Cancer Prevention Research

Commentary

See related article by Armstrong, et al., on p. 410

Not Significant But Important

James L. Mulshine[1] and Frank G. Ondrey[2]

Abstract

Armstrong and colleagues report the result of a large Phase IIb randomized trial evaluating the effectiveness of a preparation of the Bowman Birk Inhibitor compared with an oral placebo in reversing the extent of oral leukoplakia as measured visually by pathology or a battery of intermediate end points. In this editorial, we review the report of this negative clinical trials result to highlight the clinical trial process used in evaluating this previously promising chemoprevention agent. Publishing this report is important to address concerns with publication bias. The challenges in running a chemoprevention trial are reviewed with suggestions to enhance progress going forward. Conceptually, developing drugs to intercept the early stages of carcinogenesis is very attractive, but progress in this area has been slow. Two opportunities to overcome this reality are discussed. These measures include the broader use of neoadjuvant, window-of-opportunity trials with new candidate chemoprevention agents to get more textured information about the mechanistic impact of the drug exposure in previously untreated early tumor tissue. In addition, we discuss the use of new intermediate end point markers such as with optical imaging tools to obtain a more objective and quantitative assessment of drug response. *Cancer Prev Res; 6(5); 371–4. ©2013 AACR.*

Introduction

While oral cancers are not a major cause of cancer death, these cancers often cause profound debility owing to their strategic locations. Treatments to date are frequently associated with both considerable pain and functional compromise in regard to swallowing as well as phonation. Recurrent disease is a significant problem due to field cancerization (1). Despite a number of attempts, surgical management still remains the main tool for managing this condition. Therefore, there is a strong impetus to improve clinical outcomes for this disease.

The early phase of this disease provides a compelling target for therapeutic research, as leukoplakia is a well-recognized precursor with a consistent fraction of lesions progressing to invasive cancers. Previous chemoprevention trials have not identified effective tools to reliably arrest the progression of leukoplakia. However, experimental data and a Phase Ia chemoprevention trial suggested favorable activity for an oral soy extract, Bowman Birk Inhibitor compound in oral cancer (2).

On the basis of this promising result, a large Phase IIb randomized trial was conducted. As reported in this issue, Armstrong and colleagues evaluated 2 arms: one with a preparation of the Bowman Birk Inhibitor and one with an oral placebo (3). As reported, they found both arms to be equally efficacious in reversing the extent of oral leukoplakia as measured visually by pathology as well as with a battery of intermediate end points. This trial result raises a number of important issues.

First, this trial is being reported in a major cancer journal despite being a negative trial result. This can be readily justified as the trial was carefully designed and executed. The narrative outlining the trial methodology is clearly and logically presented and so this information will be appreciated by subsequent researchers attempting to define an optimal process for conducting an oral cancer chemoprevention trial. This reporting also addresses concerns about introducing bias by only reporting positive trials.

The conduct of this trial was also hindered by concerns about loss of potency of the experimental agent in the course of storage (3). The use of the Bowman Birk Inhibitor compound is underpinned by a mechanistic hypothesis related to objective inhibition of serine protease activity as documented by an established assay. Quality control assays suggested diminution in drug potency across the very long 11-year study duration especially from the early to late phase of the study. Provisions to avoid such methodologic issues are essential, but the existence of such infrastructure for chemoprevention is challenging. The authors suggest considering alternative designs to accelerate the completion of such trials.

One alternative design approach that provides enormous amount of mechanistic feedback is the "Window-of-Opportunity" neoadjuvant drug trial (4). The process with conducting a window trial is to give a brief course of drug (usually about 3 weeks) while the patient is awaiting

Authors' Affiliations: [1]Department of Internal Medicine, Rush Medical College, Rush University, Chicago, Illinois; and [2]Department of Otolaryngology, University of Minnesota Medical Center, Minneapolis, Minnesota

Corresponding Author: James L. Mulshine, Department of Internal Medicine, Vice President Research, Rush University, 1735 West Harrison Street, Suite 206, Chicago, IL 60612. Phone: 312-942-3589; Fax: 1-312-563-3377; E-mail: james_l_mulshine@rush.edu

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curative resection for a newly diagnosed but potentially curative-sized tumor. Typically, serial phlebotomy, primary tumor biopsy, and quantitative imaging study are conducted at baseline, and then the window of drug exposure is delivered. This is followed by immediate preoperative quantitative imaging after which the patient undergoes curative-intent surgery. This process provides serially acquired blood samples, tumor tissue, and quantitative computed tomography (CT) scans (4). These materials can then be comprehensively evaluated. The baseline tumor tissue allows characterization of the status of the molecular signaling. The status of the relevant pathway can then be compared with the tumor tissue resected after the 3-week drug exposure. In this way, the impact of that drug exposure on the indicated pathway can be evaluated. This approach allows for a much more integrated understanding of the actual impact of a new drug in actual patients with lung cancer while also allowing evaluation of compensatory or other tumor or host responses. With the completion of several of these trials, one could cross analyze the results to have a granular composite picture of what is driving tumor progression for oral carcinogenesis.

The first example of this neoadjuvant window approach being done successfully with lung cancer was published by Altorki and colleagues (5). In a related study by Nikolinakos and colleagues, biomarkers from tissue and serum analytes significantly correlated with activation of angiogenic mechanisms frequently inhibited by the study drug, pazopanib (6). The correlative biomarkers from tissue and serum analyses were published by Nikolinakos and colleagues who showed the significant activation of angiogenic mechanisms that was frequently inhibited by the study drug, pazopanib. Quantitative CT imaging revealed a correlation of tumor shrinkage with inhibition of candidate members of a panel of molecular angiogenic markers as well as comparable changes in expression profiling. This is a new trial structure that may provide an extraordinary amount of mechanistic information, which can be useful in subsequent science-driven, targeted drug development (4).

The neoadjuvant, window trial design used in early-stage oral cancer management is an important opportunity to obtain relevant information about candidate drugs that may also have chemoprevention activity. This relates to the fact that the tissue surrounding the resected tumor would also include variable amounts of tissue caught up in aspects of field cancerization (1). In this fashion, information may be derived as to the drug response to early previously untreated cancer cells as well as premalignant clonal populations.

Can we Accelerate Accrual to Chemoprevention Trials?

Efforts to address the issues with slow accrual to chemoprevention trials have been published (7), but the issues are multiple and complex. In the current study, the authors outline a concerted effort to consider more than 500 subjects that were identified as potential candidates for this study. After appropriate characterization, only 17% (89 subjects) of the candidates ultimately were evaluable for the study analysis (3). This challenge has been a consistent feature in the conduct of chemoprevention trials in general but for leukoplakia trials in particular. New approaches are essential if this field is to mature at a rate to allow meaningful progress. A recent publication of a workshop convened by the Institute of Medicine explored the issues associated with more rapid progress with clinical trials in general (8). However, there is even greater complexity embedded in the timely completion of a chemoprevention trial. For leukoplakia trials, more efficient provisions for rapid multi-institutional participation are crucial.

A barrier in this regard for chemoprevention trials is the obligatory need for intermediate end points to help elucidate the chemoprevention response. As there are no validated intermediate end points, defining the right assays to determine the success of the study agent involves customization for every trial. Second, providing access to robust, accurate assays at every trial site can also be challenging. This is a particular problem for leukoplakia trials since acquiring sufficient assay target tissue is often difficult.

There has been some progress with optical spectroscopy or autofluoresence screening that potentially provides a new class of tool that is particularly suited for the economical and objective assessment of the oral epithelium. The introduction of quantitative tools that can provide a more standardized metric for the chemopreventive effect of experimental agents may improve the reliability of investigational drug assessment in this context (9–11). From a strategic perspective, it may be appropriate to now ensure the integration of optical spectroscopy tools within the conduct of relevant oral cancer chemoprevention trials to accelerate progress in this field.

Active Placebo?

The authors speculated that the placebo used for this study may have beneficial chemopreventive effects independent of the mechanisms of serine protease inhibition (3). The placebo arm was found to have a major response rate of 30%. Although this may be the correct explanation, we would also point out that in an oral leukoplakia study we reported in 2004, the placebo arm using a vehicle mouth rinse was associated with a major response rate of 32% (12). In that report, we also speculated about the possibility of the placebo actually mediating a favorable chemopreventive effect, but the stronger possibility in both cases is that the variable natural history of oral leukoplakia makes assessment of drug effect difficult. Furthermore, the relationship between the change in the area of leukoplakia involvement and the eventual progression of this precursor lesion to invasive oral cancer is not fully defined. This reality is an important consideration to address in future leukoplakia chemoprevention trial designs.

An issue that emerged in the course of our study was the extent of microheterogeneity inherent in the many different

types of tissue surfaces that comprise the topical delivery of drug throughout the oral cavity. Percolation of drug across all of these varied surfaces may be a major problem in attempting to reverse intraepithelial neoplasia. We reviewed the experience with hyaluronan formulations, which may allow more favorable partitioning across chronically injured epithelial surfaces and therefore result in more favorable drug retention on cells with upregulated CD44 receptors (13–16).

It has been nearly 30 years since the first phase II clinical trials on oral leukoplakia chemoprevention were published, which ushered in prospective studies to reduce oral cancer burden through interventions in this high-risk condition. Over the course of 2 decades, several studies with retinoic acid derivatives were carried out with the ultimate large trial with isotretinoin for the prevention of secondary malignancies proving negative (17–18).

There are several ongoing strategies for oral premalignancy treatment. There is a longstanding interest in chronic inflammation and prostaglandin production during oral carcinogenesis. Further studies have noted COX-2 overexpression as a common feature of oral cancer progression (19–20). Therefore, strategies targeting NF-κB and cyclooxygenases have been used in recent or ongoing clinical trials. The nonsteroidal agent sulindac is presently in use in an ongoing clinical trial (NCT00299195).

Another strategy for leukoplakia treatment involves the PPARγ-activating drug pioglitazone. This is a relatively safe agent for type II diabetes treatment that activates the nuclear receptor PPARγ, which has been shown to heterodimerize with RXRα in a variety of malignancies. This study is open and ongoing, but accrual with this trial is slow and a great rate of accrual is necessary as well. Further accrual information regarding the ongoing pioglitizone chemoprevention trial is available at http://www.clinicaltrials.gov/ct2/show/NCT00951379?term=ondrey&rank=3 (21).

A final issue to consider is the length of time required to evaluate this agent. The mechanistic activity of the Bowman Burk Inhibitor was elucidated in the mid 1980s. The initial positive chemoprevention trial was reported in 2000. The current trial result, in a setting of a frequently incurable disease process is coming out over 25 years after the initial scientific observation. As carefully outlined in the current report, a range of significant challenges impeded the progress of this effort with the Bowman Burk Inhibitor but would more generally impede the successful development of any new chemoprevention agents. These barriers were identified and reviewed at the National Cancer Institute in 1995, and while dramatic progress has been made in many other cancer research areas, we have made little substantive progress in tackling those major barriers to advance chemoprevention research (22).

However, the strategies outlined in the National Research Council's "Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing an Agenda for 2020: Workshop Summary" contain many productive and feasible ideas that have direct relevance to accelerating chemoprevention research (8). A productive activity at this time would be to extend that general Workshop dialogue into the specific realm of chemoprevention research and define how the proposed strategies for transforming clinical trials can be adapted, including support of neoadjuvant, window trials, optical spectroscopy, and other emerging tools, to accelerate the pace of chemoprevention drug development and clinical evaluation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.L. Mulshine
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.L. Mulshine, F.G. Ondrey
Writing, review, and/or revision of the manuscript: J.L. Mulshine, F.G. Ondrey
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F.G. Ondrey

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