

Research Paper

Timing of mTORi usage and outcomes in kidney transplant recipients

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Abstract

The introduction of mammalian target of rapamycin inhibitors (mTORi) as immunosuppressive agents has changed the landscape of calcineurin inhibitor-based immunosuppressive regimens. However, the timing of mTORi conversion and its associated outcomes in kidney transplantation have conflicting results. This study investigated the effect of early or late mTORi post-transplant initiation on major transplant outcomes, including post-transplant malignancy, in kidney transplant recipients in our center. We enrolled 201 kidney transplant recipients with surviving function grafts of >3 months between 1983 and 2016. Patients were divided into three groups: early mTORi (initiated within 6 months of kidney transplantation), late mTORi, (mTORi initiation >6 months after kidney transplantation) and no mTORi. The mean creatinine at conversion was 1.46 ± 0.48 mg/dL and 1.30 ± 0.53 mg/dL for the early and late mTORi groups, respectively. During the study period, 10.5% of mTORi users and 19.2% of mTORi nonusers developed malignancy, mainly urothelial carcinoma. After adjustment for confounding factors, mTORi users were found to have a lower incidence of post-transplant malignancy than did nonusers (adjusted OR: 0.28, $P = 0.04$). No significant difference was observed between early and late mTORi users. Our results verified the potential advantages of mTORi usage in reducing cancer incidence after kidney transplantation. However, no significant result was found related to the timing of mTORi introduction. Future studies should include a longer observation period with a larger cohort.

Key words: kidney transplantation; immunosuppressant; mammalian target of rapamycin inhibitor (mTORi); outcomes; malignancy

Introduction

Advancements in surgical and medical techniques and immunosuppressive agents have led to remarkable short-term outcomes in kidney transplantation. However, with improved patient survival and an aging transplant population, long-term complications have become a major challenge [1]. The prolonged modification of the immune system of kidney transplant recipients is associated with the risk of opportunistic infection and various cancers [1].

The incidence of malignancy in kidney transplant recipients is at least 2–4-fold higher than

that in the age- and sex-matched general population [1, 2], with higher cancer-related mortality [3]. The pattern of post-transplant malignancy (PTM) varies among geographical regions. Studies from Western countries have indicated that non-melanoma skin cancer is the most common PTM [4]. By contrast, skin cancer has a lower incidence in the Asian population. In Japan, gastric and kidney cancer are the two most frequent PTMs, whereas in Korea, they are gastric cancer and lymphoma [5, 6]. In Hong Kong, non-Hodgkin lymphoma has the highest standardized incidence ratio among PTMs [7], and in Taiwan and

China, urothelial carcinoma is the most common PTM (approximately 40%) [8, 9].

Immunosuppressive therapies may directly affect cancer growth through various mechanisms. Cyclosporin and tacrolimus increase the risk of malignancy in kidney transplant recipients [10, 11], whereas mammalian target of rapamycin inhibitors (mTORi) reduce the risk [12, 13]. However, mTORi use in kidney transplantation is associated with inferior graft survival [14, 15] and increased mortality risk [16, 17]. In recent meta-analysis, Wolf S. et al found that initiation of mTORi within 3 months of kidney transplantation may reduce the future risk of malignancy [18] but in Hahn et al. analysis, mTORi treatment failed to demonstrate a reduction in cancer risk [19]. These controversial results regarding the role of mTORi and timing of introduction in transplant outcomes need further evidence for verification.

This study investigated the effect of early and late mTORi initiation on major transplant outcomes, including PTMs, in kidney transplant recipients.

Materials and Methods

Study population

This retrospective observational study included kidney transplant recipients followed up in a medical center in southern Taiwan from January 1983 to April 2016. The immunosuppressive treatment in our hospital consisted of induction therapy (methylprednisolone and basiliximab, an interleukin-2 receptor antagonist) and maintenance treatment (based on tacrolimus, mycophenolate mofetil, and prednisolone). mTORi, including rapamycin and everolimus, were included in the maintenance regimen if the graft function was stable 3 months after transplantation, minimizing the calcineurin inhibitor (CNI) dosage. Inclusion criteria were kidney transplant recipients who had mTORi as one of their maintenance immunosuppressive agents with a treatment duration of >3 months. We excluded patients who were diagnosed with malignancy before the introduction of mTORi. A total of 201 kidney transplant recipients who survived with functioning grafts for >3 months were included.

At the baseline visit, the patients' sociodemographic characteristics, medical history, and current maintenance immunosuppressive medications were recorded. Their medical histories were confirmed through doctors' chart reviews. The patients' biochemistry measurements were collected at the baseline visit, before and after kidney transplantation, and at the beginning of mTORi treatment. The patients were stratified into three

groups according to mTORi usage and time of initiation: no mTORi, early mTORi (mTORi initiation within 6 months of kidney transplantation), and late mTORi (mTORi initiation >6 months after kidney transplantation). Our patients received regular follow-up in the nephrology and urology clinics after the transplant surgery for immune status and disease progression monitoring. Screening for malignancy, including tumor marker survey, kidney and liver sonography, chest X-ray, and urine cytology, was conducted every 6 months.

Ethics statement

The study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E(II)-20150089). Written informed consent was obtained from all patients, and all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. The patients provided consent for the publication of clinical details.

Outcomes

The association of early and late mTORi initiation with major transplant outcomes in kidney transplant recipients was analyzed, which included overall survival, patient survival, first-year rejection, and PTMs.

Statistical analysis

The baseline characteristics of all the patients are expressed as percentages for categorical data and means \pm standard deviations for normally distributed continuous variables. Multivariate logistic regression analyses were performed to evaluate the association among mTORi, rejection, and PTM. Multivariate Cox regression analysis was conducted to evaluate the association between mTORi and graft failure and mortality. $P < 0.05$ was considered statistically significant. All analyses were performed using STATA statistical software, v11 (StataCorp LP, College Station, TX, USA). Graft and patient survival estimates were compared using the log-rank test. Kaplan-Meier estimates of graft/patient survivals were compared using the log-rank test. Hazard ratios for graft failure/mortality were calculated using the multivariate Cox regression analysis. Odds ratios for rejection/malignancy were examined using multivariate logistic regression analysis. Adjustments were made for the following major recipient factors: age, body mass index, diabetes mellitus, cause of end-stage renal disease, hepatitis B virus (HBV), hepatitis C virus (HCV), and immunosuppression.

Results

The baseline characteristics and demographic data of the study cohort are presented in Table 1. A total of 201 kidney transplant recipients were included, with a mean age of 46.2 ± 11.6 years and body mass index of 22.3 ± 3.7 kg/m². Of the included patients, 51.7% were men, and 11.6% and 7% were HBV and HCV carriers, respectively. The mean follow-up duration was 2368 ± 1700 days. The mean duration of mTORi use was 821.3 ± 3225 days (Table 1).

Table 1. Baseline Characteristic and Demographic Data of the mTORi User and Non-users

	No mTORi (N=78)	Early mTORi (N=39)	Late mTORi (N=84)	Total (N=201)
Age at Tx, years	46.8±10.7	45.8±12.4	45.8±12.1	46.2±11.6
Male, %	46.2%	48.7%	58.3%	51.7%
BMI, Kg/m ²	21.6±2.8	22.3±4.3	22.9±4.1	22.3±3.7
Initial Cr, mg/dl	-	1.46±0.48	1.30±0.53	-
HBV	9 (12.7%)	3 (7.9%)	10 (12.5%)	22 (11.6%)
HCV	7 (10.1%)	3 (7.9%)	3 (3.8%)	13 (7%)
DM	12 (15.4%)	12 (30.7%)	18 (21.4%)	42 (20.9%)
Hypertension	63 (80.8%)	30 (76.9%)	60 (71.4%)	153 (76.1%)
Living donor	7 (9.0%)	4 (12.3%)	3 (3.6%)	14 (7.0%)
Induction	51 (78.5%)	31 (91.2%)	59 (88.1%)	141 (84.9%)
Tacrolimus	69 (89.6%)	36 (92.3%)	64 (76.2%)	169 (84.5%)
MMF	67 (85.9%)	39 (100%)	81 (96.4%)	187 (93.0%)
Steroid-free in 3 m	6 (8%)	14 (35.9%)	14 (17.1%)	34 (16.9%)
Follow-up days	2420±1993	1643±1072	2656±1555	2368±1700
Overall graft failure	27 (34.6%)	7(18%)	18(21.4%)	52 (25.9%)
Back to dialysis	17 (21.8%)	4 (10.3%)	11 (13.1%)	32 (15.9%)
Mortality	11 (14.1%)	3 (7.7%)	9 (10.7%)	23 (11.4%)
Rejection in 1 yr	5 (6.4%)	5 (12.8%)	10 (11.9%)	20 (10.0%)
Post-Tx	15 (19.2%)	5 (12.8%)	8 (9.5%)	28 (13.9%)
Malignancy				

Abbreviations: Tx: transplant; BMI, body mass index; Cr, creatinine; HBV, hepatitis B; HCV, hepatitis C; DM, diabetes mellitus; MMF, mycophenolate mofetil; m, month; yr, year.

The mean creatinine level at conversion was 1.46 ± 0.48 mg/dL and 1.30 ± 0.53 mg/dL for the early and late mTORi groups, respectively (Table 1). Most patients received the interleukin-2 receptor antagonist Simulect® (Novartis Pharma Stein AG, Switzerland) as the induction agent (84.9%). The maintenance regimens consisted mostly of tacrolimus (84.5%) and mycophenolate mofetil (MMF, 93.0%). Of the included patients, 16.9% had steroid-free maintenance treatment for 3 months after transplantation (Table 1). The overall mortality rate was 11.4%, mainly due to cardiovascular events, followed by PTM and infection (Table 2).

Of the 201 patients, 28 (13.9%) developed PTM, 15 of whom (19.2%) were mTORi nonusers. The most common PTM was urothelial carcinoma (n = 10), followed by hepatocellular carcinoma (n = 7) (Table 3).

Table 2. Causes of Death between mTORi users and Non-users

	No mTORi (N=78)	Early mTORi (N=39)	Late mTORi (N=84)	Total (N=201)
Cardiovascular	4	2	3	9
Infection	2	0	3	5
Malignancy	3	1	3	7
Others	2	0	0	2
All	11	3	9	23

Table 3. Types of Malignancy

Type of malignancy	Frequency
Breast cancer	1
Colon cancer	1
Cervix cancer	1
Hepatocellular carcinoma	7
Lung cancer	2
Lymphoma	1
Pancreas cancer	1
Prostate cancer	2
Renal cell carcinoma	1
Urothelial carcinoma	10
Peritoneal carcinomatosis	1
Total	28

We compared overall graft and patient survival with and without mTORi use. In the multivariate analysis, no significant association was noted between these two groups, but the early mTORi group exhibited a trend of better survival outcomes than did the other groups (Figure 1A, 1B). mTORi users had higher incidents of graft rejection 1 year after transplantation, but this association was not significant in multivariate analysis (adjusted OR: 1.40, $P = 0.59$; Figure 2). After adjustment for confounding factors, mTORi users had a lower incidence of PTM than did nonusers (adjusted OR: 0.28, $P = 0.04$), but no significant difference was observed between early and late mTORi users (Figure 3).

Discussion

In this study, we examined the timing of mTORi usage and its related outcomes and reviewed the incidence of PTM in kidney transplant recipients. mTORi users had a lower incidence of PTM than did nonusers. However, no differences were observed between early and late mTORi users in patient survival, graft survival, or acute rejection.

mTORi exert complex effects on the immune system due to the multiple roles of the mTOR signaling pathway in the immune cascade [20]. mTOR pathway inhibition interferes with cell growth and proliferation and suppresses the immune response by interfering with T-cell proliferation [21, 22]. Compared with CNIs, mTORi have less direct nephrotoxicity. mTORi combined with low-dose cyclosporine lowers skin cancer incidence [23, 24]. In the CONVERT trial, kidney transplant recipients with

sirolimus and a CNI-free regimen had a lower overall incidence of malignancies (2.1 vs 6.0 malignancies per 100 person-years of exposure) [23]. However, in the ZEUS study, which compared everolimus with CNI elimination versus a standard CNI regimen, malignancy was reported in 1.6% of everolimus-treated patients compared with 6.4% in the standard CNI group [25]. These results imply that mTORi provide protection against PTM.

Compared with the general population, kidney transplant recipients have a higher risk of cancer, especially skin cancer and virus-related cancers [1, 29]. Cancers with higher standardized incidence ratios observed in organ transplant recipients are nonmelanoma skin cancers, followed by Kaposi sarcoma and posttransplant lymphoproliferative disease [26]. Urothelial carcinoma is the most common PTM in Taiwan [27, 28]. The most common PTMs in our study were urothelial carcinoma and

hepatocellular carcinoma. In a nationwide cohort population-based study, Tsai et al. demonstrated that heart, lung, kidney, and liver transplant recipients had a three-fold risk of de novo cancer compared with the general population [29]. Kidney transplant recipients were associated with a standardized incidence ratio of 10.93 (95% CI, 9.20–12.99) for urinary tract malignancies, among which bladder cancer was the most common [29]. The high prevalence of HBV and HCV infection in Taiwan may explain the increased risk of hepatocellular carcinoma in organ transplant recipients, but this association requires further exploration by comparing kidney transplant recipients with and without HBV and HCV.

The mTORi-based immunosuppressive regimens were introduced in CNI minimization/withdrawal strategies to prevent CNI-associated nephrotoxicity. Early conversion of CNI to mTORi within the first 6 months of transplantation has been proposed as a potential strategy to reduce CNI toxicity [30]. However, an increased risk of graft loss was observed in mTORi-treated patients. In the ZEUS study, patients were randomized to everolimus or cyclosporine arms at 4.5 months post-transplant, and a higher biopsy-confirmed acute rejection (BCAR) was observed in the everolimus arm [31,32]. In the CONCEPT study in which patients were randomized at 3 months, the BCAR rate was 17% in the sirolimus arm compared with 8% in the cyclosporine arm. Most rejection occurred in the sirolimus arm when steroids were discontinued at 8 months after transplantation [33]. To investigate the effect of late conversion of mTORi (>6 months post-transplantation), the CONVERT trial revealed no significant difference in renal benefit, BCAR, graft, and patient survival [34]. In our study, minimization in the CNI dosage was noted in the

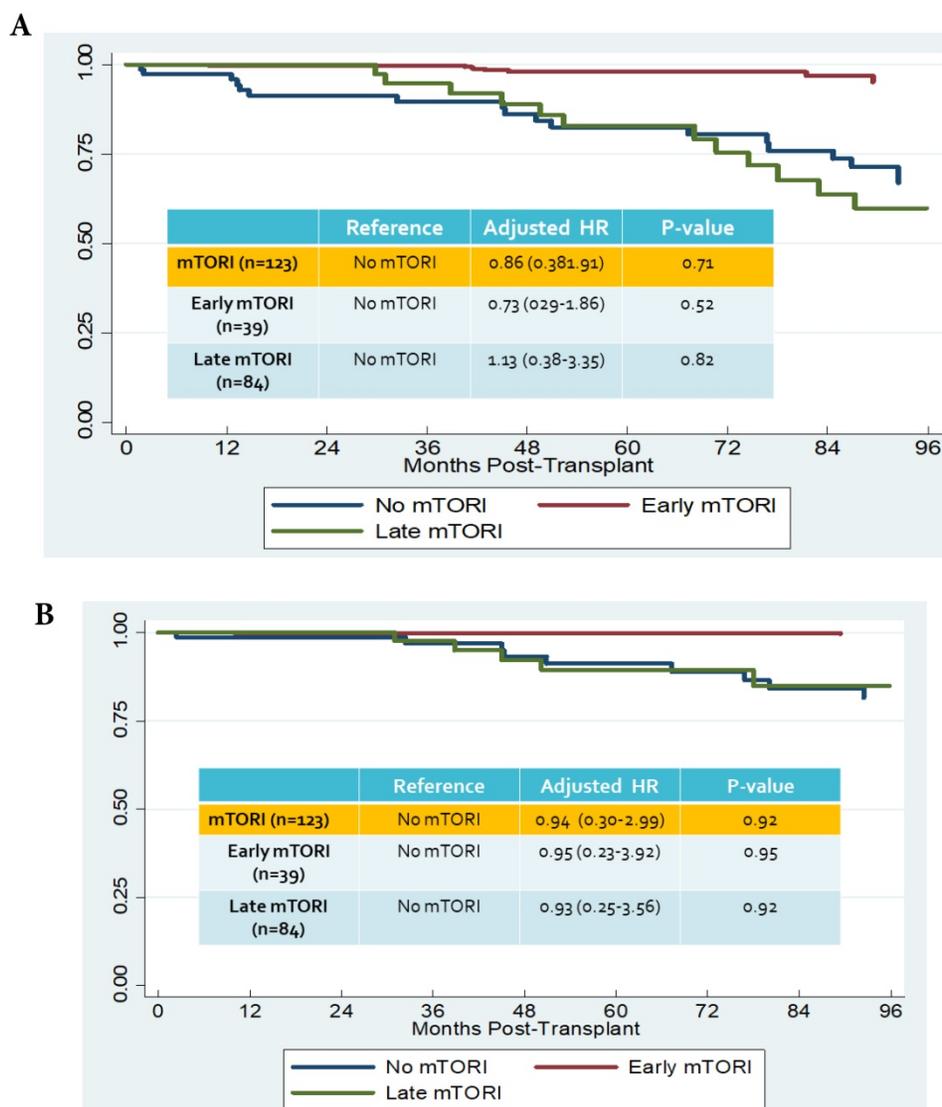
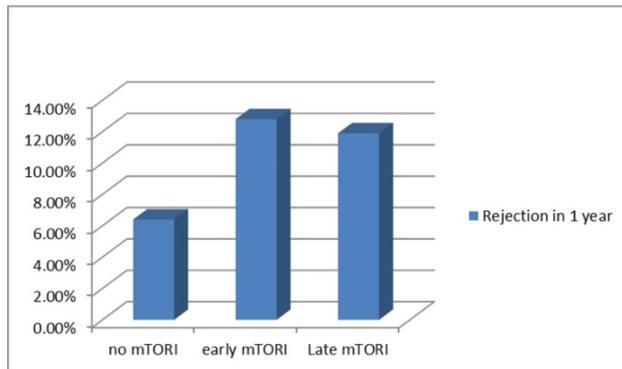


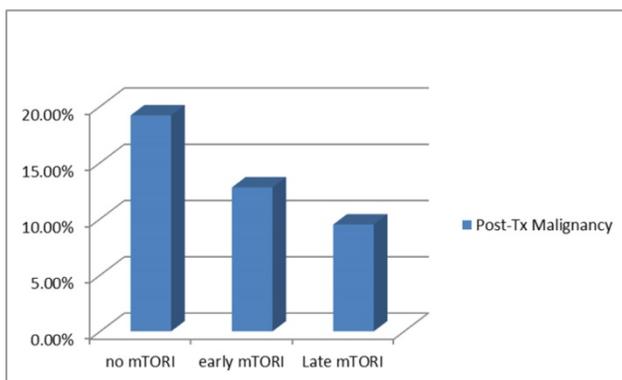
Figure 1. A. Overall graft survival in mTORi User and Non-users. Figure 1B. Patients survival in mTORi User and Non-users.

mTORi user group, but this was not significantly associated with patients' survival, graft survival, or acute rejection.



	Reference	Adjusted OR	P-value
mTORi (n=123)	No mTORi	1.40 (0.41-4.82)	0.59
Early mTORi (n=39)	No mTORi	1.57 (0.38-6.45)	0.52
Late mTORi (n=84)	No mTORi	1.25 (0.30-5.23)	0.76

Figure 2. Rejection Rate in 1 year of mTORi User and Non-users.



	Reference	Adjusted OR	P-value
mTORi (n=123)	No mTORi	0.28 (0.08-0.96)	0.04
Early mTORi (n=39)	No mTORi	0.64 (0.18-2.24)	0.49
Late mTORi (n=84)	No mTORi	0.35 (0.11-1.09)	0.07

Figure 3. Post-transplant Malignancy rate in mTORi User and Non-users.

This study has several limitations. First, it was a single-center observational study with a small cohort. Second, the follow-up period was short, which might not reflect longer-term graft outcomes and PTM incidence. Third, sirolimus and everolimus were studied as a class (mTORi) due to the small number of everolimus used. Finally, the modification of immunosuppressive agents in kidney transplant recipients might affect this study's ability to correlate the effect of the dose effect of immunosuppressive agents on PTM incidence.

Conclusion

In our cohort of renal transplant recipients, mTORi use was associated with a decreased risk of

PTM. However, no difference in mortality, graft loss, and PTM was noted in patients with early conversion to mTORi (within 6 months of kidney transplantation). The most common PTMs were urothelial and hepatocellular carcinoma. The discrepancy in cancer occurrence highlighted the need for developing specific strategies for cancer surveillance in kidney transplant recipients.

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Competing Interests

The authors have declared that no competing interest exists.

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