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Kaposi's sarcoma in renal transplant recipients—the impact of proliferation signal inhibitors

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Abstract

The incidence of Kaposi's sarcoma (KS) is greatly increased in renal transplant recipients compared with the general population, with particular prevalence in certain ethnic groups where it can occur in up to 5% of transplant recipients. The increased incidence of disease in transplant populations may, in part, be attributed to the choice of immunosuppressive regimen, with calcineurin inhibitor (CNI)-based immunosuppression being associated with the development of the tumour. A number of small studies have recently demonstrated that conversion to proliferation signal inhibitors (PSIs) along with the concomitant withdrawal of CNIs leads to a rapid resolution of both cutaneous and visceral Kaposi's lesions. In agreement with these data the abrupt onset of KS has been observed following the withdrawal of PSIs. Histological examination of lesions from patients with KS supports data from animal models which suggests that PSIs inhibit tumour angiogenesis through impaired vascular endothelium growth factor production, a key element in the development of the tumour. Previously unpublished data on renal transplant recipients from a number of European and Australian centres have been pooled to provide further insight into the use of PSIs in the management of post-transplant KS. Both members of the PSI class, everolimus and sirolimus, along with CNI withdrawal lead to regression of KS lesions in 11 out of 12 patients. Conversion to PSIs was generally well tolerated with stable renal function maintained in most patients and no episodes of acute rejection recorded. PSIs provide a potential treatment option in the management of post-transplant KS and should be considered for use in renal transplant recipients who develop the disease.

Keywords: Kaposi's sarcoma; post-transplant malignancy; proliferation signal inhibitors/mammalian target of rapamycin inhibitors; renal transplant recipients

Introduction

Kaposi's sarcoma (KS) is a skin tumour of multicentric origin, characterized histologically by endothelium-lined vascular spaces and spindle-shaped cells [1]. KS presents as single or multiple lesions on mucosal surfaces, including the skin, lungs, gastrointestinal tract and lymphoid tissue [1,2]. This article reviews the increased risk and pathogenesis of KS post-transplantation, specifically highlighting the impact of immunosuppressive regimens in renal transplant recipients. In particular, data suggest a potential role for proliferation signal inhibitors (PSIs; also known as mammalian target of rapamycin inhibitors) everolimus (Certican®, Novartis Pharma AG, Basel, Switzerland) and sirolimus (Rapamune®, Wyeth Pharmaceuticals, USA) in the management and prevention of KS.

Pathogenesis

KS is seen as both an endemic disease in African and Mediterranean populations, and as an epidemic disease associated with human herpes virus (HHV) 8 [3]. In healthy adults, HHV-8 infection is not associated with any specific, severe illness, although reported symptoms at the time of seroconversion in infected individuals include transient lymphadenopathy, diarrhoea, fatigue and skin rash [4]. Control of infection in healthy individuals appears to be mediated via an antiviral T-cell response to viral lytic proteins [4]. The development of KS is thought to be associated with reactivation of HHV-8 in transplant recipients, however, reactivation of the virus does not confirm development of the disease, as observed in the United States, where prevalence of KS in solid organ transplant recipients was 0.5%,

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lower than the estimated 20% rate of HHV-8 [1]. The mechanism through which KS develops is unclear [5], although recent evidence suggests that development involves initial latent HHV-8 infection of endothelial cells and subsequent conversion to spindle cells [6]. This is followed by a proliferative phase and expression of a lytic cycle protein, viral G-protein–coupled receptor (vGPCR). In endothelial cells, the vGPCR oncoprotein increases the secretion of vascular endothelial growth factor (VEGF) and up-regulation of its receptor, fetal liver kinase-1/kinase domain receptor (Flk-1/KDR). This activation, along with other paracrine events, plays a pivotal role in the development of the final tumour [6].

Epidemiology

The epidemiological profile of KS in transplant recipients is summarized in Table 1. The majority of cases of KS occurs in patients from Mediterranean, Jewish, Arabic, Caribbean or African ethnic groups [2,7]. The incidence of KS in transplant recipients may be as high as 500 times that in healthy individuals [2,7]. KS often occurs early after transplantation with the time to the onset of disease ranging from 5 to 21 months post-transplant [1,2,5,7], however, it has been reported as late as 18 years post-transplant [7]. The prevalence of KS in transplant recipients varies depending on geographical location, ranging from 0.5% in Western countries, such as the USA, to 5.3% in Saudi Arabia [7].

The effects of specific immunosuppressive agents on the incidence of KS has also been evaluated, with ciclosporin (CsA)-based regimens appearing to be associated with a higher incidence of the tumour than those based on azathioprine [2]. Moreover, reports suggest that KS in patients receiving CsA is more severe than that in patients receiving azathioprine [8]. An association between KS and low-dose corticosteroids has also been observed by some authors, with Vincent *et al*. [9] reporting KS in two elderly women receiving treatment for rheumatological disease. Reduction or discontinuation of immunosuppression is generally the first step in managing KS, balancing likely loss of the graft from rejection against loss of life from KS. Therefore, conversion to alternative immunosuppressive agents is an attractive option. Conversion from CsA to low therapeutic doses of mycophenolate mofetil (MMF), for example, may lead to regression of KS [10,11]. The proliferation signal inhibitors (PSIs) sirolimus and everolimus, however, may, through specific effects on VEGF, provide the greatest promise as immunosuppressive agents with anti-neoplastic activity [12].

Table 1. Summary of epidemiological characteristics of Kaposi's sarcoma in transplant recipients [1,2,7]

Incidence – general population	0.01–0.06%
Male:female ratio	3:1
Racial or ethnic background	Mainly Mediterranean, Jewish, Arabic, Caribbean or African
Average time to development after transplant	13–21 months
1-year incidence after transplantation	46%

Conversion to proliferation signal inhibitors

The potential role for sirolimus in the management of post-transplantation KS was first noted by Campistol *et al*. [6], in a report on two renal transplant recipients with KS who underwent complete regression after conversion to sirolimus. Both patients presented with multiple cutaneous KS while receiving CsA-based immunosuppression. The first patient was converted from CsA and MMF to sirolimus (3 mg/day), with resolution of the lesions within 3 months. In the second patient, continuation of CsA and withdrawal of azathioprine and prednisone had no effect on the lesions. Additional reductions in CsA dose led to no alteration in the existing lesions, and no new lesions, over 6 years. The patient was eventually converted to sirolimus (3 mg/day), with gradual disappearance of the lesions 2 months later. Both patients maintained good renal function after conversion [6]. The following year, a number of reports of KS regression in renal transplant recipients were published. Gutíerrez-Dalmau *et al*. [13] carried out a retrospective chart review of seven patients with cutaneous KS. After conversion to sirolimus from calcineurin inhibitor (CNI) therapy, six patients showed regression of their lesions in a mean time of 8.1 months, with the seventh patient showing almost complete regression after 9 months. Renal function was maintained in six patients, with acute renal failure unrelated to sirolimus reported in the remaining patient [13]. In a prospective study of conversion from CsA to sirolimus in 15 renal transplant recipients, Stallone *et al*. [5] showed that all KS lesions underwent complete regression within 3 months. Continuing remission from KS was confirmed by histological examination 6 months after conversion, and no episodes of acute rejection or changes in renal graft function were reported in any of the patients. Immunohistochemical analysis of the lesions from these patients showed a significant increase in components of the angiogenesis-signalling pathways known to be disrupted by the PSIs, compared with normal skin from the same patients (Figure 1) [5]. Recently, regression of visceral KS after conversion to

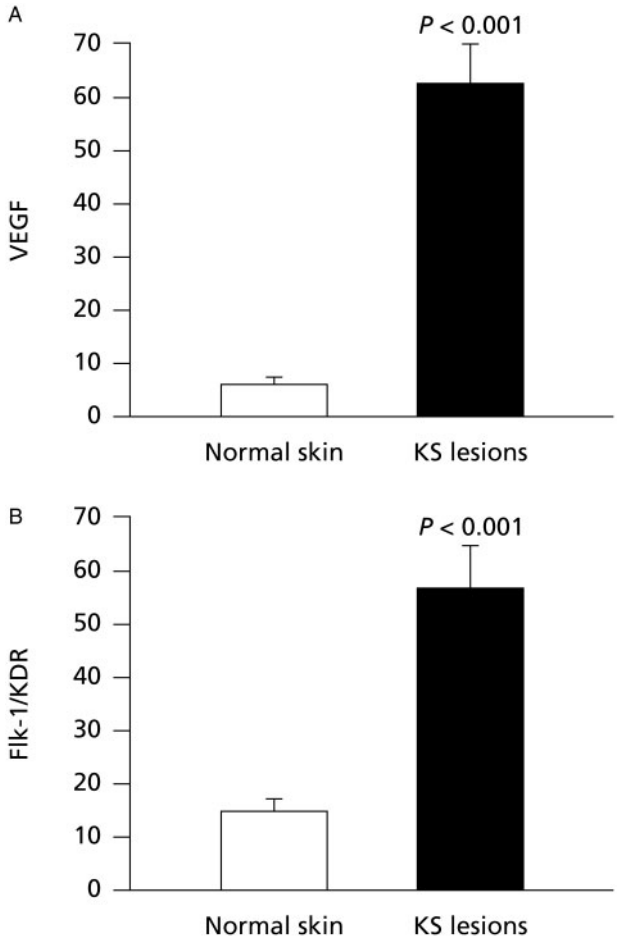

Fig. 1. Expression of the angiogenesis-related signalling proteins (A) vascular endothelial growth factor and (B) foetal liver kinase-1/kinase domain receptor is significantly increased in Kaposi's sarcoma lesions compared with normal skin [5] (Reprinted with permission from Massachusetts Medical Society). VEGF, vascular endothelial growth factor; Flk-1/KDR, foetal liver kinase-1/kinase domain receptor.

sirolimus has also been reported, with complete regression of visceral and cutaneous lesions occurring in a transplant recipient within a few months of conversion [14]. In accordance with these data, abrupt onset of KS was reported in a renal transplant recipient following the withdrawal of sirolimus [15]. Recent studies have suggested a possible mechanism for the action of PSIs on preventing angiogenesis in tumours [5]. Animal models have demonstrated that PSI activity impairs VEGF production and limits the response of endothelial cells to VEGF stimulation, therefore inhibiting tumour progression [16]. Furthermore, a recent study demonstrated that Kaposi's sarcomagenesis involves stimulation of tuberin phosphorylation by vGPCR and activation of mammalian target of rapamycin (mTOR) through both direct and paracrine mechanisms [17]. Inhibition of mTOR with sirolimus prevented vGPCR sarcomagenesis, highlighting a potential role for mTOR in the initiation of KS.

To gain a better understanding on how conversion to a PSI can improve post-transplant outcomes relating to KS, previously unpublished patient data from transplant physicians in multiple centres across Europe and Australia have been pooled to provide a more extensive patient population for analysis and treatment guidance (Table 2). This analysis only included renal transplant recipients who were converted to PSIs following the development of KS. Twelve renal transplantation recipients identified from six different transplant centres were converted to PSIs (everolimus, $n = 4$; sirolimus, $n = 5$).The range of PSI blood levels was 3–9 ng/ml in patients receiving everolimus and 5–12 ng/ml in patients receiving sirolimus; CNIs were withdrawn in all patients. Following conversion, resolution of lesions was observed in 11 patients, with stable renal function and no episodes of acute rejection reported. In one patient, the introduction of a PSI along with CsA withdrawal did not lead to resolution of KS and chemotherapy was introduced. This patient also experienced proteinuria and pneumocystosis following conversion. Conversion to PSIs was generally well tolerated in all patients with only one patient experiencing adverse events (skin disorders and hyperlipidaemia).

Summary

KS is a common long-term complication in renal transplant recipients, with an increased incidence compared with the general population, and being especially prevalent in Mediterranean and African populations. There is increasing clinical data suggesting that conversion to PSIs in patients with KS causes regression of lesions through effects on VEGF signalling. This immunosuppressive regimen may, therefore, reduce the impact of KS on the long-term outcomes of kidney transplantation.

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Table 2. Clinical experience of proliferation signal inhibitors in post-transplantation Kaposi's sarcoma from six European and Australian Transplant centres

Patient number	Patient age (years)	Patient gender M/F	Date of trans-plantation	Histology of tumuor	Time from transplant to diagnosis of KS	Original immunosuppressive regimen	Date of conversion to PSI	PSI trough blood levels	CNI minimization/ withdrawal	Current follow-up	Duration patient is KS free
1	56	M	04/11/2003	KS	3.5 months	CsA FTY 720 MP	Sirolimus initiation 12/03/2004	Sirolimus 8.2–10.2 ng/ml	CNI withdrawal 09/02/2004	Stable renal function Creatinine: 1.58 mg/dl Free of malignancy since 10/04	32 months
2	29	M	05/05/2003	KS involves skin lung stomach	24 months	MMF CsA MP	Everolimus initiation 21/07/2005 MMF withdrawal 21/07/2005 Received doxorubicin	Everolimus 7–8 ng/ml	CNI withdrawal 24/06/2005	Stable renal function Creatinine: 1.4 mg/dl Complete resolution in skin, lung, stomach Currently on everolimus/MP No adverse events	5 months
3	66	M	04/05/2005	KS involves skin	3 months	MMF CsA MP	Everolimus initiation 31/08/2005	Everolimus 8–9 ng/ml	CNI withdrawal 31/08/2005	Stable renal function Creatinine: 1.0 mg/dl Resolution of skin lesions Currently on MMF/everolimus/MP No adverse events	4 months
4	28	M	10/11/1999	KS involves lymph nodes, skin	24 months	MMF Tac MP	Sirolimus initiation 10/02/2003 MMF withdrawal 10/02/2003	Sirolimus 5–6 mg/ml	CNI withdrawal 19/02/2001	Stable renal function Creatinine: 1.5 mg/dl Resolution of lympha-denopathy and skin lesions. Currently on sirolimus/MP No adverse events	48 months
5	57	M	21/12/04	KS	5 months	CsA CS	Sirolimus initiated 24/5/2005	Sirolimus 6–8 ng/ml	CsA withdrawal	Stable renal function Creatinine: 198 µmol/l Proteinuria up to 6 g/day after conversion decreasing to 1 g/day under CEI. Resolution of KS BUT after chemotherapy— No impact of CsA withdrawal and sirolimus Over-immunosuppression with pneumocystosis lung infection	3 months

6	47	M	26/3/04	KS	11 months	CsA CS FTY 2.5 mg/day	Sirolimus initiated 17/2/05	Sirolimus 6–8 ng/ml	CsA withdrawal	Stable renal function Creatinine: 128 μmol/l Proteinuria: 0.63. Poor skin tolerance of sirolimus skin rash and pruritis. Increased LDL (introduction of statins) triple therapy: sirolimus 2 mg, MMF 500 mg, CS 5 mg	12 months
7	39	M	14/04/2005	KS, HHV8	48 months	CsA, MMF, MP	21/04/2005 switch from CNI to sirolimus, MMF, MP	Sirolimus 6–10 ng/ml	CsA withdrawal	No recurrence, graft function stable	65 months
8	43	M	30/08/2006	KS	62 months	CsA, MMF, MP	06/09/2006 switch from CNI to everolimus, MMF, MP	Sirolimus 5–8 ng/ml	CsA withdrawal	No recurrence, graft function stable	63 months
9	66 years	F	09/03/05	KS	15 months	Tac, MMF, PDR	20/06/2006 Switch to everolimus 1.5 mg bd.	Everolimus 3–7 ng/ml		Resolution of all KS plaques over 2 months. Stable renal function Creatinine 200 μmol/l Leg DVT 6 months after conversion	4 months
10	62	M	1990	KS	6 months	CSA + AZA + PDR	Sirolimus initiated 10/1999	Sirolimus 8–12 ng/ml	CsA withdrawal	Perfect follow-up	72 months
11	68	M	2001	KS	3 months	CSA, MMF + PDR	Sirolimus initiated 06/2001	Sirolimus 8–12 ng/ml	CsA withdrawal	Acute renal failure associated to aseptic shock-dialysis. KS disappear	48 months
12	72	M	2006	KS	6 months	CSA + MMF + PDR	Sirolimus initiated 10/2006	Sirolimus 8–12 ng/ml	CsA withdrawal	Recent conversion Progressive involvement	

CEI, converting enzyme inhibition; CNI, calcineurin inhibitor; CsA, ciclosporin A; CS, corticosteroids; HHV8, human herpes virus 8; KS, Kaposi's sarcoma; LDL,low-density lipoprotein; MMF, mycophenolate mofetil; MP, methylprednisolone; PDR, prednisone; PSI, proliferation signal inhibitor; Tac, tacrolimus.

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