Seminars in Oncology 43 (2016) 390–394

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/ysonc

Cutaneous squamous cell carcinomas in solid organ transplant recipients: emerging strategies for surveillance, staging, and treatment

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ARTICLE INFO

Keywords:
Cutaneous squamous cell carcinoma
Solid organ transplant recipients
Management
Surveillance
Treatment

ABSTRACT

The incidence of cutaneous squamous cell carcinomas (SCCs) in immunosuppressed solid organ transplant recipients (SOTRs) is 65- to 250-fold greater than in the general population. In addition, SCC in SOTRs is more aggressive than in the general population. SOTRs must undergo skin cancer screenings at intervals based on their risk stratification. The incidence of SCC in SOTRs varies with the type, intensity, and duration of the immunosuppressive regimen. Notably, patients on sirolimus have lower incidence of SCC compared to patients on calcineurin inhibitors. Revision of immunosuppressive regimen to include sirolimus may be a viable preventative measure against SCC in SOTRs who are high at risk for developing SCCs. Retinoids are also emerging as a means of chemoprophylaxis against development of new SCCs in high-risk patients. Treatments of SCC include electrodesiccation and curettage, surgical resection, cryosurgery, radiation, and systemic chemotherapy such as 5-fluorouracil and cetuximab.

1. Overview of squamous cell carcinomas in solid organ transplant recipients

The incidence of cutaneous squamous cell carcinomas (SCC) in fair-skinned immunosuppressed solid organ transplant recipients (SOTR) has been estimated to be 65- to 250-fold greater than in the general population [1,2]. In comparison, the incidence of basal cell carcinoma (BCC) is elevated only about 6- to 10-fold in SOTRs [3,4]. SCC is the most common skin cancer in SOTRs, being approximately four times more common than BCC. This ratio is an inversion of the ratio seen in the general population [2]. SCCs represent an even greater health burden to SOTRs than their increased incidence alone would indicate. A study of 153 SOTRs with SCCs found that SCCs in SOTRs tended to be more aggressive, and are associated with greater tumor depth, higher probability of recurrence, and greater incidence of perineural or lymphatic invasion. The same study found that BCCs, on the other hand, were not more aggressive in SOTRs than in the control population [5]. SCCs in SOTRs were also associated with aggressive subclinical extension [6]. SOTRs with cutaneous SCC of the head and neck were found in one recent study to present more frequently with high-risk pathologic features and to go on to have inferior outcomes compared with immunocompetent patients [7]. Pain is the most consistent sign of invasiveness [8]. Data from the Cincinnati Tumor Registry indicated that 5.2% of all SOTRs died from a skin malignancy, with 62% attributed to SCCs [9].

2. When do SOTRs need skin cancer screening?

As in the general population, ultraviolet radiation (UV) is the single most important carcinogen in SCCs of SOTRs. UVB radiation causes direct damage to DNA by inducing covalent bond formation between adjacent pyrimidines to create pyrimidine dimers, which are the signature mutation of UV damage [10]. UVA is less mutagenic than UVB and indirectly damages DNA by forming reactive oxygen species [10]. It is essential that SOTRs be educated about UV avoidance and skin protection. Patients should be counseled to use broad-spectrum sunscreens, avoid outdoor activities from 10 AM to 4 PM, wear sun-protective clothing such as long sleeves and wide-brimmed hats, and refrain from tanning.

Factors other than UV exposure, such as age, skin color, and past medical history, including exposure to medications such as

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http://dx.doi.org/10.1053/j.seminoncol.2016.02.019
0093-7754/

voriconazole, are also important predictive variables for incidence of SCC after transplantation [11]. Urwin et al conducted a study of 363 white (Fitzpatrick skin phototypes I–IV) renal transplant recipients in Brisbane, Australia, to create a predictive index that can be used to stratify patients into three risk groups [12]. The three risk groups have recommended first post-transplant skin cancer screening at 6 months, 2 years, and 5 years post-transplant, corresponding to at least 70% probability of being free of skin cancer until that time. At Yale Transplant Dermatology Clinic, we adapted these findings to create a six-question instrument to stratify SOTRs into three different intervals first post-transplant skin cancer screening interval, as shown in Table 1.

Because the predictive index was developed based on patients in Brisbane, Australia, a location of fairly low latitude (27 degrees South) and high incident solar ultraviolet radiation, the predictive index may not be directly applicable to temperate regions of the world, including most of the United States and Europe. Indeed, cumulative incidence of SCCs after transplant is known to be lower in regions with lower UV irradiation such as the Netherlands [13]. However, the predictive index devised by Urwin et al demonstrates the relative importance of past skin cancer history, sun exposure, age, and skin color, and provides a rubric for determining when an SOTR needs skin cancer screening [12].

3. Converting to sirolimus

The incidence of SCCs in SOTRs increases with the duration of immunosuppressive therapy. In Australia, the cumulative incidence of skin cancer in SOTRs was 7% after 1 year of immunosuppressive therapy [14] and 82% after 20 years [15]. The incidence of SCCs in SOTRs is also correlated with higher levels of immunosuppressive medications [1]. CD4 counts are significantly lower in SOTRs with skin cancer than those without [16].

Immunosuppressive regimen choice can affect incidence as well: a retrospective study showed that kidney transplant recipients who were receiving prednisolone, azathioprine, and cyclosporine had a risk of SCC that was three times as high as the risk among those receiving prednisolone and azathioprine without cyclosporine [17]. Most significantly, Euvrard et al conducted a randomized controlled trial comparing sirolimus to calcineurin inhibitors in kidney transplant recipients who had had at least one SCC [18]. Twenty-two percent of the sirolimus group developed at least one additional SCC in contrast to 39% in the calcineurin inhibitor group. The median time to onset was 15 months versus 7 months ($P = .02$).

Table 1
Individual risk factors and predictive index.

Questions asked to assess risk	Points for "yes" responses
Have you ever had a skin cancer?	5
Are you outside for more than one hour per day?	2
Are you older than 50 years of age?	2
Have you lived in a hot climate for more than 30 years?	2
Have you ever experienced sunburn as a child or a teen?	1
Is your skin tone light or very fair in color? (Fitzpatrick skin phototype I)	1
Points	First post-transplant screening
7 and greater	6 months
5-6	2 years
4 and below	5 years

Although sirolimus resulted in a lower incidence of SCC than calcineurin inhibitors, it is not without serious adverse events. There were 0.938 serious adverse events per patient in the sirolimus group, compared to 0.250 serious adverse events per patient in the calcineurin group. Twenty-three percent of patients in the sirolimus group had to discontinue sirolimus due to adverse events. The most common adverse events were edema (37%), acneiform eruption (28%), aphthous ulcers (24%), and proteinuria (20%). Therefore, some transplant centers may be reluctant to use sirolimus. However, in both the aforementioned randomized control study by Euvrard et al and a similar study, the SCC-preventative effect of switching to sirolimus was found to be largest for patients who have had one prior SCC, and was minimal for patients who have had multiple prior SCCs [2,18]. This suggests that patients may benefit from switching to sirolimus after their first post-transplant SCC, if there are no known contraindications to its use [19].

4. Retinoid chemoprophylaxis against SCCs in high-risk patients?

Topical and systemic retinoids, derivatives of vitamin A, have also been investigated as a means of chemoprophylaxis against the development of new SCCs in high-risk patients [20].

Weinstock et al studied the use of high-dose topical tretinoin for non-melanoma skin cancer development in a population of 1,131 veterans. No differences in cancer-related end points or in actinic keratosis counts were observed between treatment and control groups. Thus, high-dose topical tretinoin has been shown to be ineffective in reducing the risk of developing SCCs in high-risk patients [21].

Harwood et al retrospectively evaluated the efficacy of low-dose systemic retinoids (etretinate and acitretin) in the chemoprevention of SCCs in a population of 32 SOTRs with at least one histologically proven SCC. They found that SOTRs who received prophylactic systemic retinoids at dosages of 0.2–0.4 mg/kg/d developed significantly less SCCs in the first 3 years of treatment. The side effect profile of treatment was generally well tolerated, although six of the patients in whom treatment was interrupted had an abrupt increase in SCCs [22].

Several trials have been conducted specifically on the use of acitretin chemoprophylaxis in renal transplant recipients (RTRs). No significant difference has been observed in the time to development of first SCC after initiation of acitretin or placebo [20,23–25]. However, in one small randomized controlled trial, a 78% reduction in the risk of SCC development in patients taking 30 mg/d acitretin compared with patients taking a placebo (relative risk [RR] 0.22, 95% confidence interval [CI] 0.06–0.90) was noted. Another randomized crossover trial in 14 RTRs found that after 2 years the number of SCCs in patients on acitretin was significantly lower ($P = .002$). [23] Most patients began developing SCCs at approximately the rate of the placebo group when acitretin treatment was stopped, indicating the need for continuous treatment. Common side effects reported included mucocutaneous dryness, hair loss, musculoskeletal pain, and increased triglyceride and cholesterol levels. Pooled data from two studies found no significant difference in adverse events in the acitretin treatment group compared with the placebo group [20,23–25].

Although the data is promising, further studies on the efficacy and long-term safety of acitretin as a chemoprophylactic agent in high-risk patients are needed to establish validated guidelines for its use under this indication. The US Food and Drug Administration (FDA) categorizes acitretin as a pregnancy category X drug and contraception should be used concurrently with treatment, and for 3 years following treatment. Given the frequent mucocutaneous