

The Incidence of Cancer and Potential Role of Sirolimus Immunosuppression Conversion on Mortality Among a Single-Center Renal Transplantation Cohort of 1,816 Patients

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ABSTRACT

Introduction. The chronic use of immunosuppressive drugs in renal transplant recipients increases the risk of developing de novo malignancies. Herein we analyze the incidence of de novo tumors and the potential role of sirolimus to improve cancer-specific survival among a cohort at a single center.

Methods. This retrospective analysis of our 1,816 patients allografted between January 1983 and December 2009 sought subjects who developed de novo tumors. Epidemiological and clinical data were examined using Mann-Whitney and Pearson's chi-square or Fisher exact tests for statistical comparisons of continuous and categorical variables, respectively. Kaplan-Meier survival curves were used to determine cancer-specific survival according to type of neoplasia and immunosuppressive regimen, namely, conversion to sirolimus.

Results. One hundred patients (5.5%) were diagnosed with a de novo malignancy. The 110 different cancers were diagnosed at a median interval of 73 months after kidney transplantation. The overall cancer-specific survivals at 1 and 5 years after cancer diagnosis were 87.0% and 76.9%, respectively. The 15 patients converted to sirolimus showed no difference in survival.

Conclusion. The observed frequencies of cancer in our center are consistent with the literature. Among our cohort, sirolimus did not significantly impact survival among subjects who had de novo malignancies.

THE QUALITY of life and survival rates for end-stage renal disease patients who are on dialysis are improved after successful kidney transplantation. However, de novo malignancies after kidney transplantation have become a major concern in recent years.¹ Cancer-specific mortality among renal transplant recipients is not negligible. In fact, in the next 20 years, cancer is expected to be one of the most important causes of death among this group of patients.² Several factors have been associated with the increased incidence of de novo malignancies among transplant recipients, namely sun exposure,³ extent and duration of immunosuppression,^{4,5} concomitant viral infection,⁶ and longer pretransplantation dialysis periods.⁷ Among the risk factors associated with de novo malignancies in this setting, the advanced age of the transplanted population and the long-term immunosuppressive therapy are important contributors to an increased number of malignancies.⁸

The management of the immunosuppressive regimen in recipients who have de novo cancer after transplantation is

complex and difficult. Dose reduction or withdrawal of immunosuppression seeks to recover the recipient's defective immune system; however, it may be detrimental to graft function and survival. Ideally, the immunosuppressive regimen should not be a risk factor for cancer development. To address this concern, sirolimus, a macrocyclic lactone, has shown interesting properties. After many trials in animal models,⁹ conversion from cyclosporine to sirolimus in human renal transplant recipients who have cancer has resulted in complete regression of posttransplant Kaposi's sarcoma¹⁰ and lymphoproliferative diseases¹¹ while maintaining graft

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Table 1. Epidemiological, Clinical Characteristics and Cancer-Specific Survival of Renal Transplant Patients With de Novo Malignancy According to Type of Neoplasm

Characteristic	Cutaneous	Hematological	Gynecological	Gastrointestinal	Urological	Miscellaneous	Overall
Male/female	31/11	9/2	0/17	10/5	11/2	3/4	61/39
Age at renal transplantation (y)	45.5 (38–54.75)	37 (33.5–44)	39 (30–52)	51 (46–55.5)	47 (41–56)	49 (35–53)	44 (36.75–54)
Duration of dialysis until transplantation (mo)	44 (27–72)	30 (16–36)	45 (31–66)	40 (25.5–55.5)	30 (16.5–54)	36 (9.5–80)	41 (19–68)
Time interval of tumor development after transplantation (mo)	73.5 (28–131.75)	125 (72–155.5)	42 (11–76)	103 (50–125.5)	105 (40–137)	43 (23.5–60.5)	73 (28–127)
Cancer-specific survival at 1-/5-years after cancer diagnosis (%)	97.8/95.5	81.8/54.5	94.1/78.4	42.9/42.9	84.6/67.7	100/53.3	87.0/76.9

function. Therefore, switching from cyclosporine to sirolimus may have a potential role to treat malignancy in transplanted patients without increasing the risk of graft rejection.

These malignancies can have three sources: transfer from the donor, recurrence of a pre-existent malignancy, and de novo.^{12–14} However, in this setting, the majority are de novo malignancies.^{12–14} Some cancers are markedly increased in solid organ transplant recipients: in particular, skin cancer, non-Hodgkin's and Hodgkin's lymphoma, Kaposi's sarcoma, anogenital cancer, renal cell carcinoma, hepatocellular carcinoma, and some sarcomas.^{15–21} In contrast, the incidence of the most common solid tumors in the general population—lung, prostate, colorectal, breast—is only modestly increased.^{15–21} Thus, it is essential not only to carefully screen the patient and donor before transplantation, but also to prevent posttransplant malignancies with general preventive measures. Therefore, excessive immunosuppression should be avoided and the best immunosuppressive regimen chosen.^{22,23} This article reports the incidence of de novo malignancies among renal transplant recipients in a single transplantation center and assesses the impact on survival of changing the immunosuppressive regimen by the introduction of sirolimus.

METHODS

This retrospective analysis of all 1,816 patients undergoing renal transplantation between January 1983 and December 2009 was performed using our prospective database and approved by the Institutional Review Board. We analyzed subjects developing de novo cancers under immunosuppression. We excluded patients

with a pretransplantation diagnosis of cancer and those for whom donor-transmitted cancer was suspected.

The collected data included: patient age at transplantation, gender, duration of pretransplantation dialysis, donor type, immunosuppressive regimen, time to de novo tumor development, tumor type, treatment, and follow-up.

After diagnosing a de novo tumor, the usual procedure until 2003, was reduction in immunosuppression; thereafter, newly diagnosed patients were converted from a calcineurin inhibitor to a sirolimus regimen.

Follow-up visits were performed monthly. Screening for malignancy included annual abdominal ultrasound (including native kidneys and renal graft) as well as a dermatologic examination, in addition to procedures universally recommended for the general population.

The follow-up was defined as the time that had elapsed from transplantation to cancer-related death, death unrelated to cancer, or last visit with no evidence of de novo malignancy with a functioning allograft.

Continuous variables are reported as median values and interquartile range (IQR); categorical variables, as the number of occurrences (*n*) and their frequency (%). Mann-Whitney and Pearson's chi-square or Fisher exact tests were used for statistical comparisons of continuous and categorical variables, respectively. Kaplan-Meier survival curves were plotted to determine cancer-specific survival according to type of cancer and immunosuppressive regimen (conversion or not to sirolimus). All tests were two-sided with a significance level set at 0.05. Statistical analysis was performed using MedCalc v.11.1.1.0 (MedCalc Software bvba, Mariakerke, Belgium).

RESULTS

Among the 1,816 renal transplant recipients, 100 (5.5%) subjects were diagnosed with 110 different de novo neo-

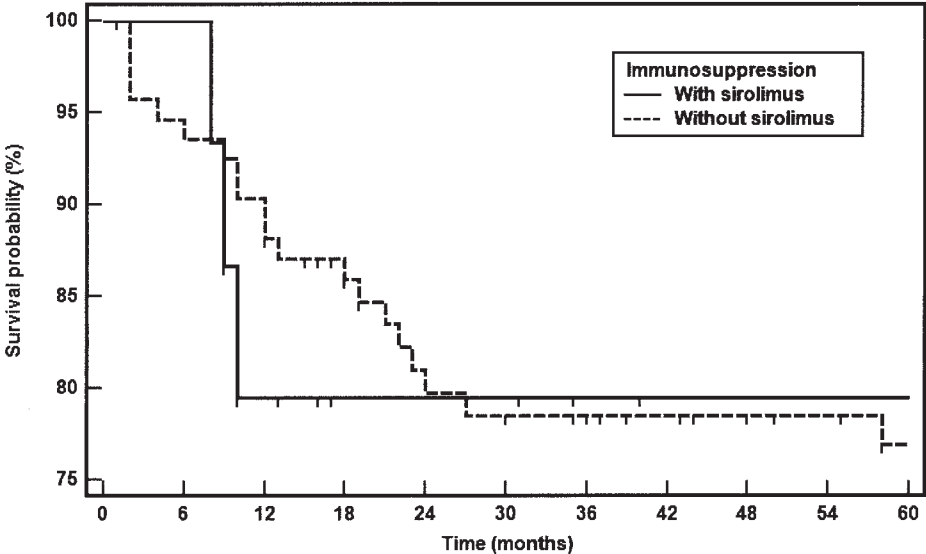
Table 2. Epidemiological, Clinical Characteristics and Cancer-Specific Survival of Renal Transplant Patients With de Novo Malignancy According to Immunosuppression Regimen (With or Without Conversion)

Characteristics	Conversion to Sirolimus	No Conversion to Sirolimus	P Value
Male/female	8/7	53/32	.57*
Age at renal transplantation (y)	41 (34.5–49.5)	46 (37–55)	.26†
Duration of dialysis until transplantation (mo)	30 (16–57)	41.5 (23.5–73.5)	.29†
Time interval of tumor development after transplantation (mo)	114 (50–125.5)	66.5 (25–128)	.24†
Cancer-specific survival at 1-/5-years after cancer diagnosis (%)	79.4/79.4	88.2/76.9	.84‡

*Fisher's exact test.

†Mann-Whitney test.

‡Chi-square test.



Number at risk											
Group: With sirolimus											
15	15	10	7	7	7	5	4	4	4	4	4
Group: Without sirolimus											
95	87	80	72	64	61	59	57	53	52	49	49

Fig 1. Cancer-specific survival curves according to immunosuppression regimen.

plasms which were identified at a median time from transplantation of 73 months (IQR 28–127). Only two patients received a living donor organ. **Table 1** shows the general features of the renal transplant recipients with de novo malignancy according to type of neoplasm. Sixty-one patients were male; the overall median age at renal transplantation was 44 years (IQR 36.75–54), the median duration of

dialysis until transplantation was 41 months (IQR 19–68), and the overall cancer-specific survival at 1 and 5 years after cancer diagnosis was 87.0% and 76.9%, respectively. Forty-two patients received antithymocyte globulin induction therapy. Maintenance immunosuppression consisted of cyclosporine + prednisolone (n = 57), cyclosporine + azathioprine + prednisolone (n = 24), cyclosporine + mycophenolate

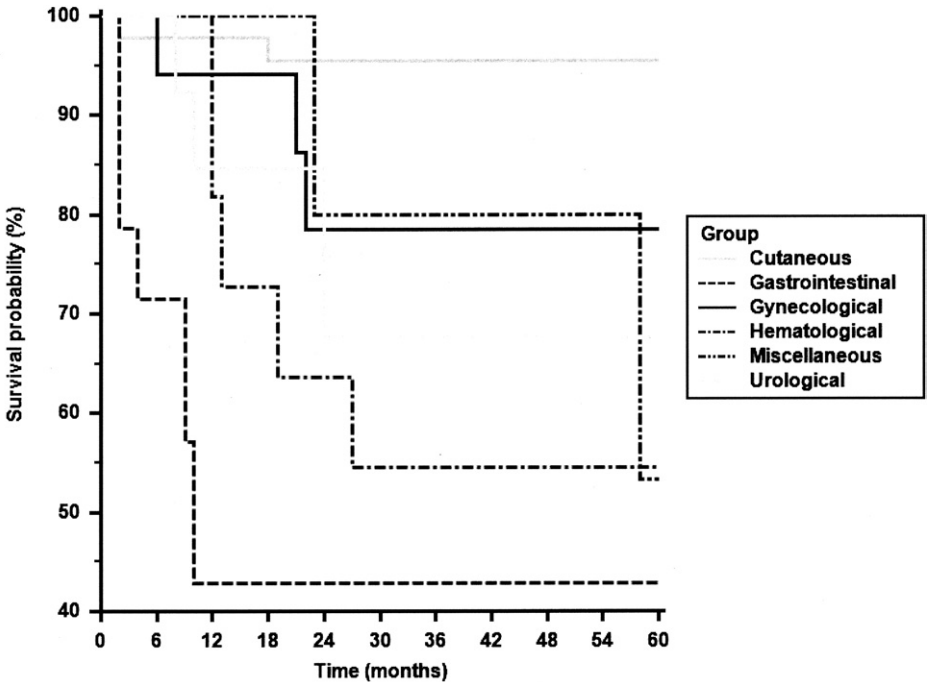


Fig 2. Cancer-specific survival curves according to tumor type.

mofetil + prednisolone (n = 12), tacrolimus + mycophenolate mofetil + prednisolone (n = 6) and isolated tacrolimus (n = 1).

Fifteen patients who had de novo malignancies were converted to sirolimus. No statistically relevant differences were observed concerning clinical characteristics or tumor-specific survival between patients converted or not to sirolimus (Table 2). Table 3 depicts the distribution of cancer types and mortality according to immunosuppression regimen. The cancer-specific survival curves according to immunosuppressive regimen and tumor type are shown in Figures 1 and 2.

DISCUSSION

In our cohort, the global incidence of 5.5% (100 patients who developed 110 de novo malignancies) is consistent with the literature.¹⁸ The relative frequency of de novo malignancies was also similar to previous studies, with a significant predominance of cutaneous (melanoma and non-melanoma) neoplasms; whereas other malignancies, such as colorectal, prostate, and stomach cancer, showed only slight increases.^{18,24–26}

Regarding cancer-specific survival, no significant differences were noted between sirolimus conversion or no-

sirolimus regimens. Because sirolimus was only recently introduced in our clinical practice, our cohort exhibits a shorter follow-up for the this regimen. Also, the number of patients who have de novo malignancies under immunosuppressive regimens with sirolimus was smaller (although every recent patient with de novo malignancy has been converted to a sirolimus immunosuppressive regimen) which limits the comparisons and may justify the lack of a significant difference in survival. Comparing the two groups according to immunosuppressive regimen, potentially more aggressive tumors in the sirolimus group could account for the lack of survival benefit. Gastrointestinal tumors have a dismal prognosis, whereas cutaneous neoplasms show the best survival. Finally, the pattern of initial immunosuppression and its heterogeneity in patients who develop de novo cancers may have important roles influencing the survival of these patients.

Sirolimus displays a different immunosuppressive mechanism from cyclosporine. It complexes with FK binding protein complex 12, thereafter binding with high affinity to the mammalian target of rapamycin. Conversion from cyclosporine to sirolimus in renal allograft patients who have de novo Kaposi's sarcoma¹⁰ or de novo lymphoproliferative disease¹¹ was associated with regression of the

Table 3. Distribution of Cancer Types and Number of Deaths According to Immunosuppression Regimen (With or Without Conversion to Sirolimus)

Type of Cancer	N	%	Conversion to Sirolimus		No Conversion to Sirolimus		P Value*
			Total	Deceased	Total	Deceased	
Skin BCC	18	16.4	—	—	18	—	1
Skin SCC	18	16.4	1	—	17	1	
Melanoma	1	0.9	—	—	1	1	
Kaposi sarcoma	6	5.5	2	—	4	—	
Other skin cancer	3	2.7	—	—	3	—	
NHL	9	8.2	2	—	7	4	0.45
Hodgkin lymphoma	2	1.8	—	—	2	1	
Breast	7	6.4	1	—	6	2	1
Ovary	2	1.8	—	—	2	1	
Cervix	3	2.7	1	—	2	—	
Vulva	6	5.5	—	—	6	—	
Stomach	6	5.5	2	1	4	2	1
Duodenum	1	0.9	—	—	1	—	
Colon	5	4.5	2	1	3	1	
Liver	3	2.7	—	—	3	3	
Kidney	6	5.5	2	—	4	—	1
Urothelium	3	2.7	1	1	2	1	
Prostate	4	3.6	—	—	4	1	
Lung	1	0.9	—	—	1	1	1
Soft tissue sarcoma	1	0.9	—	—	1	1	
Mouth	1	0.9	—	—	1	—	
Parotid gland	1	0.9	—	—	1	—	
Thyroid	3	2.7	1	—	2	—	
	110	100	15	3	95	20	1

BCC, basal cell carcinoma; SCC, squamous cell carcinoma; NHL, Non-Hodgkins lymphoma.

*Fisher's exact test.

malignancy with a survival benefit. In a single-center study of 1,008 renal transplants followed up for 5 years, a combination regimen of sirolimus plus corticosteroid resulted in a reduction in the incidence of non-melanoma skin cancers as well as of native renal cell carcinoma.²⁷ However, sirolimus has its own set of side effects, such as dyslipidemia, bone marrow suppression, reduced or delayed wound healing, decreased insulin sensitivity, and impaired male fertility²⁸; additionally, grafts can leak more proteins when treated with sirolimus.²⁹ Furthermore, the use of a de novo sirolimus-based, calcineurin inhibitor-free regimen has a distinct learning curve, requiring appreciation of these side effects, patient education, and careful monitoring of blood levels. In a large, primarily European, multicenter trial, a low-dose sirolimus regimen yielded worse outcomes owing to an excess acute rejection rate.³⁰

Thus, it is important to have data that properly assess the safety and advantage of preventing and even treating de novo malignancies after transplantation with sirolimus, to balance the difficult side effect profile.

We acknowledge some limitations in our study: the small number of patients, its retrospective nature, varying follow-up intervals, heterogeneity of neoplasms, and tumor behavior, as well as variable immunosuppression limits our ability to draw conclusions. Nevertheless, our study provides additional data in a large cohort of transplant patients. Previous reports suffer from the same limitations. Therefore, it is important to have powerful data with larger series (which are still lacking in the literature). It is of paramount importance to conduct randomized clinical trials to elucidate the best immunosuppressive regimen with the lowest risk of developing de novo cancer, and with fewer side effects.

It is strictly important to have evidence-based data to know if differences among immunosuppressive drugs in carcinogenic activity are clinically relevant in terms of survival; if the immunosuppressive therapy should be adapted to pretransplant malignancy risk; and, lastly, what is the best approach to manage the immunosuppressive regimen after a renal recipient develops a de novo malignancy.

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