Complete Response of Urothelial Carcinoma to Chemotherapy in Renal Allograft Recipients: A Two-case Study

CHIA-CHI LIN1,3, CHIH-HUNG HSU1,3 and YEONG-SHIAU PU2

Departments of 1Oncology and 2Urology, National Taiwan University Hospital; 3Cancer Research Center, National Taiwan University College of Medicine, Taipei, Taiwan, R.O.C.

Abstract. Background: The risk of urothelial carcinoma (UC) is increased in patients with end-stage renal disease. Standard regimens for UC (e.g., M-VAC) carry substantial toxicity, which could be exacerbated in patients with end-stage renal disease receiving transplantation, because of the need to take immunosuppressants for life. Patients and Methods: Patients who had histopathologically-diagnosed UC with distant metastasis were enrolled. Pure adenocarcinoma and squamous cell carcinoma were excluded. No prior systemic chemotherapy, including adjuvant or neoadjuvant therapy, was allowed. The patients were required to have a serum creatinine level ≤1.3 mg/dl or a creatinine clearance ≥40 ml/min, as well as normal bone marrow and liver functions. Patients were required to have one or more measurable lesions, sized 1 cm or greater, by radiographic studies and they provided informed consent before the treatment. Treatment. The TP-HDFL regimen was given as: paclitaxel 70 mg/m² 1-hour intravenously (i.v.) on days 1 and 8; cisplatin 35 mg/m² 24-hour (i.v.) on days 2 and 9; and 5-fluorouracil 2,000 mg/m² and leucovorin 300 mg/m² 24-hour (i.v.) on days 2 and 9; repeated every 21 days. Concomitant immunosuppressive treatments were maintained during chemotherapy. Results: From 2003 to 2004, two female renal allograft recipients developed renal pelvis UC with para-aortic and lung metastasis, respectively. They received four to six cycles of the TP-HDFL regimen and achieved complete response. There was neither significant toxicity, nor immunosuppressant dose-adjustment. The patients remained disease-free for 1 year, respectively, after completion of the chemotherapy. Conclusion: The TP-HDFL regimen showed activity and can be safely used in renal allograft recipients with metastatic UC.

The risk of urothelial carcinoma (UC) is increased in patients with end-stage renal disease (1, 2). Although UC is a relatively chemosensitive malignancy, standard regimens such as M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) carry substantial toxicity (3). The toxicity may be exacerbated in patients with end-stage renal disease who receive kidney transplantation, because such patients need to take immunosuppressive agents for life. Two renal allograft recipients with stage IV UC, who showed complete responses to weekly paclitaxel, cisplatin and infusional high-dose 5-fluorouracil plus leucovorin (TP-HDFL) (4, 5), are presented.

Patients and Methods

Patients. Patients who had histopathologically-diagnosed UC with distant metastasis were enrolled. Pure adenocarcinoma and squamous cell carcinoma were excluded. No prior systemic chemotherapy, including adjuvant or neoadjuvant therapy, was allowed. The patients were required to have a serum creatinine level ≤1.3 mg/dl or a creatinine clearance ≥40 ml/min, as well as normal bone marrow and liver functions. The patients had at least one measurable lesion, sized 1 cm or greater, by radiographic studies and they provided informed consent before the treatment.

Response and toxicity evaluation. The tumor response was evaluated by RECIST criteria (6). Toxicity was evaluated by National Cancer Institute Common Toxicity Criteria version 2.0. Patients were removed from the treatment protocol when either the maximum response had been achieved, progressive disease had occurred, or intolerable toxicity had developed.

Results

Case 1. A 37-year-old woman had chronic glomerulonephritis, which led to end-stage renal disease 6 years before presentation. She had undergone continuous ambulatory peritoneal dialysis since that time. She underwent cadaveric kidney transplantation 5 months before presentation, and took cyclosporin 125 mg/day and prednisolone 10 mg/day as immunosuppressants. Painless gross hematuria occurred. She
underwent left nephroureterectomy 3 weeks later. The pathological diagnosis was UC grade 2 of the left renal pelvis with peri-pelvic soft tissue and renal parenchyma involvement. Lymphatic vascular involvement and peri-neural invasion were noted. One peri-renal lymph node revealed metastasis. The pathological stage was T3N1M0. Follow-up MRI 2 months later showed left para-aortic lymphadenopathy, without other distant metastasis, heterogeneous enhancement of the right native kidney consistent with suspicious renal tumor, and hydronephrosis and hydronephrosis of the transplanted kidney (Figure 1). The serum creatinine was 1.3 mg/dL and creatinine clearance was 46 ml/min. The Karnofsky performance status (KPS) then was 100%. Chemotherapy with four cycles of the TP-HDFL regimen was given. The renal function and peak and trough levels of cyclosporin remained unchanged. No grade III/IV toxicity occurred. Follow-up MRI after two cycles of chemotherapy showed disappearance of the para-aortic lymphadenopathy and atrophy of the right native kidney (Figure 1). The patient underwent right nephroureterectomy and para-aortic lymph node dissection 1 month after completion of chemotherapy. The pathological finding was complete response (i.e., no residual tumor in either the right kidney or para-aortic lymph nodes), except for slight dysplasia in the right ureter. The patient was then regularly monitored in our clinic and has been free of cancer for 2 years.

Case 2. A 62-year-old woman, who had chronic glomerulonephritis which led to end-stage renal disease 10 years before presentation. She had undergone hemodialysis since then. The subject underwent living-donor kidney transplantation 1 year before presentation. She had taken tacrolimus 2 mg/day, mycophenate 250 mg/day and prednisolone 5 mg/day as immunosuppressants. Painless gross hematuria had occurred. She underwent radical cystectomy and bilateral nephroureterectomy 2 weeks later. The pathological diagnosis was multifocal UC grade 3 of the bilateral renal pelvis, left ureter and urinary bladder, with neither peri-pelvic soft tissue nor renal parenchyma involvement. There was lymphatic vascular involvement without peri-neural invasion. Twelve peri-renal and iliac lymph nodes did not reveal metastasis, and the pathological stage was T2N0M0. The patient complained of a persistent cough and dyspnea 9 months after the operation.

A chest CT scan showed multiple nodules in both lungs with diffusely increased interstitial lung markings in the bilateral lower lungs (Figure 2). There was neither liver, nor para-aortic lymph node metastasis, and the serum creatinine was 1.0 mg/dL and creatinine clearance was 54 ml/min. The KPS then was 70%. Chemotherapy with six cycles of the TP-HDFL regimen was given and the immunosuppressive agents were maintained during chemotherapy. The renal function and peak and trough levels of tacrolimus remained unchanged. Grade III leukopenia occurred once during treatment. It was not associated with fever and did not result in chemotherapy dose-modification. There were no other grade III/IV toxicities. Follow-up chest CT scan after four cycles of chemotherapy showed complete response (disappearance of multiple nodules in both lungs and interstitial lung markings) (Figure 2). The patient was regularly monitored in our clinic and has been free of cancer for 1 year.

Discussion

Urothelial carcinoma in patients with end-stage renal disease presents difficulty in the choice of an appropriate therapeutic option, since the safety of conventional regimens in renal transplant recipients has been questioned (7, 8). Cisplatin-based chemotherapy is the treatment of choice for metastatic UC in patients with normal renal function, but even in these patients the toxicity of the standard M-VAC regimen is considerable, with 20% to 30% of patients suffering from febrile neutropenia, 10% to 20% from grade 3 and 4 mucositis, and 3% to 4% having treatment-related mortality (3). Consequently, research continues for new drugs and combinations with a better therapeutic index.

The regimen used in these patients was developed at the National Taiwan University Hospital on the basis of experience with metastatic UC. This weekly infusional cisplatin plus high-dose 5-fluorouracil and leucovorin-based regimen carried moderate / high efficacy and low / moderate toxicity. Grade III/IV leukopenia and thrombocytopenia occurred in 1-14% and 0-6%, respectively. These cases demonstrated the safety of the TP-HDFL regimen for use in renal allograft recipients.

There is controversy regarding the need for continued administration of immunosuppressants during systemic chemotherapy, since immunosuppressive agents were demonstrated to induce cancer progression in in vitro and in vivo experiments (10). The two presented cases exemplify the efficacy of the TP-HDFL regimen when used for renal allograft recipients, who can continue to take immunosuppressive therapy to preserve the graft without compromising the efficacy of chemotherapy. On the basis of the promising results recorded in these patients, we are planning a phase II study of the TP-HDFL regimen in renal allograft recipients with UC.

References

Figure 1. MRI of abdomen before and after treatment. Right renal pelvis cancer (A, arrow). Complete regression (B, arrow) after treatment.


Figure 2. CT of chest before and after treatment. Multiple nodules in lung (A, arrows). Complete regression (B, arrows) after treatment.


Received February 2, 2006
Revised April 5, 2006
Accepted April 8, 2006