Aspirin for colorectal cancer with *PIK3CA* mutations: the rising of the oldest targeted therapy?

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A recent report in *The New England Journal of Medicine* by Liao and colleagues highlights the benefit of aspirin use in a molecular defined subgroup of patients affected by metastatic colorectal cancer (CRC). Authors concluded that it is very likely that the regular use of aspirin after CRC diagnosis is associated with longer survival among patients with mutated-*PIK3CA* tumors. In contrast, aspirin has no effect on cancer-specific survival in patients with wild-type *PIK3CA* CRC (1). The phosphatidylinositol 3-kinase (PI3K) signaling pathway plays an important role in carcinogenesis of CRC. Activating mutations in *PIK3CA* occur in two "hotspots" located in exon 9 (E542K, E545K) and exon 20 (H1047R) in approximately 15% of CRCs (2). *PIK3CA* encodes for a lipid kinase that regulates signaling pathways downstream of the Epidermal Growth Factor Receptor (EGFR), and its mutations hamper sensitivity to the anti-EGFR monoclonal antibodies cetuximab or panitumumab registered for metastatic CRC treatment (3,4). Activation of PI3K enhances PTGS2 (prostaglandin-endoperoxide synthase 2, also known as cyclooxygenase-2) activity and prostaglandin E2 synthesis, inhibiting apoptosis of CRC cells. The long standing knowledge of the inhibitory effect of aspirin on PTGS2 may therefore suppress cancer-cell growth and induce apoptosis by blocking the PI3K pathway (1).

Several studies demonstrated that aspirin reduces the incidence of colon polyps, and its preventive effect is detectable even when given at low doses (75 mg daily). After CRC diagnosis, aspirin use reduces recurrence of adenomas (relative risk 0.65 *vs.* placebo) (5). Recently, a randomized trial in patients affected by Lynch syndrome showed that two years of aspirin 600 mg/die improved CRC-specific outcome (HR 0.63 for CRC incidence) (6). The observation that aspirin reduces the formation of colonic polyps provides the rationale for the use of this drug in the cancer prevention setting. Among participants in a large study of cardiovascular prevention, after long-term follow-up, any dose of daily aspirin displayed cancer preventive effect by lowering by 24% the risk of CRC at 10 years (7). In a pooled analysis of 35,535 patients from 6 randomized trials, aspirin use reduced the risk of developing metastatic CRC and the risk of death from CRC, and this effect was maintained with low aspirin dose (8). However, use of aspirin for primary CRC prevention faces an increased risk of bleeding (9), so a selection of patients who are likely to benefit from this drug is warranted. On the other hand, in the secondary prevention of CRC, Chan and colleagues reported that, after surgical removal of primary tumor, aspirin use reduces the risk of CRC overexpressing COX-2 among patients from two large cohorts (Nurses' Health Study and Health Professionals Follow-up Study, started in 1976 and 1986, respectively) (10). These results were confirmed in a subsequent analysis of the same cohorts with a 29% CRC mortality risk reduction in the same subgroup of patients whose cancers over-express the enzyme COX-2 (11).

In their recent pivotal study, Liao *et al.* provided clinical hints for a bridging between molecular bases of CRC progression and pharmacogenomic of aspirin. In particular, they identified a subgroup of patients in whom the mutation of *PIK3CA* appears to be associated with reduced risk of mortality from CRC. This is the first study demonstrating the association between a specific genetic alteration which is relevant for cancer progression and a reduction in CRC mortality with the use of aspirin. Authors reported indeed a remarkable improvement in CRC-specific mortality and overall survival in a small subgroup of patients (mutated *PIK3CA* who used aspirin regularly after CRC diagnosis *vs.*

non-users), with a multivariate HR for CRC death of 0.18 (95% CI: 0.06-0.61, P<0.001) and 0.54 (95% CI: 0.31-0.94, P=0.01) for death from any cause. Conversely, tumors with wild-type *PIK3CA* did not benefit from aspirin use.

Although the hypothesized mechanism of action and data shown are compelling, caution is needed prior considering these results as practice-changing. Firstly, as acknowledged by authors, the statistical sample is limited (the patients with tumor harboring *PIK3CA* mutations who received aspirin were 62), and the use of multiple statistical tests on the same sample may increase the probability of making observations due to chance. Secondly, interpretation of results is hampered by the lack of detailed follow-up data including subsequent cancer treatments (i.e., adjuvant chemotherapy) which could impact on survival. Thirdly, it cannot be excluded that the use of self-prescribed aspirin, which was reported in many cases by patients for analgesic purposes, may have been associated with wider use of diagnostic investigations and, at least in symptomatic patients, with an anticipation in the detection of relapse, thus leading to an overall better CRC-related outcome.

In conclusion, the study of Liao *et al.* is providing compelling evidence toward a rationale use of aspirin in molecularly defined subgroup of CRC, but requires validation in independent cohorts of patients. Such studies should have mortality from CRC as primary endpoint and specific follow-up including cancer treatments. In Asia, the randomized ASCOLT trial (12) is undergoing to evaluate the efficacy of aspirin 200 mg daily for stage III and high-risk stage II CRC. It would be of great interest to assess whether the predictive role of *PIK3CA* mutation will be confirmed in this cohort of patients.

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