SHORT COMMUNICATION

Risk Factors for *De Novo* Squamous Cell Carcinoma Development in Renal Transplant Recipients with a Previous Squamous Cell Carcinoma

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Cutaneous squamous cell carcinoma (SCC) is the most common post-transplant tumour in renal transplanted recipients in Sweden. Five percent of the renal transplanted population develop SCC within 10 years of transplantation. Five years after transplantation the incidence of a first SCC is increased 52-fold, and the incidence of all SCCs is increased 121-fold in renal transplant recipients compared with the general population (1). Half of the patients with a first SCC and three-quarters of those with 2 or 3 SCCs are at risk of multiple subsequent SCC and, finally, of metastatic SCC within 10 years after transplantation. These patients are in need of intense skin surveillance. However, the risk factors that indicate the need for intensified skin surveillance have not been completely identified (1–3).

Table I. Analysed risk factor

	All ($n=73$)	No Dn SCC ($n=42$)	Dn SCC ($n=31$)	*p*-value
Age at 1st transplantation[a]	51.9 (38–62)	53.1 (38–61)	50.8 (38–63)	0.97
Age at 1st SCC[a]	60.8 (54–66)	61.8 (54–66)	60.7 (54–66)	0.96
Time 1st transplantation to 1st SCC[a]	9.4 (4–16)	9.8 (4–15)	8.1 (4–16)	0.68
Age at baseline SCC[a]	65.2 (58–69)	64.5 (57–68)	65.4 (60–72)	0.36
Time 1st transplantation to baseline SCC[a]	11.6 (6–23)	10.3 (6–19)	14.1 (7–24)	0.31
Skin type (Fitzpatrick's), *n* (%)				
I–II	40 (55)	24 (57)	16 (52)	0.80
III–IV	33 (45)	18 (43)	15 (48)	
Sun exposure, *n* (%)				
Low to moderate	36 (49)	21 (50)	15 (48)	1.00
High	37 (51)	21 (50)	16 (52)	
Clinical assessment of skin, *n* (%)				
Normal or aged skin	21 (29)	15 (36)	6 (19)	0.19
AK, solar lentigines, field cancerization	52 (71)	27 (64)	25 (81)	
Histology of base SCC, *n* (%)				
In situ	37 (51)	21 (50)	16 (52)	1.00
Invasive	36 (49)	21 (50)	15 (48)	
Number previous SCC, *n* (%)				
1	25 (34)	21 (50)	4 (13)	<0.001
2	14 (19)	9 (21)	5 (16)	
>2	34 (47)	12 (29)	22 (71)	
Azathioprine, *n* (%)				
No	47 (64)	29 (69)	18 (58)	0.46
Yes previously	26 (36)	13 (31)	13 (42)	
Mycophenolate mofetil, *n* (%)				
No or stopped	43 (59)	27 (64)	16 (52)	0.34
Yes	30 (41)	15 (36)	15 (48)	
mTOR inhibitor, *n* (%)				
No or < 3 months	54 (74)	32 (76)	22 (71)	0.79
Yes >15 months	19 (26	10 (24)	9 (29)	
Sex, *n* (%)				
Female	21 (29)	10 (24)	11 (36)	0.31
Male	52 (71)	32 (76)	20 (64)	

[a]years, median (IQR) Dn: *de novo*; IQR: interquartile range; SCC: squamous cell cancer; AK: actinic keratosis.

MATERIALS AND METHODS

In this prospective clinical observational study at Uppsala University Hospital, Sweden, 73 kidney or simultaneous pancreas and kidney transplanted patients were included. All patients had at least one post-transplant SCC *in situ* or invasive SCC diagnosed from September 2006 to December 2012 and they were followed for 2 years (4). The aim was to identify the risk factor or risk factors that are the most significant in predicting *de novo* SCC.

This study was approved by the Regional Ethical Review Board in Uppsala (Dnr 2007/032) and registered with ClinicalTrials.gov (NCT02241564).

The recorded risk factors for *de novo* SCC, as well as a comparison between patients developing and not developing *de novo* SCC are presented in **Table I**. Skin types were assessed according to Fitzpatrick's classification (5). Sun exposure was assessed based on anamnestic information. Patients with low and medium sun exposure were classified as Group 1 (low risk) and those with a history of active sun bathing (before transplantation or continuously) were classified as Group 2 (high risk). Group 1 had normal skin status according to age or minor skin lesions such as aged skin, telangiectases, elastosis, and some solar lentigines. Group 2 had actinic keratosis, many solar lentigines or more advanced lesions, such as numerous actinic keratoses and field cancerization.

Immunosuppression. All patients except one had calcineurin inhibitor (CNI)-based maintenance immunosuppression, and all patients except 4 (5%) had corticosteroids in combination with CNI at inclusion. Nineteen patients in the study used everolimus as maintenance immunosuppression for >21 months.

Statistical analyses were performed using software R version 3.1.1 (The R Foundation for Statistical Computing, Vienna, Austria).

The sample size was small compared with the number of potential explanatory variables and it was unlikely *a priori* that statistical significance alone would be able to identify all prognostic covariates. Therefore, besides Cox regression analysis of all candidate variables, we removed covariates 1 at the time to determine which could be excluded with the smallest deterioration in predictive value.

RESULTS

During follow-up 31 patients (42%) developed *de novo* SCC, of which 15 (48%) were *in situ* SCC and 16 (52%) were invasive SCC (Table I).

Patients with more than one previous cutaneous SCC had a 5-fold (1–21) higher risk

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(R^2) of a subsequent skin SCC, and patients with more than two cutaneous SCC had a 14-fold (3–63) higher risk (R^2) compared with patients without a previous SCC ($p < 0.001$) (Table SI[1]). Lower age at baseline SCC contributed more than the remaining risk factors to *de novo* SCC when the covariates were removed (not shown). Histology of the baseline SCC did not correlate to the histology of the subsequent SCC.

DISCUSSION

In most skin classifications of transplanted patients, patients with a first skin SCC belong to the higher risk group. It is essential to identify all patients with SCC because SCC can lead to metastasized disease in immuno-compromised patients. SCCs are among the most immunogenic types of cancers, and the risk of subsequent SCCs decreases dramatically when immunosuppression is interrupted (6). mTOR inhibitors probably affect SCCs (7) and SCC is the only tumour type where different features of the cancers have been found in the transplanted population compared with the general population (8). Still, almost half of the patients with a first SCC do not develop a *de novo* skin SCC within 10 years. This finding means that 95% of all renal transplanted patients in Sweden are not at risk of numerous *de novo* and later metastasizing SCCs (1).

Although several investigated risk factors are known to contribute to the development of SCC, the detailed description of the skin based on signs of sun damage did not help to predict risk in our model (1, 9, 10).

The finding that the number of previous SCCs correlates with the development of *de novo* SCCs is in accordance with earlier studies, and seems to be the strongest predictive risk factor (1, 3, 11, 12).

Risk factors of a *de novo* SCC after having at least one SCC earlier have been investigated in 2 retrospective studies: multiple skin cancers at first dermatological visit, skin type I and renal transplantation before 1984 were the most important contributors to a *de novo* SCC with a history of at least one previous SCC (3, 11).

One weakness of this study is the limited number of patients, i.e. the parameters shown to contribute to *de novo* SCCs are probably significant, but the other parameters might be underestimated. For example, we found the histology of the baseline SCC did not correlate with that of a *de novo* SCC. This finding differs from the results of 2 retrospective studies (11, 12).

mTOR inhibitors have, in earlier studies, been associated with reduced number of *de novo* SCC (*in situ* and invasive) and prolonged interval between baseline and *de novo* SCC (13–15). The protective effect seems, however, to depend on the number of previous SCC lesions; the fewer SCCs the better anti-tumour effect (15). In our study mTOR inhibitors did not contribute to a more advantageous skin SCC development than calcineurin-based immunosuppressive protocols. A bias for this risk variable was that only patients with advanced skin lesions were willing to change the main immunosuppression to mTOR inhibitors.

From a clinical and resource-saving perspective, it is essential to make an early identification of patients most prone to develop *de novo* SCC. Based on our findings, patients with more than one SCC, particularly in combination with lower age at diagnosis of SCC, should be followed up more intensively than those without a previous SCC. Also, although ultraviolet exposure is a known risk factor for SCC in the skin, our results show that patients with a lower grade of clinical signs of sun damage are also at risk for development of *de novo* SCC.

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