Pioglitazone, Nuclear Receptors, and Aerodigestive Prevention

Frank G. Ondrey

There has been intense interest in nuclear receptor targeting for cancer prevention. With the exception of estrogen antagonism in breast carcinoma there has not been widespread adoption or success of this strategy in clinical cancer prevention. Keith and colleagues have performed a careful study, which utilized the PPARγ nuclear receptor agonist, pioglitazone, a common type 2 diabetes agent, in subjects at risk for lung carcinoma. Although the results are not promising with this strategy, the study provides evidence for feasibility accrual and biomarker strategies that could be utilized to gain additional insight in future trials.

There are over 100 nuclear receptors and cofactors (also known as orphan receptors). They have been a preclinical and clinical target for cancer prevention for over 30 years. The preclinical literature is replete utilizing antiestrogens, antiandrogens, vitamin D metabolites, and vitamin A derivatives in prevention scenarios. Classic nuclear receptor hetero-dimerization patterns produce myriad transcriptional effects after nuclear translocation and receptor activation. Furthermore, they may exhibit casual binding partner arrangements to produce additional exploitative anticarcinogenesis effects. As one example, complex nuclear receptor interactions may nudge immature cells toward differentiation and apoptosis while simultaneously producing anti-inflammatory effects in immunoregulatory cells of the milieu in target tissues (1–3). However, they may exhibit untoward effects in nontarget organs, which cause toxicities thus limiting their utility in clinical cancer prevention. Specific agents, particularly retinoic acids and their congeners have been tested in a large series of aerodigestive cancer prevention clinical trials for over 30 years, yet there efficacy has not been established to an extent that allows their common clinical use in a prevention setting. In all cases the side effects of first-generation retinoids on nontarget tissues (e.g., producing hypertriglyceridemia) caused dose reductions as clinical trials progressed to an extent where biologically important activity was lost and clinical trials were negative (4). In aerodigestive cancer prevention, all studies failed by the phase III level. However, retinoid use still continues in some advanced cancer settings where higher toxicity is deemed acceptable (5).

PPARγ activators like, thiazolidinediones (specifically pioglitazone), are better tolerated and less toxic, so they represent a strategy where PPARγ and retinoid X receptor heterodimers preclinically prevent carcinogenesis progression with acceptable toxicity (6). This has been a typical rationale for utilizing thiazolidinediones for aerodigestive cancer prevention in clinical studies.

In this study, Keith and colleagues performed an exceptionally well-designed double-blind placebo-controlled clinical trial of the PPARγ activator pioglitazone in a high risk population for lung cancer. Current and former smokers underwent bronchoscopy to establish endobronchial dysplasia, and were treated with 30 mg daily pioglitazone for 6 months. At the conclusion of treatment the subjects were reevaluated for response with bronchoscopy. Cell proliferation indices, dysplasia reversal, and reduction of inflammatory indices were principal endpoints in the study. The results of the study did not demonstrate meaningful improvements in histology of the pioglitazone-treatment group, however former smokers with high degrees of dysplasia exhibited trends in improved histology. There were some improvements in an inflammatory index with treatment as well, particularly those with mild inflammation at baseline. The pioglitazone group also exhibited a decrease in proliferative index that trended toward statistical significance ($P = 0.077$) but was likely without biological relevance in this population. In sum, the trial was not overwhelmingly positive with significant utility only occurring in a small subgroup of the cohort.

Thiazolidinedione drugs have continued to be in use for aerodigestive clinical trials based on promising preclinical studies. They have an acceptable safety profile, although there is indeed a “black box warning” for
occurrence of fluid retention and congestive heart failure that can occur in approximately 3%-4% of diabetics on these agents. There is also a second warning for potential increases in bladder cancer that can occur in diabetics taking such agents in long term. Keith and his colleagues found acceptable toxicity with 30 mg daily dosing of pioglitazone for 6 months. Their study group contained patients with the most advanced preneoplasias, as they might portend the greatest cancer risk. They found acceptable Common Terminology Criteria for Adverse Events grade toxicities in the study population.

There are many difficulties with executing these trials and Keith and colleagues were able to target patients in their practice that have high clinical trial accrual and high compliance. This is laudatory. Nonetheless, it often takes several years to complete such a trial and perform all necessary primary and secondary analyses. Given these constraints, it is important to ponder mechanisms to perform such intervention studies while gaining maximal information about the preneoplastic condition and its natural history while gathering improved understanding of the agents and their effects. One issue is that pharmacodynamic endpoints that are hypothesis driven and reasonable are sparse in these study populations, and proliferative indices employing markers like Ki 67 may be more suitable in circumstances that are more kinetic and with higher cell growth/turnover (i.e., cancer). Cell proliferative markers require further analyses in these prevention settings. None of these have been validated in a preclinical setting in aerodigestive malignancy.

These trials provide an opportunity for preventive oncologists to dissect aerodigestive trial strategies, markers, and mechanisms to improve odds with subsequent trials. First, to glean more information from biopsy specimens, additional techniques should be employed in subsequent prevention trials. For example, multiplexed biomarkers [NanoString, RNA-seq, high throughput immune histochemistry (IHC), etc.] could (and are) being utilized in such trials to discover more about “on versus off target effects of the agents,” particularly in those selective patients that have excellent responses or progressive disease. In this trial, 30 mg pioglitazone was the dose chosen, yet maximal FDA dose for the agent is 45 mg daily; would there be additional benefit in the prevention setting of increasing doses of nontoxic agents above the FDA-approved dose? The road to feasibility may be a difficult regulatory issue, but currently there is a dismal unmet need for aerodigestive prevention agents. One way to circumvent the oral dosing to boost bioavailability could be targeted delivery with aerosols, nanoparticles, mucoadhesive patches, and gels, mouthwashes, etc. to maximize tissue effects at accessible anatomic sites like the mouth or tracheobronchial tree (7–9). These strategies would all involve much additional research to examine efficacy preclinically, but again would offer opportunities in this prevention setting. There is interest the transdermal tamoxifen derivative (endoxifen) for breast cancer prevention, which may improve tissue levels of the agent while circumventing systemic toxicity. In addition, combination prevention with multiple agents, perhaps one orally and the other by aerosol, could be an additional strategy. Currently, combination chemoprevention strategies are being explored with FDA-approved drugs. Actoplus Met, a metformin pioglitazone combination agent is being studied in a window-of-opportunity trial in oral cancer (ClinicalTrials.gov Identifier: NCT02917629). Other combination prevention strategies have been successful in colon cancer (10), so there is a precedent for combination prevention with multiple agents.

In any case, nuclear receptor chemoprevention strategies involving are now in forth decade and we still lack an effective agent for aerodigestive prevention. Strong consideration should be given to examining high throughput biology in these studies, while strengthening tissue targeting with direct epithelial delivery. NCI programs like PREVENT (https://prevention.cancer.gov/major-programs/prevent-cancer-preclinical) can be very helpful in advancing strategies, but interesting preclinical results and strategies are not translated often enough to target populations due to resourcing and exceptional difficulty in rapid accrual.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Received July 9, 2019; revised August 2, 2019; accepted August 2, 2019; published first September 19, 2019.

References


Cancer Prevention Research

Pioglitazone, Nuclear Receptors, and Aerodigestive Prevention

Frank G. Ondrey


Updated version

Access the most recent version of this article at:
doi:10.1158/1940-6207.CAPR-19-0341

Cited articles

This article cites 10 articles, 5 of which you can access for free at:
http://cancerpreventionresearch.aacrjournals.org/content/12/10/641.full#ref-list-1

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, use this link
http://cancerpreventionresearch.aacrjournals.org/content/12/10/641.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.