UC Irvine

UC Irvine Previously Published Works

Title

Ocular toxic effects of fenretinide.

Permalink

<https://escholarship.org/uc/item/0pq1v85r>

Journal

Journal of the National Cancer Institute, 82(12)

ISSN

0027-8874

Authors

Modiano, MR
Dalton, WS
Lippman, SM
et al.

Publication Date

1990-06-01

DOI

10.1093/jnci/82.12.1063

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

References

- (1) BAJETTA E, NEGRETTI E, GIANNOTTI B, ET AL: Phase II study of interferon alpha-2a (rIFN alpha-2a) and dacarbazine (DTIC) in metastatic melanoma (MM). *Proc ASCO* 8:286, 1989
- (2) KERR R, PIPPEN P, MENNEL R, ET AL: Treatment of metastatic malignant melanoma with a combination of interferon alpha-2a (Ifn alpha-2a; Roferon) and dacarbazine (DTIC). *Proc ASCO* 8:288, 1989
- (3) VOROBIOF D, FALKSON G, VOGES CW: DTIC versus DTIC and recombinant interferon alfa 2b (rIFN 2b) in the treatment of patients (PTS) with advanced malignant melanoma (MM). *Proc ASCO* 8:284, 1989
- (4) KIRKWOOD JM, ERNSTOFF MS: Potential applications of the interferons in oncology: Lessons drawn from studies of human melanoma. *Semin Oncol* 13:48-56, 1986
- (5) KIRKWOOD JM, ERNSTOFF MS, GIULIANO A, ET AL: Clinical trials of interferon alfa-2B (Intron A, alpha IFN) in melanoma: Review of phase I, II, and III studies. Presented at the Fourteenth International Cancer Congress, Budapest, August 1986

Ocular Toxic Effects of Fenretinide

Manuel R. Modiano,* William S. Dalton, Scott M. Lippman, Leonard Joffe, Ann R. Booth, Frank L. Meyskens, Jr.

Retinoids, the natural and synthetic analogues of vitamin A, inhibit growth and induce differentiation in many animal and human malignant cell types, and they show clinical promise as chemopreventive antineoplastic agents (1-3). Isotretinoin has been the most widely used synthetic retinoid in cancer treatment and cancer prevention trials. However, its toxic effects, primarily mucocutaneous and teratogenic, make it difficult to tolerate, since continued exposure to the retinoid is required to maintain its effect (1,2).

We have recently completed a phase II trial of fenretinide in advanced malignancies (4). Fenretinide was administered in doses of 300-400 mg/day to 16 patients with advanced, metastatic, refractory breast cancer, 15 with melanoma, five with Kaposi's sarcoma, and one with mycosis fungoides. Although fenretinide was inactive in advanced dis-

ease, its toxic effects were mild and reversible. Toxic effects included a 45% elevation over baseline of serum triglycerides in 6% of the patients, a 13% elevation of serum cholesterol in 20% of patients, and mild mucocutaneous toxic effects in 52%.

In addition, 10% suffered from nyctalopia (decreased night vision), which resolved when treatment was discontinued. One of these patients had reversible electroretinographic changes consisting of a significant decrease in the amplitude for scotopic (dark-adapted, or rod-mediated) vision on electroretinogram, which did not occur until after 1 month of treatment. This decrease was observed predominantly in the B-wave for rods on the electroretinogram and developed while the patient was receiving the higher dose of fenretinide (400 mg/day). Amplitude decreases for this patient's right eye were as follows: the pretherapy A-wave amplitude (normal, 150-250 μ V) was 190 μ V, decreasing to 160 μ V after 2 months of treatment, and the B-wave amplitude (normal, 365-550 μ V) dropped from 430 to 290 μ V after 2 months of therapy. No changes in the A-wave amplitude were recorded for the left eye, but the B-wave amplitude dropped from 430 to 340 μ V after 2 months on fenretinide. These changes reversed after fenretinide was discontinued. Patients were given fenretinide for 15-300 days (mean, 52).

Kaiser-Kupfer et al. (5) have also looked at the effect of fenretinide on the electroretinogram. They reported on electroretinograms for three of five patients with basal cell carcinoma who were receiving fenretinide at a dose of 800 mg/day. In two of these patients, dark-adaptation thresholds were elevated and the electroretinogram shows that amplitude for rod-mediated vision was depressed. Both developed nyctalopia within 3 weeks of treatment.

Costa et al. (6) also found reversible nyctalopia in one of 25 patients treated with 300 mg of fenretinide per day over 6 months. These comparisons suggest that

the ocular toxic effects of fenretinide may be dose related. The ocular side effects of fenretinide, which resemble those of other synthetic retinoids (7), may be due to the interference of these agents with vitamin A metabolism. This hypothesis is supported by a recent pharmacokinetic evaluation of patients receiving this treatment (8), which revealed that fenretinide caused a reduction in serum retinol levels.

References

- (1) LIPPMAN SM, KESSLER JF, MEYSKENS FL JR: Retinoids as preventive and therapeutic anticancer agents (part I). *Cancer Treat Rep* 71:391-405, 1987
- (2) LIPPMAN SM, KESSLER JF, MEYSKENS FL JR: Retinoids as preventive and therapeutic anticancer agents (part II). *Cancer Treat Rep* 71:493-515, 1987
- (3) LIPPMAN SM, MEYSKENS FL JR: Retinoids for the prevention of cancer. In *Nutrition and Cancer Prevention: The Role of Micronutrients* (Moon TE, Micozzi E, eds). New York: Marcel Dekker, 1987, pp 243-271
- (4) MODIANO MR, DALTON WS, LIPPMAN SM, ET AL: Phase II study of fenretinide (N-[4-hydroxyphenyl]retinamide) in advanced breast cancer and melanoma. *Invest New Drugs*. In press
- (5) KAISER-KUPFER MI, PECK GL, CARUSO RC, ET AL: Abnormal retinal function associated with fenretinide, a synthetic retinoid. *Arch Ophthalmol* 104:69-70, 1986
- (6) COSTA A, MALONE W, PERLOFF M, ET AL: Tolerability of the synthetic retinoid fenretinide (HPR). *Eur J Cancer Clin Oncol* 25:805-808, 1989
- (7) EDWARDS L, ALBERTS DS, LEVINE N: Clinical toxicity of low-dose isotretinoin. *Cancer Treat Rep* 70:663-664, 1986
- (8) PENG Y-M, DALTON WS, ALBERTS DS, ET AL: Pharmacokinetics of N-4-hydroxyphenyl-retinamide and the effect of its oral administration on plasma retinol concentrations in cancer patients [published erratum appears in *Int J Cancer* 44:567, 1989]. *Int J Cancer* 43:22-26, 1989

Received April 16, 1990; accepted April 17, 1990.

M. R. Modiano, W. S. Dalton, L. Joffe, A. R. Booth, University of Arizona, Arizona Cancer Center, Tucson, AZ.

S. M. Lippman, The University of Texas M. D. Anderson Cancer Center, Houston, TX.

F. L. Meyskens, Jr., University of California, Irvine Clinical Cancer Center, Irvine, CA.

*Correspondence to: Manuel R. Modiano, M.D., Department of Cancer Prevention and Control, Arizona Cancer Center, 1515 N. Campbell Ave., Rm. 1995, Tucson, AZ 85724.