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Pediatric solid organ transplantation is a risk factor for future cancers

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Abstract

Authors' conclusions: transplanted pediatric patients are at a higher risk of cancer than the general population. The most frequent histological type is non-Hodgkin's lymphoma, with a greater risk during the first year after transplantation, in the receptors with high susceptibility to primary infection by Epstein Barr virus and in the intestinal posttransplant.

Reviewers' commentary: This is the study with the largest sample in pediatrics to date, and demonstrates a higher risk of tumor development in solid organ transplant patients, compared to the general population. In the study, EBV infection is suggested to have a probable role as a determinant in the appearance of them, so that future action against infection by this virus may be of key importance.

Key words: solid organ transplantation, cancer, Epstein-Barr virus.

El trasplante de órgano sólido en Pediatría es un factor de riesgo para futuros cánceres

Resumen

Conclusiones de los autores del estudio: los pacientes pediátricos trasplantados tienen mayor riesgo que la población general de padecer cáncer. El tipo histológico más frecuente es el linfoma no Hodgkin, con un riesgo mayor durante el primer año postrasplante, en los receptores con alta susceptibilidad a infección primaria por virus de Epstein Barr (VEB) y en los postrasplantados intestinales.

Comentario de los revisores: se trata del estudio con mayor muestra en Pediatría hasta la fecha y describe el mayor riesgo de aparición de tumores en los pacientes trasplantados de órgano sólido respecto a la población general. Sugiere la infección por VEB como determinante en la aparición de algunos de ellos, por lo que la actuación futura frente a la infección por este virus puede ser clave.

Palabras clave: trasplante órgano sólido, cáncer, virus Epstein-Barr.

STRUCTURED ABSTRACT

Objective: to assess the potential risk of cancer and its risk factors in paediatric transplant recipients.

Design: analytical retrospective longitudinal observational study conducted in the framework of the US Transplant Cancer Match (TCM) Study.

Setting: the data were retrieved from the Scientific Registry of Transplant Recipients (SRTR) database, which has records of all solid organ transplantations performed in patients aged less than 18 years in 16 states of the United States between 1987 and 2011.

Study population: out of 18 150 transplantations in patients aged less than 18 years included in the TCM Study (45% of all solid organ transplantations in the United States), 17 958 were selected, corresponding to 16 732 individuals, and 1% were excluded because the recipients did not belong to any of the included race categories.

Risk factor assessment: the unit of analysis was transplantation of a solid organ. The authors assessed demographic and

clinical patient characteristics, the indication for transplantation, patient EBV serology status before transplantation and the race of transplant recipients.

Outcome measurement: the primary endpoint was the development of cancer classified according to the third edition of the *Classification of Diseases for Oncology*. At-risk time spanned from the transplant date or the start of cancer registry coverage to the first of the following events: death, graft failure, retransplantation, loss to followup or end of cancer registry coverage. Followup extended beyond 18 years of age. The authors summarised the results by means of standardised incidence ratios (SIRs) calculated by the direct method (dividing observed cancer counts among recipients by expected counts based on the general population rates) for total cancer and for specific types of cancer. Since non-Hodgkin lymphoma (NHL) was the most frequent type of cancer, the authors also calculated specific SIRs for NHL by age, transplanted organ, time to development of cancer and EBV status. The authors performed multivariate Cox regression to examine associations with potential risk factors.

Main results: of the 18 150 selected transplant recipients, 17 958 were included in the analysis (1% excluded). Of the total, 54.3% were male, 54.5% were aged less than 9 years, and 53.8% were Caucasian, and the median duration of followup was 4 years (interquartile range [IQR]: 1-7 years). The EBV status was known in 48% of the patients, of who 46% were seronegative. A total of 392 cancers were diagnosed, with a SIR of 212.95% (95% confidence interval [95 CI]: 188 to 238). The most frequent type was NHL (SIR: 18.5%; 95 CI: 13 to 26), with an increased incidence relative to the general population independently of age, years since transplantation and EBV status. The risk factors for NHL identified in the multivariate analysis were first year after transplant, EBV seronegative status, transplant type (heart, lung and intestine), and duration of immunosuppression, although there were no significant differences based on age, sex or race.

Conclusion: paediatric transplant recipients are at higher risk of developing cancer compared to the general population. The most frequent cancer type was non-Hodgkin lymphoma, with a higher risk in the first year post transplant, in recipients susceptible to primary infection by EBV and in intestine transplant recipients.

Conflicts of interest: one of the authors is employed by Grail (a company dedicated to the early detection of cancer), the rest declared no conflicts of interest.

Funding source: none noted.

COMMENTARY

Justification: in recent years, there has been an increase in the number of transplantations in Spain and worldwide. In Spain, 4821 organ solid transplantations were performed in 2016, and 136 were performed in recipients aged less than 15 years in 2015, which amounts to an annual rate of 3 transplantations per million individuals, above the European average.[1] Previous studies have described an increased risk of tumour development in paediatric transplant recipients.[2] Since the life expectancy of these patients has increased and thus there is more time for malignancy to occur, studying the conditions under which tumours develop is evidently relevant in order to establish preventive measures, where possible, or even to plan the followup of patients.

Validity or scientific rigour: the population was well defined, as were the predictor variables. The method for data collection was appropriate, the diagnoses were confirmed, and only 1% of the population was excluded. The time at risk of cancer was well defined. The authors used standardised incidence rates based on general population registries and assessed the independent effect of different risk factors on tumour development in transplant recipients with a Cox regression model. The median duration of followup was 4 years and the median time elapsed between transplantation and tumour development was 2.5 years, so the duration of followup seems sufficiently long, although it is not possible to know the long-term incidence of tumours in this group of patients or the incidence of tumour types for which the expected number of cases during the followup was less than 1.

Clinical relevance: during the followup, the incidence of cancer in transplant recipients was 19 times greater than the one in the general population (SIR: 19.1 [95 CI: 17.3 to 21.1]), with a predominance of NHL, whose incidence was 212 times that in the general population, and especially high in patients aged less than 5 years, intestine transplant recipients, in the first year post transplantation and in EBV-seronegative recipients, with the incidence of NHL in the latter group being 2.7 times greater than the incidence in EBV-seropositive recipients (hazard ratio [HR]: 2.71; 95 CI: 1.82 to 4.05). Excluding NHL, the incidence of tumours was 6 times greater compared to the general population (SIR: 5.89; 95 CI: 4.86 to 7.08). The effect size in tumour development seems considerable, as does the increased incidence in EBV-seronegative recipients. Although this effect would not in principle alter the decision to perform transplantation, it may be key in shaping the followup plan for these patients. The cancer incidence in transplant recipients was similar to those published in previous studies,[2,3] as was the increased incidence of tumours in solid transplant recipients that were EBV-seronegative; in the future, the latter patients may be eligible for vaccination which, while not currently available, may become a beneficial intervention.[4-6]

Applicability to clinical practice: the paediatric sample in this study is the largest analysed to date. It describes the increased risk of developing certain tumours compared to the general population, and suggests that EBV infection is a key risk factor, especially for the development of NHL, so in the

future vaccination against this virus may play an important role in preventing infection at a later date, and perhaps become an effective preventive measure.

Conflicts of interest: the authors of the commentary have no conflicts of interest to declare.

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