THE RISK OF POST-TRANSPLANT MALIGNANCY

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Abstract

Introduction. *Transplantation-related malignancies have become a major cause of post-transplant complications. Localization of a cancer in a renal graft is rare and needs a complex approach.*

Objective. *To assess the prevalence of the post-transplant malignancy and the characteristics of malignancies located on the renal graft.*

Method. *We performed a retrospective study on 827 patients transplanted in our institution between January 2000 and December 2010. Recipients were classified according to the immunological risk and the type of immune suppression received. The treatment of malignancies located at the renal graft aimed at preserving the renal graft function.*

Results. *The overall de novo malignancy prevalence was 9.43%, higher for the TMP group (10.98%) and lower for the CMP group (5.93%), p<0.0223. The prevalence of malignancies affecting the renal graft was 1.09 (9 cases). Renal cell carcinoma accounted for 2 cases and PTLD for 0.85% (7 cases). In the case of malignancy of the renal graft, the mean time from transplantation to diagnosis was 11.33 months (range 4-18 months) for PTLD and 33.67 months (range 17-60 months) for renal cell carcinoma.*

Conclusion. *The use of tacrolimus increased the standardized incidence ratio of post-transplantation malignancies. Induction with polyclonal antibody is associated with an increased risk for malignancy.*

Keywords: renal transplantation, malignancy, prevalence.

RISCUL DE CANCER POST-TRANSPLANT

Rezumat

Introducere. *Afecţiunile maligne au devenit o cauză importantă de complicaţii post-transplant. Localizarea cancerului la nivelul grefei renale este o situaţie rară, ce necesită o abordare complexă.*

Obiectiv. *Evaluarea prevalenţei generale a afecţiunilor maligne post-transplant şi a caracteristicilor malignităţilor localizate pe grefa renală.*

Metodă. *A fost realizat un studiu retrospectiv pe 827 de pacienţi transplantaţi în instituţia noastră în perioada ianuarie 2000 - decembrie 2010. Primitorii au fost grupaţi în funcţie de riscul imunologic şi tipul de imunosupresie primită. Tratamentul afecţiunilor maligne localizate la nivelul grefei renale a vizat conservarea funcţiei grefei renale.*

Rezultate. *Prevalenţa globală a malignităţilor de novo a fost 9,43%, mai mare pentru grupul TMP (10,98%) şi mai mică pentru grupul CMP (5,93%), p=0,0223. Prevalenţa afecţiunilor maligne ce afectează grefa renală a fost 1,09 (9 cazuri). Carcinomul cu celule renale a reprezentat 2 cazuri, iar PTLD 0,85% (7 cazuri). În cazul malignităţilor grefei renale, durata medie de la transplant la diagnostic a fost*

11,33 luni (interval 4-18 luni) pentru PTLD şi 3,67 luni (interval 17-60 luni) pentru carcinomul cu celule renale.

Concluzii. *Utilizarea tacrolimusului a crescut rata incidenţei standardizate a malignităţilor post-transplant. Inducţia cu anticorpi policlonali este asociată cu un risc crescut pentru malignităţi.*

Cuvinte cheie: transplant renal, afecţiune malignă, prevalenţă.

INTRODUCTION

Advances in immune suppression, transplantation surgery and laboratory tests, improve significantly patients' and graft survival after kidney transplantation. Longer survival for patients and grafts has led to an increased rate of transplantation-related malignancies, which has become a major source of post-transplant complications [1-4], limiting the life expectancy of kidney transplant recipients.

The incidence of *de novo* malignancies is significantly higher in renal transplantation recipients than in the general population, patients on dialysis or patients on the transplant waiting list [5] and is increased by the use of more potent immunosuppressive drugs [4]. The prevalence of malignancy is reported to be 14% in first 10 years and increases up to 40% at 20 years post transplantation [6,7].

OBJECTIVE

To assess the prevalence of post-transplant malignancy and the characteristics of malignancies located on the renal graft.

MATERIAL AND METHOD

We performed a retrospective study on 827 patients transplanted in our institution between January 2000 and December 2010. Recipients mean age was 42 years (range: 2 to 68 years). All patients received immunosuppression according to the immunological risk group.

High immunologic risk patients criteria include: high PRA ≥ 50%, history of immunization (re-transplant, history of early graft loss due to immunologic causes, prior positive cross-match), deceased donor graft, simultaneous pancreas and kidney transplantation. Intermediate immunologic risk patients were considered patients with: PRA: 10% - 50%, without history of immunization, age less than 14 years, over 3 mismatches and low immunologic risk were adult patients at first transplant, with 0-2 HLA mismatches, PRA < 10%, age > 60 years.

Induction of the immunosuppression was done in high and intermediate risk patients using anti lymphocyte polyclonal antibody (ALA) for 3 to 10 days. Since 2002, the intermediate risk recipients received induction with tacrolimus starting 3 days prior to transplantation. Low risk recipients received induction with cyclosporine 3 days prior to transplantation.

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Maintenance immunosuppression protocols include CyA in association with MMF and Prednisone (CMP). Since 2002, Tac was used mainly for high and intermediate risk patients to achieve potent immunosuppression in association with MMF and prednisone (TMP).

The prevalent malignancies over the follow-up period was assessed in terms of type and level of immunosuppression used.

PTLD was classified upon 2001 OMS classification [8]. The other malignancies were classified with regard to the appropriate classification system [9].

In the case of malignancies located on the renal graft, the initial treatment aimed at preserving the renal graft function.

All patients with renal cell carcinoma on renal graft underwent nephron sparing surgery whenever possible, followed by immunosuppression reduction.

PTLD treatment was adapted to the specific form of disease in an individual patient (the extent of the disease and the degree of acute illness of the patient) [10]. When suitable, medical treatment was combined with nephron sparing surgery or cryoablation to remove renal graft tumors. Patients with early lesions were treated by reducing immunosuppression and antiviral therapy with Acyclovir. For polymorphic or monomorphic PTLD localized in the renal graft, the treatment included also, monoclonal anti-B-cell antibody (anti CD20). The chemotherapy using standard CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone) treatment was reserved for patients with extended polymorphic and monomorphic PTLD. If patients did not respond to the treatment, the immunosuppression withdrawal and transplantectomy was decided.

RESULTS

Malignancy rates according to type of immunosuppression used are presented in Table I.

Seventy post-transplant *de novo* cancers and 8 non-melanoma skin cancers were found on a 10 years follow-up. The overall prevalence was 9.43%, higher for the TMP group (10.98%) and lower for the CMP group (5.93%). The difference was statistically significant, $p<0.0223$. Kidney and urinary tract malignancies (1,57%) and Kaposi sarcoma (1,69%) were the most prevalent malignancies in renal transplant patients.

The immunological risk (Table II) was similar in both groups, when compared patients with *de novo* malignancies with those without. The induction with anti

lymphocyte globulin (ALG) was significantly associated with malignancy in the CMP group: 14 (93,33%) versus 137 (57,56%), p=0.066. In the case of the TMP group, the induction with ALG lack significantly relation with the presence of malignancy: 34 patients (53.97%) versus 266 patients (52.06%), p>0,05.

Acute rejection episodes (Table II) requiring intensification of the treatment were more frequent in the CMP group (19.33%) when compared with TMP group (11.15%). In both groups, treatment of the rejection episodes was significantly statistically associated with the presence of malignancy: 14 cases (53.33%) versus 46 (19.33%), p=0.0019 for the CMP group and 12 cases (19.05%) versus 57 (11.15%), p=0.0848 for the TMP group.

Renal graft located malignancy

The prevalence of malignancies affecting the renal graft was 1.09 (9 cases). Renal cell carcinoma counts for 2 cases and PTLD for 0.85% (7 cases).

Of the PTLD cases, 1 was an early lesion, 2 were polymorphic forms, 4 were monomorphic.

The mean time from transplantation to diagnosis was 11.33 months (range 4-18 months) for PTLD and 33.67 months (range 17-60 months) for renal cell carcinoma. Early onset of the PTLD was encountered in 4 cases (57.17 %). Sex ratio was 2:1 (male/female). The patient characteristics, treatment and outcome are listed in Table III.

Treatment of clear cell renal cell carcinoma located on the renal graft

One patient, with localized renal graft tumor was treated by heminephrectomy followed by immuno-suppression reduction. At five years, the patient had functional graft.

Another case was treated by laparoscopic ultrasound guided tumor cryoablation. The patient underwent switch to rapamycin. The serum creatinine was 1.9 mg/dL at one year.

Table I. Incidence of post-transplant malignancy.

	CMP group		TMP group		Total	
Transplants	253		574		827	
Nr. malignancies	15	5.93%	63	10.98%	78	9.43%
Skin	2	0.79%	6	1.05%	8	0.97%
Stomach		0.00%	1	0.17%	1	0.12%
Lung, bronchia	1	0.40%	5	0.87%	6	0.73%
Kaposi sarcoma	3	1.19%	11	1.92%	14	1.69%
Breast	1	0.40%	6	1.05%	7	0.85%
Cervix uteri	1	0.40%	5	0.87%	6	0.73%
Kidney, ureter, urethra	2	0.79%	11	1.92%	13	1.57%
PTLD	5	1.98%	18	3.14%	23	2.78%

CMP: Cyclosporine A, Mycophenolate mophetil, prednisone regimen, TMP: Tacrolimus, Mycophenolate mophetil, prednisone regimen.

Table II. Distribution of malignant cases in regard to immunosuppression induction, the immunologic risk group and requirement for rejection treatment.

		CMP group				TMP group			
Malignancy		Yes		No		Yes		No	
Number of patients		15		238		63		511	
		N	%	N	%	N	%	No	%
Immunological risk									
	High	10	66.67%	125	52.52%	41	65.08%	273	53.42%
	Intermediate	2	13.33%	49	20.59%	14	22.22%	118	23.09%
	Low	3	20.00%	64	26.89%	8	12.70%	120	23.48%
Induction with ALG		14	93.33%	137	57.56%	34	53.97%	266	52.06%
Rejection treatment		8	53.33%	46	19.33%	12	19.05%	57	11.15%

CMP: Cyclosporine A, Mycophenolate mophetil, prednisone regimen, TMP: Tacrolimus, Mycophenolate mophetil, prednisone regimen, ALG: polyclonal anti lymphocyte globulins.

Table III. Patients with graft located malignancy.

Nr	Type of malignancy	treatment	outcome
1	RCC	heminephrectomy, immunosupression reduction	functional graft
2	RCC	cryotherapy, immunosupression reduction	functional graft
3	Early lesion	immunosupression reduction	functional graft
4	polymorphic PTLD	immunosupression reduction, anti CD20 monoclonal antibodies, cryoablation	functional graft
5	polymorphic PTLD	immunosupression withdrawal, anti CD20 monoclonal antibodies, CHOP	death (medullary aplasia)
6	monomophic PTLD	immunosupression reduction, anti CD20, Ganciclovir, cryoablation	functional graft
7	monomophic PTLD	immunosupression withdrawal, CHOP, transplantectomy	dialysis, alive
8	monomorphic PTLD	immunosupression reduction, acyclovir, CHOP	functional graft
9	monomorphic PTLD	immunosupression withdrawal, CHOP	dialysis, alive

RCC: Renal cell carcinoma, PTLD: Post-transplant lymphoproliferative disorder.

Treatment of graft localized PTLD

In the case of early lesion PTLD, the treatment consists of immunosuppression reduction with functional graft at follow-up.

In the case of polymorphic PTLD, one patient underwent cryoablation followed by switch to rapamycin and administration of anti CD20 monoclonal antibodies. The graft was functional at five years. One patient with systemic disease involving mediastinal lymph nodes, the lung and the spleen, was treated by immunosuppression withdrawal, anti CD 20 and chemotherapy (CHOP regimen). The patient died due to medullar aplasia.

In the case of graft localized monomorphic PTLD, the patient underwent cryoablation of the nodular lesion, immunosuppression reduction or switch to rapamycin, Ganciclovir, and anti CD20 monoclonal antibodies, with functional grafts. One patient had monomorphic disseminated PTLD involving the graft and the bone marrow and altered renal graft function. The immunosuppression was stopped followed by renal graft removal and chemotherapy (CHOP regimen). At four years, the patient is on dialysis.

We encountered one single case of high grade non-Hodgkin lymphoma, involving the graft and the mesenteric lymph nodes. The immunosuppression was discontinued and the patient was cured with standard chemotherapy (CHOP). He was dialyzed for four years, without recurrences.

DISCUSSIONS

Over the past 50 years, the medical community has witnessed great advances in both immunosuppressive drugs and strategies leading to better patient and graft survival rates. However, there are adverse effects and risks related to long-term use which pose a number of challenges to the clinician. Immunosuppressive therapies have to be tailored to meet the individual patient's characteristics and to balance the risks and benefits of these medications.

Because patients are not equal in regard with the chances of rejection, individualized protocols were developed considering main risk factors for to provide less aggressive but efficient immunosuppression.

One of the most significant prognostic laboratory tests is the PRA level but the simple fact of being a cadaver donor graft increases significantly the risk of kidney rejection. The number of HLA miss-matches are correlated with the graft survival on long term but only for renal grafts transplanted from a cadaver donor. In the case of renal transplant from a living donor, HLA matching has a reduced impact on the risk of rejection. A threshold set on HLA haploidentity is established with regard to major statistics [11,12]. The degree of immunization is another risk factor for rejection, especially for humoral rejection due to either preformed circulating antibody or memory lymphocyte reactivation.

Even in cases of cadaver donors, graft allocation should be considered besides immunological constraints, also the medical emergency waiting time for a transplant and availability of the required resources to perform the specific transplant [13].

New and improved immunosuppressive medications allow long term renal graft survival, but the longer the survival, the higher the risk of development of malignant tumors or cardiovascular disease. Post-transplant malignancy morbidity and mortality have become an important limitation for kidney transplantation [3,14].

The reported incidence and prevalence of different malignant diseases varies largely in different series. At 10 years 15 to 20% of the recipients will develop a malignant tumor, most of them being skin tumors and lymphoproliferative disorders [1,14]. The risk is 3-5 times higher compared with the general population, especially for the patients who received cell-depleting antibodies [2,14]. Calcineurin inhibitors increase the risk of malignancy, while rapamycin inhibitors have shown antineoplasic activities, firmly established for the treatment of post-transplant Kaposi's sarcoma [14].

Probability of graft transmitted malignancies is higher as the older donors are accepted. In fact, the etiology of post-transplant malignancy is multifactorial [3].

In our experience, prevalence of the *de novo* malignancies over a 10 year period was 9.43%. Immunosuppression regimens with tacrolimus reduces the rejection rate from 19.33% to 11.15%, when compared with cyclosporine regimens, but significantly increases the risk of newly developed malignancies (10.98% versus 5.93%, $p<0.0223$).

When assessing the risk group distribution of the patients with *de novo* malignancies, there are no significant differences. Yet, induction with ALG was more frequent in patients who developed post-transplant malignancies and received cyclosporine based regimens but not for those who received tacrolimus based regimens.

History of rejection treatment was significantly more frequent in patients who developed *de novo* malignancies either for those treated with cyclosporine or tacrolimus based immunosuppressive regimens.

Location of a *de novo* post-transplant malignancy on the renal graft is a rare event. In our experience, the most frequent situation was PTLD, sometimes with nodular forms. Whenever possible, minimal invasive, nephron-sparing surgery was done in order to preserve the renal graft function. Duration from transplantation to diagnosis was lower in the case of PTLD mainly due to the preexisting viral infections and secondary to immunosuppression which allows expression of oncogene. For renal cell carcinoma located on the renal graft, the longer the period, the increased chance of development of a malignancy.

Renal cell carcinoma in transplanted kidneys is less aggressive comparing with occurrence in native kidneys. Treatment will vary depending of tumor size and characteristics. To date, renal graft removal was performed

in most patients, which then returned to replacement treatment. The approach to these tumors has changed in recent years, and nephron-sparing surgery is being done in selected cases (small tumor size, eccentric tumor location, or a good blood flow to the rest of graft parenchyma). If these patients are followed up closely, the quality of life gained comparing with hemodialysis, justifies this type of surgery.

CONCLUSIONS

The use of tacrolimus has increased the standardized incidence ratio of posttransplant malignancies. Induction with polyclonal antibody is associated with an increased risk for malignancy.

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