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Malignancies in 2753 Kidney Recipients Transplanted During a 39-Year Experience

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ABSTRACT

An increased development of malignancies has been related to modern potent antirejection drugs. The purpose of this retrospective study was to assess the incidence and risk factors for invasive malignancies among 2753 kidney recipients (KRs), who were transplanted in two periods within our 39-year experience; before (group I) versus after (group II) the introduction of calcineurin inhibitors (CNIs). In group I, formed by 703 KRs under conventional therapy, 45 (6.4%) patients developed a malignancy, while in group II, treated with CNIs, of over 2050 KRs, 182 (8.9%) developed a malignancy different from noninvasive skin cancer. The incidence of malignancies was higher in the group of patients treated with CNIs (8.9% vs 6.4%), despite the shorter follow-up period. Moreover, the malignancy was more precocious in the CNI group, namely a mean time of onset of 75 versus 154 months in the conventionally treated group. The older mean age of recipients in group II affected by malignancies (43.6 years vs 34.6 years of the group I) played a significant ($P < .001$) role when associated with the more powerful immunosuppressive effect of CNIs, while recipient gender, dialysis period, donor source, and retransplants seemed to have few effects on malignancy development. Recipients over 60 under CNIs showed a 21% incidence of malignancies.

CALCINEURIN INHIBITORS (CNIs) are associated with improved results and lower incidence of rejection among kidney transplant recipients (KTRs). However, one of the most dreaded side effects of these powerful drugs is an increased incidence of de novo malignancies. The aim of this study was to examine the incidence of malignancies as well as the impact of the cancer on graft and patient survivals in two periods within our 39-year experience including 2753 kidney recipients treated with different immunosuppressive drugs.

PATIENTS AND METHODS

We examined a series of 2753 KTRs, most of whom (87.6%) were engrafted from deceased donors between May 1969 and December 2007, with regard to the onset of malignancies other than noninvasive skin cancers. At the beginning of our activity, conventional therapy including steroids and azathioprine was prescribed for 703 patients (group I), including 78 children, 49 grafts from living donors, 6 en bloc cases, and 20 second transplantations. In the second period, since February 1983, we adopted CNIs (cyclosporine and tacrolimus) in 2050 KTRs (group II), including, 270 children, 293 living donor grafts 5 en bloc cases 3 horseshoe kidneys, 178 retransplants, and 24 simultaneous transplants of other organs.

The incidence of malignancies, recipient age and gender, period of dialysis, donor source (deceased donor or living donor), donor age, time of malignancy onset after transplantations and impact of malignancy on graft and patient survivals were separately considered in these two groups.

RESULTS

In our 39-year experience, we detected 227 (8.2%) malignancies other than noninvasive skin cancers. In group I, the follow-up period was 369.9 ± 46.2 months (range = 300–474 months). In this period, 45/703 patients (6.4%) developed an invasive malignancy at 3 to 275 months after transplantation. They included 30 male (66.7%) and 15 female patients of mean age 34.6 ± 8.6 years (range = 13–50 years); the mean donor age was 29.1 ± 11.0 years (range = 4–57 years). The graft came from a deceased donor in 42 cases and a living donor in three cases. The

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0041-1345/09/$–see front matter
doi:10.1016/j.transproceed.2009.03.032

incidence of malignancy, investigated on the basis of recipient age, was 2.6% in 79 children of ages 2 to 18 years; 7.1% in 604 patients aged 19 to 50 years; and 0% among 20 patients aged 51 to 60 years. The mean posttransplant time of onset of the malignancy was 136.8 ± 68.4 months (range = 3–275 months). The more frequent kinds of cancers were: hepatocarcinoma (22.2%), melanoma and metastatic skin cancer (11.1%); lymphoma, cancer of uterus, or native kidneys (6.6% each); prostate, Kaposi's sarcoma, stomach, colon, bladder cancer (4.4% each); lung, breast, native kidney, transplanted kidney (2.2%), and others (16.1%). Within the first posttransplant year, only one patient died from a lung cancer. Another 16 KTRs died from 2 to 30 years after transplantation, and eight lost their grafts as a consequence of de novo malignancy between 2 and 30 posttransplant years. Eleven patients with cancer died from causes different from their malignancy. Nine patients are still living with their well-functioning graft after immunosuppressive therapy reduction or withdrawal. No significant differences were observed in 658 patients under conventional therapy, who had no invasive malignancy, with regard to recipient age and gender, donor age, donor source, and retransplantations. The mean time on dialysis was longer for nonmalignancy patients (46.8 vs 29.9).

In group II, the follow-up period was 165.0 ± 85.5 months (range = 12–309 months); 182/2050 (8.9%) recipients treated with CNIs developed a cancer from 2 to 298 months after transplantation. They included 114 male and 68 female patients, mean age of 43.6 ± 13.8 years (range = 3–70 years). The source of their grafts in 155 cases was a deceased donor, and in 27 cases a living donor. The mean donor age was 39.4 ± 17.3 years (range = 0.1–76 years). The mean posttransplant time of onset of the malignancy was 73.5 ± 64.7 months (range = 2–227 months), which was significantly shorter than that of group I. Kaposi's sarcoma was the most frequent malignancy with a rate of 17.6%, followed by lymphoma (14.8%), lung cancer (6.6%), chest (6.8%), native kidneys (6.0%), melanoma and invasive skin cancer (4.4%), stomach (3.8%), hepatocarcinoma (2.7%), transplanted kidney (2.7%), prostate (2.7%), bladder (2.2%), and other various types of cancer (30.8%). No significant differences were observed in 1868 patients under CNI therapy, who had no invasive malignancy, with regard to recipient gender, months under dialysis, donor age, donor source, and retransplants. The patients who had no invasive malignancy were younger than those with malignancies (37.0 vs 43.6 years; $P < .05$). The incidence of malignancy was also investigated on the basis of the recipient age: 262 children aged 2 to 18 years had 4.2%, incidence of malignancy while 1361 patients aged 19 to 50 years showed an incidence of 8.2%; and 361 patients aged 51 to 60 years had a 12.5% rate of invasive malignancy, and 66 patients over 60 years showed an incidence of 21.2%. Within the first posttransplant year, two patients died from Kaposi's sarcoma. The other 76 KTRs died from malignancies from 12 to 265 months. Moreover, 36 patients lost their grafts as a consequence of malignancy or immunosuppression withdrawal in a lapse of time ranging from 1 and 20 years posttransplantation. Ninety seven patients are still living, 59 of them with well-functioning grafts and 38 on dialysis; five patients were lost to follow-up after 6 to 12 years. At 3 months, 6 months, and 1, 2, 3, 4, and 10 years, cancer patient survivals in the CNI therapy group were 100%, 98%, 96%, 93%, 90%, 87%, and 76% versus 99%, 98%, 98%, 97%, 97%, 96%, 93% in the CNI therapy group without cancer, while graft survival was 98%, 96%, 92%, 89%, 84%, 79%, and 62% in the CNI therapy group with cancer versus 92%, 91%, 90%, 88%, 85%, 82%, and 70% at the same time points in the group of CNI therapy without cancer.

DISCUSSION

De novo malignancy is becoming increasingly recognized as a major cause of morbidity, graft failure, and mortality among transplant patients. It may reflect not only the longer observation period due to improved graft and patient survival, the better diagnostic techniques, the better control of cardiovascular and infective diseases, but also the greater recipient age and treatment with excessive immunosuppression.[1]

In our experience, the incidence of malignancies was higher among the group of patients treated with CNIs when compared to those prescribed conventional therapy (8.9% vs 6.4%), despite the fact that the mean follow-up period was significantly ($P < .0001$) shorter in the CNI group (165.0 vs 369.9 months). Moreover, the malignancy was much more precocious in the CNI group, when compared with conventionally treated subjects, namely mean time of onset of 73.5 vs 136.8 months ($P < .001$). The older recipient age associated with the more powerful immunosuppressive effect of CNIs may have determined this effect, while recipient gender, donor source, longer period under dialysis, and retransplants seemed to have little impact on malignancy development. As far as the various kinds of cancer are concerned, some malignancies, such as Kaposi's sarcoma and lymphoma, appear to be strictly connected with CNI therapy.

Minimization of immunosuppression, early detection of malignancies, identification of patients at risk for cancer, prevention, and use of new drugs represent the future challenges of transplantation.

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