Cancer Prevention Research

Perspective

Perspective on Kreul et al., p. 1368

Difluoromethylornithine: The Proof Is in the Polyamines

Joanne M. Jeter and David S. Alberts

Abstract

In this issue (beginning on page 1368), Kreul and colleagues report a retrospective review of long-term efficacy and toxicity for subjects participating in a phase III study of difluoromethylornithine (DFMO) for prevention of nonmelanoma skin cancer (NMSC). They conclude that those treated with DFMO had a nonsignificant, persistent decrease in NMSC after completion of treatment and that treatment with DFMO did not result in late toxicity after the discontinuation of treatment. We review the data on DFMO as a chemopreventive agent for skin and other cancers, discuss the necessary qualities of a cancer chemopreventive agent, and reflect on the requirements for a well-conducted cancer chemoprevention study, including the rationale for long-term follow-up in cancer prevention studies. *Cancer Prev Res; 5(12); 1341–4. ©2012 AACR.*

Introduction

Nonmelanoma skin cancers (NMSC) rarely result in mortality, but these cancers have considerable impact on the U.S. population and health care systems due to their high incidence and associated costs and morbidity (1). Although these cancers are not routinely reported to cancer registries, the estimated incidence of NMSCs in 2010 exceeded 2 million in the United States alone (2). Ultraviolet (UV) radiation has been identified as a key carcinogen; however, campaigns for sun avoidance and sunscreen use have done little to stem the tide of these tumors (3). Another significant risk factor for nonmelanoma skin cancers is immunocompromise, either from medications or medical conditions causing immunosuppression. For these reasons, investigation has turned to the possibility of chemoprevention of NMSCs.

Difluoromethylornithine in Cancer Treatment

Difluoromethylornithine (DFMO), an irreversible inhibitor of ornithine decarboxylase (ODC), has attracted considerable interest initially as a cancer treatment and, more recently, as a preventive agent for cancer, due to its inhibition of the polyamine pathway and cell turnover. Polyamines cause cell proliferation through regulation of gene expression, and elevated tissue levels of both ODC and polyamines are associated with epithelial cancers (4). In addition, UV radiation has been linked to the induction of *ODC* and subsequent tumor development, whereas inhibition of *ODC* induction prevents tumor formation (5–8).

Initial studies of DFMO involved its use in the treatment of cancer. An early-phase clinical trial of oral DFMO found that thrombocytopenia was the dose-limiting toxicity; gastrointestinal adverse effects were observed as well (9). Phase II studies in breast, colon, and small-cell lung cancers failed to show antitumor activity with single-agent DFMO, and the addition of DFMO to conventional chemotherapy for solid tumors and lymphomas had no significant effect on rate of disease progression (10–12). In addition, several of the later studies revealed a high incidence of reversible otoxicity, which caused discontinuation of treatment in a significant proportion of patients. Additional trials were conducted with DFMO in treatment of glioblastoma multiforme and gliomas, but despite promising early results in these tumor types, phase III studies ultimately showed no significant clinical benefit (13–15). A Phase I clinical trial of DFMO has been initiated to treat children with neuroblastoma as well (16).

Difluoromethylornithine in Cancer Prevention

In the 1990s, research on DFMO began to shift from its use as a chemotherapeutic agent to its potential as a chemopreventive agent. Dose-finding studies conducted in individuals who were free of cancer after surgical resection or who were otherwise at high risk of developing malignancy showed that loss of high-tone auditory acuity was the dose-limiting toxicity (17, 18). The dose for use in further prevention studies was established at 500 mg/m^2/d, approximately one third of that used in the cancer treatment clinical trials. Phase II studies for the prevention of cervical and breast cancers with DFMO had disappointing results (19, 20), as did a phase III randomized, placebo-controlled trial for bladder cancer prevention (21). However, results from studies in prostate (22), colon (23), and skin (24)

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cancers were promising. The chemopreventive potential of DFMO was realized in the landmark clinical trial by Meyskens and colleagues, which showed that the combination of sulindac and DFMO reduced recurrence of colon adenomas by 60% overall and reduced the recurrence of advanced colon adenomas by nearly 92% (25). Recent data suggest a role for polyamines in esophageal carcinogenesis and support the evaluation of DFMO as a chemopreventive agent in patients with Barrett's esophagus (26). A preventive trial of DFMO in patients with high-risk neuroblastoma in remission is currently ongoing (NCT01586260).

Difluoromethylornithine in Nonmelanoma Skin Cancer Prevention

Topical and oral formulations of DFMO have been explored as chemopreventive agents for NMSCs. A 6-month course of a topical DFMO preparation in individuals with moderate to severe actinic keratoses on the lateral forearms resulted in a statistically significant 23.5% reduction in the number of lesions as compared with placebo (27). The primary toxicity from this treatment was dermatologic, with 14.6% of subjects experiencing moderate to severe local inflammatory reactions. No significant systemic toxicities were seen. Biomarker studies from this clinical trial showed significant reductions in the tissue levels of spermidine, a polyamine, as well as a decrease in the percentage of cells expressing p53 protein (28). Another placebo-controlled study, investigating topical DFMO, topical triamcinolone, or the combination of these drugs, showed a statistically significant reduction in nuclear abnormalities found in skin biopsies after 6 months of use of these medications (29).

The study reported in the current issue of this journal is an update of a randomized, placebo-controlled study of oral DFMO in the prevention of NMSC (30). Subjects in the initial report were 291 individuals with a prior history of skin cancers, and study medications were taken for 4 to 5 years. Overall, a nearly significant reduction in new NMSCs was seen in subjects treated with DFMO (260 vs. 363, $P = 0.069$), primarily driven by a highly significant decrease in the incidence of basal cell carcinomas. ODC activity and levels of putrescine were significantly reduced in skin biopsies of subjects taking DFMO, and mild ototoxicity was observed in 45.2% of DFMO users as compared with 33.6% of subjects on placebo. The median follow-up for the original report was 4.5 years. The current report updates both the efficacy and toxicity data from this study with extended follow-up up to 12 years (31). The event rates for NMSC, basal cell carcinoma, and squamous cell carcinoma in the posttreatment phase were all lower in the DFMO group than in the placebo group. None of these results reached statistical significance; however, there was no evidence of a "rebound" increase in the rate on DFMO withdrawal. The previously observed significant reduction in basal cell carcinomas in the DFMO group did not persist in this later analysis; however, the DFMO group had a lower rate of squamous cell carcinomas in the second analysis than in the original report. These findings provide clinical insights into the effects of DFMO on basal cell and squamous cell carcinogenesis. The lack of sustained chemopreventive effect suggests that DFMO works at a later stage in the process of development of basal cell carcinomas, whereas the late decrease in squamous cell carcinoma incidence may be indicative of an effect on early disease in squamous cells. In addition, this retrospective review of the medical records showed no significant differences between the groups in terms of medical conditions after the completion of the study period. This report is particularly important as previous studies of DFMO have had limited follow-up, with data extending out to only 1 to 3 years.

DFMO Meets the Criteria for an Effective Chemopreventive Agent

The current report on long-term follow-up of a phase III trial of oral DFMO adds to the accumulating data that indicate this medication's use as a chemopreventive agent. Overall, DFMO has shown dramatic reductions in carcinogenic risk for adenomatous polyp recurrence (when combined with sulindac) as well as reductions in the risk of NMSC recurrence when used as a single agent. Its oral formulation at doses of up to 500 mg/m^2 seems safe in relatively healthy populations treated for up to 5 years with no lingering toxicities encountered over an extended period of follow-up. Finally, it seems that the oral formulation would be reasonably priced for daily consumption, given its well-described chemical synthesis and long-term stability.

The importance of long-term follow-up for cancer chemopreventive studies cannot be overstated. The goal of prevention is not merely to aid the body in weathering the course of an episode of disease but to allow the patient to remain disease-free for the long term, if not indefinitely. For many individuals at high risk of disease, the optimal duration of treatment needed to keep premalignant lesions from becoming malignant or to keep subclinical disease from having clinically detectable manifestations remains unknown. The best-described cancer prevention agent to date, tamoxifen, has been shown to extend its chemoprotective effects beyond the time that the medication is actually taken: reduction of breast cancer risk has been shown for 10 years or more beyond the standard 5-year treatment period (32, 33). On the other hand, other preventive medications such as retinoids do not seem to exert benefit beyond the period of active treatment (34).

Just as cancer survivorship initiatives have emerged to address the long-term effects of chemotherapeutic drugs, the unintended long-term effects, both beneficial and toxic, must be understood for cancer preventive agents as well. Review of long-term data from osteopenia studies of raloxifene indicated its potential for breast cancer prevention, which was subsequently confirmed in the STAR trial (35). Similarly, the cardiovascular adverse effects of COX-2 inhibitors became apparent through long-term cancer prevention studies (36).

Because of the length of time required for cancer to develop, late-stage clinical prevention trials must have

primary endpoints of cancer incidence or incidence of clearly established cancer precursor lesions. By their very nature, these trials must take place over a period of several years. However, extended follow-up beyond the end of the trial is crucial to determine continued benefit and late toxicity. Only with these data will we be able to conduct a full assessment of the risk–benefit ratio associated with a chemopreventive agent.

Disclosure of Potential Conflicts of Interest

J.M. Jeter is consultant/advisory board member of NIH. No potential conflicts of interest was disclosed by the other author.

Authors' Contributions

Conception and design: J.M. Jeter, D.S. Alberts
Development of methodology: D.S. Alberts
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.M. Jeter, D.S. Alberts
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.M. Jeter, D.S. Alberts
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.M. Jeter, D.S. Alberts
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