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Original Article

High Incidence of Transitional Cell Carcinoma in Kidney Transplant Recipients in Eastern Taiwan

*Jing-Liang Chen[1,2], Guan-Jin Ho[3], Ying-Chin Yang[3], Ming-Hui Shih[4], Kuei-Chun Chou[4], Ming-Che Lee[3,5]**

[1]*Department of Urology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan*
[2]*Graduate Institute of Human Genetics, Tzu Chi University, Hualien, Taiwan*
[3]*Department of Surgery, Buddhist Tzu Chi General Hospital, Hualien, Taiwan*
[4]*Department of Nursing, Buddhist Tzu Chi General Hospital, Hualien, Taiwan*
[5]*Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan*

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Abstract

Objective: A higher incidence of urinary tract transitional cell carcinoma (TCC) has been reported in both long-term hemodialysis patients and kidney transplant (KTX) recipients in Taiwan than in other countries. Herein, we report a high incidence of urinary tract malignancy, especially TCC, in KTX recipients in eastern Taiwan.

Patients and Methods: We retrospectively reviewed the medical records, clinical data, and outcomes of 102 KTX recipients in Tzu Chi General Hospital from 1992 to 2008. Overall graft and patient survival, incidence of posttransplant malignancy, and cumulative incidence of TCC after KTX were investigated.

Results: During a mean follow-up of 45.5±38.5 months after KTX, 12 malignancies were diagnosed in nine recipients. The incidence of posttransplant malignancy in all recipients was 8.2%. TCC was diagnosed in four patients, and all these patients presented with painless gross hematuria and hydronephrosis. Three patients had tumor involvement in the upper urinary tract. TCC occurred at a mean of 56±70.7 months after KTX, and the cumulative incidence of TCC was 4.7% in the first 3 years after transplant. Only one patient with triple cancer died of disseminated cholangiocarcinoma of the distal common bile duct during a mean follow-up of 15.8±9.5 months after surgical treatment of TCC.

Conclusion: KTX recipients are at extremely high risk of TCC in eastern Taiwan, with an incidence of 3.9%. The cardinal signs of posttransplant TCC are painless gross hematuria and hydronephrosis of the native kidney. Careful, timely urological screening in KTX recipients warrants early diagnosis and good prognosis after aggressive surgical management. (*Tzu Chi Med J* 2009;21(2):118–122)

*Corresponding author. Department of Surgery, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien, Taiwan.
E-mail address: mclee@tzuchi.com.tw

1. Introduction

In the last four decades, hundreds of thousands of patients with chronic renal failure have survived because of dialysis and transplantation—two of the most striking medical successes of the past 40 years in the management of end-stage renal disease (ESRD). Kidney transplantation (KTX) in selected patients can not only improve quality of life, but also prolong survival. However, posttransplant malignancy, one of the adverse effects of KTX, has emerged as an important prognostic factor. An increased incidence of malignant transformation in transplant recipients was recognized as early as the 1970s, and this effect was ascribed to the administration of immunosuppressive medications [1–3]. Skin tumors, followed by lymphoma, are the most common malignancies in transplant recipients [4]. The malignancy rate in the urinary tract including the kidney (parenchyma and collecting system), ureter, bladder and urethra in KTX recipients was rarely reported in the early era of KTX [5,6], but in the 1990s, a high incidence of up to 18% was reported in northern Europe [7]. Also, a high cumulative incidence of transitional cell carcinoma (TCC) that reached 17.5% in 10 years after KTX has been demonstrated in Taiwan [8]. In the present study, the incidence and type of posttransplant malignancy, especially urinary tract malignancy, are investigated in KTX recipients.

2. Materials and methods

The medical records of KTX recipients who underwent regular follow-up at transplant clinics in Tzu Chi General Hospital from May 1992 to March 2008 were retrospectively reviewed. Recipients who underwent KTX in other institutions and who were referred to our hospital for regular follow-up were all included in this study. The incidence and type of malignancy were assessed. The immunosuppressive regimen for induction therapy was intravenous methylprednisolone (MP) alone, at a dosage of 1000 mg (or 10 mg/kg if body weight < 60 kg) before reperfusion of the kidney graft intraoperatively. The routine maintenance therapy was triplicate immunosuppressive agents including MP or prednisolone, calcineurin inhibitors, either cyclosporin A (CsA; Neoral®, Novartis, Basel, Switzerland) or tacrolimus (TAC; Prograf®, Astellas Fujisawa, Osaka, Japan) and mycophenolate mofetil (MMF; Cellcept®, Roche, Nutley, NJ, USA). MP was administered intravenously on the day of transplantation, at a dose of 200 mg/day. The dosage was tapered to 20 mg/day within 7 days and then changed to oral prednisolone 20 mg/day. The dosage of prednisolone was gradually reduced to a maintenance dose of 5 mg/day by the fourth month. TAC was also started on the day of transplantation, at a dose of 0.1–0.15 mg/kg/day. The dosage was adjusted to maintain a blood trough level in whole blood of 8–12 ng/mL for 1 or 2 months postoperatively, and 5–10 ng/mL thereafter. Administration of CsA was started at a dose of 8–10 mg/kg/day on the day of transplantation, and was adjusted to maintain a CsA trough level in whole blood of 400–700 ng/mL for 3 months after transplantation, 200–400 ng/mL for another 3 months, and then around 100 ng/mL by the seventh month after transplantation. MMF was started at a dose of 2000 mg/day immediately after transplantation, and was reduced to 1000 mg/day 1 month after transplantation.

Any episode of acute cellular rejection was first treated by pulse therapy with MP 1000 mg (or 10 mg/kg if body weight < 60 kg) by intravenous injection for 3–5 days. A monoclonal antibody, muromonab-CD3 (OKT-3; Ortho Biotech Products, L.P., Horsham, PA, USA), at a dose of 10–15 mg/kg for 5–7 days, was administrated only to those patients whose acute rejection was confirmed by graft biopsy and were refractory to pulse therapy.

Urine examination, renal function tests and trough levels of calcineurin inhibitors were examined monthly. Routine surveillance of malignancy including tumor markers such as carcinoembryonic antigen, carbohydrate antigen 19-9, cancer antigen 125, cancer antigen 15-3, and α-fetoprotein, and imaging studies such as chest roentgenography and ultrasonography of the abdomen and renal graft, and a skin examination were performed annually. Pap smears and mammography for female recipients and serum prostate specific antigen for male recipients were also checked annually. For all patients with chronic viral hepatitis, serum α-fetoprotein and liver ultrasonography were routinely examined every 6 months. For early detection of urinary tract malignancies, patients with any persistent microscopic hematuria (RBC > 8/HPF) or gross hematuria would receive an additional urological examination to identify the source of the blood. Urine cytology and endoscopic examination such as cystoscopy and/or ureteroscopy were the most frequent modalities used for further interpretation. Any suspicious lesion under endoscopic examination was biopsied. Once *de novo* malignancy was confirmed by pathological examination, computed tomography was performed for preoperative staging.

TCC was staged according to the TNM system (American Joint Committee on Cancer Staging System, 6th edition, 2001). In the lower urinary tract, a transurethral resection (TUR) of the tumor was performed if the clinical stage was T_1 or earlier, whereas a radical resection was done if the pathological examination of the TUR tumor showed muscular invasion. Adjuvant chemotherapy with bladder instillation of mitomycin C was indicated in patients with superficial TCC after TUR. In the upper tract, a radical nephroureterectomy was done if urine cytology or biopsy demonstrated malignant cells.

The graft and patient survival and the cumulative incidence of TCC were calculated by Kaplan-Meier estimates. The patient and graft survival was calculated from the date of the first transplantation to the date of graft failure with need for dialysis, patient death, or the end of this study. Descriptive statistics were expressed as mean±standard deviation (SD) or a percentage. Data were processed and analyzed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA) for Windows.

3. Results

There were 102 KTX recipients, 55 men and 47 women, with a mean age of 48.5±11.4 years, included in this study. The graft and patient survival at 1, 3, and 5 years after transplantation were 92.6%, 89.9% and 78.3%, and 97%, 92.5% and 82.2%, respectively (Fig. 1). At a mean follow-up of 45.5±38.5 months after KTX, 12 *de novo* malignancies were diagnosed in nine KTX recipients. The incidence of malignancy in all KTX recipients was 8.2% (Table 1). One patient had double cancers (lung cancer and Kaposi's sarcoma of the intestine) and another developed three cancers (cholangiocarcinoma of the distal common bile duct, TCC of the lower urinary tract, and basal cell carcinoma of the skin) during the follow-up period. Four of the recipients who developed *de novo* malignancies had TCC, with incidences of 3.9% in all KTX recipients and 44.4% in all recipients who developed malignancy. The mean time to occurrence of TCC was 56±70.7 months after transplantation. The cumulative incidence of TCC was 4.7% in the first 3 years after KTX.

Either microscopic or gross hematuria without pain was the first clinical presentation in these four TCC patients. Hydronephrosis was also found in three patients. All TCC patients underwent endoscopic biopsy and the pathological examination confirmed the diagnosis before definite surgery. One of the three patients with upper tract TCC had bilateral lesions pathologically. All patients with upper tract TCC underwent radical nephroureterectomy and bladder cuff resection and one patient with superficial TCC in the lower tract received TUR of the bladder tumor plus intravesical chemotherapy with mitomycin C. During a mean follow-up of 15.8±9.5 months, all grafts and patients survived except for one recipient with triple cancer who died of disseminated cholangiocarcinoma about 22 months after the diagnosis of TCC with a functioning graft.

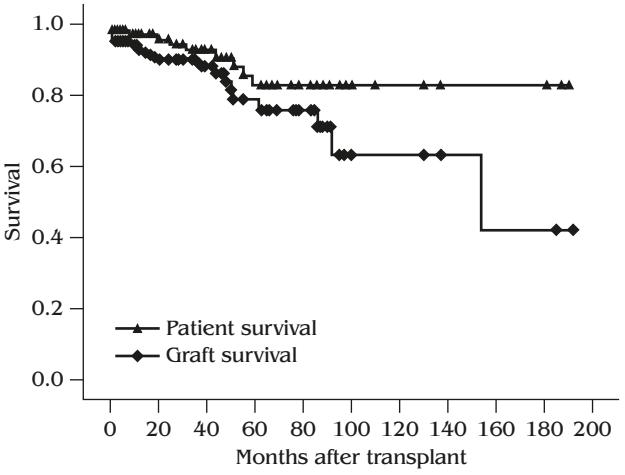

Fig. 1 — Overall graft survival was 92.6% at 1 year, 89.9% at 3 years and 78.3% at 5 years after kidney transplantation. The overall patient survival at 1, 3 and 5 years was 97%, 92.5% and 82.2%, respectively.

Table 1 — Data on *de novo* malignancy in 102 kidney transplant recipients

Age	Gender (M/F)	Cancer type	Cancer time since ESRD (mo)	Cancer time after transplantation (mo)	Type of surgery	Patient survival (Y/N)	Graft survival (Y/N)
66	F	TCC	167	161	Right nephroureterectomy	Y	Y
38	F	Cervical SCC	192	132	Conization	Y	Y
41	F	RCC	115	43	–	N	N
68	M	NPC	48	36	–	N	N
66	M	HCC	49	22	Left hepatectomy	Y	Y
54	M	1. Lung adenocarcinoma 2. Intestinal Kaposi's sarcoma	91	7	Left lung lobectomy	N	N
52	M	TCC	91	29	Bilateral nephroureterectomy	Y	Y
68	M	1. Cholangiocarcinoma 2. TCC 3. BCC	51	7	Pancreaticoduodenectomy, bilateral nephroureterectomy, wide excision of BCC	N	N
52	F	TCC	111	27	TUR-BT	Y	Y

F=female; M=male; TCC=transitional cell carcinoma; SCC=squamous cell carcinoma; RCC=renal cell carcinoma; NPC=nasopharyngeal cancer; HCC=hepatocellular carcinoma; BCC=basal cell carcinoma; TUR-BT=transurethral resection of bladder tumor; Y=survived; N=did not survive.

4. Discussion

The overall incidence of *de novo* malignancy after KTX has been reported to be three to 10 times higher than in the general population [9–11] and three times higher than in hemodialysis patients [12]. In Western countries, the most common type of posttransplant malignancy was non-melanoma skin cancer and the main type of malignancy in the urinary tract was renal cell carcinoma (RCC) [13], with an incidence of 4.6% in all KTX recipients [14]. On the contrary, in our series, the most common type of posttransplant malignancy was TCC. It occurred in 3.9% of all KTX recipients and 44.4% of all patients with posttransplant malignancy. Similar results have been reported from a Taiwanese series. Wu et al demonstrated a 4.1% overall incidence of TCC in KTX recipients and a 43.5% incidence in all patients with posttransplant malignancy [8]. Similarly, a 3.1% incidence of TCC in KTX recipients and a 62.5% incidence in all patients with posttransplant malignancy was reported by Wang et al [15]. It is interesting that the incidence of TCC and RCC in ESRD patients and KTX recipients is somewhat different between Taiwan and neighboring countries such as Japan. The incidence of urinary tract TCC and RCC in patients under maintenance dialysis was 0.89% and 0.26% in Taiwan, and 0.1% and 0.61% in Japan, respectively [12,16]. In Japan, the incidence of RCC in KTX recipients was 3.6% [17]. Both dialysis patients and transplant recipients had higher incidences of TCC in Taiwan. Old age, compound analgesics, Chinese herb usage, and underground water intake as well as female gender have been considered risk factors [8]. In the present study in eastern Taiwan, the population distribution, dietary habits, and medication and genetic components were similar to those in other areas of Taiwan. But unlike other geographic areas of Taiwan, there is less industrial pollution and no reported arsenic contamination of groundwater in eastern Taiwan. However, the incidence of urinary tract malignancy, especially TCC in kidney transplant recipients, was still high. The incidence of urinary tract TCC and RCC in patients who had undergone kidney transplantation was 3.9% and 1.0%, respectively, in our study. This indicates that environmental contamination might not be the only factor that contributes to the development of these posttransplant malignancies. Other major risk factors for urinary tract TCC in KTX recipients such as genetic difference, long-term hemodialysis [12,18], and pathophysiology from ESRD such as diabetes mellitus, and ingestion of analgesics [19,20] or aristolochic acid in Chinese herbs [21,22] may still need to be considered in the difference in incidence between Taiwan and other countries. This needs to be investigated further.

Painless hematuria was the major clinical presentation in KTX recipients with TCC, as in previous reports [8,23]. In addition, hydronephrosis is the main sign if the upper urinary tract is involved. Therefore, aggressive intervention such as endoscopic examination including cystoscopy and/or ureteroscopy, and washing cytology is indicated when TCC of the urinary tract is suspected. Once TCC is documented, an early bilateral radical nephroureterectomy is suggested because of the high risk of simultaneous development of small urothelial malignancy in the opposite tract, which occurs in up to 57.1% of cases, and is difficult to detect accurately [23].

5. Conclusion

KTX recipients in eastern Taiwan have a high risk of TCC, with an incidence of 3.9%. The cardinal signs of TCC in KTX recipient are painless gross hematuria and hydronephrosis of the native kidney. Careful, timely urological screening of KTX recipients warrants an early diagnosis and good prognosis after aggressive management.

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