Cancer Screening of Renal Transplant Patients Undergoing Long-Term Immunosuppressive Therapy

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ABSTRACT

Objective. With this study we aimed to research the effects of immunosuppressive drugs, their cumulative doses, and viral infections on development of malign tumors in patients who have undergone treatment for 5 years.

Methods. We examined 100 patients who underwent renal transplantation from 2004 to 2009. Patients had mycophenolate mofetil and steroid in addition to cyclosporine, sirolimus, or tacrolimus as immunosuppressive treatment. For malignancy screening, physical examination, radiologic and endoscopic screening were done, and immunosuppressive drugs and their cumulative doses, age, sex, body mass index (BMI), dialysis history, and viral infection history were investigated.

Results. The mean age of patients was 42.03 ± 11.30 years. There were 1 colon cancer patient, 1 retroperitoneal liposarcoma, 1 renal oncocytoma, 3 Kaposi sarcoma patients treated with cyclosporine; in those treated with Tac there were 1 basal cell carcinoma, 1 Kaposi sarcoma, 2 thyroid carcinoma, 1 breast carcinoma, 1 bladder carcinoma, 1 renal cell carcinoma, and 1 colon carcinoma patients. The mean age of patients having carcinoma was statistically significant compared with those without cancer ($P < .01$). The prednisolone cumulative dose was significantly higher in carcinoma patients than in patients without carcinoma ($P < .01$).

Results. The use of long-term chronic immunosuppressive therapy may increase the development of cancer. The risk of carcinoma increases with increasing drug dose and time period of the immunosuppressive drug. There was not a negative effect on cancer prevalence in patients with cyclosporine or tacrolimus. But the cumulative dose of steroids significantly increased malignancy occurence.

LATELY, renal transplantation has become the sole and most preferred therapy modality for end-stage renal disease (ESRD) patients. In the early post-transplantation period, the most encountered complication is acute rejection, whereas in later periods infections and carcinogenesis are more frequent. It is known that the risk of malignity is 3–5 times higher in renal transplant recipients [1–3]. Some immunosuppressive drugs has pro-oncogenic properties. Cyclosporine (CsA), calcineurin inhibitors, azathioprine (Aza), and prednisone increase the risk of cancer development by diminishing DNA repair mechanisms. Herman et al reported that CsA has significant effect on decrease of DNA repair ratio compared with Aza and prednisone [4].

In the present study, we screened renal transplant patients undergoing immunosuppressive treatment for ≥5 years and researched the effects of immunosuppressive drugs, their cumulative doses, and viral infections on occurrence of malignant tumors.

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0041-1345/15
http://dx.doi.org/10.1016/j.transproceed.2015.04.073

Table 1. Demographic Features

	All Patients (n = 100)	Malignancy (n = 14)	No Malignancy (n = 86)	*P* Value
Sex (F/M)	43/57	6/8	37/49	>.05
Age (y)	42.03 ± 11.3	51.07 ± 13.37	40.56 ± 10.28	.009
Dialysis period (y)	3.28 ± 2.99	3.43 ± 2.44	3.25 ± 3.08	>.05
Body mass index	26.08 ± 4.51	26.14 ± 5.4	26.07 ± 4.39	>.05
Pre-transplantation renal disease (*n*)				>.05
Glomerulonephritis	24	4	20	
Polycystic kidney disease	8	2	7	
SLE	5	–	5	
Diabetes mellitus	29	6	23	
Hypertension	16	2	14	
IgA nephropathy	4	–	4	
Unknown	14	1	13	
Donor source (living/cadaveric)	94/6	13/1	81/5	>.05
Post-transplantation period (y)	10.13 ± 3.83	12.86 ± 6.22	9.69 ± 3.13	>.05

PATIENTS AND METHODS

One hundred renal transplant patients who were admitted from 2004 to 2009 were included. In the postoperative period, CsA was used in 19, sirolimus in 16 and tacrolimus (Tac) in 65 patients. All patients were using mycophenolate mofetil (MMF) and steroid along with the above regimes. CsA was administered at 200–300 ng/mL for the 1st 3 months, tapered to 100–200 ng/mL thereafter, and after the 1st year given at a dose of 50–150 ng/mL. Tac was administered as continuation therapy at a dose of 4–8 ng/mL. MMF was administered at 1.5–2 g/d for 2 weeks and thereafter at 1–1.5 g/d. The methyl prednisolone dose was 6–10 mg/kg/d on the day of surgery and the following 2 days. The daily dose of prednisolone was tapered to 40 mg at the post-transplantation 10th day. In the following 1st 3 months the dose was tapered to 10 mg as oral treatment. In case of acute rejection, patients were treated with pulse steroid and antithymocyte globulin.

For malignancy, physical examination and laboratory, radiologic, and endoscopic screenings were done. Patients' immunosuppressive regime, cumulative doses, age, sex, body mass index, dialysis period, post-transplantation period, viral infections, and biochemical analysis were recorded.

Statistical Methods

For statistical analysis, NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 statistical software were used. For the comparison of 3 and more groups which had nonnormal distributions, Kruskal-Wallis analysis was applied. For the detection of the group that causes difference, Mann-Whitney *U* test was used. Comparison of the qualitative data was performed with the use of Pearson chi-square test, Fisher exact test, Fisher-Freeman-Halton test, and Yates continuity correction test (Yates-corrected chi-square). Multivariate logistic regression analysis was used to detect the most significant risk factor of steroid cumulative dosage for malignancy.

RESULTS

From 2004 to 2009, 100 cases ($n = 43$ female; $n = 57$ male) were included. The age of cases were in the range of 17–72 years at a mean of 42.03 ± 11.30 years ($P > .05$). The mean age of malignant tumor patients (51.07 ± 13.37 y) was significantly higher compared with those without malignant tumors (40.56 ± 10.28; $P = .009$).

Among the patients treated with CsA there were 1 colon cancer, 1 retroperitoneal liposarcoma, 1 renal oncocytoma, and 3 Kaposi sarcoma patients. Among those treated with Tac there were 1 basal cell carcinoma, 1 Kaposi sarcoma, 2 thyroid carcinoma, 1 breast carcinoma, 1 bladder carcinoma, 1 renal cell carcinoma, and 1 colon carcinoma patients.

The mean age of cases with malignancy was 51.07 ± 13.37 years and of those without malignancy was 40.56 ± 10.28 years. According to malignancy condition, the ages of patients with malignancy were higher than the ages of patients without malignancy ($P = .009$).

Regarding body mass index, dialysis period, and post-transplantation periods, there was no significant statistical difference between the 2 groups ($P > .05$; Table 1).

Nineteen percent of the patients were receiving CsA, and the mean cumulative dose was 289,598.68 ± 112,535.18 mg. There was no significant relationship detected between the cumulative dose of CsA and malignancy ($P > .05$). Sixteen percent of the patients were receiving sirolimus, and its cumulative dose was 11,360.63 ± 21,699.50 mg. There was no malignancy detected in any of the sirolimus-receiving patients. Sixty-five percent of the cases were receiving Tac, and its cumulative dose was 5,748.69 ± 3,297.85 mg. There was no significant relationship between the Tac cumulative dose and occurrence of malignancy in these patients. All cases were receiving MMF along with the above drugs, and its cumulative dose was 3,246.98 ± 1,683.94 mg. When we compared the 2 groups according to occurrence of malignancy, there was no significance detected between the cumulative MMF dose and malignancy status ($P > .05$). The mean cumulative dose of steroid was 9,969.25 ± 7,866.85 mg. The cumulative dose of the steroid was significantly higher in the malignancy group compared with the nonmalignancy group ($P = .001$; Table 2).

When we evaluated the effect of Tac and steroid dosages on malignancy, the results were statistically significant according to logistic regression analysis. It was calculated that the odds ratio of the effect of steroid dosage was 1.160 (95%