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Author
Meyskens, Frank L, Jr

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Commentary

American Society of Preventive Oncology Distinguished Career Achievement Lecture 2006—Enjoy the Journey: The Long and Winding Road of Chemoprevention Agent Development

Frank L. Meyskens, Jr.
Chao Family Comprehensive Cancer Center, University of California, Irvine, California

The Spring Years: The Early Days

My career in chemoprevention derived from an attempt to find a better treatment for cutaneous malignant melanoma (1). This led me to the exploration of retinoids as therapeutic modalities in a number of malignant conditions with the identification of activity in several epithelial malignancies (2-5), particularly squamous cell carcinoma and peneplastic lesions of the skin (3, 4), as well as in cutaneous T-cell lymphoma (6). These positive results provided strong clinical support for our own subsequent work in chemoprevention of cervical intraepithelial neoplasia and for those investigators who later undertook chemoprevention trials of retinoids in oral leukoplasia and secondary head and neck cancers (7, 8) as well as for the prevention of squamous cell cutaneous cancers and actinic keratoses (9-11).

In the late 1970s, there was also a lot of interest in the differentiation effects of retinoids on leukemic cells. An interesting trial of high-dose vitamin A in patients with chronic myelogenous leukemia (Southwest Oncology Group 79-84) was started, and in 1994, the results were finally reported. A substantial increase in relapse-free and total survival was evident (12), but more targeted therapy was being developed that eventually led to Imatinib (Gleevec). Whether retinoids and Imatinib should be combined is probably worth pursuing at an investigational level as drug resistance seems to occur in many patients.

In a memorable Gordon conference in 1978, I met Michael Sporn. We had a lengthy conversation, and my interest in chemoprevention was sparked. At that time, the gynecologic group at the University of Arizona was very strong, leading to an interest in the potential prevention of cervical cancer. As we wished to avoid the systemic toxicity of retinoids, and concern about teratogenic effects was high, we decided to develop the retinoid h-trans-retinoic acid and to deliver it to several important lessons:

- Developing chemoprevention agents is hard work.
- Modesty efficacy alone is not enough to engender acceptance in the medical community.
- Even fairly mild toxicity is a deal breaker.
- Biomarkers needed to be developed that inform and hasten the process of developing chemoprevention compounds into drugs (ref. 20 for one of the earliest discussions of this topic).
- The field of chemoprevention was, at that time, in the process of separating into public health (low dose, no toxicity whatsoever) and medical approaches (acceptable dose, toxicity proportionate to risk).
- Again, at that time, intraepithelial neoplasias were being identified as important targets for chemoprevention although the issue did not surface widely until many years later (21).

The Summer Years: Difluoromethylornithine and Bowman-Birk Inhibitor Concentrate

The lessons learned in the early years coincided with my move from the University of Arizona to the University of California, Irvine in 1989. After much internal debate, I decided to leave the retinoids behind, including two Program...
Projects (a moment of temporary insanity). We then set out to develop chemoprevention agents that were nontoxic and efficacious. Our first choice was difluoromethylornithine. This compound was rationally developed as an inhibitor of ornithine decarboxylase, the key enzyme in polyamine synthesis, and showed great promise in in vitro therapeutic models. We and others were, however, unable to show significant anticancer activity in the clinical setting (22).

Nevertheless, a series of studies in animal models was done in the 1980s that suggested that difluoromethylornithine was an effective chemoprevention agent, particularly against colon cancer (23, 24). These observations led to a series of clinical chemoprevention studies in concert with my Arizona colleague Gene Gerner (25-27). For all these trials, patients who had had a prior colonic adenoma were our target population. The basic strategy was this: because we knew the highest dose at which the drug would be given in a therapeutic trial, we implemented a dose de-escalation design. In the initial 1-month trial, the goal was to achieve a dose that no longer modulated polyamines and a placebo group was conducted in which the goal was to show polyamine modulation and no toxicity. An analysis of the results indicated that a dose of 200 mg/m²/d decreased polyamines, and that side effects in the difluoromethylornithine group were no greater than that seen in the placebo arm (26).

At that point, in about 1997, we were faced with a critical decision: How should we do the randomized phase III trial in which change in the number of colon adenomas would be the end point? Should the study be difluoromethylornithine alone versus placebo or should difluoromethylornithine be combined with another agent? If another drug, which? Most likely, a nonsteroidal anti-inflammatory drug. If a nonsteroidal anti-inflammatory drug, then nonspecific or specific? A lot of discussion ensued, and we elected to start a randomized phase IIb trial in which the combination of low-dose difluoromethylornithine and low-dose sulindac was the active arm. The end point was to be a comparison, between treatment and placebo, of the modulation of colonic polyamine and prostaglandin levels and other markers and recurrence and biology of adenomatous polyps. Accrual has been completed, and all patients passed their 3-year colonoscopy evaluation in October 2005; there are other markers and recurrence and biology of adenomatous polyps. Accrual has been completed, and all patients passed their 3-year colonoscopy evaluation in October 2005; there are other markers, such as the marker neu in serum and oral keratinocytes, were in the anticipated direction (34, 35). Based on these results, phase IIb 6-month randomized trial was initiated in patients with oral leukoplakia. Eighty of the projected 140 patients have been accrued; four new sites, in different geographic areas, have been added as subject accrual has been exhausted in the initial sites. We anticipate completing this trial by 2008.

This odyssey over the past 17 years has led to several important realizations:

1. The development of chemoprevention agents is very hard, takes a long time, and is not for the faint of heart.
2. Trying to develop agents without major pharmaceutical backing is dicey and complex at best.
3. Implementation of combination chemoprevention is going to be tough.
4. Appropriate markers for drug development may or may not be relevant as surrogates for the disease end point.

The Autumn Years: New Thoughts and New Directions

We need to take a giant step back and examine what we are trying to accomplish with chemoprevention. A few comments and questions to think about:

1. “Proof of principle” of the effectiveness of chemoprevention has been shown in a number of situations, perhaps most convincingly for breast cancer and colon adenomas. And yet, adoption into medical practice has not occurred. Why not? Is it not only a matter of finding a drug with strong efficacy and little toxicity (consider statins for cardiovascular disease); is cancer too diverse in its physiologic/molecular makeup to warrant a drug approach for prevention? Is it something more fundamental?

2. Dietary epidemiologic observations for a number of molecules suggest protection against a number of malignancies. In general, these observations have not been validated in randomized trials. Is the problem solely one of measurement (36) or, as we and others have suggested, is it a more fundamental conundrum (37, 38)?

3. Should we be developing chemoprevention only for high-risk individuals (certainly the approval process is easier; e.g., celecoxib for familial adenomatous polyposis, Bacillus Calmette-Guerin for in situ bladder cancer, and diclofenac for actinic keratoses)? Then, is the market large enough for pharmaceutical companies to become involved? Is the risk-benefit ratio worth it?

4. How should oncologists engage other subspecialties? Should chemoprevention even be part of the oncology management portfolio? Will coverage for prevention occur more efficiently and universally if oncologists are not the physician of record?

There are many more issues that need to be explored, especially in the broader context of prevention and health maintenance. Recently, an update of IEN has begun to explore some of these issues (39), but much more needs to be discussed and explored, and a deep examination of the field needs to occur.
In the meantime, we are trying to continue our logical approach on two major fronts: new agents and new ideas. Within the next few months, we will be launching the following early-phase innovative trials:

1. A phase IIa trial testing Erlotinib as an intervention against intraductal pancreatic mucinous neoplasms (S. Lipkin, Protocol PI).
2. A phase IIa dose-finding trial among current smoking patients with prevalent aberrant crypt foci to understand the effects of tobacco carcinogens on normal mucosa and aberrant crypt foci (R. Carroll, Protocol PI).
3. A phase IIb placebo-controlled randomized trial in patients with a prior melanoma to test the efficacy of lovastatin on atypical nevi (K. Linden, Protocol PI).

In all these studies, extensive biomarkers will be measured. Our other novel contribution involves an experimental and epidemiologic reexamination of the pathogenesis of human melanoma. The background for this adventure is discussed in ref. 40. We have done a large number of studies involving biophysical, chemical, and molecular approaches as well as reexamined the epidemiologic data (19, 41, 42). We have come to the following conclusion: the oxidation of melanin and its conversion from an antioxidant to pro-oxidant early in the pathogenic process of melanoma genesis is a key (?) first epigenetic event in the development of human melanoma. This observation has enormous implications for thinking about the etiology, prevention, and treatment of melanoma (19, 41).

The Winter Years: Thinking about the Next Generation

A major emphasis in the next decade (my last decade?) will be hiatus. I offer these visions. Kurzweil argues that in 2050, we should be prepared to live like a cherry blossom tree.

Cherry Blossom Time

Nature recurse. Why not?
It’s as if the universe is quantum Wu Li, and I was Newtonian,
Or perhaps, on a good day, Einsteinian.

But on earth, Winter’s bare limbs become Spring’s rapture of white and pink,
and I just look more grey.

If the past is not permissible and the future is always a possibility, what does that make today?

I guess it’s the day I noticed that I am no longer young. Though my mind is twenty-five, the body is no longer in sync.

Perhaps a personal trainer will do the trick, and I can learn to bloom again, like a cherry blossom tree.

Frank L. Meyskens, Jr.

References

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