Clinics in Oncology

Editorial
Published: 24 Apr, 2017

Hereditary Colon Cancer Syndromes: Optimal Management in 2017

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Editorial

Colorectal Cancer (CRC) is the third most common cancer in the United States [1]. Almost one-third of the cases show familiar predisposition and a genetic syndrome is identified in approximately 5% of newly diagnosed patients [2]. Hereditary colorectal cancer syndromes can be divided into polyposis and non-polyposis (Table 1); the most common is Lynch Syndrome (LS) secondary to Mismatch Repair (MMR) gene mutations causing Microsatellite Instability (MSI). Mutations in one of the MMR genes are highly prevalent in the western hemisphere; the prevalence is estimated to range between 1:370 and 1:3100 [3,4]. The cumulative incidence for CRC at 70 years in patients with LS can be up to 70% [5,6]; the risk depends on the genotype, with the highest risk for *MLH1* and *MSH2* mutation carriers (72 *vs.* 54 and 18% for MSH6 and MPS2 mutation carriers respectively) [7]. The CRC risk by age 40 approaches 100% for *APC* mutation carriers. Patients and/or families that meet clinical criteria for LS but tumors lack MMR gene mutations are considered to have familial colorectal cancer type X [8].

Who should be tested and how?

There is evidence that almost one-third of LS cases will be missed if only patients fulfilling clinical (Amsterdam [9] and revised Bethesda [10]) criteria are tested [11]. Screening all patients who develop CRC before the age of 70 and patients above the age of 70 who fulfill the revised Bethesda criteria using tumor PCR for detection of MSI or immunohistochemistry for lack of expression of MMR proteins is recommended by the National Comprehensive Cancer Network (NCCN) and is cost-effective [12,13]. As 12% of sporadic CRC cases have MSI secondary to biallelic *MLH1* promoter methylation or a CpG island hypermethylation phenotype, specialized testing through simultaneous detection of somatic MLH1 promoter methylation or *BRAFV600* mutation is required [14-16]. Mutation specific testing is advised if one of the polyposis syndromes is suspected [17].

Simultaneous detection of multiple different germline pathogenic mutations through Next-Generation Sequencing (NGS) is an alternative method for detection of carriers. In patients with suspected LS who had germline DNA testing at a commercial laboratory, 5.6% had mutations in non-MMR genes; 21% of those cases were in *BRCA1/2* and 13% in other high-penetrance cancer predisposition genes [18]. Two-thirds were in moderate-penetrance genes and monoallelic *MUTYH* mutations. In a recent study, the prevalence of germline mutations for high- and moderate-penetrance genes detected by NGS was 10%; half of those patients carried a high-penetrance gene mutation [19]. Three percent of the overall study population had an MMR gene mutation and 2% a mutation not related to LS. Ninety-seven percent of the patients with MMR gene mutation met clinical criteria for testing but the clinical history was not suggestive of the genotype in one-third of the patients with non-MMR gene mutations. For example, half of the patients with *APC* or *MUTYH* mutation lacked diffuse colorectal polyposis. It should be noted though that in about two-thirds of those patients, the mutation was in a gene not typically associated with CRC like *BRCA1/2.* One-third of the patients had a Variant of Unknown Significance (VUS). In another study incorporating germline NGS testing for cancer susceptibility genes, 16% of patients with early onset CRC (age <50 years) were found to have a genetic cancer syndrome; half of the patients had LS [20]. Three percent of the cases had a mutation not specifically related to CRC and in half of these cases the mutation was in a moderate-penetrance gene. In 23 (31%) of the 72 patients with a pathogenic mutation, testing was not recommended based on NCCN guidelines; in 60% of those cases the mutation was in a colon cancer related gene like *APC* or *MUTYH*. One-third of the patients had a VUS. It is currently unclear whether NGS should be used for detection of hereditary CRC syndromes but it appears that it is most useful for detection of non-MMR gene mutations.

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Received Date: *27 Mar 2017*
Accepted Date: *21 Apr 2017*
Published Date: *24 Apr 2017*

Citation:
Fountzilas C, Kaklamani V. Hereditary Colon Cancer Syndromes: Optimal Management in 2017. Clin Oncol. 2017; 2: 1264.

Table 1: Hereditary Colorectal Cancer Syndromes [11,17,45-50].

Syndrome	Genotype	Cancers (Risk)	Other Phenotypic Features
• Non-Polyposis Syndromes			
Lynch Syndrome (AD)	• MLH1 • MSH2 • EPCAM	• CRC (22-74%) • Endometrial (14-54%) • Gastric (up to 13%) • Ovary (4-20%) • Urothelial (up to 25%) • Hepatobilary (up to 4%) • Small bowel (up to 12%) • Brain (1-4%) • Sebaceous tumors/Muir-Torre syndrome (up to 4%)	• Right-sided CRC • Poor differentiation • Medullary growth pattern • Mucinous features • Signet-ring cells • Crohn-like reaction • Lymphocytic infiltration
	• MSH6	• CRC (10-22%) • Endometrial (17-71%)	
	• PMS2	• CRC (9-20%) • Endometrial (10-15%)	
Constitutional MMR deficiency Syndrome (AR)	• Biallelic MMR gene mutation	• High risk for early onset LS-associated tumors • Hematological tumors	• Café-au-lait macules • Axillary/inguinal freckling • Lisch nodules • Neurofibromas • Pilomatricomas
• Polyposis Syndromes			
Familiar Adenomatous Polyposis (FAP) Syndrome	• APC	• Colorectal (~100%) • Duodenal/periampullary (4-12%) • Thyroid (1-2%) • Gastric (up to 1%) • Hepatoblastoma (<1%) • Medulloblastoma/ Turcot syndrome (1-2%) • Pancreatic • Biliary • Distal small bowel	• Multiple colonic adenomas (>100) • Multiple polyps throughout the GI tract • Desmoid tumors (Gardner syndrome) • Epidermoid cysts • Osteomas • Congenital retinal pigment epithelial hypertrophy
Attenuated FAP (AD)	• APC (far distal or proximal gene mutations, exon 9 mutations	• CRC (69%) • Duodenal/periampullary (4-12%) • Thyroid (1-2%)	• Multiple colonic adenomas (20-100)
MUTYH-related adenomatous polyposis (AR)	• MUTYH	• CRC (80%) • Duodenal (4%)	• Multiple colonic adenomas (<100)
Polymerase proofreading-associated polyposis (AD)	• POLE • POLD1	• CRC • Endometrial (POLD1)	• Multiple colonic adenomas (<100)
Peutz-Jeghers Syndrome (AD)	• STK11	• Breast (32-54%) • Pancreatic (11-36%) • Gastric (29%) • Small bowel (13%) • Ovarian stromal tumors (21%) • Uterine (9%) • Lung (7-17%) • Testes (9%) • Cervix (10%)	• Multiple colonic hamartomas • Mucocutaneous pigmentation
Cowden Syndrome (AD)	• PTEN	• Breast (25-50%) • Thyroid (3-10%) • Endometrial (7-17%) • CRC (9-16%)	• Colonic hamartomas • Trichelemmomas • Oral papillomas • Cutaneous lipomas
Juvenile polyposis syndrome (AD)	• SMAD4 • BMPR1A	• Gastric/Duodenum (21%)	• Colonic hamartomas • Arteriovenous malformations • Telangiectasia • Epistaxis
Hereditary mixed polyposis syndrome (AD)	• GREM1	• CRC	• Multiple colon adenomas, hamartomas, and serrated polyps (<20)

AD: Autosomal Dominant; AR: Autosomal Recessive; CRC: Colorectal Cancer; GI: Gastrointestinal; MMR: Mismatch Repair

Primary prevention of CRC

Intensive early endoscopic surveillance and/or prophylactic colectomy are recommended for the major hereditary CRC syndromes [17]. Screening colonoscopy every 3 years in non-affected MMR mutation carriers resulted in a decrease in CRC incidence and mortality [21,22]. The time from development of adenoma to development of carcinoma is significantly accelerated in patients with LS (3 *vs.* 10 years in sporadic cases), providing rational for more frequent screening colonoscopy (every 1-2 years) [23]. Polyps in Familiar Adenomatous Polyposis (FAP) appear at the mean age of 15 years necessitating initiation of endoscopic screening at puberty [24]. Endoscopic screening (and subsequent surgery) decreases the risk of developing CRC and improves survival [25,26]. Timely prophylactic total colectomy with or without rectal sparring is recommended in patients with FAP [17].

Chemoprevention has been evaluated as primary prophylaxis in patients with hereditary CRC syndromes with the most promising agents being Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, significantly decreased adenoma formation in patients with large or multiple adenomas at baseline by 33 to 45% in phase III trials but its cardiovascular safety remains a concern [27,28]. In a randomized,

Table 2: Summary of NCCN recommendations for management of hereditary CRC syndromes [51].

Syndrome	Screening Colonoscopy	Prophylactic Colectomy	Extracolonic malignancies	Chemoprevention
LS	• Start at age 20-25 years • If CRC diagnosed before age 25 years start 2-5 years prior to the age of onset • Repeat every 1-2 years	• Not recommended	• Consider prophylactic hysterectomy and bilateral salpingo-oophorectomy • EGD with extended duodenoscopy starting at age 30-35 years • Annual endometrial sampling • Annual urinalysis starting at age 30-35 years	• Potential role for aspirin
FAP	• Start at age 10-15 • Repeat annually	• Recommended • Timing individualized	• EGD starting at age 20-25 years • Annual physical examination including thyroid exam • Abdominal MRI or CT within 1–3 years post-colectomy	• Potential role of NDAIDs
AFAP	• Start at late teen years • Repeat every 2-3 years	• Consider surgery if the patient has high (>20, >1 cm in size, advanced histology) polyp burden	• No recommendations	• Potential role of NDAIDs
MAP	• Start at 25-30 years • Repeat every 2-3 years	• Consider surgery if the patient has high (>20, >1 cm in size, advanced histology) polyp burden	• No recommendations	• Potential role of NDAIDs
PJS	• Start at late teen years • Repeat every 2-3 years	• Not recommended	• Start at age 25 annual mammography/breast MRI/ biannual breast exam • CT/MR enterography at age 8-10 yers • EUS/MRCP every 1-2 years starting at age 30-35 years • Annual pelvic/testicular exam	• Not recommended
JPS	• Start at age 15 • Repeat every 2-3 years	• Not recommended	• EGD every 2-3 years starting at age 15	• Not recommended

AFAP: Attenuated Familiar Adenomatous Polyposis; CRC: Colorectal Cancer; CT: Computerized Tomography; EGD: Esophagogastroduodenoscopy; EUS: Endoscopic Ultrasound; FAP: Familiar Adenomatous Polyposis; JPS: Juvenile Polyposis Syndrome; LS: Lynch Syndrome; MAP: MUTYH-Associated Adenomatous Polyposis; MR: Magnetic Resonance; MRCP: Magnetic Resonance Cholangiopancreatography; NCCN: National Comprehensive Cancer Network; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, PJS: Peutz Jeghers Syndrome

double blind, placebo-controlled trial, 77 individuals with FAP with at least 5 colonic polyps were randomized to celecoxib or placebo [29]. Celecoxib resulted in a significant decrease in the number and polyp size from baseline (28 *vs.* 4.5% and 30.7 *vs.* 4.9% respectively). In a second randomized placebo-controlled trial, 22 individuals with FAP who had at least 5 adenomatous polyps were randomized to the NSAID sulindac or placebo [30]. Treatment with sulindac resulted in a 44% decrease in the number and 35% decrease in the size of polyps compared to placebo. In a follow up study from the same group enrolling phenotypically normal (e.g. with no polyps) individuals with genetically confirmed FAP, treatment with sulindac did not decrease the number or size of polyps significantly compared to placebo [31]. In a double-blind, randomized phase III study of low-dose aspirin *vs.* placebo conducted in Japan, aspirin decreased mean polyp volume compared to placebo, although not significantly [32]. This study was underpowered for the primary outcome. NDAID plus the ornithine decarboxylase inhibitor eflornithine have shown synergistic effects in colon cancer chemoprevention in a murine FAP model [33]. The combination of celecoxib plus eflornithine compared to celexicob alone has been studied in a phase III trial [34]. The combination resulted in a decrease in the adenoma number and size compared to celecoxib alone but this did not reach statistical significance (13 *vs.* 1% and 40 *vs.* 27% respectively). CPP FAP-310 is an ongoing randomized, double blind, phase III trial evaluating the eflornithine and sulindac combination (compared to each as monotherapy) in individuals with FAP [35].

A summary of syndrome-specific primary recommendations is provided in Table 2. The evidence for screening for extracolonic malignancies is weak.

CRC treatment

There is a concern for decreased efficacy of flouoropyrimidine-containing chemotherapy as adjuvant therapy in stage II/III CRC in cases with a deficient MMR system [36,37]. Recent data reassure on the effectiveness of oxaliplatin-fluoropyrimidine containing regimens, but it appears that the mechanism of MMR deficiency does play a role, with LS cases showing no benefit [38]. The evidence though to withhold adjuvant chemotherapy in patients with LS when otherwise indicated (stage III, high-risk stage II) is inadequate.

An exciting new development is the use of MSI status of the tumor as a predictive biomarker for response to immune checkpoint inhibitors. Response to immune checkpoint inhibitors has been linked to high mutation and thus high neoantigen tumor burden in melanoma and non-small cell lung cancer [39,40]. MSI-high CRC has a higher mutational and neoantigen load compared to non-MSI-high CRC and shows evidence of having an immune active environment with upregulation of many negative immune checkpoint pathways [41-43]. In a phase II study by Le and colleagues, 32 patients with refractory metastatic CRC were treated with pembrolizumab at the dose of 10 mg/kg every 2 weeks; 11 had MSI-high tumors [43]. The overall response rate in these patients was 40% and the disease control rate was 90%. On the contrary, best response for patients with proficient MMR tumors was stable disease in 11% of the patients. Results appear similar with nivolumab in the CheckMate 142 trial [44].

Conclusions

Identification of hereditary CRC syndromes in the clinic is important not only for unaffected family members but also for the patients themselves. Universal screening of patients with CRC for evidence of MMR deficiency/MSI is sensitive and cost-effective. Intensive endoscopic surveillance and/or prophylactic surgery are recommended for carriers. MSI status can be a predictive marker for response to immunotherapy and provide new treatment options.

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