Trials and Tribulations of Interrogating Biomarkers to Define Efficacy of Cancer Risk Reductive Interventions

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Abstract

The challenges of clinical screening of cancer risk reductive interventions ("chemopreventive") have slowed progress in deployment of therapeutics to reverse or delay the carcinogenesis process. The preoperative or window-of-opportunity design clinical trial design enrolls subjects rapidly, has short study periods, and quantifies tissue biomarkers that reflect both anti-carcinogenesis mechanism of the risk reductive intervention and key molecular events of the carcinogenesis process for a specific epithelial target. High subject screened to on study ratios reduce the efficiency and increase cost of this research strategy. Small-sized tissue samples obtained by minimally invasive endoscopic technologies limit the number of biomarkers that can be detected and quantified, forcing investigators into choosing either a broad-based but superficial multi-mechanism exploration of signaling intermediates or a more focused analysis of multiple molecular events in a linear signaling-specific pathway. More efficient strategies of the future might involve isolation and expansion of pluripotent cells from at-risk epithelium or intraepithelial neoplastic lesions. Such a strategy would allow interrogation of key carcinogenesis-associated pathways and mechanisms in representative primary single-cell cultures amenable to genomic, proteomics, or transfection-based technologies. Cancer Prev Res; 6(2): 71–73. ©2013 AACR.

The challenges of clinical development of cancer risk reductive interventions—therapeutic index, long latency to a malignant transformation endpoint, defining an appropriate study population, recruitment barriers, biosample collection and management, analytic quality control, and clinical trial complexity—have conspired to limit the number of interventions that can be screened for cancer preventive efficacy in human subjects (1, 2). As the costs and efforts for late-phase clinical trials using a cancer incidence endpoint to define cancer risk reductive efficacy are not sustainable, the use of biomarker endpoints from the organ site at-risk as preliminary efficacy endpoints is a priority of the field. The preoperative or window-of-opportunity model of cancer risk reductive efficacy testing uses pre- and posttreatment tissue sampling of the epithelium at risk or of a neoplasm or both. The cancer risk reductive must be administered over a time period sufficient to modulate putative biomarker targets but need not be prolonged to alter morphology or cause involution of a noninvasive neoplasm. Biomarkers are assayed in the pre- and posttreatment tissues obtained from the neoplastic and matched morphologically normal tissue from the organ at-risk (1, 2). Such preoperative or window-of-opportunity models with biomarker changes after cancer risk reductive interventions have been used in the colon (3), breast (4, 5), prostate (6–9), and head and neck sites (10).

While each of these preoperative models and associated biomarker targets present unique methodologic and analytic challenges, some of the challenges can be generalized. The manuscript from Puntoni and colleagues (11) in this issue of Cancer Prevention Research highlights both the strengths and challenges of using tissue-based biomarkers for cancer risk reductive efficacy. The design of the phase IIa colon cancer risk reductive preoperative window-of-opportunity trial of Puntoni and colleagues exploits the requirement for repetitive colonoscopic procedures for some patients who have colonic adenomas of ≥1 cm. The investigators required 4 years to recruit and complete this study of 73 eligible subjects to this trial, yet approximately 5% to 10% of adenomas detected by colonoscopy are ≥1 cm (12), suggesting that the bulk of large adenomas were resected endoscopically with a single procedure. If the goal of a biomarker-based phase IIa cancer risk reductive trial is to identify potential clinical risk reductive efficacy in a quick, low-cost study, the 4 years required to complete this preoperative window-of-opportunity trial suggest that either a larger, multicenter trial will be required, higher volume endoscopy centers should be sought with higher risk patients, or the design is suboptimal. Phase IIa trials are intended to provide quick estimates of efficacy, prioritizing agents for entry into long-term trials.

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Puntoni and colleagues justify the selection of their intermediate biomarker endpoints on the basis of “inhibiting xanthine oxidase and reducing the intracellular reactive oxygen species (ROS) production by allopurinol might inhibit activation of the mitogen-activated protein kinase (MAPK)-NF-kB signaling pathways and therefore decrease cell proliferation as measured by Ki-67 and increase apoptosis as measured by TUNEL.” Yet little is known about the xanthine oxidases and their role in human carcinogenesis or relationship to changes in cellular populations. Without prospective data in rodent carcinogenesis models, it is difficult to model the effects of allopurinol-induced xanthine oxidase inhibition on carcinogenesis-associated driver signaling system intermediates that can be used as biomarkers for drug effect and mechanism-associated anti-carcinogenesis effect. With the lack of anti-carcinogenesis mechanistic data, the choice of intermediate efficacy endpoints for a phase IIa biomarker-driven clinical trial becomes difficult. Nevertheless, the data presented are intriguing because NF-kB expression in colonic crypt cells appears to be modulated with allopurinol, but the claim that allopurinol inhibits biomarkers of oxidative activation seems overly optimistic as there are many other biomarkers of oxidative activation and metabolism that have not been assayed. Moreover, important potential confounding variables, such as nonsteroidal anti-inflammatory and calcium intake, have not been analyzed despite being collected. The effects observed on the MAPK/NF-kB signaling pathway may be due to allopurinol, a combination of allopurinol, or other confounding variables.

The data presented by Puntoni and colleagues do not reflect the complexity of the metabolic, buffering, and reactive metabolites associated with intracellular oxidative stress. The same can be suggested about the authors’ statement that the MAPK/NF-kB signaling pathway has been studied. A contemporary assessment of this system would identify and quantify several phosphorylated metabolites of MAPK and its downstream intermediates. Yet, the small tissue sample mass obtained from small forceps biopsies, approximating 5 mg which produces approximately 300 to 800 µg of protein in crude homogenates, limits the biomarkers that can be studied in a phase IIa trial. Local pathologist requirements to render an accurate preinvasive diagnosis and rule-out invasive cancer further restrict the availability of adenomatous tissue for biomarker investigations. Such tissue limitations often result in less than satisfying data that can be difficult to interpret; yet the same limitations force choices about the depth of biomarker analyses that can be undertaken in a clinical trial such as the one here. These limitations require critical choices between the detailed examinations of a single carcinogenesis-associated pathway versus a more limited but broader examination of multiple pathways.

Puntoni and colleagues show both proof-of-principle and serious limitations in preoperative or window-of-opportunity strategies to define cancer risk reductive intervention efficacy using intermediate biomarkers. The 4-year window required to enroll 73 eligible participants for a repetitive sampling trial of large adenomas in a small consortium of institutions with long-term, extensive expertise in developing, implementing, and completing cancer risk reductive intervention clinical trials creates concerns about the viability and efficiency of a preoperative window-of-opportunity strategy with adenoma endpoints. A more efficient preoperative window of opportunity for biomarker-based colon cancer risk reductive efficacy assessment uses administration of the agent to patients with colon cancer for 2 to 3 weeks preoperatively. This approach, as published by Patel and colleagues (3), can be completed more rapidly but suffers from the major limitation that cancer tissue, adenomatous cells, or transitional normal appearing mucosa adjacent to invasive neoplasm may not be representative of the carcinogenesis biology driving neoplastic transformation in other at-risk populations, such as those with adenomas.

The strengths and weaknesses of the manuscript of Puntoni and colleagues highlight progress in the development and use of biomarkers in intraepithelial neoplasms in phase IIa cancer risk reductive clinical trials. They also show the limitations of such preoperative models. Can more efficient clinical models be identified for populations at-risk for colon cancer or for other organ sites, such as the breast or prostate? We have recently used a strategy of isolating stem-like cells from normal human breasts in primary culture as a platform for early-phase cancer risk reductive efficacy interrogation (13). While such proof-of-principle models are promising, their use to replace the necessary early-phase clinical trials using biomarker endpoints for efficacy evaluation of cancer risk reductive interventions remains in the early phase of research.

Disclosure of Potential Conflicts of Interest
E. Hawk is a consultant/advisory board member of Cancer Prevention Pharmaceuticals. No potential conflicts of interest were disclosed by the other author.

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