Title
Dose-related alpha-difluoromethylornithine ototoxicity.

Journal
American journal of clinical oncology, 14(4)

ISSN
0277-3732

Authors
Croghan, M K
Aickin, M G
Meyskens, F L

Publication Date
1991-08-01

Peer reviewed

Am J Clin Oncol (CCT) 14(4): 331–335, 1991.

Dose-Related α-Difluoromethylornithine Ototoxicity

Marilyn K. Croghan, M.D., Mikel G. Aickin, Ph.D., and Frank L. Meyskens, M.D.

We assessed the ototoxicity associated with oral α-difluoromethylornithine (DFMO) administration in 58 patients with metastatic malignant melanoma. One hundred seventy-nine sequential audiograms obtained from patients treated with DFMO alone (16 patients) or in combination with α2b-interferon (42 patients) were evaluated. DFMO doses ranged from 2 to 12 g/m^2/d and were given over periods of 2 to 50 weeks. Total doses ranging from 60 g/m^2 to 1390 g/m^2 were correlated with clinical effects and pure tone audiometric changes. By regression analysis cumulative DFMO dose showed a consistent and statistically significant positive relationship to hearing loss at multiple frequencies (500, 1000, 2000, 4000, and 8000 Hz). Patients with normal (threshold < 30 db) baseline audiograms demonstrated more hearing loss than those with abnormal (threshold ≥ 30 db) baseline audiograms at the higher frequency levels. Of the patients with normal prestudy hearing thresholds 10% or less developed a demonstrable hearing deficit at cumulative DFMO doses below 150 g/m^2. Conversely, up to 75% of the patients who received more than 250 g/m^2 developed a clinically demonstrable hearing loss. Other factors which adversely affected hearing included age, male gender, and the concomitant use of α2b-interferon. In summary, the risk of clinically significant hearing loss in patients treated with DFMO was primarily related to dose and the presence of a pre-existing hearing deficit.

Key Words: α-difluoromethylornithine—Ototoxicity.

Polyamines are organic cations which affect the regulation of cell growth, proliferation, and differentiation (1,2). DFMO, an irreversible inhibitor of ornithine decarboxylase, blocks the first step in the polyamine biosynthetic pathway and has been shown to have both in vitro (3,4,5) and in vivo (5,6,7) activity against a variety of human malignancies. DFMO is an effective treatment for all stages of African trypanosomiasis (8,9) and has also been shown to be highly active against *Pneumocystis carinii* pneumonia in immunosuppressed patients who have failed to respond to or are intolerant of standard therapy (10,11). In animal models DFMO is a potent antineoplastic agent used to prevent the induction of breast (12), colon (13), and skin (14) carcinomas. Clinical trials are currently evaluating the role of DFMO as a preventive anticarcinogenic agent.

Toxicities related to DFMO, administered alone or in conjunction with interferon (IFN), have been reported from several phase I-II clinical trials (5,7,15–18). Significant and sometimes dose-limiting ototoxicity has been both subjectively and objectively described (5,16–18). However, little quantitative information has been published which correlates hearing loss with administered dose of DFMO. Similarly, no information is available regarding other factors which may have influenced the onset or degree of ototoxicity. In this study, we have defined the relationship between auditory changes and cumulative DFMO dose. Other parameters which may affect hearing (such as age, gender, baseline auditory function, and concomitant administration of IFN-α2b) have also been evaluated.

From the Department of Radiation Oncology (M.K.C.), University of Arizona Cancer Center, Tucson, Arizona; Division of Disease Prevention (M.G.A.), Phoenix, Arizona; and UCI Cancer Center (F.L.M.), Orange, California.

Address correspondence and reprint requests to Dr. Marilyn Croghan, Department of Radiation Oncology, University of Arizona Cancer Center, 1501 N. Campbell Avenue, Tucson, AZ 85724, U.S.A.

PATIENTS AND METHODS

Patients with metastatic malignant melanoma entered into clinical trials of DFMO administered alone (phase I trial) or with IFN-α2b (phase I-II trials) were considered for evaluation. A signed informed consent form approved by the University of Arizona Institutional Review board was obtained from each patient prior to study entry. Only patients who had undergone prestudy audiometric testing within two weeks of study entry and had at least one repeat audiometric examination during the course of DFMO therapy were included in the study. Multiple sequential audiograms were evaluated whenever available. Hearing acuity, by pure tone testing, was recorded at 500, 1000, 2000, 4000, and 8000 Hz. Pure tone recognition at or below 30 db was considered to be within normal auditory range. Demographic information such as patient age and gender were obtained from the study entry forms.

Patients receiving DFMO alone were begun on an oral dose of 2 g/m^2 every eight hours and the dose was escalated at two-week intervals to 3 g/m^2 and then 4 g/m^2 as tolerated. Audiograms were routinely obtained on initiation (prior to the first dose) and completion (on the final day) of therapy. Patients receiving DFMO concomitantly with IFN-α2b were begun on an oral dose of 1.33 g/m^2 or 2.0 g/m^2 every eight hours on days 1 through 11 of each 14 day cycle. Audiograms were routinely obtained on initiation (prior to the first dose) of treatment and every 2–4 weeks thereafter. DFMO doses were decreased in patients with grade III/IV toxicity. No patient discontinued therapy because of ototoxicity alone. Patients whose disease was responding to treatment remained on DFMO despite the documented presence of hearing loss.

Multiple linear regression was used to explain hearing loss at each of the five frequency levels. Final equations were determined by a guided backward stepwise procedure in which retained variables were selected on the basis of statistical significance, multicolinearity considerations, and stability under single-case deletion (19). Evaluation of potential outliers was carried out in all cases.

RESULTS

Patient characteristics are shown in Table 1. Overall, 179 audiograms were evaluated from 58 patients; 16 patients received DFMO alone, and 42 patients received DFMO plus IFN-α2b. Twenty-three patients (40%) had only one audiogram after the initiation of therapy. The remaining 25 patients (60%) had two to seven sequential audiograms while receiving oral DFMO. Doses ranged from 2 to 12 g/m^2/day and were given over periods of 2 to 50 weeks.

TABLE 1. *Patient characteristics*

Males	36
Females	22
Mean age (years)	50.4
Age range (years)	15–78
Baseline hearing loss (≥30 db)	29/58 (50%)
Dose range (g/m^2)	60–1390

The regression equations obtained at frequencies of 500, 1000, 2000, and 8000 Hz are shown in Table 2. Factors considered for entry into regression equations as explanatory variables were: cumulative DFMO dose (log scale), age, gender, concomitant use of IFN-α2b, and the presence of initial hearing loss. All two-factor interactions which included cumulative DFMO dose were considered.

Cumulative DFMO dose showed a consistent and statistically significant positive relationship to hearing loss at all five frequency levels ($p = .0002$–$.0387$). Age was consistently and positively related to hearing loss ($p = .0108$–$.0524$) except at a frequency of 2000 Hz. Figure 1 shows the decibels of hearing loss with a 95% upper confidence limit for patients receiving 150 g/m^2 or 250 g/m^2 cumulative dose of DFMO. A subtle (1–2 db) but consistent increase in the degree of hearing loss was observed with increasing age. Patients with a normal baseline audiogram in the 4000 and 8000 Hz ranges had significantly more hearing loss than patients with abnormal baseline audiograms ($p \leq .001$). An insufficient number of patients presented with initial hearing loss at 500 and 1000 Hz to evaluate the effect of this parameter at these lower frequency levels. Concomitant administration of IFN-α2b increased hearing loss at 1000 and 2000 Hz ($p = .0176, .0265$), but did not significantly alter loss at 500, 4000, or 8000 Hz.

Although gender alone influenced ototoxicity (males suffered more hearing loss than females), the effect was complicated by an interaction with cumulative DFMO doses at the lower three frequencies. As graphically illustrated in Fig. 1, these findings demonstrate that the relationship between hearing loss and cumulative DFMO dose differed between the two sexes. The change in hearing occurred more rapidly for males than females, particularly at cumulative doses below 400 g/m^2.

Patients with normal prestudy hearing thresholds were evaluated to better assess the clinical significance of observed hearing loss (Fig. 2). Once again, the positive correlation between cumulative DFMO dose and ototoxicity was noted. Ten percent or less of the patients who received cumulative doses below 150 g/m^2

TABLE 2. *Regression coefficients (and p-values) of variables explaining hearing loss at five frequencies*

	Frequency (Hz)				
Variable	500	1000	2000	4000	8000
LogDose[a]	5.95	5.61	5.03	4.65	4.61
	(.0002)	(.0005)	(.0047)	(.0006)	(.0387)
Age	.1533	.1358		.1755	.2111
	(.0108)	(.0225)		(.0267)	(.0524)
Age*LogDose[b]					
Sex[c]	−23.41	−25.72	−28.86	6.11	−32.12
	(.0482)	(.0290)	(.0281)	(.0111)	(.0824)
Sex*LogDose	4.94	6.26	6.27		6.35
	(.0252)	(.0045)	(.0108)		(.0658)
IFN[d]	4.26	5.63	5.52		
	(.0730)	(.0176)	(.0265)		
IFN*LogDose					
Init[e]	[f]	[f]		−13.32	−12.06
				(.0000)	(.0012)
Init*LogDose					
Intercept	−33.11	−33.79	−23.10	−21.59	−18.85
Res St Dev[g]	9.15	9.08	10.19	11.20	12.53
R-squared	.379	.457	.331	.228	.261
N[h]	121	121	121	121	95

[a] Natural log of cumulative dose of DFMO.
[b] Blank spaces indicate zero regression coefficients. Variables with all zero coefficients are shown to emphasize that they were used in determining the final regression equation.
[c] 0 = female, 1 = male.
[d] 0 = no interferon, 1 = interferon.
[e] 0 = no initial hearing loss, 1 = initial hearing loss.
[f] Insufficient number of cases of hearing loss to permit estimation.
[g] Residual standard deviation.
[h] Sample sizes varied according to pattern of missing values.

developed a demonstrable hearing deficit. In contrast, hearing losses were observed in up to 75% of patients who received cumulative doses above 250 g/m^2 (Fig. 3). Documented hearing abnormalities occurred in the frequency range of normal voice tones (500–2000 Hz) as well as at higher frequencies (4000–8000 Hz).

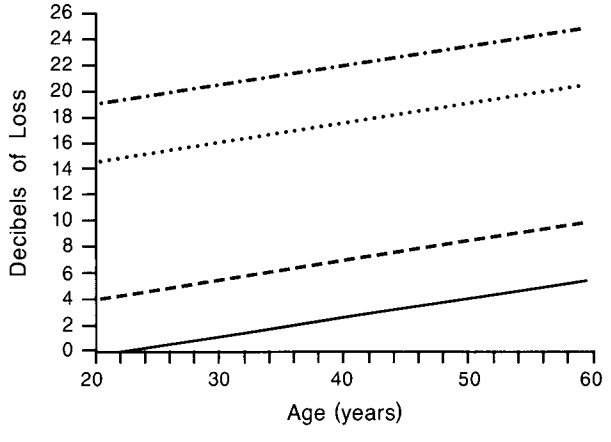

FIG. 1. Decibels of hearing loss with increasing age at a cumulative dose of 150 g/m^2 or 250 g/m^2 with a 95% upper confidence limit (CI). The solid line indicates 150 g/m^2, the dashed line 250 g/m^2, the dotted line 150 g/m^2 + 95% CI, and the alternating dotted and dashed line 250 g/m^2 + 95% CI.

DISCUSSION

In this study we have shown that DFMO ototoxicity is directly correlated with the cumulative dose received. Other factors which influenced toxicity included age,

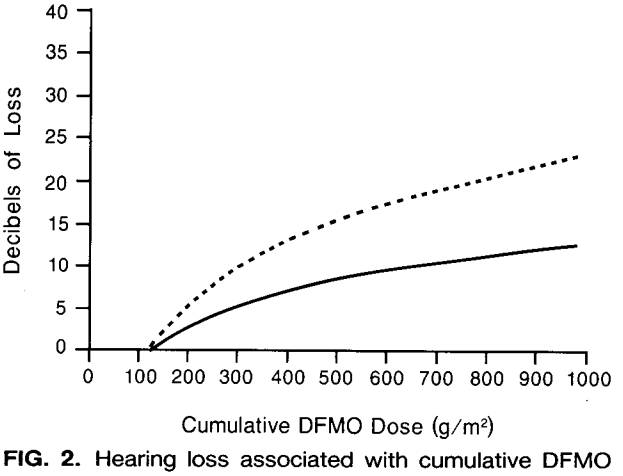

FIG. 2. Hearing loss associated with cumulative DFMO dose in males (dashed line) and females (solid line).

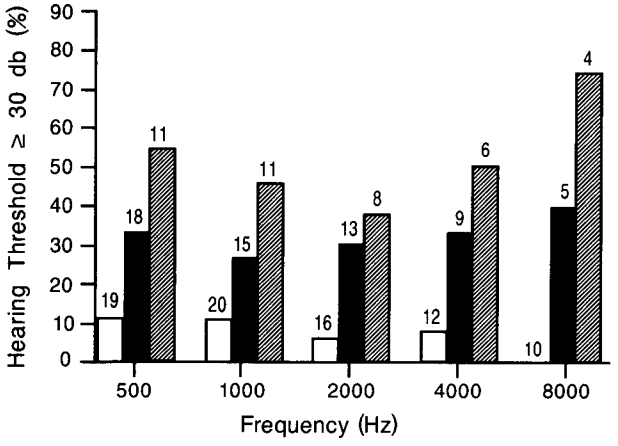

FIG. 3. Development of hearing loss in patients with normal baseline hearing thresholds. Cumulative DFMO doses of <150 g/m^2, 150 <250 g/m^2, and 250 <500 g/m^2 are represented by the white, black, and striped bar graphs, respectively.

gender, concomitant use of IFN-α2b, and the presence of an initial hearing loss. Decrements in hearing were recorded at cumulative doses as low as 60 g/m^2. The objective presence of ototoxicity did not always result in clinically detectable hearing loss. A hearing threshold below 30 db is considered to be within the normal range. In our experience, a hearing threshold of ≥30 db correlated well with a subjective complaint of hearing loss. Using this criteria, significant hearing loss was detected in less than 10% of patients receiving a cumulative dose below 150 g/m^2. Conversely, up to 75% of the patients who received more than 250 g/m^2 developed a clinically demonstrable hearing loss. Hearing deficits occurred in both the lower (500–2000 Hz) and higher (4000–8000 Hz) frequency ranges. When individual patients were examined with sequential audiograms, documented hearing loss was found to stabilize or progressively worsen, with continued DFMO administration. In this study, patients with stable or progressive disease and a good performance status at the completion of DFMO administration were generally entered into other therapeutic trials, while those with a poor or rapidly declining performance status were given supportive care only. Off-treatment audiograms were therefore either not obtained or were difficult to interpret due to the confounding presence of other experimental agents. Overall, an insufficient number of audiograms was available to objectively evaluate post-treatment hearing recovery, but we (5,18) and others (16) have previously reported rapid improvement in hearing with discontinuation of DFMO.

One potential mechanism for the development of ototoxicity may be the induction of polyamine depletion in melanin-containing transducer cells of the inner ear. However, the exact mechanism by which DFMO causes ototoxicity and therefore, the effect of additional agents on DFMO ototoxicity are currently unknown. In this study, the concomitant use of IFN-α2b resulted in increased hearing loss in the lower but not the higher frequency ranges. We have not evaluated patients concomitantly receiving other known ototoxic substances such as aminoglycosides or amphotericin B.

In conclusion, the ototoxicity associated with DFMO is directly related to the cumulative dose received. Other factors which influenced DFMO-related hearing loss included age, gender, baseline hearing acuity, and the concomitant use of agents such as IFN-α2b. This study provides important information for clinicians using high-dose (≥2 g/m^2/d) DFMO therapy in the treatment of African trypanosomiasis, *Pneumocystis carinii* pneumonia, and metastatic malignancies. Minimal ototoxicity was observed in the majority of patients who received a cumulative DFMO dose less than 150 g/m^2. Whether utilization of lower daily dose rates, such as the 0.5–2.0 g/m^2/d used in cancer prevention trials, will further reduce the observed incidence and degree of hearing loss requires further investigation.

REFERENCES

1. Raina A, Janne I. Physiology of the natural polyamines putrescine, spermedine and spermine. *Med Biol* 1975;53:121–47.
2. Pegg AE, McCann PP. Polyamine metabolism and function. *Am J Physiol* 1982;243:212–21.
3. Luk GD, Goodwin G, Marton LJ, Baylin SB. Polyamines are necessary for the survival of human small-cell carcinoma in culture. *Proc Natl Acad Sci USA* 1981;78:2355–8.
4. Kingsnorth AN, Russell WE, McCann PP, et al. Effects of α-difluoromethylornithine and 5-fluorouracil on the proliferation of a human colon adenocarcinoma of cell lines. *Cancer Res* 1983;43:4035–8.
5. Meyskens FL, Kingsley EM, Glattke T, et al. A phase II study of α-difluoromethylornithine (DFMO) for the treatment of metastatic melanoma. *Invest New Drugs* 1986;4:257–62.
6. Luk GD, Abeloff MD, Griffen CA, et al. Successful treatment with dl-α-difluoromethylornithine in established human cell variant lung carcinoma implants in athymic mice. *Cancer Res* 1983;43:4239–43.
7. Levin VA, Chamberlain MC, Prados MD, et al. Phase I/II study of DFMO and MGBG for the treatment of recurrent primary brain tumors. [Abstract]. *A Proc of Amer Acad Cancer Res* 1987;28:218.
8. Sjoerdsma A, Goden JA, Schechter PJ, et al. Successful treatment of lethal protozoal infections with the ornithine decarboxylase inhibitor, α-difluoromethylornithine. *Trans Am Phys Assn* 1984;97:70–9.
9. McCann PP, Bacchi CJ, Clarkson AB, et al. Inhibition of polyamine biosynthesis by α-difluoromethylornithine in African trypanosomes and *Pneumocystis carinii* as a basis of chemotherapy: biochemical and clinical aspects. *Am J Trop Med Hyg* 1986;35(6):1153–6.
10. Golden JA, Sjoerdsma A, Santi DV. *Pneumocystis carinii* pneumonia treated with α-difluoromethylornithine. *Western J Med* 1984;141(5):613–23.

11. Gilman TM, Paulson YJ, Boylen CT, et al. Eflornithine treatment of pneumonia in AIDS. *JAMA* 1986;256(16):2196–7.
12. Thompson HJ, Meeker LD, Herbst EJ, et al. Effect of D, L- α-difluoromethylornithine on murine mammary carcinogenesis. *Carcinog Cancer Res* 1985;45:1170–3.
13. Kingsnorth AN, King WWK, Diekema KA, et al. Inhibition of ornithine decarboxylase with α-difluoromethylornithine: reduced incidence of dimethylhydrazine-induced colon tumors in mice. *Cancer Res* 1983;43:2545–9.
14. Takigawa M, Verma AK, Simsiman RC, Boutwell RK. Inhibition of mouse skin tumor promotion and of promotor stimulated epidermal polyamine biosynthesis of α-difluoromethylornithine. *Cancer Res* 1983;43:3732–8.
15. Abeloff MD, Slovik M, Luk GD, et al. Phase I trial and pharmacokinetic study of intravenous and high dose oral α-difluoromethylornithine (DFMO). [Abstract]. *Proc ASCO* 1984;3:34.
16. Abeloff MD, Rosen ST, Luk GD, et al. Phase II trials of α-difluoromethylornithine, an inhibitor of polyamine synthesis in advanced small cell lung cancer and colon cancer. *Cancer Treat Rep* 1986;70:843–5.
17. Talpaz M, Plager C, Quesada J, et al. Difluoromethylornithine and leukocyte interferon: a phase I study of cancer patients. *Eur J Cancer Clin Oncol* 1986;22:685–9.
18. Croghan MK, Booth A, Meyskens FL. A phase I trial of recombinant interferon-α and α-difluoromethylornithine in metastatic melanoma. *J Biol Response Mod* 1988;7:409–15.
19. Draper N, Smith H. *Applied regression analysis.* New York: John Wiley; 1966.