Prospects of Chemoprevention of Human Cancers with the Synthetic Retinoid Fenretinide

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Abstract

Fenretinide or N-(4-hydroxyphenyl)retinamide is a vitamin A analogue synthesized in the United States in the late 1960s. This retinoid shows a preferential accumulation in breast instead of liver, is effective in the inhibition of chemically induced mammary carcinoma in rats, and has proved to be less toxic than many other vitamin A analogues. The Milan Cancer Institute has put a particular effort in this molecule in both the experimental and clinical fields. We have demonstrated, in animals and humans, that fenretinide induces a rapid reduction of retinol plasma concentration, that its blood levels remain constant during administration for as long as 5 years, and that the drug is able to accumulate in the human breast. To date, 2969 stage I breast cancer patients have been randomized to evaluate the efficacy of this retinoid to prevent contralateral new primaries, 709 subjects have been accrued in a prevention trial of basal cell carcinoma of the head and neck, and 153 patients entered a study the preliminary results of which already show the capability of fenretinide to prevent recurrences and new localizations of oral leukoplakia. Further studies on fenretinide will be aimed at evaluating its preventive efficacy in superficial bladder and prostate cancers and at exploring possible synergism with tamoxifen and interferons in breast cancer and skin cancer, respectively.

Introduction

Retinoids are known since their discovery to play a crucial role in cellular and tissue differentiation, but their poor clinical tolerability has always prevented a large use of these agents as anticarcinogens. Retinoids are capable to suppress tumor promotion (1) and to modify some properties of fully transformed malignant cells (2), probably by activating and/or repressing specific genes (3). Major efforts have been put into the identification of new synthetic analogues of vitamin A to enhance their organ specificity and reduce their systemic toxicity (1). It is important to stress that drug tolerability is a major issue in cancer chemoprevention, for the obvious reason that what may be acceptable to fight the established disease will never be considered suitable for merely reducing a risk.

Interesting data are coming from the laboratory, in terms of both a better understanding of the mechanisms of action of retinoids and their possible interactions and synergism with other agents such as antiestrogens. There is a growing mass of knowledge on nuclear retinoic acid receptors which are possibly the mediators of the carcinogenesis inhibition induced by retinoids. The potential chemopreventive effect of retinoids in breast cancer, for example, raises the question of whether these tumors express retinoic acid receptors (4) and whether the reciprocal modulations of retinoids and antiestrogens on their respective receptors (4) are the molecular basis for the increased ability of retinoids and antiestrogens to inhibit breast cancer cell growth in combination (1).

The Synthetic Retinoid Fenretinide

Approximately 1500 different retinoids have been synthesized by modifying either the ring structure, the side chain, or the terminal group of the molecule to obtain more efficacy and fewer side effects. The most interesting vitamin A analogue presently studied for breast cancer chemoprevention is the synthetic retinoid fenretinide or 4-HPR (5). 4-HPR was synthesized in the United States in the late 1960s by R. Gander, and its biological activity was assayed by Sporn and Newton (6) who also showed the preferential accumulation of this compound in breast instead of liver. The inhibition of chemically induced mammary carcinoma in rats by 4-HPR was fully described by Moon et al. (7). This compound has since been studied extensively and has proved to be less toxic than many other retinoids (7, 8). On the basis of all these data, 4-HPR has been proposed for chemopreventive evaluation in human breast cancer.

The original idea of studying this retinoid in a population of early stage breast cancer patients was developed at the Milan Cancer Institute in the early 1980s (9) to evaluate the possible reduction of the incidence of contralateral new primaries. The concept was that patients treated for an early cancer have a good prognosis but also a known risk of developing a contralateral breast tumor, totally independent from the biological point of view. The first advantage of this model is that the incidence of contralateral breast cancer is well assessed, i.e., about 0.8%/year, and that this figure remains stable for the first 10 years after surgery in patients who have experienced a primary in the breast. Secondly, because these patients are already under medical control with periodical follow-up, it is much easier to have them participate in the study for the required lengthy period of time. Thirdly, compliance in these patients is expected to be higher than in the general population.

In 1984 we designed the first protocol of a randomized clinical trial to evaluate the efficacy of 4-HPR in preventing contralateral breast cancer. The study was awarded a National Cancer Institute grant in 1985 but put on hold a few months later because of toxicity data arising from clinical studies with 600- and 800-mg daily doses (10). With the aim of verifying a possible dose relationship of the reported side effects (night blindness and erythema), we conducted a Phase I randomized study, starting in January 1986 and lasting for 1 year, which led us to identify the best tolerated dose (200 mg/day with a 3-day treatment interruption at the end of each month) (11, 12).

Simultaneously, pharmacological studies were performed on 4-HPR and other studies were started to evaluate its clinical efficacy in basal cell carcinoma of the head and neck, and in oral leukoplakia at the Milan Cancer Institute (Table 1), and in superficial bladder cancer at the Genoa Cancer Institute.

Pharmacological Studies

Most studies on the pharmacokinetics of 4-HPR and on the effect of this retinoid on retinol plasma levels have been conducted in breast cancer patients who participated in the Phase I trial and who continued to be treated and followed for 5 years as the patients of the ongoing Phase III trial (11, 12). In this group of patients, who can be considered as a vanguard cohort since they started 4-HPR treatment 1 year in advance, a series of planned studies were performed. The plasma concentrations of 4-HPR, of its main metabolite 4-MPR, and of retinol...
CHEMOPREVENTION STUDIES WITH THE RETINOID FENRETINIDE

In all the studies, patients are randomized to 4-HPR, 200 mg/day, with a 3-day treatment interruption at the end of each month versus no treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>End points</th>
<th>Incidence</th>
<th>Eligible subjects</th>
<th>Years of F-U</th>
<th>Patients entered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Contralateral breast carcinoma</td>
<td>0.8%/yr within 10 yr</td>
<td>Breast cancer patients pT1-pT2N-M0 operated on within 10 yr (ages 33-68 yr)</td>
<td>5</td>
<td>2969</td>
</tr>
<tr>
<td>Leukoplakia</td>
<td>Local recurrences and new localizations</td>
<td>40% within 3 yr</td>
<td>Leukoplakia patients with negative histology of cancer after CO2 laser excision (ages &lt;70 yr)</td>
<td>1</td>
<td>153</td>
</tr>
<tr>
<td>Carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>Recurrences</td>
<td>20%</td>
<td>Head and neck basal cell carcinoma patients after radical excision (ages &lt;80 yr)</td>
<td>1</td>
<td>709</td>
</tr>
<tr>
<td></td>
<td>New localizations</td>
<td>30-40% within 3 yr</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*I, intervention; F-U, follow-up.

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were measured by high performance liquid chromatography (13) after different doses and at different times during and after treatment.

**Retinol Plasma Level Reduction.** During the Phase I study, it was shown that, as previously reported in rats (15), 4-HPR causes in humans an early reduction of retinol plasma concentrations (13). Twenty-four h after a single dose of 200 mg, the concentrations of retinol and of its specific transport protein RBP are reduced in all the treated patients with average reductions of 38 and 26%, respectively. The reduction of retinol plasma concentration is proportional to the dose. In patients whose blood was collected 12 h after 5 months of daily administrations, the concentration of retinol blood levels was significantly reduced by an average of 71%. After the 3-day interruption, retinol plasma concentrations increased in all patients; 2 of 18 women completely recovered their baseline values, while the average reduction was 38%.

We have recently shown that the reduction of retinol plasma levels is associated with the interaction of 4-HPR with RBP (the specific transport protein of retinol in plasma) and with interference with the RBP-transferrin complex formation (18).

**Monitoring of 4-HPR, 4-MPR, and Retinol Plasma Concentrations during 5-Year Chronic Treatment.** As is generally the case with chemopreventive agents, the ongoing prevention studies foresee 4-HPR administration for long periods of time, i.e., 1 and 5 years. Daily chronic administration of 4-HPR at the dose of 200 mg results 14 h after drug intake in average 4-HPR concentrations of 350 ng/ml, i.e., approximately 1 μM (Fig. 3), which are constant throughout the treatment period. The concentrations of 4-MPR, which are similar to

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**Fig. 1.** Relationship between 4-HPR doses (mg/day) and 4-HPR, 4-MPR, and retinol plasma levels. Plasma of 14, 14, 15, and 18 patients receiving 100, 200, and 300 mg 4-HPR and placebo, respectively, was collected 12 h after 5 months of daily administrations. Points, means; bars, SD. Reproduced from Ref. 13 with permission.

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were measured by high performance liquid chromatography (13) after different doses and at different times during and after treatment.

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**Fig. 2.** Retinol plasma level reduction during daily treatment and after 3-day treatment interruption with 200 mg 4-HPR. Plasma of 18 patients was collected at baseline, during daily treatment (i.e., median, 15 h; range, 10-24 h), and after the 3-day drug interruption (i.e., median, 87 h; range, 83-96 h). The concentration of each patient is reported as percentage of baseline value.

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those of the parent drug, slightly but significantly increase during the first 35 months of treatment, but after 5 years, they are similar to those found at 5 months. Saturable accumulation of this metabolite, which is more polar than the parent drug, might explain this behavior. Retinol concentrations are reduced from 493 to approximately 170 ng/ml (i.e., by 65%), and this reduction is constant during the 5-year treatment.

**Kinetics of Elimination after 5-Year Chronic Treatment.** After 5-year treatment, 4-HPR was cleared from plasma with an average $t_{1/2}\beta$ of 27 h as evaluated in blood collected from 12 to 86 h after the last drug intake in 14 patients (Table 3). The rate of 4-HPR elimination was lower than that of the parent drug with an average $t_{1/2}\beta$ of 54 h. Comparison between retinol and 4-HPR average $b$ values indicates that, in the range of time examined, the ratio between the rate of 4-HPR elimination ($b = -0.03293$) and the rate of retinol recovery ($b = +0.01278$) is 2.58. The half-life of 4-HPR after 5-year treatment is consistent with those found after 1 and 28 daily doses (Table 4). In contrast to 4-HPR, an increase in the half-life of its metabolite 4-MPR occurs following multiple doses. The reported constant 4-HPR concentrations during 5-year treatment, together with the finding of a constant half-life, suggest that 4-HPR pharmacokinetic parameters do not change during long term multiple dose regimen.

Long term elimination of 4-HPR and 4-MPR, as well as retinol recovery following drug discontinuation after 5-year continuous treatment, has been investigated during a 12-month period (Fig. 4). At 6 and 12 months after drug interruption, 4-HPR concentrations were at the limits of detectability (0.01 µM), whereas the concentrations of 4-MPR were approximately 5 times higher. Baseline retinol concentrations (500 ng/ml) were already recovered after 1 month.

**Distribution of 4-HPR in the Human Breast.** Evaluation of 4-HPR concentrations in breast biopsies of a small sample of patients confirms the ability of this retinoid to accumulate in the breast as already demonstrated in rodents (7) and, as previously reported, in other breast cancer patients (19). Table 5 reports the concentrations of 4-HPR and 4-MPR found in plasma and in breast tissue fragments of 3 patients treated with 4-HPR before surgery. The concentrations of 4-HPR were in all but one sample 1.4—8.2-fold those in plasma. 4-MPR, which is more lipophilic than the parent drug, accumulated in the breast to an even higher extent and this was particularly evident after long term treatment. This might be relevant for the chemopreventive effect of this retinoid since this metabolite has the same potency as 4-HPR in *in vitro* differentiation assays (20). Both 4-HPR and 4-MPR highest concentrations were found in fat. Evidence that this retinoid accumulates not only in fat but also in the epithelial cells of the breast is given by the fact that the concentrations of 4-HPR and those of 4-MPR in the nipple discharge, which is secreted by the breast gland, are 10 and 30 times higher, respectively, than those found in plasma (Table 6).

**Fenretidine Breast Cancer Chemoprevention Study**

On the basis of experimental data showing the peculiar accumulation of 4-HPR in the rodent mammary gland (7) and of its good tolerability in humans (11, 12), a large randomized chemoprevention trial was started at the Milan Cancer Institute in 1987 with the assumption that, if 4-HPR will succeed in preventing second primaries in breast cancer patients, it would possibly be useful for a wider group of high risk subjects, like the ones belonging to families at high incidence of the disease (21).

Study participants are breast cancer patients between the age of 33 and 68 years. In order to be eligible, patients must have had an operated breast cancer (T1, T2) and be without axillary lymph node involvement and without evidence of local recurrence and/or distant metastases. They must have normal metabolic, liver, and renal function tests besides normal WBC, RBC, and platelet count. Due to the

**Table 3** Regression coefficients ($b$) and $t_{1/2}\beta$ (mean ± SD) after 5-year 4-HPR treatment at 200 mg/day

<table>
<thead>
<tr>
<th>Compartment</th>
<th>$b$</th>
<th>$t_{1/2}\beta$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-HPR</td>
<td>-0.03293 ± 0.00434</td>
<td>13 ± 4.41</td>
</tr>
<tr>
<td>4-MPR</td>
<td>-0.01362 ± 0.00336</td>
<td>25 ± 13.92</td>
</tr>
<tr>
<td>Retinol</td>
<td>+0.01278 ± 0.00253</td>
<td>20 ± 13.92</td>
</tr>
</tbody>
</table>

*a c.v., coefficient of variation. Reproduced from Ref. 14 with permission.

**Fig. 4.** Time course up to 12 months after drug interruption of 4-HPR, 4-MPR, and retinol in patients treated for 5 years. Plasma of 23 patients was collected at 1, 2, 3, 6, and 12 months, respectively, after drug interruption. Plasma concentrations at 1 day (14—24 h) are also reported. Points, means; bars, SD. Reproduced from Ref. 14 with permission.

**Table 4** 4-HPR and 4-MPR $t_{1/2}\beta$ in single and multiple dose studies in humans

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Treatment period</th>
<th>4-HPR (h)</th>
<th>4-MPR (h)</th>
<th>From</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>1 day</td>
<td>20 ± 5.9</td>
<td>20 ± 14.7</td>
<td>R. W. Johnson Pharm. Res. Inst., 1984</td>
</tr>
<tr>
<td>150</td>
<td>28 days</td>
<td>27 ± 5.9</td>
<td>45 ± 9.4</td>
<td>R. W. Johnson Pharm. Res. Inst., 1984</td>
</tr>
<tr>
<td>200</td>
<td>5 yr</td>
<td>24 ± 4.4</td>
<td>54 ± 13.9</td>
<td>C. Fornelli, 1993</td>
</tr>
</tbody>
</table>

*a Mean ± SD.

Fig. 3. Plasma concentration of 4-HPR, 4-MPR, and retinol during 5-year chronic treatment. Plasma of 7 patients was collected at 14 h (range, 12—19 h) after the last drug intake at 5, 12, 35, and 60 months of treatment. Baseline retinol concentrations are also reported. Points, means; bars, SD. * P < 0.05 by Dunnet's t test versus 5 months. Reproduced from Ref.14 with permission.
teratogenic effect of 4-HPR, they must not conceive or be pregnant during the study and for 6 months after the end of intervention. An accurate clinical examination and a baseline mammography of the contralateral breast are performed on all patients, and all the characteristics of the mammary gland are carefully recorded. Patients are randomized to receive 200 mg 4-HPR daily for 5 years (with a 3-day drug holiday at the end of each month) versus no treatment. The aims of the follow-up, which will last for 2 years, are to evaluate the efficacy of the drug, to monitor the disease, and to obtain information on the mechanism of action of 4-HPR. Mammography will be repeated every year mainly to monitor the contralateral breast gland. A sample of mammograms will be reviewed in blind by a senior radiologist. Needle biopsy will be performed on all lumps considered suspicious by clinical examination and/or mammography. The main measurements of efficacy will be physical examination and mammography of the contralateral breast. Mammography will be taken first at baseline and then every year to detect contralateral tumors; a senior radiologist will review a random sample of mammograms under blinded criteria. The patient’s compliance will be assessed by four elements: confidence patient/physician; pill count; serum assay of 4-HPR and 4-MPR; and number of control visits. "Confidence patient/physician" is the most important point. Before joining the study, each patient will be counseled by the investigating physician on the aims of the study, the expected drug effects, and side effects. After the informed consent form has been signed by the patient, a behavioral agreement will be discussed in order to enhance long term maintenance of drug administration. It will be explained to the patient that it is important to take the drug daily, both capsules, and at a regular time, after dinner, to increase the bioavailability of 4-HPR.

By June 1, 1993, 2969 patients had been randomized (1494 in the 4-HPR group and 1475 in the control group). Compliance to protocol is high, and tolerability of the drug is good, thus confirming the results of the Phase I study (11, 12). The incompleteness of accrual and the insufficient median follow-up do not allow at present the publication of any preliminary result of this trial.

**Fenretinide Oral Leukoplakia Chemoprevention Study**

The oral leukoplakia study with 4-HPR began at the Milan Cancer Institute in September, 1988. Patients eligible for entry have been operated on for previously untreated homogeneous or nonhomogeneous oral leukoplakias and have benign postoperative histology. These subjects are at risk of developing new precancerous lesions after surgical excision of the lesion and oral cavity tumors as well. Diagnostic procedures include: (a) a photograph of the lesion; (b) careful oral examination and dental mapping (where the lesion is apparently related to badly fitted dentures or broken teeth, patients are advised to seek dental treatment); (c) biopsy of suspicious lesions and areas staining with toluidine blue; (d) metabolic tests, liver function tests, renal function tests, blood work-up (WBC, RBC, and platelet count), and chest X-ray. Laser resection is performed under local anesthesia and the lesion is excised with at least 0.5-cm margins (in depth and laterally) of normal tissue.

All randomized patients are urged to improve oral hygiene, have dental treatment if necessary, stop drinking alcohol, and stop smoking. Patients are randomized to receive 200 mg 4-HPR daily for a maximum of 52 weeks (with a 3-day drug holiday at the end of each month) versus no treatment. All patients are checked every 2 months. Checkup includes clinical examination and metabolic, liver, and renal function laboratory tests. When toxicity occurs, patients are checked at monthly intervals. All suspected lesions are photographed, biopsied, and evaluated under blinded criteria by a head and neck surgeon. New lesions located more than 2 cm from the first-treated leukoplakia are considered new localizations. Control group patients are followed in the same way as those in the 4-HPR group. In a previous study (22), we found that in operated patients the chance of developing relapses or new localizations is 40% after 3 years and 23% within 1 year of surgery. Thus, a 3-year study with 190 patients should detect at least a 15% difference between the two arms in the probability of developing these events, assuming that this difference is concentrated in the first year after surgery (23). As of June 1, 1993, of the 284 patients who had been operated on for oral leukoplakias, 153 were randomized into the trial (74 in the 4-HPR arm and 79 in the control arm). The distribution of the series according to risk factors (age, sex, smoking, and alcohol habits) shows that with the exception of age, the two arms are well balanced for all factors considered.

Unfavorable events have been recently published (24) and the update results are reported in Table 7. Nineteen patients had recurrences (9 in the control group and 10 in the 4-HPR group) and 15 had new localizations (12 in the control group and 3 in the 4-HPR group). On the basis of these figures, the risk of recurrence and new localizations in the two groups who completed the intervention can be calculated as 6% in the 4-HPR group and 30% in the control group (Fig. 5).

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**Table 5 4-HPR and 4-MPR concentrations (ng/ml or ng/g) in plasma and in breast samples**

Plasma was collected 12 h after the last dose, immediately before surgery.

<table>
<thead>
<tr>
<th>Patient 1: 4-HPR, 200 mg for 7 days</th>
<th>Patient 2: 4-HPR, 300 mg for 5 days</th>
<th>Patient 3: 4-HPR, 100 mg for 168 days + 200 mg for 84 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-HPR</td>
<td>R*</td>
<td>4-MPR</td>
</tr>
<tr>
<td>Plasma</td>
<td>216</td>
<td>140</td>
</tr>
<tr>
<td>Breast tumor</td>
<td>499</td>
<td>2.3</td>
</tr>
<tr>
<td>Breast normal tissue</td>
<td>567</td>
<td>2.6</td>
</tr>
<tr>
<td>Breast muscle</td>
<td>311</td>
<td>1.4</td>
</tr>
<tr>
<td>Breast fat</td>
<td>1776</td>
<td>8.2</td>
</tr>
</tbody>
</table>

* R, tissue ng/g/plasma ng/ml; ND, not detected. Reproduced from Ref.14 with permission.

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**Table 6 4-HPR and 4-MPR concentrations (ng/ml) in plasma and nipple discharge**

4-HPR, 200 mg/day, was administered for 15 days. Blood and nipple discharge were collected 22 h after the last dose.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>4-HPR</th>
<th>R*</th>
<th>4-MPR</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>212</td>
<td>140</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>Nipple discharge from Right breast</td>
<td>2900</td>
<td>14</td>
<td>5740</td>
<td>24</td>
</tr>
<tr>
<td>Left breast</td>
<td>2600</td>
<td>12</td>
<td>8220</td>
<td>34</td>
</tr>
</tbody>
</table>

* R, nipple concentrations/plasma concentrations. Reproduced from Ref.14 with permission.

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**Table 7 First unfavorable events in 4-HPR and control patients after excision of oral leukoplakias**

<table>
<thead>
<tr>
<th>No.</th>
<th>Control</th>
<th>4-HPR</th>
<th>At months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>19</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>New occurrence</td>
<td>15</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>New primary</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

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Fig. 5. Risk of developing local relapses and new leukoplakias. ----. control; ---, 4-HPR group.

Fenretinide Tolerability

One of the main reasons which attracted the attention of oncologists on 4-HPR is its good tolerability compared to other retinoids. As has been shown by a randomized Phase I study of different doses of 4-HPR (11), no acute or severe toxicity is observed with this retinoid. The same occurs with long term p.o. administration of 200 mg daily of 4-HPR, as shown by the evaluation of 53 patients treated for 42 months (12). Dermatological tolerability is good and no liver function abnormalities are observed (12, 25). The only limitation to the extensive use of 4-HPR is the occasional side effect of impaired dark adaptation. Estimation of this side effect by dark adaptometry measurements (26), by the Goldmann-Weekers method, which is very sensitive in detecting subclinical vitamin A deficiency, has shown that in women treated with 200 mg 4-HPR daily, there is a 23% incidence of mild and a 26% of moderate alterations of dark adaptometry which are associated with the drug-induced decline of plasma retinol levels. However, about 50% of the treated patients with altered dark adaptometry were asymptomatic and the alterations of dark adaptometry are promptly reversible upon drug interruption. Toxicity of the ocular surface, which is frequently observed upon administration of natural and synthetic retinoids, is negligible in 4-HPR-treated patients (26). Because the negative side effect of dark adaptation is associated with the decrease of retinol plasma levels induced by 4-HPR, it is suggested to prescribe a 3-day drug holiday at the end of each month.

Future Developments and Open Questions

Although no final and confirmed results are available on the efficacy of 4-HPR in prevention of tumors in humans, we believe that this compound deserves special attention for a number of reasons, both biological and clinical, namely the constancy of its plasma levels during long term administration (14) and its potential efficacy in tumors other than breast, like prostate (27) and bladder. In patients resected from superficial bladder cancer and at risk of recurrence 4-HPR, has shown to be capable of reversing DNA aneuploidy (28).

As regards further investigations, it might be noted that data in Sprague-Dawley rats have shown the superiority of the combined treatment of 4-HPR with tamoxifen to that of either agent alone in blocking progression of incipient neoplastic lesions (29). The tolerability of these two agents has recently been assessed in previously untreated metastatic breast cancer patients (30), and no significant adverse effects on renal, hepatic, hematologic or lipid values were recorded, nor were there nyctalopia, photophobia, cheilitis, and pruritus. The perspective of the availability of different agents separately capable of inhibiting tumor occurrence and/or progression in hormone-dependent and -independent breast cancers seems very intriguing. The hypothesis that tamoxifen could prevent estrogen receptor-positive tumors and retinoids the estrogen receptor-negative tumors is at present purely theoretical but worth further investigation, particularly since the two agents have been shown to activate the same molecular mechanism (31).

Another field of research which could become of clinical interest in the near future is the combination of 4-HPR with differentiation-poitive cytokines as well as other differentiating agents which may be able to develop a superior activity compared to the one of the single agents given alone. A controlled study of 4-HPR with α-interferon in advanced basal cell carcinoma patients is in progress at the Milan Cancer Institute.

Another aspect which needs to be better defined is the length of intervention. Our experience in oral leukoplakia seems to suggest that the effect of 4-HPR is closely related to the exposure to the drug. We are therefore exploring both the extension of the systemic treatment from 1 to 2 years and the topical administration of 4-HPR with or without oral intake at lower doses.

Finally, the issue of possible dose increase also must be addressed. The presently prescribed regimen (200 mg daily with a 3-day drug holiday each month) is based on our first Phase I study in which 1 of 25 cases of impaired dark adaptation was recorded after 6 months of treatment with 300 mg daily. However, this negative side effect appears in only a small percentage of subjects. The incidence of pathological electroretinograms in 53 patients was 0.61% at 37–42 months (12). It is thought that higher doses, like 300 or 400 mg, could be well tolerated for relatively short periods (3–4 months) and with a longer drug holiday (5 days at the end of each month). If this approach proves to be acceptable, a new regimen of 4-HPR could be designed to allow high dose induction treatments to be followed by long term administration of lower doses.

Acknowledgments

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References

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