Fenretinide Activity in Retinoid-Resistant Oral Leukoplakia

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Abstract

Purpose: To test the hypothesis that the retinamide N-(4-hydroxyphenyl)retinamide (fenretinide) would be clinically active potentially via receptor-independent apoptosis and receptor-dependent effects in natural retinoid-resistant oral leukoplakia patients—the first test of this hypothesis in any in vivo setting.

Experimental Design: A phase II trial of fenretinide (200 mg/d for 3 months) in oral leukoplakia patients who had not responded (de novo resistance) or who had responded and then relapsed (acquired resistance) to previous treatment with natural retinoids. We analyzed apoptosis via the terminal deoxynucleotidyl transferase–mediated nick end labeling in situ DNA fragmentation assay.

Results: We accrued 35 evaluable patients with retinoid-resistant oral leukoplakia, 12 (34.3%) had partial responses to fenretinide (95% confidence interval, 19.2-52.4%), and response was associated with acquired resistance to natural retinoids (P = 0.015, Fisher’s exact test). Nine responders progressed within 9 months of stopping fenretinide. Toxicity was minimal and compliance was excellent. Mean apoptosis values (SE) increased from 0.35% (0.25%) at baseline to 1.18% (0.64%) at 3 months (P = 0.001, sign test); this increase did not correlate with clinical response. The increases in 3-month mean serum concentrations of fenretinide (0.23 μmol/L) and N-(4-methoxyphenyl)retinamide (0.57 μmol/L) correlated with decreased retinol concentrations [Spearman correlation coefficient of −0.57 (P = 0.001) and −0.43 (P = 0.01), respectively].

Conclusions: Low-dose fenretinide was clinically active and produced a small increase in apoptosis in retinoid-resistant oral leukoplakia.

With an annual incidence of over 300,000 new cases worldwide, oral cancer is the most common cancer of the head and neck. It causes high morbidity and has a 5-year mortality rate of >50%, which has not decreased in over 20 years (1, 2).

Leukoplakia is the most common premalignant lesion in the oral cavity and is associated with an increased risk of oral cancer either at the leukoplakia site or elsewhere in the oral cavity (3). The degree of cancer risk is associated with the presence of dysplasia and various molecular alterations (4, 5), and there is no standard approach for reducing this risk. Chemoprevention is a major approach under investigation for reducing the cancer risk of oral leukoplakia, also called intraepithelial neoplasia (IEN), and thus for reducing the burden of oral cancer.

Retinoids are among the most extensively studied class of chemoprevention agents in oral IEN to date, and natural retinoids, including retinyl palmitate and 13-cis-retinoic acid (13cRA; which is a natural metabolite of vitamin A and is present endogenously in human serum), are the best-studied retinoids in this setting (6–10). Short-term (3-6 months) natural retinoid therapy was significantly clinically active in randomized oral IEN trials. Most responding oral IEN, however, recurred within months of stopping treatment. Although prolonged retinoid treatment can delay progression, oral IEN becomes resistant to treatment over time, eventually progressing in association with persistent genotypic alterations and cancer development (11, 12). De novo or acquired resistance has proven to be a major obstacle to the use of natural retinoids in the setting of advanced oral IEN, which needs better treatment to prevent or delay oral cancer development (11).

The classic signaling pathways for the effects of 13cRA and other natural retinoids involve the nuclear retinoid receptors—retinoic acid receptors (RAR) and retinoid X receptors. It is
thought that the major effect of natural retinoids, mediated by the RARs and retinoid X receptors, is to modulate cell growth and differentiation. Translational studies have shown that 13cRA activates the transcription of genes, such as RAR-β, containing retinoic acid response elements in their promoter regions (13).

The retinamides are synthetic retinoids that can potentially induce apoptosis in cancer cells via a retinoid receptor-independent mechanism in addition to having retinoid receptor-dependent effects (14, 15). The retinamide N-(4-hydroxyphenyl)retinamide (4-HPR, or fenretinide) can induce apoptosis via reactive oxygen species, mitochondrial membrane permeability transition, activation of members of the activator protein-1 transcription factor family and of caspase-8, ceramide generation, and inhibition of nuclear factor-κB activation (16–20). Fenretinide can induce apoptosis in cancer cell lines resistant to natural retinoids that work via the classic retinoid-receptor signaling pathways and in receptor-knockout cells (refs. 21–24; summarized in ref. 17). These data suggest that fenretinide (a) may overcome de novo or acquired resistance to 13cRA or other natural retinoids and (b) may eliminate premalignant clones via apoptosis, which would allow effective short-term treatment of oral IEN. We hypothesized that fenretinide would be clinically active in oral IEN via receptor-independent apoptosis in de novo retinoid-resistant lesions and via receptor-independent and receptor-dependent effects in lesions with acquired resistance. The phase II translational study of short-term therapy with fenretinide in natural retinoid-resistant oral IEN is the first test of this hypothesis in vivo.

Patients and Methods

Patient eligibility. All patients had bidimensionally measurable advanced oral IEN, as defined previously (9), that was resistant to a natural retinoid. Lesion resistance was defined as (a) never responding (including no change or progressing) or (b) responding initially but subsequently progressing on prior retinoid therapy. All patients came from our National Cancer Institute randomized trial of 13cRA versus retinyl palmitate, except one who was resistant to 13cRA given off protocol. Other eligibility criteria included adequate renal, hematologic, and hepatic function and a Zubrod PS <2. The protocol was approved by the M. D. Anderson Cancer Center Institutional Review Board, and informed, signed consent was required from each patient.

Clinical trial design. We tested oral fenretinide (200 mg/d) for 3 months in a single-arm phase II trial that included a monthly 3-day drug holiday to prevent fenretinide-related ocular toxicity. The primary end point was the clinical response of oral IEN; secondary end points included toxicity and changes in the biomarkers discussed below. Patients were accrued in two stages, per a standard phase II design (described in the “Statistical Considerations” section), and evaluated every 3 months for 1 year. Fenretinide was supplied by R.W. Johnson Pharmaceutical Research Institute. The full 200 mg dose of fenretinide was recommended to be taken at breakfast. Patients were seen at monthly intervals and evaluated for compliance, drug-related toxicity, and serum drug concentrations. Response and toxicity were assessed according to standard criteria (9).

Serum evaluations for fenretinide, N-(4-methoxyphenyl)retinamide, and retinol. Concentrations of fenretinide and its major metabolite N-(4-methoxyphenyl)retinamide (4-MPR) and retinol were measured in serum samples obtained at two time points (baseline and 3 months of treatment), frozen at −70°C, and protected from light exposure. Determinations of fenretinide and 4-MPR concentrations were made using a previously validated high-performance liquid chromatography assay with 4-ethoxyphenylretinamide as an internal standard (25). The chromatographic separation was done on a Vydac 201TP column (0.46 × 25 cm). The isocratic mobile phase consisted of 55% acetonitrile, 10% n-butyl alcohol, 35% water, and 0.01 mol/L ammonium acetate. The UV detector was programmed at 364 nm for the first 12 minutes, 325 nm for the next 3 minutes, and 364 nm for the last 8 minutes to correspond to the elution times of fenretinide, retinol, and 4-MPR/4-ethoxyphenylretinamide, respectively. Serum concentrations were measured in blood collected before breakfast – 24 hours after the 200 mg dose of the previous morning (at breakfast).

Apoptosis assay: terminal deoxynucleotidyl transferase–mediated nick end labeling. Apoptosis in tissue biopsies was analyzed by the terminal deoxynucleotidyl transferase–mediated nick end labeling method as follows: formalin-fixed, paraffin-embedded tissue sections were deparaffinized in xylene, rehydrated in a series of ethanol solutions (100–50%), and first treated with 0.2 N HCl for 10 minutes at room temperature and then with proteinase K (20 μg/mL) for 30 minutes at 37°C. The endogenous peroxidase activity was blocked by incubation in a 3% methanolic hydrogen peroxide solution for 5 minutes at room temperature. Subsequently, the sections were incubated with terminal deoxynucleotidyl transferase buffer (Trevigen, Inc., Gaithersburg, MA) for 5 minutes and then transferred to a terminal deoxynucleotidyl transferase enzyme mixture containing terminal deoxyribonucleotidyl transferase buffer, terminal deoxynucleotidyl transferase at 1:400 (Roche Biomedical Corp, Indianapolis, IN), biotinylated dUTP at 1:200 (Roche), and 400 μmol/L MnSO4 and incubated at 37°C for 60 minutes. To detect the positive signal, the sections were incubated with the ABC kit (Vector Laboratories, Burlingame, CA) for 30 minutes in the dark. This was followed by incubation with 3-amino-9-ethylcarbazole (Sigma Chemical Co., St. Louis, MO) solution for 30 minutes to visualize the peroxidase complex. Finally, the sections were mounted with Aqua mount medium under coverslips. Deoxynucleotidyl transferase was omitted to create negative controls. A positive control consisted of cytospun cells, which were obtained from an APO-BRDU Apoptosis kit (Phoenix Flow Systems, San Diego, CA) or from head and neck cancer cells previously treated with 10 μmol/L fenretinide for 12 hours. The stained sections were reviewed independently by two pathologists with an Olympus microscope. The percentage of positive cells was calculated after counting the total cells and positively stained cells.

In situ mRNA hybridization studies of RAR-β expression. Non-radioactive in situ hybridization of RAR-β was done using digoxigenin-labeled antisense riboprobes on formalin-fixed, paraffin-embedded tissue biopsies, as described previously (13). The binding specificity of the antisense riboprobes was verified using sense probes as controls. Staining was scored as either detectable or undetectable. RNA quality was verified by in situ hybridization of retinoid X receptor-α mRNA, which is expressed constitutively in oral epithelium.

Statistical considerations. We used a Simon’s optimal two-stage design for phase II trials. The first stage was designed for 12 patients. With no response or one response in the first stage, the trial would be terminated and fenretinide would be considered inactive. With two or more responses in the first stage, the trial would continue and accrue 23 additional patients. Fenretinide would be considered active if ≥5 patients responded and inactive if <5 responded. The design would have type I and type II error rates controlled at the 10% level with response rates of 10% and 30% under the null and alternative hypotheses, respectively. Descriptive statistics and frequency tabulation were used to summarize the patient characteristics and toxicity profile. χ2 test (or the Fisher’s exact test for small samples) was applied to associations between unpaired categorical variables, and sign test was applied to associations between paired categorical variables. We calculated the Spearman’s rank correlation for associations between retinol, fenretinide and 4-MPR levels in serum. All P values were based on two-sided tests.

Results

A total of 38 patients were registered to this two-stage study. Three of the 12 patients accrued in the first stage responded,
and so we initiated the second stage and accrued a total of 35 evaluable patients. Of the three registered patients who were not evaluable, one never started therapy and so was excluded from all analyses and two were excluded from the response analyses for reasons unrelated to fenretinide—death from a pulmonary embolism 23 days after starting the study in one case; refusal of further treatment only 2 days after starting fenretinide because of a sinus infection in the other case. Of the 35 evaluable patients, 10 had initially responded to previous retinoid treatment but then progressed, and 25 had not responded to previous retinoid treatment.

The patient characteristic data are based on all 37 patients evaluable for toxicity. There were 25 men and 12 women and 31 White, 4 Hispanic, 1 Black, and 1 Asian patients. The mean age (SD) was 60.1 (13.4) years; median age was 61 years (range, 26-84). The most common primary lesion sites were the buccal mucosa (n = 15) and ventrolateral tongue or floor of mouth (n = 11). Dysplastic lesions occurred in 10 patients. Baseline smoking statuses were as follows: never (n = 6), former (n = 19), and current (n = 12). Baseline alcohol use statuses were as follows: never (n = 10), former (n = 11), and current (n = 16).

The 3-month response data (in the 35 patients evaluable for response) were as follows: 0 complete responses, 12 partial responses, 15 cases of stable disease, and 8 cases of progressive disease. Nine of the 12 responding patients progressed within 9 months of stopping fenretinide. The primary study end point of overall 3-month clinical response (complete responses + partial responses) was 34.3% (95% confidence interval, 19.2-52.4%). Prior clinical response to natural retinoids (see Patients and Methods) was significantly associated with subsequent response to fenretinide (P = 0.015, Fisher’s exact test)—the response rates to fenretinide were 70% for previous responders versus 20% for previous nonresponders (Table 1).

The mean compliance (percentage of drug taken divided by drug prescribed for each patient) was 98.4%. No patient took <80% of drug, 3 took 80% to 90%, and 32 took >90%. Toxicity occurred in 15 patients and consisted primarily of mucocutaneous dryness, which was grade 1 in 14 patients and grade 2 in 1 patient (skin dryness).

Serum concentrations of fenretinide, 4-MPR, and retinol are listed in Table 2. The mean 3-month fenretinide and 4-MPR concentrations were 0.23 and 0.57 μmol/L, respectively, and the maximum concentrations were 0.66 and 1.76 μmol/L, respectively. Fenretinide concentrations directly correlated with 4-MPR concentrations (Spearman correlation coefficient of 0.66, P < 0.0001; Fig. 1A). After 3 months of treatment, the increase in fenretinide correlated with decreased retinol levels (Spearman correlation coefficient of −0.57, P = 0.001; Fig. 1B). Similarily, the 3-month 4-MPR concentrations also correlated with the decrease in retinol concentrations (Spearman correlation coefficient of −0.43, P = 0.01; Fig. 1C). The combined fenretinide and 4-MPR concentrations at 3 months also correlated with decreased retinol concentrations (Fig. 1D). There was no significant difference between male and female patients in either their baseline or posttreatment serum retinol levels.

One patient had posttreatment fenretinide and 4-MPR levels of 0 and a 3-month clinical response of “no change.” Four patients had posttreatment fenretinide levels of 0 but 4-MPR levels >0. Three-month clinical responses in these four patients were partial in two and no change in two. We found no correlations between clinical response and the serum level of fenretinide, 4-MPR, or fenretinide plus 4-MPR (data not shown).

The terminal deoxynucleotidyl transferase–mediated nick end labeling data are presented in Table 3. The absolute apoptosis values were low at baseline mean (SE) values of 0.35% (0.25%) and were higher at 3 months, 1.18% (0.64%). Comparing the apoptotic values at baseline with those at 3 months shows that values increased in 18 patients, remained the same in 10, and decreased in 3 (P = 0.002, sign test). There was no correlation between apoptosis and IEN response (P = 0.35, Fisher’s exact test).

We also examined RAR-β expression in oral IEN. RAR-β mRNA was not detected at baseline in 2 of the 37 patients evaluated for clinical response and/or toxicity. We evaluated RAR-β expression both at baseline and 3 months in 30 patients, including the two without detectable baseline RAR-β expression. Both of these patients had positive RAR-β mRNA expression at 3 months, and their clinical outcomes were a

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### Table 1. Association between prior clinical responses to retinoids and responses to fenretinide in the current study

<table>
<thead>
<tr>
<th>Prior clinical responses</th>
<th>Current clinical responses</th>
<th>PR</th>
<th>NC or PD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR or PR</td>
<td></td>
<td>7</td>
<td>3 (30%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>NC or PD</td>
<td></td>
<td>5</td>
<td>20 (80%)</td>
<td>25 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>12</td>
<td>23 (65.7%)</td>
<td>35 (100%)</td>
</tr>
</tbody>
</table>

NOTE: Two-sided Fisher’s exact test, P = 0.015.

Abbreviations: PR, partial response; NC, no change; PD, progressive disease.

### Table 2. Serum fenretinide (4-HPR), 4-MPR, and retinol levels in registered eligible patients

<table>
<thead>
<tr>
<th>Time point/retinoid</th>
<th>μmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n = 36)</td>
<td>All 0</td>
</tr>
<tr>
<td>4-HPR</td>
<td>All 0</td>
</tr>
<tr>
<td>4-MPR</td>
<td>All 0</td>
</tr>
<tr>
<td>Retinol</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.93 ± 1.01</td>
</tr>
<tr>
<td>1st quartile, 2nd quartile, 3rd quartile</td>
<td>2.08 ± 0.77, 3.49</td>
</tr>
<tr>
<td>Range</td>
<td>1.79-7.33</td>
</tr>
<tr>
<td>3 mo (n = 35)</td>
<td></td>
</tr>
<tr>
<td>4-HPR</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.23 ± 0.19</td>
</tr>
<tr>
<td>1st quartile, 2nd quartile, 3rd quartile</td>
<td>0.10 ± 0.81, 0.39</td>
</tr>
<tr>
<td>Range</td>
<td>0.00-0.66</td>
</tr>
<tr>
<td>4-MPR</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.57 ± 0.38</td>
</tr>
<tr>
<td>1st quartile, 2nd quartile, 3rd quartile</td>
<td>0.28 ± 0.55, 0.77</td>
</tr>
<tr>
<td>Range</td>
<td>0.00-1.76</td>
</tr>
<tr>
<td>Retinol</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.52 ± 0.80</td>
</tr>
<tr>
<td>1st quartile, 2nd quartile, 3rd quartile</td>
<td>0.90 ± 1.42, 1.90</td>
</tr>
<tr>
<td>Range</td>
<td>0.4-3.5</td>
</tr>
</tbody>
</table>
partial response in one and stable disease in the other. Baseline RAR-β mRNA expression was lost after fenretinide treatment in one patient who had clinically stable disease after treatment. The remaining 27 patients (in the group tested for baseline and 3 months RAR-β) had IEN expressing RAR-β mRNA before and after fenretinide treatment, with partial responses in 8, stable disease in 12, and progressive disease in 7. We did not assess the association between clinical response and RAR-β mRNA expression because of the positive expression of RAR-β mRNA both before and after treatment in the vast majority of the 30 assessable patients.

Discussion

Fenretinide was clinically active in patients with oral IEN that was resistant to a natural retinoid. We originally hypothesized that this activity would result in part from retinoid receptor–independent apoptosis, which would eliminate premalignant clones and allow effective short-term oral IEN therapy. Apoptosis induction, however, did not correlate with fenretinide clinical activity. The activity of fenretinide seemed to have been mediated by RAR signaling, as suggested by the following results: present response to fenretinide and RAR-β mRNA expression because of the positive expression of RAR-β mRNA both before and after treatment in the vast majority of the 30 assessable patients.

Table 3. Apoptosis in registered eligible patients

<table>
<thead>
<tr>
<th>Time point</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n = 37)</td>
<td>0.35 ± 0.25</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td></td>
</tr>
<tr>
<td>1st quartile, 2nd quartile, 3rd quartile</td>
<td>0.0, 0.0, 0.0</td>
</tr>
<tr>
<td>Range</td>
<td>0.0-9.4</td>
</tr>
<tr>
<td>3 mo (n = 31)</td>
<td>1.18 ± 0.64</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td></td>
</tr>
<tr>
<td>1st quartile, 2nd quartile, 3rd quartile</td>
<td>0.0, 0.3, 0.5</td>
</tr>
<tr>
<td>Range</td>
<td>0.0-19.3</td>
</tr>
<tr>
<td>Baseline to 3 mo increase (n = 31)</td>
<td></td>
</tr>
<tr>
<td>Increase by ≥1%</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td>Increase by &lt;1%</td>
<td>14 (37.8%)</td>
</tr>
<tr>
<td>No change</td>
<td>10 (27.0%)</td>
</tr>
<tr>
<td>Decrease</td>
<td>3 (8.1%)</td>
</tr>
</tbody>
</table>
cancer patients (26) that leads us to conclude that fenretinide tissue levels were not high enough (3-5 \( \mu \)mol/L) to induce receptor-independent apoptosis in the present study. Fenretinide levels were \(~\sim\) 5-fold higher in breast tissue than in plasma at the 200 mg/d dose but still reached only 1.63 \( \mu \)mol/L (26), which is suboptimal for induction of apoptosis in vitro (26). Furthermore, fenretinide is thought to accumulate in breast tissue partly because of fat cells in the breast, and fat cells are unlikely to play an important role in oral IEN.

We now hypothesize that the specific mediator of fenretinide effects in the present study may have been RAR-\( \gamma \), which is the predominate retinoid receptor in normal oral epithelium and, as we have previously shown, is not lost in oral IEN (13). Fenretinide reportedly preferentially transactivates RAR-\( \gamma \) (27) and our previous work has shown that knocking out RAR-\( \gamma \) in F9 cells blocks the differentiation activity of low-concentration fenretinide (21). Although not specific to RAR-\( \gamma \), other data also support retinoid receptor mediation in the present study (14, 15). Our group has found that the same dose and schedule of fenretinide (200 mg/d) that were used in the present study reduced the expression of human telomerase reverse transcriptase catalytic subunit in lung premalignancy patients (28). Human telomerase reverse transcriptase suppression by low-dose fenretinide may be RAR-mediated because RAR/retinoid X receptor heterodimers can bind and activate estrogen response elements, which have been identified in the human telomerase reverse transcriptase promoter (29). We concluded that RAR-\( \beta \) did not play a major role in the present study because RAR-\( \beta \) was present at baseline in all but two of our previously treated patients (which is consistent with RAR-\( \beta \) up-regulation by natural retinoids; ref. 13).

Although statistically significantly increased (versus baseline), the postfenretinide apoptosis index was modest in degree and, as mentioned above, did not correlate with clinical response. Fenretinide tumor–preventive and apoptosis-induction effects also did not correlate in a recent in vivo study in mouse skin carcinogenesis (30). In vitro studies by our and other groups have shown that very high concentrations of fenretinide (3-5 \( \mu \)mol/L) are necessary for inducing apoptosis and are \(~\sim\) 10-fold higher than the serum fenretinide concentrations (mean, 0.23 \( \mu \)mol/L; maximal, 0.66 \( \mu \)mol/L) achieved in our patients with the current fenretinide dosing regimen (31). Therefore, we believe that the modest level of apoptosis we observed in this trial resulted from an RAR-dependent mechanism and not from RAR-independent effects of fenretinide.

Although serum fenretinide concentrations in our study vary from some previous reports (32, 33), several factors can contribute to such differences, including the variable disposition of fenretinide pharmacokinetics, timing of the prior fenretinide dose and blood collection, timing between taking fenretinide and meal intake, and food taken with fenretinide (e.g., a high-protein or high-fat meal may enhance fenretinide bioavailability; ref. 34). Concentrations in the current study [mean fenretinide, 0.23 \( \mu \)mol/L (or 90.05 ng/mL); mean 4-MPR, 0.57 \( \mu \)mol/L (or 230.9 ng/mL)] are similar to concentrations (fenretinide, 104.5 ng/mL; 4-MPR, 201.6 ng/mL) in another study by our group of the same daily fenretinide dose and schedule (35). The sums of fenretinide and 4-MPR concentrations are also similar in our present and earlier study. Formelli et al. (32) have reported higher concentrations than we do here but the difference likely is due in large part to different timing of the test [\(~\sim\) 24 hours (present) versus \(~\sim\) 8 to 12 hours (Formelli)] following the dose. Also, different meals were taken with fenretinide—breakfast (present study) versus dinner (Formelli study), and dinner may contain more protein and thus increase fenretinide serum levels (versus breakfast).

Baseline serum retinol concentrations seem to be higher than have been reported in the literature (36). Retinol levels increase with age, reaching a plateau at or near age 60, which is the mean age of our study population. Although our observed retinol concentration is higher, its SD value overlaps that of the previously reported mean concentration (36). Furthermore, our baseline retinol concentration is similar to that reported in another study by our group of the same daily fenretinide dose and schedule (35), conducted in patients with similar characteristics of age, gender, and smoking status. Participants in cancer prevention studies tend to be health-conscious volunteers, and so the participants in our current and prior prevention studies may have taken supplemental vitamin A that boosted serum vitamin A concentrations above the norm.

A recent Italian adjuvant trial in patients with resected oral IEN found that fenretinide at 200 mg/d (the same dose as in our trial) for 1 year significantly prevented relapse or new lesion development (37). These and our data show fenretinide activity in adjuvant and primary oral IEN treatment settings and thus support future clinical trials of (a) fenretinide combined with other agents that potentially can enhance fenretinide clinical activity (38) and (b) promising new retinamides demonstrating significantly greater activity (versus fenretinide) in head and neck cancer cell lines (31).

References


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