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Perspective

Clinical trials update: Tertiary prevention of colorectal cancer

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Colorectal cancer (CRC) is a major cause of cancer incidence and mortality worldwide. However, the past two decades have brought major advances in CRC screening and therapeutics, including advances in surgery, radiation therapy, chemotherapy, and targeted biologic therapy. As a result, the incidence and mortality of CRC have declined and there are now an increasing number of CRC survivors. Upon completing their initial course of therapy, patients with CRC have a keen interest in adopting dietary and lifestyle activities in an attempt to reduce the risk of recurrent cancer. That particular moment in time has been eloquently referred to as the "teachable moment" for oncologists – a time when patients are receptive and willing to consider adopting lifestyle practices for the purposes of risk reduction.[1] Even after the initial course of therapy, CRC patients represent an important "high-risk group" to be targeted for preventive therapeutics via clinical trial enrollment. There are now observational data supporting the importance of dietary[2,3] and lifestyle behaviors (such as physical activity)[4,5] on survival after CRC diagnosis. However, data are lacking from large-scale clinical trials in support of concrete recommendations for preventing CRC recurrence in the survivorship setting. With the growing population of CRC survivors and advances in the understanding of several well-tolerated therapeutic agents, there has been renewed interest in developing strategies for CRC risk reduction among CRC patients. This is reflected in the current state of the United States National Cancer Institute (NCI)-supported cooperative group clinical trials system, where three large randomized, controlled clinical trials have emerged that will hopefully optimize our approach to risk reduction among CRC survivors over the next decade and beyond. Each of these trials involves a prolonged intervention period using oral medications to inhibit colorectal carcinogenesis through separate mechanisms, and they will be discussed here.

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3-HYDROXY-3-METHYLGLUTARYL-COENZYME A REDUCTASE INHIBITORS

3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (i.e., "statins") have been shown to have anti-cancer properties, such as inhibition of cellular growth and induction of apoptosis. Initial enthusiasm from observational reports detailing the potential benefit of statins in reducing the risk of CRC[6] or advanced stage CRC[7] have been muted by subsequent reports showing no benefit.[8] Congruent with these latter reports, a study was recently presented at the AACR Frontiers of Cancer Prevention meeting in Philadelphia last November, 2010. In a planned analysis of statin use and CRC incidence in participants

of the Women's Health Initiative Study, no benefit was observed for women adhering to statin use.[9] However, no clinical trial data are available to clarify the discordant results from these various observational studies. Additionally, the potential for statins to have benefit in CRC is intriguing as they are fairly well tolerated and (in contrast to other agents used in CRC prevention) provide cardio-protective effects by lowering cholesterol levels. Ultimately, the clinical utility of these agents for the purposes of CRC prevention will be determined through well-designed, prospective clinical trials. A trial put forth by the National Surgical Adjuvant Breast and Bowel Project (NSABP) is now open to accrual and was designed to address the utility of statins as CRC prevention in a population of colon cancer survivors. The trial is titled "Rosuvastatin in Treating Patients With Stage I or Stage II Colon Cancer That Was Removed By Surgery," also known as NSABP P-5 (NCT01011478; Study Chair, B. Boman),[10] and will enroll 1740 patients with stage I or II colon cancer. Patients will be randomized to receive rosuvastatin 10mg daily or placebo daily for 5-years followed by a 2-year follow-up duration. The primary endpoint will be to compare the effect of rosuvastatin vs. placebo on the 5-year occurrence of colorectal adenomatous polyps, metachronous colorectal carcinoma, or colon cancer recurrence, and biomarker analyses from tissue and blood are planned. Results are expected in January 2020.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs exert their antiproliferative effects in the colon by inhibiting prostaglandin synthesis through reversible cyclooxgenase binding. A great body of experimental,[11-16] epidemiologic,[17-21] and clinical trial-based evidence[22-26] supports the notion that NSAIDs have anticancer properties in the colonic epithelium and are associated with CRC risk reduction at various stages of carcinogenesis. In the setting of secondary prevention, randomized clinical trials demonstrated that COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs) decrease the risk of adenoma recurrence, but at the cost of increased cardiovascular events.[27,28] As such, COX-2 selective NSAIDs cannot be recommended for CRC prevention outside of the research setting. A key concept of therapeutic prevention is defining the risk and targeting interventions to high-risk groups with an acceptable tolerability. Therefore, while NSAIDs may not be indicated in the setting of primary or secondary CRC prevention, the potential efficacy afforded by NSAIDs may offset potential toxicities among patients at a higher risk for disease recurrence, such as CRC patients. Several observational studies have demonstrated that regular use of NSAIDs is associated with survival improvements for CRC patients in the survivorship period.[29-31] However, large clinical trials involving NSAID use in non-metastatic CRC patients have not been conducted until now. Such is the population targeted for intervention in the intergroup trial Cancer and Leukemia Group B (CALGB) 80702, "Oxaliplatin, Leucovorin Calcium, and Fluorouracil With or Without Celecoxib in Treating Patients With Stage III Colon Cancer Previously Treated With Surgery" (NCT01150045; Principle Investigator, J. Meyerhardt).[32] This trial randomizes stage III (i.e., lymph node positive) patients to receive 3 years of treatment with celecoxib 400 mg daily vs. placebo after completion of variable-length adjuvant chemotherapy for stage III colon cancer. In total, 2500 patients will be enrolled in this trial, which opened to accrual throughout the U.S. in the June of 2010. The primary endpoint is disease-free survival, and results are anticipated in February 2013.

POLYAMINE SYNTHESIS INHIBITORS

Polyamine synthesis inhibitors have gained interest in light of their reported clinical efficacy in colorectal adenoma patients. Polyamines are naturally occurring substances found in the diet and produced in epithelial tissues. This occurs through conversion of arginine-derived ornithine by the rate-limiting enzyme ornithine decarboxylase (ODC) to form the major polyamines putrescine, spermidine, and spermine.[33] Polyamines are involved in cellular processes such as tissue growth and repair, cell proliferation, and regulation of transcription. However, in excess, they result in cancer formation within the epithelial tissues and are implicated in colorectal carcinogenesis. Eflornithine (difluoromethylornithine, DFMO) is a suicide inhibitor of ODC and, through this action, inhibits polyamine synthesis. Because of concerns for ototoxicity at high doses (which was reported originally at a dosages 20–30-times the dose of DFMO used in modern day clinical trials), a series of dose de-escalation phase II clinical trials demonstrated efficacy against polyamine biomarkers in the target tissue of origin.[34,35] More recently, a phase III trial was reported involving combination chemoprevention with eflornithine and sulindac treatment on colorectal adenoma recurrence.[36] Sulindac, like other NSAIDs, has polyamine-inhibitory properties via induction of spermidine spermine acetyltransferase (SSAT) and resultant cellular polyamine export.[33] Together, eflornithine and sulindac decrease the cellular polyamine pools. In the phase III trial, compared with placebo, eflornithine plus sulindac produced a 70% reduction in recurrent adenomas and a 91.5% reduction in advanced adenomas.[36] The trial was halted by the Data Safety and Monitoring Board after achieving these efficacy endpoints. Thus, only 267 of the planned 375 patients were enrolled. On the heels of these

results, investigators at SWOG and the NCI-Division of Cancer Prevention have developed a phase III clinical trial among CRC patients to investigate the utility of these agents in the tertiary prevention setting. The trial is titled SWOG 0820: "A Double Blind Placebo-Controlled Trial of Eflornithine and Sulindac to Prevent Recurrence of High Risk Adenomas and Second Primary Colorectal Cancers in Patients with Stage 0-III Colon Cancer, Phase III" (Study Coordinators: J. Zell, P. Brown).[37] Eligibility includes patients with rectosigmoid or colon cancer, stage 0, I, II, or III at diagnosis. Patients will be enrolled 1 year post-operatively and will be randomized into one of four arms in a 2x2 factorial design for a 3-year intervention period: Eflornithine 500 mg by mouth daily with sulindac 150 mg by mouth daily, eflornithine + sulindac placebo, eflornithine placebo + sulindac, or double placebo. Stratification will occur based on stage and accounting for receipt of adjuvant chemotherapy. Projected accrual will be 1340 patients and the primary endpoint is a reduction in high-risk adenomas and second primary CRCs. Translational pharmacogenetic analyses are proposed as secondary endpoints. It is anticipated that accrual will commence in Spring 2011, and initial results are anticipated in 2019 (with 5-year follow-up data to follow at a later date to determine durability of effect).

CONCLUDING REMARKS

Seeing the promise and potential for CRC risk reduction in high-risk populations, the U.S. NCI and cooperative oncology group systems have invested substantial resources toward testing prevention agents in patients during the CRC survivorship period. It is hoped that this shift in focus will yield tangible results for CRC survivors. Beyond the primary objectives in each of these trials, it is hoped that the trials will become valuable resources for future translational research. Such research may help to clarify the risk–benefit and risk avoidance (risk-risk), which will ultimately influence future CRC prevention strategies.

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