Measurement of Plasma Concentration of Gemcitabine and Its Metabolite dFdU in Hemodialysis Patients with Advanced Urothelial Cancer

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Objective: We investigated the pharmacokinetics of gemcitabine and its metabolite in two male patients (52 and 56-year-old) with advanced urothelial cancer receiving hemodialysis three times a week.

Methods: Gemcitabine, 1000 mg/m² in 100 ml of saline, was intravenously administered for 30 min. The concentration of gemcitabine and its metabolite 2',2'-difluorodeoxyuridine (dFdU) was measured at several given time points using a high-pressure liquid chromatography assay. Pharmacokinetic parameters were determined using the two-compartment modeling program.

Results: Gemcitabine was rapidly eliminated from plasma even in patients with renal dysfunction. No obvious differences in pharmacokinetic parameters such as the t½, AUC and Cmax of gemcitabine were observed between the patients on hemodialysis and those with normal renal function in previous reports. On the other hand, dFdU showed a sustained level until hemodialysis was initiated. Hemodialysis could reduce the plasma dFdU level by approximately 50%.

Conclusions: According to the previous information, no dose modification of gemcitabine may be required for patients with renal impairment or hemodialysis. However, gemcitabine should be given with caution because only limited information is available, and the clinical effect of sustained and/or accumulated dFdU is unknown.

Key words: urothelial neoplasm – gemcitabine – renal impairment – hemodialysis – pharmacokinetics

INTRODUCTION

Urothelial cancer arising from the renal pelvis, ureter and bladder is a common malignancy in the urological field. Systemic chemotherapy is the mainstream treatment for patients with metastatic urothelial cancer. Combination therapy with methotrexate, vinblastine, adriamycin and cisplatin (M-VAC) is a standard regimen for urothelial cancer that has been approved by the Ministry of Health, Labour and Welfare in Japan. Recently, the efficacy of gemcitabine (2', 2'-difluorodeoxycytidine) with cisplatin (GC) has been proven by a randomized control trial mainly conducted in Europe (1,2). Since GC has comparable efficacy and overall survival with lower incidences of adverse events such as high-grade neutropenia and mucositis than M-VAC, it has become part of the first-line regimen for metastatic urothelial cancer in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (3) and PDQ of the National Cancer Institute (4). Although gemcitabine has been approved only for treatment of non-small cell lung cancer, pancreatic cancer and biliary tract cancer in Japan, a phase II clinical trial for urothelial cancer has just been completed and now it is under review for expansion of the indication.

When urothelial cancer is localized in the renal pelvis and ureter, ipsilateral nephroureterectomy with a bladder cuff is a standard method for cure of the disease. However, some patients show impairment of renal function after surgery. Although even bilateral nephroureterectomy may be considered for bilateral disease, anephric patients definitely need
hemodialysis. In addition, urothelial cancer develops in patients receiving hemodialysis for other reasons such as glomerulonephritis and diabetic nephropathy. Thus, systemic chemotherapy may be considered even for patients with impaired renal function or hemodialysis.

Interviews revealed that although gemcitabine is not contraindicated for patients with renal impairment, it should be used with caution because of insufficient information about the pharmacokinetics and safety profiles of such patients (5). Thus, we investigated the pharmacokinetics of gemcitabine and its metabolite in patients with advanced urothelial cancer receiving hemodialysis in the present study.

PATIENTS AND METHODS

Two hemodialysis patients received gemcitabine administration to treat urothelial cancer.

CASE 1

A 56-year-old man underwent augmentation cystoplasty using the ileal segment for a contracted bladder induced by tuberculosis and right nephrectomy for right renal tuberculosis when he was 10 and 22 years old, respectively. Renal function gradually deteriorated and eventually resulted in hemodialysis [4 h using a dialyzer (PES 190DS, Nipro, Co., Japan)] with a blood flow of 250 ml/min and a dialysate flow of 500 ml/min) three times a week when he was 44. When he was 56, he noticed clot discharge from the urethra. Cystoscopy and computed tomography (CT) demonstrated invasive bladder cancer arising from the trigone. Radical cystectomy with pelvic lymph node dissection following laparoscopic left nephroureterectomy was performed. Pathological grade 3 urothelial cancer invaded the surrounding fat tissue (pT3b) with multiple lymph nodal involvement (pN2). At 2 months after surgery, multiple lung, liver and lymph nodal metastases and ascites induced by peritonitis carcinomatosa developed. Systemic chemotherapy using gemcitabine was given in an interval day of hemodialysis. Low-grade fever after administration of gemcitabine was observed. Chemotherapy was ceased because there was no remarkable effect observed and control of the bone pain was mandatory by a palliative method. He died of the disease three months after the last administration of the drug.

RESULTS

The peak plasma concentrations of gemcitabine were obtained at 30 min in case 1 and at 15 min during the infusion in case 2 (Table 1). Gemcitabine was rapidly eliminated from plasma and it was under the detection level at 60–90 min. The \( t_{1/2} \) was approximately 12 min (Table 2). The areas under the concentration-time curve (AUC) of gemcitabine were 5.4 and 4.5 \( \mu g/ml \cdot h \) in cases 1 and 2, respectively. On the other hand, dFdU showed a sustained plasma level for 24 h. The AUCs of dFdU were 369.1 and 509.7 \( \mu g/ml \cdot h \) in cases 1 and 2, respectively. Although hemodialysis reduced the plasma concentration of dFdU by approximately 50%, it was still in the detectable range. The clearance rates of dFdU by hemodialysis were 142.6 and 120.9 ml/min in cases 1 and 2, respectively.
The difluorine-substituted deoxycytidine analogue gemcitabine is a prodrug that does not have cytotoxic activity (5). Intracellular phosphorylation by deoxycytidine kinase causes gemcitabine to metabolize to its active metabolites, gemcitabine di- and triphosphate. Gemcitabine diphosphate inhibits ribonucleotid reductase, which is responsible for DNA synthesis. In addition, gemcitabine triphosphate incorporated into the DNA strand terminates DNA synthesis and exerts cytotoxic activity against various solid cancers. Intravenously administrated gemcitabine is rapidly metabolized to a noncytotoxic metabolite, dFdU, by cytidine deaminase. dFdU is excreted in urine and its elimination depends on renal function.

Gemcitabine application for patients with impaired renal function or hemodialysis will increase if it is approved for treatment of urothelial cancer in Japan. However, only a few studies have investigated the pharmacokinetics and safety profile of gemcitabine in patients with impaired renal function or hemodialysis (7–10). In particular, there are no data available for Japanese patients. Thus, it is mandatory to accumulate pharmacokinetic and clinical information from Japanese patients with impaired renal function or hemodialysis.

In this study, gemcitabine was rapidly eliminated from plasma even in patients with renal dysfunction. No obvious differences in pharmacokinetic parameters such as the $t_{1/2}$, AUC and $C_{max}$ of gemcitabine were observed between the patients on hemodialysis and those with normal renal function in previous reports (11–14). Similar findings that the pharmacokinetics of gemcitabine are not influenced by renal function have been reported (7–10). On the other hand, dFdU showed a sustained level until hemodialysis was initiated because the patients had no or little urine output as previously reported (7–10). Kiani et al. (8) reported that the AUC of dFdU in patients on hemodialysis was approximately 10-fold that in a historical control with normal renal function. Hemodialysis could reduce the plasma dFdU level by approximately 50% as previously reported (8,9). It is highly probable that hemodialysis two or three times before the next administration of gemcitabine may result in complete elimination of dFdU from plasma.

It has been believed that dFdU does not cause adverse events. Several reports demonstrated that there were no specific adverse events induced by gemcitabine in patients with impaired renal function or hemodialysis compared with patients with normal renal function (8–10). On the other hand, Venook et al. (7) reported that patients with elevated creatinine levels seemed to have increased sensitivity to Gemcitabine because various adverse events such as severe skin toxicity were observed. Matsuda (15) demonstrated that gemcitabine should be administered with caution for patients with a long history of hemodialysis because treatment needed to be stopped due to grade 3 hematological toxicity in two Japanese patients on hemodialysis for a long time. Kiani et al. (8) recommended that hemodialysis should start 6–12 h after administration of the drug to minimize potential side effects induced by dFdU.

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<th>Table 2. Pharmacokinetic parameters in patients on hemodialysis</th>
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AUC, area under the concentration-time curve; Cl, clearance rate; $C_{max}$, maximum concentration; $t_{1/2}$, half time.
According to previous information, no dose modification may be required for patients with renal impairment or hemodialysis. However, Gemcitabine should be given with caution because only limited information is available, and the clinical effect of sustained and/or accumulated dFdU is unknown. Furthermore, it will be necessary to investigate the efficacy and safety of gemcitabine treatment in patients with impaired renal function or hemodialysis.

Conflict of interest statement
None declared.

References