Assessing Toxicity in Cancer Chemoprevention Trials: The Other Side of the Coin

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Clinical cancer chemoprevention started by studying natural agents presumed to be virtually free of toxicity. Beginning with these agents, however, the history of the major cancer chemoprevention trials has showed that evaluating adverse effects is every bit as important as evaluating preventive efficacy. Clinical trials have taught us invaluable lessons about the nature of serious toxicity in chemoprevention—adverse effects on the primary end point, unanticipated side effects, and anticipated side effects—and about the complex risk-benefit ratios of preventive agents. We now know that there is no free lunch with chemopreventive agents, whether natural or not. This Perspective will discuss the toxicity lessons we have learned and continue to learn from clinical trials of natural and molecular-targeted and other synthetic agents.

Natural Agent Toxicity

The first 20 to 30 years of clinical cancer prevention research focused on interventions with “natural substances,” including vitamins, minerals, fiber, and other dietary constituents. A prime motivation for investigating these agents was the assumption that natural substances and vitamins would be safe. We all knew that chemoprevention agents destined to be used by healthy, at-risk participants must, first and foremost, have few if any side effects. What could be safer than vitamins and micronutrients, many of which have been available “over-the-counter” and are taken by countless people daily?

Clinical investigations of natural agents were supported by the rapidly expanding field of nutritional epidemiology as well as by their presumed safety. Many such studies had shown an inverse relationship between the quality of diet and cancer incidence (1). Improved laboratory techniques extended these studies to include measurements of serum vitamins and micronutrients. These findings corroborated those of the earlier studies: individuals with serum concentrations of nutrients in the lowest quartile or quintile had the highest incidence of cancer. Although these studies have multiple confounders and an association does not mean causality, they provided evidence (along with several in vivo animal studies) supporting the hypothesis that dietary supplementation may decrease cancer incidence. Thus, vitamins and micronutrients became the agents of choice for the first generation of cancer chemoprevention trials. What could be more “natural, intuitive, or holistic” for preventing cancer than to modify the diet or correct a dietary deficiency with a simple supplement?

Unfortunately, this approach had several flaws. It made the broad assumptions that (a) we know the specific constituents of foods that are important in cancer causation and prevention (if indeed there are any!), (b) manipulating the intake of one or more of these constituents will decrease cancer incidence, and (c) intervention for a few years relatively late in preinvasive carcinogenesis can delay or prevent cancer. Although most investigators acknowledged these limitations, they also agreed that the straightforward hypothesis of nutrient supplementation deserved testing. In designing these trials, however, a further assumption was made: “more is better.” Instead of administering supplements to raise serum levels to the highest quartile achieved through an optimal diet (the approach suggested by the nutritional epidemiologic studies), investigators in many cases chose supplement doses that raised serum or body stores from 10 to 20 times physiologic levels. We were blindsided by our underlying assumption that “vitamins are safe.” Instead of testing physiologic doses of supplements to correct an underlying deficiency, we were testing pharmacologic doses.

Rigorous clinical investigation of nutritional supplements as pharmacologic agents was all but nonexistent before the era of chemoprevention. Vitamin therapy was more in the realm of complementary and alternative medicine and was not commonly studied by the medical community. This field did not draw serious laboratory and clinical attention until the late 1970s with investigations of the retinoids vitamin A and its family of derivatives; ref. (2). Other issues also have affected preclinical and clinical investigations of natural agents. Vitamins and most nutritional supplements are not patentable and so are outside the interest of the for-profit pharmaceutical industry. They also are regulated far less rigorously by the Food and Drug Administration and thus have not had the required standard premarket evaluation in animal models or careful phase I/II/III testing in humans required of pharmaceutical drugs, or molecular-targeted and nontargeted synthetic drugs, being developed for therapy. Reports of natural agent toxicity/side effects in the literature are anecdotal or involve accidental overdoses by health enthusiasts.

Another unique aspect of high-dose supplementation with vitamins and dietary constituents must be considered. These are not synthetic foreign compounds but are normally occurring dietary constituents. Our mammalian, human physiology has evolved over millions of years with concentrations of these compounds within a narrow range that is sometimes deficient because of nutritional deprivation, but rarely in excess. They are in our daily foods and are present in changing amounts from fetal development until death. They are required for optimal cellular function and normal growth and...
development. Whereas clinical deficiency syndromes are well known, syndromes resulting from excess intake of these compounds were rare before the era of supplement use. Little is known about the dose/response/toxicity relationships of many natural agents.

Large, long-term, placebo-controlled prevention trials in both cancer and cardiovascular disease testing vitamin and mineral supplementation provided a setting where, for the first time, these agents were carefully evaluated clinically. Prevention trials that can randomize tens of thousands of healthy individuals between an active intervention and placebo give unprecedented statistical power for finding small differences between treatment groups. Given this degree of scrutiny, it should not be surprising that the first generation of phase III trials of high-dose vitamin supplementation found unexpected adverse effects. The Alpha-Tocopherol and Beta-Carotene study and Carotene and Retinol Efficacy Trial were lung cancer prevention trials that studied β-carotene and α-tocopherol and β-carotene and retinol, respectively; both trials found a statistically significantly increased incidence of lung cancer and cardiovascular disease (likely due to β-carotene; refs 3, 4). A trial testing the retinoid 13-cis retinoic acid on the incidence of second primaries in patients with stage I lung cancer found a harmful effect of the drug in active smokers (5), and multiple trials of α-tocopherol have found an increased incidence of heart disease and mortality (6, 7). A colon polyp prevention trial of folate supplementation found a 67% increased risk of what the authors described as “advanced lesions” (8). Last, a recent meta-analysis of mortality in 68 randomized trials of “antioxidant supplements” found increased mortality associated with taking the supplements (9). It seems that increasing the dose of a vitamin (10 or 20 times the recommended daily allowance) is similar to prescribing a 10 times dose of almost any drug; efficacy may not improve and harm may ensue. These lessons must be remembered when designing trials of the current generation of dietary constituents, such as certain carotenoids, calcium, vitamin D, resveratrol, and curcumin.

With these unexpected toxicity results, the first 30 years of clinical chemoprevention research with dietary constituents have been enlightening. We have learned that vitamins/micronutrients at high doses should be regarded the same as any other drug; they are pharmacologically active agents, have a dose-response relationship, and can cause harm. We have learned that these compounds have little cancer preventive activity in a well-nourished, nondeficient population and can increase cancer incidence when administered in supraphysiologic doses. Our working hypothesis was that these agents could decrease cancer incidence with few if any side effects. We were wrong on both counts.

**Synthetic (Molecular Targeted) Agent Toxicity**

**Selective estrogen receptor modulators, 5α-reductase inhibitors, and cyclooxygenase-2 inhibitors**

Although considerable interest in natural agents for cancer prevention still exists, the use of molecular-targeted or nontargeted pharmaceutical agents is gaining attention. Trials with this group of agents were initiated with the National Surgical Adjuvant Breast and Bowel Project–led P1 study of the selective estrogen receptor modulator tamoxifen in women at increased risk for invasive breast cancer (10). Studies in a similar population followed with the selective estrogen receptor modulator raloxifene (11) and a Southwest Oncology Group study of the 5α-reductase inhibitor finasteride in men at increased risk for prostate cancer (12). As opposed to the trials with micronutrients, these selective estrogen receptor modulator and 5α-reductase studies have produced significant reductions in cancer risk, but not without serious adverse effects—mainly endometrial cancer with tamoxifen and possibly increased high-grade prostate cancer with finasteride—that have seriously limited their clinical acceptance for cancer prevention.

Targeted drugs currently available in the clinic and potentially useful for prevention have completed preclinical and phase I/II/III testing and in many cases have years of clinical use and safety evaluation. Their adverse and molecular effects frequently are well described, albeit not in healthy populations but in patients with a targeted disease. By selecting drugs that have a long history of clinical use and which target specific signaling pathways, investigators believed they could better predict and reduce the adverse events. Placebo-controlled prevention trials enrolling tens of thousands of healthy volunteers, however, subject these agents to rigorous evaluations, as undergone by natural agents. In such trials, previously unrecognized side effects (not seen in smaller, shorter-term trials in a target disease) may become apparent. For a prime example, smaller, shorter trials in arthritis and familial adenomatous polyposis gave no hint of an unexpected increased incidence of cardiovascular events and mortality found recently with cyclooxygenase-2 inhibitors in large-scale cancer and other prevention trials (13). It is important to remember that differences in treatment and placebo may not always be as obvious as cardiovascular deaths, hypertension, or clinical diabetes but can be as subtle as an increase in mean blood sugar or blood pressure. From the public health perspective, modest changes such as these may be important when treating healthy population. Therefore, a careful evaluation of side effects is imperative even when studying approved pharmaceuticals with a known adverse effect profile. In the context of prevention, less common adverse effects may have major effects on the clinical utility of an agent.

**Difluoromethylornithine**

In this issue of the journal, McLaren and colleagues (14) report their comprehensive assessment of difluoromethylornithine (DFMO)-associated ototoxicity in a phase III clinical trial of DFMO plus sulindac. They previously reported that this combination had marked activity in preventing sporadic colorectal adenomas with few side effects (15). DFMO is an irreversible inhibitor of ornithine decarboxylase and is a potent inhibitor of colon carcinogenesis in animal models (16). It was initially introduced as a cancer therapeutic agent but had limited activity and significant ototoxicity. Sulindac, a nonspecific cyclooxygenase inhibitor, has long been available in the clinic as an anti-inflammatory agent. It too had been shown to be a potent inhibitor of colon polypl formation before the phase III trial (17).

The authors were well aware of the importance of evaluating the incidence and severity of side effects in the context of a chemoprevention trial. DFMO was given for 36 months at a dose high enough to affect the target enzyme and low enough, it was hoped, to avoid unacceptable ototoxicity. (Sulindac also...
was given at a relatively low dose.) The trial had an imbedded protocol to carefully evaluate the longitudinal effect of treatment on hearing. They now report an average hearing difference of 0.50 dB and, at 6 or more months after treatment, a 1.08 dB difference in hearing threshold between the active treatment and placebo groups. These findings were not statistically or clinically significant. At least a 15 dB hearing loss from baseline was detected in 9.3% of patients on DFMO plus sulindac versus 2.9% on placebo (P = 0.02). Although small and not clinically perceptible, these findings were indeed real (albeit detectable only through carefully planned testing).

McLaren and colleagues are to be congratulated for their careful study of these agents. We now know that 3 years of treatment with low doses of DFMO and sulindac can cause detectable ototoxicity. As the clinical evaluation of these agents continues, it will be important to closely monitor participants for adverse effects. Like modest effects on blood sugar or blood pressure, subtle low-dose DFMO effects on hearing in the long term may have important implications for the public health. Regardless of the potential to reduce colon polyp incidence, only a full understanding of the range and severity of side effects will enable us to determine the clinical benefits of this combination for colon polyp prevention.

Translational Toxicity Assessment

Preclinical toxicity screening based on the known mechanism(s) of a drug would be extremely helpful in selecting drugs for clinical testing and planning the evaluation of adverse effects. DFMO offers a paradigm for such assessments.

Dramatic ototoxicity of DFMO seen in phase I therapy trials stimulated translational assessments of this side effect (18–20) prior to the phase III DFMO-related ototoxicity assessments reported by McLaren and colleagues (14). Studies of DFMO and certain other ornithine decarboxylase inhibitors suggested toxic effects on hearing (18). Therefore, approaches for reducing DFMO ototoxicity include lowering the dose (as was done in the phase III DFMO plus sulindac trial; ref. 15), developing analogues with less ototoxicity (19, 21), and developing new agents aimed at targets related to (e.g., downstream) ornithine decarboxylase.

Studies imbedded within the phase III DFMO-sulindac trial suggest that a subset of patients with higher ototoxicity risk seems to be defined by single nucleotide polymorphism affecting about 5% of Caucasians (22). If confirmed in larger studies, this work suggests that another strategy for circumventing DFMO toxicity would be the use of pharmacogenomics to identify participants at risk for ototoxicity and either exclude them or at least counsel them on their risk for toxicity.

Conclusions and Future Directions

The large, placebo-controlled prevention trials have served an important role for the public and medical community. Whether for prevention or therapy, many drugs and vitamins and minerals previously thought to be safe can have undesirable effects in carefully conducted studies. Our knowledge is only limited by how closely we interrogate participants [as done comprehensively by McLaren and colleagues (14)] and the sample size and duration of a trial. Deciding to prescribe or take any drug should always include a careful consideration of the risk-benefit ratio. Tolerance for adverse effects differs widely and represents one of the prime differences in selecting an agent for prevention or therapy. For cancer prevention, the bar on tolerability is set high. Although all participants of a prevention trial are exposed to potential toxicity, only a small percentage (depending on the level of risk) experience the potential benefits. We should move forward with the study of potential chemoprevention agents, but each intervention should be carefully studied in phase II and III trials for efficacy and adverse effects. Only agents having strong evidence of efficacy and few if any side effects should be advanced to a large-population confirmatory phase III trial. This process of clinical screening can be greatly enhanced by preclinical/translational assessments of known or suspected toxicity, as has been done by McLaren and colleagues and others in the case of DFMO-related ototoxicity (18–22). Unexpected adverse cardiovascular effects have been quite prominent in past chemoprevention trials and so should be evaluated early in chemoprevention drug development. When planning confirmatory clinical phase III trials, side effect and efficacy evaluation must have equal importance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


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