Strategies for Identification and Clinical Evaluation of Promising Chemopreventive Agents

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Strategies for chemopreventative drug development are based on the use of well-characterized agents, intermediate biomarkers correlating to cancer incidence, and suitable cohorts for efficacy studies. Since

Introduction

Cancer chemoprevention is defined as the use of specific chemical compounds to prevent, inhibit, or reverse carcinogenesis. As shown in Figure 1, cancer development in humans requires an average of 20 to 40 years,[1-6] and the scope of chemoprevention encompasses all phases of this process--from healthy subjects at normal risk; to populations at intermediate risk from environmental and lifestyle factors, genetic predisposition, and precancerous lesions; to previous cancer patients at high risk for second primary malignancies.

Chemoprevention is a relatively new medical science. It is only during the past 5 years that results of clinical intervention trials with chemopreventive drugs have begun to appear in the literature. For example, a 1990 seminal trial by Hong and colleagues demonstrated that 13-cis-retinoic acid (iso-retinoin [Accutane]) prevented second primary cancers in patients with previous squamous-cell carcinoma of the head and neck.[7] Second primaries were seen in 24% (12 patients) of the placebo group but in only 4% (2 patients) of the treatment group.

Of course, such clinical trials represent only a fraction of current knowledge about human chemoprevention. Epidemiologic studies, ranging from descriptive assessment of dietary influences to prospective case-control analyses with specific micronutrients and drugs, have provided and continue to furnish leads for definitive intervention trials. For example, the protective effects of aspirin in the colon were substantiated by such studies.[8-10] Chemoprevention is not the same as cancer chemotherapy. These two treatment modalities are compared and contrasted in Table 1. A primary distinction is the timing and duration of intervention. Chemoprevention is applied throughout the long process of carcinogenesis depicted in Figure 1, before invasive disease develops. Chemopreventive treatment is intended to be long term, conceivably up to a lifetime in high-risk subjects. A consequence of this long duration of treatment in relatively healthy subjects is a requirement for agents with very low toxicity. In contrast, chemotherapeutic agents are administered after invasive disease is detected. Many such agents are given to cancer patients for short periods or in discrete cycles under conditions in which side effects are expected and carefully monitored and palliative treatment can be administered to lessen their immediate impact.

A second fundamental distinction relates to the goals of the two treatment modalities relative to cancer. Chemotherapy seeks to increase survival and remission of invasive disease and to prevent metastases, whereas chemoprevention tries to prevent or prolong the time to the onset of cancer. Because of these differences, the developmental paths for chemotherapeutic[11] and chemopreventive agents[12] are divergent. In particular, cancer incidence generally is not a feasible end point for the evaluation of chemopreventive drugs because of the long time needed for carcinogenesis and the relatively low incidences of cancers, even in high-risk populations.

Despite the differences between chemoprevention and chemotherapy, there are areas of conceptual and practical overlap between the two modalities. For instance, chemopreventive agents can be used as adjuvant therapies to prevent recurrences or new primary tumors in patients who have already been treated for cancer. This use was defined by Hong et al[7] in the trial with isotretinoin cited above.

Also, some of the mechanisms of chemopreventive and chemotherapeutic action are similar.
Cytotoxicity was the primary mechanism of early chemotherapeutic agents. Many newer chemotherapeutic agents are cytostatic and have mechanisms similar to those of some chemopreventive agents; ie, they slow the growth and progression of dysplastic cells (eg, by inducing terminal differentiation or apoptosis). A significant feature of chemoprevention is that it intervenes at the early stages of carcinogenesis when normal cell order and function are partially preserved. Chemoprevention strategies can be designed to target these preserved pathways before they are lost during the accelerating disorder that ends in the uncontrolled cell growth of cancer.

As suggested above, a significant aspect of chemoprevention is the end points selected for intervention trials. Numerous chemoprevention studies have used well-recognized precancerous lesions as end points. For example, patients with familial adenomatous polyposis (FAP) develop large numbers of colorectal adenomas beginning in their teens and, if untreated, have a 90% chance of progressing to colorectal cancer by 50 years of age.[13] In a small phase II trial in patients with FAP, Giardiello et al[14] showed that 9 months of sulindac (150 mg bid) caused a mean decrease in polyp number to 44% of baseline (p = .014) and a mean reduction in polyp diameter to 35% of baseline (P less than .001), although no patient had complete resolution of all polyps. During the 3-month follow-up, polyp size and incidence increased but remained significantly lower than baseline. Also, Meyskens et al[15] showed that all-trans-retinoic acid (Vesanoid) was effective in causing regression of cervical intraepithelial neoplasia (CIN), a precursor to cervical carcinoma.

These studies represent the vanguard effort in clinical trial design and evaluation of precancerous lesions and earlier biomarkers as surrogate end points for chemoprevention. Hong and Lippman[16,17] and Lipkin[13,18,19] were early contributors to the conceptualization of intermediate biomarkers as end points for chemoprevention. Our group and others have continued to expand this approach and formalize its application to chemopreventive drug development.[12,20-26] In the comparison between chemoprevention and chemotherapy above, we noted the importance of the safety of chemopreventive drugs during long-term administration. Approaches to eliminate toxicities that would preclude the use of highly efficacious agents is another significant component of chemopreventive drug development. The objective of this paper is to describe these current strategies and current progress in the development of chemopreventive drugs.

Bases for Successful Chemoprevention Strategies

We have previously presented a multidisciplinary approach to the development of chemopreventive drugs[12,23-27] and have collaborated with the FDA to provide guidance for applying this approach.[12] The strategy considers experimental and epidemiologic evidence that defines cancer risk at major target sites, as well as the underlying molecular, cellular, and tissue level mechanisms that contribute to the development and progression of human cancers. As previously described,[27] we have identified three critical components to the successful development of chemopreventive drugs:

1. Well-characterized agents with the potential for inhibiting the target cancer;
2. Biomarkers correlating with cancer incidence for measuring chemopreventive effect; and
3. Suitable cohorts for clinical efficacy studies.

Agents

The most important criterion for a chemopreventive agent is evidence of chemopreventive efficacy, in particular, a high likelihood that the agent will be active in preventing cancer at the target site. We have already discussed the requirement for low toxicity, and thus, evidence of a high margin of safety is also necessary to warrant consideration of an agent for clinical evaluation. This second criterion implies that sufficient prior clinical use or preclinical efficacy, toxicity, and pharmacodynamics data are available to allow estimation of an efficacy/safety ratio. Often, studies to determine the optimal dose and dosing regimen are performed as part of early clinical efficacy trials.

A third criterion is that there is a logical, presumed mechanism of chemopreventive activity of the agent. Such mechanisms guide the selection of both cohorts and end points for clinical trials. For example, an antiproliferative agent such as 2-difluoromethylornithine (DFMO [Eflornithine]) may be most effective against cancers with a pronounced proliferative component, such as the development of colon cancers from hyperproliferative tissue and adenomas. An antimutagenic agent such as oltipraz may be more effectively evaluated in a cohort such as smokers, who are constantly exposed...
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End points. The chemopreventive agents must be able to affect the disease or risk of disease within short-term phase II trials to measure efficacy and to identify and standardize intermediate biomarker surrogates.

In early stages of chemopreventive drug evaluation, clinical research efforts focus primarily on cohorts--direct measures of proliferation and differentiation, mutations, changes in expression and activity of cell growth regulators, and, possibly, less direct biochemical indicators of growth and proliferation--may prove to be valuable as potential end points.

As has been elegantly described by Fearon and Vogelstein for the development of colorectal cancer,[28] carcinogenesis is a multipath, stochastic process.[22] Except for IEN, which essentially comprises all the varying changes that occur, this multiplicity of pathways complicates the validation of single intermediate biomarkers as surrogate end points, since they may appear on only one or a few of the many possible causal pathways. Consequently, panels of biomarkers, particularly those representing the range of carcinogenesis pathways, may prove more useful as surrogate end points.

Clearly, it must be possible to change the expression of an intermediate biomarker/surrogate end point with chemopreventive agents. Intraepithelial neoplasia can be modulated, as demonstrated by the chemoprevention trials cited above that used colorectal adenomas and CIN as end points. While they will more often be risk biomarkers used primarily for identifying cohorts for chemoprevention studies, genetic lesions or their encoded products can also provide biomarkers that can be modulated in certain circumstances. Although acquired genetic lesions would not be excised by a chemopreventive agent, one can assume that some agents will confer a selective advantage for cells not carrying the lesion over those that do. In this instance, the biomarker would be the quantitative reduction in genetically altered cells at the tissue level.

The surrogate end point should have short latency compared with cancer incidence--ideally, months or a few years, compared with the 20- to 40-year period that may be required for cancer development. Intraepithelial neoplasia, even in its early stages, would appear to occur too late for effective chemoprevention studies in asymptomatic subjects. However, as will be discussed below, some cohorts with previous IEN are at high risk for recurrence or new lesions within the time frame of a chemoprevention study.

Some cohorts chosen for chemoprevention trials may be available for too short a period to allow modulation of the lesions most closely related to cancer. For example, we are carrying out trials in patients scheduled for surgery for early-stage prostate cancer and for breast lesions. The biopsy samples in these trials may be most useful for exploring changes in proliferation indices and other early biomarkers rather than actual progression of histologic lesions. Despite the brief duration of the associated trials (1 or 2 months), studies in these cohorts may provide valuable information on modulation of selected biomarkers that are known to be associated with cancer risk.

Cohorts

In early stages of chemopreventive drug evaluation, clinical research efforts focus primarily on short-term phase II trials to measure efficacy and to identify and standardize intermediate biomarker surrogates. The chemopreventive agents must be able to affect the disease or risk of disease within...
the relatively short treatment duration of such trials (many span 6 months or less; some may last up to 3 years). There are cohorts at high risk for cancer who are not good candidates for phase II chemoprevention trials, even though they will be targets for chemopreventive intervention. An example is patients at risk because of germ-line mutations (eg, BRCA1) or other family history who do not also have premalignant lesions.

From a practical standpoint, the chemopreventive effect should also be easily measured in the subject population. Tissues that are more accessible and that can be monitored in a relatively noninvasive manner provide better sites for definitive efficacy trials than do less accessible tissues. This does not mean that chemopreventive agents will be ineffective in the more difficult settings, but rather, that initial demonstration of activity may be best carried out in situations where fewer obstacles to measurement exist.

Often, the cohorts in these phase II chemoprevention clinical trials are cancer patients or patients with previous high-risk lesions who have undergone prior treatment. These patients are constantly monitored for possible recurrences and new lesions. It is important that chemoprevention trials work within the constraints of standard treatment so that patients are not at unusual risk. For example, in trials in patients with small colon adenomas (0.5 to 1.0 cm), this may result in frequent monitoring and removal of any adenomas larger than 0.5 to 1.0 cm.[29] As suggested above, in early phase II trials where the primary goal is identification and standardization of biomarkers as end points, normal treatment may also lead to very short-term trials prior to surgery in patients who are scheduled for excision of cancers or high-risk tissue, eg, prostate carcinoma or ductal carcinoma in situ (DCIS) of the breast.

In larger phase II trials and pivotal phase III trials, the emphasis is on efficacy evaluation with the standardized and validated biomarkers. These trials are generally of longer duration and are carried out in cohorts that do not initially present IEN severe enough to warrant surgery but are at high risk for progression within a 1- to 5-year time frame. Examples are individuals with atypical breast hyperplasia and multiple biomarker abnormalities, such as estrogen (ER) and epidermal growth factor receptor (EGFR) overexpression, p53 mutations, HER-2/ neu, and aneuploidy;[30] patients with prostate intraepithelial neoplasia (PIN);[31] and patients with previous colorectal adenomas.[13] or superficial bladder cancers.[32] Cohorts currently being studied in chemoprevention trials that provide the characteristics for biomarker standardization and efficacy evaluation have been discussed elsewhere[24,26,27] and are listed in Table 2.

Promising Chemopreventive Drugs/Drug Classes

Various factors must be taken into consideration in the development of chemopreventive drugs. To illustrate these considerations, three representative chemopreventive drugs/drug classes are discussed below: the retinoid, all-trans-N-(4-hydroxyphenyl) retinamide (4-HPR, fenretinide), the potent antiproliferative agent DFMO, and the nonsteroidal anti-inflammatory drug (NSAID) class.

4-HPR

A synthetic amide of all-trans-retinoic acid, 4-HPR is an antiproliferative and differentiation-inducing agent[25] with less toxicity than its parent compound and other efficacious retinoids. An important mechanism contributing to the antiproliferative activity of 4-HPR appears to be induction of apoptosis.[25,33] Another activity that may be associated with its antiproliferative effects is inhibition of the induction of ODC, a critical enzyme in polyamine biosynthesis; polyamine biosynthesis has been implicated in cell proliferation[34,35]. Other relevant activities are inhibition of prostaglandin synthesis[36] and tyrosine kinase activity, as well as enhancement of immunoglobulin secretion.[37]

Fenretinide may also have a very specific antiproliferative effect on terminal end buds in mammary glands.[38] It has been shown to be an effective inhibitor of mammary gland carcinomas in rats and mice.[39-42] In addition, 4-HPR also has shown chemopreventive activity against tumors in hamster lung, mouse skin, rat colon, mouse bladder, and rat and mouse prostate.[42] It has demonstrated synergistic activity in combination with tamoxifen (Nolvadex) in the mammary gland; with DFMO against bladder and lung tumors and lymphoma; and with vitamin E and selenite in the lung.

Phase II clinical trials of 4-HPR as a chemopreventive agent against tumors in the breast, bladder, lung, cervix, and oral cavity are in progress. Besides demonstrating the chemopreventive efficacy of 4-HPR itself, these trials are intended to investigate development strategies that can be applied to future generations of retinoids and to provide data for the validation and standardization of intermediate biomarkers for carcinogenesis.
As with other efficacious retinoids, toxicity complicates the development of 4-HPR as a chemopreventive drug. For 4-HPR, the primary concern is ophthalmic toxicity (reduced night vision) due to depletion of retinol (vitamin A) levels in the eye. Two methods to reduce this toxicity are being evaluated. The first is introduction of a periodic drug holiday to allow for recovery of retinol levels. For example, the National Cancer Institute (NCI) is sponsoring a phase III trial in patients surgically treated for stage I/II breast cancer that will assess the ability of 5 years of treatment with 4-HPR to prevent a second primary in the contralateral breast; 2 years of follow-up is planned.[43-45] A preliminary phase I study found 200 mg/d of 4-HPR with a 3-day holiday each month to be well-tolerated for long-term treatment.[44] Interim results are very encouraging. There is also some indication of a protective or delaying effect of 4-HPR against ovarian cancer.[46]

The second toxicity-reducing strategy explores the potential synergistic activity of 4-HPR with other chemopreventive agents. As noted above, 4-HPR and tamoxifen have demonstrated such activity against rat mammary cancers. A short-term phase II trial is now in progress that is evaluating the effects of the two agents in combination and singly on intermediate biomarkers in breast biopsy tissue of patients with mammographically detected lesions requiring biopsy (DCIS).[47] This is the presurgical cohort described above that will be treated in the 2- to 4-week period between diagnostic and excisional biopsies. Intermediate biomarkers evaluated will include DCIS grade, nuclear polymorphism, ploidy, and proliferation indices. Should synergy be observed, a dose titration study could be undertaken to identify lower, presumably less toxic doses of the two agents to provide the optimal efficacy/toxicity ratio.

DFMO

2-Difluoromethylornithine is a potent, irreversible inhibitor of ODC that slows both the growth of tumor cells and the promotion and progression phases of carcinogenesis. The potential of DFMO as a chemopreventive drug is based on activity against cancers with pronounced proliferative phases, such as those in the rat and mouse colon, mouse bladder, rat mammary gland, and mouse skin.[41,48] The demonstrated synergistic chemopreventive activity of DFMO with 4-HPR is described above; DFMO is also synergistic with oltipraz in the bladder and piroxicam in the rat colon.[48]

Pharmacodynamics have been an important consideration in setting development strategies for DFMO. Since most of the ingested DFMO is excreted unchanged in feces and urine, the primary cancer targets for DFMO are the colon and bladder, which receive high exposure to the agent. A phase II trial in patients with previously resected superficial bladder cancer is in progress, and another trial in patients with previous colon adenomas is scheduled. In both trials, primary end points are prevention of new lesions and effects on proliferation biomarkers. Phase II trials in other targets associated with proliferation are also underway, most notably, in a presurgical breast cohort (as described above for 4-HPR) and in patients with CIN III. Very preliminary results in the CIN III trial are promising.[Dr. Michele F. Mitchell, personal communication, January 1996]

The toxicity of DFMO--ie, reversible loss of hearing acuity--could also be problematic for its development as a chemopreventive agent. Therefore, the identification of a reliably effective dosing regimen with acceptable side effects will be a criterion for continued development of this agent. In fact, a phase II study of DFMO in colon cancer patients is currently in progress to identify the optimal chronic dose that is effective without producing side effects, especially ototoxicity.[49]

NSAIDs

The nonsteroidal anti-inflammatory drugs (eg, aspirin, ibuprofen, piroxicam, and sulindac) have demonstrated considerable activity against colon and bladder cancers in preclinical chemopreventive efficacy studies.[41,50-53] Early clinical studies also support the potential activity of sulindac and aspirin. As cited above, sulindac has shown dramatic effects in causing the total or near-total regression of adenomatous colorectal polyps in patients with FAP.[14,54] Also, as mentioned above, aspirin use reduced the relative risk of death from colon cancer in prospective studies,[8,10] and, in patients with previous colorectal adenomas, it lowered the risk of new adenomas.[9]

A primary mechanism of action of NSAIDs is inhibition of cyclooxygenase activity in prostaglandin synthesis. This inhibition may contribute to the chemopreventive efficacy of these drugs. However, prostaglandin E2 (PGE2) in the gut promotes protective mucosal secretions, and it is well-known that the lowered gut prostaglandin levels resulting from NSAID administration are associated with one of...
the major side effects of chronic NSAID treatment—gastrointestinal ulceration and bleeding. Likewise, prostaglandins in the kidney and thromboxanes in platelets are important to normal physiologic function, and their inhibition is associated with renal tubule toxicity and excessive bleeding, respectively. The challenge is to develop chemopreventive strategies that retain the ability of NSAIDs to inhibit carcinogenesis-associated activities without depressing the protective effects of normal prostaglandin synthesis.

Several approaches to accomplish these goals are being evaluated. One is based on the discovery of the inducible form of cyclooxygenase (COX-2), which is predominant at inflammation sites and in macrophages and synoviocytes.[55] Constitutive cyclooxygenase (COX-1) predominates in the stomach, gastrointestinal tract, platelets, and kidney[56] in the absence of inflammation. The NSAIDs that have demonstrated chemopreventive activity inhibit both forms of the enzymes, but other compounds selectively inhibit COX-2—for example, a recently synthesized NSAID, NS-398.[57] Similarly, nabumetone (Relafen) demonstrates higher specificity for COX-2 than COX-1 and less toxicity than other NSAIDs.[58] Should the inflammatory or other activities associated with COX-2-mediated prostaglandin synthesis be a factor in carcinogenesis, such agents may prove to be desirable alternatives for the NSAIDs currently being developed.

A second strategy is combination of the NSAID with a drug such as the prostaglandin analog misoprostol (Cytotec), which protects against NSAID-induced gastrointestinal toxicity.[59] Another possibility is the combination of an NSAID with another chemopreventive agent. For example, the combination of DFMO with an NSAID is of high interest for evaluation against colon cancer because of the synergistic chemopreventive activity of DFMO and piroxicam in the rat colon.[48] The identification of low doses of NSAIDs that provide chemopreventive efficacy but less toxicity may also be possible. For example, a clinical dose-titration study found that doses of aspirin as low as 80 mg once daily were effective in reducing rectal PGE2 and PGF1α.[60] These doses are less than the dose of 325 mg every other day that has been found to protect against heart disease[61] and are significantly lower than the 325- or 500- mg qid doses used in the treatment of arthritis and other types of inflammation.

Finally, in-depth evaluation of the pharmacologic properties of the NSAIDs may lead to a new generation of NSAID derivatives that retain their chemopreventive activity but are devoid of toxicity. An example is the sulindac metabolite, sulindac sulfone. Unlike its parent compound, the sulfone suppresses prostaglandin synthesis to only a minimal extent but has chemopreventive activity in the rat colon[62,63] and mammary gland.[64] It is currently in the early stages of clinical development as a chemopreventive agent in patients with FAP.

Current and Future Chemoprevention Trials

Table 4 lists current phase II chemoprevention trials being sponsored or funded by the NCI Chemoprevention Branch. Protocols have been developed for 10 cancer targets—prostate, breast, colon, esophagus, lung, bladder, cervix, oral cavity, skin, and liver. These studies do not include all of the ongoing clinical research in chemoprevention, but rather, exemplify current trends in thinking on chemoprevention.

The most important aspect of current efforts is the identification and validation of surrogate end points at the target sites. As stressed above, painstaking work in characterizing surrogate end points and their relationship to earlier intermediate biomarkers is a component of most of the trials. In studies with well-established precancerous lesions, such as colorectal adenomas, the focus is already beginning to shift to evaluation of efficacy.

Table 5 summarizes the current plan for pivotal trials to demonstrate chemopreventive activity for promising agents at major targets. It should be noted that the agents discussed here are first-generation compounds and serve as models for evaluation of future agents and combinations with higher potency and less toxicity, derived using strategies such as the approach described above for NSAIDs. Separating toxicity from efficacy and circumventing toxicity with drug- and target-specific strategies are the major challenges for chemoprevention research.

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