Adjuvant Chemotherapy With Gemcitabine Plus Cisplatin for Kidney Transplant Patients With Locally Advanced Transitional Cell Carcinoma

A Single-center Experience

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ABSTRACT

Background. The purpose of the present study was to evaluate the effects and safety of adjuvant chemotherapy with gemcitabine plus cisplatin in kidney transplant patients with locally advanced transitional cell carcinoma.

Methods. A total of 22 kidney transplant patients with locally advanced transitional cell carcinoma were assessed. Eleven patients who underwent surgery and received adjuvant chemotherapy were enrolled in the study. They were compared with 11 matched patients who were treated with surgery alone. The chemotherapy regimen was gemcitabine 800 mg/m^2 on days 1, 8, and 15 and cisplatin 70 mg/m^2 on day 2. A single treatment cycle lasted 28 days. Because of the potential concerted reaction between the immunosuppressant regimen and the chemotherapeutic agents, drug toxicities were closely observed, and a dose reduction of the chemotherapeutic agents was planned according to the toxicity grade. There was a 75% drug dose reduction for grade 2 hematologic toxicities and grade 1 nephrotoxicity, and there was a 50% drug dose reduction for grade 3 hematologic toxicity and grade 2 nephrotoxicity. Patients who developed grade 4 hematologic toxicity or grade 3 to 4 nephrotoxicities were withdrawn.

Results. Eleven patients completed a total of 29 cycles. At a median follow-up time of 21 months, the mean overall survival time was longer than that of the observation group ($P = .043$). The incidence of hematologic toxicities was higher, resulting in a dose reduction of the chemotherapeutic agents in 45.5% of patients. Gastrointestinal reactions were most common in patients with nonhematologic toxicities. Grade 1 nephrotoxicity was reported in 3 patients; no other grade of nephrotoxicity was observed. Levels of serum creatinine and blood urea nitrogen were not obviously reduced during chemotherapy.

Conclusions. Our study data suggest that kidney transplant patients with locally advanced transitional cell carcinoma may derive an overall survival benefit from the administration of adjuvant chemotherapy with gemcitabine plus cisplatin after surgery. The drug toxicities were acceptable, and nephrotoxicity was mild.

WITH the prolonged survival time after kidney transplantation, cancer tends to become the main cause of mortality in kidney transplant recipients [1]. The common cancer sites differ between patients in Western countries

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and China. Nonmelanoma skin cancer and lymphoma are more commonly found in Western countries, whereas transitional cell carcinoma (TCC) is the most frequently reported cancer in China [2]. Although surgical treatment is performed, TCC in kidney transplant recipients leads to a poorer prognosis than in the general population because of its multiple-site occurrence, greater invasiveness, and higher recurrence rate [3,4].

Recently, adjuvant chemotherapy with gemcitabine plus cisplatin (GC) has been recommended as an effective treatment for patients with locally advanced and metastatic TCC. However, because of concerns regarding the nephrotoxicity of chemotherapeutic drugs (particularly cisplatin), few kidney transplant recipients receive adjuvant chemotherapy after surgery. In our hospital, 11 kidney transplant patients with locally advanced TCC were administered GC adjuvant chemotherapy between June 2011 and October 2013. The aim of the present retrospective study was to evaluate the effects and safety of adjuvant chemotherapy in kidney transplant patients.

PATIENTS AND METHODS

Patients

A total of 22 patients with histologically proven TCC of the native upper urinary tract or bladder after kidney transplant were recruited. The kidney transplant procedures were performed in accordance with the ethical standards detailed in the Declaration of Helsinki. The patients, including 2 men and 20 women (age range, 47–71 years; mean age, 59.6 ± 6.1 years), were diagnosed with urinary system TCC at 22 to 134 months (mean time, 60.8 ± 25.2 months) after renal transplantation. All patents were treated with nephroureterectomy combined with bladder cuff excision or cystectomy, depending on the TCC site. The pathologic grade ranged from G2 to G3, and the TNM stage ranged from pT3N0M0 to pT4N1M0 (Table 1).

The following immunosuppressant regimens were implemented: cyclosporine (CsA) + mycophenolate mofetil (MMF) + prednisone, 11 patients; CsA + azathioprine + prednisone, 6 patients; tacrolimus + MMF + prednisone, 3 patients; and rapamycin + MMF + prednisone, 2 patients. Twenty-two patients were divided into 2 groups: the adjuvant chemotherapy group (AC group) included 11 patients who underwent surgery and adjuvant chemotherapy, and the observation group included 11 patients who underwent surgery only. Eleven patients in the AC group underwent GC adjuvant chemotherapy within 8 weeks after the operation. They demonstrated good performance status (Eastern Cooperative Oncology Group performance status), bone marrow reserve, liver function, and graft function. The serum creatinine levels ranged from 51 to 110 μmol/L (mean, 78.7 ± 14.8 μmol/L), and the blood urea nitrogen levels ranged from 2.1 to 9.8 mmol/L (mean, 5.1 ± 1.7 mmol/L).

Methods

The 11 patients in the AC group were administered gemcitabine intravenously at 800 mg/m^2 on days 1, 8, and 15 plus cisplatin at 70 mg/m^2 intravenously on day 2. The cycles were repeated every 28 days. The hematologic and nonhematologic toxicities were graded according to the World Health Organization adverse reaction grading standards. Because of the nephrotoxicity of CsA and the myelosuppression of MMF and azathioprine, the dosages of the chemotherapeutic drugs were adjusted according to their graded toxicities. A 75% drug dose reduction was used for grade 2 hematologic toxicities and grade 1 nephrotoxicity; a 50% drug dose reduction was used for grade 3 hematologic toxicities and grade 2 nephrotoxicity. Patients who progressed to grade 4 hematologic toxicities or to grade 3 or 4 nephrotoxicity were withdrawn from study. Recombinant human granulocyte colony–stimulating factor and recombinant human interleukin-11 were administered to treat hematologic toxicities when patients developed high-grade toxicities. The immunosuppressant dosage remained unchanged during chemotherapy.

Table 1. Patient Characteristics and Comparative Analysis Results Between the AC Group and the Observation Group

Characteristic	AC Group (n = 11)	Observation Group (n = 11)	*P*
Age, y			
≥60	5	5	.999
<60	6	6	
Sex			
Male	0	2	.476
Female	11	9	
ECOG performance status			
0	1	3	.497
1	8	7	
2	2	1	
Site of tumor			
Upper urinary tract	7	8	.999
Bladder	4	3	
Grade			
G2	4	5	.999
G3	7	6	
T stage			
T3	9	8	.999
T4	2	3	
Lymph nodal status			
Negative	8	9	.999
Positive	3	2	

Abbreviations: AC, adjuvant chemotherapy; ECOG, Eastern Cooperative Oncology Group.

Statistical Analysis

For clinical characteristics, *P* values were calculated by using the Fisher exact test. Survival outcomes were estimated with the Kaplan-Meier method and then compared by using the log-rank test. A 5% or lower *P* value was considered to be statistically significant. All statistical analyses were performed by using SPSS version 19.0 software (IBM SPSS Statistics, IBM Corporation, Armonk, NY, United States).

RESULTS

Patient Characteristics

The clinical characteristics are described in Table 1. There were no clinically significant differences between the 2 groups. The follow-up time ranged from 6 to 38 months (mean time, 21.0 ± 7.3 months). The 11 patients who received adjuvant chemotherapy completed a total of 29 cycles (mean number of cycles, 2.6 ± 0.8), and none