Sirolimus use improves cancer-free survival following transplantation:
A single center 12-year analysis

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Introduction:

The introduction of calcineurin inhibitors [CNIs] to steroid-based anti-rejection regimens decreased the incidence of acute rejection and improved long-term graft survival. (1,2) However, CNIs have been found to lead to an increased risk of malignancy. The risk of developing malignancy following transplantation has been tied to both dosage and length of exposure to immunosuppressant therapy. (1,2)

Over the last 15 years, Sirolimus has emerged as a successful immunosuppressant agent with low associated nephrotoxicity. Many studies evaluating the efficacy of Sirolimus coupled with CNIs have suggested that the combination of these medications results in an additive immunosuppressant effect with potential minimization of side effects/toxicities. (3,4)

The work presented here reflects our 12-year experience with Sirolimus substituting for traditional long-term steroid-based immunosuppression regimens following renal transplantation.
we aimed to determine the long-term consequences of our Sirolimus implementation protocol on rates of malignancy following transplantation.

Methods:

From April 2003 to December 2013, 563 kidney transplant recipients at Albany Medical Center (mean follow-up: 72 months, range:36–120) were entered in an early steroid withdrawal protocol with Sirolimus used as part of long-term immunosuppression.

We compared outcomes in our SBP (Sirolimus based protocol) recipients with the results from a control cohort of patients maintained on chronic steroids (December 2001to December 2002; n= 65). Both cohorts of patients were induced with 4-5 mg/ kg of Thymoglobulin depending on hematologic considerations and a Solu-medrol taper (375-20 mg) over 6 days.

Immunosuppression protocols for the SBP are summarized in table 1.

Table 1

Immunosuppression regimen	
Induction	
Thymoglobulin	0.5-1.0 mg/kg/day for total dose of 4-5 mg/kg*
Solu-medrol	Day 0 - 375 mg, Day 1 - 200 mg, Day 2 - 160 mg, Day 3 - 12 0 mg, Day 4 - 80 mg, Day 5 - 4 0 mg, Day 6 20 mg
Tacrolimus	8-10 ng/ml on Discharge
Mycophenolate Mofetil	Day 0 - Day 5 - 2 g/day, Day 6 - 1 g/day
Sirolimus	Day 6 - 8-10 ng/mlb
Maintenance	
Tacrolimus	Discharge - Day 90 - 8-10 ng/ml, then 2 ng/ml[a]
Mycophenolate Mofetil	1 g/day
Sirolimus	8-10 ng/ml[b]

*Dose reduced secondary to thrombocytopenia/leukopenia.
[a] 12-h. trough.
[b] 24 h. trough.

Steroid protocols maintained a 12 h Tacrolimus trough level of 8-10 ng/ml in addition to steroids (4-8 mg daily following discharge) and Mycophenolate Mofetil (1 g/day).

Pre-transplant cancer screening was standardized for all patients. All patients underwent a thorough history and physical exam as well as a chest X-ray. All female patients were required to have yearly Pap smears. All female patients over 40 years old underwent mammography with subsequent follow up mammograms per standard recommendations. Female patients over 50 years old were required to obtain yearly mammograms. Men over 50 years old were required to have a screening PSA with repeat testing every 4 years. All patients over 50 years old were required to undergo screening colonoscopy with follow up colonoscopy per standard recommendations.

Results:

Sirolimus-based immunosuppression results in equivalent cancer diagnoses compared to standard [steroid-based] regimens:

There were no significant differences between the control and SBP groups in the rates of these pre-transplant cancer diagnoses ($p > 0.05$) (including Non-Melanoma Skin Ca, Breast Ca, Cervical Ca, Urothelial Ca and Prostate Ca). Patients were followed up to 12 years post-transplantation and monitored for new cancer diagnoses. For skin, breast, cervical, urothelial, and prostate cancers, the prevalence of post-transplant diagnoses were statistically equivalent between the standard [steroid based] and SBP groups ($p > 0.05$).

12-year follow-up data did demonstrate a statistically significant difference in the rates of post-transplant lymphoproliferative disorder (PTLD) in the control [steroid-based] vs. SBP groups (5.88% vs. 0.5%, respectively< 0.05)

Additionally, the rate of cancer-related mortality in the sirolimus-based group was also found to be significantly lower (2.94% vs. 0.025%, $p = 0.01$).

Kaplan-Meier curves demonstrate improved cancer-free survival 10-12 years post-transplant [Fig. 1]. we identified a more profound improvement in cancer-free survival among patients in the SBP group ($p = 0.05$, Fig. 1). This effect is most evident close to 120 months post-transplantation [Fig. 1]. Patient survival rates remain equivalent throughout our study [$p = 0.22$].

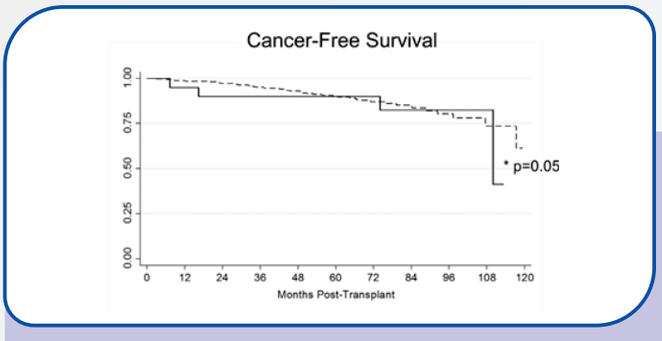

Fig1. Cancer- free survival was equivalent amongst our groups, but diverges around 100 months following transplantation. At 120 months following transplant an advantage is seen for patients on SBP [p= 0.05]

Discussion:

Sirolimus has been shown to have significant anti-tumor properties. the mTOR pathway is an important component in the pathogenesis of both renal cell and lung carcinomas. (5,6)

The ability of Sirolimus to inhibit mTOR, blocking critical steps in PI3 Kinase and Akt signaling pathways has led to its development as a potential chemotherapeutic drug for multiple malignancies. (7,8)

This study represents the longest experience with a patient population that was initiated with Sirolimus post-transplant and maintained on Sirolimus long-term. Therefore, the effects of Sirolimus use may compound over time, allowing for improved cancer free survival but also delaying the development of cancer and improving cancer-related outcomes.

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