Androgenic Therapy for Advanced Breast Cancer in Women

A Report of the Cooperative Breast Cancer Group

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A randomized clinical trial of calusterone and testolactone according to the protocol of the Cooperative Breast Cancer Group (CBCG) produced objective remissions of advanced breast cancer in 28% of women receiving calusterone and 18% of those given testolactone. Effectiveness of the calusterone has prompted a dose-response study by the CBCG to determine the most effective dose of this androgen for use in treatment of breast cancer.

ANDROGENIC therapy for advanced breast cancer in women has been used for several decades and produces objective regression rates for metastatic lesions in the range of 10% to 20%. The precise mechanism of action of a male hormone in such treatment is not completely understood and may be entirely unrelated to androgenic effects, although most of the androgens effective in the therapy of breast cancer are also associated with virilization of the patient. A search for new androgenic agents undertaken by the Cooperative Breast Cancer Group (CBCG) of the National Cancer Institute during the past few years has resulted in clinical evaluation of many drugs, and this report details a phase 2 study of two androgenic compounds—calusterone (17β-Hydroxy-7β,17-dimethylandrost-4-en-3-one, NSC 88536) and testolactone (17α-oxa-D-homoandrosta-1,4-diene-3,17-dione, NSC 23759) (Figure)—according to the basic protocol of the CBCG.

Materials and Methods

The main principles of the basic CBCG protocol for drug appraisal are (1) randomized assignment of patients to receive drugs under study, based on menopausal age and dominant metastatic site, (2) objective criteria for regression of disease while on therapy, and (3) use of two impartial investigators for review of patients' response to therapy by examination of serial roentgenograms, photographs of lesions, and measurements of metastatic foci. A patient is considered to have an objective regression of cancer while receiving therapy if more than 50% of all lesions decrease in size while all other lesions remain static or more than 50% of nonosseous lesions decrease in size while all osseous lesions remain static and no new lesions appear during therapy.

Previous phase 1, 2 and 3 clinical evaluation by the CBCG of testolactone and phase 1 and 2 studies of calusterone[1] indicated that these drugs induce objective regressions of lesions in advanced female breast cancer. Calusterone was originally produced as a fortuitous by-product during synthesis of 7α-methyl testosterone compounds.[2] This epimer seemed to have little biologic activity in animals, but clinical trial in a group of women with advanced breast cancer demonstrated that it produced objective regressions when administered orally at a dosage of 200 mg daily.[3] When a double bond is introduced between the first and second carbon atoms, testolactone loses all characteristic biologic activity of its parent testosterone, including virilization, and has been most effective at an oral dosage of 1 gm daily (findings of the CBCG, written communication, 1972). The present study evaluated these drugs at these dosages in two similar groups of women (Table 1), randomized according to the protocol of the CBCG such that 109 patients received the calusterone and 115 received the testolactone.

Results

According to criteria of the CBCG protocol, 28% of patients receiving calusterone (30 of 109) had an objective remission of advanced metastatic disease with a mean duration of therapy of 11.9 weeks and a one-year survival rate of 59%. By these same criteria, 18% of women receiving testolactone (21 of 115) had an objective remission with median duration of therapy of 12.0 weeks and a one-year survival rate of 59% (Table 2).

Table 1.—Data on Patients Treated

	Calusterone	Testolactone
Age (yr)		
Mean	57.6	59.4
Median	57.0	59.0
Range	31.0-81.0	35.0-84.4
	(N=108)	(N=115)
Years post-menopausal		
Mean	9.2	11.0
Median	7.8	8.0
Range	0.1-25.9	0.1-33.5
	(N=91)	(N=92)
Duration of disease (yr)		
Mean	3.9	4.2
Median	2.4	3.0
Range	0.0*-22.6	0.0*-20.6
	(N=109)	(N=114)
Dominant site of lesion (No. of patients)		
Local	13	16
Osseous	24	26
Visceral	72	73

*Primary inoperable cancer.

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Table 2.—Regression Ratio by Treatment

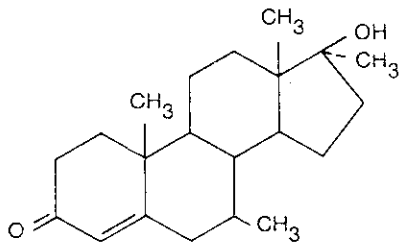
Dominant Site of Lesion	Castrated Less Than 1 Yr	No. of Yrs Post-Menopausal 1-5	6-10	>10	Total
Calusterone					
Local	1/1 (1.00)	0/2	0/2	4/8 (0.50)	5/13 (0.38)
Osseous	0/1	2/7 (0.29)	2/6 (0.33)	3/10 (0.30)	7/24 (0.29)
Visceral	0/0	3/23 (0.13)*	5/16 (0.31)	10/33 (0.30)*	18/72 (0.25)
Total	1/2 (0.50)	5/32 (0.16)	7/24 (0.29)	17/51 (0.33)	30/109 (0.28)
Testolactone					
Local	1/1 (1.00)	1/3 (0.33)	1/3 (0.33)	1/9 (0.11)	4/16 (0.25)
Osseous	0/1	1/10 (0.10)†	2/5 (0.40)	3/10 (0.30)	6/26 (0.23)
Visceral	1/2 (0.50)	2/19 (0.11)†	2/12 (0.17)	6/40 (0.15)‡	11/73 (0.15)
Total	2/4 (0.50)	4/32 (0.13)	5/20 (0.25)	10/59 (0.17)	21/115 (0.18)

*Two patients received <15 days of therapy. †One patient received <15 days of therapy. ‡Six patients received <15 days of therapy.

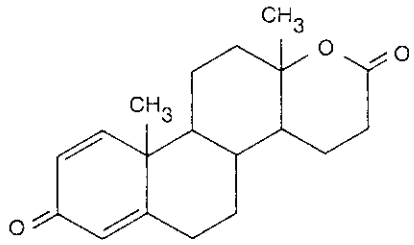
A statistically significant difference in the mean duration of disease (time elapsed prior to start of treatment with test compound) between women who had regressions (5.8 years) and those who did not (3.5 years) suggests that this variable may have some predictive value in dealing with advanced breast cancer patients. As would be expected, the mean duration of disease for women having regressions while being treated with calusterone (5.6 years) was significantly greater ($P<.01$) than that for women who did not (3.3 years) and the mean duration of disease for remissions on testolactone (5.9 years) was significantly greater ($P<.05$) than that for women treated with the same compound who did not show regressions (3.8 years). The median test also disclosed a statistically significant difference ($P<.01$) in the median duration of therapy between women with regressions (40.6 weeks) and those who did not respond (9.6 weeks).

Various clinical abnormalities such as hepatic dysfunction, gastrointestinal symptoms, and others occur in women receiving androgenic therapy. In the present study, severe or life-threatening problems arose in four instances in patients receiving testolactone and in two instances among those given calusterone. Mild to moderate abnormalities were reported 23 times in the former group and 45 times in the latter (including two patients who developed hepatic dysfunction). A total of 30 women treated with calusterone displayed abnormalities as compared with 19 among those receiving testolactone.

Gordan et al[1] have suggested that nonhormonal chemotherapy may adversely influence subsequent response of advanced breast cancer to androgenic compounds. In the present study, 18 patients had received such chemotherapy before the treatment with calusterone was started and six of these (35%) demonstrated objective regressions as a result of the androgen therapy. Thirteen women given testolactone had had previous exposure to chemotherapy and three of these (23%) had objective regressions from the androgen. It seems unlikely in the patients studied here that exposure to nonhormonal chemotherapy prior to androgenic therapy affected subsequent response to the androgen.



Calusterone



Testolactone

Comment

Promising preliminary studies of calusterone showed objective regression rates in excess of 50%[2] with a distinct lack of androgenicity so that a protocol, randomized study by the CBCG seemed imperative to evaluate a drug which appeared to produce a regression rate in advanced breast cancer more than 2.5 times that of most other androgens. In the present study testolactone was used as the reference compound because it also had previously demonstrated efficacy without virilization.

The objective remission rate reported earlier for calusterone[1] was not obtained in the present evaluation, but its effectiveness was well demonstrated. The dosage used to date has been empirical and it is impossible to state unequivocally that 200 mg daily is optimum to achieve the greatest number of objective regressions. The results reported here have been the impetus for a CBCG study of dose-response randomizing 20 mg of fluoxymesterone (α9-fluoro-11β,17β-dihydroxy-17α-methy-4-androst-10-3-one) daily against 100, 200, and 400 mg per day, respectively, of calusterone. This dose-response evaluation should define optimum dosage of the calusterone in producing objective regressions of advanced female breast cancer.

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Nonproprietary and Trade Names of Drugs

Calusterone—*Methosarb.*
Testolactone—*Teslac.*
Fluoxymesterone—*Halotestin, Ultandren, Ora-Testryl.*

References

1. Gordan GS, Wessler S, Avioli LV: Calusterone in the therapy for advanced breast cancer. *JAMA* 219:483-490, 1972.

2. Campbell JA, Babcock JC: Synthesis of some 7α- and 7β-methyl steroid hormones. *J Am Chem Soc* 81:4069-4074, 1959.

3. Gordan GS, Halden A, Walter RM: Anti-tumor efficacy of 7β,17α-dimethyltestosterone (calusterone) in advanced female breast cancer. *Calif Med* 113:1, 1970.