Original Article

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Incidence of Post-transplant Malignancy after Renal Transplantation: Single Center Analysis

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Background: Immunosuppression after kidney transplantation is associated with increased risk of malignancy, which has become the second most common cause of death among kidney transplant recipients. In this review, we report the incidence of malignancies after kidney transplantation in a single center and evaluate the incidence, characteristics, relationship to immunosuppressive drugs and discuss what clinicians must consider during a follow-up of patients after kidney transplantation.
Methods: Between May 1978 and September 2013, a total of 748 kidney transplant patients who were able to undergo a follow-up process through electronic medical records were enrolled in this retrospective cohort study to determine the potential incidence and types of malignancy that may occur after kidney transplantation and the associated impact on patients and graft survival.
Results: Among 748 patients, 63 cases of malignancy appeared in 54 patients (7.2%). Gastrointestinal cancer (12 cases, 19%) and post-transplant lymphoproliferative disorder (12 cases, 19%) were the two most common types of malignancy. The second most common type of malignancy was urinary tract malignancy in 10 patients. Two different types of malignancy were diagnosed in nine patients during our follow-up. The overall graft survival in malignancy patients was better, which may mean that malignancy did not affect the overall graft loss.
Conclusions: Clinicians should be aware of the incidence of malignancy in transplant patients and perform routine examinations for early detection of malignancy.

Key Words: Malignancy, Kidney transplantation, Incidence, Multiple primary cancer
중심 단어: 악성종양, 신이식, 발생률, 다발성 원발성 악성종양

INTRODUCTION

Kidney transplantation is clearly accepted as the best treatment for end stage renal disease patients who need renal replacement therapy. Several studies have proven that kidney transplantation is associated with lower risk of mortality and improves quality of life than patients on long-term dialysis(1-3). Although the development of many immunosuppressive drugs has decreased the incidence of acute graft rejection after kidney transplantation, complications including infection, malignancy, and cardiovascular events are increasing(4,5). And malignancy has become the second most common cause of death among kidney transplant recipients(1). Several studies showed that immunosuppression after organ transplantation is associated with increased risk of posttransplant lymphoproliferative disorder (PTLD) and squamous cell carcinoma(6-8). Beyond gender, age, genetic risk, conventional risk factors, pre-existing cancers, there are several mechanism theories that explain the contribution of immunosuppressive agents to tumor growth after transplantation. First, most of the immunosuppressive protocols are designated to reduce lymphocyte reactivity that results in decreased alloreactivity to the

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transplant and less immune surveillance(9). In addition, malignancy occurs by DNA damage or interfering with DNA repair mechanisms. Azathioprine (AZA) inhibits DNA repair and induces DNA mutations by codon misreads(10). Cyclosporine (CsA) has been shown to accelerate carcinogenesis by interfering with DNA damage repair and by up-regulating expression of tumor growth factor β and vascular endothelial growth factor(11). Furthermore, enhanced angiogenesis, tumor invasion, metastasis and Epstein-Barr virus-induced B-cell expansion have been shown in the use of calcineurin inhibitors(12).

In this review, we report the incidence of malignancies after kidney transplantation in a single center study and evaluate the incidence, characteristics, relationship to immunosuppressive drugs and discuss what clinicians must consider on following up patients after kidney transplantation.

MATERIALS AND METHODS

Between May 1978 and September 2013, 748 kidney transplant patients who were able to follow-up through electronic medical records were enrolled in this retrospective cohort study to determine the incidence and types of malignancy occurring after kidney transplantation and their impact on patients and graft survival. All data were collected and analyzed from kidney transplant patients' clinical notes and computerized records including pathology and radiology reports. The immunosuppressive therapy was based on CsA/tacrolimus, mycophenolate mofetil (MMF)/AZA and steroids. Before 1985, patients received AZA and steroids. Between 1986 and 1998, patients received dual maintenance immunosuppression with CsA and AZA. After 1998, AZA was replaced by MMF as second maintenance drug, and tacrolimus was used as other choice of CsA. Kidney transplant patients are routinely screened for detecting malignancies. Blood tests including tumor markers were examined twice per year. Gastrointestinal (GI) endoscopic examinations and abdominal ultrasonography were performed annually. Among these patients, 63 cases of malignancy from 54 patients were diagnosed and treated. We compared these malignancy patients with total population of renal transplant patients in a single center and studied this group with types of malignancy, incidences, interval between transplantation and cancer diagnosis, prognosis, and graft survival. Data were analyzed with SPSS ver. 18.0 (IBM Co., Armonk, NY, USA) and Kaplan-Meier method was used to calculate graft survival curve.

RESULTS

1. Patient characteristics

Seven hundred forty-eight patients were enrolled in this study. The mean age of patients was 38.2±10.8 years (range, 15～70) and the male/female ratio was 1.91:1. Among these patients, 326 patients (43.6%) received kidney from living-related donor, 367 patients (49.1%) from living-unrelated donor, and 55 (7.4%) from deceased donor. AZA was used in 51 patients (6.8%), CsA in 591 patients (79.0%), and tacrolimus in 106 patients (14.2%) as main maintenance immunosuppressive drug. Acute rejection was observed in 210 patients (28.1%).

Sixty-three cases of malignancy appeared in 54 patients (7.2%). Mean age of cancer patients group was 44.0±9.6 years (range, 28～66) which was older than cancer-free patients group (37.7±10.7 years) and the male/female ratio was 1.57:1. Thirteen malignancy patients (24.1%) received kidney from living-related donor and 38 patients (70.4%) from living-unrelated donor which was larger portion than cancer-free patients. Only three patients received kidney from deceased donor. Most of malignancy patients (88.9%) were using CsA as main immunosuppressive drug and six patients (11.1%) were using tacrolimus (Table 1).

2. Types and incidences of malignancy

GI cancer (12 cases, 19%) and PTLD (12 cases, 19%) were the two most common type of malignancy (Table 2). Stomach cancer (seven cases, 11%) was the most common type in GI cancer. Both colon cancer and hepatocellular carcinoma was seen in two patients and pancreas tumor in one patient. Twelve cases were PTLD which were affecting various organs (two cases, stomach; two cases, intestine; five cases, neck; two cases, kidney; and one case, lung). Second most common type of malignancy was urinary tract malignancies in 10 patients (seven cases, native kidney; one case, transplanted kidney; and two cases, bladder). Female genital

Table 1. Characteristics of patients

Characteristic	Total patients (n=748)	Cancer-free patients (n=694)	Cancer patients (n=54)
Age (yr)	38.2±10.8 (15~70)	37.7±10.7 (15~70)	44.0±9.6 (28~66)
Gender (male:female)	491:257 (65.6:34.4)	458:236 (66.0:34.0)	33:21 (61.1:38.9)
Donor			
Living-related	326 (43.6)	313 (45.1)	13 (24.1)
Living-unrelated	367 (49.1)	329 (47.4)	38 (70.4)
Cadaver	55 (7.4)	52 (7.5)	3 (5.6)
Immunosuppression			
Azathioprine	51 (6.8)	51 (7.3)	0
Cyclosporine	591 (79.0)	543 (78.2)	48 (88.9)
Tacrolimus	106 (14.2)	100 (14.5)	6 (11.1)
Acute rejection	210 (28.1)	198 (28.5)	12 (22.2)
Viral infection			
CMV	37 (4.9)	35 (5.0)	2 (3.7)
EBV	4 (0.5)	4 (0.6)	0

Data are presented as mean±SD (range) or number (%).
Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus.

Table 2. Type of malignancy and time of diagnosis after renal transplantation

Variable	No. (%)	Mean age at diagnosis (yr)	Mean time of diagnosis (mo)[a]	Response to treatment	
				Good	Poor
Stomach cancer	7 (11.1)	53.7±8.8 (40~68)	127.9±42.6 (63~178)	5	2
Colon cancer	2 (3.2)	43.5±6.4 (39~48)	128.5±91.2 (64~193)	1	1
Hepatocellular carcinoma	2 (3.2)	50.0±11.3 (42~58)	98.5±115.2 (17~180)	0	2
pancreas tumor	1 (1.6)	66	149	1	0
Lymphoma	12 (19)	45.4±10.8 (24~60)	104.3±59.8 (12~204)	9	3
Kaposi sarcoma	4 (6.3)	48.2±15.4 (31~66)	50.5±68.1 (4~149)	3	1
Skin cancer	2 (3.2)	63.5±9.2 (57~70)	123.5±82.7 (65~182)	1	1
Breast cancer	4 (6.3)	50.0±14.4 (30~63)	53.5±40.0 (18~108)	2	2
Thyroid cancer	6 (9.5)	50.8±9.8 (37~65)	129.3±55.0 (68~193)	6	0
Urinary tract cancer	10 (15.9)	56.8±8.4 (44~68)	104.6±75.3 (10~251)	10	0
Prostate cancer	2 (3.2)	66.0±2.8 (64~68)	126.5±61.5 (83~170)	2	0
Female genital cancer	7 (11.1)	46.4±9.4 (38~62)	109.6±71.9 (16~224)	6	1
Lung cancer	3 (4.8)	57.0±9.2 (49~67)	28.3±14.5 (14~43)	0	3
Brain tumor	1 (1.6)	59	65	1	0
Total	63 (100)	51.7±10.9 (24~70)	101.7±63.7 (4~251)	47	16

Data are presented as mean±SD (range).
[a]The period from transplantation to the diagnosis of malignancy.

malignancies (uterus, cervix, and ovary) were seen in seven patients and prostate cancer in two patients. Kaposi sarcoma (four cases, 6.3%), skin cancer (two cases, 3.2%), breast cancer (four cases, 6.3%), thyroid cancer (six cases, 9.5%), lung cancer (three cases, 4.8%), and brain tumor (one case) were diagnosed during follow-up. The mean age at malignancy diagnosis was 51.7±10.9 (range, 24~70) and the mean time interval between malignancy diagnosis and transplantation was 101.7±63.7 months (range, 4~251). Patient with diagnosis of PTLD at neck was the youngest patient at his age of 24- and 70-year-old male patient was the oldest patient who was diagnosed as basal cell carcinoma at nose. Shortest time interval was Kaposi sarcoma (4 months) and longest one was urothelial carcinoma at renal pelvis of

Table 3. Patients with multiple primary malignancies

Sex/age	First malignancy			Second malignancy		
	Type	Pathologic diagnosis (stage)	Time of diagnosis (mo)[a]	Type	Pathologic diagnosis (stage)	Time of diagnosis (mo)[a]
M/56	Stomach	Adenocarcinoma (I)	147	Urinary bladder	Urothelial carcinoma *in situ*	147
F/34	Sigmoid colon	Adenocarcinoma (III)	64	Uterus	Endometrioid carcinoma (II)	73
M/54	Pancreas	IPMN[b]	149	Skin, forearm	Kaposi's sarcoma	150
M/22	PTLD	Diffuse large B cell lymphoma	30	Thyroid	Papillary carcinoma (I)	189
M/59	PTLD	Diffuse large B cell lymphoma	12	Urinary bladder	Urothelial carcinoma *in situ*	86
M/55	Skin, left 3rd toe	Kaposi's sarcoma	4	Skin, nose	Basal cell carcinoma	182
M/36	Thyroid	Papillary carcinoma (I)	112	Kidney, native	Papillary renal cell carcinoma (I)	167
M/47	Kidney, native	Renal cell carcinoma (I)	26	Lung	Papillary adenocarcinoma	28
M/52	Lung	Bronchioloalveolar carcinoma (II)	43	Kidney, native	Papillary adenoma	49

Abbreviations: IPMN, intraductal papillary mucinous neoplasm; PTLD, posttransplant lymphoproliferative disorder.
[a]The period from transplantation to the diagnosis of malignancy; [b]Intraductal papilary mucinous neoplasm (radiologic diagnosis).

transplanted kidney (251 months). Two different types of malignancy were diagnosed in nine patients during our follow-up. All but one patient were diagnosed with malignancies in different periods. Most of them were male but various types of malignancy can occur in any period (Table 3).

3. Treatment modalities and prognosis

Among seven gastric cancer patients, four patients underwent subtotal gastrectomy, and three patients received endoscopic mucosal resection (EMR). Two patients who underwent surgery recurred with peritoneal seeding, while other two patients with surgery and EMR treated patients were not recurred yet. Colon cancer patients underwent surgery and one patient recurred with liver and brain metastasis. Both HCC patients had hepatitis B virus infection and they received radio frequency thermal ablation and transarterial chemoembolization repeatedly, but HCC recurred and expired due to hepatic failure. Eight patients with lymphoma received chemotherapy and four patients received surgical resection. Among them, nine patients were in complete remission during follow-up, two patients were expired for other reasons and PTLD recurred in one patient. Three patients with Kaposi sarcoma and two patients with other skin cancer were treated by surgical excision and their prognosis was good, but in one patient with Kaposi sarcoma who was treated with surgical excision, chemotherapy, and radiotherapy recurred again. Three patients with breast cancer were treated by surgery and chemotherapy and one patient received chemotherapy alone due to multiple organ metastasis. All of thyroid cancer, urinary tract malignancies and prostate cancer patients showed good prognosis after surgical removal (nephrectomy, transurethral resection of bladder). All female genital malignancy patients were treated with surgical removal and combination chemotherapy in three patients, while lung metastasis was seen in one case of cervical cancer. Lung cancer patients show a poor prognosis despite treatment. Among 63 patients, 47 patients showed good response to treatment which means cancer was not recurred during follow-up and 17 patients showed poor response to treatment which means cancer was recurred with peritoneal seeding or distant metastasis (Table 2).

4. Graft survival

Among 748 total patients, median follow-up period was 118.5 months, range from 0 to 419 months. Seventy cases died with a functioning graft due to other reasons (pneumonia, cardiovascular attack, myocardial infarction) and two cases with graft failure which was marked as 0 month follow-up. Overall graft survival in cancer patients was better than in cancer-free patients (P=0.035). In other words, malignancy did not affect overall graft loss (Fig. 1).

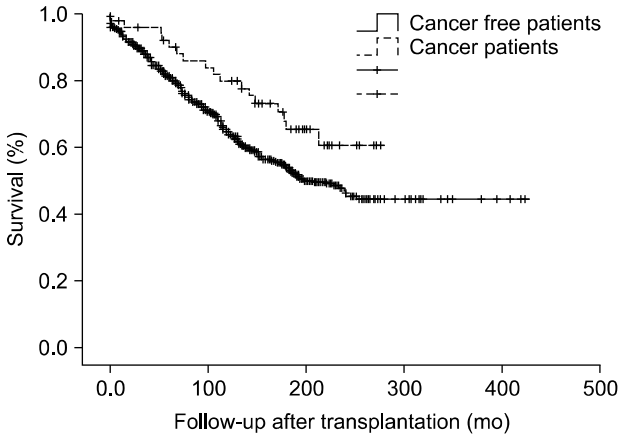

Fig. 1. Cumulative graft survival of cancer patients and cancer free patients.

DISCUSSION

Although preferentially managing infectious and cardiovascular complications after kidney transplantation is crucial, posttransplant malignancy has become an essential cause of increasing mortality and morbidity nowadays. According to several previous reports, most prevalent malignancies after kidney transplantation is Kaposi's sarcomas, non-Hodgkin lymphomas and nonmelanoma skin cancers with 10 to 20 times greater than in the general population(13). Also viral-associated tumors and urogenital tumors seemed to take a large proportion of malignancy after kidney transplantation(14). Ro et al.(15) reported 4.3% malignancy development in a 37-year follow-up in a single center study, and Kim et al.(16) showed 4.2% of malignancy incidence pattern after renal transplantation among 757 patients. In the previous Korean study, the incidence of malignancy was distributed 1.2% to 4.3%, and this was increased during the follow-up periods(16). In our study, malignancies after kidney transplantation were developed in 52 of 748 patients (7.2%) and GI malignancy (stomach cancer) was the most common. Most of the other studies in Western countries and even in Eastern Asia, except in Japan, GI cancers occurred in relatively low rate compared to our study. Kaposi's sarcomas, non-Hodgkin lymphomas and nonmelanoma skin cancers seemed to be the most common malignancies in those studies(17). There were four cases of Kaposi sarcoma in our study, and the mean interval of diagnosis was 50.5±68.1 months in those cases. Among these patients, one patient was diagnosed as Kaposi sarcoma 4 months after renal transplantation which was the shortest time interval of diagnosis in our study. According to some reports, Kaposi sarcoma and lymphoma was diagnosed in the early stage of posttransplantation(18-20). Berber reported 50% of the patients displayed Kaposi sarcoma in the first posttransplant year(18). Dominant effect of the immunosuppressive agents in the early stage of posttransplantation is associated with relatively early onset of specific malignancies such as Kaposi sarcoma and lymphoma(18).

We found nine patients diagnosed with two different types of malignancies after renal transplantation. The incidence rate of multiple primary cancer after kidney transplantation was 16% which was higher than recent study (8.1%) based on general population(21). Eight of nine patients were male and all patients were diagnosed double primary cancer before age 60. Only one patient was diagnosed with different malignancies at the same period who had stomach and urothelial cancer. Type of the malignancy seemed to be various and could be diagnosed at any period. Further prospective research and concern will be required to figure out the risk, predisposing factors, and prognosis associated with different type of malignancy after transplantation.

Our study has some limitations. Due to a single center study, malignancy incidence after kidney transplantation was too small to compare with those in the general population. For more accurate comparison, calculating standardized incidence rate would be helpful but there were limitations in our study. Tremblay et al. reported that in the era of using antithymocyte globulin and adding CsA or tacrolimus, there is a statistically significant increase in cancer incidence compared to the era mainly using AZA and steroid(22). And several studies suggested that sirolimus might reduce the incidence of malignancy(23). Bang(24) showed relatively low malignancy rate using tacrolimus (3.4%) compared with CsA (7.6%), and Kasiske et al.(14) also suggested tacrolimus was associated with a lower incidence of skin cancer. In our study, 53 malignancy patients received kidney transplantation between 1986 and 1998 and 10 patients received kidney transplantation after 1998. We couldn't figure out malignancy category specifically related

to immunosuppressive agents, because most of them (92.6%) were using CsA as immunosuppressive drug and only four patients (7.4%) were using tacrolimus. Another limitation is that, in our study, graft survival in cancer patient group was better than in cancer-free patient group (P=0.035). This value is statistically significant, but in clinical point of view, malignancy may not affect overall graft loss. To evaluation the graft survival result, adequate number of malignant patient population and further study including multivariate analysis will be needed.

CONCLUSION

Among these 63 cases of malignancy patients, 47 patients (74%) showed a good prognosis with early diagnosis and prompt management. However, other patients showed a poor prognosis with either recurrence of malignancy or peritoneal seeding. Advanced stage at diagnosis might be the reason for poor prognosis. In conclusion, we suggest that clinicians and patients should be aware of incidence of malignancy in transplant patients and perform routine examinations for early detection of malignancy for proper treatment.

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