Malignancies after kidney transplantation are associated with an increased risk of graft loss but not of chronic rejection

Tiziana Cena, Claudio Musetti, Marco Quaglia, Michele Battista, Corrado Magnani, Piero Stratta, Vincenzo Bagnardi
Nephrology and Kidney Translant, Univ. Piemonte Orientale, Novara, Italy
Unit of Medical Statistics and Cancer Epidemiology, University of Eastern Piedmont and CPO Piemonte, Novara, Italy.
Department of Statistics and Quantitative Methods, University of Milan-Bicocca, Milan, Italy
claudio.musetti@med.uniupo.it

BACKGROUND

Nowadays patient survival after a malignancy is as high of 71.3% at 10 years after the diagnosis of a first non-cutaneous malignancy (NCM).

However it is not clearly known how the diagnosis of a malignancy may affect graft function as compared to patients without malignancy.

On the one side, patients with a malignancy usually reduce their immunosuppressive (IS) therapy and are frequently exposed to "nephrotoxic" therapies. On the other side, virus-related malignancies may appear in patients are particularly "sensible" to IS: thesepatients may be less likely to develop a chronic rejection as they might already be correctly immunosuppressed even with a low-dose IS treatment.

Aim of this study is to evaluate the impact of NMSCs and NCMs on death-censored graft survival in a cohort of recipient of their first KTx, using a multivariate Cox model adjusted by known risk factors and considering malignancies as a time-dependent risk factor.

METHODS

Design: retrospective analysis of a prospective cohort of patients (n=682), enrolled between November 1998 and March 2013.

Inclusion criteria

- Adult patients receiving their first kidney transplant from a deceased donor
- Minimum follow up of six months.

Data Collection

Primary outcome/event: death censored graft failure (=chronic dialysis)

Malignancy was diagnosed histologically. NMSC might rarely have been diagnosed on clinical bases (when treated with cryotherapy).

Reduced immunosuppression (Red-IS): any single drug therapy OR steroids + mTOR-inhibitor or mycophenolate.

Statistical Methods

All study variables were evaluated as risk factors with univariate analyses; known and significant risk factors were included in a multivariate Cox model (forward stepwise procedure) for time-dependent variables (NCM and NMSC).

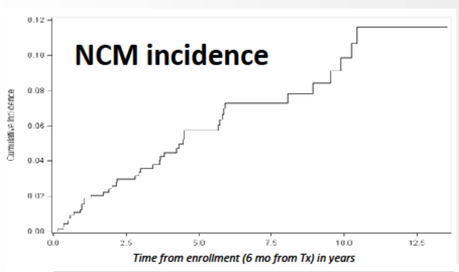
Moreover we evaluated graft survival in patients with a NCM from the time of NCM diagnosis and looked for risk factors with univariate analyses (chemotherapy, surgery, radiation therapy and reduction of IS).

RESULTS - 1

Parameter	Median (IQR)
Recipient Age (years)	53 (43-64)
Male Recipients	426/682 (62.5)
HCV Positive	43/682 (6.3)
Donor Age	55 (43-67)
Cold ischemia time (hours)	19 (16-22)
Delayed Graft Function	147/682 (21.6)
Induction therapy:	
None	78/682 (11.4)
Anti IL2 receptor	517/682 (75.8)
ATG	87/682 (12.8)
Maintenance IS therapy	
Tacrolimus – MMF/AZA +/- ster.	531/682 (77.9)
Cyclosporine– MMF/AZA +/- ster.	44/682 (6.5)
Other	107/682 (15.7)
1+ acute rejection (within 6 mo)	38/682 (5.6)
Creatinine at 6 months (mg/dL)	1.6 (1.3-2.0)
Creatinine >= 2.0 mg/dL	206/679 (30.3)
Urinary proteins at 6 mo. (g/24h)	0.20 (0.1-0.4)
Urinary proteins >= 0.5 g/24h	109/673 (16.2)

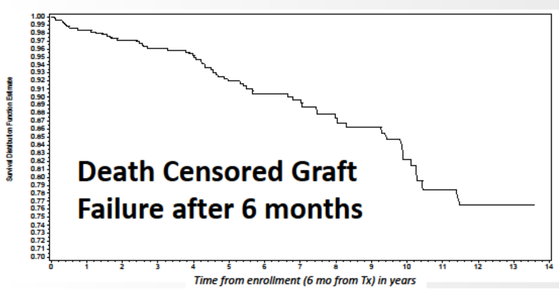
Over a total follow up of 3185 patient-years from the sixth post-KTx month (mean 4.67 years/patient), 50 patients developed a NMSC (10-years incidence: 11.1%) and 41 a NCM (10-years incidence: 9.1%).

During the follow up 37 patients died, particularly 10/41 (24.4%) patients with a NCM died as compared to 27/641 (4.2%) deaths among patients without a NCM (p<0.001).



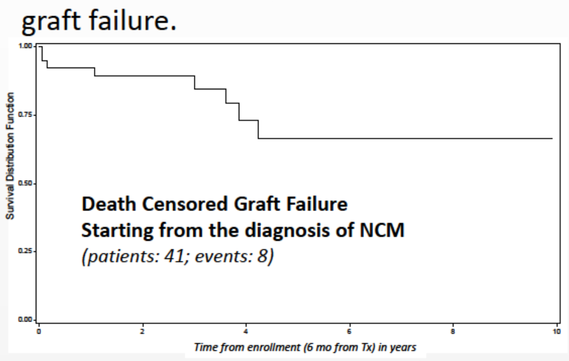
Death censored graft survival

In the entire cohort, we observed 63 graft losses (10-years death-censored graft survival: 85%), of which 38/63 (60.3%) due to chronic rejection and 25/63 (39.7%) for other causes.



Post-malignancy graft survival

Among 41 patients with a NCM, 10 patients (24.4%) died and 8 (19.5%) experienced graft failure.



The causes of graft loss were 2/8 (25%) chronic rejection, 2/8 (25%) a "de novo" nephropathy (1 myeloma kidney and 1 immunotactoid glomerulonephritis), 1/8 (12.5%) relapse of IgA nephropathy on an ECD kidney (best eGFR = 24 ml/min/1.73m2), 1/8 (12.5%) chronic pyelonephritis, 1/8 (12.5%) chronic pyelonephritis and reflux following radical prostatectomy and 1/8 (12.5%) graft nephrectomy for a RCC.

Death censored graft survival after NCM
Univariate model. Patients: 41; Events: 8

Covariate	HR (IC 95%)	p-value
IS Reduction	0.82 (0.21-3.32)	0.79
Surgery	0.59 (0.15-2.34)	0.45
Chemotherapy	0.72 (0.17-3.03)	0.66
Radiationtherapy	0.39 (0.05-3.14)	0.37

Among patients with a NCM, 20/41 (48.8%) reduced their IS therapy, as compared to 40/614 (6.5%; p<0.001) among other patients. Moreover the rate of graft failure in patients with a NCM who reduced IS therapy was 4/20 (20%), as compared to 4/21 (19.1%) in those who did not (rate ratio: 1.05). However, in patients without a NCM, the rate of graft failure in patients who reduced IS therapy was 8/40 (20%), as compared to 45/574 (7.8%) in those who did not (rate ratio: 2.56; p=0.016).

Death censored graft survival.
Multivariate model – Role of IS reduction.

Covariate	HR (95%IC)	p
Donor Age (per year)	1.030 (1.009-1.050)	0.004
Acute rejection	3.199 (1.636-6.255)	0.001
Creat ≥ 2 mg/dL	2.864 (1.538-5.334)	0.001
U-Prot ≥ 0.5 g/24h	2.215 (1.239-3.958)	0.007
NCM	2.782 (1.147-6.750)	0.024
IS Reduction (time-dependent)	1.483 (0.694-3.170)	0.309

RESULTS - 2

Death censored graft survival: risk factors.
Multivariate model. Patients: 682; Events: 63.

	Model including NMSC		Model including NCM	
Donor Age (per year)	1.03 (1.01-1.05)	0.010	1.02 (1.00-1.04)	0.019
Acute rejection	3.11 (1.63-5.92)	<0.001	3.27 (1.71-6.26)	<0.001
6 mo. Creat ≥ 2 mg/dL	3.19 (1.76-5.77)	<0.001	3.16 (1.74-5.73)	<0.001
6 mo. U-Prot ≥ 0.5 g/24h	2.16 (1.24-3.78)	0.007	2.30 (1.31-4.03)	0.004
NMSC	0.78 (0.29-2.07)	0.622	-	-
NCM	-	-	2.69 (1.17-6.18)	0.020

Death censored graft survival: causes of failure.
Multivariate model. Patients: 682; Events: 63.

	Chronic Rejection (events: 38)		Other Causes (events: 25)	
Donor Age (per year)	1.03 (1.00-1.05)	0.028	1.02 (0.99-1.05)	0.290
Acute rejection	3.63 (1.62-8.18)	0.002	2.90 (0.95-8.92)	0.060
6 mo. Creat ≥ 2 mg/dL	2.79 (1.31-5.96)	0.008	3.84 (1.44-10.22)	0.007
6 mo. U-Prot ≥ 0.5 g/24h	2.82 (1.40-5.66)	0.004	1.61 (0.62-4.13)	0.33
NCM	0.98 (0.22-4.48)	0.98	8.18 (2.77-24.18)	<0.001

DISCUSSION

*We defined in **a time-dependent analysis the hazard ratio of graft failure associated with a diagnosis of NMSC (HR=0.78, p=0.62) or NCM (HR=2.69; p=0.02).***

The association of NCM with graft failure has not yet been investigated as a time-dependent variable: indeed many different studies investigated graft survival since the diagnosis of a NCM, but they are not able to compare directly patients with a NCM with those without a NCM and may not be able to adjust for all known malignancy-independent risk factors.

Interestingly, in patients with an NCM, only a minority of grafts are lost to chronic rejection (25%), which is somehow unexpected because transplant physicians commonly taper the IS therapy after a malignancy, exposing patients to a potentially increased risk of rejection.

Actually the increased risk associated with NCM is due to other causes (HR=8.18; 95%CI = 2.77-24.18). NCM therapies (which may be nephrotoxic) were associated with a not significant reduction of risk of graft loss. Therefore, the increased risk of graft failure may be attributed malignancy associated nephropathies.

In our cohort NCMs act as an effect modifier of the relationship between IS reduction and graft loss. This finding may be consistent with the hypothesis speculating that patients who develop a malignancy are particularly susceptible to chronic IS at "standard doses".

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Claudio Musetti
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