Clinical Trials

Major finding: The PI3K inhibitor pictilisib plus anastrozole suppresses luminal B breast cancer proliferation.

Clinical relevance: PI3K inhibitor effects on preoperative proliferation were assessed in a window-of-opportunity trial.

Impact: Pictilisib in combination with anastrozole may be effective as a preoperative treatment.

PICTILISIB PLUS ANASTROZOLE REDUCES PROLIFERATION IN ER$^+$ BREAST CANCER

PI3K–mTOR pathway genes are commonly mutated in estrogen receptor (ER)–positive breast cancer, and preclinical and clinical data have indicated that PI3K–mTOR pathway inhibition may enhance endocrine therapy, prompting Schmid and colleagues to perform a phase II preoperative window-of-opportunity study investigating the effects of the PI3K inhibitor pictilisib in combination with the aromatase inhibitor anastrozole on tumor cell proliferation. This study randomly assigned 75 postmenopausal women with newly diagnosed operable ER$^+$, HER2$^-$ breast cancer to receive anastrozole alone (26 patients) or anastrozole plus pictilisib (49 patients). Treatment was given for 14 days prior to surgical resection and adjuvant therapy. At least two tumor biopsies were taken at baseline and at the end of treatment, and used for immunohistochemistry. The primary end point was inhibition of tumor cell proliferation measured by change in Ki67 staining before and after treatment. Ki67 staining decreased in all but 3 patients, and the group receiving pictilisib and anastrozole had a greater mean suppression (83.8%) than the group receiving anastrozole alone (66.0%). Subanalysis of the molecular subtypes revealed that anastrozole plus pictilisib reduced luminal B tumor proliferation, whereas there was no effect on luminal A tumor proliferation. There were no significant correlations observed between PI3K mutation status and pictilisib response. Treatment-related adverse events for pictilisib and anastrozole were consistent with previous studies, with the anastrozole plus pictilisib group having more adverse events than the anastrozole-alone group, including fatigue, rash, nausea, and diarrhea. All adverse events were rapidly reversible, and reducing the dose of pictilisib reduced skin toxicity. The results of this phase II trial indicate that the addition of pictilisib to preoperative anastrozole hormone therapy reduces tumor proliferation in patients with luminal B breast cancer, but further insight is needed to understand why the effects were independent of PI3K mutation status and specific to luminal B subtype tumors. ■

Schmid P, Pinder SE, Wheatley D, Macaskill J, Zammit C, Hu J, et al. Phase II randomized preoperative window-of-opportunity study of the PI3K inhibitor pictilisib plus anastrozole compared with anastrozole alone in patients with estrogen receptor–positive breast cancer. J Clin Oncol 2016 Mar 14 [Epub ahead of print].

Metastasis

Major finding: Quiescent stem-like disseminated latent tumor cells evade NK-mediated immunosurveillance.

Mechanism: Autocrine *DKK1* expression drives quiescence and downregulation of NK ligands in latent metastases.

Impact: Reactivation of NK ligands in quiescent latent metastases may be a potential therapeutic strategy.

AUTOCRINE WNT INHIBITION DRIVES IMMUNE EVASION AND LATENCY OF METASTASES

Patients with highly malignant tumors often relapse after treatment of the primary tumor due to metastatic colonization, which occurs prior to diagnosis. However, elucidation of the molecular mechanisms underlying disseminated tumor cell latency has been difficult due to the lack of adequate preclinical models. Malladi and colleagues injected nude mice with fluorescently labeled metastatic breast and lung cancer lines and isolated latency competent cancer (LCC) cells from target organs harvested before the appearance of overt tumors in most mice. Orthotopic implantation of LCC cells exhibited similar tumorigenic properties as the parental lines and greater metastasis-initiating potential. Pulse-chase experiments with a thymidine analogue revealed that LCC cells entered quiescence more frequently than the parental cells *in vitro* and *in vivo*. Depletion of natural killer (NK) cells resulted in outgrowth and increased metastases of lung LCC cells *in vivo*. Bioinformatic analyses of gene signatures showed that LCC cells closely resembled stem and progenitor cells, and that LCC exhibited decreased expression of NK cytotoxicity gene signatures. Consistent with these findings, LCC cells exhibited overexpression of SRY-box 2 (*SOX2*) and *SOX9*, two stem cell–associated transcription factors which were required for LCC oncosphere formation *in vitro* and metastatic seeding *in vivo*, and were resistant to NK-mediated cytolysis *in vitro*. Analysis of quiescent LCC cells revealed the reduction of WNT, MYC, and NFκβ signaling. Consistent with these findings, dickhopf WNT signaling pathway inhibitor 1 (*DKK1*) was expressed in LCC cells *in vitro* and *in vivo*, as well as in disseminated tumor cells which arose in mice orthotopically implanted with breast cancer patient-derived xenografts. Mechanistically, upregulation of *SOX2* resulted in autocrine *DKK1* expression, which attenuated WNT signaling to drive LCC cells into quiescence, which induced the downregulation of NK cell activators. Together, these results describe the autocrine mechanism by which disseminated tumor cells enter quiescence and evade immune surveillance while maintaining the potential for tumor initiation and outgrowth. ■

Malladi S, Macalinao DG, Jin X, He L, Basnet H, Zou Y, et al. Metastatic latency and immune evasion through autocrine inhibition of WNT. Cell 2016;165:45–60.