The Paradox of Sirolimus-Induced Immunosuppression and Tumor Control

Lisette Stucki Vincent Piguet

Department of Dermatology and Venereology, University Hospital Geneva, Geneva, Switzerland

Immunosuppression favors tumor growth [1]. This fact is well known by the dermatologist who has to take care of highly frequent skin cancers in solid organ transplant recipients under immunosuppressive therapy [2]. Surprisingly, sirolimus seems to combine immunosuppressive and anticancer properties, thereby apparently challenging the idea that immunosuppression favors tumor growth. In a recent issue of the *New England Journal of Medicine*, researchers from the University of Bari have reported that sirolimus has an antitumoral effect on Kaposi's sarcoma (KS) in kidney transplant recipients [3]. In the Italian study, a group of 15 patients had developed cutaneous KS while receiving classical immunosuppressive agents (cyclosporin). After stopping cyclosporin A and introducing sirolimus, all patients had a total regression of KS within 3 months [3]. These findings confirmed and extended case reports suggesting that sirolimus could be beneficial for patients with iatrogenic KS [4]. In this issue of *Dermatology*, González-López et al. [5] describe a case of iatrogenic KS probably precipitated by withdrawal of sirolimus and possibly by concomitant thrombosis. These exciting observations indicate that sirolimus has an unusual combination of immunosuppressive and antitumor properties.

KS is a common complication of immunosuppression induced by HIV infection or by immunosuppressive regimens administered to recipients of solid organ transplants. Four types of KS have been described: classical KS occurring in older men from Mediterranean and Jewish lineage, endemic KS in certain areas of Africa, AIDS-

associated KS and iatrogenic KS in patients receiving immunosuppressive treatment [for a review, see 6–8]. Regression of iatrogenic KS upon removal of immunosuppressive therapy is well demonstrated, which indicates that KS is reversible if host immunity is restored. Human herpesvirus 8 (HHV-8) infection is necessary (although not sufficient) for the development of all forms of KS. The role of HHV-8 in the pathogenesis of KS might explain, at least in part, why host immunity is critical in controlling KS growth [for a review, see 6, 7].

Sirolimus, formerly known as rapamycin, is a macro-lide antibiotic, highly lipophilic, produced by *Streptomyces hygroscopicus* fermentation and has been originally identified in 1975 as an antifungal agent [9]. It was subsequently developed as an immunosuppressive drug for solid organ transplantation 15 years later [10]. Sirolimus belongs to a new class of immunosuppressors. Its mode of action shares some similarities with inhibitors of calcineurin, FK-506 and cyclosporin A [for a review, see 11]. Sirolimus, FK-506 and cyclosporin A bind to the intracellular immunophilin FK-506-binding protein, but unlike FK-506 and cyclosporin A, sirolimus does not inhibit T-cell-receptor-induced calcineurin activity. Instead, sirolimus inhibits a multifunctional serine/threonine protein kinase called mammalian target of rapamycin (mTOR). This key protein kinase is involved in the transduction signal of cytokines (interleukin 2 and growth factors), but also controls cell growth by regulating many cellular processes, such as protein synthesis and cell cycle progression [12].

Sirolimus inhibition of the mTOR signaling network is likely to explain its antimitotic effects. mTOR signaling is hyperactivated in many tumor types. mTOR signaling results from a balance of activation by proto-oncogenes including PI3K, Akt and inhibition by tumor suppressor genes including PTEN, TSC1 and TSC2 [13]. PTEN is one of the most frequently mutated tumor suppressor genes found in human cancers, such as those of the prostate, breast, lung and endometrium and melanoma. 85% of patients with Cowden syndrome (facial trichilemmomas, oral papillomatosis, palmar pits associated with thyroid, breast or pancreatic cancers) have mutations of the PTEN gene [for a review, see 12]. TSC1 and TSC2 are also familiar to the dermatologist since mutations in TSC1 and TSC2 were first identified in patients suffering from tuberous sclerosis (epilepsy, low intelligence and angiofibromata) [for a review, see 12].

Posttransplantation malignancies are responsible for a large percentage of death in the years following organ transplantation. Sirolimus has proven its efficacy in significantly reducing the incidence of de novo skin or solid internal tumors in comparison with cyclosporin in renal posttransplantation patients [14, 15]. The complex interplay of sirolimus and the mTOR signaling pathway might well explain the powerful antineoplastic effect of sirolimus on iatrogenic KS. In addition, sirolimus inhibits angiogenesis by downregulating vascular endothelial growth factor, probably via the mTOR signaling pathway [16, 17]. The levels of vascular endothelial growth factor and its receptor are generally very high in KS, most probably due to the presence of HHV-8 which upregulates the expression of those molecules in the endothelial cells [18]. This additional antiangiogenic effect of sirolimus might also contribute to the control of iatrogenic KS.

In dermatology, sirolimus has been mainly evaluated as a steroid or cyclosporin-sparing agent. In severe psoriasis, systemic sirolimus in monotherapy appeared to be ineffective, but in combination with subtherapeutic doses of cyclosporin, therapeutic doses of sirolimus showed a similar efficacy when compared to cyclosporin in monotherapy [19]. Topical sirolimus has also shown systemic and cutaneous penetration with some degree of clinical efficacy in psoriasis [20].

Sirolimus is overall a potent immunosuppressive drug, and its use requires a careful monitoring including prophylactic protection against *Pneumocystis carinii* pneumonia and cytomegalovirus reactivation. Blood level monitoring is crucial (4–12 ng/ml), because of the great variability of bioavailability of this molecule depending on the food intake and other drugs absorbed. Side effects

of sirolimus are usually dose dependent and reversible. The most frequent side effects are leukopenia, thrombocytopenia, hyperlipidemia, arthralgia, edema and skin lesions. Rare cases of capillary leak syndromes are also associated with sirolimus [21]. Skin lesions associated with sirolimus treatment are also frequent with different degrees of severity, including xerosis, aphthous ulcerations, pathologies of the pilosebaceous apparatus including acne-like eruptions [22], hidradenitis suppurativa, chronic skin folliculitis and nodular inflammation of the cervical region [23].

So far, sirolimus has not been very frequently used in dermatology, maybe because of its inefficacy in monotherapy in psoriasis and its frequent skin adverse reactions. Nevertheless, its lack of nephrotoxicity, its immunosuppressant and antitumoral properties should make sirolimus an attractive drug for the dermatologist in the future, possibly as a cyclosporin/corticosteroid-sparing agent and in dermatosis with increased tumor risk such as mucosal erosive lichen planus or dermatomyositis [24]. Interestingly, CD4 counts in HIV patients under highly active antiretroviral therapy were not severely affected by kidney transplantation and subsequent immunosuppressive regimens (including sirolimus) [25]. It is therefore reasonable to think that other forms of KS might also benefit from sirolimus. Several questions remain however. Whether the antineoplastic effect of sirolimus occurs at similar doses to immunosuppression remains to be determined. It is unclear if sirolimus modifies HHV-8 levels in KS patients, and long-term studies on the efficacy of sirolimus in KS patients are unavailable. Nevertheless, sirolimus 'kills two birds with one stone' due to its unique combination of anticancer and immunosuppressant properties. This highly useful profile makes sirolimus a very attractive candidate drug in a variety of diseases including skin diseases.

References

- Dunn GP, Old LJ, Schreiber RD: The three Es of cancer immunoediting. *Annu Rev Immunol* 2004;22:329–360.
- Euvrard S, Kanitakis J, Claudy A: Skin cancers after organ transplantation. *N Engl J Med* 2003;348:1681–1691.
- Stallone G, et al: Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005;352:1317–1323.
- Campistol JM, Gutierrez-Dalmau A, Torregrosa JV: Conversion to sirolimus: a successful treatment for posttransplantation Kaposi's sarcoma. *Transplantation* 2004;77:760–762.
- González-López MA, Rodrigo E, González-Vela MC, Fernández-Llaca H, Arias-Rodríguez MA, Val-Bernal JF: Posttransplant Kaposi's sarcoma restricted to the site of a previous deep venous thrombosis: abrupt onset after withdrawal of sirolimus. *Dermatology* 2006;213:30–33.
- Hengge UR, et al: Update on Kaposi's sarcoma and other HHV8 associated diseases. 1. Epidemiology, environmental predispositions, clinical manifestations, and therapy. *Lancet Infect Dis* 2002;2:281–292.
- Hengge UR, et al: Update on Kaposi's sarcoma and other HHV8 associated diseases. 2. Pathogenesis, Castleman's disease, and pleural effusion lymphoma. *Lancet Infect Dis* 2002;2:344–352.
- Kempf W, Cathomas G, Burg G, Trüeb RM: Micronodular Kaposi's sarcoma – A new variant of classic-sporadic Kaposi's sarcoma. *Dermatology* 2004;208:255–258.
- Vezina C, Kudelski A, Sehgal SN: Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. *J Antibiot (Tokyo)* 1975;28:721–726.
- Calne RY, et al: Rapamycin for immunosuppression in organ allografting. *Lancet* 1989;ii:227.
- Reynolds NJ, Al-Daraji WI: Calcineurin inhibitors and sirolimus: mechanisms of action and applications in dermatology. *Clin Exp Dermatol* 2002;27:555–561.
- Guertin DA, Sabatini DM: An expanding role for mTOR in cancer. *Trends Mol Med* 2005;11:353–361.
- Hay N: The Akt-mTOR tango and its relevance to cancer. *Cancer Cell* 2005;8:179–183.
- Kahan BD, et al: Low incidence of malignancy among sirolimus/cyclosporine-treated renal transplant recipients. *Transplantation* 2005;80:749–758.
- Kauffman HM, Cheriak WS, Cheng Y, Hanto DW, Kahan BD: Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation* 2005;80:883–889.
- Guba M, et al: Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med* 2002;8:128–135.
- Brugarolas JB, Vazquez F, Reddy A, Sellers WR, Kaelin WG Jr: TSC2 regulates VEGF through mTOR-dependent and -independent pathways. *Cancer Cell* 2003;4:147–158.
- Masood R, et al: Vascular endothelial growth factor/vascular permeability factor is an autocrine growth factor for AIDS-Kaposi sarcoma. *Proc Natl Acad Sci USA* 1997;94:979–984.
- Reitamo S, et al: Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2001;145:438–445.
- Ormerod AD, Shah SA, Copeland P, Omar G, Winfield A: Treatment of psoriasis with topical sirolimus: preclinical development and a randomized, double-blind trial. *Br J Dermatol* 2005;152:758–764.
- Kaplan MJ, et al: Systemic toxicity following administration of sirolimus (formerly rapamycin) for psoriasis: association of capillary leak syndrome with apoptosis of lesional lymphocytes. *Arch Dermatol* 1999;135:553–557.
- Kunzle N, Venetz JP, Pascual M, Panizzon RG, Laffitte E: Sirolimus-induced acneiform eruption. *Dermatology* 2005;211:366–369.
- Mahe E, et al: Cutaneous adverse events in renal transplant recipients receiving sirolimus-based therapy. *Transplantation* 2005;79:476–482.
- Nadiminti U, Arbiser JL: Rapamycin (sirolimus) as a steroid-sparing agent in dermatomyositis. *J Am Acad Dermatol* 2005;52:17–19.
- Kumar MS, et al: Safety and success of kidney transplantation and concomitant immunosuppression in HIV-positive patients. *Kidney Int* 2005;67:1622–1629.