

Treatment Approaches for Actinic Keratosis

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by the surgeon remains vague. Our trial did not include patients with suspicious nodes, and therefore we cannot answer the question regarding removal of more than the suspicious node. However, the fact that removal of clinically negative but histologically positive nodes in more than half the patients in our trial did not change the prognosis may indicate that removal of more than a bulky node might not be indicated. This interpretation was supported by data from an international lymphadenectomy trial¹ in which the removal of single suspicious nodes before randomization was allowed, but the addition of systematic lymphadenectomy did not translate into better survival.

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Since publication of their article, the authors report no further potential conflict of interest.

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Treatment Approaches for Actinic Keratosis

TO THE EDITOR: Jansen et al. (March 7 issue)¹ provide landmark data regarding field-directed therapy for actinic keratosis. Although many patients may benefit from treatment for actinic keratosis because of the decreased risk of progression to squamous-cell carcinoma, active surveillance can be an alternative. Prospective studies in which the estimated percentage of actinic keratosis lesions that will progress to squamous-cell carcinoma is 0.1% per lesion per year have shown that many cases of actinic keratosis regress spontaneously and 40% of squamous-cell carcinomas arise in clinically normal-appearing skin.² A randomized, double-blind, placebo-controlled trial of topical fluorouracil for chemoprevention of keratinocyte carcinoma in high-risk patients showed a 75% reduction in the risk of squamous-cell carcinoma at 1 year; however, the number needed to treat to prevent one squamous-cell carcinoma was 33, and no differences were seen between the control group and the treatment group at 4 years.³ Treatment of actinic keratosis in lower-risk patients would probably be associated with a higher number needed to treat and greater potential for harm.

We advocate for shared decision making and appropriate information framing when deciding on management options for actinic keratosis.⁴ We also recommend a balancing of treatment efficacy, adherence, cost, and side effects, as well as the patient's risk of squamous-cell carcinoma and the patient's wishes.^{5,6}

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THE AUTHORS REPLY: We agree with Navarrete-Dechent and colleagues that shared decision making and appropriate information on the risk of squamous-cell carcinoma are very important. However, data on the percentage of actinic keratosis lesions that will progress to a squamous-

cell carcinoma are sparse, and the variance in the suggested risk of progression is wide, ranging from 0.025% to 16% per actinic keratosis lesion per year. Furthermore, there is evidence that field-directed treatment reduces progression to squamous-cell carcinoma, and in our trial we observed a greater increase in health-related quality of life in the fluorouracil group than in the other groups.¹ Data are lacking to support a wait-and-see policy in terms of patient satisfaction.

In deciding whether or not to treat actinic keratosis, the above-mentioned items and the possible side effects of treatment, as well as the patient's motivation for treatment, are important considerations. If patients decide not to receive treatment, advice regarding contacting a physician in case of symptoms such as pain, bleeding, and fast growth of the lesion is warranted.² Moreover, patients should be notified that actinic keratosis can be regarded as a biomarker, and they must be aware of the risk of keratino-

cyte cancer. Good surveillance, as Navarrete-Dechent and colleagues suggest, might be an option for some patients, but data from a prospective trial to study the benefits of this strategy are lacking.

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Since publication of their article, the authors report no further potential conflict of interest.

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Methotrexate for Prevention of Cardiovascular Events

TO THE EDITOR: Low-dose methotrexate is widely used as first-line therapy for rheumatoid arthritis and other chronic diseases, and its use is supported by recommendations in the United States¹ and Europe.² However, data from large, placebo-controlled trials regarding the risks of methotrexate therapy have been limited. It is therefore of considerable interest that Ridker et al. (Feb. 21 issue)³ found that the prevalence of known side effects of methotrexate was generally low in the Cardiovascular Inflammation Reduction Trial, probably owing to a trial design that featured an initial run-in phase during which patients could leave the trial in the event of methotrexate-related side effects. Subsequently, the risks that were attributable to methotrexate therapy (the between-group differences in incidence rates) were less than 1 event per 100 patient-years for major hepatic and mucosal events, 1.5 events per 100 patient-years for leukopenia, and 1.6 events per 100 patient-years for gastrointestinal events. In contrast to these reassuring findings, the unexpected observation that methotrexate therapy was associated with higher rates of non-basal-cell skin

cancer than placebo is reminiscent of the risk of squamous-cell carcinoma that has been associated with tumor necrosis factor (TNF) inhibitors.⁴ Taken together, these data on the safety of methotrexate therapy provide a solid background against which other first-line treatment options for rheumatoid arthritis, including conventional, biologic, and targeted synthetic medications, can be considered.

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