those obtained with intravenous administrations. Adult female Wistar rats bearing C6 brain tumor were randomized into four-groups. Groups 1 (G.1) to 3 (G.3) received intra-arterial injection and Group 4 (G.4) received intravenous administration of [³H]SarCNU. G.1 (slow infusion rate) was administered 1 ml of [³H]SarCNU solution over 60 min (0.017 ml/min), Group 2 (G.2; medium infusion rate): 0.2 ml over 5 min (0.04 ml/min), G.3 (fast infusion rate): 1 ml over 5 min (0.2 ml/min), and G.4 (intravenous infusion): 1 ml intravenously over 5 min. Quantitative autoradiographic method was used to measure the concentration and the distribution of [³H]SarCNU in the brain and the brain tumors. The tissue uptake constant of SarCNU in both viable (tumor tissue excluding necrosis) and peak regions (the area of tumor containing top 20% of the tracer concentration) of the intra-arterial injection groups were significantly higher (p < 0.0001) than those in the intravenous group. The mean concentrations of the viable tumor in the intra-arterial groups were 2.92 (G.1), 16.06 (G.2), and 20.8 (G.3) times higher than those of intravenous group. Between the intra-arterial groups, the mean concentration in the viable tumors of G.1 (slow flow rate) was significantly (p < 0.0001) lower than in G.2 and G.3. However, there was no significant difference between G.2 and G.3. In three intra-arterial groups the mean concentration delivery ratios of the brain tumors were high and ranged from 3.07 (G.3) to 3.87 (G.2), but there was no significant difference between them. Only G.4, intravenous group, showed significantly (p < 0.005) lower concentration delivery ratio, 1.26. These results suggest that higher infusion rate in the intra-arterial chemotherapy could have an effect not only on the streaming phenomenon which results in the brain toxicities, but also on the increase in the concentration and the sufficient distribution of a drug in tumors. By finding chemotherapeutic agents to which tumors show high sensitivity and using intra-arterial administration of these agents at more effective flow rate, better clinical results could be achieved in the treatment of patients with malignant brain tumors.

Introduction

Clinical results in the treatment of malignant gliomas have not been satisfactory despite extensive therapeutic efforts. The effect of a chemotherapy treatment is influenced by the concentration of a drug in tumor, tumor exposure time to a drug, and an intracellular half-life of a drug [1]. To increase the concentration of chemotherapeutic agents in the tumor might be one of available methods to improve the clinical effects in treatment of malignant gliomas. High dose intravenous administration of chemotherapeutic agents has been used to increase tissue concentration of chemotherapeutic drugs. However, the approach has been greatly limited
by severe side effects including bone marrow suppression and organ toxicity, even though some rescue methods have been applied; such as autologous bone marrow or autologous blood stem cell transplantations [2–4]. Intra-arterial administration of chemotherapeutic agents is one of the attractive methods to increase the drug delivery and to decrease potentially systemic toxicity, particularly with drugs that are rapidly cleared by the peripheral circulation [5,6]. Pharmacological modeling has suggested that intra-arterial delivery can result in a 200–500% increase in brain levels over intravenous administration during the first passage through a tumor area [7–10]. In the experimental brain tumors, a higher concentration of drugs in tumor have been obtained after an intra-arterial administration than those achieved after one intravenous administration [9–11].

Experimental studies of intra-arterial chemotherapy for the brain tumors have shown the significantly better effects on the brain tumor than the intravenous chemotherapy. However, the clinical effects of intra-arterial chemotherapy on the patients with malignant brain tumors are limited and the incidence and severity of side effects by the intra-arterial administration could not be ignored. The streaming phenomenon, non-mixing distribution of drug in the blood, after intra-arterial chemotherapy at a low flow rates may cause the focal toxicities in the brain. The flow rate of intra-arterial administration may also affect concentrations and distributions of drugs in the brain tumors.

In vivo experimental studies have shown that in the tumor-bearing rats an intra-arterial administration prolonged the survival in comparison to an intravenous administration [9,12]. Nevertheless, the clinical results of an intra-arterial chemotherapy especially those using 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) have been termed controversial [13,14] and furthermore, the intra-carotid chemotherapy has been often described to be too toxic [13,15] as a possible treatment. The major complication of the procedure with BCNU is focal toxicity in the brain and retina [16]. The streaming phenomenon, and non-uniform distribution of a drug in the blood has been suggested as a main reason for the neurotoxicity after an intra-arterial chemotherapy, because of excessively high concentration of the drug delivered to the brain by the blood stream [14–18]. This streaming phenomenon is influenced by the infusion rate, and could be reduced by an increase in the infusion rate [11,18]. A streaming phenomenon, in addition to the irregular mixing of a drug, influences the drug delivery to the brain [15–18]. However, few studies have investigated how the infusion rate or the streaming phenomenon would influence the concentration or the distribution of drugs in the brain tumors.

Collins et al. noted that drugs with high first-pass extraction and high total-body clearance (rapid metabolism) were appropriate for intra-arterial administration [19]. Today, there are some chemotherapeutic agents available for intra-arterial chemotherapy. Among them, BCNU [13,14,19–21] and cisplatin [22–24] have mainly been used for the patients with malignant brain tumors. However, the clinical results of the intra-arterial administration of these chemotherapeutic agents on malignant brain tumors have not been satisfactory [13,14,20,23], because of serious side effects, e.g. focal toxicities in the brain and retina [14,24–26]. Though there have been only a few clinical reports showing low incidence of serious neurotoxicities after intra-arterial chemotherapy [20,27], the most common reason for not continuing these intra-arterial chemotherapy has been the brain and ocular toxicities especially in BCNU study [28]. According to a major report from the Brain Tumor Cooperative Group (BTCG) [14] in 448 patients with malignant gliomas, 9.5% of 167 patients who received intra-carotid administrations of BCNU developed irreversible encephalopathy on CT scan and 15.5% of patients developed ipsilateral visual loss. It has been concluded that the intra-carotid BCNU (dissolved in an ethanolic solution) administered by the methods used in that study had no effect on prolonging survival.

In this study we used SarCNU, a derivative of sarcosinamide synthesized by Suami et al. [29], a sarcosinamide congener of BCNU. It has been shown to have a potential as an anti-tumor drug; it is more cytotoxic than BCNU in assays using human glioma cells [30] and has less systematic toxicity and to the bone marrow [31]. SarCNU also has a high tumor to brain ratio because its entry into cells depends on a specific carrier mechanism [32]. We examined the influences of the infusion flow rate on the concentration and distribution of this drug in the rat brain and the brain tumors after an intra-arterial (intra-carotid; i.a.) administration of SarCNU (sarcosinamide chloroethyl-1-nitrosourea) at various infusion rates. From the data presented, an optimum infusion rate was derived which we believe would reduce streaming phenomenon, and at the same time would result in an efficient delivery of the drug to the brain tumors.