Feasibility of Pre- and Postoperative Gemcitabine-plus-Cisplatin Systemic Chemotherapy for the Treatment of Locally Advanced Urothelial Carcinoma in Kidney Transplant Patients

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ABSTRACT

Objective. To investigate the feasibility of pre- and postoperative gemcitabine-plus-cisplatin (GC) adjuvant chemotherapy for the treatment of locally advanced urothelial carcinoma in kidney transplant patients.

Methods. Seven kidney transplant patients diagnosed with locally advanced urothelial carcinoma were treated with a pre- and postoperative GC adjuvant chemotherapy between January 2008 and March 2012. Gemcitabine (800 mg/m^2) was administered at as an intravenous infusion on days 1 and 8. A total cisplatin dosage of 100 mg/cycle was administered on 2 days (50 mg/d on days 2 and 3) as an intravenous infusion. A single treatment cycle lasted 21 days. At the beginning of chemotherapy, the cyclosporine (CSA) dosage was reduced by 25 mg/d (on day 1 through day 8) if the blood CSA concentration was well maintained and did not fluctuate significantly. In addition, mycophenolate mofetil was reduced by 500 mg/d, while azathioprine was reduced by 25 mg/d (on day 1 through day 16). One cycle of GC neoadjuvant chemotherapy was given before operation, and several GC cycles were given after operation according to the patients' situation. Retrospective analysis was performed on the clinical data, chemotherapy regimen, chemotherapy efficacy, and side effects of the 7 patients.

Results. The 7 patients were all treated with 1 course of presurgical chemotherapy. The seven patients completed 24 treatment cycles of chemotherapy in total. The average GC medication period per patient was 3.4 cycles. The postsurgery follow-up was 6 to 36 months (average-22.1); all of the patients survived. There was 1 case of complete remission (14.5%), 2 of partial remission (28.5%), and 4 of stable disease (57%), with one case of T4N1M0 and three cases of T3N0M0. The overall efficacy was 43%. The toxicity and side effects associated with the GC regimen were largely associated with myelosuppression. The other side effects included reversible nephrotoxicity, gastrointestinal tract and skin reactions, as well as phlebitis. Hematologic toxic reactions included reversible leukopenia, thrombocytopenia, and anemia. There was 1 case of degree III anemia and 1 case of degree II; 5 cases of degree III and 1 of degree II leukopenia; and 3 of degree II thrombocytopenia. Gastrointestinal reactions included nausea, vomiting, and constipation. There were 2 cases of degree III and 4 cases of degree II nausea and vomiting as well as 2 cases of degree III and 3 cases of degree II constipation. There were 3 cases of degree I phlebitis (43%) and 2 cases of degree I skin erythema. The nephrotoxicity reactions were all reversible. Both liver function and grafted kidney function were not significantly altered after chemotherapy compared with prior to

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chemotherapy. None of the patients suffered renal allograft rejection after chemotherapy; none required additional antirejection drug treatments. The original antirejection treatment regimen was restored after the patients completed the chemotherapy treatment cycles.

Conclusion. We confirmed the efficacy of applying a GC regimen to treat locally advanced urothelial carcinoma in kidney transplant patients. The side effects were tolerable and reversible with minor impacts on graft function.

WITH RECENT ADVANCES in kidney transplant techniques and the development and application of a new generation of immunosuppressive agents, an increasing number of kidney transplant patients have achieved long-term survival with a transplanted kidney. However, the high incidence rate of post-transplant tumors, especially urinary malignancies, seriously affects the long-term survival of kidney transplant patients.[1–3] Through a summary and meta-analysis of 15 domestic reports, Mingqian Peng et al[3] found that the total incidence rate of post-transplant tumors was 1.5%, and Jun Lin et al[4] reported an incidence rate of 1.46% (23/1580). Our previous study[5] revealed that post–kidney transplant transitional cell carcinoma (TCC) was characterized by multiple-site occurrence and high invasiveness and that TCC was prone to local tissue invasion and distant metastasis.

As a new chemotherapy regimen, the combination of gemcitabine and cisplatin (GC) has been increasingly used to treat locally advanced urothelial carcinoma and has achieved good efficacy.[6,7] The Chinese Urological Diseases Diagnosis and Treatment Guidelines[8] and the National Comprehensive Cancer Network[9] recommend that the GC regimen be used as the standard first-line chemotherapy to treat locally advanced urothelial carcinoma. For locally advanced bladder cancer patients who are suitable candidates for surgical treatments, the neoadjuvant chemotherapy regimen can control local lesions, lower the tumor levels, eliminate metastatic microlesions, and therefore increase long-term survival rates[10,11]; for T3 to T4 tumor patients in particular, a more significant improvement of the survival rate can be achieved.[12] However, for the treatment of locally advanced urothelial carcinoma in kidney transplant patients, the application of pre- and postoperative GC regimens as adjuvant chemotherapy is rarely seen due to concerns for graft function and the possible synergistic toxicities and side effects caused by immunosuppressant and chemotherapy drugs. Both domestic and international reports on this topic are sparse. For the present study, 7 kidney transplant patients with locally advanced urothelial carcinoma were treated with pre- and postoperative GC adjuvant chemotherapy in our clinic between January 2008 and March 2012. The total treatment course was 24 cycles. The data were retrospectively summarized, and the feasibility, efficacy, toxicity, and side effects of pre- or postoperative GC regimen adjuvant chemotherapy were analyzed.

PATIENTS AND METHODS

Patients

Seven patients with locally advanced urothelial carcinoma that developed after kidney transplant were recruited for this study, including 1 man and 6 women (Table 1). All 7 patients received their transplanted kidney from a living donor. All kidney transplant procedures were in accordance with the Declaration of Helsinki. The age of the patients ranged from 55 to 70 years with an average age of 60.8 years. The time since the kidney transplant at the diagnosis of locally advanced urothelial carcinoma was 1 to 16 years, with an average of 10.1 years. None of the 7 patients had received previous systemic chemotherapy or radiotherapy. Postoperation pathologic specimens showed the locations of the urothelial carcinoma lesions included 3 cases in the unilateral native upper urinary tract, 2 cases in the bilateral native upper urinary tract, 1 case in the bladder, and 1 case in the bladder combined with the bilateral native upper urinary tract. The pathologic subtypes included 6 cases of transitional epithelial cell carcinoma and 1 case of moderately differentiated squamous cell carcinoma in combination with transitional cell carcinoma. The clinical TNM classification of malignant tumors included 4 cases of T3N0M0 and 3 cases of T4N1M0. The pathologic grade was classified as G3 in 6 cases and G2 in 1 case. The Karnofsky performance status score for all patients was $\geq$70. Aspartate aminotransferase (AST) levels in blood were 12 to 23 U/L (average 18.6 U/L). Alanine aminotransferase (ALT) levels in blood were 10 to 24 U/L (average 19.7 U/L). Serum creatinine levels were 54 to 107 μmol/L (average 80.7 μmol/L). Blood urea nitrogen levels were 2.96 to 7.56 mmol/L (average 5.64 mmol/L). The white blood cell counts (WBC) were $\geq 4.0 \times 10^9$/L, and the blood platelet counts were $\geq 100 \times 10^9$/L. The hemoglobin concentrations were $\geq$100 g/L. Urinary protein was negative for all patients.

Methods

Chemotherapy regimen and schedule. Gemcitabine (Haerbin Gloria Pharmaceutical Co Ltd, Haerbin City, Heilongjiang Province, China) was administered at 800 mg/m^2 as an intravenous infusion on days 1 and 8. The total cisplatin dosage was 100 mg/cycle and was administered on 2 different days (50 mg/d on days 2 and 3) as an intravenous infusion. One treatment cycle lasted 21 days. Tropisetron hydrochloride (5 mg) was given intravenously before and after the administration of gemcitabine and cisplatin. Intravenous hydration and diuretics were given on days 2, 3, and 4. All of the patients routinely received oral administration of leucogen during chemotherapy. Alprostadil (10 μg/d) was administered intravenously on day 1 through day 8 as a vasodilator therapy. Patients who developed degree III or greater granulocytopenia during chemotherapy were treated with recombinant human granulocyte colony-stimulating factor to accelerate the WBC recovery.

After a chemotherapy cycle of 21 days, the patients were allowed to recover for 1 week. The initiation of the next chemotherapy cycle was determined based on the patients' WBC and the status of the recovery of their liver and kidney functions. All patients needed to complete at least 2 treatment cycles to determine the treatment efficacy; patients responding to the treatment were given a maximum of 6 treatment cycles. The evaluation criteria included the following: complete remission (CR), defined as the tumor being completely undetectable for at least 4 weeks; partial remission (PR), defined as at least a 30% reduction in the sum of the longest diameters, without appearance of new lesions for at least 4 weeks; stable disease (SD), defined as a reduction in the baseline sum of the longest diameters that is less than PR level or an increase that is less than the progressive disease (PD) level; and PD, defined as an increase in baseline sum of the longest diameters of greater than 20% or the appearance of new lesions. The sum of CR and PR represented the total efficacy.[13] The assessment of adverse reactions was determined by the World Health Organization adverse reaction grading standards.

Adjusted immunosuppressant regimen. The immunosuppressant regimens of the 7 kidney transplant patients at the time of diagnosis of locally advanced urothelial carcinoma included 5 cases of cyclosporine (CSA) + Mycophenolate mofetil (MMF) + prednisone, 1 case of CSA + azathioprine (Aza) + prednisone, and 1 case of rapamycin + MMF. The blood CSA concentrations of the 6 patients who received CSA were 76 to 107 ng/mL, with an average of 87.7 ng/mL. At the beginning of chemotherapy, the CSA dosage was reduced by 25 mg/d (on day 1 through day 8) if the blood CSA concentration was well maintained and did not fluctuate significantly. On day 9 of the chemotherapy, the serum creatinine level was measured. If the serum creatinine level did not significantly differ compared with the level prior to chemotherapy, the CSA dosage was restored to the level given prior to the chemotherapy. If the serum creatinine level was significantly elevated, the use of the reduced CSA dosage was prolonged by 1 week, after which the serum creatinine level was measured again to determine whether the original CSA dosage should be restored. Between day 1 and day 14 of the chemotherapy, MMF was reduced by 500 mg/d, while Aza was reduced by 25 mg/d. On day 15 of the chemotherapy, the WBC was measured. If the WBC was not significantly different compared with the count prior to chemotherapy, the MMF or Aza dosage was restored to the level used prior to chemotherapy. If the WBC was significantly reduced, the use of the reduced MMF or Aza dosage was prolonged by 1 week, after which the WBC was remeasured to determine whether the original dosage should be restored. The prednisone dosage remained unchanged during chemotherapy.

Operation Methods. One cycle of GC neoadjuvant chemotherapy was given before operation and several GC cycles were given after operation according to the patients' situation. The operation approaches included 3 cases of radical resection of the unilateral native upper urinary tract with bladder cuff excision, 2 cases of radical resection of the bilateral native upper urinary tract with bladder cuff excision, 1 case of palliative endoscopic resection of bladder tumor with bilateral iliac artery embolization, and 1 case of radical resection of the bilateral native upper urinary tract with cystectomy and transplant nephrostomy.

RESULTS

Short-Term Efficacy

All 7 patients underwent 1 course of GC chemotherapy and completed a total of 24 treatment cycles. The average medication period per patient was 3.4 cycles. The post-surgery follow-up time was between 6 and 36 months, with an average follow-up time of 22.1 months. Two patients underwent two treatment cycles, 2 patients underwent 3 treatment cycles, 2 patients underwent 4 treatment cycles, and 1 patient underwent 6 treatment cycles. There was 1 case of CR (14.5%) with T3N0M0; 2 cases of PR (28.5%) with T4N1M0; and 4 cases of SD (57%), with 1 case of T4N1M0 and 3 cases of T3N0M0. The total efficacy was 43%.

Toxicity and Side Effects

The toxic reaction was assessed in all 7 patients. Hematologic toxic reactions included leukopenia, thrombocytopenia, and anemia, all of which were reversible. There was 1 case of degree III anemia (14%), 1 case of degree II anemia (14%), 5 cases of degree III leukopenia (71.4%), and 1 case of degree II leukopenia (14.2%). The 6 patients who developed leukopenia were all treated with recombinant human granulocyte colony-stimulating factor to accelerate the WBC recovery. There were 3 cases of degree II thrombocytopenia (43%). Nonhematologic toxic reactions included gastrointestinal reactions, phlebitis, skin erythema, and nephrotoxicity. Gastrointestinal reactions included nausea, vomiting, and constipation. There were 2 cases of degree III nausea and vomiting (28.6%), 4 cases of degree II nausea and vomiting (57.1%), 2 cases of degree III constipation (28.6%), and 3 cases of degree II constipation (43%). There were 3 case of degree I phlebitis (43%) and 2 cases of degree I skin erythema (28.6%; Table 2). The nephrotoxicity was reversible. A total of 4 patients suffered transient renal dysfunction, and the creatinine level in 2 of the patients who received CSA was twice that of the level prior to the chemotherapy within the first week of cisplatin administration. The creatinine level was then restored to the level prior to the chemotherapy by reducing the CSA dosage and administrating alprostadil (10 μg/d) as a vasodilator therapy. The creatinine level was restored to the level prior to chemotherapy before the end of the first treatment cycle. Blood AST levels after 24 chemotherapy cycles ranged from 10 to 27 U/L with an average of 18.7 U/L. ALT blood levels ranged from 12 to 29 U/L with an average of 21.6 U/L. Serum creatinine levels ranged from 83 to 156 μmol/L with an average of 110.7 μmol/L. Blood urea nitrogen ranged from 4.27 to 9.01 mmol/L with an average of 6.4 mmol/L, suggesting that liver and kidney function did not change significantly overall during the treatment regimen. The urinary protein analysis was negative in all of the patients. There was no renal allograft rejection in any of the patients.

DISCUSSION

The high incidence of malignancy is currently considered an important risk factor that affects the long-term survival of kidney transplant patients.[3] Urothelial carcinoma in Chinese individuals is characterized by a high incidence rate, multiple-site occurrence, and high invasiveness and is

Table 1. Clinical Data of the 7 Patients

Patient No.	Age/ gender	Diagnosis time (mo)	Immunosuppressant	Tumor location	Pathologic subtype	Pathologic (primary tumor stage)	Follow-up (mo)	Type of response
1	61/M	96	R + M	Bladder	TCC	T4N1M0/G2	Survived (18)	PR
2	57/F	14	C + M + P	Unilateral upper urinary tract	SCC + TCC	T3N0M0/G3	Survived (15)	SD
3	68/F	108	C + A + P	Unilateral upper urinary tract	TCC	T4N1M0/G3	Survived (12)	SD
4	55/F	72	C + M + P	Bilateral upper urinary tract + bladder	TCC	T4N1M0/G3	Survived (28)	PR
5	55/F	84	C + M + P	Bilateral upper urinary tract	TCC	T3N0M0/G3	Survived (27)	SD
6	60/F	120	C + M + P	Unilateral upper inum	TCC	T3N0M0/G3	Survived (19)	SD
7	70/F	192	C + M + P	Bilateral upper urinary tract + bladder	TCC	T3N0M0/G3	Survived (36)	CR

Note: The diagnosis time was defined as the period from the renal transplantation to the time when locally muscle-invasive and metastatic TCC was diagnosed. C, cyclosprosine; M, mycophenolate mofetil; P, prednisone; R, rapamycin; A, azathioprine; FK, bullok reusable; TCC, transitional cell carcinoma; SCC, squamous cell carcinoma; PR, portral remission; SD, study disease; CR, complete remission.

prone to local tissue invasion and distant metastasis.[1,3–5] For patients with advanced urothelial carcinoma, the efficacy of platinum agent-based systemic chemotherapy is well established.[9,10] However, for kidney transplant patients who have locally advanced urothelial carcinoma, the current widely used immunosuppressants, including CSA, MMF, Aza, and tacrolimus (FK506), when used with the available chemotherapy drugs cause many synergetic toxic side effects, including myelosuppression, digestive disorders, metabolic disorders, and nephrotoxicity. Therefore, before treating these patients with chemotherapy, it is necessary not only to assess the efficacy of the chemotherapy regimen but also to consider the protection of graft function and the tolerance of patients' systemic organs to the synergic toxicity and side effects from chemotherapy drugs and immunosuppressants. To meet these requirements, clinicians should first choose a chemotherapy regimen that has a confirmed efficacy and milder toxicity and side effects and then reduce the relative dosage of the chemotherapy drugs and immunosuppressants to decrease the possibility of systemic side effects and graft function damage as much as possible.

There are two types of GC regimens for treating locally advanced bladder cancer, a 21-day cycle and a 28-day cycle. Clinical experiments outside of China have revealed that the 21-day and 28-day regimens exhibited similar clinical efficacies, although the 21-day regimen produced milder toxicity and side effects. Therefore, based on a comprehensive analysis of efficacy, toxicity, side effects, and expense, we adopted the 21-day regimen for this study. Our data indicate that the average medication period per patient was 3.4 cycles. Within a follow-up of 6 to 36 months, there was 1 case of CR and 2 cases of PR. The total efficacy was 43%, which is consistent with the chemotherapy efficacy reported in nontransplant patients with advanced bladder cancer. These results suggest that a modified GC regimen that was customized to match the medication characteristics of kidney transplant patients resulted in a similar efficacy as the conventional regimen in the short term.

Our results demonstrate that the primary toxicity and side effects of the GC regimen were myelosuppression and gastrointestinal reactions, respectively. The myelosuppression from the GC regimen was largely caused by gemcitabine, which resulted in an additive effect on myelosuppression with the immunosuppressant MMF or Aza (these 2 reagents are highly selective for lymphocytes). The gemcitabine dosage used for nontransplant patients is typically 1000 to 1250 mg/m^2. To avoid possible additive myelosuppression effects, we adjusted the gemcitabine dosage to 800 mg/m^2 and kept the medication schedule and cycle unchanged. In addition, we adjusted the dosage and schedule of MMF or Aza administration as described in the Methods section, routinely gave patients leucogen orally, and gave recombinant human granulocyte colony-stimulating factor to patients who developed a granulocytopenia greater than degree II to accelerate WBC recovery. In our study, there was 1 case of degree III anemia, 1 case of degree II anemia, 5 cases of degree III leukopenia, 1 case of degree II leukopenia, and 3 cases of degree II thrombocytopenia. The patients who developed anemia and thrombocytopenia recovered on their own without any special treatment. The WBCs in the 6 patients who developed greater than II degree leukopenia were restored to normal levels after the treatment with granulocyte colony-stimulating factor. These results suggest that the myelosuppression reaction was reversible. Notably, the most severe myelosuppression reaction during the GC regimen did not occur when gemcitabine was administered on day 1 and day 8 but occurred on day 16 after the

Table 2. Major Side Effects After the Chemotherapy

	Hematologic side effects (case)			Nonhematologic side effects (case)				
	Anemia	WBC reduction	PLT reduction	Nausea and vomitting	Constipation	Phlebitis	Skin erythema	Kidney toxicity
Degree I	—	—	—	—	—	3	2	—
Degree II	1	1	3	4	3	—	—	2
Degree III	1	5	—	2	2	—	—	2

WBC, white blood cell; PLT, platelet.

treatment cycle started. This result is similar to the myelosuppression curve in nontransplant patients. By day 16, most patients have already been discharged from the hospital and begun their follow-up visits; therefore, after being discharged from the hospital, patients should undergo blood tests for the prevention of serious adverse reactions, such as severe infections caused by leukopenia (kidney transplant patients are a high-risk population for various infections). MMF or Aza should not be restored to the original dose unless the blood test on day 15 is normal.

Although the overall graft function after the treatment did not change significantly compared with the function prior to chemotherapy, in our preliminary study, 2 patients developed a rapid deterioration of graft function over the short term, suggesting that GC regimen-induced toxicity to the transplanted kidney remains a critical problem that requires attention. The study by Benisovich et al[14] demonstrated that the simultaneous administration of cisplatin and CSA to patients who develop malignancies after kidney transplantation could maintain stable graft function. The risk factors for graft function damage in our study included drug-induced nephrotoxicity and the possible presence of chronic renal allograft rejection. Drug-induced nephrotoxicity was mainly caused by the simultaneous administration of cisplatin and CSA. Cisplatin is primarily metabolized by the kidney after entering the body, and its metabolites cause oxidative damage to renal tubular cells and inhibit tubular brush border cells and the organic ion transport system, which subsequently causes hydropic degeneration and local necrosis of tubular epithelial cells. Electron microscopy revealed that tubular segments exhibited brush border microvilli fusion, mitochondrial vacuolization, and endoplasmic reticulum expansion accompanied with degranulation, lysosomes, and an increased number of vacuoles. Cisplatin can induce the highest level of nephrotoxicity among all of the platinum agents. CSA-induced nephrotoxicity mainly manifests as a glomerular afferent artery contraction that reduces the blood supply for the glomeruli and subsequently causes glomerulosclerosis. Simultaneous damage to both the glomeruli and tubules could lead to a rapid deterioration of graft function. Because both the anticancer effect and the nephrotoxicity of cisplatin are positively correlated to its dosage, we reduced the total cisplatin dosage to 100 mg per treatment cycle and administered it on 2 different days (50 mg/d). Meanwhile, we reduced CSA by 25 mg/d and administered the vasodilator alprostadil to reverse the CSA-induced nephrotoxicity. In addition, hydration and diuresis were given to patients to maximally reduce nephrotoxicity. After the 2 patients who developed degree III nephrotoxicity in our preliminary study were treated as described previously, their graft function recovered. Our overall results were consistent with those of previous reports. No patients exhibited renal allograft rejection after the completion of chemotherapy, and no additional antirejection drugs were needed. The original antirejection regimen was restored after the completion of chemotherapy.

In summary, we confirmed the efficacy of a modified GC regimen in combination with the appropriate adjustment of the immunosuppressant dosage in the treatment of locally advanced urothelial carcinoma in kidney transplant patients. Side effects were tolerable and reversible, and the impact on graft function was mild. In this study, systemic chemotherapy was used to treat locally advanced urothelial carcinoma in kidney transplant patients, and the study subjects were highly selective. The number of cases in this study was small, and the follow-up time was short; thus, the applicability of our results may be limited, and they require further confirmation by in-depth studies with a higher number of cases.

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