Opportunistic Infections Among Long Term Survivors of Kidney Transplantation: Defining Risk Factors

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Introduction

- Kidney transplant (KT) recipients are at increased risk for opportunistic infections (OIs) in the 2-6-month post-transplant period[1]
- After that period, the risk of opportunistic infection decreases
- An increased risk of OI after 6 months is typically associated with an increase in immunosuppression
- However, little is known regarding the incidence of OI among long term survivors of KT (i.e ≥ 10 years)

Objectives

•To describe the incidence of very late opportunistic infections (VLOIs) in long term survivor of KT

•To define any risk factors associated with VLOIs in KT recipients

Methods

- A retrospective chart review of patients age ≥18 who underwent KT between 2003 and 2009, followed up at Yale New Haven Hospital, and survived ≥10 years post-transplant was performed.
- Data collected were as follows: demographics, comorbidities, and transplant data including age at time of KT, indication for KT, induction and maintenance immunosuppression and infection occurring 10 years after KT.
- VLOIs were defined as opportunistic infections that occurred 10 years or more of KT. The AST on Infectious Disease Monitoring definitions was used to categorize opportunistic infections.[2]
- Data related with VLOIs were collected including date of infection, clinical and microbiologic data, absolute lymphocyte count (ALC), treatment of rejection within 1 year of infection, and status at 30-days after diagnosis of infection.
- Simple logistic regression was performed to determine clinical characteristics associated with risk for VLOIs.

Results

Table 1. Characteristics of 16 patients with very late-onset opportunistic infections

Characteristics	Patients With Opportunistic Infections (n = 16)
Age at time of transplant	
18-39	6 (37.5%)
40-59	6 (37.5%)
60-79	4 (25%)
Median Years From Transplant to Last Follow Up (range)	14.2 (10-37)
Alive at Time of Study	11 (68.8%)
Living Donor	7 (43.8%)
Retransplantation	1 (6.2%)
Male	10 (62.5%)
Race	
Asian	2 (12.5%)
Black	3 (18.8%)
Hispanic	3 (18.8%)
White	8 (50%)
Induction Immunosuppression	
Basiliximab	3 (18.8%)
Daclizumab	1 (6.2%)
Methylprednisolone	7 (43.8%)
Thymoglobulin	3 (18.8%)
Unknown	2 (12.5%)
Maintenance Immunosuppression Regimen	
Belatacept and prednisone	1 (6.2%)
Belatacept, mycophenolate, and prednisone	4 (25%)
Cyclosporine, mycophenolate, and prednisone	1 (6.2%)
Tacrolimus and prednisone	4 (25%)
Other	4 (25%)
Mean Charlson Comorbidity at Time of Diagnosis (SD)	6.3 (3.6)
Comorbidities	
Hepatitis C+	2 (12.5%)
Diabetes Mellitus	6 (37.5%)
Renal disease requiring Renal Replacement Therapy	2 (12.5%)
Cardiovascular Disease	5 (31.3%)
Cerebrovascular Injury	4 (25%)
Malignancy	4 (25%)
Number of Ver y Late Onset Opportunistic Infection (OI)	
1	6 (37.5%)
2	5 (31.3%)
3+	5 (31.3%)
Mean Absolute Lymphocyte Count (103/µL) at time of OI	0.78

Table 2. Individualized data from 16 patients with very late-onset opportunistic infections

Patient	Age at Time of Transplant	Diagnosis for Kidney Transplant	CCI	H/o DM (1=Yes; 2=No)	On Dialysis at Time of OI (1=Yes; 2=No)	CMV Status	Maintenance Immunosuppression	Total Number of Very Late Infections	Treatment for Rejection Within 1 Year of OI (1=Yes; 2=No)	OI Timing (years s/p transplant)	Age at Time of OI (years)	Type of OI	Pathogen	ALC at time of Infection (10^3/µL)	30-Day Outcome
1	25	Analgesic Nephropathy	3	2	1	D+/R-	Tacrolimus + Mycophenolate + Prednisone	2	1	10	35	Pneumonia	Adenovirus	0.5	Alive
2	63	DM 2	7	1	2	D-/R+	Tacrolimus + Mycophenolate + Prednisone	2	2	11	73	Viremia	CMV	1.1	Alive
3	47	Hypertensive Nephropathy	4	2	2	D?/R-	Cyclosporine + Mycophenolate + Prednisone	1	2	15	62	Esophagitis	HSV + Candida	0.6	Alive
4	50	DM 1	7	1	2	D-/R+	Belatacept + Prednisone	3	2	12	63	Esophagitis	Candida	0.7	Alive
5	72	MPGN	9	2	2	D-/R+	Tacrolimus + Prednisone	5	2	15	87	Meningitis	Cryptococcus	0.2	Deceased
6	45	DM 1	15	1	2	D-/R+	Tacrolimus + Mycophenolate + Prednisone	10	1	13	59	Colitis	CMV	0.6	Alive
7	70	DM 2	8	1	2	D-/R+	Belatacept + Mycophenolate + Prednisone	3	2	11	81	Pneumonia	PJP	0.2	Alive
8	43	Glomerulonephritis	3	2	1	D-/R+	Belatacept + Mycophenolate + Prednisone	1	2	11	54	Pneumonia	PJP	0.6	Alive
9	31	DM 1	14	1	1	D?/R-	Tacrolimus + Prednisone	6	2	29	59	Pneumonia	PJP	0.2	Alive
10	33	Hypertensive Nephropathy	4	1	2	D?/R-	Belatacept + Mycophenolate + Prednisone	1	2	10	43	Pneumonia + Fungemia	PJP + Cryptococcus	0.2	Deceased
11	26	Hypertensive Nephropathy	4	2	2	D-/R+	Sirolimus + Prednisone	2	2	33	59	Colitis	Adenovirus	1.1	Alive
12	67	Hypertensive Nephropathy	3	2	2	D-/R+	Everolimus + Prednisone	1	2	12	79	Viremia	CMV	0.2	Deceased
13	41	Obstructive Nephropathy due to Neurogenic Bladder	4	2	2	D+/R-	Belatacept + Mycophenolate + Prednisone	1	2	10	51	Pneumonia	PJP	0.6	Alive
14	32	Polycystic Kidney Disease	2	2	2	R+	Tacrolimus + Mycophenolate + Prednisone	2	2	15	46	Pneumonia	PJP	0.6	Alive
15	43	Hypertensive Nephropathy	4	2	2	R+	Sirolimus + Mycophenolate + Prednisone	1	2	10	53	Skin	VZV	1.4	Alive
16	34	Polycystic Kidney Disease	3	2	2	D?/R-	Sirolimus + Prednisone	1	2	15	50	Skin VZV	1.4	Alive	

Results

- Of the 332 KTRs, 16 (4.8%) developed a VLOI with a total of 18 infections.
- Among 16 patients with VLOI, half were White and most were male.
- The mean age at time of transplant was 45 (S.D 15.5) and the mean post-transplant follow-up was 15.8 years (S.D. 7.5).
- The mean ALC at the time of VLOI was 780/µL (S.D. 430).
- Two patients (12.5%) had acute rejection of their transplanted kidneys within 1 year of VLOI.
- Pathogens implicated in VLOI were the following: PJP, (n=6), *Candida* (n=2), CMV (n=1), Cryptococcus (n=2), Adenovirus (n=2), VZV (n=2), and HSV (n=1)
- Types of infections included pneumonia (n=7), GI (n=5), CNS (n=3), skin/soft tissue (n=1)
- Two patients had 2 concurrent VLOIs (1 had PJP and disseminated cryptococcal infection and 1 had HSV and candida esophagitis)
- Thirty-day mortality for VLOI was 18% (n=3)
- VLOI incidence was associated with years from date of transplant [OR 1.3, p=0.02], cerebrovascular disease [OR 4.45, p=0.02], and lower ALC [OR 5.9, p<0.05].
- Although not statistically significant, there was a trend towards an association between increasing Charlson Comorbidity index and increased incidence of VLOI [OR 1.24, p=0.09].

Discussion/Conclusion

- Overall, the incidence of VLOIs (beyond 10 years post transplant) was low among this population of long-term survivors of kidney transplant.
- These VLOIs infrequently occurred in the setting of intensified immunosuppression.
- Low ALC is an independent predictor of VLOIs in this population
- Cerebrovascular disease as a comorbidity may be a surrogate marker of physiologic function in aging transplant recipients.
- Risk of VLOIs increases as one ages.
- VLOIs in our cohort was associated with poor outcomes.
- Despite stable immunosuppression in most long-term survivor of KT, certain patients may remain at risk for VLOIs. VLOIs should be considered a differential amongst those with low ALC and those with advanced age.
- Appropriate prophylaxes should be considered for those at risk.

References

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