Excretion of cytosine arabinoside in saliva after its administration at high doses

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High-dose cytosine arabinoside (cytarabine) is widely used, either alone or in combination with other chemotherapeutic agents, for the treatment of refractory hematological malignancies. Its pharmacology in plasma and cerebrospinal fluid has been extensively examined. In this study, we measured the concentration of cytarabine in saliva of nine patients with hematological malignancies who received high-dose cytarabine. Cytarabine at a dose of 3 g/m^2 was administered i.v. over 2 h. Saliva samples were collected before initiating cytarabine infusion, within 15 min after the completion of infusion and 2 or 4 h after infusion. The concentration of cytarabine was measured by HPLC methods. All nine patients showed a detectable level of cytarabine in saliva within 15 min after the completion of infusion (0.58 ± 0.48 μg/ml), which was equivalent to 5% of its plasma concentration; however, the drug was no longer detectable in saliva thereafter. These findings suggest that cytarabine is excreted in saliva during and shortly after its administration at a high dose. *Anti-Cancer Drugs* 17:597–598 © 2006 Lippincott Williams & Wilkins.

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Introduction

High-dose cytosine arabinoside (cytarabine) is widely used for the treatment of hematological malignancies, especially for refractory acute leukemia or malignant lymphoma [1,2]. In hematopoietic stem cell transplantation (HSCT), high-dose cytarabine is also used as a component of the conditioning regimen, usually in combination with total body irradiation (TBI) or other chemotherapeutic agents [3,4]. The primary toxicities of high-dose cytarabine include myelotoxicity, nausea/vomiting, central nervous system disturbance, keratoconjunctivitis and mucositis [1]. Mucositis, particularly stomatitis, contributes to morbidity and secondary systemic infections in patients with profound neutropenia. It is believed that cytarabine-induced oral mucositis is primarily due to the inhibition of mucosal DNA synthesis by cytarabine in the blood. However, there have been only a few reports describing the behavior of cytarabine in saliva, which is also postulated to cause mucosal damage in synergy with cytarabine in the blood [5,6]. In the present study, we examined the concentration of cytarabine in saliva after its high-dose administration to elucidate its pharmacokinetics in saliva.

Patients and methods

Patients and treatment

We examined patients with acute myelogenous leukemia or myelodysplastic syndrome who received high-dose cytarabine as part of a conditioning regimen for allogeneic HSCT. The patients received cytarabine at a dose of 3 g/m^2 every 12 h for 4 days after receiving TBI (12 Gy), as we have previously reported [3]. During the days of high-dose cytarabine infusion, the patients also received hydrocortisone i.v. (200 mg/day) for the prophylaxis of hypersensitive reaction to the high-dose cytarabine. They also received cyclosporin A or tacrolimus with short-term methotrexate for the prophylaxis of graft-versus-host disease.

Sample collection and measurement of cytarabine concentration

On the first day of cytarabine infusion, blood and saliva samples were obtained simultaneously before initiating cytarabine infusion, within 15 min after the completion of infusion and 2 or 4 h after infusion. The samples were collected in heparinized tubes containing tetrahydrouridine to prevent deamination of the cytarabine. Concentrations of cytarabine in plasma and saliva were measured by HPLC, using the method described by Bury and Keary [7]. Briefly, after being deproteinized and neutralized, the samples were placed in an L-column ODS (Chemicals Evaluation and Research Institute, Tokyo, Japan). Absorbance of the column effluent at 274 nm was monitored using an UV detector. This assay system was able to detect cytarabine at levels as low as 0.04 μg/ml.

Grading of stomatitis

We used the National Cancer Institute Common Toxicity Criteria to grade stomatitis as follows: grade 0, none;

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grade 1, painless ulcers, erythema and/or mild soreness in the absence of lesions; grade 2, painful erythema, edema or ulcers, but can swallow; grade 3, painful erythema, edema or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support; grade 4, severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia. The graded degree of stomatitis of each patient was evaluated and recorded every day from the day of HSCT to day 28, and the maximum grade of each patient was considered to be his or her grade.

Results

Our subjects consisted of nine patients, five with acute myelogenous leukemia and four with myelodysplastic syndrome, whose median age was 43 years (range 27–58). Their mean plasma and saliva concentrations of cytarabine are shown in Table 1. Cytarabine was not detected in samples obtained before administration in any of our nine patients. The mean concentration of cytarabine in plasma was $12.72 \pm 5.82\,\mu g/ml$ within 15 min after completion of infusion. Cytarabine was detectable in saliva of all patients at a mean concentration of $0.58 \pm 0.48\,\mu g/ml$, which accounted for approximately 5% of the plasma concentration. Between 2 and 4 h after cytarabine infusion, its plasma concentration was very low, but still detectable. Cytarabine was no longer detectable in saliva, however, at 2–4 h after infusion. Regarding the incidence and severity of stomatitis, six of our nine patients developed grade 2 or 3 stomatitis and no patients developed grade 4 stomatitis.

Discussion

In the present study, we examined patients receiving high-dose cytarabine ($3\,g/m^2$) in order to determine its levels of excretion in saliva. All nine patients showed detectable levels of cytarabine in saliva immediately following high-dose cytarabine infusion. The pharmacology of high-dose cytarabine has been extensively investigated using plasma and cerebrospinal fluid [1,8,9]. Since cerebrospinal fluid exhibits little, if any, deaminase activity, the half-life of cytarabine in cerebrospinal fluid is significantly prolonged compared to that in plasma. Although cytarabine was detectable in saliva, it was detectable only shortly after the completion of cytarabine infusion, almost in parallel with the plasma concentration. These findings strongly suggest that the excretion of cytarabine in saliva is through diffusion from plasma.

The pharmacokinetics of high-dose cytarabine in saliva have yet to be fully examined; to date, there have been few reports describing the presence of cytarabine in saliva after its infusion [5,6]. To the best of our knowledge, the present study is the first to clearly demonstrate cytarabine concentrations in saliva during high-dose cytarabine therapy. It is plausible that the excretion of cytarabine in saliva could contribute to the development of stomatitis, which is one of the toxicities of high-dose cytarabine, particularly when it is used in combination with other chemotherapeutic agents or with radiation [3,4]. Indeed, six of our nine patients developed grade 2 or 3 stomatitis in this study. Our patients also received TBI and methotrexate in addition to cytarabine, which makes it difficult to clearly distinguish the effects of cytarabine in saliva on the subsequent development of stomatitis. Although higher cytarabine concentrations in plasma and other chemoradiotherapy are likely to play a more important role in the development of stomatitis, the mean concentration of cytarabine in saliva was $0.58\,\mu g/ml$, which is above the level necessary to inhibit DNA synthesis [8,10]. Further investigation of the area under the concentration curve of cytarabine in saliva is needed to clarify the drug exposure to mucosa. However, these findings suggested that not only cytarabine in the plasma, but also the drug in saliva might partly contribute to the development of stomatitis in synergy with other chemoradiotherapy.

In the present study, we found that excretion of cytarabine in saliva is observed after high-dose cytarabine therapy and that its concentration was above the level at which it interferes with DNA synthesis. Future study to further elucidate the behavior of cytarabine in saliva is required.

Table 1 **Mean cytarabine concentration ($\mu g/ml \pm SD$; $n=9$) after high-dose infusion as measured by HPLC assay**

Time after completion of cytarabine infusion	Plasma	Saliva
<15 min	12.72 ± 5.82	0.58 ± 0.48
2–4 h	0.19 ± 0.13	0

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