Clinical experience with topical tretinoin in the treatment of cervical dysplasia.

https://escholarship.org/uc/item/2vw472xf

Journal of the American Academy of Dermatology, 15(4 Pt 2)

0190-9622

Meyskens, F L, Jr
Surwit, E S

1986-10-01
Clinical experience with topical tretinoin in the treatment of cervical dysplasia

Frank L. Meyskens, Jr., M.D., and Earl S. Surwit, M.D. Tucson, AZ

Dysplasia of the uterine cervix is a recognized preneoplastic condition. Because of the observed ability of retinoids to reverse other dysplastic conditions in vitro and in vivo, a number of clinical studies have been carried out of the effect of these agents on cervical dysplasia, with the object of developing a means of chemoprevention of cervical malignancies in women at risk. We have conducted phase I and II trials of topical tretinoin (retinoic acid and Retin-A) delivered by means of a cervical cap and inert collagen sponge system. The results of these studies warranted a phase III trial, which is now underway. The outcome of the latter investigation will have important implications, not only for the management of patients with cervical dysplasia but also for therapeutic approaches to other precancerous conditions. (J AM ACAD DERMATOL 15:826-829, 1986.)

Vitamin A and both its natural and synthetic derivatives (retinoids) can block the phenotypic expression of malignancy by transformed cells, regardless of whether transformation was initiated by physical, chemical, or viral agents. The retinoids also inhibit the proliferation of many transformed cell lines, and retinoid-treated cells frequently show evidence of differentiation or maturation. In vivo, retinoids have shown chemopreventive activity in animals treated with chemical carcinogens and tumor viruses and have brought about regression of a number of transplanted tumors.

Several mechanisms may be involved in the antitumor activity of these compounds. Important among these are their general stimulation of the host's immune response and possibly also their enhancement of the antigenicity of new tumor cells. They may also exert a direct cytotoxic effect through disruption of lysosomal membranes or other cellular membranes.

From the Department of Internal Medicine, Arizona Cancer Center. Reprint requests to: Frank L. Meyskens, Jr., M.D., Professor of Medicine, Acting Head of Hematology/Oncology, Department of Internal Medicine, Arizona Cancer Center, Sixth Floor Facility, Tucson, AZ 85724.

Other modes of action of the retinoids may involve their binding to cytosolic receptors. For example, some retinoids have been shown to possess antipromoter activity, by which cells' progression to malignancy is reversed. This effect is correlated with the drugs' inhibition of the synthesis of ornithine decarboxylase, presumably via their binding of intracytoplasmic receptors, translocation to the cell nucleus, and alteration of mRNA.

The antipromoter effect of retinoids makes them obvious candidates for investigation as chemopreventive agents in preneoplastic conditions such as dysplasia of the uterine cervix. Several such studies have in fact been carried out, including our phase I and phase II trials of locally delivered tretinoin.

A major problem with pharmacologic intervention in human precancerous conditions is the toxicity that accompanies almost any therapeutic agent. In contrast to many therapeutic drug regimens, prophylactic regimens are liable to be extended, increasing the patient's exposure to the risk of toxic effects. Furthermore, the risk/benefit ratio must always be less favorable for treatment of even a high-risk precursor condition than it is for the resulting disease itself. Yet developing ef-
fective chemopreventive agents for high-mortality conditions such as cervical malignancy is extremely important.

One approach to the toxicity problem, clearly, is to develop agents with improved therapeutic ratios. To some degree, this has been done with retinoids. Analogs have been synthesized that show much less local and systemic toxicity than the naturally occurring retinoids. An alternative approach is to deliver the compound selectively to local or regional areas, thus avoiding systemic effects.

We have used the latter approach in our preliminary investigations of the use of topical tretinoin to reverse cervical dysplasia. We are now engaged in a phase III trial of this agent, using a cervical cap with a collagen sponge insert to deliver the drug directly to the treatment site.

CLINICAL EXPERIENCE WITH TOPICAL TRETINOIN IN CERVICAL DYSPLASIA

We first tested an inert collagen sponge and diaphragm system to deliver tretinoin to the cervix. The diaphragm permitted an undesirable leakage of the retinoid preparation onto the vaginal mucosa and the vulva. Other side effects were mild, however, and we noted early changes in the intraepithelial neoplasias of the patients studied.

These results encouraged us to develop a collagen sponge and cervical cap that delivered the tretinoin effectively and eliminated the problem of leaking. In our tests of various drug vehicles, an inert cream base proved most practical. This delivery system was used in our phase I and II studies and will also be used in the current phase III trial.

Phase I trial

The phase I investigation showed that both tretinoin and the delivery system were well tolerated. The subjects in the study had mild or moderate intraepithelial dysplasia. Based on known skin and mucosal toxicity, a cream-based concentration of 0.05% tretinoin was selected as the starting dose. This dose was escalated according to a modified Fibonacci scale. The delivery device and drug were changed daily for 4 consecutive days. Side effects were assessed by clinical and colposcopic examination.

Colposcopically directed biopsy specimens revealed mild or moderate dysplasia in all 36 patients enrolled in the study. The lesion and entire squamocolumnar junction were completely visualized. Results of endocervical curettage were negative in all patients and pretreatment Papanicolaou smear results were consistent with those of the ectocervical biopsy.

The cervical cap and collagen sponge insert (Fig. 1) have been described extensively. To apply the drug, we loaded the sponge with 1 ml of fresh tretinoin preparation. We then positioned the sponge cap device around and against the cervix. Patients returned daily for replacement of the insert with one containing fresh drug.

We evaluated toxicity by clinical examination, colposcopy, and colpophotographs. Liver function tests were performed before entry into the study and again on the fourth day of therapy.

The systemic side effects we noted were mild and not clearly related to the tretinoin dose. Patients demonstrated acceptable cervical side ef-
ects (1+ to 2+) at all dosage levels tested. In most cases we did not see cervical changes by colposcopy until after 2 days of application. Mild inflammation was the most frequent side effect and was seen in 22 patients. A moderate increase in vascularity, the next most common side effect, occurred in 19 cases.

Vaginal side effects occurred at every dose level. They were mild to moderate at tretinoin concentrations of 0.05% to 0.372%. Patients given a tretinoin concentration of 0.48% developed a moderate amount of discharge. One of these patients developed bleeding and prolonged vaginal burning after the last drug application.

In 12 of the studied patients the disease disappeared completely. Of these subjects, four had mild dysplasia, six had moderate dysplasia, and two had severe dysplasia. Ten of the 12 patients with a complete response have now been followed up for at least 12 months. Dysplasia recurred at 18 months in one patient whose biopsy specimens were negative at 12 months.

This study suggested that tretinoin delivered to the cervix via a collagen sponge–cervical cap insert was feasible and well tolerated. Using [3H]-retinoic acid, we demonstrated uptake into cervical tissue without systemic absorption.9 The absence of significant systemic side effects after 4 days of treatment suggested that the development of a local maintenance retreatment protocol was reasonable. A dose of 0.37% appeared appropriate for a phase II trial.

Phase II trial

Twenty-three patients with mild, moderate, or severe dysplasia were selected for a phase II efficacy study.10 One milliliter of tretinoin solution was applied to the sponge, and the cervical cap was carefully positioned as before to ensure placement of the cap around and against the cervix. A new cap device loaded with tretinoin was inserted on 4 consecutive days. The patients returned at 3, 6, and 9 months for follow-up and maintenance treatment, which consisted of 0.372% tretinoin inserted daily with the cap for 2 days.

Twenty patients were finally evaluated in phase II. Ten of the 20 patients showed complete disappearance of the disease. In seven of these complete responders, the original cervical dysplasia had totaled 25% to 50%. Three patients had 75% cervical involvement at the start of treatment.

Acceptable cervical toxicity (mild to moderate) was seen in 18 patients during the induction treatments. Vaginal toxicity occurred more frequently during induction than in the three maintenance treatments. During induction, 12 patients had mild or no toxicity. Increased vaginal discharge and itching were the most frequent side effects. These systemic side effects occurred more often during induction (9/23 patients) than in three maintenance treatments (3/16 patients).

The absence of significant side effects during induction and maintenance treatments suggests that using retinoids as a chemopreventive agent in cervical dysplasia was a valid concept. Similar conclusions have recently been reached by Romnev et al.,11 who conducted a feasibility study of topical retinyl acetate delivered by a vaginal applicator.

Phase III trial

As a result of the activity of tretinoin seen in our earlier trials, a phase III double-blind study has been designed and is now underway at our center. The study should be able to determine definitively whether tretinoin or another retinoid is an effective chemopreventive agent for cervical malignancy. To date 60 patients have been accrued for this trial. We will compare the efficacy of 0.372% tretinoin in a cream vehicle with the vehicle used alone.

Whatever the outcome of this particular investigation, it is important to continue studying the roles of the retinoids in chemoprevention. These agents have great potential for treating preneoplastic conditions, if they are used rationally and with a thorough understanding of their biologic roles.

REFERENCES

3. Lotan R: Effects of vitamin A and its analogues (reti-
Topical tretinoin in cervical dysplasia

Gary L. Peck, M.D. Bethesda, MD

In several studies between 1962 and 1978, topical tretinoin was proved capable of producing complete regression of actinic keratosis and basal cell carcinoma. But because its efficacy is not comparable to that of other modalities, topical tretinoin is currently used only as an adjunct to topical 5-fluorouracil in the treatment of actinic keratosis. One recent report found topical tretinoin ineffective in the chemoprevention of actinic keratosis. Although the oral synthetic retinoids isotretinoin and etretinate have been used in the prevention and treatment of cutaneous malignancy, the potential exists for chronic toxicity from the prolonged systemic therapy that appears necessary for maintaining the chemopreventive effect. For this reason, it may be appropriate to study further the preventive as well as therapeutic effects of topical tretinoin and other retinoids for actinic keratosis and skin cancer. If they prove safe and effective, the use of topical retinoids in the prevention and treatment of cutaneous tumors may be the most significant clinical application of these drugs. (J Am Acad Dermatol 15:829-835, 1986.)

Vitamin A deficiency is potentially a precan-cerous disease. It provides researchers a con-ceptual link between the treatment of benign dermatoses and the prevention and treatment of malignancies with retinoids. One feature of this deficiency is a squamous metaplasia characterized by increased cell proliferation and hyperkeratosis of a variety of epithelia. These morphologic abnormalities are also found in some cutaneous disorders of keratinization such as psoriasis.1

From the Dermatology Branch, National Cancer Institute, National Institutes of Health.
Reprint requests to: Dr. Gary L. Peck, Senior Investigator, Dermatology Branch, National Cancer Institute, National Institutes of Health, Building 10, Room 12N238, Bethesda, MD 20892.