

Chapter 18: Cancer of the Skin and Lip

- 18.1: We recommend that KTRs, especially those who have fair skin, live in high sun-exposure climates, have occupations requiring sun exposure, have had significant sun exposure as a child, or have a history of skin cancer, be told that their risk of skin and lip cancer is very high. (1C)**
- 18.2: We recommend that KTRs minimize life-long sun exposure and use appropriate ultraviolet light blocking agents. (1D)**
- 18.3: We suggest that adult KTRs perform skin and lip self-examinations and report new lesions to a health-care provider. (2D)**
- 18.4: For adult KTRs, we suggest that a qualified health professional, with experience in diagnosing skin cancer, perform annual skin and lip examination on KTRs, except possibly for KTRs with dark skin pigmentation. (2D)**
- 18.5: We suggest that patients with a history of skin or lip cancer, or premalignant lesions, be referred to and followed by a qualified health professional with experience in diagnosing and treating skin cancer. (2D)**
- 18.6: We suggest that patients with a history of skin cancer be offered treatment with oral acitretin, if there are no contraindications. (2B)**

KTRs, kidney transplant recipients.

Background

Skin cancers include basal cell carcinoma, squamous cell carcinoma and malignant melanomas.

Fair-skin individuals are Caucasians and especially those with blond hair and light complexion (626).

High sun-exposure climates are in areas of the world that are near the Equator, and those that have poor ozone-layer protection.

Appropriate ultraviolet light/sun avoidance includes the use of shade and avoidance of sunlight during peak hours of radiation, wearing protective clothing and the use of ultraviolet light blocking sunscreens.

Skin and lip self-examination is accomplished by close inspection of all skin areas, using a mirror and/or the assistance of a family member, such as a spouse.

Qualified health professionals with experience in diagnosing skin cancer include physicians, physician's assistants or nurse practitioners with experience in diagnosing skin cancer.

Qualified health professionals with experience in diagnosing and treating skin cancer include dermatologists, physicians or surgeons with experience in diagnosis (including skin biopsies and their interpretation) and treatment of skin cancer.

Acitretin has been used at doses between 0.2 and 0.4 mg/kg/day in RCTs to prevent skin cancers.

Rationale

- Patients who are at high risk can be identified.
- Patient behaviors can reduce the risk.
- Educating patients who are at high risk will encourage them to undertake behaviors that will reduce that risk.
- Sun exposure is a risk factor for skin cancer.
- Avoiding sun exposure may reduce the incidence of skin cancer.
- Self-examination will detect skin cancer at an earlier stage than other measures.
- Early detection and treatment will reduce the morbidity and mortality of skin cancer.
- Skin and lip examination by a qualified health professional can detect skin cancer early.
- Advice to undertake regular skin self-examination is poorly recalled and implemented.
- Acitretin may reduce the risk for recurrent squamous cell skin cancer in KTRs.
- Although adverse effects associated with the use of acitretin are common, and often necessitate discontinuing therapy, the benefits may outweigh harm in selected KTRs.

Skin cancers occur with a much higher incidence in KTRs compared to the general population. In addition, risk factors for skin cancers in the general population are also likely to be risk factors for skin cancer in KTRs. These include: fair skin, living in high sun-exposure climates, having occupations with sun exposure, having had significant sun exposure as a child, or having a history of skin cancer (627).

Most measures for reducing the risk of skin cancer (described in guideline statements above) require patient cooperation. Although there are only limited RCT data

demonstrating that informing KTRs of their increased risk for skin cancer helps to reduce that risk, the benefits of patient education are very likely to outweigh harm (628).

There is evidence that geographical locations associated with increased sun exposure are associated with increased risk of skin cancer in both KTRs and the general population (629). There is also evidence in the general population that the use of sunscreen reduces the incidence of squamous cell cancer (630). Although there is no evidence in KTRs that avoidance of sun exposure or the use of sun blockers reduces skin cancer, potential benefits likely outweigh harm. Sun can be blocked by staying in shaded environments, wearing protective clothing, a wide-brim hat and sunglasses that block ultraviolet light. There is a concern that use of sunscreens may lead to behaviors which increase total sunlight exposure (631).

It is plausible that self-examination will lead to earlier detection of skin cancer than less frequent skin examinations by health-care providers (632). It is also plausible that early detection will lead to early treatment, and thereby reduce morbidity and mortality. However, skin self-examination has not been shown to be effective in reducing overall cancer-specific mortality and morbidity in either the general population or in KTRs. Nevertheless, since the costs and adverse effects of self-screening are low, the use of education programs to encourage self-examination, especially in areas of high prevalence of skin cancer, is justified.

American (627) and European (633) transplantation professional guidelines recommend skin cancer screening in KTRs, monthly skin self-examination and at least annual total body skin examination by a dermatologist or expert physician (634). The USPSTF concluded that there is insufficient evidence to recommend for or against population skin cancer screening using total skin examination (635), while The American College of Preventive Medicine recommended screening for high-risk individuals (636).

Advice to undertake regular skin examination is poorly recalled and implementation is thus not reliable (637). Nonetheless, in a community-based RCT of regular skin screening, the intervention group reported considerably higher rates of performance (638). Visual inspection by KTRs is also likely not to be as reliable for detecting skin cancer as regular skin examinations by qualified health professionals. Studies in the general population have shown that individuals with adequate training and experience, for example dermatologists, detect skin cancer earlier than general practitioners (639). General practitioners with experience may perform as well as dermatologists in some areas (640). In the absence of experienced general practitioners, resources may be insufficient to allow KTRs to be seen annually by a dermatologist. Therefore, a strategy that combines primary screening with referral of suspicious lesions to a dermatologist may be most cost-effective. Pa-

tients who have had a skin cancer are much more likely to develop a second lesion than patients with no history of skin cancer (641). Therefore, patients who have had a skin cancer are more likely to benefit from regular screening by a dermatologist, or health-care professional with comparable training. Early diagnosis and removal of skin cancers is essential to reduce disfiguring surgery and to prevent mortality from advanced or metastatic lesions.

There is a paucity of RCT data assessing whether the benefits of altering the immunosuppressive medication regimen to reduce the incidence of skin cancer outweigh harm. For example, in a recent RCT, KTRs 10–15 years after transplant were randomly allocated to convert CNI to sirolimus (N = 555) vs. remaining on CNI (N = 275) (119). At 2 years of follow-up, 12 (2.2%) in the conversion group vs. 21 (7.7%) in the CNI group had investigator-reported skin cancer ($p < 0.001$). However, the number of adverse effects in the sirolimus conversion arm was higher than those in the CNI control arm. Indeed, the Drug Safety Monitoring Board halted enrollment for patients with eGFR 20–40 mL/min/1.73 m² early, because in this stratum (N = 77) the composite safety end point (first occurrence of biopsy-proven acute rejection, graft failure or death) was significantly higher in the conversion vs. the control group (119). The Work Group concluded that it remains unclear whether there is a high-risk population of KTRs in which benefits from converting one immunosuppressive regimen to another to reduce skin cancer outweigh harm.

In three RCTs, which together included a total of 93 KTRs (10–15 years after transplant), those treated with acitretin for 6–12 months demonstrated a reduction in the rate of formation of new skin cancers compared to untreated controls, with no differences between doses of 0.2 and 0.4 mg/kg/day (642). In these trials, several individuals had adverse effects attributed to therapy (642); however, these adverse effects generally resolved upon discontinuation of treatment. Adverse effects that resulted in treatment withdrawal included: headache (N = 3), dyslipidemia (N = 2) musculoskeletal complaints (N = 2) and skin rash (N = 2). In addition, the duration of treatment and follow-up were relatively short in these trials. Altogether, the Work Group concluded that there is moderate-quality evidence that there are tradeoffs to prophylaxis with acitretin (see Evidence Profile in Supporting Table 52 at <http://www3.interscience.wiley.com/journal/118499698/toc>); some KTRs may consider that the benefits of treatment outweigh the harm.

Research Recommendations

- A RCT is needed to better define the optimal dose and the benefits and harm of acitretin to prevent recurrent skin cancer in KTRs.