Chemoprevention Considerations in Patients with Hereditary Colorectal Cancer Syndromes

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KEYWORDS

- Chemoprevention • Hereditary colon cancer syndromes
- Familial adenomatous polyposis • Lynch syndrome
- Hamartomatous polyposis syndromes

KEY POINTS

- Nonsteroidal anti-inflammatory medications are the most widely studied chemoprevention agents in hereditary colorectal cancer syndromes, although novel agents influencing non-COX pathways are being evaluated in human trials.
- Chemoprevention has been shown to be efficacious for colorectal polyposis and duodenal polyposis in patients with familial adenomatous polyposis and for cancer reduction in Lynch syndrome.
- Chemoprevention can be considered for use in select patients as an adjunct to standard of care in patients with hereditary gastrointestinal cancer syndromes.
- The goals, risks, and benefits of chemoprevention therapy should be carefully considered before embarking on their clinical use.

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INTRODUCTION

Hereditary colorectal cancer syndromes (HCCS) are associated with benign and malignant tumors within and outside of the intestinal tract (**Table 1**). Their onset occurs in childhood or young adult life, and in familial adenomatous polyposis (FAP), will lead to colorectal cancer (CRC) unless colectomy is performed.[1] Endoscopic management, often beginning at a young age, is standard, although surgery may be required. Disease reduction with chemoprevention in HCCS targets enzymatic pathways of carcinogenesis (**Table 2**) and is an area of investigation. Chemoprevention use outside of a clinical trial requires appropriate patient selection (**Table 3**), establishment of treatment goals, and knowledge of the efficacy and safety of the agent.

FAMILIAL ADENOMATOUS POLYPOSIS

Most chemoprevention research in FAP has focused on inhibition of the cyclooxygenase (COX) pathway through the use of nonsteroidal anti-inflammatory medications (NSAIDs) with adenoma reduction as the clinical end point. Although some agents have shown success in preventing or reducing adenomas in the intestinal tract, none reduce the incidence of or mortality from cancer. Major cancer risks in FAP include the colorectum, duodenum, stomach, and thyroid. Desmoid tumors, although nonneoplastic, contribute to significant morbidity and mortality in FAP and may impact surgical approaches to disease management. Effective chemoprevention has the potential to mitigate the impact of FAP directly through reduced disease manifestations or symptom burden (eg, pain) and/or indirectly by averting or postponing surgery. Life-altering surgeries figure prominently in the management of FAP and can thwart attainment of important life goals in education, work, relationships, and family.[2] Delaying surgery by polyp control may be particularly important in adolescents and young adults who are still in the process of defining and establishing goals that will be central to their identities.[3]

Colorectal Polyposis

Colorectal polyposis control has been the primary target of most chemoprevention studies in FAP because CRC is the greatest health threat to these patients.

Early trials assessed the efficacy of chemoprevention by the impact on findings on flexible sigmoidoscopy (FS) rather than colonoscopy. One of the first randomized controlled trials (RCT) was a 9-month study of 22 participants with rectosigmoid polyps (18 of whom had not previously undergone colon surgery) assessing the efficacy of sulindac, a nonspecific COX inhibitor, at a dose of 150 mg twice daily compared with placebo.[4] Significant reductions in both polyp number (by 44%) and diameter (by 35%) were observed in the sulindac arm. Notably, 3 months after sulindac discontinuation, the size and number of polyps increased but was still lower than at baseline. No side effects were attributed to sulindac, but the investigators stated that sulindac is unlikely to replace colectomy as primary therapy for colorectal polyposis. Another placebo-controlled RCT assessed the utility of sulindac for the prevention of rectosigmoid polyp development over 4 years in 41 young individuals with a pathogenic variant (PV) in *APC* and no polyps on baseline FS.[5] Sulindac was dosed at 75 mg or 150 mg twice daily based on weight. No significant difference in polyp occurrence was noted between the study arms. Importantly, 11 patients (27%) were withdrawn from the study for polyposis progression, 6 in the sulindac and 5 in the placebo arm. Of 34 patients completing at least 40 months of treatment, the mean number and size of adenomas in the sulindac and placebo arms were 5.9 versus 7.5 and 0.70 mm versus 1.2 mm, respectively. Adverse events did not differ significantly

Table 1
Hereditary colorectal cancer syndromes, associated genes, and frequent clinical features

Syndrome	Genes	Features
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM*	Colorectal, gynecologic, urothelial, brain, gastric, small bowel, skin carcinoma
Familial adenomatous polyposis	*APC*	Colorectal, gastric and duodenal adenomas; colorectal, duodenal, gastric, thyroid, and brain cancers; osteomas; Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE); soft tissue tumors; desmoid tumors
MutYH-associated polyposis	*MUTYH*	Colorectal and duodenal adenomas; colorectal, duodenal, thyroid cancer; desmoid tumors
NTHL1-associated polyposis	*NTHL1**	Colorectal and duodenal adenomas; breast, endometrial, urothelial, brain, and colorectal cancers
Polymerase proofreading associated polyposis	*POLE, POLD1*	Colorectal adenomas; endometrial, colorectal, and brain cancers
Peutz-Jeghers syndrome	*STK11*	Mucocutaneous pigmentation, panintestinal hamartomatous polyps, breast, gastric, small bowel, colorectal, pancreatic, lung, and gynecologic/testicular cancers
PTEN hamartoma tumor syndrome	*PTEN*	Panintestinal hamartomatous polyps, esophageal glycogen acanthosis, skin lesions, macrocephaly, breast, thyroid, renal, endometrial, and colorectal cancers
Juvenile polyposis syndrome	*BMPR1A, SMAD4*	Gastric and colorectal hamartomatous polyposis, gastric and colon cancer; SMAD4: hereditary hemorrhagic telangiectasia overlap syndrome

Table 2
Molecular targets for chemoprevention in hereditary colorectal cancer syndromes

Medication	Classification
Sulindac	Nonselective COX inhibitor
Celecoxib	Selective COX-2 inhibitor
Rofecoxib	Selective COX-2 inhibitor
Aspirin	Nonselective COX inhibitor
Eicosapentaenoic acid	Anti-inflammatory
Difluoromethylornithine	Ornithine decarboxylase inhibitor
Rapamycin/sirolimus/everolimus	mTOR inhibitor
Erlotinib	EGFR inhibitor
Guselkumab	Immune modulation
Erlotinib-sulindac	
Rapamycin/sirolimus	
Frameshift peptide vaccines	
Nivolumab and other checkpoint inhibitors	

Abbreviations: COX, cyclooxygenase; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin.

between the arms, and sulindac was reported to be well tolerated. Mucosal prostaglandin and thromboxane B2 levels were significantly lower than baseline in the sulindac arm at the end of treatment.

A 6-month RCT of celecoxib, a selective COX-2 inhibitor, at 400 mg, 100 mg, or placebo, twice daily demonstrated a significantly reduced number of colorectal polyps (by 28%) and burden (by 31%) on colonoscopy in the 400-mg arm, compared with reductions of 4.5% and 4.9% in the placebo arm.[6] No significant difference was noted between the placebo and celecoxib 100-mg arm. Both celecoxib doses were reported to be well tolerated, and adverse event did not differ between the celecoxib groups and the placebo group. In 1999, under US Food and Drug Administration (FDA)

Table 3
Potential benefits of chemoprevention in patients with hereditary colorectal cancer syndromes

FAP	LS	Hamartomatous Polyposis Syndromes
Delay colectomy • Children and young adults • Desmoid prone individuals	Decrease cancer risk • Colorectal • Endometrial	Decrease extraintestinal manifestations • Soft tissue • Vascular • Neurologic
Prevent or delay duodenectomy • Individuals with advanced-stage duodenal polyposis		Modulate polyposis burden • Gastric • Small bowel • Colorectal
Prevent secondary surgery • Individuals with advanced-stage rectal or pouch polyposis		Decrease symptoms from polyposis and improve quality of life • Protein losing enteropathy • Gastrointestinal bleeding • Diarrhea

Abbreviation: LS, Lynch syndrome.

accelerated approval regulations, 21 CFR part 314, subpart H, celecoxib was approved at 400 mg twice daily as an adjunct to endoscopy for colorectal polyposis in adults with FAP. In 2011, the study sponsor voluntarily withdrew the FAP indication for celecoxib because the FDA required a postmarketing study as a condition of approval under subpart H, which was not completed as planned.

In a phase 1, 3-month, dose escalation trial of celecoxib in 18 children aged 10 to 14 years, no clinically meaningful differences in adverse events were seen between placebo and the 3 weight-based celecoxib doses.[7] Compared with baseline, the end of treatment number of polyps increased by 39% in the placebo arm, whereas a significant reduction of 44% was observed in the highest dose group, 16 mg/kg/d, which corresponds to the adult dose of 400 mg twice daily. A 5-year, international, pediatric, placebo-controlled RCT designed to study the effectiveness of 16 mg/kg/d of celecoxib in reducing the progression of colorectal polyposis defined as the occurrence of 20 or more polyps, more than 2 mm in size after excision of all baseline colorectal polyps greater than 2 mm in size, was performed.[8] The trial was halted due to low enrollment. Of the 106 children randomized, the number of patients with progression of polyposis (12.7% vs 25.5%) and the time to progression (2 vs 1.1 years) favored the celecoxib group.

A previously available selective COX-2 inhibitor, rofecoxib, showed promise in a series of 8 Israeli patients treated with 25 mg daily for a mean of 16 months.[9] The drug was well tolerated without significant adverse events, and the rate of polyp formation was lowered between 70% and 100% versus baseline polyp counts. The same dose of rofecoxib was studied in a 9-month, placebo-controlled, RCT in 21 Japanese adults.[10] A significant reduction in both the number and size of polyps was observed in the rofecoxib arm without differences in adverse events between treatment arms.

Aspirin irreversibly inhibits both COX-1 and COX-2 isoenzymes. The impact of aspirin at 600 mg/d with or without resistant starch at 30 g/d versus placebo on the number of rectosigmoid polyps was evaluated in an international RCT in children and young adults between ages 10 and 21 years in the Colorectal Adenoma/Carcinoma Prevention Programme (CAPP) 1 study.[11] Of the 206 randomized patients 33 had at least 1 follow-up annual endoscopy and were included in the primary analysis. At a median of 17 months of treatment no significant reduction in the number of polyps was noted in any arm. A trend for a smaller mean size of the largest polyp, 3.8 mm versus 5.5 mm, was observed in patients who were treated for 1 or more year in the aspirin versus nonaspirin arms, and 3 mm versus 6 mm for patients treated for more than 1 year. The investigators posit that the effect of aspirin may be on disease progression rather than on inhibition of initiation. No serious adverse events were noted in the trial participants.

Aspirin 100 mg daily, mesalazine 2 g daily, or both together were compared versus placebo in an 8-month RCT of 104 Japanese patients aged 16 to 70 years with intact colons.[12] Polyps 5 mm or more in size were removed at baseline colonoscopy. The primary end point was the proportion of patients with polyps 5 mm or more at the end of treatment. Thirty percent of patients exposed to aspirin versus 50% of patients not on aspirin met the end point (for an adjusted odds ratio of 0.37 [95% confidence interval [CI],0.16 to 0.86]). No benefit was seen with mesalazine. No serious drug-related adverse events occurred, and grade 1 to 2 upper gastrointestinal symptoms were seen in 12% of patients who received aspirin plus mesalazine, and in 4% of those who received aspirin or mesalazine.

Levels of polyamines and the key enzyme that regulates their production, ornithine decarboxylase (ODC), are elevated in polyps in patients with FAP.[13]

Diflouromethylornithine (DFMO), also known as eflornithine, is an irreversible inhibitor of ODC and has been studied in combination with other agents in FAP to assess for any synergistic effect.

In a 6-month RCT the effect of DMFO (at a dose of 0.5 g/m^2/d rounded down to the nearest 250 mg) plus celecoxib 400 mg twice daily versus celecoxib alone on the number of adenomas in a defined area in the intact colon or rectum (in patients with prior colectomy) was compared in 112 adults with FAP.[14] No significant difference in the polyp count (−13.0% for celecoxib + DFMO vs −1.0% for celecoxib, P = .69) or secondarily in polyp burden (−40% for celecoxib + DFMO vs −27% for celecoxib, P = .13) was demonstrated. The video-based, blinded, assessment of global polyp change favored combination therapy (−0.80 vs −0.33, P = .03) over celecoxib alone. No DFMO-related ototoxicity, adverse cardiovascular outcomes, or significant increase in adverse events in the combination arm was noted. The investigators attributed the lack of added benefit with DMFO to the low baseline burden of polyps and use of still images to capture the primary end point, which were hard to standardize between examinations and may have inaccurately represented true disease burden.

A recent international RCT in 171 adult patients compared eflornithine 750 mg daily in combination with sulindac 150 mg daily to either agent alone on first FAP-related disease progression in the duodenum, in intact colon, or in the postcolectomy rectum or ileal pouch.[15] Patients were stratified on the basis of polyp burden and surgical status (precolectomy, rectal or ileal pouch polyposis, or duodenal polyposis). Disease progression was defined as need for surgery, advanced adenoma requiring excision by endoscopy, the occurrence of high-grade dysplasia, or duodenal polyposis stage progression. No difference was noted for the primarily end point or in adverse events between study arms. In the preplanned secondary efficacy analysis stratified by subgroup, disease progression in patients with an intact colon occurred in 17%, 46%, and 42% (for a hazard ratio [HR], 0.30; 95% CI, 0.07–1.32 for combination vs sulindac, and HR, 0.20; 95% CI, 0.03–1.32 for combination vs eflornithine). The mean time to progression was 39.3 months (95% CI, 37.1–41.6), 25.2 months (95% CI, 24.2–26.1), and 19.7 months (95% CI, 18.2–21.1) in the combination, sulindac, and eflornithine arms, respectively. No differences were noted in the secondary analysis in the postcolectomy or duodenal polyposis arms. The results of combination treatment in the 37 patients in the precolectomy arm are compelling, and additional trials in this population are warranted.

Adenomatous Polyposis Coli (APC) inactivation and epidermal growth factor receptor (EGFR) signaling promotes COX expression and intestinal polyps. Murine models of FAP demonstrated that a combination of sulindac and an EGFR inhibitor decreased intestinal adenomas by 87%.[16] In a prespecified secondary analysis[17] of a single-center, 6-month RCT of 92 adult patients with FAP comparing sulindac 150 mg twice daily plus erlotinib 75 mg daily versus placebo on duodenal polyposis,[18] the change in number of polyps in the intact colorectum, ileal pouch, and rectum was assessed.[17] Eighty-two patients had lower gastrointestinal data available. The number of polyps was significantly lower in the sulindac-erlotinib compared with placebo arm in patients with an intact colon (−69.4% [95% CI, −28.8%–109.2%]) and an ileal pouch (−121.7% [95% CI, −280% to −71.6%]). No difference was noted between arms in patients with an ileorectal anastomosis. Grade 2 and 3 adverse events were reported twice as common in the treatment than (44%) in the placebo group (22%). Most common was an erlotinib-induced acneiformlike rash, which occurred in 68% of the treatment group and 22% of the placebo group (P<.001). Rash treatment included topical cortisone and/or clindamycin. Although the effectiveness of the combination was

shown, the toxicity as demonstrated in this trial limits its clinical potential in FAP at doses studied.

Foods or plant derivatives have also been studied in patients with FAP. The minimal side effect profile of naturally occurring compounds provides an advantage if effective for chemoprophylaxis and safe. Curcumin and quercetin are plant-derived polyphenols with antioxidant and anti-inflammatory properties. The effectiveness of a combination of both compounds at a dose of 480 mg and 20 mg both 3 times daily, respectively, for 6 months was studied in 5 adults postcolectomy and showed a significant decrease in the number (60.4%) and size of polyps (50.9%).[19] In a follow-up trial, 44 adults with an intact colon, ileorectal anastomosis, or ileal anal pouch, and 5 or more polyps, were randomized to curcumin 1.5 g twice per day or placebo for 12 months. The primary outcome was the number of polyps on FS. In contrast to the pilot study, no significant difference in the number or size of polyps was observed.[20]

Limited data suggest that long-term use of ascorbic acid, an antioxidant, induces regression of rectal adenomas in FAP. In a single-center RCT, 49 patients with an ileorectal anastomosis received 3 g/d ascorbic acid or placebo; 36 patients were evaluable. Over 18 months, a significant reduction in the number of polyps as assessed by 3 monthly sigmoidoscopies was noted in the ascorbic acid group at 9 months only versus in the placebo group.[21] A trial randomized 58 patients to 4 g/d of ascorbic acid plus 400 mg of alpha-tocopherol per day, a wheat fiber supplement at 22.5 g/d, or placebo.[22] No effect on rectal polyps was noted in any treatment arm.

Eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid, has been shown to have antineoplastic activity in a 6-month RCT, of 55 European adults with a history of ileorectal anastomosis and at least 3 rectal polyps.[23] Treatment included EPA free fatty acid at 2 g daily or placebo, and the primary end point was the number of polyps in a tattooed area in the rectum. Secondary end points included the sum of the polyp diameters in the photographed area and global rectal polyp burden score by blinded video review. EPA resulted in a significant decrease in all parameters with a 22.4% reduction in polyp number compared with placebo wherein all parameters worsened. Currently, a phase 3, multicenter, 2-year, European RCT study is underway to determine whether EPA-FFA can reduce the number of rectal polypectomies compared with placebo in adults with FAP and previous colectomy with ileorectal anastomosis.

Black raspberries (BRBs) contain multiple compounds including calcium; vitamins A, C, and E; selenium; folic acid; quercetin; b-sitosterol; ellagic acid; ferulic acid; and anthocyanins. These substances have demonstrated chemopreventive activity in vitro and in murine models of FAP. In a phase 1b study, 14 adult patients with at least 5, 2-mm rectal polyps were treated with BRB suppositories (each containing 720 mg BRB powder) administered at bedtime and randomized to either 20 g of BRB placebo powder administered orally as a slurry (60 g/d total) or 20 g of placebo BRB powder slurry 3 times daily for 9 months.[24] A reduction in rectal polyp number (-3.5, $P = .069$) and burden (-8.5, $P = .036$) was observed. No additional benefit was noted on adenoma end points in patients randomized to oral BRB powder. BRBs significantly decreased proliferation, DNA methylation methyl transferase 1 protein expression, and p16 promoter methylation in adenomas from responders but not from the 3 nonresponders.

Agents with novel mechanisms of controlling polyposis in FAP are being studied. In murine models of FAP, the mechanistic target of rapamycin (mTORC1) pathway is activated and is associated with an increased expression of mTOR protein in intestinal polyps, whereas inhibition of the mTOR pathway has been shown to decrease mTOR activity and suppress both the number and size of polyps, and prolong mouse survival.[25]

The effect of the mTOR inhibition by sirolimus, a rapalogue of rapamycin, on rectal or pouch polyps was reported in a case series of 4 adult patients with InSiGHT Polyposis Stage 3.[26] Sirolimus was initiated at a dose of 2 mg once daily and adjusted to achieve a target sirolimus blood level range of 5 to 8 μg/L; 18 adverse events, related to both drug dose and blood level, with toxicity grades 1 to 3 were noted, and 1 patient withdrew due to adverse events. The size of 5 marked polyps decreased in 80% of polyps evaluated. An increase in apoptosis and decrease in proliferation was seen in 3 of 4 patients. The investigators suggested that sirolimus was promising for polyposis in the rectal remnant and ileal pouch but associated with numerous adverse events likely due to the narrow therapeutic window of classical mTOR inhibitors. A new formulation of rapamycin with drug particles embedded in a pH-sensitive methacrylic acid copolymer (eRapa) was found to produce consistent blood concentrations in a phase Ib trial of men with low-grade prostate cancer undergoing surveillance.[27] At present, a phase IIa, dose escalation, 12-month trial with eRapa is underway in the United States to assess the safety and effect of eRapa on colorectal polyp burden in patients with FAP.

Inflammatory features associated with activation of the interleukin (IL) 23/IL-17/JAK/STAT3 pathway have been demonstrated in polyps from patients with FAP and linked to growth and progression of CRC. An FDA-approved human monoclonal antibody known as guselkumab that inhibits IL-23-specific intracellular signaling and downstream pathways is currently being evaluated in a 24-week, placebo-controlled RCT to determine if monthly administration of subcutaneous guselkumab can reduce polyp burden in the duodenum, rectum or ileal pouch.

Duodenal Polyposis

Duodenal polyposis affects nearly 100% of patients with FAP, and advanced-stage duodenal polyposis may require duodenectomy to prevent duodenal cancer. Duodenal cancer is a leading cause of cancer and cancer deaths in patients with FAP once colectomy has been performed. The duodenum with its intimate association with the pancreatic-biliary duct complex and associated organs make duodenectomy a technically demanding surgery associated with substantial morbidity. Studies on extracolonic risk management and quality of life after duodenal surgery[28,29] are sparse, but one recent report on pancreatico-duodenectomy (PD) in patients who had previously undergone IPAA for FAP provides evidence that avoidance of PD through management of adenomas may confer clear benefits.[29] Results of that study showed that one-quarter of the patients undergoing PD developed diabetes, with a resulting drop in quality-of-life scores. Therefore, there is a compelling need for chemoprevention in the duodenum.

Sulindac has not convincingly been shown to reduce duodenal polyposis. In an RCT, 24 patients with Spigelman stage III or IV duodenal polyposis received either sulindac 200 mg twice daily or placebo for 6 months.[30] No difference in polyposis was noted between arms by blinded review of pretreatment and posttreatment videotape recordings. Duodenal mucosal epithelial cell proliferation was significantly reduced in patients in the sulindac arm. In a secondary analysis of this trial, a significantly greater number of patients exposed to sulindac versus placebo had regression of duodenal polyps less than 3 mm (9 of 11, 82% vs 2 of 11, 38%) and fewer new polyps (2 of 11, 18%, vs 5 of 12, 42%).[31]

In a 6-month RCT, celecoxib, when compared with placebo, led to an improvement of duodenal polyposis as assessed by blinded video review at a dose of 400 mg twice daily ($P = .03$), but no effect was noted at 100 mg twice daily.[32] Compared with patients on placebo, those on celecoxib 400 mg twice daily had a 14.5% reduction in

the involved duodenum versus 1.4% (P = .436), and in a subanalysis those with greater than 5% of the duodenum covered by polyps at baseline showed a 31% reduction in involved areas compared with 8% on placebo (P = .049). Baseline or end-of-treatment polyp characteristics such as polyp size, number, and Spigelman stage were not reported.

FAP mouse models have shown a pronounced effect of sulindac in combination with erlotinib, an inhibitor of EGFR tyrosine kinase activity on duodenal polyps. In a single-center, 6-month RCT, the combination of erlotinib 75 mg daily with sulindac 150 mg twice daily was compared with placebo and reduced the duodenal polyp burden (19 mm between-group difference, P<.001) and number of polyps (8 mm between-group difference, P<.001).[18] Adverse events were more common in patients in the combination versus the placebo arm including an acneiformlike rash (87% vs 20%, P<.001) managed with topical cortisone and/or clindamycin therapy. Notably, 73% of patients in the combination arm required erlotinib dose reduction versus 28% in the placebo arm. Results are pending from an open-label study in the United States using erlotinib 350 mg once weekly on duodenal polyp burden in FAP.

The RCT comparing eflornithine 750 mg daily in combination with sulindac 150 mg daily, to either agent alone, on FAP-related disease progression demonstrated an increase in Spigelman stage or excision of duodenal polyps in 27% (15 of 56) in the combination arm, 19% (11 of 58) in the sulindac arm, and 21% (12 of 57) in the eflornithine arm without obvious benefit on duodenal polyposis in any of the study arms.[15]

LYNCH SYNDROME

Lynch syndrome (LS) the commonest hereditary cause of CRC is the genesis of 3% to 5% of CRC[33] and 10% of endometrial cancer (EC) in women younger than 50 years.[34] Colonoscopy and polypectomy reduce CRC incidence and mortality in LS.[35,36] Despite recommended surveillance colonoscopy every 1 to 2 years in LS,[37] a recent study showed that CRC occurred in 8.4% at 10 years and was independent of whether colonoscopy was performed at 1- to 3-year intervals.[38] The heightened cancer risk and accelerated CRC pathway make LS an attractive target for chemoprevention.

Colorectal Neoplasia

The RCT, CAPP-2 randomized 861 individuals with LS to aspirin 600 mg/d, resistant starch 30 mg/d, or both.[39] After a mean treatment of 25 months, no difference in the incidence of adenoma or CRC was observed between arms. In longer-term follow-up, resistant starch had no effect on CRC incidence,[40] but over 10 years of observation, patients who received aspirin for 2 years had a substantial reduction in CRC (HR, 0.65; 95% CI, 0.43–0.97) with a relatively low-risk safety profile.[41] The aspirin effect was apparent after 5 years of initiating aspirin and sustained for up to 20 years. This “legacy effect”[42] suggests that initiating aspirin for at least 2 years in younger patients, when the risk of aspirin-related adverse effects such as major bleeding are less common, may be more effective and safer than incepting it in older patients. A subgroup analysis of CAPP-2 identified obesity as an independent risk factor for CRC, which was mitigated with aspirin,[43] suggesting that aspirin might be most beneficial in obese patients with LS. An RCT, “CAPP-3,” is underway to assess the efficacy of 100 mg, 300 mg, or 600 mg of daily aspirin on CRC incidence. Based on current evidence, guidelines suggest consideration of aspirin for CRC prevention in LS, but the optimal dose is unknown.[37,44]

Observational data in LS showed an association between CRC risk and use of aspirin and/or ibuprofen (HR, 0.41; 0.28–0.61), multivitamins (HR, 0.55; 0.40–0.75),

or calcium (HR, 0.46; 0.30–0.71) compared with nonusers, and appeared stronger for longer duration of exposure.[45,46]

The impact of NSAIDs on biomarkers in LS was tested in a 4-week study in 22 patients with LS or meeting the Amsterdam criteria and found that sulindac 150 mg twice daily increased proximal, but not distal, colon epithelial cell proliferation and had no effect on apoptosis compared with placebo.[47] A phase Ib, 6-month study randomized 80 patients with LS and Lynch-like syndrome to daily naproxen 220 mg versus 440 mg versus placebo and found no difference in adverse events between arms.[48] Mucosal prostaglandin E_2 levels were significantly reduced with naproxen compared with placebo. Naproxen downregulated genes in cell cycle dynamics and upregulated immune genes with a dose-dependent effect, thus playing a role in the activation of the immune system of the colorectum. A phase 1, nonrandomized trial of atorvastatin 20 mg with or without aspirin 325 mg is currently underway to assess any synergistic effects of these agents on colorectal biomarkers in LS.

Preclinical studies suggest an association between tumor neoantigens and the immune microenvironment in the DNA mismatch repair (MMR)-deficient adenoma-carcinoma pathway.[49] These findings are key to understanding why tumor vaccines or immune checkpoint inhibitors may work in LS. MMR-deficient crypts seem to be the earliest epithelial abnormality identified in colorectal mucosa in LS. MMR-deficient cells generate immunogenic frameshift peptide (FSP) neoantigens and can elicit host immune responses.[50] Checkpoint blockade therapies targeting PD-1/PD-L1 are highly effective for treatment of advanced MMR-deficient CRC[51] and are being studied as immunopreventive agents in LS. A phase 2, 3-month, study of nivolumab in adults with LS and a personal history of advanced neoplasia will assess its impact on the incidence of adenomas, LS-related cancers, and biomarkers of immunologic activity. Vaccines are a promising strategy in LS, and work has shown strong immunogenicity in animal models.[52] A phase 1/2a study of an FSP vaccine was conducted in 22 patients with advanced MMR-deficient CRC.[53] Of 19 analyzed patients, all showed FSP-specific immune humoral and cellular immune responses after vaccination. Three patients had grade 2 local injection site reactions, and no severe adverse events occurred. Another phase 1/2 vaccine study is underway testing frameshift-derived neoantigen-loaded dendritic cells in patients with LS.

Endometrial Cancer

Little data on chemoprevention on non-CRC in LS are available. Epidemiologic studies have shown that progestin-containing contraceptive pills reduce EC in average risk women. A phase 2 biomarker study of progestin-containing OCP or depo-medroxyprogesterone acetate (depoMPA) demonstrated that both agents significantly decreased endometrial epithelial proliferation and induced microscopic endometrial changes characteristic of progestin effect after 3 months of treatment in 51 women with LS or hereditary non-polyposis colorectal cancer (HNPCC).[54] The long-term CAPP-2 results noted a trend toward fewer EC among women in the aspirin than placebo arm (HR, 0.50; 95% CI, 0·22–1·11).[41] Findings from both studies suggest benefit in EC but warrant further study in LS.

Hamartomatous Polyposis Syndromes

The phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome, Peutz-Jeghers syndrome (PJS), and juvenile polyposis syndrome (JPS) are rare intestinal hamartomatous polyposis syndromes associated with benign and malignant intestinal and extraintestinal cancers. Cancers develop through hamartoma-carcinoma

pathway or transformation of the adjacent epithelium of the abnormal stromal environment.[55] Data on chemoprevention are limited in these syndromes.

Patients with a PV in *PTEN* have abnormal PI3K-AKT-mTOR signaling, and targeting P13K, AKT1, mTOR, or PDK1 could be a means for chemoprevention.[56] The mTOR inhibitor sirolimus was found to regress mucocutaneous lesions in mice with *PTEN* gene deletion[57] and, in case reports in children, to attenuate abdominal lipomatosis and thymus volume,[58] soft tissue vascular lesions in forearm,[59] and hamartomas of the chest, mediastinum, abdomen, and pelvis.[60]

An open-label study with sirolimus 2 mg daily for 56 days in 18 patients with *PTEN* PVs showed regression of gastrointestinal and skin lesions with favorable modulation of mTOR pathways on immunohistochemistry, improved cerebellar function, and was well tolerated.[61] An open-label, 12-month, 10-patient study of sirolimus 2 mg daily on colorectal polyposis is underway in individuals with a PV in *PTEN*.

The intestinal hamartomatous polyposis syndromes PJS, due to a germline PV in *STK11* (also known as *LKB1*), and JPS, due to PVs in either *BMRPR1A* or *SMAD4,* are associated with increased risks of CRC and gastric cancer, and in the case of PJS, breast, pancreas, lung, gonadal, and gynecologic cancers.

Polyps in patients with PJS and in LKB1 knockout mice models have elevated COX-2 levels.[62,63] Initiation of celecoxib before and after the development of polyposis led to a reduction in murine tumor burden and vascularity of polyps.[63] Celecoxib 400 mg daily was administered to 8 patients with PJS for 6 months to determine the effects on gastric polyps. Based on video recordings from EGDs, 2 of 6 patients had a significant reduction in gastric polyps at end of treatment.[63]

LKB1 is a serine/threonine protein kinase with mTOR as its major downstream effector. Sirolimus also has been shown to decrease polyp size and vascularity and tumor burden in murine models of PJS.[64,65] An open-label, phase 2,12-month study of the mTOR inhibitor everolimus at 10 mg daily to assess its effect on large gastrointestinal polyps was terminated before completion. Three patients completed therapy, and all developed stomatitis causing dose reductions, but no other serious adverse events were noted. Unfortunately, there was insufficient polyp burden to draw any conclusions.[66] At present, a trial assessing the safety and efficacy of sirolimus in decreasing polyp burden in children and adults with PJS is enrolling.

No chemoprevention studies in JPS exist. Juvenile polyposis of infancy (JPI) caused by the combined loss of function of *PTEN* and *BMPR1A* presents in the first 2 years of life and has a severe phenotype characterized by gastrointestinal bleeding, diarrhea, protein-losing enteropathy, and early mortality. Sirolimus has been shown successful in case reports in patients with JPI in improving gastrointestinal bleeding, protein-losing enteropathy, patient growth, and reducing intestinal polyp burden.[67,68]

A multicenter cohort of 25 patients with JPI at mean age of 13 months reported the effect of mTOR inhibition on adverse events, disease progression, time to colectomy, and mortality in 7 patients compared with children who received standard-of-care treatment.[69] The risk of colectomy (HR, 0.27; 95% CI, 0.07–0.95), change in serum albumin (mean increase = 16.3 g/L), and hemoglobin (mean increase = 2.68 g/dL), and mortality (0% vs 22%) favored the sirolimus group. The investigators report that mTOR inhibitor therapy was well tolerated over a follow-up of 30 patient-years, and no serious adverse events were reported.

SUMMARY

No chemoprevention agents for the HCCS are FDA approved. A variety of studies demonstrate modest efficacy of NSAIDs including sulindac, selective COX-2

inhibitors, and aspirin on reducing colorectal polyps in adults with FAP and preventing CRC in LS. Celecoxib regresses colorectal polyposis in children and may have a modest effect in duodenal polyposis in adults. Combination chemoprevention holds promise for more effectiveness than single agents for polyposis, but daily erlotinib and sulindac benefits occur at the expense of toxicity. RCT data for nutraceutical benefit exist only for EPA in FAP. The mTOR pathway seems important in polyposis because animal models and descriptive studies using mTOR inhibitors have suggested benefit and more RCT evidence is being generated. Immunopreventative strategies may prove highly effective in LS. The long-term durability and safety of many agents is unknown and will not substitute for endoscopic and surgical management of HCCS.

CLINICS CARE POINTS

- There are no FDA-approved agents for chemoprevention for patients with HCCS.
- Chemoprevention use for patients with HCCS is adjunctive to standard of care, including endoscopy and surgery.
- Chemoprevention may blunt polyposis burden and progression in familial adenomatous polyposis and the typical endoscopic features of polyps.
- Chemopreventive agents have toxicity, and the long-term benefit and risk of chemoprevention is unknown.

AUTHOR CONTRIBUTIONS

C.A. Burke: concept, design, drafting, critical revision, final approval, and accountability for work; C. Macaron, G.N. Mankaney, M. Haider, M. Mouchli, K. Hurley: drafting, critical revision, final approval, and accountability for work.

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