



Lung cancer in renal transplant recipients: A case-control study



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ARTICLE INFO

Keywords:

Lung cancer
Kidney transplantation
Thoracic surgery
Thoracic malignancies

ABSTRACT

Introduction: Solid organ transplant patients are at heightened risk of several cancers compared to the general population. Secondary to a higher number of procedures and better survival after transplantation, cancer is a rising health concern in this situation. Limited data exist for lung cancer (LC) after renal transplantation. We report here the most important series of renal transplant recipients with lung cancer.

Methods: Retrospective study of all cases of LC diagnosed in three French Renal Transplant Units from 2003 to 2012. A control group consisted of non-transplant patients with LC matched with the cases for age (< 30; 30–50; 50–65; > 65 years), gender and diagnosis date. We recruited two controls for each case.

Results: Thirty patients (median age 60 years; range 29–85; male/female ratio 80/20%) with LC were analysed. LC incidence was 1.89/1000 person-years over the period 2008–2012. All patients were former or active smokers (median 30 pack-years). Transplanted patients had significantly more comorbidities, mainly cardiovascular disease. The median interval of time from kidney transplantation (KT) to diagnosis of LC was 7 years (range 0.5–47 years). LC was incidentally diagnosed in 40%. Most patients (70%) had advanced LC (stage III or IV) disease. Stage of LC at diagnosis was similar in cases and controls. Surgery and chemotherapy were proposed to the same proportion of patients. In cases, mortality was cancer related in 87% and median survival time after diagnosis was 24 months. Survival was not significantly different between the 2 groups.

Conclusion: Despite frequent medical and radiological examinations, diagnosis of LC is usually made at an advanced stage and the overall prognosis remains poor.

1. Introduction

Pulmonologists have now to manage frequently the pulmonary complications of kidney transplant recipients: 3486 renal transplantations have been performed in 2015 (French Biomedecine Agency) and more than 30,000 kidney transplant recipients (KTRs) are alive with a functioning graft in France. As significant progress has been made in the

prevention and treatment of infections, cancer has become, with cardiovascular diseases, a major cause of morbidity and mortality in solid organ transplantation [1,2]. Lung cancer (LC) is a leading cause of mortality in these patients. To better understand the epidemiological characteristics and prognosis of LC in renal transplant recipients, we studied patients with LC in three cohorts of Renal Transplant Units in the Paris area. We sought to determine demographic characteristics,

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smoking habits, and the clinical and pathological presentation of LC. We matched transplanted patients with non-transplanted patients in order to compare baseline characteristics, treatment and prognosis of LC in these two groups.

2. Methods

We conducted a ten-year retrospective cohort study from 01/01/2003 to 31/12/2012 in three hospitals in the Paris area (Hôpital Foch, Suresnes; Hôpital Necker-Enfants Malades, Paris; Hôpital Bichat-Claude Bernard, Paris).

All HIV uninfected renal transplant recipients who had been transplanted for more than three months when the LC occurred were included. Cases were identified by cross-checking databases from the Nephrology Unit and the Respiratory Diseases Unit. All patients had a histologically proven diagnosis of LC. The diagnosis was performed according to the American Joint Committee on Cancer Staging System for LC.

LC incidence was determined among renal transplant recipients of Foch and Necker-Enfants Malades hospitals in the last 5 years (2008–2012).

Data were extracted from the hospital database and completed with the original paper file. The following data were collected: demographic variables, pre-transplant renal disease, dialysis duration, cigarette smoking habits, immune-suppressive treatment before and after LC diagnosis, LC histological subtype, clinical stage, specific treatment administered, complications, survival time, and cause of death.

Controls were non-transplanted patients with LC treated in Foch hospital matched with cases for age (< 30; 30–50; 50–65; > 65 years), gender and diagnosis date. If more than two eligible controls were identified for a given case, controls were selected at random.

Survival data were collected from general practitioners and in the hospital files. All patients were studied until their death or December 31, 2013. Kaplan–Meier survival curves were used to estimate survival of the patients after the diagnosis of LC and compared by log rank.

We compared baseline characteristics using the *t*-test for normally distributed variables such as tobacco consumption or smoking duration. Normal distribution was controlled by a Shapiro-Wilk test. The chi-square test was used for categorical variables such as tumor type and stage at diagnosis. We considered *p*-values ≤ 0.05 to be statistically significant.

This study was approved by the Ethical committee of the French Society of Pulmonology (CEPRO 2015-006).

3. Results

We diagnosed 30 lung cancers in kidney transplant recipients between 2003 and 2012. Demographic characteristics and indications for renal transplantation of patients are summarized in Table 1.

During the period 2008–2012 at Foch and Necker Hospitals, the population of transplanted patients was of 11123 person-years. Twenty one patients were diagnosed with LC. Thus, the incidence of LC was 1.89/1000 person-years and 2.55/1000 person-years among male renal transplant recipients.

The median time since transplantation in the whole group of patients was 7 years (from 0.5 to 47 years). In their history there was a median of 3 years of dialysis before transplantation (up to 10 years). During the 2003–2008 period, half of the patients (6/11) received cyclosporin A; then tacrolimus (14/18; 77%) in the more recent period. Only two patients were treated with an mTOR inhibitor before LC diagnosis. TMP-SMX was given to all transplanted patients as prophylaxis of *Pneumocystis jirovecii* pneumonia.

Characteristics of LC, treatment and survival of patients and controls are detailed in Table 2. All patients were former or active smokers (unknown for one). As expected, transplanted patients had more frequent cardiovascular co-morbidities (hypertension, ischemic heart

disease). LC was stage IV in 18 patients, IIIB in 1, IIIA in 2, IIA/IIB in 3 and stage IA/IB in 6 patients. Distribution of histological types differed, with more squamous cell carcinoma in renal transplant patients. Management of LC was not different between patients and controls. Patients with localized diseases were treated by surgical resection [10] or by targeted radiotherapy [1]. None had radiochemotherapy. The majority of patients with disseminated disease received platine based chemotherapy as first line treatment (12/13). The anti-angiogenic monoclonal antibody Bevacizumab was not used. Tyrosine kinase inhibitors were used, only in second or third line regimen (four patients). Because of better renal tolerance, the carboplatine-based doublet was administered to all but one renal transplant recipients. Immunotherapy was not available at the time of this study but would have raised the problem of graft rejection. Infection-induced admissions were more frequent in the transplanted group ($p = 0.019$). The rate of other causes of admission was similar in the two groups. The changes in immunosuppressive regimen after cancer diagnosis were variable, depending on chemotherapy initiation (detailed in Table 1). mTOR inhibitors were introduced in four patients after LC treatment (alive: 1, deceased of progressive cancer: 2 and sepsis: 1, range 4–72 months).

Kaplan–Meier survival curves are presented in Fig. 1. The log rank test showed no differences. Six of the 30 transplanted patients were alive at the latest news with a median follow up time of 20 months. Half of the 24 deceased patients survived less than 6 months. Deaths of patients with limited stage cancer (I, II or IIIA) were related to infections (*Mycobacterium avium* 1, sepsis 2), post-surgery complications [2] or cancer progression [2]. Most stage IV deaths (15/16) were caused by cancer progression except one patient who died of sepsis. We did not find survival differences between patients diagnosed by routine examination ($n = 13$) and those with symptoms ($n = 17$) (Fig. 2). Eleven out of 60 non-transplanted patients were still alive with a median duration of follow up of 10 months. At least 96% (47 out of 49 deceased controls) died because of cancer progression, one cause of death is unknown and one died of stroke.

4. Discussion

To our knowledge, we report here the largest group of LC in renal transplant recipients. Risk and prognosis of LC after transplantation is highly variable, depending on the type of transplantation and the immunosuppressive regimen [3]. Indeed, patients at highest risk are lung and heart-lung recipients [4,5]. The Respiratory Diseases Department in Foch Hospital is also specialized in Lung Transplantation. During the period 1988–2011, LC occurred in 12 out of 402 lung transplanted patients (AM Hamid personal data). As incidence and prognosis differ between groups of transplanted patients, we chose to focus on KTRs.

Incidence of LC in KTRs was 1.89/1000 person-years during the period 2008–2012 (2.55 person-year in men), consistent with previous studies [6]: Incidence of LC has been demonstrated to be moderately increased in the majority of studies, varying from 0,91/1000 PY (7 217 KT recipients, median duration of follow-up of 5.2 years) in an Italian study [7] to 2,3/1000 PY (mean incidence during the first three years post-transplantation) in a North-American study [8].

All patients were current or former smokers. We did not find any significant difference in smoking habits between patients and controls. Consequently, as in the general population, our cohort is mainly composed of male smokers but it can be outlined that transplanted patients are younger than the LC population in France: around 60 years old instead of 65 years old (INCA data, 2012). Noticeably, despite regular clinical monitoring (40% of cases were diagnosed by routine radiological exam), most patients had advanced LC at the time of diagnosis: 60% were stage IV, similar to controls. Our data's are concordant with a previous study in solid organ transplant patients (24 patients, 10 KT recipients) showing that despite 58% of fortuitous diagnosis, 83.4% had stage III–IV LC [9]. This is quite similar to LC diagnosed in persons living with HIV [6,10] or in heart transplant recipients [11].

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