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Editorial

EDITORIAL

What to Do With the Participants/Patients in Phase III Clinical Cancer Trials That Have Been Stopped by the FDA

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The two companion papers in this issue of the Journal are unique in that they address one way to salvage useful information when a drug is declared persona non grata by the US Food and Drug Administration (FDA), thereby obviating continuation of its use in a clinical trial (1,2).

But first, before launching into the major thrust of this editorial, some historical background is needed for the broader audience that is interested in the general topic of clinical trials. Starting in the early 90s, a widespread interest in specific cox-2 inhibitor observational studies and promising mechanistic data held the promise that high specificity would lead to enhanced efficacy and preclude some of the toxicities experienced in patients receiving nonsteroidal anti-inflammatory drugs (NSAIDS) (3). A large number of randomized four-arm 2x2 chemoprevention trials were launched in the late 90s and early 2000s in patients with precursors to colorectal cancer.

In parallel, an interest in supplemental selenium for the prevention of prostate cancer, based on promising observational results and supportive mechanistic data, led to the launch of several phase III randomized selenium trials in patients at risk for prostate (4) and other cancers. At the time that concern was raised about the cardiovascular side effects of cox-2 inhibitors, the selenium trials were ongoing and too early to analyze. An excess of serious bleeding episodes was detected in the cox-2 inhibitor trials, and randomized trials involving this class of compounds were stopped by the FDA (5).

This editorial does not address design or other issues related to the original trial , nor does it focus on important interpretations when trials are stopped, such as the interpretation of clinical trials, particularly prevention investigations that are stopped early or challenges to data monitoring committees when regulatory authorities intervene (6,7).

What to do with all these patients?

In prior stopped or suspended trials, patients simply came off the trial and little to no useful information was gleaned. A simplified flow diagram of the follow-up trial is provided in Figure 1 to assist the reader in following the narrative. Complex flow diagrams of patients are provided in the manuscripts.

These investigations took a novel approach to this question, and my comments are focused on the information about outcomes and toxicities gained by morphing the stopped trial to a suspended one followed by a unique approach and a follow-up trial. After a brief hiatus, and with FDA, National Cancer Institute, and institutional review board concurrences, those patients who were in the cox-2 inhibitor (celecoxib in this trial) plus selenium arm or the selenium arm alone were offered selenium, and the majority of eligible patients were rerecruited to the follow-up described (1). Patients in the celecoxib arm only and those on the combination were offered follow-up by surveillance, and many received a colonoscopy (2).

Now let's examine here the overall conclusion of these two papers.

First, the carefully stated conclusion that "selenium supplementation is not recommended for preventing colorectal adenomas in selenium replete individuals" (1): The design and analysis of this follow-up study in which selenium was restarted in participants who had been in the selenium only or the selenium plus celecoxib arm (now sans celecoxib) were impeccable. Although the overall results indicated that selenium did not affect overall recurrence of adenomas, a planned subgroup analysis of participants with advanced adenoma at baseline showed that adenoma recurrence was reduced in patients receiving selenium. Toxicity analysis demonstrated no difference in new-onset type 2 diabetes (T2D), although subanalysis detected a

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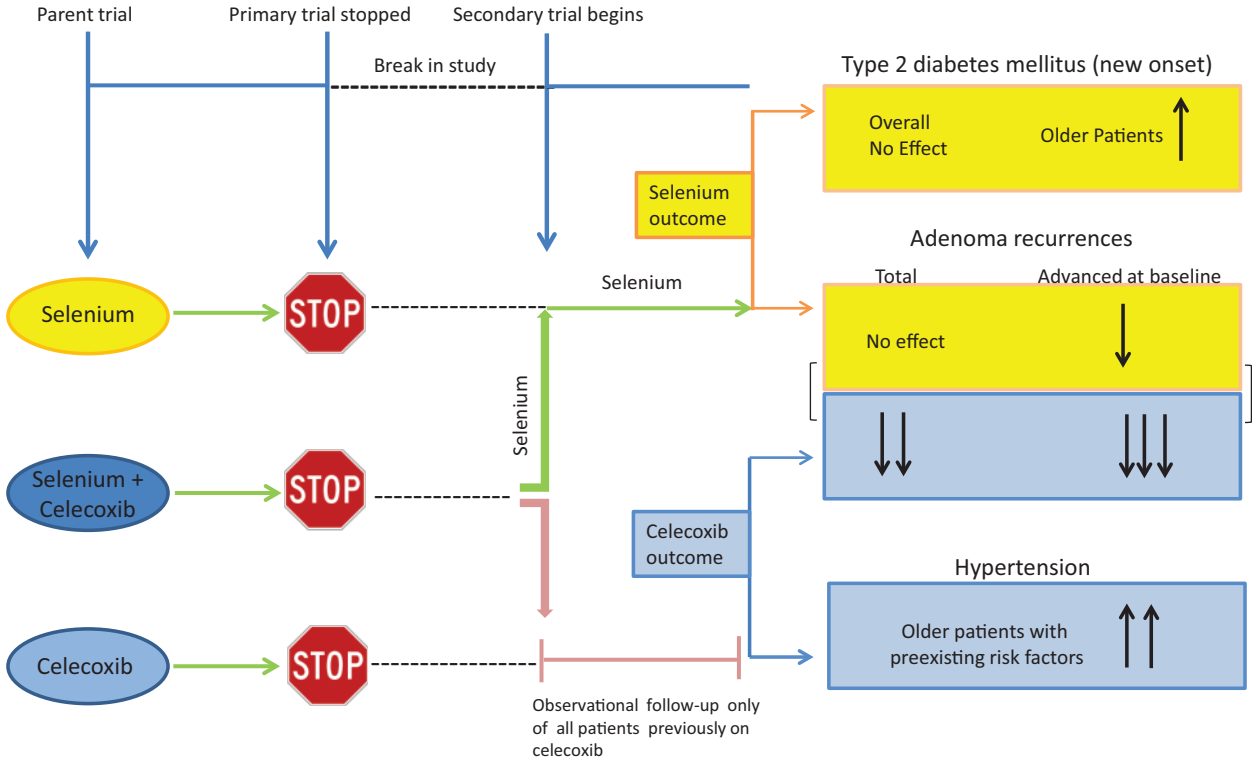

Figure 1. Simplified flow diagram with qualitative assessment of outcomes and toxicities. ↑ ↓ = some increased or decreased benefit or harm; ↑↑ ↓↓ = significant clinical benefit with increase in favorable outcome and neutral or decreased change in toxicity; ↓↓↓ = significant clinical benefit with increase in outcomes and marked decreased to no toxicity.

statistically significant increase in new T2D in older individuals taking selenium, as has been demonstrated in a meta-analysis of side effects of randomized control trials of selenium (8).

Second, "Limited duration celecoxib presents adenoma recurrence in patients with prior high-risk adenomas, in whom strategies to minimize cardiovascular toxicity might be feasible" (2). Overall the extensive analysis of the outcomes of the placebo and celecoxib arms supports this very limited conclusion as even after being off study for 12 months, fewer participants in the two prediscontinuation celecoxib arms had fewer overall and advanced adenomas on their 12-month colonoscopy in the resumed follow-up, with the effect being greatest in participants with previous advanced adenomas. Disappointingly, however, follow-up of patients previously receiving celecoxib demonstrated a substantial risk of hypertension in patients who had preexisting cardiovascular risk factors.

These two manuscripts present extensive and complex statistical analyses that merit review and discussion in a specialty journal. In fact, one may argue that a day-long symposium on the implications for more effective management and utilization of stopped or suspended randomized prevention (or treatment) trials would be a useful outcome: particularly as the field is at a major tipping point with very few promising compounds on the horizon, the continued nonadoption of several effective chemoprevention compounds including tamoxifen, the general disinterest of US-based pharmaceutical companies in prevention, and the emerging role of precision medicine (and the promise of precision prevention). The recent analysis and publication of several long-term (20+ years) follow-up studies of low-dose aspirin in lowering the incidence of many cancers suggest that trying to identify other effective natural products should continue, but in a more sophisticated, holistic, and integrated manner than that followed to date (9,10). After all, acetylsalicylic acid represents the most successful compound to evolve from a prototypical natural product and has been a commercial product since 1899 (11). Or perhaps we should just drink willow bark tea as our ancestors have done for over 2000 years (12)!

Notes

Dr. Meyskens is Co-Founder and Medical Advisor to Cancer Prevention Pharmaceuticals.

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