Clinical Trials

Major Finding: Patients with HPV16$^+$ cervical cancer and high T-cell responses to an HPV16 vaccine survived longer.

Concept: Vaccine dose and the inclusion of PEGylated type I IFN had no effect on tumor shrinkage or survival.

Impact: This trial should prompt larger studies and work to identify biomarkers of strong T-cell response.

STRONG HPV VACCINE RESPONSE PREDICTS BETTER SURVIVAL WITH CHEMOTHERAPY

Although some clinical success has been achieved with vaccines in premalignant lesions caused by human papillomavirus type 16 (HPV16), responses to vaccine monotherapy in HPV16-induced cancers is limited by cancer-induced immunosuppression. In a study of 77 patients with advanced, recurrent, or metastatic HPV16$^+$ cervical cancer, Melief, Welters, and colleagues tested the effects of an HPV16 vaccine (ISA101) with standard carboplatin–paclitaxel chemotherapy with or without PEGylated type I IFN, with vaccine administration timed for optimal chemotherapy-mediated alleviation of immune dysfunction. Most patients (98.9%) reported chemotherapy-induced side effects, but few were deemed attributable to vaccine treatment. Vaccine-related side effects were mainly systemic allergic reactions, which affected 15.3% of patients and were serious in 6.9% of patients (almost all in the group receiving the highest vaccine dose), and injection-site reactions, which were not serious and affected 69.4% of patients. In the 64 patients evaluable for T-cell response, all exhibited responses specific to the HPV16 oncoproteins E6 and E7 without generally enhanced immune function. Notably, although vaccine dose did not affect the amount of tumor shrinkage or overall survival (OS), patients who mounted strong (greater than median) HPV16-specific immune responses to the vaccine exhibited greater OS than patients with weak (less than median) responses, with median OS values of 16.8 and 11.2 months in each group, respectively. The inclusion or exclusion of PEGylated type I IFN had no impact on tumor size or OS. In all, this study demonstrated that the HPV16 vaccine ISA101 in combination with carboplatin–paclitaxel chemotherapy is generally well tolerated, with a safety profile similar to that of chemotherapy alone. Limitations of the study include the small number of patients included and the lack of a chemotherapy-only control arm. Research to better establish the clinical efficacy of ISA101 and identify biomarkers predicting strong immune response is warranted, and a randomized, placebo-controlled trial examining ISA101's synergy with anti–PD-1 (observed elsewhere) in patients with HPV16$^+$ recurrent or metastatic oropharyngeal cancer is in progress. ■

Melief CJM, Welters MJP, Vergote I, Kroep JR, Kenter GG, Ottevanger PB, et al. Strong vaccine responses during chemotherapy are associated with prolonged cancer survival. Sci Transl Med 2020; 535:eaaz8235.

Drug Development

Major Finding: Inhibition of BET protein bromodomains BD1 and BD2 produces unique phenotypes in disease models.

Concept: Inhibition of BD1 but not BD2 restricts cancer growth, but both modulate immunity and inflammation.

Impact: This shows that these domains have distinct roles and that selective targeting may be of interest.

SELECTIVE INHIBITION OF BET PROTEIN DOMAINS HAS FUNCTIONAL RELEVANCE

The inhibition of BET proteins, which are epigenetic readers that contain two tandem bromodomains (BD1 and BD2) for chromatin binding and transcription activation, has yielded promising results in preclinical and clinical studies of hematologic and solid cancers. The first-generation BET inhibitors currently under investigation exhibit equal affinity for BD1 and BD2, and little is known about the potentially unique functions of these two bromodomains. To address this knowledge gap, Gilan, Rioja, and colleagues used structure-based design to develop highly selective BD1 and BD2 inhibitors termed iBET-BD1 and iBET-BD2, respectively. Experiments using a variety of human cancer cell lines revealed that iBET-BD1 had similar effects as a pan-BET inhibitor, inhibiting proliferation and resulting in cell-cycle arrest and apoptosis, and *in vivo* experiments using a mouse model of acute myeloid leukemia showed that iBET-BD1 provided a greater increase in survival than iBET-BD2. According to nascent RNA–sequencing experiments, the transcriptome of iBET-BD1–treated cells resembled that of cells treated with a pan-BET inhibitor, whereas iBET-BD2–treated cells showed little transcriptomic perturbation. Further experiments revealed that BD2 was dispensable for chromatin binding by BET proteins and, hence, maintenance of preexisting transcriptional states; however, BD2 was important for initial binding of BET proteins to chromatin to facilitate induction of gene expression. Additionally, functional *in vitro* assays showed that, despite not affecting cancer-cell proliferation or survival, BD2 inhibition, like BD1 inhibition, exerted immunomodulatory effects, inhibiting the production of effector cytokines. This along with some prior findings raised the possibility that, although selective BD2 inhibition is not effective in cancer, it may be valuable in some immunoinflammatory diseases. This notion was supported by results from experiments in a rat model of rheumatoid arthritis, a mouse model of psoriasis, and a mouse model of nonalcoholic fatty liver disease. Collectively, these findings establish unique functions for BD1 and BD2 and suggest that current therapeutic strategies based on BET targeting in cancer and immunoinflammatory diseases may be refined by selective targeting of either domain. ■

Gilan O, Rioja I, Knezevic K, Bell MJ, Yeung MM, Harker NR, et al. Selective targeting of BD1 and BD2 of the BET proteins in cancer and immuno-inflammation. Science 2020 Mar 19 [Epub ahead of print].

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