Clinical Trials

Major finding: A phase I study shows that navitoclax monotherapy elicits durable responses in CLL.

Mechanism: Navitoclax is a BH3 mimetic that selectively targets the antiapoptotic protein BCL-2.

Impact: BCL-2 is clinically validated as a useful therapeutic target in CLL.

TARGETED BCL-2 INHIBITION IS EFFECTIVE IN CHRONIC LYMPHOCYTIC LEUKEMIA

Elevated expression of the antiapoptotic protein B-cell lymphoma 2 (BCL-2) is a hallmark of chronic lymphocytic leukemia (CLL) and is thought to drive the accumulation of mature leukemic lymphocytes. Roberts and colleagues report the results of a phase I study in which 29 patients with relapsed or refractory CLL were treated with navitoclax, a BCL-2 homology domain 3 (BH3) mimetic agent that selectively binds BCL-2 and BCL-x_L, thus inducing the mitochondrial apoptotic pathway by preventing BCL-2–mediated sequestration and inactivation of proapoptotic proteins. Strikingly, 90% of patients with peripheral blood lymphocytosis achieved at least a 50% reduction in lymphocytosis within days of starting navitoclax treatment, which was associated with increased apoptosis of circulating CLL cells, confirming the on-target effects of navitoclax. The median progression-free survival of CLL patients treated with navitoclax was 25 months. Nine patients (31%) achieved a partial response, and stable disease was observed in 18 patients. The responses were durable, as 7 patients maintained features of stable disease for more than 12 months after starting navitoclax. The most common serious adverse event was grade 4 thrombocytopenia, which was anticipated due to the known role of BCL-x_L in platelet homeostasis. To identify potential biomarkers for the response to navitoclax, the expression of BCL-2 family proteins was analyzed in a subset of patients. No correlation between BCL-2 level and response was observed; however, navitoclax is also thought to kill cells expressing the related prosurvival factor MCL-1 by displacing its inhibitor, BIM, from a stable complex with BCL-2. Consistent with such a mechanism of action, high BIM:MCL-1 ratios were associated with achievement of a partial response. These findings establish BCL-2 as a valid therapeutic target in CLL and indicate that navitoclax has promising single-agent activity in heavily pretreated CLL patients. ■

Roberts AW, Seymour JF, Brown JR, Wierda WG, Kipps TJ, Khaw SL, et al. Substantial susceptibility of chronic lymphocytic leukemia to BCL2 inhibition: results of a phase I study of navitoclax in patients with relapsed or refractory disease. J Clin Oncol 2011 Dec 19. [Epub ahead of print].

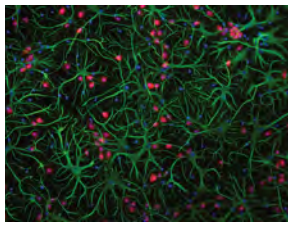
Chemotherapy

Major finding: Disruption of SMO-dependent signaling increases blood–brain barrier permeability.

Mechanism: Perivascular astrocytes secrete SHH, and endothelial cells express PTCH-1 and SMO.

Impact: Modulation of Hedgehog signaling could affect drug delivery or cell migration to the CNS.

HEDGEHOG SIGNALING REGULATES BLOOD–BRAIN BARRIER INTEGRITY



The blood–brain barrier (BBB) limits the entry of blood-borne molecules to the central nervous system (CNS) and thus poses a significant obstacle to the delivery of systemic chemotherapy. The BBB consists of specialized endothelial cells that are tightly bound by junctional proteins to restrict the passage of solutes and astrocytes that surround the CNS vasculature. Alvarez and colleagues investigated the role of the Hedgehog (Hh) pathway in the maintenance of BBB integrity because deregulated Hh signaling and BBB disruption are common features of multiple sclerosis, which is marked by aberrant entry of circulating leukocytes into the CNS and subsequent demyelination and neuronal damage. Sonic hedgehog (SHH) expression was observed in cultured human astrocytes, and active, secreted SHH was present in astrocyte-conditioned media. BBB endothelial cells did not express SHH but expressed high levels of the SHH receptor components Patched-1 (PTCH-1) and Smoothened (SMO), suggesting that astrocyte-mediated paracrine signaling activates the Hh pathway in BBB endothelial cells. Systemic pharmacologic disruption of Hh signaling with cyclopamine or conditional deletion of *Smo* in endothelial cells increased BBB permeability in mice as measured by serum protein and leukocyte CNS extravasation, which was correlated with decreased junctional protein expression. These findings provide insight into the maintenance of BBB integrity and suggest that pharmacologic modulation of BBB permeability has the potential to improve delivery of chemotherapeutic agents to the brain or prevent migration of cancer cells into the CNS. ■

Alvarez JI, Dodelet-Devillers A, Kebir H, Ifergan I, Fabre PJ, Terouz S, et al. The Hedgehog pathway promotes blood-brain barrier integrity and CNS immune quiescence. Science 2011;334:1727–31.

Note: *Research Watch* is written by *Cancer Discovery* Science Writers. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit *Cancer Discovery* online at www.AACR.org/CDnews.