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Significant Risk Factors for Occurrence of Cancer After Renal Transplantation: A Single Center Cohort Study of 1265 Cases

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ABSTRACT

Occurrence of cancer after renal transplantation remains a major problem, and the second cause of death. We performed a retrospective analysis of first cancer, first skin cancer, and first organ cancer (including posttransplant lymphoproliferative disease [PTLD]) among 1265 cases from 1979 to 2006. The occurrence of cancer was clearly a time-dependent event justifiying the use of Kaplan-Meier survival and Cox regression methods. The 10-year cumulative incidences of first cancer, first skin cancer, and first organ cancer were 24.6%, 14.5%, and 14.5%, respectively. Recipient age was a major, independent risk factor for the 3 endpoints with a 6% increased relative risk for each year increment ($P < .0001$). Female gender was also a major, independent risk factor, but only for skin cancer ($P = .0002$). We could not demonstrate any difference between the immunosuppressive drugs used for induction or maintenance therapy, especially between antithymocyte globulin (ATG) vs anti-CD25, cyclosporine vs tacrolimus, and azathioprine vs mycophenolate mofetil. Large cohorts are needed with strict stratifications for recipient age and gender to detect any difference, if any, among the drugs.

OCCURRENCE OF CANCER after renal transplantation is a frequent event[1–5] in part related to immunosuppression and to viral infections/diseases. Currently, we use potent immunosuppressive drugs with a sharp decrease in acute rejection frequency to about 15% to 20%. The choice among the drugs should be guided by the balance between potency and adverse events including cancer.[2,3] In addition, cancer is the second cause of death, mainly organ cancers and posttransplant lymphoproliferative diseases (PTLD). The goal of this study was to establish the cumulative incidences of first cancer, first skin cancer, and first organ cancer, seeking to sort out the independent, significant risk factors for such occurrence.

MATERIALS AND METHODS

The Recipients

The retrospective and monocenter cohort included all 1265 cases performed at our center from March 1979 to December 2006: namely, 1070 first procedures, use of 1186 cadaveric donors, and overall 840 male recipients. Overall, recipient mean (SD) age and median age were 45.6 (13.5) and 47 years, respectively but clearly increasing in the recent decade. Induction treatment was used in only 644 cases (50.9%), with antithymocyte globulin (ATG) in 323, basiliximab in 193, daclizumab in 107, and OKT3 in 21. Maintenance therapy changed over time, namely, azathioprine-prednisone from 1979 to July 1984 (n = 108); cyclosporine-based from August 1984 to March 1996 (n = 798), and thereafter tacrolimus-based (n = 355). Only 4 recipients started on sirolimus with no calcineurin inhibitor (CNI). The second drug was azathioprine (AZA) in 741 subjects; mycophenolate mofetil (MMF) in 217; sirolimus in 32; malononitrilamide (MNA) in 8; and none in 267 cases. All recipients received prednisolone which was usually withdrawn at 18 months if no problem had occurred. The analyses were performed by an intention-to-treat method.

Endpoints

The primary endpoint was occurrence of the first cancer (date and type: skin vs organ vs PTLD). The secondary endpoints were occurrence of the first skin cancer (date and type: basal vs squamous vs melanoma vs Kaposi) and occurrence of the first organ cancer (including PTLD; date and organ involved).

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0041-1345/09/$–see front matter
doi:10.1016/j.transproceed.2008.12.013

Statistics

The occurrence of cancer is clearly a time-dependent event. We used appropriate statistical methods such as Kaplan-Meier (K-M) survival without the event and Cox regression analyses in both uni- and multivariate modes. Categorical covariates were analyzed by both K-M and Cox models, but continuous covariates could be tested only by Cox analysis.

RESULTS

Cancer Prevalence

Overall, 230 subjects experienced at least 1 cancer: 119 skin, 90 organ, and 21 PTLD. At current follow-up, we have observed overall 130 skin, 106 organ, and 23 PTLD cancers.

Cumulative Incidences of Cancer at 10 Years Posttransplantation

The 10-year cumulative incidences were 24.6%, 14.5%, and 14.5% for first cancer, first skin cancer, and first organ cancer (including 2.5% for PTLD), respectively. These percentages were lower for women compared with men, but only significant for skin cancer (8.2% vs 17.0%; $P = .002$ by Fisher Exact Test).

Recipient Age at Transplantation

Recipient age at the time of operation was a major, independent factor for occurrence of first cancer, first skin cancer, and first organ cancer (relative risk [RR] = 1.06 [1.05–1.08]; $P < .0001$ for all 3 endpoints). K-M survival without first cancer confirmed decreased survival with the following age categories: 16 to 39, 40 to 59, and ≥60 years.

Recipient Gender

Female gender was protective for first cancer (RR = 0.66 [0.49–0.88]; $P = .005$) and for first skin cancer (RR = 0.45 [0.29–0.68]; $P = .0002$) and in this case remained independent.

Induction Treatment

We were unable with a Cox model including recipient age and gender to demonstrate any increased role of induction therapy or its type. The cancer risk was similar for ATG vs anti-CD25 vs no induction.

Maintenance Treatment

We were unable to demonstrate any difference among various immunosuppressive treatments.

DISCUSSION

The 10-year cumulative incidence of first cancer was low at our center: 24.6%. This is much lower than that in sun-exposed countries like Australia, where the rate is >50%.[5] Finally, the incidence of skin cancer vs organ cancer (including PTLD) was similar in our study. The recent increase in prostate cancer may be due to systematic serum prostatic antigen determinations every year.

Recipient age was a major, independent risk factor[2,4,5] with an increased risk of 6% for each year increment in age at operation. This factor was so powerful that it precluded demonstration of any additional risk factor among induction and maintenance treatments. So in practice, the current cyclosporine- and tacrolimus-based treatments show the same cancer risk. We observed similar data for AZA vs MMF. Our experience with sirolimus is limited, thus precluding any support for a protective role which is still not firmly established in clinical practice.[2,3] In addition, we demonstrated that women were protected against skin cancer, but we have no good explanation for this observation. Usually, women expose themselves more to the sun, but they are also much more sun-protected on sun-exposed areas. It is well established that efficient sun protection decreases the number of squamous cell carcinomas.

The positive point of this study is that it represents a large monocentric experience. Large multicenter cohort studies need to be strictly analyzed by gender and by recipient age to note any difference among immunosuppressive protocols.[5]

REFERENCES

1. Penn I: Occurrence of cancers in immunosuppressed organ transplant recipients. Clin Transpl 147, 1998

2. Wimmer CD, Rentsch M, Crispin A, et al: The Janus face of immunosuppression—de novo malignancy after renal transplantation: the experience of the Transplantation Center Munich. Kidney Int 71:1271, 2007

3. Bosmans JL, Verpooten GA: Malignancy after kidney transplantation: still a challenge. Kidney Int 71:1197, 2007

4. Villeneuve PJ, Schaubel DE, Fenton SS, et al: Cancer incidence among Canadian kidney transplant recipients. Am J Transplant 7:941, 2007

5. Webster AC, Craig JC, Simpson JM, et al: Identifying high risk groups and quantifying absolute risk of cancer after kidney transplantation: a cohort study of 15,183 recipients. Am J Transplant 7:2140, 2007