

LACK OF EFFECT OF COUMARIN IN WOMEN WITH LYMPHEDEMA AFTER TREATMENT FOR BREAST CANCER

CHARLES L. LOPRINZI, M.D., JOHN W. KUGLER, M.D., JEFF A. SLOAN, PH.D., THOM W. ROOKE, M.D., SUSAN K. QUELLA, R.N., PAUL NOVOTNY, M.S., REX B. MOWAT, M.D., JOHN C. MICHALAK, M.D., PHILIP J. STELLA, M.D., RALPH LEVITT, M.D., LOREN K. TSCHETTER, M.D., AND HAROLD WINDSCHITL, M.D.

ABSTRACT

Background Lymphedema of the arms can be a serious consequence of local and regional therapy in women with breast cancer. Coumarin has been reported to be effective for the treatment of women with lymphedema; we undertook a study in which we attempted to replicate those findings.

Methods We studied 140 women with chronic lymphedema of the ipsilateral arm after treatment for breast cancer. The women received 200 mg of oral coumarin or placebo twice daily for six months and then the other treatment for the following six months. The end points of the study consisted of the volume of the arm (calculated from measurements of hand and arm circumference) and the answers on a questionnaire completed by the patient about symptoms potentially related to lymphedema.

Results The volumes of the arms at 6 and 12 months were virtually identical, regardless of whether coumarin or placebo was given first. After six months, the average volume of the affected arm increased by 21 ml during placebo treatment and 58 ml during coumarin treatment ($P=0.80$). In addition, answers on the patients' questionnaires were similar in the two treatment groups. After six months, only 15 percent of the women in the coumarin group and 10 percent of those in the placebo group reported that the study medication had helped a moderate or large amount ($P=0.19$). Coumarin was well tolerated, except that it resulted in serologic evidence of liver toxicity in 6 percent of the women.

Conclusions Coumarin is not effective therapy for women who have lymphedema of the arm after treatment for breast cancer. (N Engl J Med 1999;340:346-50.)

©1999, Massachusetts Medical Society.

LYMPHEDEMA is an important long-term complication of local and regional therapy in women with breast cancer. It can result in cosmetic deformity, loss of functional ability, physical discomfort, and recurrent episodes of cellulitis and lymphangitis. It is more common in women who are obese¹ and in women over the age of 60 years, presumably because of the loss of connections between lymph vessels and veins.² Physical therapy can be effective in reducing the lymphedema but requires special training that is not widely available.^{3,4}

Coumarin (5,6-benzo- α -pyrone, or 1,2-benzopyrone) and related drugs have been reported to reduce lymphedema,⁵⁻¹⁰ possibly through stimulation of proteolysis by tissue macrophages. In addition to

findings that it decreases the pain and discomfort caused by lymphedema, coumarin has been reported to reduce the incidence of cellulitis or lymphangitis and to soften slowly the brawny edema that is often found in conjunction with lymphedema. In 1993, Casley-Smith et al. reported in the *Journal* the results of a double-blind, crossover trial of coumarin in 31 women with postmastectomy lymphedema and 21 men and women with lymphedema of the leg of various causes.¹⁰ Coumarin was reported to be more effective than placebo in reducing the volume of edema fluid in the arm, in reducing skin temperature, and in increasing the softness of the limb tissue. We undertook the current study in an attempt to confirm these results in women who had lymphedema after treatment for breast cancer.

METHODS

Subjects

The subjects of the study were 140 women 33 to 84 years old with unilateral lymphedema of the arm attributed to earlier local or regional treatment of breast cancer (surgery or radiation therapy). In each case, both the woman and her physician had determined that the lymphedema was sufficiently severe to warrant treatment. The lymphedema had to have been present for at least one year and was not immediately reversible by elevation or compression of the arm. All the women were ambulatory. Women were not eligible for the study if they had taken coumarin previously, were currently undergoing radiation therapy or chemotherapy (with the exception of tamoxifen given as an adjuvant to local or regional treatment), had changed their regimen of physical therapy for lymphedema during the preceding month, or had an indwelling venous device; if they had an infection of either arm, had evidence of residual active cancer, had a life expectancy of less than 2 years, or had bilateral edema of the arms; if they were pregnant or nursing; or if they had a history of hepatitis or evidence of liver dysfunction (i.e., serum aminotransferase or conjugated bilirubin concentrations >50 percent above the upper limit of normal), a history of alcohol abuse, or a history of venous thrombosis in the preceding 12 months.

At the time of enrollment, a complete history was obtained from each woman, and a physical examination and liver-function tests were performed. In addition, the women completed a questionnaire designed to assess swelling, pressure, tightness, heaviness, and loss of mobility of the arms, which they graded from 0 to 3

From the Mayo Clinic and Mayo Foundation, Rochester, Minn. (C.L.L., J.A.S., T.W.R., S.K.Q., P.N.); the Illinois Oncology Research Association Community Clinical Oncology Program (CCOP), Peoria (J.W.K.); Toledo Community Hospital Oncology Program CCOP, Toledo, Ohio (R.B.M.); Siouxland Hematology-Oncology Associates, Sioux City, Iowa (J.C.M.); Ann Arbor Regional CCOP, Ann Arbor, Mich. (P.J.S.); Meritcare Hospital CCOP, Fargo, N.D. (R.L.); Sioux Community Cancer Consortium, Sioux Falls, S.D. (L.K.T.); and CentraCare Clinic, St. Cloud, Minn. (H.W.). Address reprint requests to Dr. Loprinzi at the Mayo Clinic, 200 First St., SW, Rochester, MN 55905, or at loprinzi.charles@mayo.edu.

according to the following scale: 0, none; 1, mild; 2, moderate; and 3, severe. These questionnaires also inquired about any infection in the affected arm. Measurements were taken of the circumference of each hand just distal to the thumb, of each wrist at its narrowest point, and of each arm 30, 40, and 50 cm proximal to the tip of the middle finger, as far as possible before the axilla was reached. The volume of each arm was calculated from these measurements as described by Casley-Smith¹¹ and according to the formula for the volume of a cylinder. The women were also given written instructions that provided details about the planned study procedures and educational information about lymphedema. The study was approved by the appropriate institutional review committees, and all the women gave written informed consent.

Study Design

The women were stratified according to six characteristics (age, therapy for breast cancer, history of cellulitis in the involved arm, duration of lymphedema, time since surgery or radiation therapy, and tamoxifen therapy) and then randomly assigned to receive coumarin (two 100-mg tablets twice daily) or placebo (two identical lactose tablets twice daily) for six months, followed by the other treatment for six months. The coumarin and placebo tablets were provided by Drossapharm Pharmaceuticals (Basel, Switzerland).

The women were examined monthly, and on each occasion they were asked to complete questionnaires that included the items on the prestudy questionnaire as well as questions about whether they thought that the study medication was helpful, how often they took the study medication, and whether they had nausea, vomiting, diarrhea, or other symptoms that might be related to the medication. At the end of each six-month treatment period, the circumference of the hands and arms was measured in the same way as before the study.

Initially, we planned to measure serum aminotransferase concentrations at the end of each treatment period. However, as we have reported previously,¹² two women had abnormal values three or four months after treatment started (the measurement was performed in one woman in whom jaundice developed and in another at the discretion of the attending physician). We therefore measured serum aminotransferase concentrations in the other women after three to four months of the initial treatment and then one and three months after crossover to the opposite treatment. Treatment was stopped if serum aminotransferase concentrations were two or more times the upper limit of normal.

The efficacy of treatment was judged according to changes in arm volume, which was calculated from measurements of circumference by the method of Casley-Smith,¹¹ and according to the women's answers on the questionnaires.

Statistical Analysis

At the end of each treatment period, Student's *t*-tests and Wilcoxon's rank-sum tests were used to compare the average circumference of the affected arm at each measurement site, after normality had been established or refuted by Shapiro-Wilk testing.¹³ The average ratio of the circumference of the affected arm to that of the normal arm was compared in the same way at each site. The arm-circumference measurements were then combined into volumetric data for each arm at each time point according to the method of Casley-Smith¹¹ and by application of the formula for the volume of a cylinder.

We evaluated the volumetric data using the geometric relations for arm measurements and the SAS Data Step Graphics Interface program.¹⁴ According to this method, the circumference measured at each site was used to construct ellipses with the geometric formula relating the circumference of an ellipse to its area. A second equation was formed by relating the relative length of the major and minor axes of each ellipse. The two equations, each with two unknown variables, were then solved to obtain the equation for an ellipse that represented the shape of the arm at each site. These ellipses were then joined by straight lines of the appropriate lengths, and a representation of the curvature of the hand was

constructed with an additional ellipse. For each woman, the representation of the normal arm was then overlaid with the representation of the affected arm. Simulations demonstrated that the resulting image accurately reflected changes in arm volume.

The incidence scores for responses to the questionnaires were compared between the groups at the end of each treatment period by simple tests for the equality of binomial proportions. Ordinal responses were analyzed by standard Wilcoxon's rank-sum tests. All the statistical tests were two-sided.

RESULTS

Of the 140 women enrolled in the study, 1 was found to be ineligible (she had a history of hepatitis) and 1 withdrew from the study (she never took any study medication after randomization). For analyses of toxicity, data from all 139 women who took any study medication (including the ineligible woman) were included. For the evaluation of efficacy, data were obtained on 130 of the 138 remaining women (94 percent) at 6 months and 113 (82 percent) at 12 months. Six women discontinued treatment before the evaluation at 6 months, and 12 more stopped before the 12-month evaluation. One woman was reportedly murdered after her six-month evaluation. Arm-volume data were not obtained in several additional cases in which women did not return for arm measurements; data were available for 120 at 6 months and 93 at 12 months.

The characteristics of the women in the two study groups were similar (Table 1), as were their answers to

TABLE 1. BASE-LINE CHARACTERISTICS OF WOMEN WITH BREAST CANCER AND LYMPHEDEMA ACCORDING TO STRATIFICATION FACTORS.*

CHARACTERISTIC	COUMARIN FIRST, PLACEBO SECOND (N=67)	PLACEBO FIRST, COUMARIN SECOND (N=71)	P VALUE
	percent		
Age			0.86
<60 yr	51	48	
≥60 yr	49	52	
Therapy for breast cancer			0.90
Mastectomy without radiation therapy	48	45	
Mastectomy with radiation therapy	34	38	
Breast-conserving surgery with radiation therapy	18	17	
History of cellulitis in affected arm			0.99
Yes	30	30	
No	70	70	
Duration of lymphedema			0.99
1-2 yr	31	31	
>2 yr	69	69	
Time since surgery or radiation therapy to chest wall or axilla			0.97
<2 yr	12	15	
2-4 yr	33	28	
>4 yr	55	56	
Tamoxifen therapy			0.99
Yes	45	45	
No	55	55	

*Because of rounding, not all percentages total 100.

questions on the base-line questionnaire about arm pressure, tightness, heaviness, swelling, and loss of mobility.

Results of a crossover analysis demonstrated that there was no evidence of a carryover effect, and therefore results for each treatment were combined. After the administration of coumarin or placebo for six months, there were no significant differences from base line in total or distal edema; volume of the affected arm; ratio of the volume of the affected arm to that of the normal arm; or circumference of the hand, wrist, or arm at points 30, 40, and 50 cm from the tip of the middle finger. The average volume of the affected arm increased by 21 ml with placebo and 58 ml with coumarin. The volumes of both the affected and the normal arms were similar in the two groups at all times (Fig. 1). Our assessment of the influence of evaluation on the results included analyses of the effects of variability between patients, treatment period, treatment sequence, base-line scores, severity of lymphedema, duration of lymphedema, age, handedness, use of tamoxifen, and history of cellulitis. Regardless of the covariates included in the analysis, coumarin had no effect that differed from that of placebo on any of the end points related to efficacy.

Analysis of the data provided by the monthly questionnaires also supported this finding. The women's responses to questions about arm swelling, pressure, tightness, heaviness, and loss of mobility were similar for coumarin and placebo during both periods

and demonstrated some positive changes with time but no differential effects associated with treatment (Fig. 2). The frequency of infections of the arm was similar during the coumarin and placebo periods.

After each six-month period the women were asked whether they thought that the study medication was helping them. Their responses did not suggest that coumarin had benefit during either period (Table 2). After 12 months the women were asked which of the two treatment periods (the first or the second) they preferred. Of the 87 women who answered this question, 51 percent did not prefer one period over the other, 24 percent preferred the coumarin period, and 25 percent preferred the placebo period.

The results of the monthly questionnaires with respect to compliance revealed that 88 percent of the women took at least 90 percent of their study medication during the first six months, and 81 percent did so during the second six months. There were no differences between treatments in compliance.

With regard to side effects, the information obtained from the questionnaires and by history taking at 6 and 12 months did not suggest any differences in the incidence of nausea, vomiting, or diarrhea between coumarin treatment and placebo. However, as we have previously reported,¹² the incidence of hepatotoxic effects was substantially higher with coumarin than with placebo. In none of the women did serum aminotransferase concentrations reach 2.5 times the upper limit of normal during the

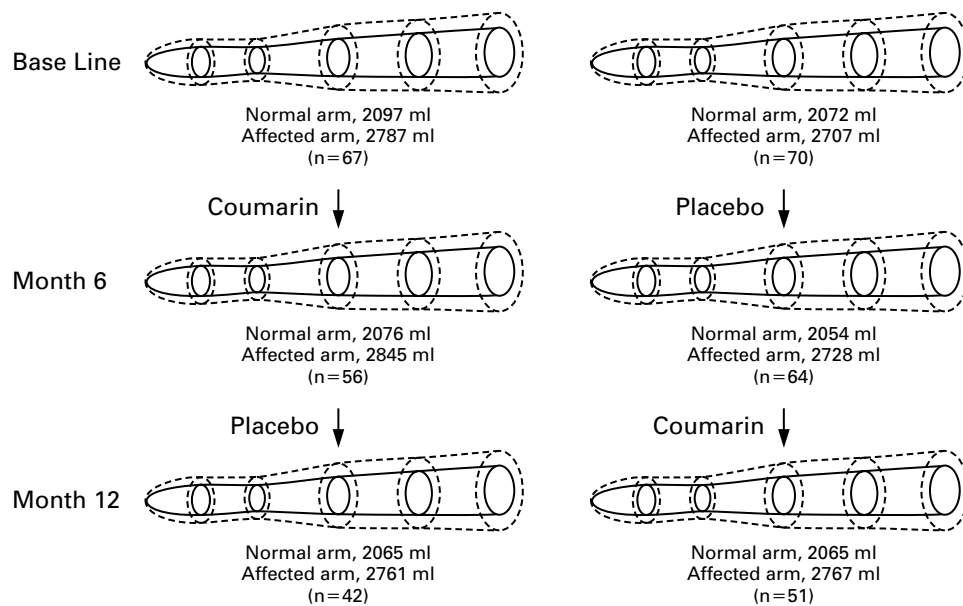


Figure 1. Mean Volumes of the Arms in the Women Receiving Coumarin and Placebo in a 12-Month Crossover Study. The affected arm (dashed line) and normal arm (solid line) are shown; circles represent sites at which the circumference was measured. The sizes of the involved arms and of the contralateral control arms remained remarkably similar despite treatment.

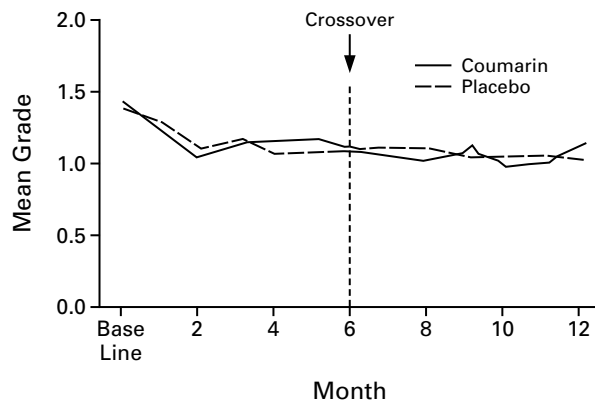


Figure 2. Grading of Arm Symptoms on Questionnaires by Women in the Two Treatment Groups.

Arm symptoms assessed by the women were swelling, pressure, tightness, heaviness, and loss of mobility. Symptoms were graded according to the following scale: 0, none; 1, mild; 2, moderate; and 3, severe.

TABLE 2. BENEFIT PERCEIVED BY THE WOMEN WHILE RECEIVING COUMARIN OR PLACEBO.*

WOMEN'S ASSESSMENT OF BENEFIT	COUMARIN FIRST, PLACEBO SECOND (N=67)	PLACEBO FIRST, COUMARIN SECOND (N=71)	P VALUE
	percent		
At mo 6†			0.19
No, did not help	59	71	
Yes, helped a little	26	19	
Yes, helped a moderate amount	9	8	
Yes, helped a large amount	6	2	
At mo 12‡			0.08
No, did not help	51	67	
Yes, helped a little	31	28	
Yes, helped a moderate amount	10	2	
Yes, helped a large amount	8	2	

*Because of rounding, not all percentages total 100.

†Data were missing for 13 of the women who received coumarin first and for 19 of the women who received placebo first.

‡Data were missing for 28 of the women who received coumarin first and for 28 of the women who received placebo first.

placebo period, whereas in nine women (6 percent) the concentrations became high during treatment with coumarin ($P=0.006$). The most prominent instance of hepatotoxicity occurred in a woman in whom jaundice developed and the serum bilirubin concentration rose to 19.3 mg per deciliter (330 μmol per liter) while she was receiving coumarin. In these nine women the test results became normal after coumarin treatment was stopped (treatment was stopped when the elevated values were recorded).

DISCUSSION

In our study we found that coumarin did not alleviate lymphedema and that coumarin-related hepatotoxic effects were more common than has been previously reported. We designed our protocol to duplicate that of a study by Casley-Smith et al., who reported that coumarin alleviated lymphedema.¹⁰ We are unable to explain the difference between the results of the two studies. The previous trial involved 31 women with lymphedema of an arm, whereas we studied 140 women. All the women had lymphedema after treatment for breast cancer, and review of the baseline characteristics of the women in the two studies suggests that they were similar. The circumferences of the arms were measured similarly in both studies.

Previous studies suggested that coumarin caused hepatotoxic effects in fewer than 1 percent of patients, and indeed it was claimed that hepatotoxicity was not clearly associated with this drug.^{15,16} Thus, our finding of hepatotoxic effects in 6 percent of the women in our study was unexpected. We were unable to identify any predisposing factors, such as therapy with tamoxifen or high body weight. During our trial, the deaths of patients receiving coumarin in other countries led to the removal of the drug from the market in at least two countries.

In conclusion, we found that coumarin was ineffective for ameliorating lymphedema of the arm in women who had undergone local or regional therapy for breast cancer.

Supported in part by grants (CA-25224, CA-37404, CA-35113, CA-35415, CA-35103, CA-63848, and CA-37417) from the National Cancer Institute.

We are indebted to Dr. John Casley-Smith for his help in reviewing the protocol after it was developed.

APPENDIX

This study was conducted as a trial of the North Central Cancer Treatment Group. Additional participating institutions and investigators included the following: Duluth Community Clinical Oncology Program (CCOP), Duluth, Minn. (J.E. Krook); Rapid City Regional Oncology Group, Rapid City, S.D. (L.P. Ebbert); Carle Cancer Center CCOP, Urbana, Ill. (A.K. Hatfield); Iowa Oncology Research Association CCOP, Des Moines (R.E. Morton); Cedar Rapids Oncology Project CCOP, Cedar Rapids, Iowa (M. Wiesenfeld); Missouri Valley Cancer Consortium, Omaha, Nebr. (J.A. Mailiard); Ochsner CCOP, New Orleans (C.G. Kardinal); Scottsdale CCOP, Scottsdale, Ariz. (R. Wheeler); Geisinger Clinic and Medical Center CCOP, Danville, Pa. (S. Nair).

REFERENCES

1. Say CC, Donegan W. A biostatistical evaluation of complications from mastectomy. *Surg Gynecol Obstet* 1974;138:370-6.
2. Pezner RD, Patterson MP, Hill LR, et al. Arm lymphedema in patients treated conservatively for breast cancer: relationship to patient age and axillary node dissection technique. *Int J Radiat Oncol Biol Phys* 1986;12:2079-83.
3. Casley-Smith JR, Casley-Smith JR. Modern treatment of lymphoedema. I. Complex physical therapy: the first 200 Australian limbs. *Australas J Dermatol* 1992;33:61-8.
4. Zanolta R, Monzeglio C, Balzarini A, Martino G. Evaluation of the results of three different methods of postmastectomy lymphedema treatment. *J Surg Oncol* 1984;26:210-3.
5. Jamal S, Casley-Smith JR, Casley-Smith JR. The effects of 5,6 benzo-

- [a]-pyrone (coumarin) and DEC on filaritic lymphoedema and elephantiasis in India: preliminary results. *Ann Trop Med Parasitol* 1989;83:287-90.
6. Braun HD, Becker T, Meyer U. Behandlung von Stauungserscheinungen nach Ablatio mammae und Bestrahlung: Erfahrungen mit physikalischer Therapie und Venoruton. *Munch Med Wochenschr* 1971;113:1630-3.
 7. Casley-Smith JR, Jamal S, Casley-Smith J. Reduction of filaritic lymphoedema and elephantiasis by 5,6-benzo- α -pyrone (coumarin), and the effects of diethylcarbamazine (DEC). *Ann Trop Med Parasitol* 1993;87:247-58.
 8. Casley-Smith JR, Wang CT, Casley-Smith JR, Zi-Hai C. Treatment of filarial lymphoedema and elephantiasis with 5,6-benzo- α -pyrone (coumarin). *BMJ* 1993;307:1037-41.
 9. Piller NB, Morgan RG, Casley-Smith JR. A double-blind, crossover trial of 0-(β -hydroxyethyl)-rutosides (benzo-pyrones) in the treatment of lymphoedema of the arms and legs. *Br J Plast Surg* 1988;41:20-7.
 10. Casley-Smith JR, Morgan RG, Piller NB. Treatment of lymphedema of the arms and legs with 5,6-benzo- α -pyrone. *N Engl J Med* 1993;329:1158-63.
 11. Casley-Smith JR. Measuring and representing peripheral oedema and its alterations. *Lymphology* 1994;27:56-70.
 12. Loprinzi CL, Sloan JA, Kugler J. Coumarin-induced hepatotoxicity. *J Clin Oncol* 1997;15:3167-8.
 13. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). *Biometrika* 1965;52:591-611.
 14. SAS/GRAPH software: reference, version 6. Vol. 1. Cary, N.C.: SAS Institute, 1990:599-736.
 15. Cox D, O'Kennedy R, Thornes RD. The rarity of liver toxicity in patients treated with coumarin (1,2-benzopyrone). *Hum Toxicol* 1989;8:501-6.
 16. Casley-Smith JR, Casley-Smith JR. Frequency of coumarin hepatotoxicity. *Med J Aust* 1995;162:391.