Comment re: Continuous Rather than Intermittent Administration of Fenretinide in Leukoplakia

To the Editor: The article by William et al. (1) reports the lack of activity of high-dose fenretinide (1,800 mg/m²/d, given as 900 mg/m² twice daily) in patients with oral leukoplakia. The same authors had previously shown that a lower dose of fenretinide (i.e., 200 mg/d, once daily) for 3 months was effective (34% partial responses) with a trough drug concentration in plasma at steady state ($C_{ss,\text{min}}$) averaging 0.230 ± 0.19 μmol/L (2). To increase the activity, the authors conducted a new trial (1) in which fenretinide was administered at higher doses (900 mg/m² twice daily) but with a different dosing schedule (i.e., in four 3-week cycles with 1 week on drug followed by 2 weeks off). The trial was stopped early because only 20% of the treated patients showed a partial response. The lower activity of fenretinide was presumably due to the lower extent of drug exposure. In this study, $C_{ss,\text{min}}$ averaged 0.122 ± 0.093 μmol/L, which is approximately two times lower than that observed in the previous study of fenretinide administered at a dose of 200 mg/d for 3 months.

We had previously shown that the same low dose tested by the authors in the first trial (i.e., 200 mg/d, 100 mg twice daily) for 12 months significantly prevented relapses and new lesions in patients with resected oral leukoplakia (3) and that the effect lasted up to 19 months after randomization (4). Plasma drug concentrations in this study were determined at 4 or 12 months in 31 patients and at different time intervals (1-24 hours) from the last drug intake. The average drug concentration during the two daily dosing intervals ($C_{ss,\text{av}}$) ranged from 0.52 to 0.75 μmol/L, whereas trough concentrations ($C_{ss,\text{min}}$) averaged 0.50 μmol/L. Thus, fenretinide plasma concentrations in our study were four times higher than those reached by administering high but intermittent doses (1).

The comparison of fenretinide activity in these three leukoplakia trials that measured $C_{ss,\text{min}}$ indicates that fenretinide activity might not be associated with the rate of drug exposure ($C_{\text{max}}$) but rather to the extent of drug exposure (area under the curve) because higher doses separated by washout periods were less effective than were lower doses administered continuously. Thus, because the tolerability of fenretinide was good in all three trials, the data suggest that a continuous rather than an intermittent dosing schedule should provide the optimal therapeutic effect. Consistent with this hypothesis, the results of the correlative in vitro studies reported by William et al. (1) seem to favor, for the premalignant line, chronic (3 days) rather than short (1 day) treatment.

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References

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