Occurrence of malignancies after kidney transplantation in adults: Slovak multicenter experience

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Malignancies are one of the three major causes of renal recipient´s death with a functioning graft after cardiovascular diseases and infections. Among the variety of risk factors, including conventional and specific to transplant recipients, the duration of immunosuppressive therapy, the intensity of therapy, and the type of immunosuppressive agent all have an impact on development of post-transplant malignancy. The aim of our retrospective study was to document the incidence, the type of malignancies, the patient/graft survival in the group of kidney transplant recipients in Slovak Republic, and to identify the factors which influenced the outcome. We analyzed the data of 1421 patients who underwent renal transplantation from deceased or living donors in the period from 2007 to 2015 in the Slovak transplant centers. The incidence of malignant tumors was 6%, the malignancy was diagnosed in 85 patients at the age of 54.1 ± 9.8 years, more frequently in men (68.2 %; P < 0.0001). The mean time of malignancy occurrence was 45 months after transplantation. The most frequent malignancies were skin cancers– basal cell carcinoma (BCC) in 17.6%, squamous cell carcinoma (SCC) in 8.2%, and malignant melanoma (MM) in 2.4% of patients, followed by non-skin tumors such as renal cell carcinoma (RCC) in 16.5%, cancer of colon in 12.9%, prostatic cancer in 9.4%, breast cancer in 9.4%, cancer of lung in 7.1%, post-transplant lymphoproliferative disease (PTLD) in 2.4%, cancer of urine bladder in 2.4%, and cancer of sublingual gland in 1.17% of patients. Surgical treatment was used in 40% of patients, chemotherapy in 7.1%, radiotherapy in 2.4%, treatment with biological agents in 15.3%, combined therapy in 29.4% and palliative treatment in 5.9% of patients. 55.3% of patients underwent conversion from other immunosuppressive agents into mTORi at the time of malignancy occurrence. The remission was achieved in 48.2% of patients, 28.2% of patients were in the oncology treatment in the end of the year 2015, and 23.5% of patients died. There was no difference in the kidney function at the time of malignancy occurrence (s-creat 133.7 ± 59.8 µmol/l) and one year later (s-creat 131.1 ± 47.9 µmol/l) (P = 0.7768). The patients after successful treatment more frequently suffered from BCC (P = 0.0140), did not undergo palliative treatment (P = 0.0033), but were more frequently treated surgically (P < 0.0001).

Key words: malignancy, kidney transplantation, immunosuppression, mortality

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; MM, malignant melanoma; RCC, renal cell carcinoma; PTLD, post-transplant lymphoproliferative disease; s-creat, serum creatinine level; TAC, tacrolimus; CyA, cyclosporine A; MMF, mycophenolate mofetil; CS, corticosteroids; mTORi, mTOR inhibitor; Basil/Dacl, basiliximab/daclizumab; Thymo, rabbit anti-thymocyte globulin; IVIG, intravenous immunoglobulin; PP, plasmapheresis; MO, malignancy occurrence; RT, renal transplantation; vs., versus; USRDS, United States Renal Data System; RTRs, renal transplant recipients; KDIGO, Kidney Disease: Improving Global Outcomes

The survival of patients who undergo renal transplantation has been improved over the past three decades. In the short term, renal transplantation offers a good prospect of survival, however, the life expectancy beyond 10 years is still considerably less than in general population [1]. Rates of malignancy compete with cardiovascular disease as the leading cause of death (40 – 50% of deaths after the first-year post-transplant) with a functioning graft; accounting for 27% of deaths in renal transplant recipients [2]. This reflects the increasingly power-

ful induction and immunosuppressive regimes along with the increasing duration of immunosuppression due to improved survival beyond one year [3]. Registry data show that the risk

Table 1. Demographic and clinical characteristics of patients with malignancy

2007 – 2015	n = 85 (100%)	P value
Recipient gender		
Male	58 (68.2%)	< 0.0001
Female	27 (31.8%)	
Recipient age (years) *	54.1 ± 9.8	
First transplantation	79 (92.9%)	
Re-transplantation	6 (7.1%)	
Deceased donor	71 (83.5%)	
Living donor	14 (16.4 %)	< 0.0001
Donor gender		
Male	71 (83.5%)	
Female	14 (16.5%)	
Primary cause of renal failure		
Diabetes	9 (10.6%)	
Glomerulonephritis	27 (31.8%)	
Cystic kidney disease (ADPKD)	5 (5.9%)	
TIN	26 (30.6%)	
Hypertension	8 (9.4%)	
Other	10 (11.8%)	
Induction		
Without	57 (67.1%)	
Basil/Dacl	21 (24.7%)	
Thymo	7 (8.2%)	< 0.0001
Immunosuppressive treatment at the time of transplantation		
TAC	55 (64.7%)	
CyA	28 (32.9%)	
mTORi + CNI	2 (2.4%)	
MMF	83 (97.6%)	
CS	84 (98.8%)	
Immunosuppressive treatment at the time of malignancy occurrence		
TAC	60 (70.6%)	
CyA	20 (23.5%)	
mTORi + CNI	2 (2.4%)	
MTORi	2 (2.4%)	
MMF	79 (92.9%)	
CS	62 (72.9%)	
History of antirejection treatment		
CS	28 (32.9%)	
Thymo	2 (2.4%)	
IVIG + PP	9 (10.6%)	
Rituximab	3 (3.5%)	

TAC, tacrolimus; CyA, cyclosporine A; MMF, mycophenolate mofetil; CS, corticosteroids; mTORi, mTOR inhibitor (mammalian target of rapamycin); Basil/Dacl, basiliximab/daclizumab; Thymo, rabbit anti-thymocyte globulin; IVIG, intravenous immunoglobulin; PP, plasmapheresis
*The results are presented as a mean ± SD

of *de novo* malignancies is increased in transplant recipients with relative risk 3 – 5 times compared with the general population [4]. Malignancies after kidney transplantation are often more aggressive and with worse prognosis compared with the general population and patients on dialysis. Cancer is more common in older patients, and more common after transplantation than while on dialysis [5]. Among the variety of risk factors including conventional (such as increasing age, cigarette smoking and sun exposure) and specific to transplant recipients, the duration of immunosuppressive therapy, the intensity of therapy and the type of immunosuppressive agent all have an impact on development of post-transplant malignancy [6, 7]. There are multiple mechanisms through which immunosuppression is believed to increase the risk of developing cancer in transplant patients. The first mechanism is that long-term immunodeficiency may increase the risk of oncoviral-driven malignancy [8]. Second, the impaired immunosurveillance of neoplastic cells due to nonspecific mode of action of most immunosuppressive drugs is thought to play a role. Finally, some immunosuppressive drugs may have pro-oncogenic properties. The organ transplant recipients receive several combinations of immunosuppressive agents therefore it has been suggested that the duration and intensity of immunosuppressive treatment as well as the type of agent can affect the cancer risk [3, 8, 9]. For example, the calcineurin inhibitor, cyclosporine A, has been demonstrated to cause significant reduction in DNA repair mechanisms as well as azathioprine and prednisolone to a smaller extent, which may in part contribute to the elevated cancer risk observed in transplanted patients [10]. Azathioprine relates to development of skin tumors possibly because of increased photosensitivity to ultraviolet light. The polyclonal antithymocyte antibodies used for induction and antirejection therapy appear to be related to an increased incidence of post-transplant lymphoproliferative disorders, particularly virally induced cancers [3, 8]. This effect was not observed with monoclonal anti-interleukin 2 antibodies. The proliferation signal inhibitors (m-TOR inhibitors) appear to be associated with the reduced risk of some malignancies [11]. Mycophenolate mofetil (MMF) is a selective and reversible inhibitor of inosine monophosphate dehydrogenase which is essential for lymphocyte proliferation. The data of carcinogenic effects of MMF are conflicting. Studies demonstrate that MMF has mutagenic effect in vitro and can enhance tumor invasiveness, however, MMF has also been associated prevention of in vitro tumor dissemination [8].

Research has shown that transplant recipients are at increased risk of many different cancers. An analysis of the United States Renal Data System (USRDS) shows that compared with an age adjusted population the incidence of common cancers such as colon, lung, prostate or breast cancer was approximately doubled in renal transplant recipients while the increase in incidences of other cancers ranged from 3-increase for bladder and testicular cancer to 15-times increase for kidney malignancies with an inci-

dence of more than 20% of lymphomas and non-melanoma skin cancers [12]. Some of these cancers can be caused by infectious agents. A non-Hodgkin lymphoma can be caused by Epstein-Barr virus infection [13] and liver cancer by chronic infection with the hepatitis B (HBV) and hepatitis C viruses [14].

The aim of our retrospective study was to document the incidence, the type of malignancies, the patient/graft survival in the group of kidney transplant recipients in Slovak Republic, and to identify the factors which influenced the outcome.

Patients and methods

Patients. We analyzed the data of 1421 patients at the age of 54.1 ± 9.8 who consecutively underwent renal transplantation from deceased (n = 1299) or living (n = 122) donors in the period between 01st JAN. 2007 and 31st DEC. 2015 at the Slovak transplant centers of the University Hospital Bratislava, the University Hospital Košice, the University Hospital Banská Bystrica, and the University Hospital Martin. We identified malignancy in 85 patients (6%), 58 men (68.2%) and 27 women (31.8%). The demographic and basic clinical characteristics of renal transplant recipients with malignancy are summarized in Table 1.

Statistical analysis. We used the certified statistical program – Medcalc version 13.1.2 – for statistical evaluation with application of the following statistical analyses: Student t test, chi-square test. We considered $P < 0.05$ to be statistically significant.

Results

Incidence of malignancies. The incidence of tumors was 6%, the malignancy was diagnosed in 85 patients at the age of 54.1 ± 9.8 years more frequently in men (68.2%; $P < 0.0001$). The average time of malignancy occurrence was 49.2 ± 34 months after transplantation with the median of 45 months after transplantation. The most frequent tumors were skin cancers – basal cell carcinoma in 15 patients (17.6%), squamous cell carcinoma in 7 patients (8.2%), and malignant melanoma in 2 patients (2.4%) followed by renal cell carcinoma in native kidneys in 14 patients (16.5%) and cancer of colon in 11 patients (12.9%). Sporadically, we observed post-transplant lymphoproliferative diseases and carcinomas of prostate, breast, lung, uterus, urine bladder, and esophagus (Tab. 2).

Treatment of malignancies. More than 50% (47 patients, 55.3%) of patients underwent conversion from other immunosuppressive agents into mTORi at the time of malignancy occurrence, surgical treatment was applied in 40% of patients (n = 34) with significant positive impact on patient´s survival in 65.9% patients treated surgically ($P < 0.0001$). Biological agents (15.3%) and combined therapy (29.4%) were applied relatively more frequently – usually mTORi conversion after surgical treatment. Chemotherapy was applied less frequently (7.1%), sporadically radiotherapy and palliative treatment (Tab. 3).

Patient and graft survival. During the period of observation (01st JAN. 2007 – 31st DEC. 2015), remission was achieved in 48.2% of patients, while 28.2% of patients were still on oncology treatment (Tab. 6). 28.2% of patients with malignancy (n = 20) died, 13 patients in the first year after malignancy occurrence, the rest of patients (n = 7) died after one year of tumor diagnosis. The higher risk of dead was related to renal cell carcinoma in native kidneys (died vs. cured patients: 20% vs. 7.3%), colon cancer (30% vs. 19.5%) and lung cancer (10% vs. 2.4%). The best prognoses showed non-melanoma skin cancer (43.9% vs. 5%) (Tab. 6).

There was no difference in the kidney function at the time of malignancy occurrence (s-creat 133.7 ± 59.8 μmol/l) and one year later (s-creat 131.1 ± 47.9 μmol/l) ($P = 0.7768$). The average level of serum creatinine at the time of tumor diag-

Table 2. Incidence of cancer in graft recipients

2007 – 2015	n = 85 (100%)
Time of malignancy occurrence after transplantation (months)	49.2 ± 34.0
BCC	15 (17.6%)
SCC	7 (8.2%)
Malignant melanoma	2 (2.4%)
RCC in native kidneys	14 (16.5%)
Colon	11 (12.9%)
Prostate	8 (9.4%)
Breast	8 (9.4%)
Lung	6 (7.1%)
Uterus	4 (4.7 %)
PTLD	2 (2.4%)
Urine bladder	2 (2.4%)
Esophagus	2 (2.4 %)
Sublingual gland	1 (1.2%)
Graft RCC	1 (1.2 %)
Gallbladder	1 (1.2 %)
Thyroid	1 (1.2 %)

BCC, basal cell carcinoma; SCC, squamous cell carcinoma; RCC, renal cell carcinoma; PTLD, post-transplant lymphoproliferative disease

Table 3. Treatment of malignancies

2007 – 2015	n = 85 (100%)
Conversion into mTORi	47 (55.3%)
Surgical treatment	34 (40.0%)
Chemotherapy	6 (7.1%)
Radiotherapy	2 (2.4%)
Biological agents	13 (15.3%)
Combined therapy	25 (29.4%)
Palliative therapy	5 (5.9%)

mTORi, mTOR inhibitor

Table 4. Kidney function at the time of malignancy occurrence and one year later

2007 – 2015	s-creat at the time of MO (μmol/l) *	s-creat one year later (μmol/l) *	P value
All patients (n = 85)	133.7 ± 59.8	131.1 ± 47.9	0.7768
Without conversion (n = 38)	139.1 ± 47.8	146.0 ± 50.9	0.5385
Conversion to mTORi (n = 47)	132.0 ± 68.3	122.3 ± 43.8	0.4008

MO, malignancy occurrence; s-creat, serum creatinine level; mTORi, mTOR inhibitor
*The results are presented as a mean ± SD

Table 5. Kidney function according to conversion into mTORi

2007 – 2015	Without conversion (n = 38)	With conversion (n = 47)	P value
s-creat at the time of MO (μmol/l) *	139.1 ± 47.8	132.0 ± 68.3	0.5944
s-creat one year later (μmol/l) *	146.0 ± 50.9	122.3 ± 43.8	0.0219

MO, malignancy occurrence; s-creat, serum creatinine level; mTORi, mTOR inhibitor
*The results are presented as a mean ± SD

nosis in non-converted group of patients (n = 38) was 139.1 ± 47.8 μmol/l and one year later it was 146.0 ± 50.9 μmol/l (P = 0.5385). In the mTORi converted patients (n = 47), the average level of s-creat at the time zero was 132.0 ± 68.3 μmol/l and 12 months later it was 122.3 ± 43.8 μmol/l (P = 0.4008) (Tab. 4). When we compared the renal function at the time of malignancy occurrence and 12 months later in both groups of patients (those without and with conversion into mTORi), we found statistically significant lower levels of serum creatinine in the group of patients one year after conversion into mTORi (P = 0.0219). There was no significant difference of s-creat in both groups at the time of malignancy occurrence (P = 0.5944, Tab. 5).

Factors influencing outcomes. Finally, we compared the impact of various demographic characteristics, the mean time of malignancy occurrence after transplanta-tion, the type of malignancy, and the selected oncological treatment on the patient´s survival (Tab. 6). The worst prognosis was surprisingly observed in the group of patients without induction treatment (P=0.0310) compared with those who received the inhibitor of interleukin-2 receptor or anti-thymocyte globulin. Successfully treated patients more frequent suffered from BCC (P = 0.0140), did not undergo palliative treatment (P = 0.0033) but more frequent were treated surgically (P < 0.0001). Other factors such as the recipient age, the order of transplantation, the primary cause of renal failure, the immunosuppressive treatment at the time of transplantation and malignancy occurrence, the history of antirejection treatment, and the time of malignancy occurrence after transplantation did not significantly influenced the patient survival with malignancies (Tab. 6).

Table 6. Comparison of characteristics of cured patients and died patients

2007 – 2015	Cured patients (n = 41)	Died patients (n = 20)	P value
Mean (%)	73.2	55	0.1585
Recipient age (years) *	54.3 ± 12	54.7 ± 6.9	0.8907
First transplantation (%)	92.7	95	0.7353
Second transplantation (%)	4.9	5	0.9886
Third transplantation (%)	2.4	0	0.4885
Primary cause of renal failure			
Diabetic nephropathy (%)	9.8	10	0.9805
Glomerulonephritis (%)	41.5	25	0.2116
Cystic kidney disease (%)	2.4	5	0.5941
TIN (%)	34.1	35	0.9451
Hypertension (%)	7.3	15	0.3469
Other (%)	4.9	10	0.3469

Table 6. Comparison of characteristics of cured patients and died patients (continued)

2007 – 2015	Cured patients (n = 41)	Died patients (n = 20)	P value
Induction			
Without (%)	63.4	90	0.0310
Basil/Dacl (%)	24.4	10	0.1878
Thymo (%)	12.2	0	0.1059
Immunosuppressive treatment at the time of transplantation			
TAC (%)	68.3	70	0.8938
CyA (%)	29.3	30	0.9555
mTOR + CNI (%)	2.4	0	0.4885
MMF (%)	97.6	100	0.4885
CS (%)	97.6	100	0.4885
Immunosuppressive treatment at the time of malignancy occurrence			
TAC at the time of MO (%)	68.3	65	0.7982
CyA at the time of MO (%)	19.5	35	0.1905
mTOR + CNI at the time of MO (%)	4.9	0	0.3181
mTOR at the time of MO (%)	4.9	0	0.3181
MMF at the time of MO (%)	90.2	95	0.5253
CS at the time of MO (%)	80.5	60	0.0901
History of antirejection treatment			
CS (%)	34.1	30	0.7507
Thymo (%)	2.4	0	0.4885
IVIG + PP (%)	9.8	10	0.9805
Rituximab (%)	4.9	0	0.3181
Time of malignancy occurrence after RT (months) *	40.1 ± 24.4	47.7 ± 37.6	0.4118
Type of malignancy			
Breast (%)	7.3	10	0.7202
RCC (%)	7.3	20	0.1472
BCC (%)	34.1	5	0.0140
SCC (%)	9.8	0	0.1508
Prostate (%)	9.8	10	0.9805
Lung (%)	2.4	10	0.2001
Colon (%)	19.5	30	0.3638
Uterus (%)	7.3	5	0.7353
Graft RCC (%)	2.4	0	0.4885
Gallbladder (%)	0	5	0.1522
Thyroid (%)	2.4	0	0.4885
Esophagus (%)	4.9	0	0.3181
Oncology treatment			
Palliative (%)	0	20	0.0033
Surgical (%)	65.9	10	< 0.0001
Chemotherapy (%)	2.4	10	0.2001
Radiotherapy (%)	2.4	5	0.5941
Without any treatment (%)	7.3	20	0.1472
Conversion into mTOR at the time of MO (%)	43.9	65	0.1249

BCC, basal cell carcinoma; SCC, squamous cell carcinoma; MM, malignant melanoma; RCC, renal cell carcinoma; PTLD, post-transplant lymphoproliferative disease; s-creat, serum creatinine level; TAC, tacrolimus; CyA, cyclosporine A; MMF, mycophenolate mofetil; CS, corticosteroids; mTORi, mTOR inhibitor; Basil/Dacl, basiliximab/daclizumab; Thymo, rabbit anti-thymocyte globulin; IVIG, intravenous immunoglobulin; PP, plasmapheresis; MO, malignancy occurrence; RT, renal transplantation

*The results are presented as a mean ± SD

Discussion

Malignancy after renal transplantation is an important medical problem during the long-term follow up. The prognosis of transplant patients with cancer is worse than in the general population with aggressive course and short survival times. The type of malignancy is different in various countries and dependent on genetic and environmental factors [11, 15]. The incidence of tumors in our register was 6% in the follow up period from 1 to 7 years, the average time of malignancy occurrence was 49.2 ± 34 months after transplantation, while the median was 45 months after transplantation. The incidence of malignant tumors in our study is comparable with the data in the literature which show development of malignant tumors in 15 to 20% of graft recipients after 10 years [16].

It is well known that renal transplant recipients (RTRs) are at greater risk of developing cancer compared to the general population [4]. This is especially true for cancers associated with viral infections and skin tumors [8, 17, 18]. Some cancers are common in the general population and occur at higher incidence in RTRs (e.g. cervical cancer, colon cancer and renal cell carcinoma) and therefore they require special attention [13, 18]. Our observations were in accordance with the literature data as the most common type of malignancy after transplantation in our cohort of patients were skin tumors in the rate of 28.2%, especially non-melanoma tumors, followed by non-skin tumors such as renal cell carcinoma in native kidneys in rate of 16.5% and cancer of colon in the rate of 12.9% of patients. We didn´t confirm a higher occurrence of cervical cancer in cohort of our patients as the incidence was only 4.7% in the followed-up period.

The malignancy was the reason of death in 1.4% patients from our cohort of 1421 patients who underwent renal transplantation in the follow-up period, where overall mortality from various reasons was 163 deaths (11.5%), and consequently the mortality among the patients with malignancy was twice as high (23.5%) as the overall mortality and comparable with 27% of deaths after the first-year post-transplant documented by Pilmore et al. [2]. The most common cause of death in our group of cancer patients were renal cell carcinoma, colon and lung cancer, but without statistical significance (p = 0.1472, 0.3638, 0,2001). Significantly mostly cured were the patients with non-melanoma skin cancer, especially those with BCC (p = 0.0140). Significantly better prognosis in our group of patients was related to early diagnosis establishment and immediate surgical treatment (P < 0.0001) mostly due to BCC and cured non-skin cancers.

In view of higher cancer incidence and poor prognoses, prevention and screening may play an important role in reducing the burden of cancer in renal transplant recipients. Every dialysis patient on the waiting list should undergo a regular screening program before transplantation as well as regular screening after transplantation to detect and treat a potentially malignant tumor at early stage. According to the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the monitoring, management, and treatment of kidney transplant recipients [18], routine cancer screening is recommended for all transplant individuals because the early detection will lead to early treatment, and thereby will reduce the morbidity and mortality caused by malignancies. After the development of cancer, the survival of transplant recipients is poor, and treatment options are limited by the transplant or comorbidities. It is thus important to consider the options for preventative measures and screening RTRs, which can theoretically deliver benefits of lower morbidity and mortality through reduced incidence or early interventions. It would be useful to arrange a prospective study focusing on the impact of the screening frequency on detection of early stage cancer, the patient compliance with screening and diagnostic procedures, and immediate radical treatment when the malignancy was recognized.

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