RESEARCH WATCH

Clinical Trials

**Major finding:** The BTK inhibitor ibrutinib is well tolerated and active in B-cell cancers.

**Approach:** The optimal biologic dose of ibrutinib was determined based on BTK active site occupancy.

**Impact:** Inhibition of BTK alone can block active BCR signaling in multiple B-cell malignancies.

SPECIFIC INHIBITION OF BTK IS EFFECTIVE IN B-CELL MALIGNANCIES

Aberrant B-cell receptor (BCR) signaling has been implicated in the development of mature B-cell malignancies. Bruton tyrosine kinase (BTK) is a key effector molecule in antigen-stimulated BCR signaling and represents an attractive therapeutic target due to its restricted expression in B lymphocytes. Ibrutinib has been developed as an orally bioavailable, irreversible BTK inhibitor that binds the kinase active site to block BCR signaling. Advani and colleagues report the results of a phase I trial of ibrutinib in 56 patients with relapsed or refractory B-cell non-Hodgkin lymphomas or B-cell chronic lymphocytic leukemia (CLL). Ibrutinib occupancy of the BTK active site in peripheral blood mononuclear cells was determined by assaying the ability of a fluorescent probe to bind BTK before and during ibrutinib treatment. Ibrutinib blocked the probe from binding to BTK starting 4 hours after treatment initiation and throughout the entire 4-week treatment cycle, indicating that ibrutinib-mediated inhibition of BTK is durable and complete. Importantly, BTK occupancy was ibrutinib dose dependent, allowing the authors to determine an optimal biologic dose. A maximum tolerated dose was not reached, and ibrutinib generally caused only grade 1 or 2 adverse events, likely due to the restricted expression of BTK and the rapid absorption and elimination of ibrutinib. Strikingly, 60% of evaluable patients achieved an objective response, and 16% of patients had complete responses. Of note, 3 of the 9 patients who experienced disease progression had been treated with a lower dose of ibrutinib that was not sufficient for complete BTK occupancy, further linking BTK occupancy to ibrutinib efficacy. Together, these findings underscore the central role of BTK in the growth and survival of various B-cell malignancies and support further study of ibrutinib in larger clinical trials.


Colorectal Cancer

**Major finding:** Aspirin use selectively prolonged survival in patients with PIK3CA-mutant colorectal cancer.

**Concept:** Aspirin-mediated inhibition of PTGS2 may inhibit cancer progression by downregulating PI3K.

**Impact:** PIK3CA mutation may be a predictive biomarker for adjuvant aspirin therapy in colorectal cancer.

PIK3CA MUTATIONS PREDICT FOR RESPONSE TO ASPIRIN THERAPY

Regular aspirin use has been suggested to lower cancer risk, but the underlying mechanisms are incompletely understood. Predictive biomarkers are also needed to determine which patients may benefit most from adjuvant aspirin therapy. Aspirin's role as a prostaglandin-endoperoxide synthase 2 (PTGS2; also known as cyclooxygenase-2) inhibitor may contribute to its protective effect, but molecular biomarkers other than PTGS2 expression that can be assessed in a standardized manner would be preferable. Based on previous evidence suggesting that PTGS2 inhibition downregulates phosphatidylinositol 3-kinase (PI3K) activity, Liao and colleagues hypothesized that regular aspirin use might selectively prolong survival in the 15% to 20% of patients with colorectal cancer who harbor activating mutations in PIK3CA, which encodes PI3Kα. Individuals with colorectal cancer were identified among over 170,000 participants in 2 long-term prospective cohort studies that documented information on lifestyle factors, including aspirin use. Tumor tissue specimens were collected from the hospitals that participants visited, and PIK3CA status was determined in 964 patients from whom tumor DNA and data on postdiagnosis aspirin use were available. Regular use of aspirin following diagnosis was associated with significantly longer cancer-specific and overall survival only among patients with PIK3CA-mutant tumors. Furthermore, among patients with PIK3CA-mutant tumors, 26% of those who did not use aspirin died within 5 years of diagnosis, compared with only 3% of patients who took aspirin, whereas the 5-year cancer-specific mortality was 15% for patients with PIK3CA-wild-type tumors regardless of aspirin use. Although these findings obtained with a molecular pathological epidemiology approach require confirmation in larger, independent data sets, they suggest that cross-talk between PTGS2 and PI3K may contribute to the protective effect of aspirin use in patients with cancer and that PIK3CA mutation may represent a predictive biomarker for adjuvant aspirin therapy in colorectal cancer.
