Pharmacokinetical Comparison of Anticancer Drugs in Cerebrospinal Fluid during Cerebrospinal Fluid Perfusion and Injection Chemotherapy

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The present study examined the pharmacokinetics of anticancer drugs in the cerebrospinal fluid (CSF) during CSF perfusion or injection chemotherapy. A 69-year-old Japanese woman with disseminated glioblastoma received one course of both ventricular-lumbar (V-L) and lumbar-ventricular (L-V) CSF perfusion chemotherapy, and one course of both ventricular and lumbar injection chemotherapy with methotrexate (MTX), cytosine arabinoside (Ara-C), and nimustine (ACNU). Samples of CSF from the ventricles and lumbar spinal canal were obtained via the Ommaya reservoirs. The drug concentrations in the CSF were measured by either fluorescence polarization immunoassay or high performance liquid chromatography. In the V-L CSF perfusion chemotherapy, the maximum CSF concentrations of the three drugs in the lumbar spinal canal were lower than those in the ventricles. However, the concentrations of MTX and Ara-C in the lumbar spinal canal exceeded those in the ventricles 3 hours after the perfusion. The area under the CSF concentration versus the time curves (AUC) of MTX and Ara-C in the lumbar spinal canal were 175.7 and 76.2%, respectively, of those in the ventricles. In the L-V CSF perfusion chemotherapy, the CSF concentrations of the three drugs in the lumbar spinal canal were higher than those in the ventricles. The AUCs of MTX and Ara-C in the ventricles were 15.5 and 18.4 %, respectively, of those in the lumbar spinal canal. In the ventricular CSF injection, the initial CSF concentrations of the three drugs in the ventricles were higher than those in the lumbar spinal canal. However, the CSF concentrations of MTX and Ara-C in the lumbar spinal canal exceeded those in the ventricles 12 hours after the injection. Although the concentration of ACNU in the ventricles was only detectable at 3 hours after the injection, no concentration in the lumbar spinal canal was detectable. The AUCs of MTX and Ara-C in the lumbar spinal canal were 84.6 and 29.1%, respectively, of those in the ventricles. In the lumbar CSF injection, the CSF concentrations of MTX and Ara-C in the ventricles were detectable but lower than those in the lumbar. Although the CSF concentration of ACNU in the lumbar spinal canal was only detectable at 3 hours after the injection, no concentration in the ventricles was detectable. The AUC of MTX in the ventricles was 0.31% of that in the lumbar spinal canal. These results indicate that CSF perfusion chemotherapy may thus be a more useful treatment than CSF injection chemotherapy to patients with disseminated brain tumors.

Key words — pharmacokinetics, cerebrospinal fluid, methotrexate, cytosine arabinoside, nimustine.
Introduction

The treatment of disseminated malignant brain tumors generally involves intrathecal chemotherapy with methotrexate (MTX) alone or in combination with cytosine arabinoside (Ara-C), together with local radiotherapy. However, because the maximum dose of MTX is limited by neurotoxicity, the clinical results have not been satisfactory. The pharmacokinetics of nimustine (ACNU) in lumbar cerebrospinal fluid (CSF) and the therapeutic effect of ventricular-lumbar (V-L) perfusion chemotherapy with ACNU in fifteen patients with subarachnoid dissemination of primary central nervous system tumors have been reported. Recently, a pilot study evaluating the efficacy and side effects of V-L perfusion chemotherapy with MTX and Ara-C in patients with meningeal carcinomatosis found that this therapy was effective in improving cerebral, cranial nerve, and spinal root signs and symptoms. In addition, we have reported the pharmacokinetics of MTX, Ara-C, and ACNU in lumbar CSF during V-L perfusion chemotherapy in three patients with disseminated brain tumors. We found that CSF perfusion chemotherapy enable a high concentration of anticancer drug to be administrated for dissemination in the spinal cord within a short period of time, with minimal adverse effects. In addition, the maximum concentration of anticancer drugs in discharged CSF and the duration of perfusion were inversely correlated. Furthermore, we reported a case of the CSF concentrations of MTX, Ara-C, and ACNU during V-L and lumbar-ventricular (L-V) perfusion chemotherapy in a patient with disseminated brain tumor. We found that the pharmacokinetics of anticancer drugs in ventricular CSF differ from those in lumbar CSF during L-V and V-L perfusion chemotherapy. However, there have been few reports on the pharmacokinetic comparison between the ventricles and the lumbar spinal canal of chemotherapy drugs administered by either perfusion or injection chemotherapy.

In this study, we examined the pharmacokinetics of anticancer drugs in the CSF of a patient with a disseminated brain tumor during V-L perfusion, L-V perfusion, ventricular injection, and lumbar injection chemotherapy, using the combination of MTX, Ara-C, and ACNU.

Methods

Case Reports

A 69-year-old Japanese woman weighing 39 kg had a disseminated glioblastoma that had been treated previously by partial surgical resection and radiation therapy. She underwent six courses of CSF perfusion and two courses of CSF injection chemotherapy with intervals of at least one week between each treatment. In the first, second, fifth, and sixth courses of CSF perfusion chemotherapy, the perfusion was performed for 2 hours via an Ommaya reservoir in the anterior horn of the lateral ventricle, and discharged by drainage through an Ommaya reservoir in the lumbar spinal canal (V-L route). In the third and fourth courses of CSF perfusion chemotherapy, the perfusion solution was perfused for 2 hours via the lumbar Ommaya reservoir, and discharged through an Ommaya reservoir in the anterior horn of the lateral ventricle (L-V route). For the perfusion solution in the fifth treatment (consisting of V-L perfusion chemotherapy) 20 mg of MTX, 20 mg of Ara-C, and 10 mg of ACNU were dissolved in 100 mL of artificial CSF (99.5 mL of lactated Ringer's, 0.4
mL of 7% sodium bicarbonate, and 0.1 mL of 50% glucose). For the perfusion solution in the fourth treatment (consisting of L-V perfusion chemotherapy) 10 mg of MTX, 30 mg of Ara-C, and 10 mg of ACNU were dissolved in 100 mL of artificial CSF. For the first course of CSF injection chemotherapy, the medication was injected via an Ommaya reservoir in the lumbar spinal canal. In the second course, the chemotherapy solution was injected via an Ommaya reservoir in the anterior horn of the lateral ventricle. The injection solution consisted of 10 mg of MTX, 20 mg of Ara-C, and 10 mg of ACNU were dissolved in 20 mL of saline. The drugs were immediately perfused or injected after dissolution in the artificial CSF or saline because ACNU was easily degraded in aqueous solution.

Informed written consent for the treatment was obtained from the patient. The CSF concentrations of the three drugs in both the ventricles and the lumbar spinal canal were measured during the fourth and fifth courses of CSF perfusion chemotherapy and during both ventricular and lumbar injection chemotherapy. The CSF samples were obtained from the two Ommaya reservoirs at baseline, and 2, 3, 5, 10, 30, 48, 72, and 96 hours after the initiation of perfusion and at baseline, and 3, 12, 24, 48, 72, and 96 hours after the injection. The CSF samples (2.0 mL) were collected in tubes, and immediately frozen and stored at -20°C until analysis, which was performed within 1 week.

The CSF concentrations of MTX were measured using a fluorescence polarization immunoassay (TDX, Abbott, North Chicago, IL), and the Ara-C and ACNU concentrations in the CSF were measured using the HPLC assay as previously reported9).

The half-lives anticancer drugs were estimated using a modified microcomputer program (MULTI®) with a microcomputer, model NEC PC-9801, as follows:

\[ C_{CSF} = A \exp(-k_e (t-t_i)) \]  
\[ C_{CSF} = A \exp(-\alpha (t-t_i)) + B \exp(-\beta (t-t_i)) \]  

where \( C_{CSF} \) is the CSF concentration, \( t \) is the time, \( t_i \) is the infusion time, and \( k_e \) is the elimination rate constant of one compartment model, \( \alpha \) and \( \beta \) are the elimination rate constants of two compartment model.

The values for the area under the CSF concentration of MTX and Ara-C versus the time curves (AUC) were calculated using the trapezoidal rule.

**Results**

The interval between each treatment was sufficient (at least one week) to ensure that no anticancer drugs were detectable in the CSF at the initiation of perfusion and injection chemotherapy.

In the V-L CSF perfusion chemotherapy, the maximum CSF concentrations of the three drugs in the both ventricles and lumbar spinal canal occurred at the end of the perfusion, with 75.7 μg/mL of MTX, 125.8 μg/mL of Ara-C, and 28.2 μg/mL of ACNU in the ventricles and 33.8 μg/mL of MTX, 45.6 μg/mL of Ara-C, and 2.8 μg/mL of ACNU in the lumbar spinal canal. Although the initial CSF concentrations of the three drugs in the lumbar spinal canal were lower than those in the ventricles, the CSF concentrations of MTX and Ara-C in the lumbar spinal canal exceeded those in the ventricles 3 hours after perfusion. In both the ventricles and the lumbar spinal canal, the CSF concentrations of MTX decreased with a biexponential decay pattern, whereas those of Ara-C and
ACNU decreased with a monoexponential decay pattern (Fig. 1). The AUCs of MTX and Ara-C in the lumbar spinal canal were 175.7 and 76.2%, respectively, of those in the ventricles (Table 1).

In the L-V CSF perfusion chemotherapy, the maximum CSF concentrations of the three drugs in both the ventricles and the lumbar spinal canal occurred at the end of the perfusion, with 18.3μg/
mL of MTX, 47.7 μg/mL of Ara-C, and 1.9 μg/mL of ACNU in the ventricles and 60.2 μg/mL of MTX, 188.6 μg/mL of Ara-C, and 20.8 μg/mL of ACNU in the lumbar spinal canal. The CSF concentrations of the three drugs in the lumbar spinal canal were consistently higher than those in the ventricles. In the ventricles, the CSF concentrations of MTX decreased with a biexponential decay pattern, while those of Ara-C and ACNU decreased with a monoexponential decay pattern. In the lumbar spinal canal, the CSF concentrations of the three drugs decreased with a monoexponential decay pattern (Fig. 2). The AUCs of MTX and Ara-C in the ventricles were 15.5 and 18.4%, respectively, of those in the lumbar spinal canal (Table 1).

In the ventricular CSF injection, the CSF concentrations of the three drugs at 3 hours after the injection were 66.2 μg/mL of MTX, 84.7 μg/mL of Ara-C, and 0.15 μg/mL of ACNU in the ventricles, and 18.9 μg/mL of MTX, 19.8 μg/mL of Ara-C, but no detectable ACNU in the lumbar spinal canal. The initial CSF concentrations of the three drugs in ventricles were higher than those in the lumbar spinal canal. However, the CSF concentrations of MTX and Ara-C in the lumbar spinal canal exceeded those in the ventricle 12 hours after the injection. In the ventricles, the CSF concentrations of MTX decreased with a biexponential decay pattern, whereas the concentration of Ara-C decreased with a monoexponential decay pattern. In the lumbar spinal canal, the CSF concentrations of both MTX and Ara-C decreased with a monoexponential decay pattern. Although the concentration of ACNU in the ventricles was detectable only at 3 hours after the injection, that in the lumbar spinal canal was not detectable (Fig. 3). The AUCs of MTX and Ara-C in the lumbar spinal canal were 84.6 and 29.1%, respectively, of those in the ventricles (Table 1).

In the lumbar CSF injection, the concentrations of the three drugs at 3 hours after the injection were 82.4 μg/mL of MTX, 94.2 μg/mL of Ara-C, and 0.90 μg/mL of ACNU in the lumbar spinal canal, and 0.44 μg/mL of MTX, 0.39 μg/mL of Ara-C, but no detectable ACNU in the ventricles.

![Fig. 2. Time Course of CSF Concentrations of MTX, Ara-C, and ACNU following Lumbar-Ventricular CSF Perfusion Chemotherapy](image-url)
The CSF concentrations of MTX and Ara-C in the ventricles were detectable but lower than those in the lumbar spinal canal. The CSF concentrations of MTX and Ara-C in the lumbar spinal canal, and that of MTX in the ventricles, decreased with a monoexponential decay pattern. Although the CSF concentration of ACNU in the lumbar spinal canal was detectable only at 3 hours after the injection, that in the ventricles was undetectable (Fig. 4). The AUC of MTX in the ventricles was 0.31% of that in the lumbar spinal canal (Table 1).

The CSF AUCs of ACNU in all treatments and that of Ara-C in the ventricles during lumbar CSF injection could not be estimated due to a lack of measurement points.

**Discussion**

In the present study, we compared the pharmacokinetics of MTX, Ara-C, and ACNU in both ventricular and lumbar CSF in a patient with disseminated glioblastoma during CSF perfusion chemotherapy by both the L-V and V-L routes, and CSF injection chemotherapy via the ventricles and lumbar spinal canal. Meningeal carcinomatosis is generally treated by intrathecal chemotherapy with MTX alone or in combination with Ara-C. However Bleyer and Shapiro et al. have reported that when MTX is administered by lumbar puncture, the concentration of MTX that arrives at the subarachnoid space is low. In addition, Rieselbach et al. have proposed that lumbar injections of MTX and Ara-C do not sufficiently distribute these drugs in the subarachnoid space of the brain. Similar assumptions have been made about anticancer drugs injected through an Ommaya reservoir. We previously showed that high concentrations of MTX, Ara-C, and ACNU arrive at the lumbar spinal canal during V-L perfusion for 2 hours. In the present study, when the anticancer drugs were perfused by the V-L route, the CSF concentrations of the three drugs in the lumbar spinal canal were initially lower than those in the ventricles, but were higher at 3 hours after perfu-
Fig. 4. Time Course of CSF Concentrations of MTX, Ara-C, and ACNU following Lumbar Injection Chemotherapy

MTX: ventricles = ○ ○ ○; lumbar = ● ● ●; Ara-C: ventricles = □ □ □; lumbar = ▲ ▲ ▲; ACNU: lumbar = △; t = time after the injection; solid and dotted line = computer simulation curve.

sion. Furthermore, high concentrations of MTX and Ara-C arrived at the ventricles even via the L-V perfusion route. However, the CSF AUC of MTX in the lumbar spinal canal was higher than that in the ventricles regardless of the perfusion route. These results demonstrate the efficiency of CSF perfusion chemotherapy in distribution of large quantities of anticancer drugs in CSF within a short period of time, allowing for an effective drug concentration to be maintained in the CSF for an extended period of time.

However, in contrast to MTX and Ara-C, ACNU was not as effectively distributed. When ACNU was administered by both L-V and V-L perfusion CSF chemotherapy, ACNU was initially detectable in the CSF of both the ventricles and the lumbar spinal canal at the end of perfusion, but was not detectable at 8 hours after the end of perfusion, most likely because the half-life of ACNU is very short (less than 0.4 hours). Furthermore, even at the injection site, the CSF concentration of ACNU decreased to less than 1 µg/mL at 3 hours after the end of perfusion. In an experiment involving the intraventricular injection of ACNU in dogs, Levin et al. reported that a significant amount of ACNU in the CSF is hydrolytically degraded before reaching subarachnoid regions distal to the injection site. In our patient, similar results were obtained with respect to the decomposition of ACNU.

Nakagawa et al. reported that 9 of 13 patients with meningeal carcinomatosis treated with V-L perfusion of MTX and Ara-C showed a positive response. In their treatment regimes, MTX (10 to 30 mg) and Ara-C (40 mg) were infused at 8 to 12 hour intervals on six or nine occasions via an Ommaya reservoir placed in the lateral ventricle, which was found to be effective in improving cerebral, cranial nerve, and spinal root signs and symptoms. However, they also found that the drugs displayed unacceptably high levels of toxicity when compared with that of standard intrathecal chemotherapy, indicating that this therapy needs to be investigated further to establish optimal
drug doses and repetitive perfusate volumes. We previously reported that the half-lives of MTX, Ara-C, and ACNU during V-L perfusion chemotherapy are about 4, 1, and 2 hours, respectively, and consequently, a 3 day interval between CSF perfusion chemotherapy with MTX and Ara-C appears prudent. The present patient experienced no serious complications as the interval between each CSF perfusion chemotherapy treatment was at least one week. In addition, the side effects of the anticancer drugs in the whole body were negligible, most likely because the transport of these drugs from the CSF to the rest of the body is slight, as previously reported.

In the present study, a 2 hour perfusion period was used for all treatments, however the drugs, in particular ACNU, underwent decomposition dependent on the perfusion period. We previously reported that the maximum concentration of ACNU in the lumbar discharged CSF degrades to less than 1% of the concentration in the original perfusion solution after 3 hours of V-L perfusion, due to the extremely short half-life of ACNU that took into account the rapid degradation of ACNU in solution under body temperature. These results of the present study indicate that CSF perfusion chemotherapy with anticancer drugs including Ara-C should be performed within 2 hours, and that these anticancer drugs should be immediately perfused after dissolution in artificial CSF.

In conclusion, CSF perfusion chemotherapy may be a more useful treatment than CSF injection chemotherapy in patients with disseminated brain tumors. However, CSF perfusion chemotherapy is not appropriate for patients with large metastatic deposits and obliteration of the cerebrospinal chamber. Anticancer drugs with extremely short half-life, such as ACNU, that are injected by the lumbar spinal canal route are not efficiently delivered in the whole spinal canal. Except for disseminated tumors in the lumbar spinal canal, lumbar injection chemotherapy may be not a feasible route of treatment. However, future studies on the appropriate concentrations of perfused anticancer drugs, and the possible synergistic effects of drug combinations are required.

References