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Ocular Toxic Effects of Fenretinide


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 disease, 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. Of 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 uV) was 190 uV, decreasing to 160 uV after 2 months of treatment, and the B-wave amplitude (normal, 365-550 uV) dropped from 430 to 290 uV 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 uV after 2 months on fenretinide. These changes reversed after fenretinide was discontinued. Patients were given fenretinide for 15-300 days (mean, 52).

Kaiser-Kupper 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.

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