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LETTER TO THE EDITOR

Effect of everolimus on skin cancers in calcineurin inhihitor-treated heart transplant recipients

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Non-melanoma skin cancers (NMSC) are the commonest cancers in heart transplant recipients (HTR) [1,2] and include mainly squamous-cell carcinomas (SCC) and basal-cell carcinomas (BCC). After a first SCC, all HTR develop new NMSC within 5 years and at least 25% of them develop also extracutaneous cancers [3]. Kidney transplant patients under mTOR inhibitors develop fewer NMSC compared with those receiving calcineurin inhibitors either in *de novo* treatment or after conversion [4–10]. So far, limited clinical data exist on the antitumoral properties of everolimus (EVE) [9–11]. We report for the first time the effect of EVE on NMSC in HTR.

This observational study included HTR with multiple recurrent skin tumors and/or fast growing SCC switched to EVE since 2006 among the 635 HTR followed over the same period in our center (1428 heart transplantations since 1979). All the reported patients received the initial immunosuppressive regimen following our standard institutional protocol, including polyclonal induction therapy (3–5 days, 1.5 mg/kg/day), corticosteroids, azathioprine until 2000, mycophenolate mofetil afterwards and cyclosporine (whose trough levels were adjusted to time after transplantation according to international guidelines). EVE was started at 1.5 mg/day and adjusted to obtain trough levels 3–10 ng/ml. Each visit included physical examination and standard echocardiography; endomyocardial biopsies were performed according to institutional guidelines. Dermatological assessment recorded the count of histologically proven NMSC and the presence of verrucous lesions. The number of tumors before and after EVE was compared with the Wilcoxon signed rank-test. Because of the delay necessary to assess the impact of immunosuppression alteration on NMSC, only patients with at least 1-year follow-up under EVE were studied.

Fourteen men with 115 NMSC were considered. Their mean age was 69 ± 7 years and the mean delay after transplantation 13.5 ± 5 years. Six patients had also developed other malignancies. EVE introduction was always followed by discontinuation of azathioprine and by reduction of calcineurin inhibitors. Cyclosporine was decreased (trough levels targeted at 50–80 ng/ml) in six patients, and withdrawn in seven others (depending on the initial immunosuppression regimen, history of rejection and comorbidities). Dosages of corticosteroids and mycophenolate mofetil were not significantly altered. The total number of immunosuppressants was increased after EVE introduction; no patient had a lower number of drugs and six patients had an additional immunosuppressant.

Concerning the effect on skin cancers, 10 patients were evaluable (Table 1) over a mean period of 28 months (four patients were excluded: three EVE discontinuations and one death from hepatocarcinoma). Overall, the mean number of tumors per patient that developed under EVE was significantly lower as compared with the same period before EVE (3.7 vs. 1.5, $P = 0.03$). Remarkably, the SCC/BCC ratio was halved. Seven patients did not develop further SCC. Furthermore, three of five patients with multiple verrucous (non-NMSC) lesions experienced a decrease in these lesions. However, two patients kept developing multiple NMSC despite a temporary beneficial effect; one of them experienced lymph-node metastasis of a facial SCC.

Among evaluable patients with noncutaneous malignancies before EVE introduction, two (2 and 5) did not relapse. Patient 4 developed recurrence of bladder cancer and patient 7 developed prostatic cancer 1 year after EVE introduction, but no relapse of bladder cancer.

Adverse effects occurred in all patients and led to EVE discontinuation in five of them. Discontinuation was decided shortly in three patients because of proteinuria, pneumonitis, and ileitis respectively. Two additional patients (4 and 7) discontinued EVE during months 16 and 17 because of proteinuria. These side effects regressed after EVE withdrawal. Other side effects included edema, aphthae, folliculitis, hidradenitis suppurativa, seborrheic dermatitis exacerbation, diarrhea, fever of unknown origin, and hyperlipidemia. Most side effects were controlled by EVE tapering. Patient 6 experienced a grade 1R (1B) biopsy-proven acute rejection according to the International Society of Heart and Lung Transplantation classification [12] at month 15, which was successfully treated by corticosteroid pulses. Patients 4 and 5 experienced clinically insignificant grade 1R (1A) rejection, which did not require treatment.

Table 1. Characteristics of patients and number of skin tumors before and after everolimus introduction.

Patients	Heart Disease	Age at HT	Time to first skin tumor (years)	IS regimen before EVE	IS regimen after EVE	Other nonskin cancers	EVE follow-up (months)	Skin tumors before EVE*					Skin tumors under EVE				
								SCC	BCC	Bow	AK	T	SCC	BCC	Bow	AK	T
1	ID	60	5	Cy	Cy EVE		36	2	0	0	1	3	0	0	0	1	1
2	V	64	5	Cy	Cy EVE	Prostate	26	2	1	0	1	4	0	1	0	0	1
3	IS	53	5	Cy	Cy EVE		33	1	0	0	0	1	2	1	0	1	4
4	IS	62	15	Cy CS	EVE CS	Bladder	16	4	0	1	2	7	1	0	0	1	2
5	ID	65	7	Cy CS	EVE CS	Lung prostate	37	1	0	0	0	1	0	0	0	0	0
6	ID	62	5.5	Cy CS	EVE CS		34	0	0	1	0	1	0	0	0	0	0
7	IS	56	2	Cy MMF	Cy MMF EVE	Bladder	17	2	0	0	0	2	0	0	0	0	0
8	IS	57	1	Cy AZA	EVE MMF		27	7	2	1	0	10	5	2	0	0	7
9	V	37	11	Cy CS AZA	Cy CS EVE		34	0	0	3	0	3	0	0	0	0	0
10	V	43	4	Cy CS MMF	Cy CS MMF EVE		20	1	2	2	0	5	0	0	0	0	0
Total								20	5	8	4	37	8	4	0	3	15

ID, idiopathic cardiomyopathy; V, valvular; IS, ischemic cardiomyopathy; Cy, cyclosporine; CS, corticosteroids; MMF, Mycophenolate mofetil; EVE, everolimus; AZA, azathioprine; T, total number of skin tumors; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; Bow, Bowen's disease; AK, actinic keratosis.

*To homogenize the follow-up periods, the 'before' period considered for each patient corresponded to the mean time of follow-up of the group under EVE (28 months).

Immunosuppression revision in organ transplant patients is increasingly prompted to reduce cutaneous and visceral carcinogenesis [2,13]; however, the best immunosuppressive strategy remains to be defined [2]. Before the mTOR inhibitors era, minimization was the main approach, and the tumoral regression observed thereafter in transplant patients with NMSC has been largely documented. Regression of skin tumors after secondary introduction of mTOR inhibitors has been reported mainly in Kaposi's sarcoma, whereas few data exist for patients with NMSC [7,8,10]. mTOR inhibitors are more and more prescribed for skin cancers; in HTR, EVE is also used because of its lower risk of nephrotoxicity and cardiac allograft vasculopathy [14]. Even though our patient group is rather small, we believe it is representative of the HTR population with skin cancer. Our study is the first report on the antitumoral properties of EVE in HTR with NMSC. Furthermore, the finding that the preventive effect of EVE seems to be higher on the most aggressive NMSC, i.e. SCC as compared with BCC, is original. Similarly to sirolimus [15], the antitumoral properties of EVE may be due to an anti-angiogenic effect [11]. The possibility that the benefit could be partly related also to the decrease of other immunosuppressants cannot be excluded; however, in our patients, the total number of immunosuppressive drugs was increased after EVE and no significant rejection occurred, suggesting that patients were not substantially less immunosuppressed. Remarkably, some patients seem to be nonresponders. EVE appears safe regarding graft function and may be used without calcineurin inhibitors. Adverse effects are frequent and mostly mucocutaneous, similar to those induced by sirolimus [2]. Although tolerance may be improved by EVE reduction and appropriate treatments, the rate of EVE discontinuation because of adverse effects remains considerable. Of note, our patients were rather elderly, had been immunosuppressed for several years and carried substantial comorbidities.

Our results suggest that EVE may be beneficial in HTR with skin cancers while maintaining immunosuppression, which allows tapering or withdrawal of calcineurin inhibitors. However, the frequency of adverse effects underscores the need for randomized trials to assess better the benefit–risk of EVE introduction in these patients.

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