Journal of Cellular Biochemistry Supplements 28/29:140–143 (1997)

Chemoprevention of Cancer of Uterine Cervix: A Study on Chemoprevention of Retinamide II from Cervical Precancerous Lesions

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Abstract Dysplasia of the uterine cervix is a recognized precancerous condition. Because of the observed ability of retinoids to suppress various cell lines in vitro, a number of clinical studies have examined the effect these agents have on cervical dysplasia, with the object of developing a means of chemoprevention of cervical malignancies in women at risk. Three cervical cancer chemoprevention trials with Retinamide II (RII) have been conducted at the Cancer Institute, Chinese Academy of Medical Sciences, Beijing, China.

A pilot study used RII to intervene in cases of precancerous cervical dysplasia. Twenty-seven women with mild, moderate, or servere cervical dysplasia, pathologically confirmed, were treated by RII suppositories, 10 mg QD, given intravaginally for 6 months (each course lasting 3 months). The results indicated that after the second course, the overall response rate was 96.29% and the complete response rate was 88.89%. In general, side effects were mild. A little cervical and vaginal irritation was well tolerated. In the second double-blind study, patients with precancerous cervical lesions were randomized into two groups, one treated with RII suppository intravaginally and the other with a placebo, once daily for 50 days in two courses. Precancerous lesions in 68.76% of patients in the treatment arm disappeared, with an overall effective rate of 74.29% after two courses of treatment with RII. Its curative effect was approximately that of laser beam radiation and electrocautery ($P > 0.05$), and differed significantly ($P < 0.01$) from that of traditional antiinflammatories. RII can be a major measure in prevention and treatment of cervical cancer in high-incidence areas in China. In the third trial, we are conducting a randomized double-blind study placebo controlled, in a high-incidence area of cervical cancer (Xiang-Yuan county, Shang Xi Province, China). At present, the patients are being followed up and the study will be completed after 2 years. J. Cell. Biochem. Suppls. 28/29:140–143.

Key words: chemoprevention; precancerous lesions; uterine cervix retinamide II (RII)

The world-adjusted mortality of cervical cancer in China was 14.6/100,000, next to that of Chile (15.4/100,000). Chinese-adjusted mortality was 9.98/100,000, which ranks second to stomach cancer [1]. The aim of our study on cervical cancer intervention was to treat precancerous cervical lesions that had not yet become cervical cancer.

Retinamide II (RII) was developed in the People's Republic of China. A new synthetic retinoid [2,3], it had marked anticancer effects and experimentally induced cell differentiation [4–6].

This cervical cancer chemoprevention trial using RII was conducted at the Cancer Institute of the Chinese Academy of Medical Sciences, Beijing, China [7].

MATERIALS AND METHODS

All subjects were recruited through referrals of women whose abnormal Pap smears were detected during screening at gynecologic clinics. The subjects were examined colposcopically and abnormal sites biopsied under colposcope direction.

Eligible women were 40 to 65 years of age with a histopathologic diagnosis of mild, moder-

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Received 10 March 1997; Accepted 10 November 1997

ate, and severe dysplasia (excluding carcinoma in situ) within 6 months of the day of recruitment. Voluntary participation and informed consent had to be received. Women were excluded if diagnosed as having a disease that would interfere with the intervention protocol or its evaluation, including cardiopathy, hypertension, nephritis, or diabetis mellitus, or if they were considered unreliable or not able to comply with the intervention regimen.

RII was dissolved in a cream-based vehicle, which contained palmitic acid, stored at low temperature, and shielded from high temperature. Each suppository contained 10 mg RII [7].

Toxicity was evaluated by clinical examination, including colposcopy at first, second, third, and fourth weeks and at 3 and 6 months after beginning application. Urinalysis, blood chemistry, hemogram, and liver function test were performed prior to study entry and in the first, third, and sixth months after the initial application.

The RII suppository 10 mg QD and a cotton ball with tail was given intravaginally every morning for 6 months (two courses each lasting 3 months). Subjects were instructed to remove and discard the cotton ball each night.

RESULTS

Pilot Intervention Study of Precancerous Cervical Dysplasia By RII

Twenty-seven women with mild, moderate, or severe pathologically confirmed cervical dysplasia were treated by RII suppository. No systemic side effects were found. Results of clinical examinations (including urinalysis, blood chemistry, hemogram, and liver function test) were normal at the first, second, third, and fourth weeks and at 3 and 6 months after beginning the application

In general, the topical side effects and toxicity of RII disappeared 4 weeks after cessation of application. The general side effects were mild. What little cervical or vaginal irritation occurred was well tolerated (Tables I, II).

The results indicated that after two courses, 26 of 27 patients responded. Precancerous lesions completely disappeared in 24 patients (Tables III–V). The overall response rate was 96.29% (26/27) and the complete response rate was 88.89%. Minimal cervical and vaginal irritation was well tolerated. The results of this clinical trial suggested a practical basis for additional studies of RII for chemoprevention of cervical cancer.

TABLE I. Clinical and Colposcopic Grading for Cervical and Vaginal Toxicity (Judgement Standard)

+: Mild discharge and increased cervical vascularity
++: Mild discharge, increased cervical vascularity, and visible ecchymosis
+++: Increased cervical, vascularity, moderate burning or itching or discharge with bleeding or cervical and vaginal mucosa

TABLE II. Side Effects and Toxicity of Retinamide II Topically Applied to Cervical Dysplasia

	Degree				
Week	0	+	++	+++	Total
1	1	8	5	13	27
2	14	11	1	1	27
3	22	4	0	1	27
4	27	0	0	0	27

TABLE III. Change of Colposcopy in Cervical Dysplasia Pretreatment and After 6 Months Treatment by Retinamide II Suppository

		Posttreatment		
Pretreatment		Normal	Unsatisfied	Abnormal
Normal	5	3	0	2
Unsatisfied	4	0	4	4
Abnormal	18	9	0	9

TABLE IV. Change in Papanicolaou Cytology in 27 Cervical Precancerous Lesions Pretreatment and 6 Months Posttreatment by RII Suppository*

Lesions		Posttreatment				
extent	Pretreatment	I	II	III	IV	V
I	0	0	0	0	0	0
II	2	0	2	0	0	0
III	24	1	16	7	0	0
IV	1	0	1	0	0	0
V	0	0	0	0	0	0

*According to Papanicolaou's classification.

Randomized, Double-Blind Study With Placebo on Precancerous Cervical Lesions

Patients (74 total) with precancerous cervical lesions were randomized into two double-blind groups. One group of 42 patients was treated

TABLE V. Pathological Change of Tissue Biopsy Under Colposcopy in Patients of Cervical Dysplasia Pretreatment and After 2 Courses of Treatment by RII Suppository

		Posttreatment				
	Pretreatment	Epithelic normal squamous	Chronic cervical	Mild dysplasia	Moderate dysplasia	Severe dysplasia
Mild dysplasia	14	1	12	1	0	0
Moderate dysplasia	12	2	8	2	0	0
Severe dysplasia	1	0	1	0	0	0
Total	27	3	21	3	0	0

TABLE VI. Change of Papanicolaou Cytology in Cervical Precancerous Lesions by RII and Placebo Suppository*

Groups	Lesion extent	Pretreatment	Posttreatment					
			I	II	III	IV	V	Unknown
RII	I	21	16	4	0	0	0	1
	II	19	9	8	0	0	0	2
	III	0	0	0	0	0	0	0
	IV	2	2	0	0	0	0	0
	V	0	0	0	0	0	0	0
Placebo	I	16	13	2	0	0	0	1
	II	14	10	4	0	0	0	0
	III	1	0	1	0	0	0	0
	IV	1	1	0	0	0	0	0
	V	0	0	0	0	0	0	0

*$X^2 = 0.6771$, $P > 0.05$, according to Papanicolaous, classification.

TABLE VII. Pathological Change of Tissue Biopsy Under Colposcopy in Cervical Dysplasia Pretreatment and After 2 Courses of Treatment by RII and Placebo Suppository*

Groups	Dysplasia degree	Lesions				Total
		Disappear	Decrease	No change	Aggravated	
RII	I	21	0	0	3	31
	II	3	2	0	0	5
Placebo	I	10	0	10	0	20
	II	2	2	1	0	5

*The statistical significant between RII and placebo.

with an RII suppository intravaginally and the other 32 patients with placebo, daily for 50 days (Tables VI–IX) in two courses.

Precancerous lesions in 68.75% of the patients disappeared, with an overall effective rate of 74.29% after two courses of treatment with RII. Its curative effect approximated that of laser beam radiation and differed significantly ($P < 0.01$) from that of traditional antiinflammatory.

Randomized, Double-Blind Trial in a High Incidence Area

Cervical cancer has the highest mortality rate in Xiangyuan county, Shanxi province. We are conducting a randomized double-blind placebo-controlled trial in an area of high cervical cancer incidence (Xiang-yuan county, Shanxi Province, China). We anticipate a total accrual of 152 patients, who will be followed up according to protocol for 2 years, after which the data will be analyed.

CONCLUSION

RII, a new synthetic retinoid had marked anticancer effects and induced cell differentiation by experiment. Our results showed that RII had high efficacy and low toxicity, while its minimal cervical and vaginal irritation was well tolerated. In short, RII can be a major measure

TABLE VIII. Pathological Change of Tissue Biopsy Under Colposcopy in Cervical Dysplasia 1 Year After Treatment by RII, Laser, Electrocautery, and Condensation

	Lesions					
Groups	Disappear	Decrease	No change	Aggravated	Malignant progression	Total
RII	21	4	11	0	0	36
Laser	43	8	15	0	0	61
Electrocautery	30	7	12	0	1	50
Condensation	32	21	26	0	1	80
Total	144	37	72	1	2	256

TABLE IX. Pathological Change of Tissue Biopsy Under Colposcopy in Cervical Dysplasia 2 Years After Treatment by RII Compared With Laser and Antiphliogistic Treatment

	Lesions					
Groups	Disappear	Decrease	No change	Aggravated	Malignant progression	Total
RII	27	0	8	0	0	35
Laser	48	0	11	0	0	59
Antiphliogistic	9	0	14	0	16	39
Total	110	0	35	0	16	161

in prevention and treatment of cervical cancer in high-incidence areas of China.

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