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Neoplasm Incidence in Simultaneous Pancreas and Kidney Transplantation: A Single-Center Analysis

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ABSTRACT

Background. Long-term immunosuppression is associated with an increased rate of cancer. The aim of this study was to analyze the incidence of newly diagnosed tumors in simultaneous kidney and pancreas transplantation (SPKT).

Methods. We retrospectively analyzed the incidence of a neoplasm among 360 diabetic subjects who consecutively underwent SPKT from 1985 to August 2010 in a single institution. Data were retrieved from the institutional registry. We evaluated the nature of all newly diagnosed malignant tumors, including posttransplantation lymphoproliferative disease (PTLD), to compare Kaplan-Meier survival rates with those of patients free of a neoplasm.

Results. The median follow-up was 8 years; the overall 5-year patient survival was 84%. In 25 patients the tumors were malignant. Almost one-fourth of the cancers represented skin tumors (3 squamous cell and 4 basal cell carcinomas). PTLD was diagnosed in 5 recipients. The cumulative survival of patients with malignancies was significantly lower than that in recipients without cancer (8-year survival by 38% vs 70%; $P < .001$). The mean ($\pm$SD) time to diagnosis was 6 $\pm$ 3 years. Since 2004, the 12 recipients with malignancy who were switched to sirolimus at the time of diagnosis showed survivals that were not apparently better than those who remained on the established immunosuppression (46% vs 55%; $P = .71$).

Conclusions. The risk of neoplasm development was similar to that reported by other centers. Recipients of SPKT show higher incidence of cancer, though their overall survival is still significantly better than in those usually remaining on dialysis.

Organ transplant recipients are prone to develop a variety of neoplasms, that are only rarely diagnosed in the general population.[1] Overall, the incidence of cancer is three- to fourfold higher compared with an age-matched healthy population. The spectrum of tumors differs depending on type of transplantation.[2] The probability of developing neoplasm further increases with the length of follow-up; it may reach 55%–70% at 24 years after transplantation, as reported in an Australian study.[3] The impaired immune system clearly plays a key role in cancer pathogenesis, because it is responsible for detection and elimination of oncogenic cells. It is assumed that transformed cells escape from the control of the immune system, developing to a clinical malignancy.[4] Immunosuppressive drugs contribute to oncogenesis not only indirectly by suppression of immune cells, but also by direct effects promoting tumor invasiveness, as shown in studies with cyclosporine.[5] On the other hand, the new immunosuppressant sirolimus, which acts through the mammalian target of rapamycin (mTOR) pathway, may exert protective effects on cancer development in kidney allograft recipients.[6]

Because most of the data have come from populations of renal recipients, there is less information about tumor incidence in pancreas transplantation. Of importance may be the frequent use of induction therapy and the pretransplant history of diabetes, which represent independent risk

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factors for cancer development.[7] The aim of the present study was to retrospectively analyze de novo malignancies among simultaneous pancreas-kidney recipients to compare the survivals of patients and grafts with vs without malignancy and to determine major risk factors associated with de novo cancer. In a small subgroup we tested the effects of conversion to sirolimus at the time of cancer diagnosis.

METHODS

Study Design and Data Collection

This retrospective single-center analysis examined de novo malignancy prevalence after simultaneous kidney-pancreas transplantation in type 1 diabetes patients between 1985 and 2010. We evaluated the number and type of malignant tumors and time to cancer diagnosis. Patient and graft survival rates were analyzed in the group with cancer versus recipients without a malignancy. Some recipients with a malignancy were withdrawn from a calcineurin inhibitor and switched to sirolimus and steroids at the time of diagnosis. A subanalysis compared their survival with recipients, who were diagnosed malignancy and remained on their previous immunosuppressive therapy. Kidney graft failure was defined as a return to dialysis or death. Pancreas graft failure was defined as death, return to insulin therapy, or graftectomy. Data were obtained from the institutional transplantation registry, which was actualized twice a year, and from patient medical records.

Statistics

Survival curves were plotted according to Kaplan-Meier methods with differences between curves tested using the log-rank technique at a .05 level of significance. Numeric data were expressed as mean ± SD with differences tested using nonparametric methods. Categoric data were compared using χ^2 tests. A logistic regression model of analysis was used to evaluate possible influences of age at transplantation, immunosuppression, waiting list time, hepatitis B virus seropositivity, body mass index (BMI), gender, smoking, type 1 diabetes mellitus duration, number of acute rejection episodes, and treatment of these episodes. A back-step elimination algorithm was used to eliminate confounding factors at the significance level of .05.

RESULTS

Type of Malignancy and Their Prevalence

Since 1985, 23/360 recipients of simultaneous pancreas-kidney transplantation had a diagnosis of a malignant tumor. Nonmelanoma skin cancers, observed in 7 patients, were the most frequent type. Postransplantation lymphoproliferative disease (PTLD) was observed in 5 recipients. Lung adenocarcinoma, bladder carcinoma, and peritoneal carcinoma affected in 2 recipients in each case. Other neoplasms were rare, accounting for <0.5% in each category (Table 1). The median time to cancer diagnosis was 6 ± 3 years.

Table 1. Malignancy Prevalence in Simultaneous Pancreas and Kidney Transplant (SPKT) Recipients (n = 360) Between 1985 and 2010

	n	%
Any malignancy	25	6.2
Nonmelanoma skin cancer	7	1.9
Lymfoma	5	1.3
Lung adenocarcinoma	2	0.5
Bladder carcinoma	2	0.5
Peritoneal carcinoma	2	0.5
Merkel cell carcinoma	1	0.3
Stomach adenocarcinoma	1	0.3
Carcinoma of thyroid gland	1	0.3
Kidney carcinoma	1	0.3

Demographic Data and Patient and Graft Survival

Recipients with a malignancy were significantly older than the rest of the cohort (48 ± 7.5 vs 40 ± 8.9 y; P = .039). They had waited for transplantation a shorter time than the other patients. The mean waiting list times were 469 ± 384 versus 281 ± 197 days for recipients without versus with malignancy, respectively. The mean BMI did not differ between groups, and all of them had suffered from diabetes for similar times. The groups also did not differ in smoking or gender.

Almost 90% of recipients in both groups received induction treatment with polyclonal anti–T-lymphocyte antibodies. Recipients who did not developed malignancy had been significantly more frequently treated with tacrolimus (169/335 vs 7/25; P = .029). Between the group without versus with de novo malignancy, there were no differences in the number of patients treated with cyclosporine (158/335 vs 16/25), azathioprine (62/335 vs 5/25), sirolimus (73/335 vs 3/25; mycophenolate mofetil), (184/335 vs 16/25), or steroids (323/335 vs 24/25). In the group with malignancy we observed significantly more acute rejection episodes of either the pancreas or the kidney graft (8/25 vs 33/335; P < .001; Table 2).

Because there were significant differences in several factors between the groups, we analyzed the data using a logistic regression model. Of the factors listed in Table 2, age at the time of transplantation was identified to be significantly associated with an increased risk of malignancy (P = .012, likehood ratio 1.08, 95% CI 1.017–1.146).

The median survival of recipients with malignancy was 7.8 years, which was significantly worse compared with patients free of cancer (17 y; P > .001). Only 35% of patients with cancer were alive 7 years after transplantation compared with 78% of recipients without malignancy. Consequently, noncensored cumulative pancreas graft survival was significantly worse after 8 years: 47% with versus 63% without malignancy (P = .019). Cumulative kidney graft survivals were 46% and 74% after 7 years in recipients with versus without malignancy, respectively (P < .001).

At the time of malignancy diagnosis, we switched 12 recipients from calcineurin inhibitors to sirolimus and steroids. Another 11 patients remained on their established immunosuppression. The median survival times were 267 days versus 376 days, respectively (ns).