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Research Article
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A Phase III Skin Cancer Chemoprevention Study of DFMO: Long-term Follow-up of Skin Cancer Events and Toxicity

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Abstract

Decreasing the incidence of nonmelanoma skin cancer (NMSC) is of great importance in regards to future healthcare services. Given the previously reported preventive effects of α-difluoromethylornithine (DFMO) in skin and colon cancer trials, we determined appropriate cause to update the clinical data on the subjects from the recently reported randomized, double-blind, placebo-controlled phase III skin cancer prevention study of DFMO. Our intention was to retrospectively assess the further incidence of skin cancer, other malignancies, and adverse events of patients accrued to our phase III skin cancer prevention study of DFMO. Clinical records of 209 University of Wisconsin (UW) Health subjects were reviewed, and 2,092.7 person years of on study (884.3 person years) and poststudy (1,208.4 person years) follow-up for these patients were assessed for new NMSC events and recurrence rates from the on study period, the poststudy period, and the two study periods combined. No evidence of increased significant diagnoses or serious adverse events was observed in the DFMO participants. The initially observed, marginally significant reduction ($P = 0.069$) in NMSC rates for DFMO subjects relative to placebo continued without evidence of rebound. Event rates after discontinuation from study for total NMSCs (DFMO 0.236 NMSC/person/year, placebo 0.297, $P = 0.48$) or the subtypes of basal cell carcinomas (BCC; DFMO 0.179 BCC/person/year, placebo 0.190, $P = 0.77$) and squamous cell carcinomas (SCC; DFMO 0.057 SCC/person/year, placebo 0.107, $P = 0.43$) are listed. Follow-up data revealed a persistent but insignificant reduction in new NMSCs occurring in DFMO subjects without evidence of latent or cumulative toxicity relative to placebo subjects. *Cancer Prev Res; 5(12); 1368–74. ©2012 AACR.*

Introduction

Despite respectable intentions, education on the importance of limited or protected sun exposure has not been enough to halt the rising trend of the most commonly diagnosed malignancy in the United States, nonmelanoma skin cancer (NMSC). For the year 2010, estimates expected greater than 2 million new cases of basal cell carcinoma (BCC) or squamous cell carcinoma (SCC; ref. 1). About trends note, individual use of sunscreen tends to occur only with the intention to sunbathe, if at all, and limited prospective studies of sunscreens have not observed significant protection against BCC or malignant melanoma (2, 3). NMSC has many risk factors, namely UV radiation, and with continued depletion of the ozone layer, this underrecognized epidemic is projected to increase (4, 5).

The increased incidence of NMSC especially impacts certain populations, an example being organ transplant recipients who are at increased risk (incidence $\geq 50\%$) with significant morbidity and increasing mortality (6–8). It is also alarming that women have a higher incidence of both BCC and SCC when compared with men, and this is especially evident in women under 40 years of age in whom the BCC incidence is increasing (9, 10). The financial burden of this malignancy for U.S. residents is quite substantial. One of the top 5 most costly cancers to Medicare, total yearly expenditures for NMSC care in the United States have been estimated at $426 million and $650 million for the Medicare population and for the entire U.S. population, respectively (11, 12). In regards to major implications for future healthcare services alone, decreasing the incidence of NMSC across all populations is of great importance. Unfortunately, a successful and safe chemopreventive agent against NMSC does not exist (13–16).

Polyamines have been of research interest ever since their regulatory capabilities in normal cell signaling and growth were observed. Early work by O'Brien and colleagues observed increased levels of polyamines in epithelial

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tumorigenesis (17). Epithelial carcinogenesis of skin, colon, and breast has specifically been linked to elevated levels of polyamines, spermidine, and spermine (18). Preclinical research observing chemopreventive effects of polyamine depletion led to the development of α-difluoromethylornithine (DFMO), an analog of the amino acid ornithine, which irreversibly inhibits ornithine decarboxylase (ODC), the rate-limiting step of polyamine synthesis (19). While DFMO exhibited some positive therapeutic effects in clinical trials, most of the recent focus has been toward cancer prevention effects (20, 21). This was recently highlighted by Meyskens and colleagues when they noted a significant reduction in colonic adenomas in participants taking DFMO + sulindac as compared with placebo (22).

The above data led to a single institution [University of Wisconsin (UW; Madison, WI)] phase III double-blind, placebo-controlled skin cancer prevention study, of DFMO (500 mg/m^2) for up to 5 years (23). There was a significant difference in new BCC of patients taking DFMO (163 cancers) versus placebo (243 cancers) as expressed as event rate of 0.28 BCC/person/year versus 0.40 BCC/person/year, ($P = 0.03$). The subjects showed exceptional compliance and the groups did not have a difference in toxicity/adverse events.

A key issue in the clinical viability of a chemoprevention agent after acute effectiveness and/or tolerance is the latent effectiveness and/or toxicity of the agent. Earlier chemoprevention research has observed positive and negative latent effects with chemopreventive agents. Namely, use of tamoxifen (5 years) for breast cancer prevention has observed even greater evidence of protection up to 5 to 10 years after stopping tamoxifen as compared with subjects on placebo (24). Contrary to this, early work with retinoids in oral cancer prevention has implied a rebound effect. When subjects discontinued the putative preventive agent, protective effects were not apparent due to increased development of second primary tumors (25). Also, the recent linkage between isotretinoin and inflammatory bowel disease is a concerning example of toxicity experienced years after use of a chronically administered agent (26).

Despite a wide spectrum of potential or ongoing clinical uses of DFMO, namely as a cancer preventive described earlier, as a treatment option in the management of human African trypanosomiasis (intravenous dose of 400 mg/kg per day for 14 days; refs. 27, 28), or as an anti-*Helicobacter pylori* therapy (29), the sustainability of its effects or possible latent toxicities have not been assessed.

The continued interest in DFMO as a chemopreventive agent, along with other potential uses, provided cause to update the clinical data and overall health status of the available subjects from the phase III skin cancer prevention study of DFMO to understand the sustainability of the observed DFMO effects. After UW Health Sciences Institutional Review Board approval, we manually reviewed medical records of 243 subjects who received care at UW Health. The review focused on the skin cancer events by histology, other neoplasia (invasive and noninvasive), significant other diagnoses, and survival.

Materials and Methods

Subjects

Previously, 291 participants (mean age, 61 years; 60% male) with a history of prior NMSC (mean, 4.5 skin cancers) were randomized to 500 mg/m^2/day oral DFMO ($n = 144$) or placebo ($n = 147$) for 4 to 5 years in the phase III skin cancer prevention study of DFMO, University of Wisconsin Carbone Cancer Center (UWCCC) Protocol CO9737. We pursued reviewing the clinical records of these original 291 subjects to establish what further incidence of malignancy (skin or otherwise) occurred after patients discontinued DFMO.

Study design

Approval was received to review the 243 UW Health subjects from this study; 209 clinical records were subsequently used. The 34 records not included did not have poststudy information; possible reasons for this included deaths of 7 patients (4 DFMO and 3 placebo) before the follow-up period began, lost affiliation with the UW Health, or not requiring medical assistance.

Specifically, the clinical records were reviewed by the authors (S.M. Kreul and H.H. Bailey) to assess whether the patient was living or deceased, and date of death if applicable, the date of last contact with the patient, and the ICD9 Codes for relevant diagnoses. We documented the date (month/day/year) of diagnosis for relevant diseases of NMSC, other skin cancers, other cancers, cardiovascular or vascular disease, dementia, colonic polyps, hepatic, and renal dysfunction. Data collection specifically for NMSC included lesion location, histology (basal or squamous), and total number of skin carcinomas.

Statistical considerations

The primary objective was to determine whether the reductions in NMSC rate observed in subjects randomized to DFMO for up to 5 years were maintained, strengthened, or reduced over the 5 or more years since going off-study. As with the efficacy analysis in the article for the original study, the primary endpoint used to address this was the rate of NMSC recurrence; for this study, we are interested in the interval from going off-study from CO9737 to the date of last contact for this follow-up study; the cut-off date for date of last contact was May 23, 2011. The rates of skin cancer recurrence were compared in the 209 subjects reviewed between the original randomization arms, DFMO versus placebo, using a 2-sample Student t test. For greater precision, efficacy was evaluated using the exact probability value from the permutation test obtained from the randomization distribution. A similar analysis was conducted for the original phase III DFMO article. Estimates of the mean cumulative event rate over time were obtained by fitting a nonhomogenous Poisson process $\lambda(t|z) = z\lambda 0(t)$ using the nonparametric model of Huang and colleagues and are displayed in Fig. 1A–C. Analyzing panel count data with informative observation times (30). In these models, the distributions of both the frailty variable z and observation times are considered as nuisance parameters. The way the

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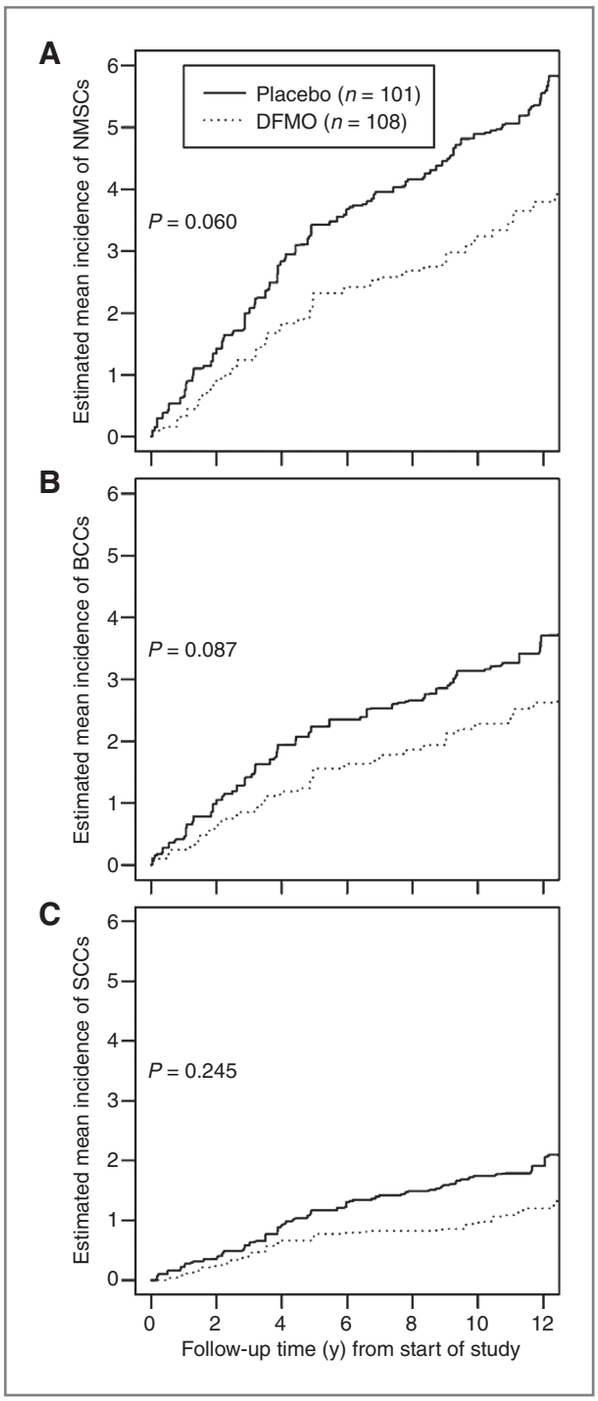

Figure 1. A–C, NMSC, BCC, SCC incidence from start of study to present ($N = 209$).

data were collected, we expect observation times to be noninformative, although these models have been found to be insensitive to assumptions of informativeness of the observation times.

For the secondary analyses, the rate of skin cancer recurrence from randomization onto CO9737 to the date of last contact for this follow-up study were compared between the original randomization arms, also with permutation test. Computations were conducted and figures were created with R software (31).

Results

Baseline characteristics of the original study cohort and the poststudy cohort are summarized in Table 1. Height and weight was used to determine body surface area, and the resulting mean and median values for randomized subjects were both 1.96 m^2. The original study population had a total of 334 subjects enrolled over 2 years into the placebo run-in phase. After 28 days of the placebo run-in, 291 subjects (87%) met the minimum compliance rate (≥80%) and were randomized to continue with blinded study treatment between September 1998 and July 2000. The mean age at enrollment was 60.9 years, with a median of 61.9 years. Among randomized subjects, 175 (60%) were male and 116 (40%) were female. Nearly all subjects (290, or 99.7%) were White, non-Hispanic with 1 Hispanic subject. Baseline variables across the 2 treatment groups seemed reasonably well balanced and consistent with randomization, with the possible exception of weight (Wilcoxon $P = 0.060$) and body surface area (Wilcoxon $P = 0.063$).

Baseline characteristics for the 209 prior study subjects that carried over into our retrospective study are summarized as the retrospective study population in Table 1. The mean age at enrollment was 60.9 years, with a median of 63.0 years. Among randomized subjects, 120 (57%) were male and 89 (43%) were female. Most subjects (208, or 99.5%) were White, non-Hispanic with 1 Hispanic subject. Baseline variables across the 2 treatment groups also seemed reasonably well balanced and consistent with randomization.

Original study results of the 291 participants randomized to oral DFMO (500 mg/m(2)/day) or placebo for 4 to 5 years revealed a marginally statistically significant ($P = 0.069$) decrease in total NMSCs (DFMO, 259 cancers; placebo, 363 cancers) in participants randomized to DFMO. Analysis by specific NMSC type revealed a statistically significant difference in new BCCs (DFMO, 162 cancers; placebo, 245 cancers; expressed as event rate of 0.28 BCC/person/year versus 0.40 BCC/person/year, $P = 0.03$). Table 2 displays results while on study for the 209 subjects, who are the focus of this retrospective review. Poststudy data of 209 study subjects displayed in Table 3 did not show a significant difference between groups in total NMSCs or individual cancer types (SCC or BCC). The BCC poststudy event rate of DFMO subjects was similar to the placebo subjects (DFMO 0.179 BCC/person/year, placebo 0.190, $P = 0.765$; Table 3). Interestingly, the poststudy period rate of SCCs decreased when compared with placebo (DFMO 0.057 SCC/person/year, placebo 0.107, $P = 0.426$. SCCs: DFMO 40, placebo 64).

Table 4 displays the combined data of the 209 subjects from study initiation to end of the current retrospective period with a follow-up from 2.3 to 12.7 years.

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Table 1. Randomized subject baseline characteristics.

Population	Treatment group		*P* value
Original study	DFMO ($n = 144$)	Placebo ($n = 147$)	
Age, y	61.6 ± 10.7	60.2 ± 11.0	
Gender			
Female	57 (39.6%)	59 (40.1%)	
Male	87 (60.4%)	88 (59.9%)	
Race			
White	144 (99.3%)	147 (100%)	
Hispanic	1 (0.7%)	0 (0%)	
Body surface area (m^2)	1.94 ± 0.23	1.99 ± 0.23	
Prior NMSC	4.2 ± 7.7	4.9 ± 5.7	0.10
Prior tumor rate	2.3 ± 3.3	2.1 ± 3.4	0.08
Retrospective study	**DFMO ($n = 108$)**	**Placebo ($n = 101$)**	
Age, y	61.4 ± 10.9	60.4 ± 11.0	
Gender			
Female	43 (39.8%)	46 (45.5%)	
Male	65 (60.2%)	55 (54.5%)	
Race			
White	107 (99.5%)	101 (100%)	
Hispanic	1 (0.5%)	0 (0%)	
Body surface area (m^2)	1.94 ± 0.23	1.96 ± 0.23	
Prior NMSC	3.2 ± 3.0	5.5 ± 6.3	0.01
Prior tumor rate	2.5 ± 3.5	2.4 ± 3.9	0.57

NOTE: For continuous data, mean ± SD is presented. For categorical data, *N* (%) are presented. Prior tumor rate is defined as the number of prior skin cancers divided by the time from initial diagnosis to randomization.

Estimates of the mean cumulative event rate over time from start of the prior study to end of the retrospective study (approximately 12 years) for NMSC, BCC, and SCC are displayed in Fig. 1A–C.

In the prior study, gastrointestinal adverse events were the most commonly observed toxicity, and nausea or diarrhea were often attributed as possibly related to study drug. Twelve study subjects died during study participation or follow-up, 7 on the DFMO arm (ages 69–78 years), and 5 on the placebo arm (ages 62–78 years). Although no deaths were felt to be possibly or probably related to the study drug, 4 deaths on the DFMO arm were previously described: congestive heart failure, a ruptured spleen and congestive heart failure, a cerebrovascular accident, and acute renal failure. We examined the medical records for diagnoses of or evidence for malignancies and noninvasive neoplasms, cardiac, vascular, endocrine, neurological, gastrointestinal, renal, hepatic, and ophthalmologic events. Table 5 compares the DFMO and placebo groups relative to general system events that occurred poststudy. We compiled cardiac conditions as chronic heart failure, valve disorders, coronary artery disease, abnormal electrocardiography (ECG),

Table 2. Cancers during study.

Treatment group	DFMO ($n = 108$)	Placebo ($n = 101$)	Overall ($n = 209$)	*P* value
Time under observation, y/avg.	463.6/4.29	420.7/4.17	884.3/4.23	
Subjects with new NSMC	70	69	139	
Total new NMSCs	207	308	515	
New NMSCs/y (SE)	0.444 (0.063)	0.701 (0.095)	0.568 (0.057)	0.012
Subjects with new BCC	57	55	112	
Total new BCCs	133	201	334	
New BCCs/y (SE)	0.294 (0.049)	0.466 (0.067)	0.377 (0.041)	0.014
Subjects with new SCC	32	43	75	
Total New SCCs	74	107	181	
New SCCs/year (SE)	0.150 (0.040)	0.236 (0.056)	0.191 (0.034)	0.223

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Table 3. Poststudy cancers

Treatment group	DFMO ($n = 108$)	Placebo ($n = 101$)	Overall ($n = 209$)	*P* value
Time under observation, y/avg.	627.2/5.81	581.2/5.75	1,208.4/5.78	
Subjects with new NSMC	49	52	101	
Total new NMSCs	146	170	316	
New NMSCs/y (SE)	0.236 (0.039)	0.297 (0.081)	0.266 (0.044)	0.484
Subjects with new BCC	44	42	86	
Total new BCCs	106	106	212	
New BCCs/y (SE)	0.179 (0.035)	0.190 (0.042)	0.185 (0.027)	0.765
Subjects with new SCC	28	22	50	
Total new SCCs	40	64	104	
New SCCs/y (SE)	0.057 (0.011)	0.107 (0.054)	0.081 (0.027)	0.426

endocarditis, abnormal heart rate, and cardiomegaly, which occurred in 23 DFMO participants versus 22 placebo participants. The renal conditions (chronic renal failure, abnormal creatinine, kidney cyst, and calculi) were noted in 4 of the DFMO group as compared with 2 in placebo. Hepatic disorders, including hepatitis, cholecystitis, hepatic and pancreatic cysts, abnormal liver function tests (transaminases, total bilirubin, alkaline phosphatase), ascites, microalbumin, and common bile duct obstruction, were observed for 9 DFMO participants and 3 placebo patients.

Discussion

Our results after updating the clinical data on subjects from the randomized, double-blind, placebo-controlled phase III skin cancer prevention study of DFMO imply that up to 5 years of DFMO did not result in latent toxicity and the initial observed insignificant reduction in NMSC and significant reduction in BCCs did not result in a "rebound" increase in rate of BCCs or SCCs after stopping DFMO. Further evaluation of rates of BCC's and SCC's in Fig. 1A–C, which depict the cumulative mean incidence of events over time (rate) suggest the following: the initial diverging rates of BCCs during the study (consistent with the observed significant reduction in BCC rate) is followed by parallel rates from years 5 to 12 implying initial protection followed by no protection or a return to baseline risk; the initial lack of any divergence in rates of SCCs between DFMO and placebo during the study imply minimal to no protection, but in the initial years poststudy (years 5–10) there is divergence of the rates suggestive of DFMO protection; the combined results of BCCs and SCCs (NMSCs) show a persistent, but not significant ($P = 0.060$), divergence in rates from year 1 to 10 consistent with the earlier results for BCCs and SCCs. These data strongly imply DFMO at 500 mg/m^2/day for up to 5 years provides a small to moderate reduction in the risk of NMSCs for up to 5 to 10 years. There is clearly no evidence of any increase in incidence of NMSCs upon discontinuation of DFMO.

From these data, it is possible to hypothesize that DFMO more strongly inhibits later stages of basal cell carcinogenesis with less effect on early carcinogenic processes, as evidenced by a near immediate decrease in BCCs during 5 years of DFMO followed by a rapid return to a rate of BCCs similar to placebo subjects (no evidence of latent protection). Contrary to BCCs, DFMO's effect on SCCs seems to be more strongly impactful on early carcinogenesis rather than later given the observed minimal if any reduction in incidence/rate during DFMO administration, but observed trend toward a reduced rate of SCCs in the 5 years after DFMO administration. As we discussed in our initial report (23), it should not be surprising if DFMO or any potential skin cancer prevention agent had differing effects

Table 4. All cancers combined

Treatment group	DFMO ($n = 108$)	Placebo ($n = 101$)	Overall ($n = 209$)	*P* value
Time under observation, y/avg.	1,090.8/10.10	1,002.0/9.92	2,092.7/10.01	
Subjects with new NSMC	76	77	153	
Total new NMSCs	353	478	831	
New NMSCs/y (SE)	0.336 (0.041)	0.509 (0.085)	0.420 (0.046)	0.060
Subjects with new BCC	70	68	138	
Total new BCCs	239	307	546	
New BCCs/y (SE)	0.231 (0.034)	0.334 (0.053)	0.281 (0.031)	0.087
Subjects with new SCC	42	47	89	
Total new SCCs	114	171	285	
New SCCs/y (SE)	0.106 (0.022)	0.175 (0.053)	0.139 (0.028)	0.245

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Table 5. Number (%) of patients with each condition poststudy

	N (%) of patients			
	DFMO (*N* = 108)	**Placebo (*N* = 108)**	**All (*N* = 209)**	***P* value[a]**
Hematologic malignancy	4 (3.7)	2 (2.0)	6 (2.9)	0.684
Prostate cancer	5 (4.6)	2 (2.0)	7 (3.3)	0.447
Noninvasive neoplasm	23 (21.3)	28 (27.7)	51 (24.4)	0.334
Cardiac[b]	23 (21.3)	22 (21.8)	45 (21.5)	1.000
Vascular disease	22 (20.4)	20 (19.8)	42 (20.1)	1.000
Diabetes mellitus type II	8 (7.4)	5 (5.0)	13 (6.2)	0.572
Neurologic disorders	22 (20.4)	17 (16.8)	39 (18.7)	0.595
Colonic polyps	16 (14.8)	11 (10.9)	27 (12.9)	0.418
Renal disease[c]	4 (3.7)	2 (2.0)	6 (2.9)	0.684
Hepatic disorders[d]	9 (8.3)	3 (3.0)	12 (5.7)	0.137
Eye disorders	7 (6.5)	7 (6.9)	14 (6.7)	1.000
Death	10 (9.3)	6 (5.9)	16 (7.7)	0.441

[a]Fisher exact test.

[b]Chronic heart failure, valve disorders, coronary artery disease, abnormal ECG, endocarditis, abnormal heart rate, and cardiomegaly.

[c]Chronic renal failure, abnormal creatinine, kidney cyst, and calculus.

[d]Hepatitis, cholecystitis, hepatic cyst, abnormal liver function tests, ascites, microalbumin, and common bile duct obstruction.

against squamous or basal cell carcinogenesis given the known differences in critical oncogenic pathways between the 2. While the relatively small size of our studies limits the ability to establish significant small to moderate changes, the consistent decreased numbers of NMSCs in participants having received DFMO is noteworthy.

As discussed earlier, key considerations toward a potential chemopreventive agent besides acute and latent protection from cancer are safety and compliance. The initial study results (23) observed high compliance (>95%), even when DFMO was in a liquid form rather than tablet, and minimal toxicity other than a significant ($P < 0.05$) increase in uniformly transient audiometric (but not clinically detectable) hearing loss in participants on DFMO. The combined toxicity data from our prospective and follow-up studies continue to imply an acceptable immediate and long-term safety profile of daily DFMO. However, as with all prevention agents, larger and/or longer prospective, randomized trials that could discern increased rates of uncommon events are still needed to more definitively establish long-term safety.

The limitations of our follow-up study include the relatively small size of our study (noted earlier), the inability to review the full 291 patients from the original study (48 patient records were not affiliated with UW Health and 34 subjects from UW Health were lost to various reasons), and the retrospective nature (follow-up guidelines from the prior study were not in place and subjects may have been more or less closely followed than previously). Events may have been missed if recorded by other providers as subjects may have sought care outside the UW Health system. This was a manual process, and errors in recording may have occurred, but data were cross-checked by study statistician and compared with article records and electronic health records. On the basis of the earlier experience, we have started incorporating prospective, long-term follow-up plans into our phase III chemoprevention trial proposals with the hopes of improving our ability to detect beneficial or detrimental latent effects.

While it could be debated whether the observed differences in NMSC between participants who took DFMO daily for up to 5 years as compared with those who took placebo are large enough to justify its continued development as a "solo" agent for cancer prevention, these results show a "biologic" signal is there. Namely, clinically safe administration of DFMO produces an alteration in skin cancer development. At a minimum, these data support the exploration of DFMO in combination with other agents, especially given the data of Meyskens and colleagues and Elmets and Athar in colon cancer and skin cancer prevention, respectively (22, 32).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Development of methodology: S.M. Kreul, K.M. Kim, A. Verma, H.H. Bailey
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.M. Kreul, G.S. Wood, A. Verma, H.H. Bailey
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T. Havighurst, K.M. Kim, G.S. Wood, A. Borich, A. Verma, H.H. Bailey
Writing, review, and/or revision of the manuscript: S.M. Kreul, T. Havighurst, K.M. Kim, E.A. Mendonça, G.S. Wood, S. Snow, A. Verma, H.H. Bailey
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References

1. Jemal A, Siegel R, Xu J, Ward E, Cancer Statistics, 2010. CA Cancer J Clin 2010;60:277–300.
2. Thieden E, Philipsen PA, Sandby-Møller J, Wulf HC. Sunscreen use related to UV exposure, age, sex, and occupation based on personal dosimeter readings and sun-exposure behavior diaries. Arch Dermatol 2005;141:967–73.
3. Green A, Williams G, Neale R, Hart V, Leslie D, Parsons P, et al. Daily sunscreen application and beta carotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomized controlled trial. Lancet 1999;354:723–9.
4. Norval M, Lucas RM, Cullen AP, de Gruijl FR, Longstreth J, Takizawa Y, et al. The human health effects of ozone depletion and interactions with climate change. Photochem Photobiol Sci 2011;10:199–225.
5. Ulrich C, Kanitakis J, Stockfleth E, Euvrard S. Skin cancer in organ transplant recipients: where do we stand today? Am J Transplant 2008;8:2192–8
6. Rogers HW, Weinstock MA, Harris AR, Hinckley MR, Feldman SR, Fleischer AB, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol 2010;146:283–7.
7. Ramsay HM, Reece SM, Fryer AA, Smith AG, Harden PN. Seven-year prospective study of nonmelanoma skin cancer incidence in U.K. renal transplant recipients. Transplantation 2007;84:437–9.
8. Bath-Hextall F, Leonardi-Bee J, Somchand N, Webster A, Delitt J, Perkins W. Interventions for the prevention of non-melanoma skin cancers in high-risk groups. Cochrane Database System Rev 2007: CD005414.
9. Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjær SK. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978–2007: rapid incidence increase among young Danish women. Int J Cancer 2010;127:2190–8.
10. Christenson LJ, Borrowman TA, Vachon CM, Tollefson MM, Otley CC, Weaver AL, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA 2005;294:681–90.
11. Chen JG, Fleischer AB Jr, Smith ED, Kancler C, Goldman ND, Williford PM, et al. Cost of nonmelanoma skin cancer treatment in the United States. Dermatol Surg 2001;27:1035–8.
12. Housman TS, Feldman SR, Williford PM, Fleischer ABJr, Goldman ND, Acostamadiedo JM, et al. Skin cancer is among the most costly of all cancers to treat for the Medicare population. J Am Acad Dermatol 2003;48:425–9.
13. Wright TI, Spencer JM, Flowers FP. Chemoprevention of nonmelanoma skin cancer. J Am Acad Dermatol 2006;54:933–46.
14. Levine N, Moon TE, Cartmel B, Bangert JL, Rodney S, Dong Q, et al. Trial of retinol and isotretinoin in skin cancer prevention: a randomized, double-blind, controlled trial. Cancer Epidemiol Biomarkers Prev 1997;6:957–61.
15. Frieling UM, Schaumberg DA, Kupper TS, Muntwyler J, Hennekens CH. A randomized, 12-year primary-prevention trial of beta carotene supplementation for nonmelanoma skin cancer in the Physicians' Health Study. Arch Dermatol 2000;136:179–84.
16. Duffield-Lillico AJ, Slate EH, Reid ME, Turnbull BW, Wilkins PA, Combs GF, et al. Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. J Natl Cancer Inst 2003;95:1477–81.
17. O'Brien TG, Simsiman RC, Boutwell RK. Induction of the polyamine biosynthetic enzymes in mouse epidermis by tumor-promoting agents. Cancer Res 1975;35:1662–70.
18. Nowotarski SL, Origanti S, Shantz LM. Posttranscriptional regulation of ornithine decarboxylase. Methods Mol Biol 2011;720:279–92.
19. Haegele KD, Alken RG, Grove J, Schechter PJ, Koch-Weser J. Kinetics of alpha-difluoromethylornithine: an irreversible inhibitor of ornithine decarboxylase. Clin Pharmacol Ther 1981;30:210–7.
20. Simoneau AR, Gerner EW, Nagle R, Ziogas A, Fujikawa-Brooks S, Yerushalmi H, et al. The effect of difluoromethylornithine on decreasing prostate size and polyamines in men: results of a year-long phase IIb randomized placebo-controlled chemoprevention trial. Cancer Epidemiol Biomarkers Prev 2008;17:292–9.
21. Izbicka E, Streeper RT, Yeh IT, Pressley O, Grant M, Andrews JV, et al. Effects of alpha-difluoromethylornithine on markers of proliferation, invasion, and apoptosis in breast cancer. Anticancer Res 2010; 30:2263–9.
22. Meyskens FL Jr, McLaren CE, Pelot D, Fujikawa-Brooks S, Carpenter PM, Hawk E, et al. Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial. Cancer Prev Res 2008;1: 9–11.
23. Bailey HH, Kim K, Verma AK, Sielaff K, Larson PO, Snow S, et al. A randomized, double-blind, placebo-controlled phase 3 skin cancer prevention study of α-difluoromethylornithine in subjects with previous history of skin cancer. Cancer Prev Res 2010;3:8–11.
24. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. Cancer Prev Res 2010;3:696–706.
25. Klaassen I, Braakhuis BJ. Anticancer activity and mechanism of action of retinoids in oral and pharyngeal cancer. Oral Oncol 2002;38:532–42.
26. Sewell JL, Mahadevan U. Of blemishes and bowels: isotretinoin and inflammatory bowel disease. Gastroenterology 2010;138:392–4.
27. Oguri H, Hiruma T, Yamagishi Y, Oikawa H, Ishiyama A, Otoguro K, et al. Generation of anti-trypanosomal agents through concise synthesis and structural diversification of sesquiterpene analogues. J Am Chem Soc 2011;133:7096–105.
28. Pépin J, Khonde N, Maiso F, Doua F, Jaffar S, Ngampo S, et al. Short-course eflornithine in Gambian trypanosomiasis: a multicentre randomized controlled trial. Bull WHO 2000;78:1284–95.
29. Barry DP, Asim M, Leiman DA, de Sablet T, Singh K, Casero RA Jr, et al. Difluoromethylornithine is a novel inhibitor of *Helicobacter pylori* growth, CagA translocation, and interleukin-8 induction. PLoS ONE 2011;6:e17510.
30. Huang C, Wang M, Zhang Y. Analysing panel count data with informative observation times. Biometrika 2006;93:763–76.
31. R. Core Development Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2011. ISBN 3-900051-07-0, Available from: www.R-project.org.
32. Elmets CA, Athar M. Targeting ornithine decarboxylase for the prevention of nonmelanoma skin cancer in humans. Cancer Prev Res 2010;3:8–11.

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