

COMPARISON OF 6 α -METHYL-9 α -FLUORO-17-ACETOXY-21-DEOXYPREDNISOLONE WITH FLUOXYMESTERONE AND METHYLPREDNISOLONE IN TREATMENT OF METASTATIC BREAST CANCER

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WE HAVE PREVIOUSLY PUBLISHED THE RESULTS of management of metastatic breast carcinoma in women with 6 α -methyl-9 α -fluoro-17-acetoxy-21-deoxyprednisolone (oxylone acetate) in a preliminary study.⁷ (This compound has been named by the International Union of Pure and Applied Chemistry as 9 α -fluoro-11 β -17-dihydroxy-6 α -methyl-9 α -pregna-1,4-diene-3,20-dione-17-acetate.) Five objective regressions were noted in 20 patients. Subsequently, this compound has been studied more extensively by us, both in primary and secondary hormonal management of patients with metastatic breast carcinoma. This report presents the results observed in 2 concurrent studies, one comparing oxylone acetate with fluoxymesterone (Halotestin) and the other comparing oxylone acetate with methylprednisolone (Medrol).

Oxylone acetate is of interest because it possesses both adrenocorticoid activity and progestational activity as shown by Glenn and co-workers.³ They also found it to be the best of a large series of steroids in the inhibi-

tion of both testosterone-sensitive and testosterone-resistant mammary fibroadenomas in the rat and a hormonally independent transplantable C3H mouse mammary carcinoma.

MATERIALS AND METHODS

Two studies were undertaken: study 1, the comparison of oxylone acetate with Halotestin as the initial additive in the hormonal management of breast carcinoma in postmenopausal women, and study 2, the comparison of oxylone acetate with Medrol in patients previously treated with 1 other hormonal agent. Both studies were randomized double-blind trials, in which the criteria for admission to the studies, and the clinical response, were those employed by the Breast Cancer Study Group of the Cancer Chemotherapy National Service Center.⁶

In study 1 the patients received either 10 mg. of Halotestin or 25 mg. of oxylone acetate orally, twice daily. All patients were examined clinically at monthly intervals for change in size of palpable tumors. A complete radiographic survey of the skeleton and chest was carried out at 4- to 6-week intervals. Also, hemoglobin levels, sulfo bromophthal-
ein retention, serum calcium, phosphorus, acid and alkaline phosphatase, and serum proteins were determined at similar intervals.

In study 2 the patients were randomized according to a random number method rather than by menopausal age and site of metastases. Therapy was given orally in identical tablets of either 25 mg. of oxylone acetate or 12 mg. of Medrol, twice daily. The same studies and parameters of disease as mentioned in study 1 were carried out in study 2. The patients selected for study 2 had previously received either androgenic or estrogenic agents, but none had received corticosteroids.

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RESULTS

Study 1. Objective remissions are summarized in Table 1. It is interesting to note that oxyllone acetate did induce objective remissions in 6 of 23 patients (26%), whereas Halotestin was effective in only 13%. The average duration of the regressions induced in the 3 patients responding to Halotestin was 30 weeks. In the 6 patients responding to oxyllone acetate the average duration of regression was 35 weeks. These differences are not significant.

Manifestations of hypercorticism were observed in 12 patients receiving oxyllone acetate. Considerable osteoporosis was observed in 2 of 6 patients on treatment with oxyllone acetate for 6 months or longer. Three patients decreased the dose of the drug to 1 tablet (25 mg.) daily, because of undesirable acne and moon facies. All these patients had been receiving the drug for 2 months or more. Minimal cushingoid changes appeared in 1 patient receiving Halotestin. Edema was seen in 2 patients receiving oxyllone acetate and in 1 receiving Halotestin. Mild facial hirsutism occurred in 7 patients with Halotestin and in 3 patients with oxyllone acetate. Hoarseness occurred in 8 patients receiving Halotestin and in only 1 patient receiving oxyllone acetate. Vaginal bleeding occurred, after discontinuance of therapy, in 3 patients treated with oxyllone acetate.

Study 2. The incidence of objective regression produced by oxyllone acetate and Medrol are recorded in Table 2. Three of 14 patients

responded to oxyllone acetate and 3 of 13 responded to Medrol. The average duration of regression was 31 weeks with oxyllone acetate and 32 weeks with Medrol.

The response to previous hormonal therapy is compared to the subsequent response in this study in Table 3. Previous response to hormonal therapy appeared to have a significant prognostic value in response to the agents employed in this study. Androgens had been the primary treatment in 26 patients and estrogen in 1. Medrol and oxyllone acetate were both more effective in patients who had previously enjoyed a hormonally induced regression, as compared to those who had failed their first administrative hormonal treatment. Thus, a failure or response with prior hormonal therapy does not predict the response to another agent, but regressions appear to occur more frequently if the initial hormonal agent produced a regression.

The side effects of both the agents in study 2 were primarily those of hypercorticism. Moon facies, acne, gastrointestinal symptoms, and osteoporosis, were slightly more severe in the oxyllone acetate group, though the frequency with both compounds was about equal. This may be related to a slight difference in the potency of the compounds at dose levels employed. Two patients in this study experienced vaginal bleeding upon discontinuance of oxyllone acetate.

DISCUSSION

Oxyllone acetate is of interest, in that it has both progestational and adrenocorticoid activity. Progestins and glucocorticoids have been shown by others to be efficacious in metastatic breast cancer.^{4,5} Therefore, the demonstration of activity in our studies for a compound possessing both kinds of hormonal activity was expected. However, the relative efficacy of oxyllone acetate in the treatment of human metastatic mammary cancer does not appear to be as great in comparison to other steroids as Glenn et al.³ found it to be in experimental mammary tumors of rodents.

With the continued evaluation of steroid compounds, it appears that a relatively fixed percentage of human breast cancer patients have hormonally responsive tumors, and that observable maximal response rates will not vary significantly between various steroidal agents when given at adequate dose levels in an adequate number of patients. The con-

TABLE 1
INCIDENCE OF OBJECTIVE REGRESSION
IN PATIENTS RECEIVING OXYLLONE
ACETATE OR FLUOXYMESTERONE

	Objective remissions/no. pt.*				
	Menopausal age, yr.				
Dominant les.	<1	1-5	5-10	>10	Total
<i>Fluoxymesterone</i>					
Breast	0/1	0/1	0/2	1/1	1/5
Osseous	1/2	0/1	0/1	0/5(1)	1/9(1)
Visceral	1/2	0/3	0/1(1)	0/3	1/9(1)
TOTAL	2/5	0/5	0/4(1)	1/9(1)	3/23(2)
<i>Oxylone acetate</i>					
Breast	1/1	0/1	0/1	1/2	2/5
Osseous	1/2	1/1	0/1	1/4	3/8
Visceral	0/2	1/2	0/3	0/3(1)	1/10(1)
TOTAL	2/5	2/4	0/5	2/9(1)	6/23(1)

*Numbers in parentheses indicate the number of patients studied for less than 2 weeks.

TABLE 2
INCIDENCE OF OBJECTIVE REGRESSION
IN PATIENTS RECEIVING OXYLONE
ACETATE OR METHYLPREDNISOLONE
AS SECONDARY HORMONAL THERAPY
FOR METASTATIC BREAST CANCER

Dominant les.	Objective remissions/no. pt.				
	Menopausal age, yr.				
	<1	1-5	5-10	>10	Total
<i>Methylprednisolone</i>					
Breast	0/0	0/0	0/0	1/3	1/3
Osseous	0/0	1/2	0/0	0/1	1/3
Visceral	0/1	0/2	0/0	1/4	1/7
TOTAL	0/1	1/4	0/0	2/8	3/13
<i>Oxylone acetate</i>					
Breast	0/0	0/1	1/2	0/0	1/3
Osseous	0/0	0/0	0/1	0/2	0/3
Visceral	0/1	1/2	0/1	1/4	2/8
TOTAL	0/1	1/3	1/4	1/6	3/14

tinued use of supermaximal doses of androgenic, estrogenic, or glucocorticoid hormones, employed for suppression of metastatic breast cancer, is certainly superphysiological. Whether or not studies employing physiological or subphysiological doses of these hormonal agents would produce comparable results cannot be stated, but such studies would be of interest. Alterations of the steroid molecule may be capable of reducing some side effects of steroid agents, but may be incapable of increasing the incidence of objective regressions in metastatic breast cancer above a fixed level, granted the trial doses employed are at supermaximal levels for each compound.

Studies that would identify the hormone-dependent breast cancer population would be of extreme importance in the scientific management of metastatic breast carcinoma, and in the investigation of dose-response relationships with various steroids. Bulbrook et al.¹ have found that patients responding to adrenalectomy and hypophysectomy have normal etiocholanolone and other 11-deoxy-17-oxy-steroid-excretion patterns, whereas those failing to respond to these procedures have depressed excretion of etiocholanolone. This is an extremely important and interesting observation and should be studied more critically in patients receiving additive hormonal therapy.

The fact that a glucocorticoid without progestational activity gave results indistinguishable from those produced by oxylone acetate, supports the concept that the progestational

function of oxylone acetate is not of primary importance in the induction of regressions in metastatic breast cancer. However, we have observed that a more potent pure progestin (6 α -methyl-17-acetoxy progesterone) employed in superphysiological doses can produce responses in metastatic breast cancer.⁸ However, the induction of withdrawal vaginal bleeding is good presumptive evidence that at least physiological doses of a progestin were being administered. Reports of the use of other progestins in breast cancer suppression have given varying results.^{2, 5}

Oxylone acetate did induce objective remissions. However, the incidence of moderately severe cushingoid side effects and the fact that a known potent adrenal glucocorticoid (Medrol) also produced objective regressions of a similar nature with less severe side effects, would support the probability that the objective regressions obtained with oxylone acetate were primarily due to the adrenal corticoid activity of the compound. We do not think oxylone acetate, at the dose levels employed, has any advantage over other agents in the management of metastatic breast cancer.

SUMMARY

- 1. 6 α -Methyl-9 α -fluoro-17-acetoxy-21-deoxy-prednisolone (oxylone acetate) was compared in a randomized double-blind study with fluoxymesterone (Halotestin) in the management of metastatic breast carcinoma.
- 2. Oxylone acetate induced regressions in 6 of 23 patients (26%) and Halotestin induced regressions in 3 of 23 patients (13%). These differences are not significant.
- 3. In a second study, oxylone acetate was compared in a randomized double-blind study

TABLE 3
CORRELATION OF RESPONSE TO
CORTICOSTEROID THERAPY WITH
RESPONSE TO PREVIOUS
HORMONAL THERAPY

Result	No. pt.	Response to prev. hormonal therapy, no. pt.	
		Failure	Regression
Methylprednisolone	13	10	3
Regression	3	1	2
Failure	10	9	1
Oxylone acetate	14	8	6
Regression	3	1	2
Failure	11	7	4

with methylprednisolone (Medrol) in patients previously treated with 1 hormonal agent. Objective regressions were obtained in 3 of 13 Medrol-treated patients, and in 3 of 14 oxyllone acetate-treated patients.

4. Objective responses were obtained with these 2 glucocorticoid drugs in 4 out of 9 patients who had responded to previous hormonal therapy, but in only 2 of 18 who had failed an initial trial on either an androgen or estrogen.

5. Oxyllone acetate at a dose of 25 mg. twice daily, produced moderately severe hypercorticoïd changes. Vaginal bleeding was observed following withdrawal in several, supporting the progestational activity demonstrated in experimental animals.

6. Oxyllone acetate at this dose level does not appear to have any advantages over other hormonal agents in the treatment of metastatic breast carcinoma in the postmenopausal woman.

REFERENCES

1. BULBROOK, R. D.; HAYWARD, J. L.; SPICER, C. C., and THOMAS, B. S.: Comparison between urinary steroid excretion of normal women and women with advanced breast cancer. *Lancet* 2: 1235-1237, 1962.
2. COLSKY, J.; SHNIDER, B.; JONES, R., JR.; NEVINNY-STICKEL, H. B.; HALL, T.; REGELSON, W.; SELAWRY, O. S.; OWENS, A., JR.; BRINDLEY, C. O.; FREI, E., III, and UZER, Y.: Comparative study of 9 α -bromo-11 β -ketoprogesterone and prednisolone in treatment of advanced carcinoma of female breast. *Cancer* 16: 502-505, 1963.
3. GLENN, E. M.; RICHARDSON, S. L.; BOWMAN, B. J., and LYSER, S. C.: Steroids and experimental mammary cancer. In PINCUS, G., and VOLLMER, E. P., Eds.: *Biological Activities of Steroids in Relation to Cancer*. New York, N.Y. Academic Press Inc. 1960; pp. 257-305.
4. GOLDENBERG, I. S., and HAYES, M. A.: Hormonal therapy of metastatic female breast carcinoma; I, 9 α -bromo-11-ketoprogesterone. *Cancer* 12: 738-740, 1959.
5. LEMON, H. M.: Prednisone therapy of advanced mammary cancer. *Cancer* 12: 93-107, 1959.
6. SEGALOFF, A.: Progress report; results of studies by Cooperative Breast Cancer Group—1956-60. In *Cancer Chemotherapy Reports*, No. 11. Bethesda, Md. Cancer Chemotherapy National Service Center. 1961; pp. 109-141.
7. TALLEY, R. W.; KELLY, J. E.; BRENNAN, M. J., and VAITKEVICIUS, V. K.: Clinical study of 6 α -methyl-9 α -fluoro-17-acetoxy-21-deoxyprednisolone (U-17323) in human breast cancer—preliminary report. In *Cancer Chemotherapy Reports*, No. 12. Bethesda, Md. Cancer Chemotherapy National Service Center. 1961; pp. 59-62.
8. TALLEY, R. W.; BRENNAN, M. J., and VAITKEVICIUS, V. K.: Unpublished data.