Incidence and Long-Term Prognosis of Cancer After Kidney Transplantation

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ABSTRACT

Background. Malignancy is an important cause of mortality in renal transplants recipients. The incidence of cancer is increased by immunosuppressive treatment and longer kidney graft survival. The aim of this study was to evaluate the incidence, prognosis and survival of posttransplant malignancies: solid organ cancer (SOC), posttransplant lymphoproliferative disorder (PTLD), and nonmelanoma skin cancer (NMSC).

Methods. We retrospectively studied the development of cancers among kidney transplants patients in our hospital from January 1979 to January 2015. We analyzed demographic and clinical characteristics, risk factors, and patient survival after tumor diagnosis.

Results. We included 1450 kidney transplants recipients with a mean follow-up was 10 years; among them, 194 developed malignancies. The mean age at presentation was 59 ± 10 years. The SOC, PTLD, and NMSC incidences were 6.2%, 1.2%, and 6%, respectively. The most common tumors were kidney (16.6%), colon (11%), bladder (10%), breast (10%), prostate (10%), and lung (8.8%). The median times to development of a SOC, PTLD, and NMSC were 6.86 (range, 3.7–12), 4.43 (range, 1.8–5.7), and 8.19 (range, 3.8–12.2) years, respectively. Risk factors associated with developing SOC and PTLD were patient age (odds ratio [OR], 1.03; $P < .001$) and time posttransplant (OR, 1.05; $P = .02$), whereas for NMSC were to be male (OR, 3.61; $P < .001$), to take calcineurin inhibitors (OR, 2.17; $P = .034$), patient age (OR, 1.05; $P < .001$) and time posttransplant (OR, 1.15; $P < .01$). The mean survival time from the diagnosis of SOC, PTLD, and NMSC were 2.09 (range, 0.1–5.3), 0.22 (range, 0.05–1.9), and 7.68 (range, 3.9–10.5) years, respectively ($P < .001$).

Conclusions. SOC occurs more frequently than other malignancies among renal transplant patients. NMSC has better survival and prognosis. Older patients and prolonged graft function have a greater risk of developing malignancies.

CANCER IS AN important cause of morbidity and mortality in kidney transplants recipients. There are reasons to believe that cancer should be more common after renal transplantation compared with general population [1–6]. Several large studies have reported a prevalence of cancer in transplanted patient ranging from 4% to 18% [5–9]. The etiology of malignancy is owing to the effects of immunosuppression and oncogenic viral pathogens [4,5,9,10]. Immunosuppressive treatment may cause DNA damage and inhibit immune surveillance mechanisms [1,6]. Certain posttransplantation malignancies may display different clinicopathologic characteristics than their de novo counterparts: fast progression, unfavorable, prognosis and poor response to treatment [2,5,11–14].

In addition, no study has yet provided information on the site of malignancy-related mortality in kidney transplantation and whether site-specific cancer mortality can be

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stratified along demographic factors. Further, in different geographic areas the distribution of posttransplant malignancy may show considerable differences [1,4,5,9].

The aim of this study was to evaluate the incidence, prognosis and survival of posttransplant de novo malignancies (solid organ cancer [SOC], posttransplant lymphoproliferative disorder [PTLD], and nonmelanoma skin cancer [NMSC]) in kidney transplant recipients at our center.

METHODS

Selection and Description of Participants

We retrospectively analyzed the development of de novo cancers among our population of kidney transplants recipients from January 1979 to January 2015. All transplanted patients were followed at our outpatient care unit as long as their transplanted kidney functioned. In case of complication, they were admitted to our department. Patient data and posttransplantation complications were registered in our database. Transplanted patients received triple immunosuppressive therapy with tacrolimus/cyclosporine, mycophenolate mofetil/azathioprine, and prednisolone; induction with anti–interleukin-2 antibody (basiliximab) or rabbit antihuman thymocyte immunoglobulin (thymoglobulin) was selected for hyperimmunized patients and in kidney–pancreas transplant recipients.

We analyzed the demographic and clinical characteristics, risk factors, and patient survival after tumor diagnosis. Kidney function (glomerular filtrate measured by the abbreviated Modification of Diet in Renal Disease formula), duration of renal replacement therapy before transplantation, posttransplant time, rejection episodes, and immunosuppression and induction regimens were collected.

Statistical Analysis

The Student t test for continuous variables (expressed as mean values ± standard deviation) and the χ^2 test for categorical variables (expressed as percentages) were used to compare data between the 2 groups: with or without cancer. The elapsed time from transplant to the tumor diagnosis was expressed as the median value and quartile range.

After identifying potential factors for the development of de novo cancers in our transplant recipients, multiple logistic regression analysis was performed to determine the influence of various parameters on SOC, PTLD, and NMSC. The Kaplan–Meier method was used for cumulative survival curves and differences were compared by the log-rank test. $P < .05$ was considered significant. Statistical analyses were performed using SPSS v12.0 software package for Windows (SPSS, Inc, Chicago, IL).

RESULTS

Patient Characteristics and Clinical Variables

There were 1450 renal transplantations performed in our hospital between January 1979 and January 2015 (1424 from deceased donors and 26 from living donors). A total of 178 were combined transplants (164/178 pancreas–kidney transplantation). The mean follow-up was 10 years.

We studied 194 transplanted patients who developed SOC, PTLD, or NMSC. Most transplant patients with cancer were male (74%) and showed a mean age at presentation of 59 ± 10 years. Patient's demographics and clinical characteristics in both groups (with or without cancer) are shown in Table 1. There were no differences between the percentage of patients under azathioprine and mycophenolate treatment in both groups.

Only 20 recipients (1.3%) in this cohort had a pretransplant history of malignancy: 8 skin cancers (5 basal cell carcinoma and 3 squamous cell carcinoma), 4 breast, 3 prostate, 2 colon, 1 renal, 1 bladder cancer, and 1 lymphoma.

Posttransplant Malignancies

Malignancies were found in 194 transplanted patients. The SOC, PTLD, and NMSC incidences were 6.2% (n = 90), 1.2% (n = 17), and 6% (n = 87), respectively. The most common tumors were renal carcinoma of the native kidney (n = 15; 16.6%), colon cancer (n = 10; 11%), bladder cancer (n = 9; 10%), breast cancer (n = 9; 10%), prostate cancer (n = 9; 10%), and lung cancer (n = 8; 8.8%). Other malignancies were cervical and thyroid cancers in 4 patients each (4.4% each tumor) and malignant brain tumor in 3 (3.3%). A low incidence was presented in Kaposi sarcoma, hepatocellular carcinoma, tongue cancer, gastric cancer, parathyroid cancer, pancreatic cancer, and other gynecologic cancers. Skin cancers were observed in 87 transplanted patients, being squamous cell carcinoma in 52% (n = 45) and basal cell carcinoma in 48% (n = 42).

The elapsed median time between transplantation and the appearance of tumors were 6.86 years (range, 3.7–12) in SOC, 4.43 years (range, 1.8–5.7) in PTLD, and 8.19 years (range, 3.8–12.2) in NMSC. Renal function was stable 1 year after tumor diagnosis.

Risk Factors for Cancer in Kidney Transplant Recipients

A separate analysis was performed for SOC/PTLD and NMSC. It was owing to their different features, prognosis,

Table 1. Demographic and Clinical Characteristics of Kidney Transplant Patients in Both Groups

Characteristic	With Cancer	Without Cancer	P
Gender (% male)	74	63.6	.007
Age at transplantation (y)	59 ± 10	53 ± 14	.016
Donor age (y)	45 ± 20	43 ± 18	.24
Duration of renal replacement therapy (y)	3.6 ± 3.8	4.06 ± 4.3	.301
Duration of renal transplant (y)	7.4 ± 5.3	4.8 ± 4.7	<.001
Cold ischemia time (h)	18.7 ± 7.5	16.6 ± 7.2	.036
Pretransplant percentage of panel reactive antibodies peak (%)	13.8 ± 27	16.6 ± 30	.96
HLA mismatching	2.4 ± 1.3	2.94 ± 1.3	<.001
Acute rejection episodes (%)	17	20	.387
MDRD at 1 year (mL/min)	54 ± 18	60 ± 20	.47
MDRD at 5 years (mL/min)	58 ± 15	61.5 ± 19	.57
Number of kidney transplants (>1)	177	1273	.829
Calcineurin inhibitors (%)	90.5	88.5	.498
Polyclonal or monoclonal antibody (%)	13	22.5	.004

Abbreviation: MDRD, Modification of Diet in Renal Disease; HLA, human leukocyte antigen.

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