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Beyond Chemotherapy - The Role of Aspirin in Resected Colorectal Cancer

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Colon cancer is the fourth most commonly diagnosed cancer, the third leading cause of death, and accounts for approximately 11% of all new cancer diagnoses in Canada.[1] Advancements in adjuvant chemotherapy have translated into clinically meaningful improvements in survival after surgical resection.[2,3,4] However, three-year disease-free survival (DFS) still remains at approximately 75% for patients with stage III colon cancer treated with oxaliplatin-based chemotherapy, underscoring the need for further therapeutic advancements in adjuvant colon cancer.

There is mounting evidence that aspirin (ASA) holds clinical utility in the management of colorectal cancer.[5,6,7] Mechanistically, ASA is proposed to exert anti-tumour effects on colon cancer primarily through cyclooxygenase-2 (COX-2)-dependent and independent mechanisms.[6] ASA inhibits COX-2, an enzyme

that is overexpressed in the majority of colorectal adenocarcinomas. COX-2 leads to increased production of prostaglandin E2 (PGE2) and subsequent activation of the phosphatidylinositol 3-kinase (PI3K)-mammalian target of rapamycin (mTOR) signalling pathways, facilitating increased colorectal carcinogenesis. Inhibition of COX-2 is thought to decrease PGE2 production and inhibit PI3K signalling.[8] ASA has also been shown to inhibit mTOR (a downstream effector of the PI3K pathway) signalling through AMPK in colorectal cancer (CRC) cells, leading to autophagy and enhanced cancer cell clearance.[9] Extra-tumorally, ASA may limit metastasis by inhibiting platelet activation through COX enzymes, proposed to enhance immune clearance of metastasizing cells by suppressing platelet-derived thromboxane A2 and restoring T cell–mediated anti-tumour activity **(Figure 1)**.[10]

In the context of cancer prevention, ASA has been previously investigated. A meta-analysis of 51 randomized controlled trials suggested that ASA reduced CRC incidence relative to placebo.[11] However, ASA remains not currently recommended for primary prevention of CRC in the general population due to variable outcomes in certain subgroups (eg, older adults), the risk of adverse events, and the duration of therapy required (U.S. Preventive Services Task Force). The strongest evidence supporting the use of ASA in chemoprevention is from patients with Lynch syndrome. Lynch syndrome is an autosomal dominant hereditary cancer syndrome caused by germline alterations that lead to loss of function variants in one or more of several key DNA mismatch repair (MMR) genes, culminating in a dysfunctional MMR pathway. In the CAPP2 study, treatment with ASA at 600 mg per day for two years significantly reduced the incidence of CRC compared with placebo (9% vs. 13%; hazard ratio [HR]: 0.65; 95% confidence interval [CI]: 0·34–0·91; p=0.019) after 10 years of follow-up.[12] In a per-protocol analysis among those who took ASA for at least two years, the HR was 0.56 (95% CI: 0.34-0.91; p=0.91). Further research is needed to determine the optimal dose of ASA for patients with Lynch syndrome. The American Gastroenterological Association recommends offering ASA to patients with Lynch syndrome for cancer prevention (Conditional recommendation).[13]

Several studies have explored the utility of adjuvant ASA in resected CRC, with the greatest benefit observed in patients with PI3K pathway abnormalities.[14-16] More recently, ALASCCA is perhaps the most paradigm-changing prospective clinical trial. This study evaluated the effect of adjuvant ASA on recurrence and survival in patients with resected CRC harbouring somatic alterations in the PI3K pathway.[17] Eligible patients had stage I–III rectal cancer and stage II–III colon

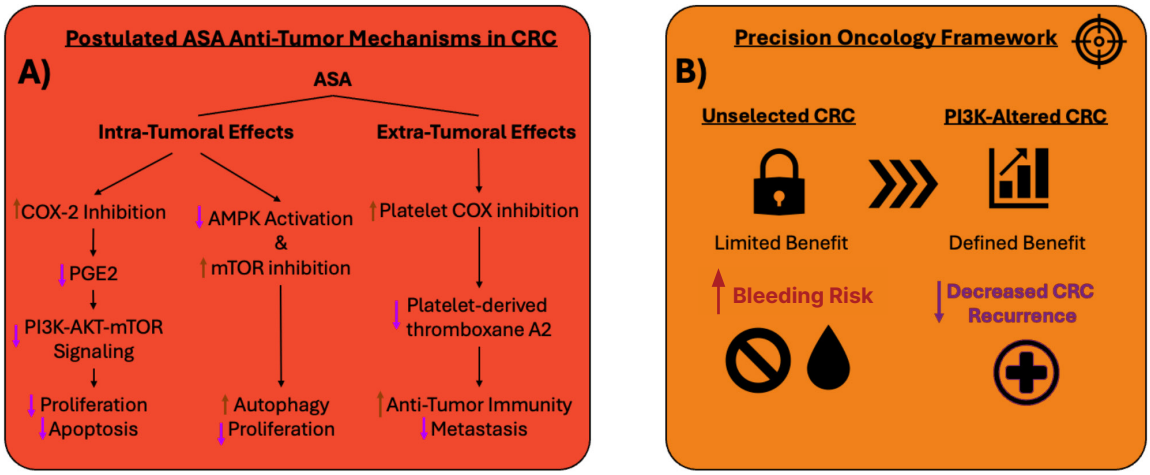

Figure 1. A) Selection of proposed intra- and extra-tumoral mechanisms of anti-tumor activity due to ASA in CRC onocogenesis. B) Importance of biomarker-driven personalization of patient selection in maximizing benefit in CRC risk reduction, specific to those individuals with actionable PI3K mutation pathway alterations; *courtesy of Scott W. Strum, MD, MSc, FRCPC, Patricia A.Tang, MD*

Abbreviations: ASA: aspirin; **CRC:** colorectal cancer; **COX-2:** cyclooxygenase-2; **mTOR:** mammalian target of rapamycin; **PGE2:** prostaglandin E2; **PI3K:** phosphatidylinositol 3-kinases.

cancer, and had either pre-specified PI3K catalytic subunit alpha hotspot mutations in exon 9 or 20 (Group A), or moderate- to high-impact somatic variants in *PIK3CA, PIK3R1*, or *PTEN* (Group B). Patients were randomized 1:1 to receive ASA 160 mg orally once daily or a placebo for three years. The estimated three-year cumulative incidence of recurrence was significantly lower with ASA compared with placebo in both molecular subgroups: 7.7% vs. 14.1% in Group A (HR: 0.49; 95% CI: 0.24–0.98; p=0.04) and 7.7% vs. 16.8% in Group B (HR: 0.42; 95% CI: 0.21–0.83). The three-year DFS favoured ASA in both Group A (88.5% vs. 81.4%; HR: 0.61) and in Group B (89.1% vs. 78.7%; HR: 0.51). Severe adverse events occurred in 16.8% of ASA-treated patients versus 11.6% with placebo; they were most commonly postoperative complications, thromboembolic events, and infections, whereas non-severe events were primarily hematologic and gastrointestinal. The number needed to treat to prevent one recurrence ranged from 6 in stage III rectal cancer to 42 in stage II colon cancer, supporting a favourable risk–benefit profile for ASA in molecularly-selected patients. This trial has supported its use in clinical practice for this subpopulation and has already been implemented into international guidelines.[18]

In contrast to the strongly positive results from ALASCCA, SAKK 41/13 was a phase III, prospective, randomized, double-blind, placebo-controlled, multi-centre trial evaluating adjuvant ASA in patients with R0-resected stage II or III colon cancer.[19] Patients with centrally confirmed activating *PIK3CA* mutations in exon 9 or 20 were randomized in a 2:1 ratio to receive ASA (100 mg daily) or placebo for three years, independent of decisions regarding adjuvant chemotherapy. Of 1,040 patients screened, 180 (17.3%) had *PIK3CA*-mutated colon cancer, and 112 were ultimately randomized. Baseline characteristics included 45.9% stage II and 54.1% stage III disease, and 63.2%–70.3% received adjuvant chemotherapy. The study did not meet its primary endpoint. Although DFS was numerically better in the ASA group, the 3-year DFS rates were 88.3% with ASA and 82.4% with placebo, with an unstratified hazard ratio of 0.57 (90% CI: 0.27–1.22; p=0.11). Compared with the positive results of ALASCCA, SAKK 41/13 evaluated a narrower range of *PIK3CA* mutations, used a lower ASA dose, excluded rectal cancer, and was underpowered due to early closure. These factors may have contributed to the lack of statistically significant results.

Important insights can also be gleaned from trials involving adjuvant ASA in molecularly unselected populations. For example, the ASCOLT trial was a prospective randomized, placebo-controlled study evaluating adjuvant ASA in patients with resected CRC.[20] Eligible patients included those with Dukes' C or high-risk Dukes' B colon cancer and Dukes' B or C rectal cancer who had completed standard adjuvant therapy. Patients were randomized 1:1 to receive either 200mg of ASA daily or placebo for 3 years. Among 1,550 patients in the modified intention-to-treat population, five-year DFS was 77.0% with ASA and 74.8% with placebo (HR: 0.91; 95% CI: 0.73–1.13; p=0.38), resulting in no statistical improvement in DFS. In the ASAC phase III clinical trial enrolling patients with CRC after radical treatment of liver metastases, they were randomized to three years of adjuvant ASA 160 mg once daily vs placebo.[21] Similarly, this trial was also negative, as ASA did not improve DFS (HR for recurrence or death 1.08 [95·44% CI 0.85–1.38]; p=0.58). Importantly, ASA was actually associated with lower overall survival (OS) than placebo (OS 76% with ASA vs 85% with placebo at 36 months [HR for death 1·64 (95% CI 1.01–2.65); p=0.045]), and more serious adverse events. Lastly, in yet another randomized phase III study, the EPISODE-III clinical trial demonstrated that 3 years of adjuvant low-dose ASA of 100mg once daily did not significantly improve DFS in an unselected R0-resected stage III adenocarcinoma from the cecum to upper rectum population: three-year DFS was 75.4% with placebo and 78.8% with ASA (HR 0.84, 95% CI 0.65–1.09; one-sided p=0.0987).[22] Results from studies such as these strongly suggest that for molecularly unselected patients, the use of ASA may not only be not beneficial, but may in fact be harmful.

In an effort to enhance the identification patients who may benefit from adjuvant ASA outside of PI3K testing, circulating tumour DNA (ctDNA) has also been evaluated. The presence of ctDNA after surgery is known to be a reasonable prognostic marker, although it's predictive value has remained more variable.[23] ctDNA was evaluated in CALBG/SWOG 80702, a phase III trial of patients with stage III colon cancer who were treated with adjuvant celecoxib (a selective COX-2 inhibitor) in addition to adjuvant chemotherapy.[24] In a post-hoc analysis, among patients with post-operative ctDNA positivity, celecoxib was associated with improved DFS (adjusted HR: 0.61; 95% CI: 0.42-0.89) and overall survival (adjusted HR: 0.62; 95% CI: 0.40-0.96) compared to

placebo. These findings persisted after stratifying for *PIK3CA* mutation status. Conversely, no such difference was observed in patients with negative post-operative ctDNA results. Therefore, ctDNA may help complement or further refine the selection of patients who may benefit from adjuvant COX-inhibitor-based therapies. The results of several trials incorporating ctDNA are pending, aiming to clarify how to integrate ctDNA in routine clinical practice (reviewed in[23]).

While ASA has shown strong promise in reducing recurrence in pre-specified populations, it carries an inherent risk profile. ASA is an irreversible inhibitor of COX enzymes, which play important roles in modulating inflammation and platelet function. ASA has been studied in large populations outside of cancer, with a well-established safety profile. In a meta-analysis of 13 trials (n=164,225) assessing the efficacy of ASA in the primary prevention of cardiovascular events, the use of ASA (at most dose levels between 75-100 mg/day) was associated with an increased rate of major bleeding (HR: 1.43; 95% CI: 1.30-1.56); number needed to harm 210) compared with no ASA.[25] This included intracranial hemorrhage and gastrointestinal bleeding. In the Physician's Health Study (n= 22,071) assessing 325 mg ASA every other day versus placebo, the relative risk of ulcer in the ASA group was 1.22 (169 for ASA vs. 138 for placebo; 95 % CI: 0.98 to 1.53; P = 0.08), and the relative risk of requiring a blood transfusion was 1.71.[26] In the ALASCCA trial, non-severe adverse events occurred in 43.4% of patients who received ASA and in 35.4% of patients who received placebo, and the most common events were hematologic and gastrointestinal. Four patients had a grade 5 serious adverse event in the ASA arm (1.3%), with one death considered potentially related to ASA use. ASA use should be avoided, or used with great caution, in patients with coagulopathies, such as hemophilia, peptic ulcer disease, or gastrointestinal bleeding, *G6PD* deficiency, uncontrolled hypertension, ASA-induced asthma/bronchospasm, and severe hepatic or renal dysfunction. In ALASCCA, patients with these comorbidities were largely excluded. The risks should always be discussed when counselling patients prior to initiating ASA, to provide context for the clinically meaningful DFS benefit in appropriately selected patients.

Overall, ASA has been shown to be highly effective in reducing recurrences in patients with resected stage I–III rectal cancer and stage II–III colon cancer, who have activating *PI3K* mutations, which encompasses up to 37% of patients in this demographic.[17] A personalized, precision oncology-based approach is important in deciding which patients will benefit most from adjuvant ASA, which is best supported by a dose of ASA 160 mg PO daily for three years. The benefits from treatment generally outweigh the adverse effects of ASA, especially in high-risk patient populations, such as stage III colon and rectal cancer, with a number needed to treat of 9 (95% CI: 6-18) and 6 (95% CI: 4-13), respectively.[17] Obtaining sequencing data in a timely, cost-effective fashion and ensuring that laboratory workflows can accommodate it is of utmost importance.

Future directions include optimizing ASA dosing and duration of therapy, as well as determining its benefit in molecular subpopulations such as those with microsatellite instability-high/deficient MMR disease, where immunotherapy has emerged as a cornerstone of treatment.[27] Further research on the role of adjuvant ASA will require refinement of biomarkers, particularly for PI3K and ctDNA subpopulations, and assessment of the biological mechanisms underpinning its clinical benefit. The CHALLENGE trial demonstrated the benefit of a structured exercise program after adjuvant chemotherapy in stage II-III colon cancer compared to health education material;[28] whether ASA has an additive benefit to a structured exercise program remains to be determined.

In conclusion, emerging data support adjuvant ASA as one of the first biomarker-directed, low-cost therapeutic strategies in CRC, with the greatest benefit observed in tumours harbouring PI3K pathway alterations. Molecular profiling remains the greatest barrier to implementing this advancement on a more global scale. ASA is considered safe and effective, has already been adopted into international guidelines, and should be considered an existing standard of care in this patient population.

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