Targeted Therapy

Major finding: EGFR inhibition in keratinocytes increases chemokine expression and immune cell infiltration.

Approach: Deletion of *Egfr* in the mouse epidermis serves as a model for EGFR inhibitor–induced skin rashes.

Impact: Use of these models may identify ways to avoid dose-limiting skin responses to EGFR inhibitors.

INHIBITION OF EPIDERMAL EGFR DISRUPTS SKIN IMMUNE HOMEOSTASIS

Small molecule and monoclonal antibody inhibitors of EGF receptor (EGFR) have shown clinical activity in EGFR-dependent cancers but cause skin toxicities such as acneiform rashes, dryness, itchiness, and infections. Such adverse events are currently the best predictors of antitumor activity, but they often negatively affect quality of life and lead to dose reduction or treatment discontinuation, which limits treatment efficacy. Mascia and colleagues analyzed the plasma of patients with ovarian cancer before and after treatment with gefitinib and noted increases in proinflammatory chemokine levels after treatment. Lichtenberger and colleagues similarly observed elevated chemokine expression in skin rash biopsies from EGFR inhibitor–treated patients compared with untreated healthy control subjects and also found evidence of increased bacterial colonization, decreased antimicrobial peptide expression, and skin barrier defects in affected patients. To gain insight into skin-specific effects of EGFR inhibition, both groups generated mouse models specifically lacking EGFR expression in epidermal keratinocytes and found that these mice progressively developed the phenotypic and histologic features of the skin lesions of EGFR inhibitor–treated patients. An early increase in proinflammatory chemokines was observed that promoted the recruitment of macrophages and mast cells, followed by infiltration of T cells, neutrophils, and eosinophils and defects in keratinocyte differentiation. Although both groups ruled out causative roles for lymphocytes and major immune signaling pathways in the EGFR-deficient skin phenotype, Mascia and colleagues found that bisphosphonate-mediated macrophage depletion partially rescued the phenotype of EGFR-deficient skin and normalized inflammatory gene expression, and Lichtenberger and colleagues observed that pharmacologic mast cell inhibition reduced infiltration of immune cells into the epidermis. Together, these findings provide insight into the role of EGFR in the epidermis and suggest potential approaches to prevent dose-limiting skin toxicities caused by EGFR inhibitors, which could improve the effectiveness of anti-EGFR therapy. ■

Mascia F, Lam G, Keith C, Garber C, Steinberg SM, Kohn E, et al. Genetic ablation of epidermal EGFR reveals the dynamic origin of adverse effects of anti-EGFR therapy. Sci Transl Med 2013;5:199ra110.

Lichtenberger BM, Gerger PA, Holcmann M, Buhren BA, Amberg N, Smolle V, et al. Epidermal EGFR controls cutaneous host defense and prevents inflammation. Sci Transl Med 2013;5:199ra111.

Clinical Trials

Major finding: The next-generation antiandrogen ARN-509 has antitumor activity in metastatic CRPC.

Approach: Preclinical and clinical efficacy data were integrated to determine the maximum efficacious dose.

Impact: Further study of ARN-509 is warranted based on its high therapeutic index and favorable safety profile.

ARN-509 IS SAFE AND EFFECTIVE IN CASTRATION-RESISTANT PROSTATE CANCER

Drugs targeting androgen receptor (AR) signaling have significant activity in many patients with metastatic castration-resistant prostate cancer (CRPC), but intrinsic and acquired resistance to these agents remains a clinical challenge. ARN-509 is a second-generation AR antagonist that has shown greater potency than first-generation AR inhibitors in preclinical models and, unlike some first-generation AR inhibitors, does not act as an AR agonist when AR is overexpressed. Rathkopf and colleagues report findings from a first-in-human phase I dose-escalation study in patients with metastatic CRPC that assessed the safety, tolerability, and pharmacokinetics of ARN-509 as well as a recommended phase II dose. The secondary objective of the trial was to evaluate antitumor activity. ARN-509 was rapidly absorbed, had linear and dose-proportional pharmacokinetics, and showed evidence of antitumor activity at all doses tested. Of 30 patients enrolled in the trial, 18 (60%) had a greater than 50% decline in prostate-specific antigen levels after ARN-509 treatment, and 4 of 7 patients with unfavorable circulating tumor cell counts converted to favorable status after receiving ARN-509. Uptake of 16β-[^{18}F]fluoro-α-dihydrotestosterone (FDHT), an indicator of AR binding capacity, declined in all patients tested in a dose-dependent manner, indicating that ARN-509 effectively bound and inhibited AR in patients. The most common adverse event caused by ARN-509 was grade 1 or 2 fatigue, and only 1 grade 3 adverse event related to treatment was reported. Because of the lack of dose-limiting toxicity, a maximum tolerated dose was not defined. Instead, a maximum efficacious dose was chosen for the recommended phase II dose based on the doses that elicited the best clinical responses and produced steady-state plasma levels in the range that led to tumor regressions in mice. These findings suggest that ARN-509 is safe and effective and provide support for its further clinical development for treatment of CRPC. ■

Rathkopf DE, Morris MJ, Fox JJ, Danila DC, Slovin SF, Hager JH, et al. Phase I study of ARN-509, a novel antiandrogen, in the treatment of castration-resistant prostate cancer. J Clin Oncol 2013 Sept 3 [Epub ahead of print].