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Risk of *de novo* cancers after transplantation: Results from a cohort of 7217 kidney transplant recipients, Italy 1997–2009

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Abstract To assess incidence and risk factors for *de novo* cancers (DNCs) after kidney transplant (KT), we carried out a cohort investigation in 15 Italian KT centres.
Seven thousand two-hundred seventeen KT recipients (64.2% men), transplanted between 1997 and 2007 and followed-up until 2009, represented the study group. Person years (PY) were computed from 30 days after transplant to cancer diagnosis, death, return to dialysis or to study closure. The number of observed DNCs was compared to that expected in the general population of Italy through standardised incidence ratios (SIR) and 95% confidence intervals (CI). To identify risk factors, incidence rate ratios (IRR) were computed.
Three-hundred ninety five DNCs were diagnosed during 39.598 PYs, with Kaposi's sarcoma (KS), post-transplant lymphoproliferative disorders (PTLD), particularly non-Hodgkin' lymphoma (NHL), lung, kidney and prostate as the most common types. The overall IR was 9.98/1.000 PY, with a 1.7-fold augmented SIR (95% CI: 1.6-1.9). SIRs were particularly elevated for KS (135), lip (9.4), kidney carcinoma (4.9), NHL (4.5) and mesothelioma (4.2). KT recipients born in Southern Italy were at reduced risk of kidney cancer and solid tumors, though at a higher KS risk, than those born in Northern Italy. Use of mTOR inhibitors (mTORi) exerted, for all cancers combined, a 46% significantly reduced risk (95% CI: 0.4–0.7).
Our study findings confirmed, in Italy, the increased risks for cancer following KT, and they also suggested a possible protective effect of mTORi in reducing the frequency of post transplant cancers.

1. Introduction

Kidney transplantation (KT) is an increasingly used medical procedure for treating End-Stage Renal Diseases (ESRD) in industrialised countries. In Italy, the overall number of organ transplants increased 1.6 fold between 1992 (with 1083 transplants carried out) and 2010 (2876 transplants).[1] This increase is largely due to the high success rate of renal transplantation in the last two decades. The introduction of highly active immunosuppressive drugs strongly contributed to lower acute rejection rates and to increased organ and patient survival rates.[2]

A large body of evidence, however, indicates that the chronic use of immunosuppressive drugs is associated with increased risks of opportunistic diseases, particularly cancers.[3–6] After 10 years of immunosuppression, KT recipients have a cumulative incidence of cancer as high as 20%.[7] As compared to the age- and sex- matched general population, a 3-to-5-fold increased risk was documented, among KT recipients, for skin cancers and urological malignancies, while for some virus-related cancers such as non-Hodgkin lymphomas (NHL) or Kaposi sarcoma (KS) the risk was up to 100-fold higher.[4,8,9] Several large scale studies on the spectrum of *de novo* cancers (DNCs) following organ transplantation were carried out in the United States,[3,6] Canada,[10] Japan,[11] Australia and New Zealand,[4,5,7] and Northern Europe.[12,13] Conversely, relatively few investigations were conducted in Southern Europe on the cancer risk of KT recipients, as compared to the corresponding general population.[9,14]

A multicentre study was thus carried out among KT transplant recipients in Italy to assess the spectrum of DNCs. Specific aims were to quantify the potentially increased risks, as compared to the general population, and to identify risk factors associated with cancer development.

2. Methods

This retrospective cohort study used clinical and epidemiological information collected among 8210 individuals who, between 1997 and 2007, underwent KT in 15 centres from northern, central and southern Italy. A total of 993 KT recipients (12.0%) were excluded from the analysis due to the presence of one of the following conditions: a previous transplant received before 1997 ($n = 688$); a cancer diagnosis within the five years preceding the transplant ($n = 40$); a DNC diagnosed within 30 days after KT ($n = 3$); a follow-up shorter than 30 days after KT ($n = 223$) and age at KT transplant below 18 years ($n = 39$).

The final cohort consisted of 7217 KT recipients (64.2% men) – who received 7299 organs. In each of the 15 participating centres, trained staff retrieved pertinent information from clinical charts and performed an audit for accuracy and consistency. The follow-up, including vital status, was updated to December 31st, 2009. Data were thereafter transposed in a standardised questionnaire which included personal information such as age at transplant, sex, area of origin and residence, as well as transplant information, i.e. date of KT, transplant centre, cause of ESRD, donor status, use of calcineurin inhibitors (CI), use of mTOR inhibitors (mTORi) and length of follow-up. Thereafter, data were entered in an electronic database for the purposes of statistical analysis.