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Malignancy incidence after renal transplantation in children: a 20-year single-centre experience

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Abstract

Background. Cancer is a well-recognized complication of organ transplantation. The pattern of malignancies that occur in the paediatric graft population is different from that in the general paediatric population and in the population of adult organ transplant recipients.

Methods. We reviewed medical records from 240 consecutive paediatric renal transplantations performed in 219 children, aged less than 19 years, in our centre between April 1987 and March 2007. Data from patients who had been transferred into adult units were extracted from the French registries of dialysis and transplantation.

Results. Among the 219 children who underwent renal transplantation during the study period, 16 (7.3%) developed malignancy. The cumulative incidence of cancer was 1.9, 4.0, 6.9 and 10.2% at 1, 5, 10 and 15 years post-transplantation, respectively. The 10-year incidence of post-transplantation lymphoproliferative disorder (PTLD) was 4.5%. Other identified cancers were Hodgkin lymphoma, Burkitt lymphomas, renal papillary carcinoma, thyroid papillary carcinoma, recurrent ovarian seminoma and skin cancer. The mortality rate was 25% (4/16).

Conclusion. Early detection of cancer in transplant recipients is of great importance. Regular screening for persistent Epstein–Barr virus (EBV) DNA viral load in patients at risk for developing PTLD is recommended. The occurrence of skin cancer in transplanted children is extremely rare during childhood, but cases can develop in early adulthood.

Keywords: child; malignancy; post-transplantation lymphoproliferative disease (PTLD); renal transplantation; skin cancer

Introduction

An increased incidence of cancer is a well-recognized complication of organ transplantation (Tx). According to a recent cohort study that had a longer follow-up duration than any previous report, the relative risk for cancer in transplanted children was two to three times higher than in the general population [1]. Cancer rates in transplant recipients are roughly equivalent to those experienced by people 20–30 years older without transplants. Although the magnitude of risk declined with increasing age for recipients over 65, the risk was still two to three times above that of the general population [1]. In other reports examining patients receiving transplants during childhood, malignancies were 10 times more frequent than expected for that age group [2,3]. This elevated risk may be in parallel with the current increasing use of immunosuppression.

Malignancies occurring after solid organ Tx probably result from a complex interplay of different factors. These include the immunological condition of the child, the immunosuppressive treatment, oncogenic viruses and other possible synergistic effects. The pattern of malignancies in paediatric renal transplant recipients differs significantly from that in adult renal allograft recipients and the general population. According to the Israel Penn Transplant Tumor Registry, which is the largest database that tracks cancer following Tx, PTLD is the most common neoplasm in paediatric transplant recipients and it occurs early after transplantation. Skin carcinomas, such as squamous cell and basal cell carcinomas, are the second most common malignancy in children [4]. According to Coutinho *et al*. [3], most patients do not present *de novo* malignancy until they have been moved to adult units and the probability of developing a malignancy is 17% at 25 years after first renal replacement therapy. The occurrence of skin cancer in transplanted children is extremely rare during childhood because ageing is a crucial factor for the development of skin cancers, which develop in early adulthood at an average age of 27 years [5].

The aim of the present study was to evaluate the occurrence of and risk factors for malignancy after renal Tx in children.

Subjects and methods

Study design and data collection

We retrospectively reviewed medical charts of all consecutive paediatric renal Tx performed between April 1987 and March 2007. Data from

patients who had been transferred to adult units were extracted from the French registries of dialysis (REIN) and transplantation (CRISTAL). The methods and quality controls of these two registries are well established and have been described elsewhere [6,7].

Population

During the study period, 240 renal Tx were performed in 219 children aged less than 19 years at the Edouard-Herriot Hospital, University of Lyon. The median age at Tx was 11.1 (range 0.6–18.6) years. There were 127 boys and 92 girls. Forty-two Tx (17.5%) were living related donor Tx and 63 (26%) were preemptive. Seventeen patients (7.8%) died. The median duration of the follow-up was 10.4 (range 0.1–20.4) years and the median age of surviving patients at last follow-up was 20.8 (range 4.1–36.5) years. Identification of malignancy was made by biopsy of the affected organ.

Immunosuppressive regimen

From 1987 to 2000, the immunosuppressive protocol consisted of antithymocyte globulins (ATG), prednisolone, azathioprine (AZA) and cyclosporine (CyA) in cases of *de novo* Tx. ATG was administered as induction therapy at a dose of 2 mg/kg/day during the first 10 days post-Tx. Prednisolone was started preoperatively at a single dose of 300 mg/m^2 followed by 60 mg/m^2/day until Day 14 post-Tx, and then was progressively reduced to 2.5 mg/m^2/day after 12 months post-Tx. AZA was given preoperatively at a dose of 3 mg/kg, was changed to 2 mg/kg/day over the first 2 months, and then to 1 mg/kg/day thereafter. CyA was started orally as soon as serum creatinine fell below 100 μmol/L. The target CyA trough blood level was 150–200 ng/mL during the first 6 months and 100–150 ng/mL thereafter. Immunosuppressive therapy changed following the year 2000. Prednisolone was then given preoperatively at a dose of 60 mg/m^2, induction therapy consisted of basiliximab at Days 0 and 4, AZA was replaced by mycophenolate mofetil (MMF), administered preoperatively at a dose of 500 mg/m^2 and then 600 mg/mg^2/day after Tx, and CyA was stared in first 48 h. Patients with a second or third Tx and those with steroid-resistant nephrotic syndrome were managed on an individual basis.

Statistical analysis

Survival time free from malignancy following Tx was estimated using a time to failure Kaplan–Meier method. The endpoint was defined as first cancer. Data were censored at time of death or at last available follow-up. Factors associated with occurrence of malignancy were assessed by univariate and multivariate analyses using a Cox proportional hazard model. A P-value <0.05 was considered statistically significant. All statistical analyses were carried out with the SAS software (version 9.1; SAS Institute, Cary, NC, USA).

Results

Incidence of malignancy post-Tx

During the follow-up, 16 out of 219 patients (7.3%) developed malignancy. The cumulative incidence of cancer was 1.9 ± 0.9% at 1 year post-Tx (205 patients at risk), 4.0 ± 1.4% at 5 years post-Tx (161 patients at risk), 6.9 ± 2.0% at 10 years post-Tx (111 patients at risk), and 10.2 ± 2.7% at 15 years post-Tx (62 patients at risk) (Figure 1).

Malignancies included 5 B-cell EBV-associated PTLD, 1 Hodgkin lymphoma, 2 Burkitt lymphomas, 2 B-cell lymphomas, 1 stage III renal papillary carcinoma, 1 thyroid papillary carcinoma, 1 recurrent ovarian seminoma, 1 patient with Bowen disease, 1 patient with squamous (SCC) and basal cell carcinoma (BCC) of the eyelid and 1 patient with BCC of the scalp (Table 1). The cumulative incidence of lymphoproliferative disorders was 4.5 ± 1.5% at 10 years post-Tx. Of the 16 children that had cancer, 4 (25%) developed malignancies within the first year post-Tx. The median age at malignancy was 15.7 years (range 3.1–24.9)

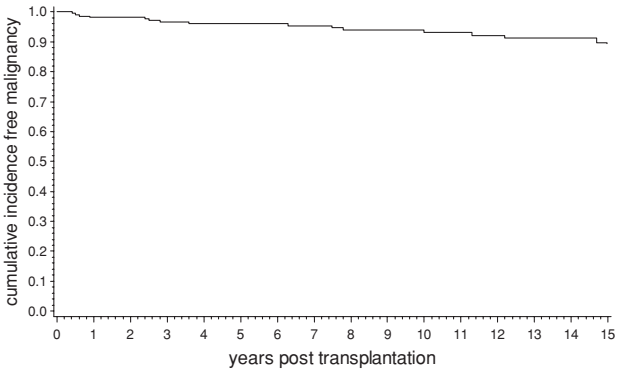

Fig. 1. Cumulative incidence free from malignancy in 219 transplant recipients.

and the median time between Tx and diagnosis of malignancy was 5.0 years (range 0.4–16.6). Using a Cox proportional hazard model, we did not find any baseline variable associated with the occurrence of malignancy (Table 2).

Characteristics of patients with malignancy post-Tx

The male to female ratio was 11:5. All donors but one were deceased donors. Primary disease, induction therapy, initial immunosuppression therapy and dialysis type before Tx are indicated in Table 1. Cyclophosphamide was administrated prior to renal Tx in two patients with steroid-resistant nephrotic syndrome at a dose of 2 mg/kg for 12 weeks (cumulative dose of 168 mg/kg). Malignancy occurred in both patients at 19 years after cyclophosphamide treatment. The youngest patient (patient 13) with skin carcinoma suffered from Fanconi anaemia, an inherited immunodeficiency known to predispose to cancer; this patient did not receive AZA or MMF due to haematological risk. In addition, this patient received androgenic treatment before renal Tx with a good response. Seven patients that presented signs of acute rejection and that were treated with methylprednisolone pulses during the first 6 months post-Tx showed a mean duration of 4.9 years (range 0.3–12.0) prior to malignancy. Monoclonal antibody OKT3 was given to two recipients because of acute rejection at 10 days after Tx for 1 patient and 5 months after Tx for the other. Diagnosis of malignancy was made at 3.6 and 7.3 years after administration of OKT3, respectively.

Three children returned to haemodialysis due to intractable rejection. In one child, this occurred at 6 years before cancer diagnosis, in the second, PTLD occurred before the return to haemodialysis, and in the third, the cancer was revealed during transplantectomy pathology study. Immunosuppression was discontinued in children who returned to dialysis. Growth hormone treatment was given to five children before renal Tx because of important growth retardation.

Six of 10 patients with PTLD experienced a mismatch in serology for EBV between recipient and donor. The delay to diagnosis of PTLD in these six patients was 4.6 years versus 3.3 years in the other four patients without EBV mismatch. Prophylactic antiviral treatment with ganciclovir was given to four children because of the EBV mismatch. Symptoms

Table 1. Characteristics of patients who developed malignancy

Pt	Primary disease	Dialysis prior to Tx	GH prior to Tx	Age at Tx	Time to diagnosis of cancer	Symptoms	Localization	Pathology	Induction	IS after Tx	Treatment (except IS)
1	SRNS	No	No	14.5 y	5 m	Adenopathy	Neck	Monomorphic monoclonal	ATG	CyA, Ste, MMF	Ganciclovir
2	PUV	PD	No	7 m	2.5 y	Adenopathy	Neck, spleen	Monomorphic monoclonal	ATG	CyA, Ste, AZA	Rituximab, ganciclovir, methotrexate
3	Lery-Weill	HD	Yes	15.5 y	11 m	Back pain	Paravertebral tumour	B-cell Lymphoma stage III	Basilix	CyA, Ste, MMF	CYM
4	ARPKD	No	Yes	12.5 y	2.5 y	Adenopathy	Neck	Hodgkin lymphoma	Basilix	FK, Ste, MMF	VBVP, radiotherapy
5	Nephrono-phtisis	PD	No	3 y	6 m	Adenopathy, splenomegaly	Neck	Polymorphic, polyclonal	Basilix	FK, Ste, MMF	Rituximab, ganciclovir
6	Denys Drash	PD	No	1.3 y	3.5 y	General symptoms	Graft	Polymorphic, polyclonal	ATG	CyA, Ste, AZA, OKT3	Transplantectomy
7	Bilateral renal hypoplasia	PD	No	1.5 y	12 y	Adenopathy	Neck	Oligoclonal PTLD	ATG	FK, Ste, AZA	Valaciclovir rituximab
8	SRNS	HD	Yes	17 y	8 y	Adenopathy	Neck	Burkitt Lymphoma	ATG	CyA, Ste, AZA	Rituximab, chemotherapy
9	SRNS	DP	No	14 y	14.5 y	Pathologic finding	Graft	Renal papillary adenoma stage III	ATG	CyA, Ste, AZA	Transplantectomy
10	Thrombosis	DP	Yes	14 y	3 y	Cutaneous lesion	Scalp	CBC	ATG	CyA, Ste, AZA	Surgical exeresis
11	Frasier	HD	No	14 y	7 m	Ultrasound finding	Ovary	Ovarian seminoma	Basilix	FK, Ste, AZA	Chemotherapy, surgery
12	ARPKD	HD	No	4 y	16.5 y	Adenopathy	Mediastinal, abdominal, spleen	B lymphoma stage IV	ATG	CyA, Ste, MMF	Rituximab, chemotherapy
13	HUS	No	No	14 y	10 y	Cutaneous lesion	Eyelid	SCC, CBC	ATG	CyA, Ste	Surgical exeresis
14	SRNS	No	Yes	12.5 y	11 y	Cutaneous lesion	Hand	Bowen disease	ATG	CyA, Ste, AZA	Surgical exeresis
15	PUV	No	No	15.5 y	7.5 y	Local mass	Thyroid gland	Thyroid papillary carcinoma	ATG	CyA, Ste, MMF	Surgery, radioactive iode
16	PUV	No	No	6.5 y	6.5 y	General symptoms mass of cavum	Graft, liver, spleen, pulmonary, pharyngeal abdominal, mediastinal	Burkitt Lymphoma	ATG	CyA, Ste, AZA	Death prior to therapy

SRNS, steroid-resistant nephrotic syndrome; ARPKD, autosomal-recessive polycystic kidney disease; PUV, posterior urethral valve; HUS, haemolytic uraemic syndrome; ERD, extra-renal depuration; Tx, transplantation; PD, peritoneal dialysis; HD, haemodialysis; GH, growth hormone; Basilix, basiliximab; ATG, antithymocyte globulin; IS, immunosuppression; CyA, cyclosporine; FK, tacrolimus; MMF, mycofenolate mofetil; AZA, azathioprine; Ste, steroids; CYM, methothrexate; aracytine, rituximab, VBVP, vinblastine; VP16, bleomycine, prednisone; y, years; m, months.

Table 2. Risk factors of malignancy post-transplantation

	Cancer ($n = 16$)	Cancer free ($n = 203$)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Recipient characteristics at first Tx						
Male gender, *n* (%)	11 (69)	116 (57)	2.2 (0.7–6.8)	0.17	2.3 (0.7–7.2)	0.15
Mean age at Tx (years)	9.4 ± 6.1	10.0 ± 5.1	1.0 (0.9–1.1)	0.70		
Period of Tx (1987–1999 versus 2000–2007)	13 (81)	133 (65)	0.9 (0.2–3.2)	0.77		
Indication for Tx, *n* (%)						
Congenital structural abnormalities	4 (25)	73 (36)	1.0 (reference)			
Glomerulonephritis	4 (25)	42 (21)	1.8 (0.6–3.4)	0.74		
Hereditary renal diseases	5 (31)	60 (30)	1.1 (0.7–1.3)	0.98		
Others	3 (19)	28 (14)	1.4 (0.6–1.9)	0.70		
GH prior to Tx, *n* (%)	5 (31)	61 (30)	1.0 (0.8–1.4)	1.00		
Preemptive Tx, *n* (%)	6 (38)	56 (28)	1.3 (0.5–3.6)	0.59		
Living related donor Tx, *n* (%)	1 (6)	39 (19)	0.3 (0.1–2.1)	0.20	0.3 (0.0–1.9)	0.18
Primary immunosuppression, *n* (%)						
AZA versus MMF	9 (56)	132 (65)	0.8 (0.6–2.2)	0.59		
CyA versus FK	12 (75)	170 (83)	0.7 (0.5–5.9)	0.75		
ATG versus IL-2 receptor antibody	12 (75)	142 (70)	1.1 (0.6–4.7)	0.78		

Tx, transplantation; GH, growth hormone; AZA, azathioprine; MMF, mycophenolate mofetil; CyA, cyclosporine; FK, tacrolimus; ATG, anti-thymocyte globulin; IL2, interleukin-2; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.

of PTLD included fever, anorexia and weakness ($n = 2$), cervical lymph node ($n = 6$), back pain ($n = 1$), as well as liver and spleen enlargement ($n = 2$). The histological typing of the PTLD was polymorphic and polyclonal in two patients, monomorphic and monoclonal in three patients, and oligoclonal in one patient.

Thyroid carcinoma was diagnosed from local symptoms of a mass, radiological imaging, and tissue biopsy. The recurrent ovarian seminoma was detected by routine ultrasonography follow-up at 6 months post-Tx, following gonadectomy in a patient with Frasier syndrome. Two malignancies were revealed upon transplant removal after intractable acute rejection (1 renal carcinoma and 1 renal PTLD).

The three skin cancers (Bowen disease of the hand, BCC of the scalp and BCC/SCC of the eyelid) were diagnosed by routine dermatological follow-up; they occurred at a mean age of 24 years and at a mean interval after Tx of 10.6 years. Two SCC and three BCC were found on a single patient.

Assessment of biochemical profiles revealed elevated lactic dehydrogenase (LDH) (>450 UI/L) in 9 of the 16 patients at the time of diagnosis of malignancy. This was observed mainly in patients with PTLD (7/10). Haematological profiles were unremarkable and renal function was not modified.

Management

The overall therapeutic approach consisted of decreasing immunosuppression exposure in all children, a discontinuation of anti-metabolites, a decrease in anti-calcineurin dose and an increase in prednisone dose. Rituximab (anti CD20, 375 mg/m^2 once a week for 4 weeks) was given to 7 of 10 patients with PTLD that expressed the CD20 antigen, and to patients entered into clinical trials for lymphomas. Chemotherapy protocols were applied to seven patients with lymphomas and monomorphic PTLD. Surgical procedures were performed in patients with skin cancers, thyroid carcinoma (sub-total thyroidectomy associated with radioactive iodine for residues) and ovarian seminoma (associated with chemotherapy).

Four patients (25%) have died (patients 2, 3, 7 and 16 in Table 1). One patient (patient 3) died from chronic encephalopathy and respiratory insufficiency at 3.5 years after EBV-related encephalitis. He had received chemotherapy that included methotrexate, aracytine and rituximab (CYM protocol). Another patient died at 3 years post-PTLD from acute gas-embolism while on haemodialysis (patient 2); this patient had received rituximab and methotrexate. The third patient died because of severe hypercalcaemia during anesthesia and surgical biopsy for Burkitt lymphoma (patient 16). This patient did not receive chemotherapy prior to death. The last death was caused by metabolic complications due to macrophage activation syndrome soon after diagnosis of PTLD (patient 7). The entire protocol for rituximab treatment had not been completed in this patient. The survival rate after treatment for malignancy was 75% with a mean time of follow-up of 5.2 years.

Discussion

EBV seronegative status, CMV disease, immunosuppression therapy, acute rejection episodes and a younger age have all been suggested to be risk factors for the development of PTLD [8]. Over-immunosuppression may lead to the breakdown of cytotoxic T-cells and EBV infection allows silent-infected cells to undergo lytic replication and ultimately B-cell transformation. Because primary infection with EBV increases the risk for PTLD, many recommend a determination of pre-transplant antibody status in recipients, a rapid detection of EBV infection in seronegative symptomatic patients, and regular screening for EBV DNA viral load in patients at risk for developing PTLD [9,10]. While examining cyclophosphamide, one study found a crude association between a cumulative cyclophosphamide

dose of >250 mg/kg and increased risk for development of malignancy, suggesting a potential carcinogenic effect [4]. In addition, CyA, OKT3, ATG, basiliximab and daclizumab have each been associated with higher risk for PTLD in some [11–13] but not all studies [14,15]. In our study, we were unable to identify any risk factors that were associated with post-Tx malignancy.

EBV-induced PTLD affects 1–10% of all paediatric renal transplant recipients [16]. The term PTLD encompasses a heterogeneous group of lymphoproliferative disorders. The lack of a standard definition that includes clear clinical and histological parameters has resulted in a wide variation in reported incidence [16]. In our centre, the 10-year incidence of PTLD was 4.5%. The incidence of PTLD is four times higher in paediatric than adult transplant recipients, since a larger proportion of children are EBV naive prior to Tx [16]. Both T-cell dependent and B-cell dependent lymphoproliferative disorders have been observed after solid organ allograft. T-cell PTLD represents only 14% of all cases but includes a poorer prognosis since 65% of patients reported in the literature died, while a few cases were associated with EBV infection [17]. B-cell dependent PTLD represent 85% of the total cases of PTLD and these are mainly associated with EBV primary infection or reactivation in children. In our patients, we did not observe any cases of T-cell dependent PTLD.

The incidence of PTLD differs by transplant type, and has been estimated at 4–15% among paediatric liver recipients, 8–20% among paediatric lung, heart and heart–lung recipients, 1–10% among paediatric kidney recipients, and 19% among intestinal transplant recipients. The higher incidences of PTLD among heart, lung and intestinal recipients can be explained by a more aggressive immunosuppressive regimen [18]. A link between PTLD development and the immunosuppressed state is further suggested by the finding that 80% of cases occur within the first year of organ Tx, during peak immunosuppression. The time from Tx to diagnosis of PTLD in the paediatric population ranges from 6 weeks to 7 years [18,19]. In our study, only one third of the patients presented with PTLD in the first year post-Tx.

PTLD should be suspected in kidney recipients that show tonsillar enlargement, lymphadenopathy, hepatosplenomegaly or general symptoms such as fever, weight loss and night sweats. Further indications are abdominal symptoms, including pain, change in bowel habit or bowel obstruction, and respiratory symptoms, such as dyspnoea or stridor [19]. In addition, increased serum LDH and uric acid concentrations may be found. In our series, LDH was high (>450 UI/L) in 7 of 10 patients with PTLD; uric acid was not measured for each patient.

A commonly used therapeutic approach for PTLD is a reduction in calcineurin inhibitors to half dose or target level and a stopping of anti-metabolite agents while continuing oral steroid treatment [19]. While using this strategy, the patient should be quickly revaluated, usually within 1–4 weeks, to determine if additional interventions are needed. Anti-CD20 monoclonal antibody therapy is widely accepted as the second line therapy if the CD20 antigen is expressed on PTLD cells. For more severe lesions or for those that do not respond, chemotherapy protocols are used [19].

The outcomes of paediatric recipients presenting with PTLD vary according to studies reported in the literature. A single-centre study reported no mortality in six paediatric kidney recipients who developed PTLD [20]. Conversely, the multicentre report from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) found that of 56 kidney recipients with PTLD, 66% lost their graft and 48% died either from malignancy or from infection [21]. In our series, all of the 4 deaths occurred among the 10 patients with PTLD. Purighalla *et al*. [22] observed that the risk for rejection following reduced immunosuppression during PTLD was 50% and that post-PTLD rejection, when left untreated, led to graft loss [22]. We did not observe rejection episodes following reduced immunosuppression in our series.

Data from the Cincinnati Transplant Tumor Registry from 1968 to 1993 showed that 208 tumours occurred in 200 renal allograft recipients. Of these patients, 65% were paediatric cases that developed tumours following Tx. In this study, a striking feature was the paucity of common tumours seen in the general paediatric population, such as retinoblastoma, Wilm's tumour, neuroblastoma, leukaemia, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma and primary brain tumours [23]. Instead, the predominant tumour observed was non-Hodgkin lymphoma.

A study that compared three different periods (5 years before starting renal replacement therapy, during dialysis, and after Tx), demonstrated that preexisting individual cancer risk factors and factors related to primary renal disease, end stage renal disease (ESRD), or dialysis can all be excluded as major contributors to the increased risk during the post-transplant period [24]. The standardized incidence ratio (SIR) for malignancy was 3.27 after transplant, as compared to 1.35 during dialysis, and 1.16 before renal replacement therapy [24].

Treatment of skin cancers has consisted of surgical excision of lesions along with adequate margins as well as a tapering of immunosuppressive regimens. Prevention of such tumours begins with adequate education of patients and their families about the importance of strict protection from the sun. Prevention also includes regular dermatological visits for early detection and ablation of premalignant lesions [25]. Anogenital cancers are the third most frequent malignancy in patients that had undergone renal Tx in childhood, accounting for 4% of tumours in paediatric transplant recipients [5]. In our series, none of the three patients with skin cancers presented anogenital lesions.

Early detection of cancer in transplant recipients is of great importance. The clinical practice guidelines committee of American Society of Transplantation has published a set of guidelines for outpatient renal transplant follow-up for the prevention of cancer [26]. While an experimental vaccine against the gp350 envelope protein is under investigation for EBV non-immune recipients [27], regular screening for persistent EBV DNA viral load in patients at risk for developing PTLD is recommended.

Conclusion

Earlier reports of cancer following renal Tx have been limited by small numbers of patients in single-centre studies

and incomplete ascertainment of cases in large registries. This is especially true in children. Large multicentre longitudinal registry studies are able to detect trends and risk factors that may not be evident in smaller studies. Transplantation is the treatment of choice for children with ESRD because it offers the best opportunities for growth, development and quality of life. However, the long-term risk for malignancies is significantly increased following renal Tx. The pattern of malignancies that occurs in the paediatric graft population is different from that in the general paediatric population and in the population of adult organ transplant recipients. Because these malignancies are an important contributor to overall mortality, clinicians should show enhanced surveillance and continued vigilance for cancer symptoms following renal replacement therapy.

Conflict of interest statement: None declared.

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