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Pharmacokinetics of Temozolomide in a Patient With Glioblastoma Undergoing Hemodialysis: A Short Communication

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Background: Temozolomide (TMZ) is an alkylating agent used to treat glioblastoma. However, the pharmacokinetics of TMZ to establish a treatment strategy for patients undergoing hemodialysis (HD) remain unclear. In this case report, we evaluated the pharmacokinetics and HD removal rate of TMZ in a patient with glioblastoma undergoing HD to determine optimal dosing of TMZ.

Methods: A 78-year-old man with glioblastoma who underwent HD 3 times a week was treated with TMZ concomitant with radiotherapy. One dose of TMZ was prescribed at 75 mg/m^2 on the day before HD and another dose of 37.5 mg/m^2 on the day before non-HD. Peak and trough concentrations (1 hour and 12 hours after dosing, respectively) were evaluated before HD and on non-HD days. HD removal rate of TMZ was calculated based on the predialyzer and postdialyzer plasma concentrations. Furthermore, the TMZ plasma concentrations were measured using liquid chromatography–tandem mass spectrometry.

Results: The mean plasma peak and trough concentrations ± SD after 75 mg/m^2 TMZ were 2917 ± 914 and 108 ± 17.6 ng/mL, respectively. Those after 37.5 mg/m^2 TMZ dosage were 1305 ± 650 and 53.8 ± 11.8 ng/mL, respectively. The mean HD TMZ removal rate was 84.9 ± 1.9%.

Conclusions: TMZ was tolerable in patients undergoing HD. Based on the data from a single individual pharmacokinetic perspective, the pharmacokinetics of TMZ in this patient undergoing HD were comparable with those observed in patients with normal renal function. In addition, it may be reasonable to administer TMZ after HD because of the high HD removal rate.

Key Words: temozolomide, pharmacokinetics, hemodialysis, glioblastoma, malignant glioma

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INTRODUCTION

Temozolomide (TMZ), an alkylating agent, is a key drug used in glioblastoma treatment. In 2005, Stupp et al.[1] reported the efficacy of TMZ therapy and concomitant radiotherapy for the treatment of glioblastoma. For newly diagnosed glioblastoma, the standard TMZ dose is 75 mg/m^2 once daily for 42 consecutive days with concomitant radiotherapy.[2]

In clinical practice, patients with glioblastoma who require TMZ administration rarely develop severe renal impairment requiring hemodialysis (HD). In a patient who develops manageable adverse events (AEs) and require HD, TMZ dose of 75 mg/m^2 can be administered once on the day before HD and another dose of 37.5 mg/m^2 can be administered on the day before non-HD, concomitant with radiotherapy.[3] Muto et al reported that TMZ can be administered to 7 patients undergoing HD without dosage reduction; however, severe lymphocytopenia and thrombocytopenia developed in 4 and 1 patient, respectively.[4] Although there are a few case reports of patients undergoing HD and receiving TMZ, to the best of our knowledge, no study has examined the pharmacokinetics of TMZ in these patients or the HD removal rate.

Little unchanged TMZ is excreted in the urine[5] because most TMZ is non-enzymatically metabolized to 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC). MTIC

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F. Tanaka, K. Irie, and M. Hirabatake conceived the study. F. Tanaka, K. Irie, N. Fukui, R. Horii, H. Imamura, M. Hirabatake, H. Ikesue, N. Muroi, N. Sakai and T. Hashida designed the study. F. Tanaka and R. Horii collected data. F. Tanaka, K. Irie, and S. Fukushima measured the plasma concentrations, and F. Tanaka and K. Irie performed the pharmacokinetic analysis. F. Tanaka drafted the manuscript. All the authors approved the final manuscript.

The authors declare no conflict of interest.

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This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kobe City Medical Center General Hospital (approval number: zn200508). The patient had impaired consciousness; therefore, a written informed consent was obtained from the patient's family.

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is further metabolized to diazonium ions, which induce DNA methylation and suppress cell growth and 5-amino-imidazole-4-carboxamide (AIC). The half-lives of both TMZ and MTIC were approximately 2 hours. AIC is an intermediate of purine biosynthesis and is mostly excreted in urine.

However, no data have been reported on the pharmacokinetics of TMZ in patients undergoing HD; thus, no standard dose for TMZ in patients undergoing HD. In addition, the protein binding rate of TMZ has been reported to be 12%–16%, suggesting a high HD removal rate; however, this has not been demonstrated. In this study, we evaluated the pharmacokinetics and removal rate of TMZ in patients with glioblastoma undergoing HD to determine the optimal TMZ dose.

CASE PRESENTATION

A 78-year-old man (body surface area: 1.54 m^2; body weight, 51.1 kg) was referred to our hospital by his previous physician because of a suspected brain tumor. The patient had chronic renal failure because of chronic glomerulonephritis and had required HD thrice every week for the previous year. After hospitalization, the patient was diagnosed with isocitrate dehydrogenase wild-type glioblastoma, and TMZ therapy was initiated for 42 days with concomitant radiotherapy (40 Gy in 15 fractions). The comorbidities included hypertension, dyslipidemia, hypothyroidism, benign prostatic hyperplasia, and cataracts in both eyes. He did not use any medications known to interact with TMZ. During this study, the patient underwent HD 3 times a week for 3 hours using a polysulfone membrane with a surface area of 1.5 m^2. Blood and dialysate flow rates were 155–200 and 500 mL/min, respectively.

Before to TMZ administration, the patient presented with grade 3 lymphocytopenia and grade 2 anemia. During 42 days of TMZ therapy with concomitant radiotherapy, lymphocytopenia and anemia deteriorated to grades 4 and 3, respectively. Twenty days after starting TMZ therapy, the patient developed fever suspicious of aspiration pneumonia and was treated with piperacillin/tazobactam for 8 days. The observed AEs were tolerable, and TMZ therapy was continued for 42 days without dose reduction. The patient remained stable after treatment.

MATERIALS AND METHODS

TMZ Administration

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kobe City Medical Center General Hospital (approval number: zn200508). The patient had impaired consciousness; therefore, a written informed consent was obtained from the patient's family.

TMZ doses of 75 mg/m^2 (120 mg) once on the day before HD and of 37.5 mg/m^2 (60 mg) once on the day before non-HD days were administered based on a previous case report.[3] The patient received HD 3 times a week. Thus, "before HD" days included 3 days and "before non-HD" days included 4 days in a week. Figure 1 represents the schedules for TMZ dosing, pharmacokinetic sampling, and HD. TMZ dosing was performed at 21:00, and pharmacokinetic sampling was performed at 22:00 (1 hour, peak concentration) and 9:00 on subsequent day (12 hours, trough concentration), after which HD was initiated on HD day. In the regular schedule, the patients received 3 doses of 75 mg/m^2 TMZ before HD days (Fig. 1A) and 3 times of 37.5 mg/m^2 TMZ before non-HD days (Fig. 1B) per week. However, days 23 (Fig. 1C) and 22 (Fig. 1D) were irregular schedules because the HD schedule was changed owing to infection control problems in our hospital.

The patient was unable to take TMZ tablets orally; therefore, the tablets were suspended in apple juice (pH 3–4) and administered via a nasogastric tube. TMZ decomposes into MTIC at pH >7 and is stable in acidic solutions.[6,7]

Efficacy and Safety Evaluation

The best tumor response was evaluated using computed tomography and was based on the Response Evaluation Criteria in Solid Tumors guidelines, version 1.1. TMZ-associated AEs were evaluated using the Common Terminology Criteria for Adverse Events, version 5.

Pharmacokinetic Sampling and Measurements

Blood samples were drawn using an acidic collection tube (VP-FC052K; Terumo, Tokyo, Japan) to prevent the hydrolysis of TMZ.[8,9] After immediate centrifugation (1500*g*, 10 minutes), plasma samples were stored at −20°C until measurement. Pharmacokinetic sampling was conducted on 8 days:4 days before HD days (day 23, 24, 36, and 38) and 4 days before non-HD days (days 22, 25, 32, and 39). The peak and trough concentrations (1 and 12 hours after dosing) were evaluated. On HD days, HD was started after trough-level sampling (12 hours, $Conc._{preHD}$), and the concentration of plasma that passed through the dialyzer ($Conc._{postHD}$) was measured to evaluate the HD removal rate of TMZ.

Bulk TMZ powder was purchased from the Tokyo Chemical Industry (Tokyo, Japan). Plasma TMZ concentration was measured using liquid chromatography–tandem mass spectrometry as described previously.[10] The linear calibration range for TMZ was 10–500 ng/mL ($R^2 > 0.999$). Samples at the peak concentrations were diluted 10-fold to be within the calibration range. The intra-assay accuracy (relative error %, n = 5) and precision (relative SD %, n = 5) were 4.7%–7.1% and 93.6%–101.9%, respectively. TMZ was stable in acidic plasma at −20°C for 1 month.

Pharmacokinetic Analysis

The elimination rate constant (K_{el}) and elimination half-life ($t_{1/2}$) of TMZ in the patient were calculated from the peak and trough concentrations using a noncompartmental analysis (Equation 1). K_{el} and $t_{1/2}$ were calculated for each dose, and the mean ± SD is presented. The HD removal rate (%) of TMZ was calculated as the concentration before and after ($Conc._{preHD}$ and $Conc._{postHD}$) HD (Equation 2). HD clearance (CL) was calculated using blood flow and the HD removal rate (Equation 3).

$$Kel\ (/h) = \frac{\ln\left(\frac{Conc._{peak}}{Conc._{trough}}\right)}{time_{trough} - time_{peak}} \quad (1)$$

$$\text{HD removal rate}\ (\%) = \frac{Conc._{preHD} - Conc._{postHD}}{Conc._{preHD}} \times 100 \quad (2)$$

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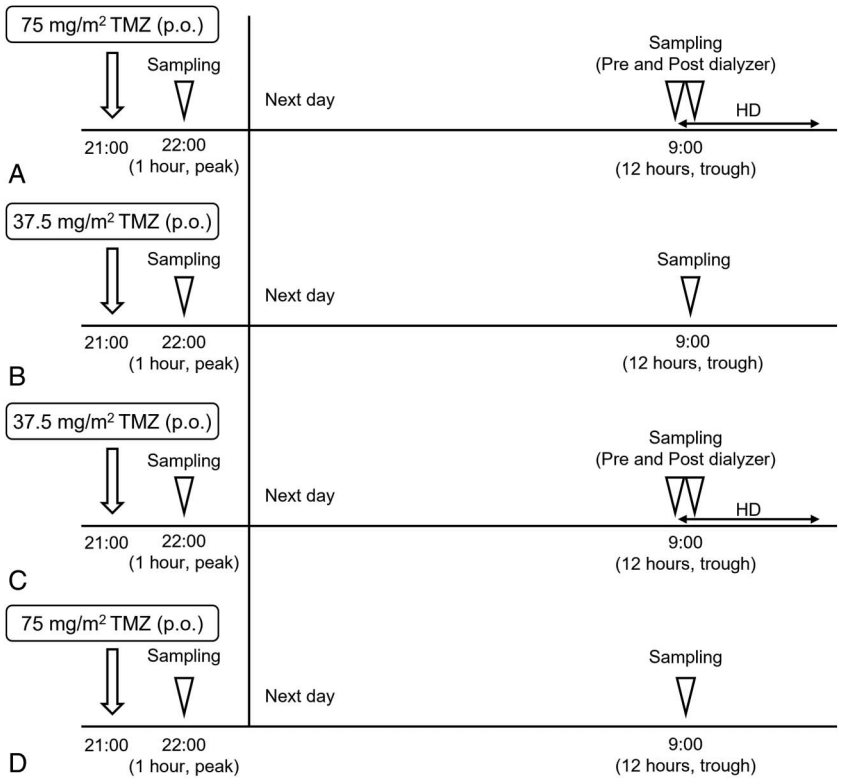

FIGURE 1. Schedule of TMZ dosing (at 21:00), pharmacokinetic sampling (at 22:00 and 9:00 on the subsequent day), and HD (at 9:00 on the subsequent day). A, Before HD days (75 mg/m^2, days 24, 36, and 38) and (B) before non-HD days (37.5 mg/m^2, days 25, 32, and 39). C, Irregular before HD days (37.5 mg/m^2, days 23) and (D) irregular before non-HD days (75 mg/m^2, days 22); C and D, were irregular schedules because the HD schedule was changed. Pharmacokinetic samplings for HD removal rate were performed before and after the dialyzer at initiation of HD.

$$\text{HD CL } (mL/min) = \textit{Blood flow} \times \textit{HD removal rate} \quad (3)$$

RESULTS

TMZ Concentrations

The mean TMZ plasma concentrations after 75 mg/m^2 (120 mg) and 37.5 mg/m^2 (60 mg) TMZ administration are shown in Figure 2, and the raw data are presented in **Supplemental Digital Content 1** (see **Table S1**, http://links.lww.com/TDM/A682). The mean ± SD of peak (1 hour) and trough (12 hours) TMZ plasma concentrations after TMZ administration at 75 mg/m^2 were 2917 ± 914 and 108 ± 17.6 ng/mL, respectively. The mean ± SD peak and trough TMZ plasma concentrations after administration at 37.5 mg/m^2 were 1305 ± 650 and 53.8 ± 11.8 ng/mL, respectively. The mean ± SD of K_{el} and $t_{1/2}$ after 75 mg/m^2 TMZ administration were 0.30 ± 0.03 /h and 2.35 ± 0.23 hours, respectively. The mean ± SD of K_{el} and $t_{1/2}$ after 37.5 mg/m^2 TMZ administration were 0.28 ± 0.06 /h and 2.57 ± 0.67 hours, respectively.

HD Removal Rate of TMZ

The HD removal rate of TMZ was evaluated 3 times after administration of 75 mg/m^2 dose, but only once after 37.5 mg/m^2 dose once because the HD schedule was changed

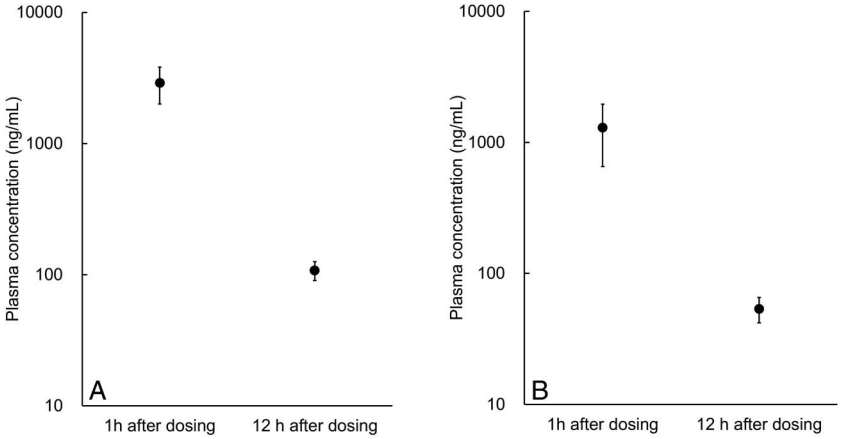

FIGURE 2. Plasma concentrations of temozolomide (TMZ) in a patient with glioblastoma undergoing hemodialysis. TMZ was administered at the dose of (A) 75 mg/m^2 (at 21:00) and (B) 37.5 mg/m^2 (at 21:00). Dots indicate mean TMZ concentrations and bars indicate standard deviations.

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owing to infection control problems in the hospital. The mean $Conc._{preHD}$ and $Conc._{postHD}$ after 75 mg/m^2 TMZ dosage were 108 ± 17.6 and 15.9 ± 1.8 ng/mL, respectively. $Conc._{preHD}$ and $Conc._{postHD}$ for 37.5 mg/m^2 TMZ dosage were 63.5 and 11.1 ng/mL, respectively. The mean HD removal rate of TMZ was 84.9 ± 1.9% based on the change in the TMZ concentration after one pass through the dialyzer. The HD CL was 131.6–169.8 mL/min (2.58–3.32 mL/min/kg).

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DISCUSSION

To the best of our knowledge, this is the first study to investigate the pharmacokinetics and removal rate of TMZ in patients undergoing HD. At the start of the TMZ treatment, the drug was administered at partially reduced doses, and the AEs were tolerable. TMZ is rapidly eliminated from the blood, and its dialyzability is high.

At physiological pH, TMZ non-enzymatically hydrolyzes to MTIC, which rapidly decomposes into an active methyldiazonium ion and an inactive compound, AIC. This nonenzymatic and non–organ-dependent elimination of TMZ can explain its rapid elimination in patients undergoing HD. Thus, it is speculated that TMZ does not accumulate in patients with chronic renal failure undergoing HD. In our case, K_{el} was calculated by avoiding HD, as shown in Figure 1. Thus, K_{el} simply shows the K_{el} for each dose. The K_{el} and $t_{1/2}$ in our patient, which is similar 37.5 and 75 mg/m^2 of TMZ, were comparable with those in a previous study reporting that, in patients with normal renal function given 150 mg/m^2 of TMZ, the K_{el} and $t_{1/2}$ of TMZ were 0.303 /h and 2.29 hours, respectively.[11] We compared the peak concentration observed in the present study with that simulated based on a previously reported population pharmacokinetic model in patients with normal renal function.[12] The simulated data are presented in **Supplemental Digital Content 2** (see **Figure S1**, http://links.lww.com/TDM/A681). The present study reported a peak concentration of 2917 ng/mL, which was within the variability calculated for patients with normal renal function, which suggests that the volume of distribution was also similar. The trough concentration was also within the variability calculated for patients with normal renal function. Therefore, no clinically meaningful pharmacokinetic changes were observed.

In the present case, lymphocytopenia and anemia worsened during TMZ therapy. However, myelosuppression is a common side effect of TMZ and radiation therapy in patients with normal renal function; the AEs observed in our patient were considered tolerable, and the administration of TMZ was completed for 42 days.

The molecular weight and protein binding rate of TMZ are 194.15 and 12%–16%, respectively,[2] suggesting that TMZ is easily removed by HD. Consistent with this expectation, the HD removal rate of TMZ in this study was 84.9%. The CL of TMZ was reported at 2.56 mL/min/kg.[11] The result of HD CL in our case may indicate that HD greatly boosts the elimination of TMZ. Therefore, TMZ should be administered after HD.

This study had some limitations. The effects of AIC metabolites were not evaluated. However, AIC is considered to have little effect on AEs because it is an endogenous intermediate in purine biosynthesis.

CONCLUSION

Here, we report the successful administration of TMZ in a patient with glioblastoma undergoing HD. TMZ (75 mg/m^2 on the day before to HD and 37.5 mg/m^2 on non-HD days) was tolerable in patients undergoing HD. Pharmacokinetic perspective based on data of a single individual revealed that TMZ was rapidly eliminated from the blood after administration. Additionally, it may be reasonable to administer TMZ after HD because of the high HD removal rate.

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