Drug Resistance

Major finding: Quantitative proteomic analysis reveals that MEK inhibition activates multiple RTKs.

Clinical relevance: Selumetinib plus sorafenib may be effective in triple-negative breast cancer.

Impact: Assessing drug-induced kinome changes may guide combination therapies for other cancers.

KINOME SIGNATURES CAN GUIDE RATIONAL COMBINATION THERAPY DESIGN

Cancer cells frequently develop resistance to single kinase inhibitors through activation of compensatory pathways that promote survival. To identify kinases whose activation promotes drug resistance, Duncan and colleagues developed a proteomics approach in which cell lysates were incubated with multiplexed beads conjugated to selective and pan-kinase inhibitors. The bound kinases were identified by mass spectrometry and drug-induced increases in binding were indicative of elevated kinase activity. Application of this method to triple-negative breast cancer (TNBC) cell lines and primary tumor samples, in which the MEK signaling pathway is elevated, revealed that multiple receptor tyrosine kinases (RTK) were activated in response to treatment with the MEK inhibitor selumetinib (AZD6244). Mechanistically, inhibition of the MEK signaling pathway promoted the proteasomal degradation of c-MYC, which subsequently led to transcriptional derepression of RTKs such as VEGFR2 and PDGFRβ. Knockdown of either of these kinases enhanced TNBC cell growth inhibition by selumetinib, indicating that this reprogramming of the kinome in response to selumetinib treatment was necessary to subvert MEK inhibition. These findings further suggested that combining selumetinib with sorafenib, a small-molecule inhibitor of both VEGFR2 and PDGFRβ, might be an effective approach in TNBC. Both were ineffective as single agents, but when combined, the 2 kinase inhibitors synergistically blocked TNBC cell growth *in vitro* and induced significant tumor regression in a genetically engineered TNBC mouse model. Together, these findings identify a potential therapeutic strategy for TNBC and establish a method for rational design of combination kinase inhibitor therapies that can potentially improve clinical responses. ■

Duncan JS, Whittle MC, Nakamura K, Abell AN, Midland AA, Zawistowski JS, et al. Dynamic reprogramming of the kinome in response to targeted MEK inhibition in triple-negative breast cancer. Cell 2012;149:307–21.

Leukemia

Major finding: Induction failure in ALL is associated with clinical and biologic heterogeneity.

Approach: Retrospective analysis was performed on patients from 14 study groups.

Impact: The current standard of care may not benefit all patients who fail induction.

SPECIFIC DISEASE FEATURES AFFECT OUTCOME AFTER INDUCTION FAILURE IN ALL

Current treatment regimens cure approximately 80% of children diagnosed with acute lymphoblastic leukemia (ALL). However, for those rare patients who do not achieve a complete remission after induction chemotherapy, the prognosis tends to be poor, and these patients are uniformly offered allogeneic hematopoietic stem-cell transplantation. Schrappe and colleagues performed a retrospective analysis of 44,017 pediatric patients diagnosed with ALL from 1985 through 2000 and discovered that clinical, biologic, and prognostic heterogeneity were associated with induction failure. A total of 1,041 patients (2.4%) failed induction therapy, with an overall 10-year survival rate of 32%. The authors found that the high-risk features generally associated with a diagnosis of ALL were overrepresented in this cohort, including older age, high leukocyte count, T-cell disease, male sex, Philadelphia chromosome positivity, and *MLL* rearrangement. Interestingly, within this poor prognosis group, patients with certain biologic features, such as high hyperdiploidy and younger age, had a significantly better rate of survival. In contrast, older age, T-cell disease, and *MLL* rearrangement were associated with a particularly poor outcome. The treatments administered to these patients also affected their prognosis and clinical outcome. Specifically, patients with T-cell leukemia fared better when they were treated with allogeneic stem-cell transplantation, whereas younger patients with precursor B-cell leukemia who received chemotherapy showed the best overall 10-year survival rate. These findings therefore suggest that stem-cell transplantation may not benefit all patients who fail induction chemotherapy. Rather, specific disease features may be used to personalize therapy and improve outcomes in patients with ALL. ■

Schrappe M, Hunger SP, Pui CH, Saha V, Gaynon PS, Baruchel A, et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med 2012;366:1371–81.