Editorial

Reexamination of Field-Directed Therapy for Actinic Keratosis

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Berman et al[1,2] recently published a 2-part series exploring the role of field-directed therapy in the management of actinic keratosis (AK). As a member of the *Cutis* Editorial Board, I applaud this comprehensive and thoughtful body of work. Nonetheless, I think it is worth a brief critical reexamination of several specific issues regarding the treatment of AK.

One Lesion or Multiple Lesions

Almost all dermatologists agree with the assertion that an AK, regardless of the nomenclature utilized or classification/grading scheme chosen, represents the initial overt manifestation of a disease continuum, which may eventuate in invasive squamous cell carcinoma (SCC).[3,4] The possibility of progression with associated morbidity or mortality is used to justify AK eradication.[5-7] Most dermatologists would concede that it is relatively uncommon when a single AK lesion is considered; however, despite a number of publications on this subject, the exact likelihood of this phenomenon remains uncertain.[8-10]

For some clinicians, the low rate of malignant transformation of an individual AK speaks against the use of field-directed therapy. We should remember that a patient presenting with a single AK is a relatively rare occurrence! Multiple lesions more commonly are observed.[11] Under these circumstances, the cumulative risk for malignant transformation dramatically increases, and an increasing number of AKs directly correlates with an increasing risk for SCC.[12,13] Thus in the average patient, field-directed therapy may be the best way to eliminate precursor lesions, lest active AKs will be missed during individual lesion-directed therapy.

Field-Directed Therapy and the Patient

Despite a variable degree of inflammation associated with field-directed therapies, this approach demonstrates notable patient-friendly aspects. For example, instead of cryotherapy-induced hypopigmented or depressed scars, field-directed therapy generally is associated with a good cosmetic outcome and even some degree of clinical skin rejuvenation.[14] One also might argue that most field-directed therapies are more humane compared to widespread use of lesion-directed cryotherapy; the latter can be uncomfortable, especially when employing longer freeze times associated with a better overall rate of AK clearance.[15]

Subclinical Lesions

Field-directed therapy is the unmasking and subsequent destruction of initially unapparent AKs, or so-called subclinical lesions. Some clinicians still question this concept, which is part of the overall theme known as field cancerization.[16] The actual direct evidence for subclinical lesions certainly is relatively scant and largely relies on a technique called reflectance confocal microscopy, which is not widely used in the United States.[17,18] Nonetheless, the evidence generated by reflectance confocal microscopy is solid, is based on reproducible objective criteria (ie, nuclear atypia, keratinocyte pleomorphism, overall architectural disarray), and is verifiable by routine histology. In addition, a plethora of indirect evidence demonstrates the presence of subclinical lesions within a cutaneous field characterized by clinically recognizable AKs.

Indirect biologic evidence for the existence of subclinical lesions includes the presence of genetic alterations (characteristic of AKs and SCCs) within the keratinocytes, immediately surrounding visible lesions. Deleterious alterations in perilesional sun-exposed skin may involve mutations in the critical p53 tumor suppressor gene, as well as in $p14^{Arf}$, $p15^{Ink4B}$, and $p16^{Ink4A}$ loci.[19-22] Increasing biochemical evidence suggests that many field-directed therapies actually reverse expression of oncogenes and/or remove patches of keratinocytes carrying mutated and therefore nonfunctional apoptotic genes.[14,23-25] These findings provide a remarkable rationale for field-directed therapy.

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Subclinical lesions also can be identified by pink fluorescence under Wood lamp illumination following topical application of both of the commercially available aminolevulinic acid photosensitizers[26] as well as by focal appearance of erythema and crusting, which accompanies topical application of 5-fluorouracil or imiquimod.[27]

The unmasking of subclinical lesions can be dramatic during field-directed therapy. In low-concentration imiquimod studies, a doubling of apparent AK lesions has been noted as coincidental with drug application.[28,29]

All of the foregoing evidence clearly supports the presence of subclinical lesions and thereby highlights the advantage of field-directed treatment of AK-bearing skin sites. Use of lesion-directed therapy alone would lead to the persistence of subclinical lesions that possess the capacity to progress to overt AK if left untreated.[20]

The basic presumption that field-directed therapy offers distinct advantages over lesion-directed monotherapy also is supported by a small-scale (n=25 in each group), direct, head-to-head comparison of initial and long-term clinical and histologic AK clearance rates when a standardized method of cryotherapy was compared with the application of either 5-fluorouracil or imiquimod. In this study, although cryotherapy performed well initially, at 1-year posttreatment the histologically confirmed clinical clearance of lesions as well as clearance of the surrounding skin was substantially superior following imiquimod or 5-fluorouracil when compared to cryosurgery.[30]

Future Directions

Due to marked differences in study design (ie, study populations, anatomic sites treated, end points measured, duration of therapy, duration of follow-up), it is virtually impossible at present to conclude with absolute assurance that one field-directed therapy inherently is superior to another. Additionally, it is impossible to choose an optimum method of combining lesion-directed and field-directed therapies (or 2 different field-directed therapies). Additional investigation ultimately will clarify this situation and will help the clinician make the most rational choice for any given patient.

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