Malignancy in Renal Transplant Recipients: A Single-Center Experience in Thailand

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Background: *Malignancy is the second most common cause of death in renal transplant patients with functioning graft and its incidence increases with time after organ transplantation.*
Objective: *To present the cumulative incidence and manifestations of malignancy among renal transplant recipients in Phramongkutklao hospital between 1987 and 2009.*
Material and Method: *To retrospectively review of the transplant charts and records of 168 kidney transplant recipients from October 1, 1987 to November 15, 2009 at Phramongkutklao Hospital. The data related to malignancy were recorded.*
Results: *The cumulative incidence of malignancy was 4/168 (2.4%) recipients with a median age of 45 years (range, 8-55 years). The median time of diagnosis of malignancy after transplantation was 7.3 years (range, 0.8-10.4 years). All four patients had posttransplantation malignancy. The diagnosis was based on pathological specimens. All of them received cyclosporine, prednisolone and azathioprine or mycophenolate mofetil as immunosuppressive regimen. Two patients had native renal cell carcinoma (RCC), one had post-transplant lymphoproliferative disorder (PTLD), the other had a malignant hemangiopericytoma. Two patients (PTLD and advanced RCC cases) are alive, one patient died of malignancy (malignant hemangiopericytoma) and the other died of infection (Pseudallescheria boydii brain abscess).*
Conclusion: *The incidence of malignancies in the present study was increased among renal transplant recipients compared to the general population especially renal cell carcinoma. Because of the higher risk to develop malignancy in transplant recipients, a close surveillance for early detection of malignancy is necessary in the long term follow-up.*

Keywords: *Malignancy, Renal cell carcinoma (RCC), Post-transplant lymphoproliferative disorder (PTLD), Transplant*

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As renal transplantation is the best means of renal replacement therapy, malignancy remains one of the life-threatening complications in the long-term follow-up of renal transplant recipients. It represents the second main cause of death in renal transplant patients with functioning graft[1]. The incidence of malignancy post renal transplantation increases with time after organ transplantation and is related to the intensity of immunosuppression. The etiology is multifactorial, probably involves the direct carcinogenic effects of some immunosuppressive medications, or impaired immune-surveillance of the host or suppressed antiviral immune activity referring to common viral-related post transplantation malignancies[2]. It may present as de novo cancer or as a recurrence of a pre-exiting malignancy or from the transmission of malignancy from the donor.

The authors sought to present the cumulative incidence and manifestations of malignancy among renal transplant recipients in Phramongkutklao Hospital between 1987 and 2009.

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Material and Method

The authors retrospectively reviewed the transplant charts and records of 168 kidney transplant recipients from October 1, 1987 to November 15, 2009 at Phramongkutklao Hospital. Permission for the present study was given by the institutional ethics committee. All recipient charts and records were reviewed for age, gender, immunosuppressive regimen, time of development of malignancy, history of malignancy of donors and recipients, history and treatment of graft rejection, clinical presentation,

pathological reports and patient outcomes. A diagnosis of malignancy was based on pathological diagnosis.

Results

Among 168 renal transplant recipients in Phramongkutklao Hospital between 1987 and 2009, there were 4 patients (two men and two women) who developed post transplantation malignancy. Their median age was 45 years (range, 8-55 years). Median time of the diagnosis of malignancy after transplantation was 7.3 years (range, 0.8-10.4 years). All of them received cyclosporine, prednisolone and azathioprine or mycophenolate mofetil as immunosuppressive regimen. Two patients had native renal cell carcinoma (RCC), one had post-transplant lymphoproliferative disorder (PTLD) as non-Hodgkin's lymphoma, the other had a malignant hemangiopericytoma.

For clinical presentations, the first patient presented with microscopic hematuria and ultrasonography revealed native renal cell carcinoma (RCC) which subsequently underwent right radical nephrectomy. He had a prior history of steroid-resistant rejection requiring OKT3 therapy twice with 17 months apart. Four years after the diagnosis of RCC, he developed *Pseudallescheria boydii* brain abscess and died because of sepsis.

The second patient was found incidentally to have asymptomatic multiple lung nodules on chest x-ray (CXR). Computed tomography of chest and abdomen revealed advanced native renal cell carcinoma with lung metastases. She was started on sorafenib, orally administered tyrosine kinase inhibitor and had the immunosuppressive regimen adjusted. The cyclosporine dosage was decreased to 25 mg twice daily and azathioprine was replaced with everolimus which was increased to 1.75 mg twice daily. Twenty-eight months later repeated CXR and computed tomography of chest revealed disappearance and regression of lung nodules. The patient has been doing well and her current serum creatinine is 1.3 mg/dL with 24-hour urine creatinine clearance of 41 mL per minute after almost 14 years of transplantation.

The third patient, a 14-year-old boy presented with fever and left upper quadrant abdominal pain, initially diagnosed as splenic abscesses. He underwent splenectomy which pathological report showed B-cell lymphoma. The patient received intravenous immunoglobulin 400 mg/kg daily for 3 days and rituximab once a week for 4 doses. Also he received intravenous acyclovir for 10 days followed by oral acyclovir for a total of 6 months and has been doing well since then. Currently his immunosuppressive regimen includes everolimus 0.75 mg orally twice daily and prednisolone 5 mg per day.

The fourth patient presented with right pelvic mass with ascites and right pleural effusion. The diagnosis was malignant hemangiopericytoma with peritoneal carcinomatosis. She died two weeks after the diagnosis of malignancy.

The history including immunosuppressive regimens, clinical presentation and pathological report are summarized in Table 1.

Discussion

The cumulated incidence of malignancy among 168 renal transplant recipients in Phramongkutklao Hospital between 1987 and 2009 was 2.4% (4 patients). Two had native renal cell carcinoma. One had post-transplant lymphoproliferative disorder (PTLD). The increased incidence of RCC and PTLD in the presented patients is in general agreement with the USRDS 2003 annual data report[3]. RCC was approximately 15-fold more common than in the general population. There was one retrospective study of malignancies in 270 renal transplant (RT) recipients from 1992 to 2007 in another center in Thailand[4]. The incidence of malignancies was 6.7% (18 cases out of 270 patients) of which the most common cancer was transitional cell carcinoma of the urinary tract followed by hepatocellular carcinoma. However, there was no report of skin cancer in that study, the same as in the present study. Compared to the data of 730 RT recipients in Taiwan with a mean follow-up duration of 72.2 ± 54.4 months, 69 cancers were diagnosed in 63 (8.6%) RT recipients. Of them, 30 cases (4.1%) were urinary tract transitional cell carcinoma (TCC). The cumulative incidence for TCC was 3.0% after 3 years of graft survival, increasing to 7.2% at 6 years and 17.5% at 10 years[5]. In contrast, of 35,765 kidney transplant recipients in the United States in 1995-2001, the cumulative incidences of malignancies at 3 years after transplantation were 7.75% for skin cancers and 7.45% for non-skin cancers. Skin cancer, prostate cancer, PTLD, breast cancer, RCC, lung cancer, colon cancer and hepatocellular carcinoma were the main cancers after kidney transplantation in the United States[3]. Incidence and type of cancer after renal transplantation vary between centers, countries and time periods. The difference of malignancy pattern might be due to genetics, geographic and environmental factors.

RCCs of native kidneys in transplant recipients were more frequently incidental findings[6]

Table 1. Summary of the history, immunosuppressive regimens of four patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age	42	48	8	55
Gender	Male	Female	Male	Female
Time of transplantation	August 1998	May 1997	August 2000	May 1995
Time of development of malignancy	4 years and 8 months (April 2003)	10 years (April 2007)	10 months (June 2001)	10 years and 5 months (October 2005)
Pathology	Renal cell carcinoma	Advanced renal cell carcinoma with lung metastases	Non-Hodgkin's lymphoma	Malignant hemangiopericytoma
Clinical presentation	Microscopic hematuria	Incidentally abnormal chest X-ray finding	Fever with left upper quadrant pain	Right pelvic mass with ascites and pleural effusion
Induction therapy	No	No	No	No
Treatment protocol	Cyclosporine Mycophenolate mofetil Prednisolone	Cyclosporine Azathioprine Prednisolone	Cyclosporine Azathioprine Prednisolone	Cyclosporine Azathioprine Prednisolone
History of rejection	Twice	Once	Twice	None
Treatment of rejection	1. Pulse intravenous methylprednisolone 1g per day x 3 days followed by OKT3 5 mg/day for 7 days in September 1998 2. Pulse intravenous methylprednisolone 1g per day x 3 days followed by OKT3 5 mg/day for 12 days in January 2000	1. Pulse intravenous methylprednisolone 1g per day x 3 days in November 1998	1. Pulse intravenous methylprednisolone 1g per day x 3 days in September 2000 and azathioprine was replaced with mycophenolate mofetil 2. Pulse intravenous methylprednisolone 1g per day x 3 days in April 2001	None
Change of Treatment protocol	No change	Cyclosporine Everolimus Prednisolone	Everolimus Prednisolone	No change
Last serum creatinine (mg/dL)	2.8	1.3 (April 2011)	1.9 (April 2011)	1.1
Death	Yes(Pseudallescheria boydii brain abscess)	No	No	Yes

or detected by periodic ultrasonography screening[7]. It was suggested all patients who are receiving dialysis therapy or who are renal transplant recipients should undergo annual abdominal ultrasonography, along with computed tomography (CT) or magnetic resonance imaging (MRI) in those with a suspected lesion[8].

The incidences of the most common cancers (colon, lung, prostate and breast) are roughly twofold higher in the first 3 years after kidney transplantation than in the US general population. This suggests that measures to reduce the risk of these malignancies, *e.g.* screening for colon cancer, smoking cessation, screening for prostate and breast cancer, might also be appropriate for transplant recipients.

The duration and the intensity of immunosuppressive therapy and the type of immunosuppressive agent have an impact on development of post-transplant malignancy. Patients receiving antibody induction (including OKT3) had a significantly higher risk for malignancy-related death compared with patients receiving no antibody induction[9]. Calcineurin inhibitors clearly favor the development of cancer by inducing somatic mutations and blocking DNA repair, blocking apoptosis and probably favoring the development of metastasis through transforming growth factor-β[1]. Azathioprine is a purine analogue that is incorporated into cellular DNA where it inhibits the purine nucleotide synthesis and interferes with RNA synthesis and metabolism. Azathioprine is listed as a human carcinogen in the 11th Report of Carcinogens of the US Department of Health and Human Services[2].

One of the authors' patients received 2 courses of OKT3 for steroid-resistant rejection and later

developed RCC. All patients received cyclosporine and three of them received azathioprine. It was shown that the new immunosuppressive agents, the proliferation signal inhibitors (PSIs) or mammalian target of rapamycin (mTOR) inhibitors, had the potential role in the prevention, modification and treatment of post-transplant malignancies in at-risk patient populations[10]. Everolimus, one of the mammalian target of rapamycin (mTOR) inhibitors, has been shown to be effective as monotherapy or synergistically with chemotherapy or radiation in experimental cancer models[11-13]. In addition, maintenance immunosuppression with mTOR inhibitors is associated with a reduced incidence of de novo malignancies[14]. So the immunosuppressive regimen is an important factor to be considered for the excellent long term outcome of renal transplant patients.

Conclusion

The incidence of malignancies in the present study was increased among renal transplant recipients compared to the general population especially renal cell carcinoma. Malignancy is one of the three major problems (in addition to cardiovascular disease and infection) in the long term follow-up of transplant recipients, suggesting malignancy should continue to be a major focus of prevention in kidney transplantation. The oncological screening for early detection and prompt treatment is recommended for transplant patients.

Potential conflicts of interest

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References

1. Campistol JM. Minimizing the risk of post transplant malignancy. Transplantation 2009; 87 (8 Suppl): S19-22.
2. Domhan S, Zeier M, Abdollahi A. Immunosuppressive therapy and post-transplant malignancy. Nephrol Dial Transplant 2009; 24: 1097-103.
3. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant 2004; 4: 905-13.
4. Ativitavas T, Jirasiritham S, Ngorsakun P, Pipatpannawong K, Mavichak V. Malignancies in renal transplant patients: 15 years experience in Thailand. Transplant Proc 2008; 40: 2403-4.
5. Wu MJ, Lian JD, Yang CR, Cheng CH, Chen CH, Lee WC, et al. High cumulative incidence of urinary tract transitional cell carcinoma after kidney transplantation in Taiwan. Am J Kidney Dis 2004; 43: 1091-7.
6. Klatte T, Seitz C, Waldert M, de Martino M, Kikic Z, Bohmig GA, et al. Features and outcomes of renal cell carcinoma of native kidneys in renal transplant recipients. BJU Int 2010; 105: 1260-5.
7. Elkentaoui H, Robert G, Pasticier G, Bernhard JC, Couzi L, Merville P, et al. Therapeutic management of de novo urological malignancy in renal transplant recipients: the experience of the French Department of Urology and Kidney Transplantation from Bordeaux. Urology 2010; 75: 126-32.
8. Tillou X, Demailly M, Hakami F, Westeel PF, Saint F, Petit J. De novo renal carcinoma in renal transplant recipients: effect of early treatment. Transplant Proc 2009; 41: 3314-6.
9. Meier-Kriesche HU, Arndorfer JA, Kaplan B. Association of antibody induction with short- and long-term cause-specific mortality in renal transplant recipients. J Am Soc Nephrol 2002; 13: 769-72.
10. Chapman JR, Campistol JM. Malignancy in renal transplantation: opportunities with proliferation signal inhibitors. Nephrol Dial Transplant 2007; 22 (Suppl 1): i1-3.
11. Mabuchi S, Altomare DA, Connolly DC, Klein-Szanto A, Litwin S, Hoelzle MK, et al. RAD001 (Everolimus) delays tumor onset and progression in a transgenic mouse model of ovarian cancer. Cancer Res 2007; 67: 2408-13.
12. Treeck O, Wackwitz B, Haus U, Ortmann O. Effects of a combined treatment with mTOR inhibitor RAD001 and tamoxifen in vitro on growth and apoptosis of human cancer cells. Gynecol Oncol 2006; 102: 292-9.
13. Manegold PC, Paringer C, Kulka U, Krimmel K, Eichhorn ME, Wilkowski R, et al. Antiangiogenic therapy with mammalian target of rapamycin inhibitor RAD001 (Everolimus) increases radiosensitivity in solid cancer. Clin Cancer Res 2008; 14: 892-900.
14. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. Transplantation 2005; 80: 883-9.

มะเร็งในผู้ป่วยหลังรับการปลูกถ่ายไต: ข้อมูลของสถาบันหนึ่งในประเทศไทย

ประเจษฎ์ เรืองกาญจนเศรษฐ์, บุริน เลาหะวัฒนะ, สิริลักษณ์ เลี่ยวเส็ง, ศรันยา กิจพาณิชย์, อดิสรณ์ ลำเพาพงศ์, ประไพพิมพ์ ธีรคุปต์

ภูมิหลัง: *มะเร็งเป็นสาเหตุมากเป็นอันดับสองของการเสียชีวิตในผู้ป่วยหลังรับการปลูกถ่ายไตที่ไตยังคงทำงานได้อยู่ และมีอุบัติการณ์เพิ่มขึ้นตามระยะเวลาหลังการปลูกถ่ายไต*

วัตถุประสงค์: *เพื่อนำเสนอข้อมูลอุบัติการณ์สะสมของมะเร็ง อาการวิทยาของมะเร็งในผู้ป่วยหลังรับการปลูกถ่ายไตในโรงพยาบาลพระมงกุฎเกล้าในช่วงปี พ.ศ. 2530 ถึง พ.ศ. 2552*

วัสดุและวิธีการ: *โดยการรวบรวมย้อนหลังของข้อมูลต่างๆ ที่เกี่ยวข้องกับโรคมะเร็งในแฟ้มประวัติของผู้ป่วยจำนวน 168 ราย ที่ได้รับการปลูกถ่ายไตในโรงพยาบาลพระมงกุฎเกล้า ตั้งแต่วันที่ 1 ตุลาคม พ.ศ. 2530 ถึงวันที่ 15 พฤศจิกายน พ.ศ. 2552*

ผลการศึกษา: *พบว่ามีอุบัติการณ์สะสมของมะเร็งร้อยละ 2.4 (พบมะเร็งในผู้ป่วย 4 รายจากทั้งหมด 168 ราย) ผู้ป่วยเมื่อได้รับการวินิจฉัยมะเร็งมีอายุเฉลี่ย 45 ปี (8-55 ปี) ระยะเวลาเฉลี่ยที่ได้รับการวินิจฉัยว่ามีมะเร็งภายหลังการผ่าตัดปลูกถ่ายไตคือ 7.3 ปี (0.8-10.4 ปี) ผู้ป่วยทั้งสี่รายได้รับการวินิจฉัยตรวจพบว่ามีมะเร็ง ภายหลังได้รับการผ่าตัดปลูกถ่ายไต โดยได้รับการวินิจฉัยจากการตรวจชิ้นเนื้อทางพยาธิวิทยา ผู้ป่วยทุกรายได้รับยา cyclosporine, prednisolone และ azathioprine หรือ mycophenolate mofetil เป็นยากดภูมิคุ้มกันสำหรับป้องกันการสลัดไต มีผู้ป่วย 2 ราย ที่ตรวจพบมีมะเร็งที่ไตเดิม ผู้ป่วย 1 ราย มี post-transplant lymphoproliferative disorder (PTLD) และอีก 1 รายมี malignant hemangiopericytoma จนถึงปัจจุบันผู้ป่วยที่มีมะเร็งดังกล่าวยังคงมีชีวิตอยู่ มีจำนวน 2 ราย (เป็นผู้ป่วยหนึ่งรายที่มีมะเร็งของไตเดิมและอยู่ในขั้นลุกลามร้ายแรง และอีกหนึ่งรายเคยมี PTLD) มีผู้ป่วยหนึ่งรายเสียชีวิตจากโรคมะเร็ง malignant hemangiopericytoma และอีกหนึ่งรายเสียชีวิตจากการติดเชื้อ (ฝีอักเสบในสมองที่เกิดจากภาวะติดเชื้อ Pseudallescheria boydii)*

สรุป: *พบอุบัติการณ์ของมะเร็งได้สูงขึ้นในผู้ป่วยหลังรับการปลูกถ่ายไตเมื่อเทียบกับประชากรทั่วไป โดยเฉพาะอุบัติการณ์ของมะเร็งที่ไต ด้วยเหตุที่ผู้ป่วยที่ได้รับการปลูกถ่ายอวัยวะมีโอกาสเสี่ยงมากขึ้นต่อการเกิดมีมะเร็งทำให้มีความจำเป็นที่จะต้องได้รับการตรวจดูแลอย่างใกล้ชิดในระยะยาว เพื่อที่จะให้ได้รับการวินิจฉัยมะเร็งตั้งแต่ระยะเริ่มแรกอย่างรวดเร็ว ในกรณีที่มีมะเร็งเกิดขึ้น*