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Clinical endpoints for developing pharmaceuticals to manage patients with sporadic or genetic risk of colorectal cancer

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Abstract

To reduce the morbidity and mortality from colorectal cancer, current clinical practice focuses on screening for early detection and polypectomy as a form of secondary prevention, complemented with surgical interventions when appropriate. No pharmaceutical agent is currently approved for use in clinical practice for the management of patients with risk of colorectal cancer. This article will review earlier attempts to develop pharmaceuticals for use in managing patients with sporadic or genetic risk of colorectal cancer. It will also discuss therapeutic endpoints under evaluation in current efforts to develop drugs for treating colorectal cancer risk factors.

Keywords

colorectal cancer (CRC); difluoromethylornithine (DFMO); non-steroidal anti-inflammatory medications (NSAIDs); sulindac; adenomatous polyps; colonoscopy; chemoprevention; sulindac

Background

Colorectal cancer (CRC) is a leading cause of death in the United States (US) with nearly 141,000 new cases and 49,000 deaths annually (1). Current medical practice employs a variety of early detection screening methods to manage patients with risk of CRC. These methods include fecal components (e.g. occult blood, DNA), serum components (e.g. carcinoembryonic antigen [CEA] and methylated DNA) and physical technologies to visualize the colorectum (e.g. flexible sigmoidoscopy, colonoscopy, CT virtual endoscopy, chromoendoscopy) (2–5). In families with known germline risk factors such as familial adenomatous polyposis [FAP] syndrome, inheritance may be determined at young age by genetic analysis of the relevant gene mutation. Despite general recommendations for screening and surveillance, only 50% of the US adults age 50 or older have undergone

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testing. As a result, late-stage diagnosis of CRC is an all too common result of those non-adherents to screening recommendations. Thus despite an 80–90% 5-year relative survival for early stage CRC, the overall survival for all stages is 65% (1).

Epidemiological studies have revealed numerous associations of dietary and lifestyle factors with CRC development (6). These observations have been the basis of several clinical trials (7) testing the hypothesis that dietary modifications could be used to reduce risk of CRC in patients with an average risk of primary prevention of CRC. Both epidemiological and experimental studies have associated inflammation with risk of CRC (8). These findings have been the basis for multiple clinical trials employing non-steroidal anti-inflammatory drugs (NSAIDs) and other agents with anti-inflammatory activity designed to reduce CRC risk in the general population. Although recent trials using agents targeting the cyclooxygenase-2 (COX-2) gene product showed activity, the relatively modest efficacy of these agents to reduce the risk of colorectal adenoma (CRA) was accompanied by an equivalent or greater risk of serious cardiovascular toxicities (9–11), leading some experts to the conclusion that these agents are not appropriate to use as primary prevention in patients with average risk of CRC (12). Current clinical management does not include any pharmaceuticals for colorectal cancer prevention among average-risk populations, or high-risk populations.

Endoscopic polypectomy appears to be effective in secondary CRC prevention strategy (13, 14). Colonoscopy, with subsequent polypectomy when indicated, does not appear to totally reduce the risk of CRC in patients with sporadic risk (15). In particular, patients with multiple or advanced lesions are more likely to have advanced lesions when seen in follow up and suggest this subset to be more aggressive than smaller, single lesions (16). In patients with genetic risk (e.g. FAP, hereditary non-polyposis colon cancer [HNPCC]), clinicians face a number of challenges managing CRC risk that are different than those in patients with sporadic risk. FAP is currently managed by surgical techniques that often involve removal of both the colon and rectum. Clinical management of these patients involves dealing with duodenal polyposis, development of desmoids tumors and complications of FAP-related operations (17). No pharmaceuticals currently have regulatory approval for use in the management of disease risk in patients with either sporadic or genetic risk of CRC and associated neoplasia. Thus, there is a significant unmet medical need to develop pharmaceuticals that could be used in secondary prevention strategies. There are unmet needs for patients who have had CRC but are currently disease free, or in FAP patients in a variety of clinical indications.

Chemoprevention Trials in General Population with Sporadic Risk

Lippman has reviewed current problems and barriers in the general field of cancer chemoprevention (18). A specific barrier to the development of drugs for patients with sporadic risk of CRC has been the absence of consensus endpoints for this need. Extended time to, and relatively low frequency of, cancer endpoints in patients with sporadic but elevated risk of CRC (e.g. patients with prior CRC, patients with ulcerative colitis or Crohn's disease) require long-term studies in large populations, making these endpoints impractical for drug development-based clinical trials. Until recently, risk factors, such as CRA, were not viewed by regulatory bodies as appropriate endpoint in cancer prevention studies. Concerns involved a number of factors; including questions about the role of CRAs in development of CRC and the assumption that endoscopic polypectomy accompanying screening and surveillance procedures would be sufficient to manage CRC risk in these patients (19). Recent studies have addressed both these issues. Observational studies by Baxter indicate that colonoscopy is associated with reduced risk of death associated with CRC occurring on the left, but not right, side (15). Also, colonoscopy is subject to issues of

quality and physician-specific variability – most dramatically demonstrated by differences in CRA detection rates related to differences in coloscopic withdrawal time (20). Assessment of these and other findings suggest that colonoscopy may not by itself be sufficient to reduce risk of CRC in all patients (21). The significance of reducing risk of colorectal cancer from the antecedent lesions cannot be underestimated. The risk of CRC morbidity and mortality was reduced but not eliminated with colonoscopy and polypectomy (13, 14) especially left-sided lesions (15). Yet, colonoscopy has significant limitations in detecting right-sided, flat-, or serrated lesions (22–24). The ‘incident’ lesions are often high-grade and may have devastating effects on the patient.

Chemoprevention trials in the general population (i.e., primary prevention) have not been effective. In average-risk patients, several agents have been proposed but with limited efficacy and concern for toxicity have prevented their recommendation and use. Recent pooled analysis of aspirin trials in the general population show a decrease in CRC risk but concerns about the safety have led to a lack of consensus about the balance of risks and benefits associated with long-term aspirin use, particularly in low-risk populations (25). The adverse side effects of nausea, dyspepsia, peptic ulcers and gastrointestinal bleeding have precluded recommendations for aspirin use. Calcium may have modest benefits as secondary CRC prevention (i.e. prevention of recurrent CRAs in patients with a history of CRA), based on several randomized studies (26–28), but differing endpoints along the spectrum of CRC has complicated its interpretation of effectiveness. In secondary analyses of multiple clinical trials suggested a modest, inverse relationship between selenium and colorectal adenoma risk (29) but there are concerns about worsening other cancers. In a Phase III trial of ursodeoxycholic acid to prevent colorectal adenoma recurrence (i.e. a secondary prevention clinical trial) there was a decrease in the treatment arm for high-grade dysplasia (30). Of concern have been the clinical trials with adverse outcomes for COX-2 inhibitors that included celecoxib and rofecoxib for which there was an increased rate of adverse cardiovascular events (31, 32). There is modest evidence of risk reduction in the general population but significant adverse effects due to drug toxicity. This increased risk with minimal benefit has precluded general recommendations for chemoprevention among practicing clinicians.

Current screening methods for the general population from the American Gastroenterological Association (AGA) (3), American College of Gastroenterology (ACG) (5), the American Cancer Society (ACS) (4) and the United States Preventative Services Task Force (USPSTF) (2) suggest initial screening for the general population to begin at age fifty, with repeat colonoscopy to be repeated in ten years if no lesions were identified. Standard screening and surveillance methods for the general population are without any recommendations for preventive pharmaceuticals. These methods rely on a variety of technologies, complemented with surgical interventions when appropriate and provide opportunity for risk-reducing, targeted pharmaceuticals to augment the standard of care.

Chemoprevention Programs in Elevated-Risk Populations with Prior Adenoma/CRC

General guidelines for people with a prior history of adenomatous polyps are similar to those recommendations for people with a prior history of CRC, namely increased frequency of colonoscopy, as shown in Figure 1. After surgery for CRC or endoscopic removal of advanced adenomas, colonoscopy is performed after one year as depicted in Figure 1. If there are additional advanced lesions detected at this time, then repeat colonoscopy is conducted in one additional year. If there are not advanced lesions, then repeat surveillance colonoscopy in 3 years.

A current Phase-III clinical trial, S0820 (ClinicalTrials.gov Identifier NCT01349881), is a double-blind, placebo-controlled, randomized control trial of eflornithine (difluoromethylornithine [DFMO]) and sulindac to prevent recurrence of high-risk adenomas and second primary colorectal cancers in patients with previous stage 0-III cancer, summarized in Table, Column 1. These agents act by lowering epithelial polyamine pools, which has been shown to have importance in colorectal carcinogenesis and prevention (33, 34). It is important to note several issues about the study design of this clinical trial. First, this trial is not in a general population, but rather in patients with moderate risk of CRC due to a previously diagnosed colon cancer (i.e. a tertiary prevention clinical trial). Second, the clinical endpoints of the trial are reduction in the aggregate endpoint; high-grade dysplasia, adenomas with villous features, large adenomas (≥ 1.0 cm), multiple adenomas (3 or more), or second primary CRC. Third, the trial is designed to follow up patients after a three year intervention period – which begins at 1-year postoperatively and ends at postoperative year 4. Additionally, a 5-year, post-intervention follow-up period has been incorporated into the trial to measure durability of effect. Given the fairly lengthy time-course from benign lesion to colorectal cancer, it may be impractical to design clinical trials lasting decades and therefore this shorter time course is required. Here, the endpoints are a decrease in the quantity and quality of colonic lesions after only three years of treatment. This model of clinically related endpoints, with a greater expected response rate, requires fewer participants, may expedite trials and has been advocated in CRC chemoprevention trials (35).

In the NCT01349881, DFMO and sulindac, will be given to patients as single agents or in combination for a total of three years as depicted in Figure 1. During this time, patients will be assessed for occurrence of metachronous (new, missed or recurrent) colorectal disease as well as toxicity from the DFMO and sulindac combination as previously described by Zell et al (36), including an assessment of cardiovascular events. While the combination of DFMO and sulindac has a modest side-effect profile, the minimum exposure with a therapeutic effect has yet to be determined. It remains to be determined whether continuous or intermittent drug treatment is more effective. While celecoxib suppressed adenomatous polyps during therapy, cessation of treatment was associated with an increased frequency of advanced CRA, compared to the same frequency in patients receiving placebo as well as significant cardiovascular toxicity (11, 37). This response may not be associated with all NSAIDs, sulindac has been shown to reduce aberrant crypt foci (ACF) without rebound effect (38). Future trials will determine if DFMO + sulindac could safely be given for shorter periods of time (i.e. for 2 years prior to a recommended surveillance colonoscopy as indicated in the example shown in Figure 1 for the recommended surveillance colonoscopy).

Another current, Phase III clinical trial has been sponsored by the National Surgical Adjuvant Breast and Bowel Project (NSABP) in collaboration with the National Cancer Institute (NCI) (ClinicalTrials.gov Identifier: NCT01011478). It is a double-blind, placebo-controlled, randomized control trial of rosuvastatin to prevent occurrence of adenomas and second primary colorectal cancers in patients with previous stage I–II colon cancer, summarized in Figure 2, column 2. Patients will receive either oral rosuvastatin or placebo once daily for five years with the primary outcome measured as occurrence of adenomatous polyps, metachronous CRC, or colon cancer recurrence in patients with resected stage I or II colon cancer. Rosuvastatin has both on-target effects to lower lipids and off-target effects to decrease inflammation (39) and will be compared to aspirin (regardless of dose) in its effect to decrease lesions, but without the toxic side-effects of aspirin.

Implicit questions remain in either trial, with DFMO + sulindac (NCT01349881) or rosuvastatin (NCT01011478). Will there be a benefit compared to existing practice measured by a reduction in the need for colonoscopy? Evaluation of both the clinical

effectiveness as well as the cost-effectiveness will be essential. The clinical effectiveness is likely measured through a reduced disease burden at fixed points in time. Yet the true risk-reduction after treatment may occur years beyond the duration of treatment while the risks occur only while in treatment. The cumulative risk of disease over time in the treatment arm may result in a decrease in severity or number of lesions thereby decreasing the disease burden as well as the cost to the health care system.

Chemoprevention Programs in Elevated-Risk Populations with IBD

In people with GI disorders like inflammatory bowel disease (IBD) there is an increased risk of malignant transformation. This increased risk necessitates increased frequency of surveillance colonoscopy, often yearly with extensive histological sampling every 10 cm. Patients with high grade dysplasia are advised to undergo prophylactic colectomy or total proctocolectomy. While there are medications available for the treatment of IBD either Crohn's disease or ulcerative colitis (UC), the standard of care is focused on risk reduction through surveillance. Crohn's disease management is centered on keeping a patient in remission including amino salicylates (sulfasalazine or mesalamine), antibiotics (ciprofloxacin or metronidazole), corticosteroids (budesonide or prednisone), immunomodulators (azathioprine or mercaptopurine) or even biologics such as infliximab or adalimumab. UC is a distinct disease but is medically managed by similar methods as Crohn's disease. There are significant opportunities for development of targeted therapeutic agents in these high-risk IBD populations.

Chemoprevention Programs in High-Risk Populations with Genetic Predisposition

There are limited options available for people at risk of genetic diseases associated with CRC. Genetic screening tests are available to assess individual risk for Hereditary Nonpolyposis Colorectal Cancer (HNPCC), also known as Lynch Syndrome as well as Familial Adenomatous Polyposis (FAP).

HNPCC, or Lynch Syndrome, results from a germline collection of pathological DNA mismatch repair (MMR) genes. Inherited mutations in *MLH1*, *MSH2*, *MSH6* and *PMS2* genes increase individual risk of CRC as well as endometrial-, ovarian-, pancreatic-, small bowel-ureter-, kidney and stomach- cancers. The gene mutations are inherited in an autosomal dominant pattern with one mutation sufficient to increase individual cancer risk. Lynch syndrome is notable for the average early onset of CRC disease but also for the predilection of right-sided lesions and accelerated carcinogenesis whereby cancers can develop from precursors in as few as 2–3 years compared to sporadic cancers development taking 8–10 years. This pattern of disease progression necessitates frequent surveillance colonoscopy every 2–3 years, with initial screening to begin between 20–25 years old (40). Further recommendations include a subtotal colectomy, as compared to a partial resection after CRC detection in a patient with Lynch Syndrome.

ASA and HNPCC-In a recent trial, investigators assessed disease risk with a pharmaceutical intervention in patients with HNPCC. Specifically, the CAPP2 trial investigated whether high dose daily aspirin would reduce the risk of colorectal cancer disease in people with HNPCC, or Lynch Syndrome, the predominant form of hereditary colorectal cancer. Their results indicated a substantially reduced cancer incidence after more than 6 years of follow up with aspirin treatment (41). While there was a reduction in the mortality of Lynch Syndrome patients with long term use of aspirin (41), targeting the polyamine pathway with combination therapy may supplement current medical management with aspirin, as suggested by the preclinical mouse models as well as the clinical efficacy of

DFMO/sulindac against right-sided lesions (34). Daily aspirin use at full dose (600–650 mg) is a major cause of gastrointestinal bleeding requiring emergency medical treatment.

FAP is a genetic syndrome caused by mutations in the Adenomatous Polyposis Coli (*APC*) tumor suppressor gene. Mutations or deletions in the 5q21–22 region of the chromosome are propagated by an autosomal dominant mode of inheritance. Related, but genetically similar diseases Attenuated FAP and MYH associated polyposis, often present with disease in adults and are major challenges in regard to endoscopic surveillance and surgical interventions. Patients with *APC* mutations have hundreds to thousands of colorectal adenomas which necessitate early, frequent surveillance colonoscopy and ultimately prophylactic colectomy. In the absence of a total colectomy, there is a near certainty of CRC developing before age 40. Colectomy with ileo-rectal reconstruction or total procto-colectomy with ileal pouch-anal reconstruction dramatically reduces their lifetime risk of colorectal cancer. However, progressive polyposis in the retained rectum, ileal pouch (and retained distal rectum) and most problematic the duodenum requires life-time medical management, endoscopies and surgical interventions. Celecoxib was a medication that had previously been approved for FAP management. It had an accelerated approval pathway by the Food and Drug Administration (FDA) in 1999, authorized by the European Medicines Agency (EMA) in 2003, only to be withdrawn by Pfizer in February 2011.

There are significant unmet medical needs in patients with FAP, who despite radical colectomy, require long-term and frequent assessment and interventions. COX-2 inhibitors had modest risk reduction at best but their cardiovascular safety concerns have not resulted in common usage in clinical practice. Efficacy measured by reduction in the number (and size) of polyps, was modest. Similar modest polyp reduction was demonstrated with fatty acids. If there was an increased benefit from pharmaceuticals then the potential benefits to FAP patients may include phenotype suppression of FAP. This would translate into deferred prophylactic colectomy, increased use of rectal preserving ileo-rectal anastomosis (IRA) rather than a pouch, and subsequent increased benefits of improved bowel function and improved fertility for women. Other quality-of-life (QOL) improvements might include reduced intra-abdominal adhesions, desmoids, as well as controlling duodenal polyposis.

FAP and DFMO/sulindac -A current clinical trial aimed at asking whether DFMO/sulindac can reduce the impact of FAP on the individual (ClinicalTrials.gov Identifier: NCT01483144) is shown in Table, Column 3. Specifically, investigators are conducting a double-blind, randomized, Phase III trial with primary outcome measures of delaying time to the first occurrence of any FAP-related event. Inclusion criteria include diagnosis of FAP or Attenuated FAP and age greater than 18 years old. If the patients have had a prior colorectal surgery, the inclusion criteria also stipulate at least 3 years since the colectomy or proctocolectomy with an ileo-rectal anastomosis (IRA) or pouch. A blocked stratified randomization of the participants based on FAP-related event prognosis with 150 patients divided among 3 groups, namely; DFMO/sulindac, DFMO, or sulindac arms, shown in Table 2. The primary outcomes of the study are to delay time to surgical intervention or clinical progression of advanced duodenal polyposis diagnosis of cancer or death itself. Secondary outcomes include evaluation of adverse events as well as regression of duodenal, rectal or pouch polyposis. Patients will be treated daily for a total of 24 months. At the 6, 12 and 18 month visits, endoscopy will be performed to assess disease progression/regression. The enrollment is estimated to be 150 patients with estimated primary completion in 2015.

Other genetic syndromes for which there may be a benefit of DFMO/sulindac are less clear. Hamartomatous syndromes, Peutz-Jeghers syndrome and Juvenile polyposis are similar to FAP in their clinical manifestations as polyposis syndromes (17), but are uncertain in their responsiveness to the combination polyamine inhibition.

Potential to decrease disease burden and increase QOL

Individuals with a genetic risk, such as HNPCC or FAP, are among those who would derive a significant benefit from targeted pharmaceutical agents. Within the treatment continuum, there are discrete stages. Initial surveillance is with frequent colonoscopies and polypectomies are the standard of clinical practice for HNPCC and/or FAP patients. While this may decrease risk of transformation of larger polyps, it does little to reduce overall disease burden. The second discrete phase for FAP patients involves surgical intervention with ileo-rectal anastomosis (IRA) or colectomy with a pouch. The transition from the initial treatment phase to the second phase (from colonoscopy to surgery) often occurs during young adulthood and is made more difficult by questions of social acceptability and fertility issues in patients in this age category. The third phase within the treatment continuum of patients with FAP centers on continued surveillance within the small intestine, surgical intervention (Duodenectomy or Whipple procedure) for advanced duodenal polyposis, and cancer treatment. The potential for a pharmaceutical treatment to decrease overall disease burden, delay life altering surgery and lower overall risk of malignant transformation underscores the need for further development of targeted, chemo-therapeutic agents in colorectal cancer. The overall time to clinically meaningful endpoints such as FAP-related surgeries would be significantly delayed, thereby decreasing the overall burden to the individual patient, decreasing the healthcare costs, but increasing the quality-of-life measures (QOL). These QOL indicators also extend to future management of the disease by Gastroenterologists and Internists, likely at local facilities as opposed to tertiary-care facilities, thereby decreasing travel time and direct cost to the patient. QOL indicators are also measured in decreased numbers and frequency of invasive procedures. Ultimately, the QOL indicator that matters most is the patient's overall well-being that includes mental health and a decrease in anxiety.

Potential for targeted pharmaceuticals to decrease overall morbidity and mortality

There are approximately one million colorectal cancer survivors and 2–3 million “polyp formers”. When these populations are added to the 140,000 people with GI disorders (including IBD) and those people genetic predispositions (50,000 with FAP and half a million with HNPCC) there are over 4 million high-risk people. A proposed, targeted therapy is poised to reduce disease burden throughout these populations, as shown in Figure 2.

Screening protocols for the general population begins at age 50. If there are 2–3 million people who are diagnosed with polyps, then repeat colonoscopies would be expected in this population. Yet, the DFMO/sulindac combination has been shown to have a 70% reduction in the total number of adenomas and a 95% reduction in multiple adenomas (34). Application of these data to the 2–3 million polyp formers would imply a reduction of 1.5–2 million lesion reductions with DFMO/sulindac. It is also clear that there would be a decrease in the associated risks of bowel perforation, bleeding, infection and cost to the healthcare system.

In another example of the potential for DFMO/sulindac, 150,000 people have IBD, with the risk of malignant transformation increased up to five-fold after a decade of the disease. This increased risk of CRC necessitates colonoscopy every 2–3 years. The combination of DFMO/sulindac has the potential to decrease the risk of disease and frequency of colonoscopy by similar orders of magnitude, seen in total adenomas (70% reduction), advanced adenomas (92% reduction) and multiple adenomas (95% reduction).

Pharmaceuticals in clinical practice

Therapeutic prevention pharmaceuticals have significant opportunity to translate into clinical practice. Defining the clinical benefit among patients with previous adenomas, there is a clear need to identify right-sided (proximal) or left-sided (distal) lesions. When the combination of DFMO/sulindac was studied for its effectiveness in reducing lesions, the risk reduction was equal between right- or left- sided lesions, however it is acknowledged that the total number of patients for this analysis was relatively small (34). While pharmaceuticals for cancer prevention in the general public are unlikely to have a significant benefit to risk ratio, there is a significant at-risk population that may derive benefit. The significance of the choice of pharmaceutical agent(s) cannot be underestimated. Other non-steroidal anti-inflammatory drugs (NSAIDs) were not as effective in their reduction of polyp burden. These features of the combination DFMO/sulindac have a very real potential to decrease CRC disease burden.

Conclusion

In CRC prevention trials, cancer is the definitive endpoint. Yet it is unlikely that CRC should be used as the completion of clinical trial as the time to develop cancer is measured in years to decades while identification and removal of the pre-neoplastic lesions may preclude CRC altogether. CRC chemoprevention trials are hampered by this lack of clinically appropriate endpoints and assessment of agent associated toxicity (42). In the general population, the lifetime risk of CRC is only 5%, so the safety profile of prevention agents will be critical. A focused approach to shorter treatment and prevention designs would identify primary effects on surrogate biomarker, endpoints and immediate secondary toxicity and lesions (43). An example of current focused clinical trials is summarized in Table 1. The three clinical trials are 2–5 years in duration with primary endpoints that include; decrease recurrence risk and delay disease related events.

While the timeframes and endpoints of clinical trials are important, so too are the side-effects of treatment protocols. Toxicity associated with DFMO/sulindac has been closely monitored and appears less than that seen in other CRC prevention clinical trials (36). It is an important clinical management strategy that among high-risk patient populations the risk of adverse effects may outweigh the benefits associated with treatment. Table 1 reflects this concern with some of the current trials excluding high-cardiovascular-risk patients.

The clinical management of high-risk populations may be augmented with the targeted therapy of DFMO/sulindac in addition to surveillance colonoscopy and surgery, especially with its reduction in metachronous adenomas (44). Similarly, such therapy may help suppress the disease burden of FAP or HNPCC by delaying surgery or even decreasing disease burden.

Biomarkers as a prognostic factor associated with disease are extremely valuable in clinical practice. Based on recent clinical trials, the polyamine pathway may also be a relevant source for biomarkers (34, 45, 46). This strategy of biomarker use has been an effective risk assessment and reduction tool in cardiovascular diseases, clearly opportunities for CRC still exist (19). Prevention trials should therefore focus on high risk populations, the assessment of toxicity and surrogate markers that can delineate them (47).

Future considerations

Advancements in individualized risk assessment by life-style and biomarkers will help to define the future of CRC prevention. As risk assessment improves the population of people that would benefit from intervention will become increasingly clear. In this way, the risk

associated with treatment will be minimized in light of the potential benefits. It may be reasonable to decrease treatment times, thereby maximizing the benefits of pharmaceuticals while decreasing the potential toxicity (42).

Expert Commentary

Colonoscopy is a screening test and surveillance tool for CRC disease. The effectiveness of colonoscopy to reduce risk of colon cancer appears to be greater among those patients with distal (left-sided), compared to distal (right sided) lesions. While only 50% of adults over 50 have had a colonoscopy, those with a prior history of disease or high-risk genetic predisposition have a pattern of increased frequency of colonoscopy. This dichotomy between underuse of screening colonoscopy in the general population and potential overuse of surveillance colonoscopy by populations with moderate to high risk of CRC is accentuated by a lack of effective pharmaceutical agents that would reduce risk-factors for CRC. Some analyses have already indicated that promising agents, such as aspirin and other NSAIDs, are neither cost effective (48) nor safe (12). Targeting moderate to high risk populations for treatment with pharmaceutical agents holds promise for both a benefit-risk ratio and cost effectiveness considerations. Targeted therapies are needed to reduce risk factors associated with CRC as well as the biomarkers used to validate efficacy of treatment. The combination of DFMO/sulindac has the potential to do both. While the toxicity of treatment appears to be low, continued research needs to evaluate risk stratification, to better assess patients whose benefit from treatment outweighs the risk of side-effects.

Five-year view

There are currently no pharmaceutical agents with regulatory body approval for use in the management of patients with risk of CRC. Similarly, there are no biomarkers that simultaneously stratify risk of disease and evaluate the effectiveness of preventative therapy. In the next five years, multiple Phase III clinical trials will be conducted with NCT01483144 to be completed in 2015. Combined, their evaluations of both DFMO/sulindac and rosuvastatin in patients with FAP and/or a prior history of CRC will clarify the role of targeted pharmaceuticals in high risk populations. Further studies will help define the minimum amount of time required for effective treatment, thereby reducing the toxicity, as proposed in Figure 1 with a short-course, intermittent dosing schedule that precedes colonoscopy. Pharmacogenomic, molecular markers and clinical characteristics of the patients will help stratification prior to treatment. This paradigm shift is akin to changes in the management of heart disease with ACE-inhibitors, beta-blockers and statins that have reduced mortality from coronary artery disease.

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4. *Cardiovascular toxicity of COX-2 therapy in general population (31)
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Key issue bullet points

1. Current management of patients with sporadic and genetic risk involves screening and surveillance colonoscopy complemented with surgical interventions when appropriate.
2. Patients with prior history of advanced adenomatous polyps, CRC, UC, Crohn's have limited medical management aimed at reducing their increased individual risk for CRC.
3. High risk groups with genetic diseases like FAP or HNPCC lack targeted therapy aimed at reducing the risk factors.
4. Recent clinical trials for CRC in the general population cost considerable time and money with significant concerns about toxicity.
5. Current clinical trials in CRC prevention use high-risk populations, have endpoints of reduced disease burden and are of shorter design.
6. Pharmaceuticals aimed at reducing risk have a significant opportunity in treating patients with prior advanced adenomatous polyps, CRC survivors, people with IBD, and genetic predispositions such as FAP and HNPCC.
7. Surrogate markers of risk are valuable to evaluate effectiveness of treatment.

Figure 1.

Possible implementation of pharmaceutical therapies in medical practice to treat CRC risk factors in patients with sporadic prior CRC. Current guidelines depicted here for surveillance colonoscopies and proposed implementation of pharmaceutical therapy to reduce occurrence of metachronous colorectal neoplasia are adapted from NCCN guidelines. One current trial (S0820 to be conducted by SWOG) proposes initiating drug therapy following the one year post-surgery surveillance colonoscopy and continuing for three years until the three year surveillance colonoscopy in patients without advanced/multiple CRAs at the one year colonoscopy. Depending upon results of the surveillance colonoscopy at year 4 in this schema, a subsequent surveillance colonoscopy would be recommended for three to five years later (presuming no advanced/multiple CRA are detected). An important element of future clinical drug trials in this setting should include a follow up surveillance colonoscopy after the end of drug treatment to identify any possible rebound effects of the therapy. If the treatment was effective, therapy could continue for some time prior to the next scheduled surveillance colonoscopy (this example shows a two year treatment interval).

Figure 2.

Patient populations that might benefit from pharmaceutical therapies that would treat risk factors for colorectal cancer (CRC) and associated sequelae. Strategies would target patients with moderate to high risk of CRC, in order to achieve optimal patient benefit-risk considerations. Patients with moderate risk of CRC would include those with prior sporadic CRC, prior sporadic advanced colorectal adenomas (CRA) and/or multiple CRA (“polyp formers”) or certain types of inflammatory bowel disease (IBD), including ulcerative colitis and Crohn’s disease. Patients with high risk of CRC would include those with certain genetic syndromes, including familial adenomatous polyposis (FAP) or hereditary non-polyposis colon cancer (HNPCC).

Table 1

Clinical trials comparison among patients with elevated CRC risk. Table 1, column 1 (NCT01349881) Prospective, double-blind, randomized, DFMO/sulindac treatment to reduce adenomas and secondary primary prevention trial in patients with previous Stage I–III CRC. Table 1, column 2 (NCT01011478) Prospective, double-blind, randomized rosuvastatin treatment to reduce adenomas and CRC in patients with previous Stage I–II CRC. Table 1, column 3 (NCT01483144) Prospective, double-blind, randomized, DFMO/sulindac treatment to delay time to FAP-related event in FAP patients.

	NCT01349881	NCT01011478	NCT01483144
Post-Adjuvant Treatment	Polyamine Inhibitors: Eflornithine 500mg/d, Sulindac 150mg/d, Placebo	Statins: Rosuvastatin 10mg/d vs. Placebo	Polyamine Inhibitors: Eflornithine 500mg/d, Sulindac 150mg/d, Placebo
Treatment Duration	3-years	5-years	2-years
Number of Patients	1340	1740	150
Stage	0-III	I or II	0-III
Exclusion of High-CV Risk Patients?	Yes	No	Yes
On-Study Timeline	1-yr post-operative	Post-operative	Perioperative
Primary endpoint	High-risk adenomas, SPCRC	Adenomas, SPCRC, recurrence	Delay FAP-related events
Results Anticipated	2020	2020	2015

High-risk FAP-population delay of disease progression. FAP patients' disease burden will be assessed, stratified and then randomized into treatment arms. Disease burden will be based on the extent of disease. Randomization of patients will be based stratification.

Table 2

NCT01483144 FAP Trial	Disease Burden	Stratification**
	Intact colon	Best-longest projected time to event
	Rectal or pouch polyposis	Intermediate
	Duodenal polyposis	Worst-shortest projected time to event
	Existing or potential desmoid disease	

** If a patient has 2 or more lesions, then the stratum for randomization will be defined by the 'worst prognosis'