Ontology, Oncology, and Preventive Economies: Developing Drugs for Cancer Prevention

Commentary on Christov et al., p. 5488

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Tumor growth is a result of an imbalance of cellular proliferation and cell death, and agents that promote apoptosis or reduce proliferation, or both, will result in impaired tumor progression. Multiple agents with promising preventive potential that slow proliferation or induce apoptosis have been identified in preclinical studies and are now available for clinical investigation. How does one select and study them practically, efficiently, and economically to select the most effective compounds?

Randomized, prospective risk reduction trials that are designed with cancer incidence as their end point are expensive and cannot realistically be conducted for all possible agents for both economic and practical reasons (1). The current clinical model of preventive agent discovery focuses on drugs already approved for the treatment of malignancy that are often at the end of their patent lives when commercial interest in their further development and sponsorship is waning. This progressive, investigational model for development of new agents that are effective in the treatment of cancer evaluates them in patients with advanced malignancy so that new drug approvals are usually for treatment of advanced disease either with the new agent alone or in combination with other established drugs. The next step in the drug developmental process is often evaluation of the promising new compound in the treatment of early disease (i.e., in the adjuvant treatment setting).

Adjuvant treatment trials with improved disease-free survival as their end point require thousands of patients and years to complete. Historically, signals of primary preventive efficacy among therapeutic agents have been gleaned from adjuvant therapy studies by observing the incidence of new primary tumors (e.g., in the colon or in the opposite breast in patients with early-stage malignancy). Useful information about toxicity is gained from these trials only after tens of thousands of person-years of observation unless the early toxicity observed is either dramatic or severe.

Primary prevention studies with cancer incidence as the end point require many thousands of subjects even when they are conducted in putatively “high-risk” individuals (1). Because of the ethical imperative to do no harm to healthy subjects, the primary focus of prevention drug development has been on safety, with efficacy often being evaluated as an additional primary end point. We have been rigid in our insistence of virtually no toxicity among the agents that we consider for primary risk reduction of human malignancy. For example, the rare risk of endometrial cancer associated with tamoxifen and the slightly higher occurrence of high-grade prostatic malignancy with finasteride have impeded their use in the primary prevention of breast or prostate malignancies, respectively.

The demonstration that a potentially effective preventive agent inhibits cellular proliferation or induces apoptosis, or does both, is a critical first step in identifying promising new preventive agents, and the model proposed by Christov et al. (2) in this issue that evaluates the preoperative response of small, early tumors to a candidate agent is both efficient and ethical in its design. It is likely to identify accurately agents that have promising cancer-preventing potential. This new model will not eliminate the need for large, prospectively randomized clinical trials to evaluate new preventive agents in humans, but it provides a strategy that will quickly reduce the number of agents that need to be considered. It will also identify those drugs with the maximum combination of inhibition of proliferation and induction of apoptosis that can be selected to move forward for additional study. An agent thus identified can be taken to a safety study in a relatively small group of individuals who are at increased risk for the target malignancy, and, after an appropriate demonstration of safety, can be taken to a larger trial with cancer incidence as the primary end point. For approved drugs (such as sulindac, meclizine, or celecoxib reported on by Christov and colleagues) where safety is well established but potential efficacy as cancer-preventive agents is newly realized, the demonstration of antiproliferative or proapoptotic properties in small, early invasive, human tumors can serve as sufficient justification to initiate large, primary prevention trials. Both the U.S. Food and Drug Administration and the U.S. Patent Office should consider the approval of new drugs and the issuance of new patents for approved drugs with additional indications for cancer risk reduction to promote commercial interest in the evaluation and development of agents that would otherwise attract little interest in the business sector.

Although the evaluation of the end points of proliferation and apoptosis requires longer durations of drug administration in humans than in laboratory rats, effects can be seen in weeks rather than months or years of study. This will be crucial when evaluating agents derived from foods that are known to be safe, such as the cruciferous vegetable constituent benzyl isothiocyanate that effectively suppresses growth of cultured human breast cancer cells by causing G2-M phase cell cycle arrest. It also induces apoptosis with a decrease in levels of proteins involved in regulation of G2-M transition, including cyclin B1 and cyclin-dependent kinase 1, induction of proapoptotic...
proteins Bax and Bak, and down-regulation of antiapoptotic proteins Bcl-2 and Bcl-xL (3). Similar apoptotic changes are induced by guggulsterone, a constituent of the Ayurvedic medicinal plant *Commiphora mukul*, in human prostate cancer cell lines characterized by appearance of subdiploid cells and cytoplasmic histone-associated DNA fragmentation caused by apoptosis induction that is not seen in normal prostate epithelial cells (4).

There will be issues related to the durability of the clinical responses reported in a clinical evaluation that uses small tumors as the basis for measuring response, and the emergence of late-appearing toxicities will always be answered only with clinical trials of longer duration. Nevertheless, the proposed model is an effective and efficient screen for rapidly identifying and selecting new agents from a panoply of compounds with promising potential for the reduction of the incidence of prevalent human malignancies.

The AACR Task Force on the Treatment and Prevention of Intraepithelial Neoplasia (IEN) has delineated the relationship between intraepithelial lesions and cancer risk as well as the clinical benefit that can be derived from reducing their burden (5). The AACR IEN Task Force has recommended focusing on established precancers as the target for new agent development. The IEN Task Force proposed several clinical trial designs that provide practical and feasible approaches to the rapid development of new agents to treat and prevent premalignant lesions that mirror the methods used by Christov and his associates. Investigators should embrace these designs as they investigate promising new compounds.

As the cancer burden increases in our aging population, we face a public health imperative to identify the most promising agents rapidly and efficiently and to bring a few, carefully selected agents to large validation trials in high-risk individuals. The sulfur-based compounds from garlic and other food sources, along with many other substances being identified in laboratories that are exceedingly promising as preventive agents, will not be evaluated as therapeutic agents but could and should be evaluated in preoperative studies in humans and taken forward into larger investigations if the antiproliferative and proapoptotic properties they have shown in cell cultures or animal models can be replicated in human tumor specimens. This efficient strategy should be more widely used by investigators seeking to identify the safest, most effective agents for human cancer prevention.

References

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