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# Sirolimus for Cutaneous Kaposi's sarcoma in Renal Transplant Recipients in a Developing Economy: A Report of Two Cases

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## ABSTRACT

Kaposi's sarcoma (KS) is a significant malignancy associated with solid organ transplantation and though regional variations exist, it is important that transplant recipients are counselled to present early when lesions are identified and that physicians promptly confirm the diagnosis and institute appropriate therapy involving switching classes of proliferation signal inhibitors. We report two cases of successful treatment of KS with the use of Sirolimus.

Sirolimus has proven efficacy against both cutaneous and visceral KS while maintaining satisfactory renal function, however the course of treatment in human subjects is yet to be determined.

## INTRODUCTION

Kaposi sarcoma (KS) is a relatively common malignancy associated with solid organ transplantation [1-3].

Its prevalence among renal transplant patients varies from one region to another, ranging from 0.17% in Africa to 4.1% in Saudi Arabia. It is thought to be related to the variation in the incidence of human herpes virus 8 (HHV-8) infection as well as the choice of immunosuppressive agents especially calcineurin inhibitors (CNI) [2,4-6]. KS is a multicentric tumour characterized by the proliferation of plump spindle cells lining slit like vascular spaces. It presents as single or multiple lesions on the skin, mucosa, lungs, gastrointestinal tract and lymphoid organs [5,6].

In transplant settings, KS is managed by withdrawal of CNI in addition to reduction of the dose of other immunosuppressants with or without ancillary treatments such as chemotherapy or radiotherapy [3]. Reports from Europe and Australia suggest improvement in KS lesions with the use of (PSIs) proliferation signal inhibitors (mammalian target of rapamycin inhibitors or mTOR) such as Everolimus and Sirolimus in addition to the withdrawal of CNI. mTOR inhibitors have been evaluated in multiple trials and have been found effective when used as a replacement or in combination with CNI-I.

Nigeria, the most populous black nation with a population estimated to be over 170 million [7] has several transplant centres but about 70% of its renal transplants is carried out in the private sector [8]. The Zenith Medical and Kidney Centre is a privately owned specialist transplant and dialysis facility located in Abuja, the federal capital of Nigeria. Out of 108 renal transplants performed during her first 3 years, two patients were confirmed to have developed cutaneous KS. This article aims to report the experience of this centre's response to the use of PSIs in the management of KS.

## CASE 1

A 67 year old man with end stage renal disease due to hypertension underwent living donor renal transplantation 32 months ago. Induction of immunosuppression was with Basiliximab and Methyl Prednisolone followed by maintenance with Prednisolone, Mycophenolate mofetil (MMF) and Tacrolimus. Though he developed post-transplant diabetes mellitus that was managed with Galvusmet (Metformin/Vidagliptine) and Lantus 10 units nocte, his transplant function remained excellent with an eGFR of 73.4 ml/min using CKD-EPI formula. He later presented with a four week history of painful and itchy hyper pigmented macules over both lower limbs about 21 months post transplantation. He was referred to a dermatologist who performed a biopsy of the lesion. Histological examination confirmed the diagnosis of

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cutaneous Kaposi's sarcoma. No visceral lesions were noted on imaging. Tacrolimus was replaced by Sirolimus (5 mg daily). Over a six week period of taking Sirolimus his lesions were noticed to have regressed with depigmentation and pain and itching having resolved. He has maintained satisfactory renal function and not suffered graft rejection.

## CASE 2

A 63 year old male in end stage renal failure due to chronic hypertension and who was seropositive for Hepatitis C virus received a kidney allograft from his younger brother two years ago. Induction of immunosuppression was with Basiliximab and Methyl Prednisolone followed by maintenance with Prednisolone, Mycophenolate sodium (Myfortic) and Cyclosporin. He presented nine months after transplantation with violaceous erythematous plaques on the trunk and lower limbs bilaterally of two weeks duration. Clinical diagnosis of Kaposi's sarcoma was made and confirmed histologically after a biopsy of the lesions. Cyclosporine was replaced by Sirolimus with marked regression of the lesions after six weeks with stable renal function eGFR of 89.8 ml/min using (CKD-EPI formula). He has no side effects and renal transplant function has remained satisfactory [9-12].

## DISCUSSION

The cases presented in this report were both cutaneous, one localized and the other had multiple cutaneous lesions. Both occurred in males in their $6^{th}$ decades. When cancers are diagnosed in post renal transplant patients, a change in the type of and dosage of immunosuppression is recommended [13]. This was done for both patients with a switch from Tacrolimus and Cyclosporine to Sirolimus. Both men showed remarkable improvement with Sirolimus use for a few weeks with regression of the lesions they presented with and as yet there has been no report of adverse effects. Their renal function has remained optimal.

The use of Sirolimus in these two patients is based on documented findings on its anti-tumor properties particularly its inhibition of proliferation signals as well as its effects on angiogenesis while not compromising renal function [14-19]. The effect of proliferation signal inhibitors on cancers is subject of on-going research [9] and its effect is being explored in the treatment of KS. Side effects which occur regularly include decreased hemoglobin and a rise in serum lipids, occasionally arthralgia, peripheral edema, gastrointestinal disturbance, skin disorders and infections may be seen as well as an increase in proteinuria [10]. Nephrotoxicity associated with sirolimus use has been demonstrated in animals but research in humans is still ongoing [11]. The patients on Sirolimus in this study have not shown any adverse reactions so far. Campistol et al. documented complete regression of KS in two patients managed with Sirolimus with a mean duration of treatment of 3 months more than a decade ago with many other similar reports over the years including regression of visceral lesions [12-15].

A prospective randomized trial in kidney transplantation comparing Sirolimus-MMF-prednisolone to Tacrolimus-MMF-prednisolone reported clinical acute rejection in 10% of the Tacrolimus group compared to 13% in the Sirolimus group (p=0.58). Their study showed that CNI-free regimen using Sirolimus-MMF-prednisolone produces similar acute rejection rates, graft survival and renal function 1-2 years after transplantation compared to Tacrolimus-MMF-prednisolone [14]. The CONVERT trial demonstrated that at 2 years, Sirolimus conversion among patients with baseline glomerular filtration rate of more than 40 mL/min was associated with excellent patient and graft survival, no difference in biopsy proven acute rejection, increased urinary protein excretion and a lower incidence of malignancy compared with CNI continuation [15]. Though it has been shown that the risk of acute rejection in patients switching from CNI to Sirolimus is not significant [14,15]. It is not clear for how long Sirolimus should be administered or whether it should be continued for the life of the allograft. Economic factors (affordability by individual patients) may be significant in a situation where immunosuppression is not funded by government.

Though the two patients in our centre did not have Human immunodeficiency virus (HIV), it must be borne in mind that the incidence of KS is even higher in post-transplant patients with HIV. Patients undergoing transplantation in Africa must be counseled about the risk of malignancy particularly KS. They all must be encouraged to report any new symptoms or lesions immediately either to their transplant centre or to the nearest qualified physician.

## CONCLUSION

While CNIs are effective for preventing acute rejection in kidney transplant recipients, long-term use may cause chronic kidney injury and is associated with increased risks of cardiovascular events, cancer and infection-associated death. Immunosuppression strategies are needed to balance risks of acute and subclinical rejection with long-term benefits of improved kidney function. KS in Africans also responds to proliferation signal inhibitors (Sirolimus). Switch to Sirolimus should be considered as first line treatment of KS before other ancillary measures are taken. Use of Sirolimus in this way may inhibit developing tumors and further help salvage renal allografts that may otherwise be lost to acute rejection.

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