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Clinical Trials

Major finding: The PI3Kδ inhibitor idelalisib has activity in previously treated B-cell non-Hodgkin lymphomas.

Approach: A phase II trial evaluated idelalisib in patients who were refractory to rituximab and an alkylating agent.

Impact: Idelalisib may be an effective therapy for indolent non-Hodgkin lymphoma regardless of subtype.

IDELALISIB IS ACTIVE IN RELAPSED AND REFRACTORY INDOLENT LYMPHOMA

The δ isoform of phosphatidylinositol 3-kinase (PI3Kδ) acts downstream of the B-cell receptor and other cytokine, chemokine, and integrin receptors to regulate B-cell development and function. Given that PI3Kδ activity is largely restricted to hematopoietic cells and often upregulated in B-cell malignancies, this PI3K isoform represents a promising therapeutic target. Gopal and colleagues report results from a single-group, open-label, phase II study of the orally bioavailable PI3Kδ inhibitor idelalisib in patients with relapsed or refractory indolent B-cell non-Hodgkin lymphomas, including follicular lymphoma, small lymphocytic lymphoma, marginal-zone lymphoma, and lymphoplasmacytic lymphoma with or without Waldenström macroglobulinemia. Eligible patients had been previously treated with at least two systemic therapies, and their disease had either failed to respond or progressed within 6 months following treatment with rituximab and an alkylating agent, which are commonly used as first-line and subsequent therapy. The primary endpoint was the overall response rate, and secondary endpoints included the time to response, duration of response, progression-free survival, overall survival, and safety. Of 122 evaluable patients, lymph node size was reduced in 110 (90%) patients, with 71 (57%) meeting the criteria for an objective response. Response rates were similar across the lymphoma subtypes. The median time to response was 1.9 months, and the median duration of response was 12.5 months, indicating that continued administration of idelalisib can lead to rapid, durable responses in patients with indolent B-cell non-Hodgkin lymphomas. The median progression-free survival was 11.0 months, and the median overall survival was 20.3 months. Idelalisib had a favorable safety profile in this patient population, with a low incidence of clinically significant hematologic toxic effects or severe adverse events and low rates of discontinuation due to toxicity. The findings that idelalisib is well tolerated and has single-agent activity in indolent non-Hodgkin lymphomas support further evaluation of this drug in larger, controlled trials. ■

Gopal AK, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014 Jan 22 [Epub ahead of print].

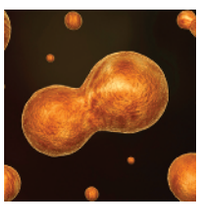
Cell Biology

Major finding: The synthesis and localization of particular lipid species changes throughout the cell cycle.

Concept: Specific lipid species and lipid biosynthetic enzymes are important for successful cell division.

Impact: The specificity of lipid composition in dividing cells suggests that individual lipids have distinct roles.

LIPID SYNTHESIS AND LOCALIZATION ARE REGULATED DURING THE CELL CYCLE



The lipid composition of membranes can affect both their mechanical properties and the activation of membrane-associated signaling pathways, but the precise cellular roles of most lipids that comprise the vast mammalian lipidome are poorly understood. Atilla-Gokcumen and colleagues hypothesized that a cell's lipid composition may change during the sweeping membrane rearrangements that accompany cell division. Indeed, a liquid-chromatography–mass spectroscopy analysis of global lipid composition in HeLa cells detected 11 lipid species that specifically accumulated during cytokinesis compared with S phase, including sphingolipids and ceramides. Several of the cytokinesis-specific species accumulated in lysates enriched for the midbody, a structure that forms at the interface between dividing cells, and several other lipids that were unchanged throughout the cell cycle specifically accumulated at the midbody during cytokinesis, prompting the authors to investigate the contributions of lipid biosynthetic enzymes to cell division. Of 244 enzymes targeted by RNA interference, knockdown of 23 provoked cytokinesis defects, and 12 were involved in the synthesis of lipids previously identified by the mass spectrometry assay. Analysis of the 3 enzymes with the strongest phenotypes, sphingomyelin phosphodiesterase 4 (SMPD4), galactosylceramidase (GALC), and diacylglycerol O-acyltransferase 2 (DGAT2), showed that their loss affected cellular lipid composition in distinct ways, but that loss of each caused mitotic delay and cell division failure marked by blebbing and distortion, likely reflecting impaired cytoskeletal organization. Together with the observation that membrane stiffness was increased in normal dividing cells, these data suggest that cells may calibrate their lipidome to accommodate the mechanical demands of cell division. The finding that cells regulate levels of particular lipid species during cell division and the identification of lipid biosynthetic enzymes required for cell division set the stage for future investigations into how lipids affect membrane physics, cell signaling, and cytoskeletal organization in dividing cells. ■

Atilla-Gokcumen GE, Muro E, Relat-Goberna J, Sasse S, Bedigian A, Coughlin ML, et al. Dividing cells regulate their lipid composition and localization. Cell 2014;156:428–39.

AACR American Association for Cancer Research

CANCER DISCOVERY

Lipid Synthesis and Localization Are Regulated during the Cell Cycle

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