The Role of Immunosuppression in Malignancies Among 351 Pediatric Renal Transplant Patients

L. Berardinelli, M. Raiteri, L. Ghio, P.G. Messa, and G. Montagnino

ABSTRACT

The incidence of de novo malignancies over a 38 year experience in 351 children ranging in age from 2 to 18 years was investigated among subjects prescribed various immunosuppressive protocols. There were 14 children (3.98%) who showed de novo malignancies, namely, 4.86 cancers for every 1000 graft-function years (GFYs). Among patients who had grafts functioning for >10 years, 7.4% suffered from cancer. Nine patients survive without a recurrence at a mean of 12.5 ± 6.6 years including 6 with graft function. Among group I who were treated with pre–calcineurin inhibitor (CNI) therapy 3 (3.8%) children (1 male and 2 females) developed a malignancy at a mean of 15.2 ± 11.9 years posttransplant (range, 7–35), for 4.65 cancers every 1000 GFYs. Two of them survive with functioning grafts. Among group II, who were treated by CNIs there were 273 children including 24 retransplants. Group II showed 11 malignancies (4.0%), for 5.04 malignancies for every 1000 GFYs. The incidence of cancer was similar in the 2 groups, undergoing different immunosuppressive regimens; however, the malignancies in the CNI- group were more precocious, compared with those of the conventionally-treated cohort.

RENAL transplantation is considered to be the best therapy for end-stage renal disease (ESRD), particularly for the pediatric population, for it is associated with better chances of growth and school attendance. The use of calcineurin inhibitors (CNIs) has offered considerable improvement in 1-year graft survival, but these powerful immunosuppressive drugs predispose the adult population to an increased risk of cancer.[1] There are few reports of malignancies among transplanted children[2,3] other than posttransplant lymphoproliferative diseases (PTLD), which represent the most common malignancies in the pediatric population, including more than 52% of all tumors.[4] The aim of this retrospective study was to analyze the incidence and characteristics of invasive malignancies among 351 children, who were transplanted between ages 2 and 18 years under different immunosuppressive treatments. The impact of a cancer on graft and patient survivals was also evaluated during the last 37 years.

PATIENTS AND METHODS

Over 2809 kidney transplantation operations performed between May 22, 1969, and December 31, 2008 include 351 performed in patients aged under 18 years. The greatest portion (86.0%) were from decreased donors (DDs). Only 36 had been transplanted with a living donor (LD) kidney. The first 78 children were treated with conventional therapy (prednisone and azathioprine), the latter 273 with calcineurin inhibitors (CNIs). Our pediatric population was grouped on the basis of the immunosuppressive therapy: before (group I) versus after (group II) the introduction of CNIs. We sought differences in risk factors for the onset of a malignancy other than a noninvasive skin cancer.

Group I, including 78 children, belonging to our early experience and treated with corticosteroids and azathioprine; had 65 (83.3%) DD kidneys with 2 en bloc, versus 13 (16.7%) from an LD. Group II was formed by 273 children treated with CNIs and, since 2000, by induction of anti–T-cell antibodies. We included 237 (86.8%) children received the kidney from a DD, 36 (13.2%) were from a related LD. There were 24 re-transplants (22 second and 2 third), 5 en bloc and 2 simultaneous kidney plus liver transplants.

This study considered only malignancies different from noninvasive skin cancers. Some risk factors, such as recipient age and gender, period of pretransplant dialysis, source of transplant (deceased donor or living donor), donor age, the incidence of malignancy and average time of onset of malignancy, follow-up

From the General Surgery and Kidney Transplantation Unit (L.B., M.R.), the Pediatric Nephrology Unit (L.G.), and the Nephrology and Dialysis Unit (P.G.M., G.M.), Policlinico University Hospital IRCCS, Milan, Italy.

Address reprint requests to L. Berardinelli, General Surgery and Kidney Transplantation Unit, Policlinico University Hospital IRCSS, Via Francesco Sforza, 35-20122, Milan, Italy. E-mail: luisa.berardinelli@unimi.it

0041-1345/10/$–see front matter
doi:10.1016/j.transproceed.2010.03.131

period, and impact of the malignancy on graft and patient survivals were investigated for both groups.

Reduction or withdrawal of immunosuppression was the therapeutic management after a diagnosis of cancer, with addition of chemotherapy as tailored to the individual patient's response, stipulated according to the prescription of the specialist.

Patients were followed from the time of transplantation until the last available visit, return to dialysis, graft nephrectomy, retransplantation, or death. Kaplan-Meier survival curves assessed patient and graft survivals, with differences calculated by the log-rank test. Moreover, the estimated incidence rates of cancer were calculated as the quotient of malignant disease incidence every 1000 years of graft function (GFY) separately for the 2 different protocols. $P < .05$ was accepted as significant.

RESULTS

A malignancy was detected among 14/351 (3.98%) children in our series, including 4 males and 10 females. It occurred at a mean of 9.1 ± 8.8 years (range, 0.6–35); the incidence rate was 4.86 malignancies for 1000 GFYs. Overall 7.4% of patients who had graft function for >10 years suffered a de novo malignancy. The data base, stratified into the 2 groups, evidenced some differences.

The incidence rate for children under conventional therapy (group I) was 4.65 malignancies for 1000 GFY versus 5.04 for children in group II, under CNI (P = NS). There were some differences in the onset time of cancer and the course of the disease. In the group I, 3 patients (3.8%; 1 male and 2 females), whose mean age at the procedure was 15.2 ± 2.6 years (range, 13–18), developed malignancies at a mean of 15.2 ± 11.9 years posttransplantation (range, 3–35). All children had received grafts from a DD. The first patient who received a graft at 18 years from a 28-year-old male DD developed an asymptomatic cancer in his right native kidney at 35 years there after, as detected by annual control sonography. Due to cardiac compromise, we performed a renal artery embolization into the kidney affected by cancer, to reduce the operative risks. He is still living with normal renal function (1.3 mg/dL) at 1.5 years after nephrectomy. The second child, a 13-year-old female recipient at transplantation is still living with normal graft function (1.1 mg./dL) at 22 years after the excision of multiple melanomas. The third patient, a 14-year-old child, died from lymphoma at 22 years and 4 months after her second transplant, which was well functioning at the time of her demise.

Among group II recipients 11 malignancies (4.0%) were treated in 3 males and 8 females of overall mean age at transplantation of 11.2 ± 5.5 years (range, 3–18). They developed de novo cancers at a mean of 7.4 ± 5.3 years postoperatively (range, 0.6–13). Among 36 transplantations using a LD, 2 children (5.5%) developed cancer; the other malignancies occurred among 9/237 (3.8%) patients transplanted with a DD kidney.

Between 1 and 10 years posttransplantation 4 cancers had an onset; the other 7 appeared between 11 and 13 years. The types of malignancies were malignant lymphoproliferative disease (n = 8; 2 cerebral lymphomas, 1 femoral lymphoma, 3 systemic lymphomas, 1 lymphatic leukemia, 1 myeloma), ovarian dysgerminoma (n = 1), Kaposi's sarcoma (n = 1), and renal cell carcinoma in the transplanted kidney (n = 1), which was evidence fortuitously by histologic findings of a graft, from a related LD requiring removal for chronic allograft nephropathy (CAN) at 8 years posttransplantation. All patients suffering from PTLD had been Epstein-Barr virus (EBV)-negative at the time of transplantation, but developed EBV primary infections there after. All PTLD patients' donors were EBV positive. Furthermore, before and/or after transplantation, all patients received a range of immunosuppressive drugs in addition to the baseline prophylactic regimen.[5]

As far as the outcomes are concerned, 2 children affected by cerebral lymphoma and 1 by acute lymphoblastic leukemia at diagnosed mean of 9.6 ± 4.5 years died with functioning grafts within a few months after the onset of the malignancy. The 3 children affected by ovarian dysgerminoma, Kaposi's disease, or myeloma lost their grafts after reduction or withdrawal of immunosuppressive treatment. A renal carcinoma was discovered at histologic examination of a graft, which was removed due to CAN. The child who lost graft function after the onset of myeloma died 3 months later due to that disease while on dialysis. The other 3 patients presently alive without a recurrence at a mean of 15.6 ± 3.8 from cancer onset years (range, 13–20). Four patients are alive with functioning grafts at 24, 17, 17, and (2 years after) transplantation and 13, 12, 3, and 1 year after the onset of the cancer without evidence of a recurrence.

DISCUSSION

The incidence of PTLD among patients under CNI treatment (2.93%) was similar to that reported in pediatric series, namely of 0.7–2.6%.[6–8] Cadaveric donor source, young age (<5 years), and male gender were not significant risk factors in our analysis, different from previously reported results.[9,10] Moreover, different from the results obtained in our center among patients of ≥50 years at transplantation, there was no significant increase in incidence among our pediatric kidney recipients despite the use of more potent immunosuppressive drugs.[11] In fact, the incidence of cancer was similar for recipients within our earlier experience of treatment with steroids and azathioprine, compared with recipients treated with CNIs. However, malignancies were more precocious in the CNI group, when compared with that of conventionally treated subjects, despite the fact that the CNI mean follow-up period was significantly shorter ($P < .0001$).

Caucasian race, recipient age <18 years, EBV seronegative recipients, cytomegalovirus infection, use of OKT3, tacrolimus, and administration of human pituitary growth hormone have all been implicated as risk factors for malignancy.[12] Better knowledge of risk factors for cancer, adoption of new drugs, and tailored modulation of immunosuppressive therapy may reduce the incidence of cancer in the future.

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