De Novo Cancer Incidence and Prognosis After Kidney Transplantation: A Single Center Analysis

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ABSTRACT

Background. Malignancy is an important cause of mortality in renal transplants recipients. The aim of this study was to evaluate the incidence, prognosis, and survival of patients developing a de novo post-transplant cancer.

Methods. Using a retrospective cohort design, we evaluated the incidence of de novo cancers among kidney transplants patients in our hospital from January 2000 to December 2012. We also evaluated the patient survival after tumor diagnosis.

Results. We included 535 kidney transplants recipients with a mean follow-up of 7.8 years; among them, 39 (7.2%) developed malignancies. Median time from transplant to cancer diagnosis was 3 years, with a median age at diagnosis of 60 years. Male patients were significantly older at time of cancer diagnosis (68.5 years) compared with women (38 years, $P < .05$), and cancer diagnosis occurred significantly earlier in men (3.5 years since transplantation) than in women (8.5 years, $P < .05$). Among 39 patients affected by a de novo post-transplant cancer, 18 patients (46.2%) died, with an average age at death of 58.5 years. The average time from cancer diagnosis to death was 1.5 years. Among the group of patients who did not develop a post-transplant cancer, 83 patients (16.7%) died, with a median age at time of death of 54.5 years ($P < .05$).

Conclusions. Kidney transplant recipients are at higher risk of developing a post-transplant cancer. Prognosis after cancer diagnosis is poor, probably as a consequence of a more aggressive behavior of cancer in transplant recipients. Intensive screening protocols could allow for an earlier diagnosis thereby improving the long-term outcome of these patients.

KIDNEY transplantation is the preferred treatment of end-stage renal disease, since it is associated with an overall improved quality of life and patient survival [1]. Advances in surgical procedures and clinical care of transplanted patients have led to an increase in survival rates, but there is an increasing evidence of a higher incidence and prevalence of infectious and neoplastic complications in patients undergoing transplantation, mostly caused by immunosuppressive therapy, essential for the success of the allograft and for the patient's own survival [1].Immunosuppression allowed for a significant reduction of the incidence of acute rejection in transplant recipients but, on the other hand, chronic administration of an immunosuppressive therapy has side effects that may

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compromise the health of the patient himself. The toxicity of this therapy is linked not only to its chronic administration, but also, and above all, to the induced immunosuppression, which if it is essential to reduce the risk of graft rejection, also exposes patients to an increased risk of developing a de novo cancer after transplantation [2].

Cancer is the third most common cause of death (after cardiovascular diseases and infections) for patients who underwent a transplant [3-7]. However, the most common neoplastic disorders in the general population, such as lung, breast, prostate, colon, and cervical carcinomas, do not appear to have a higher incidence in transplanted patients than in the general population of the same age and sex, in which these diseases are widely represented [5,6,8]. In contrast, the cancers most frequently reported in transplanted patients are often associated with oncogenic viruses infections, such as human papillomavirus, Epstein-Barr virus, and human herpesvirus 8 [8,9], and are less common tumors in the general population [5-8].

Although the higher incidence of de novo cancer in kidney transplant recipients is well documented in literature, few studies investigated the prognosis and mortality of these patients [10-12].

In this single center analysis, using a retrospective cohort study design, we have evaluated the incidence, prognosis, and survival of patients developing a de novo cancer after transplantation.

PATIENTS AND METHODS

Post-transplant de novo cancer incidence was evaluated in a population of consecutive kidney transplantations performed at a single institution between January 2000 and December 2012. Owing to the low expected cancer-related mortality, skin cancer (including melanoma), were excluded from this analysis.

All transplant candidates underwent a careful screening including total body computed tomography angiography, mammography, and colonoscopy, and serum oncologic markers. Patients were scheduled for kidney transplantation only after negative cancer screening or, in case of solid cancer detected during the screening, after at least 3 to 5 years of the disease-free period.

Post-transplant screening included yearly mammography, breast sonography, serum oncological markers evaluation, fecal occult blood test, and in patients older than 50 years, a colonoscopy every 5 years. Patients were followed according to a standardized protocol.

All patients underwent a standardized 3-drug immunosuppressive protocol, with or without induction therapy with anti-interleukin-2 receptor antibodies (Simulect, Novartis, Basel, Switzerland) or with antithymocyte globulin (ATG-Fresenius, Fresenius, Bad Homburg, Germany), basing on both donor and recipient characteristics, as previously described [13].

Statistical Analysis

Statistical analysis was performed using the SPSS software (version 21.0, SPSS, Chicago, IL). Descriptive results are expressed as percentage or as mean (± standard deviation [SD]). Bivariate analyses were performed using χ^2 test for dichotomous or categorical variables, and Student *t* test for continuous variables, where applicable. All statistical tests were two-sided, and P values $< .05$ were considered statistically significant. The contribution of every patient enrolled in the study in terms of observation time (overall follow-up) was defined calculating the interval between the 30th day after the transplantation and the date of the last observation (end date of the study or date of the outcome). In case of patients undergoing organ retransplantation, the interval between the 30th day from the first transplant and the last useful date relative to the last transplant was considered as the risk period. The date of the last follow-up for patients in whom the event has been reported coincides with the date of re-entry into dialysis. For the retransplanted ones, the date of the last re-entry into dialysis was considered as the last follow-up day. The period at risk of developing a specific type of tumor has been calculated consequently from the 30th day after the transplant up to the date of the possible diagnosis of that type of neoplasm, rather than the last follow-up or death. It must be specified that every patient, after a diagnosis of cancer, stops to contribute to the determination of the onset time for that specific tumor form, but continues to contribute to the observation time for all the other neoplasms. For the whole cohort the sum of the individual contributions by the individual patients, expressed in person-years (PYs), was considered. This measure was then used in the calculations of incidence. To compare neoplastic risk in patients undergoing organ transplantation with that of the Italian population of the same age and sex, area of living and specific period, standardized incidence rates (Standardized Incidence Rates, SIR) were used. SIR was obtained by dividing the number of observed tumor cases (all tumors) by the number of cases expected in the general population using the incidence estimates provided by the Registri Italiani di Patologia belonging to the Associazione Italiana Registri Tumori (AIRTUM).

RESULTS

Clinical characteristics of the 535 patients considered in this analysis are listed in Table 1. Mean follow-up was 7.8 years (range, 6-17.8 years).

Most recipients were men, with a median age of 48 years and received the kidney from a deceased donor. Most transplant recipients received a long-term pre-transplant dialysis and were under tacrolimus-based immunosuppression.

A total of 39 patients (7.2%), 33 men and 6 women with a median age of 60 ±12.3 years, developed 39 de novo post-transplant tumors, with a total incidence of 7.2 cases/10^3PY.Specifically, 28 solid tumors, 2 post-transplantation lymphoproliferative disorders, and 9 Kaposi's sarcomas were diagnosed (Table 2). Cancer incidence was higher in men than in women: 9.6 cases/10^3PY in men compared with 3.1/10^3PY cases in women. In the cohort of transplanted patients, 39 tumors were diagnosed. Dividing the number of cases observed with that of the expected cases (23, number obtained from Italian Cancer Registries), a SIR of 1.69 was obtained, therefore transplanted patients have a 1.69-fold higher risk than the general population of developing any tumor.For those developing a de novo post-transplant cancer, the median time between the 30th post-transplant day and the date of the first cancer diagnosis was 3 years, with a median age at diagnosis of 60 years. Male patients were significantly older at the time of cancer diagnosis (68.5

Table 1. Clinical Characteristics of the Study Cohort (535 Patients)

	Clinical Characteristics
Male (n, %)	342 (48)
Living/Deceased (n)	103/432
Age (y; mean ± SD)	48 ± 22.3
Cause of ESRD (n, %)	
Glomerulonephritis	325 (60.8)
Polycystic kidney disease	91 (17)
Diabetes mellitus	26 (4.9)
Other causes (interstitial nephritis, congenital disorders, …)	84 (17.3)
Waiting list (mo; mean ± SD)	21 ± 10.4
Pretransplant dialysis (mo; mean ± SD)	32 ± 16.3
Donor age (y; mean ± SD)	55.6 ± 15.1
Immunosuppression (n, %)	
Induction	155 (28.9)
TAC+MPA+Ster	444 (83)
CYA+MPA+Ster	60 (11.2)
EVE+MPA+Ster	31 (5.8)
BMI (kg/m^2; mean ± SD)	25 ± 4.7

BMI, body mass index; CYA, cyclosporine; ESRD, end-stage renal disease; EVE, everolimus; MPA, micopenolic acid; SD, standard deviation; Ster, steroids; TAC, tacrolimus.

years) compared with women (38 years, $P < .05$), and cancer diagnosis occurred significantly earlier in men (3.5 years since transplantation) than in women (8.5 years, $P < .05$), suggesting a significant higher risk of cancer in male recipients compared with female recipients, where there was a lower incidence and a later diagnosis.

Table 2. Incidence of Every Type of Tumor in the Study Population

	All	Incidence	M	Incidence	F	Incidence
Cancer Type (ICD-10)	Obs.	%	Obs.	%	Obs.	%
Solid Tumors						
Kidney (C64)	5	13.0%	5	15.1%		
Lung-Windpipe (C33-C34)	6	15.3%	6	18.1%		
Prostate gland (C61)	1	2.5%	1	3.0%		
Breast (50)	2	5.1%	1	3.0%	1	17.0%
Big intestine (C18)	2	5.1%	2	6.0%		
Bladder (C67)	1	2.5%	1	3.0%		
Stomach (C16)	1	2.5%	1	3.0%		
Thyroid gland (C73)	2	5.1%	2	6.0%		
Mesothelioma (C38-C45))	2	5.1%	2	6.0%		
Testis (C62)	1	2.5%	1	3.0%		
Penis (C60)	1	2.5%	1	3.0%		
CNS (C70-C72)	3	7.7%	1	3.0%	2	33.0%
Salivar glands (C07-C08)	1	2.5%	1	3.0%		
KS	9	23.0%	6	18.1%		50.0%
PTLD	2	5.1%	2	6.0%		

F, female; KS, Kaposi Sarcoma; M, male; Obs, observed; PTLD, post-transplant lymphoproliferative disorder.

Table 2 showed that Kaposi sarcoma was the most frequent neoplasia observed(23%), mostly developing during the first 2 years after transplantation, whereas a solid organ cancer developed in 28 patients.

In order to evaluate and estimate the survival rates in graft recipients in whom a de novo post- transplant cancer occurred, and to compare their life expectancy to that of transplanted patients not affected by any malignancies, additional analyses were performed taking into account time since transplantation to death and average age at death of every deceased patients. Among 39 patients affected by a de novo post-transplant cancer, 18 patients (46.2%) died, with an average age at death of 58.5 years. The average time from cancer diagnosis to death was 1.5 years. Among the group of patients who did not develop a post-transplant cancer, 83 patients (16.7%) died, with a median age at time of death of 54.5 years ($P < .05$).In both groups of patients, the median time from transplant to death was 4 years and the median time from cancer diagnosis to death, among all the deceased patients affected by malignancies, was 1.5 years, suggesting a more aggressive behavior of cancer in the transplant population.

DISCUSSION

This study demonstrated that kidney transplant recipients are at higher risk of developing a de novo post-transplant cancer. Approximately 7% of transplanted patients developed a tumor within 10 years since transplantation, showing as de novo cancer is a rather frequent complication in kidney transplant recipients, with a risk 1.6-fold higher than in the general population.

This increased risk is lower than the one reported by international studies conducted on transplanted patients [14-16], in which risk of de novo cancer in graft recipients compared with that in the general population is from 3- to 6-fold higher.The exclusion of cases of nonmelanoma skin cancer in this study largely explains this difference. In fact, in other studies not considering nonmelanoma skin tumors, the SIR of the neoplastic risk for all tumors is reduced to about 2- to 3-fold [14,16], and this is more consistent with data showed in this study. Our results even show that risk is not the same for all neoplasms, but it is particularly higher for specific tumor forms associated with viral infections such as Kaposi Sarcoma or post-transplantation lymphoproliferative disorder, and for those associated with the presence of specific risk factors such as renal tumors.

Renal cancer was the most frequently diagnosed de novo post-transplant cancer in our series, confirming the recent data of other international studies [6,14,17,18].

Polycystic kidney disease is an important risk factor for renal neoplasms, because this pathology, which can arise and/or progress even after transplantation, causes accumulation of toxic substances in nephrons. In addition, cysts cells can release growth factors responsible for the increase of cell proliferation and neoplastic progression,

although this risk seems not significantly increased after transplantation [13,19,20].

This study demonstrated that male recipients are more likely to develop a post-transplant cancer, and this could influence the long-term outcome of such patients. Prognosis in kidney transplant recipients developing a de novo post-transplant cancer is poorly investigated. In a recent study, Pendón-Ruiz de Mier et al [12] reported that the mean survival time from the diagnosis of cancer was 2.09 years, whereas in a previous study the same group [11] reported similar graft and patient survival among kidney-transplant recipients developing a cancer after transplantation compared with recipients without cancer. More recently, Benoni et al [10] demonstrated that kidney transplant recipients with a post-transplant cancer had a worse survival compared with nontransplant patients with cancer.

Our study confirmed these observations: cancer diagnosis significantly affected post-transplant survival, and patient survival after diagnosis of a post-transplant cancer is only 1.5 years.

However, if a post-transplant cancer negatively affects recipient's survival rates (almost 50% of patients in whom de novo cancer occurred died) and therefore represents an important mortality risk factor, on the other hand, the average age at death is higher for this group of patients rather than for those ones in whom a de novo cancer has not developed.

Further analyses should be conducted in order to explain the reasons leading to this phenomenon. Perhaps a higher incidence of tumors in older patients than in younger ones could justify why the average age of death of patients with de novo cancer is higher than that of patients in whom the event did not occur. Moreover, an earlier onset of cardiovascular diseases, which could complicate prognosis of graft recipients leading them to death precociously, could be an explanation of this result.Although this study presents some important findings, we are conscious of its limitations: the study sample is relatively small; however, this is a single center analysis and this allowed for a homogeneous analysis of clinical outcomes of patients, without confounding factors, such as different race, immunosuppressive protocols, or post-transplant screening. We have not identified the risk factors for developing a post-transplant cancer; however, this is beyond the aim of the study, which aimed to evaluate the incidence and prognosis of de novo post-transplant cancer.

In conclusion, post-transplant cancer significantly affects patient survival after kidney transplantation. These findings highlighted that prevention of post-transplant cancer-related morbidity and mortality is a fundamental target in kidney transplant programs. The introduction of specific pretransplant screening protocols and a specific patient management, on the basis of risk of developing a post-transplant neoplasm, is certainly necessary to reduce the incidence of cancer or at least to anticipate tumor diagnosis, as cancers after transplantation have a more aggressive behavior with a high mortality.

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