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A DOSE-RESPONSE EVALUATION OF ANDROGENS IN THE TREATMENT OF METASTATIC BREAST CANCER

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A comparative double-blind clinical trial of two androgens, one at two dose levels the other at three dose levels, in the treatment of metastatic breast cancer, was conducted by 10 members of the Cooperative Breast Cancer Group. The two androgens studied were dromostanolone propionate at 100 mg and 200 mg three times weekly and 7α-methyl-19-nortestosterone acetate at 10 mg, 33 mg, and 100 mg weekly. The latter compound is a much more potent androgen and the hypothesis to be tested was whether or not a much more potent androgen could induce a greater incidence of regressions. The rates of regression observed in this study were as follows: dromostanolone propionate at 100 mg, 22%, at 200 mg, 16% (the p value for the difference is 0.325); 7α-methyl-19-nortestosterone acetate at 10 mg, 15%, at 33 mg, 22%, and at 100 mg, 28% (the difference between the lowest and highest dose-response rates being 0.05%). This study suggests that at least a log dose increase of a potent androgen is required to obtain an increased objective remission rate, whereas a one tenth of a log dose increase of a weaker androgen is not associated with an increased response rate. Abnormalities occurring during therapy with 7α-methyl-19-nortestosterone acetate, whether drug- and/or disease-related, decreased with increasing doses. The reason for this is not clear. No difference in total survival was observed between any of the treatment groups, but patients who had regressions had longer median survival than those who were classified as failures to therapy.

ANDROGENS HAVE BEEN TESTED AND STUDIED extensively in the management of patients with recurrent breast cancer. There has been some, but not excellent, correlation between the degree of androgenicity demonstrated by these agents as compared with the objective regression rate. In 1963, Campbell et al.[2] reported a new class of androgenic steroids, one of which was 7α-methyl-19-nortestosterone acetate (NSC-69948). In rats, Lyster and Duncan[4] found this compound to be 6.5 times as active as testosterone propionate in stimulating seminal vesical growth and 23 times as potent a myotropic agent. Pilot studies in humans revealed this compound to be a very potent androgenic compound, and it seemed reasonable to use this drug as therapy for advanced female breast cancer.

In the present randomized, double-blind study, 7α-methyl-19-nortestosterone acetate was compared with dromostanolone propionate (Drolban®), NSC-12198, an agent with previously demonstrated efficacy in breast cancer.[1] Three doses of 7α-methyl-19-nortestosterone

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Supported, in part, by individual National Cancer Institute (NCI) grants; all the authors function under the aegis of the Cooperative Breast Group, Grant Number CA-03364. Miss Waters is a participant in the NCI Contract, Number PH-43-NCI-65-573.

The following five investigatiors also contributed cases to this study: Fred J. Ansfield, MD, University of Wisconsin Medical Center, Madison, Wis.; Thomas L. Dao, MD, Roswell Park Memorial Institute, Buffalo, N.Y.; Anne C. Carter, MD, Downstate Medical Center, State University of New York, Brooklyn, N.Y.; Martin G. Goldner, MD, the Jewish Hospital of Brooklyn, Brooklyn N.Y.; Ralph C. Wilde, MD, University of Pittsburgh, Pittsburgh, Pa.

The authors wish to thank Mrs. Anne C. Ulbrich for her assistance in the editing and preparation of this paper.

Received for publication May 14, 1973.

acetate (10 mg, 33 mg, and 100 mg) were compared with two doses of dromostanolone propionate (100 mg and 2000 mg). Dromostanolone propionate was selected as the comparison agent, rather than testosterone propionate, because of its ready solubility in oil at these two concentrations. The drugs were administered intramuscularly three times weekly.

Previously, 7α-methyl-19-nortestosterone acetate was studied at a dose level of 10 mg three times per week, and a remission ratio of 6/25 (24%) was noted.[6] In another evaluation,[5] the drug was given at three dose levels, 31.6 mg, 50 mg, and 100 mg three times weekly; regressions were observed in 5 of 16 patients, 13 of whom were treated more than 2 weeks. There appeared to be correlation between incidence of regression and degree of masculinization.

Ten principal investigators contributed a total of 527 patients to the present study; 27 patients were ineligible according to protocol criteria. Therefore, data on 500 of the 527 patients are included in this analysis.

The criteria and procedures followed in the conduct of this study were according to Protocol I—"A Cooperative Study to Evaluate Experimental Steroids in the Therapy of Advanced Breast Carcinoma."[3,7] This protocol requires the following:

1. The patient will have proven and progressive metastatic breast cancer.
2. No prior hormonal therapy, with the exception of oophorectomy, will have been given.
3. Measurable lesions must be present; presence of osteoblastic lesions only is not considered measurable.

Classification of a patient having a regression depends on the following:

1. Fifty percent measurable lesions decrease in size with no increase in size of any other lesion and/or no new lesions developing.
2. Conversion of lytic bone lesions to osteoblastic lesions is a criterion of objective regression.
3. A decrease in amount of effusion of pleural or peritoneal cavities does not constitute a regression.
4. Development of increased osteoblastic metastases in a patient having osteoblastic metastases as well as other measurable lesions at onset of therapy is considered a failure to therapy.
5. All patients treated are reviewed by two outside investigators who make independent judgments as to response or failure to therapy.

RESULTS

Comparison of treatments: To investigate the extent to which patients receiving the five treatments were comparable as to age, number of years postmenopausal, duration of disease, and dominant site of lesion, studies were made by treatment according to these variables. No differences were noted between any of these groups.

Regression rates: A main consideration in evaluating a treatment is the observed regression rate. The highest regression rate was observed with 100 mg of 7α-methyl-19-nortestosterone acetate (28.2%), and the lowest rate (15.3%) was observed with 10 mg of the same agent; the dose of 33 mg produced a regression rate of 22.3%. The regression rate with dromostanolone propionate was 22.4% for patients receiving 100 mg and 16.2% for those receiving 200 mg (the p value for the difference is 0.325). The difference observed between these two dose levels may be explained in terms of random selection of patients.

The three dose levels of 7α-methyl-19-nortestosterone acetate when tested for linear *regression** show significance ($2 = 4.61$, df = 1, $p < 0.05$). The relationship between regression rate and the logarithm of the dosage level is statistically significant, and the dosage-response curve is essentially linear (Fig. 1).

Tables 1 and 2 present regression ratios by categories, based on dominant site of lesion and number of years postmenopausal. By definition, patients treated on Cooperative Breast Cancer Group protocols are classified according to the lesion with the most ominous prognosis, i.e., patients with local recurrence and osseous metastases are classified as predominantly osseous metastases and patients with osseous metastases and lung, or liver, or brain metastases are classified as predominantly visceral metastases. Thus, a patient with a single lung metastasis and numerous lytic bone metastases, who shows healing of most of the bone metastases and no change in the lung lesion, will have been classified as a regression.

* This is a statistical usage of the term *regression* to indicate a problem which considers the frequency distribution of one variable (in this case, regression rate) when another variable (in this case, dosage) is held fixed at each of several levels. The term does not indicate the regression of disease.

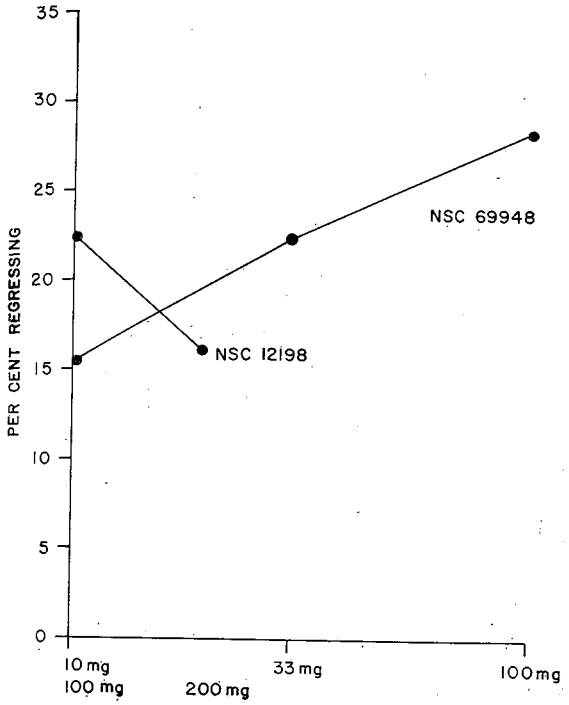

FIG. 1. Dose-response ratios on a semi-logarithmic plot. Percentage of patients regressing for two dose levels of NSC-12198 and three dose levels of NSC-69948. Percentage responding is indicated on the ordinate, and dose is on the abscissa. NSC-12198 is presented as 1/10 the dose and NSC-69948 is presented as the actual dose plotted on a logarithm scale. (Note: The factor 1/10 was arbitrarily selected.)

The highest observed regression rate for patients classified as local, and the highest observed regression rate for patients classified as visceral, were observed in the group of patients treated with 100 mg of 7α-methyl-19-nortestosterone acetate, 56.2% and 26.8%, respectively. The highest observed regression rate for patients classified as osseous (38.5%) was in the group of patients treated with 100 mg of dromostanolone propionate. For patients in the less than one year postmenopausal category, and for patients in the greater than 10 years postmenopausal category, the highest observed regression rates, 40% and 30.8%, respectively, were in the group of patients treated with 100 mg of 7α-methyl-19-nortestosterone acetate. The highest regression rate for patients in the 1 to 5 years postmenopausal category (29.2%) was observed in the group treated with 100 mg of dromostanolone propionate; and the highest for patients in the 6 to 10 years postmenopausal cateogry (29.2%) was observed in the group treated with 33 mg of 7α-methyl-19-nortestosterone acetate.

Duration of regression: Data for duration of regressions are crude estimates. The lowest median duration of regression (6.6 months) was observed in patients treated with 100 mg of dromostanolone propionate; the highest median duration of regression (12.2 months) was observed in patients treated with 10 mg of 7α-methyl-19-nortestosterone acetate. Thus, there is a discrepancy between the percentage of regressions observed and the duration of regressions.

Duration of therapy: The lowest median duration of therapy (13.4 weeks) was observed for 100 mg of 7α-methyl-19-nortestosterone

TABLE 1. Regression Ratio (and Proportion Regressing), by Treatment, Dominant Site of Lesion, and Number of Years Postmenopausal

Dominant site of lesion	No. years postmenopausal: Castrated <1 yr.		1–5 yrs.		6–10 yrs.		>10 yrs.		Total	
				NSC-12198 (100 mg)						
Local	0/1	(—)	3/4	(0.75)	0/4	(—)	0/2	(—)	3/11	(0.27)
Osseous	—	(—)	2/9	(0.22)	0/2	(—)	8/15	(0.53)	10/26	(0.38)
Visceral	1/4	(0.25)*	2/11	(0.18)*	1/10	(0.10)†	2/23	(0.09)*	6/48	(0.13)
TOTAL	1/5	(0.20)	7/24	(0.29)	1/16	(0.06)	10/40	(0.25)	19/85	(0.22)
				NSC-12198 (200 mg)						
Local	0/2	(—)	0/2	(—)	0/2	(—)	1/6	(0.17)	1/12	(0.08)
Osseous	1/3	(0.33)	2/4	(0.50)	2/7	(0.29)	4/14	(0.29)*	9/28	(0.32)
Visceral	0/4	(—)*	2/11	(0.18)‡	1/8	(0.13)*	0/17	(—)†	3/40	(0.08)
TOTAL	1/9	(0.11)	4/17	(0.24)	3/17	(0.18)	5/37	(0.14)	13/80	(0.16)

* One patient received less than 15 days of therapy.
† Two patients received less than 15 days of therapy.
‡ Three patients received less than 15 days of therapy.

TABLE 2. Regression Ratio (and Proportion Regressing), by Treatment, Dominant Site of Lesion, and Number of Years Postmenopausal

Dominant site of lesion	No. years postmenopausal: Castrated <1 yr.		1–5 yrs.		6–10 yrs.		>10 yrs.		Total	
				NSC–69948 (10 mg)						
Local	0/1	(—)	1/4	(0.25)	1/4	(0.25)	1/6	(0.17)	3/15	(0.20)
Osseous	0/4	(—)	1/10	(0.10)	2/5	(0.40)*	4/21	(0.19)	7/40	(0.18)
Visceral	0/2	(—)	0/16	(—)†	1/10	(0.10)	6/28	(0.21)*	7/56	(0.13)
TOTAL	0/7	(—)	2/30	(0.07)	4/19	(0.21)	11/55	(0.20)	17/111	(0.15)
				NSC–69948 (33 mg)						
Local	0/1	(—)	0/2	(—)	2/6	(0.33)*	2/10	(0.20)	4/19	(0.21)
Osseous	0/1	(—)	1/7	(0.14)	2/4	(0.50)	4/13	(0.31)	7/25	(0.28)
Visceral	0/6	(—)†	4/19	(0.21)	3/14	(0.21)	9/38	(0.24)‡	16/77	(0.21)
TOTAL	0/8	(—)	5/28	(0.18)	7/24	(0.29)	15/61	(0.25)	27/121	(0.22)
				NSC–69948 (100 mg)						
Local	1/3	(0.33)	2/4	(0.50)	—	(—)	6/9	(0.67)	9/16	(0.56)
Osseous	1/2	(0.50)	1/7	(0.14)*	2/7	(0.29)	1/15	(0.07)†	5/31	(0.16)
Visceral	2/5	(0.40)	0/9	(—)*	4/14	(0.29)†	9/28	(0.32)*	15/56	(0.27)
TOTAL	4/10	(0.40)	3/20	(0.15)	6/21	(0.29)	16/52	(0.31)	29/103	(0.28)

* One patient received less than 15 days of therapy.
† Two patients received less than 15 days of therapy.
‡ Four patients received less than 15 days of therapy.

acetate and the highest (16.7 weeks) for 100 mg of dromostanolone propionate.

Survival: Survival curves were constructed from life-table analyses (Fig. 2). Fifty per cent of patients given 100 mg of dromostanolone propionate survived 10 to 11 months and 50% of patients given 200 mg of the same drug survived 9 to 10 months. With 7α-methyl-19-nortestosterone acetate, 50% of patients given 10 mg survived 11 to 12 months, those given 33 mg survived 8 to 9 months, and those given 100 mg survived 8 to 9 months. As would be expected from previous survival studies of patients receiving androgen therapy, patients who experienced regressions had longer median survivals than the nonregressors for all drug dosage regimens.

The median duration of survival of responders and nonresponders for each drug dose category was as follows:

dromostanolone propionate
100 mg responders 18+ months failures 7 to 9 months
200 mg responders 18+ months failures 6 to 7 months

7α-methyl-19-nortestosterone acetate
10 mg responders 21+ months failures 8 to 9 months
33 mg responders 24–25 months failures 8 months
100 mg responders 22 months failures 5 to 6 months

Abnormalities present during therapy: The majority of abnormalities were due to virilism induced by therapy with these androgens. In general, it can be stated that the longer the patient was on therapy the more likely she was to develop signs of virilism. Abnormalities of severe or life-threatening degrees were defined as those requiring discontinuance of therapy or introduction of extreme therapeutic measures to control symptoms. However, not all abnormalities were drug-induced; some were disease-induced. In the analysis of the data, no distinction was made between the abnormalities related to the drug and those produced by disease.

It is of interest that in patients treated with dromostanolone propionate, the least potent androgen, there were only five abnormalities reported, involving three patients (3.5%) who received 100 mg (two patients had severe to life-threatening symptoms), but 37 abnormalities reported involving 22 patients (27.5%) who received 200 mg (12 patients had severe to life-threatening symptoms).

In patients treated with 7α-methyl-19-nortestosterone acetate, there was no dose-related increase in abnormalities as might have been predicted. Thirty-eight abnormalities were reported involving 29 patients (26.1%) who received 10 mg (14 patients had severe to life-threatening symptoms); 20 abnormalities

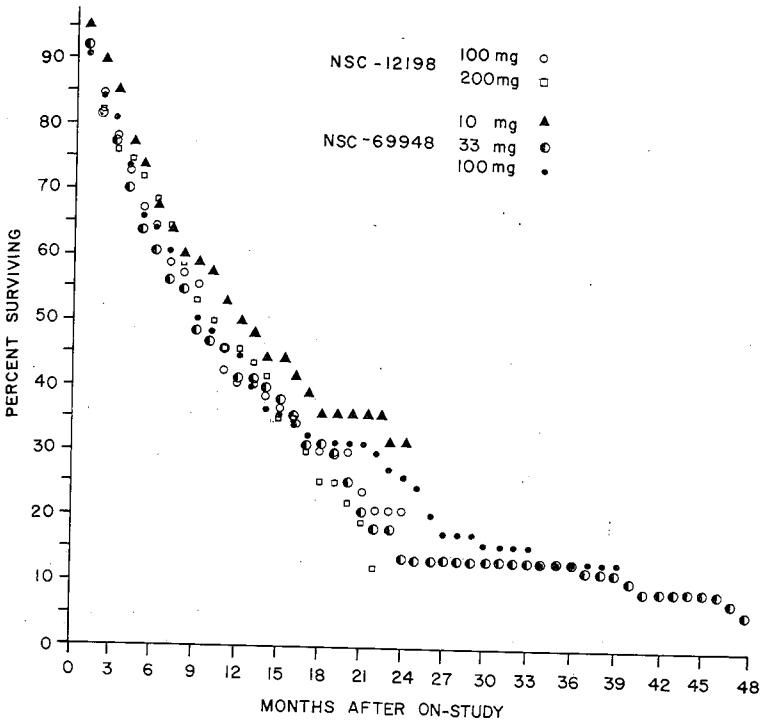

FIG. 2. Percentage of patients surviving for specified numbers of months after on-study (computed by the life-table method) —two dose levels of NSC-12198 (dromostanolone propionate) and three dose levels of NSC-69948 (7α-methyl-19-nortestosterone acetate).

were reported involving 16 patients (13.2%) who received 33 mg (9 patients had severe to life-threatening symptoms) and 10 abnormalities were reported involving 9 patients (8.7%) who received 100 mg (three patients had severe to life-threatening symptoms). The relationship between the abnormality rate and the dosage level of the 7α-methyl-19-nortestosterone acetate is highly significant ($\chi^2 = 11.02$, $p < 0.01$). However, it is difficult to explain this, as the abnormalities due to drug were not separated from the abnormalities due to disease. Also, since virilism in most androgen therapy is related to duration of therapy as well as dose, it is important to point out that patients receiving 100 mg of 7α-methyl-19-nortestosterone were on therapy a median of only 13.4 weeks as compared to a 13.9 week median for patients receiving 10 mg and a 15.7-week median for patients receiving 33 mg. Thus there is no adequate explanation for all the discrepancies.

Comparison of responders and nonresponders: There were 105 patients who had regressions and 395 patients who did not respond. It is of interest to investigate the type of patient most likely to respond to these two androgens. Age, number of years postmenopausal, and duration of disease at on-study were compared, and, using the t-test for two independent groups, the differences observed for these three variables were not statistically significant.

Also, comparisons were made for these three variables: age, number of years postmenopausal, and duration of disease at on-study, according to androgen and dosage regimen. No significant differences were noted.

Using the median test, the median duration of therapy for patients with remissions (42.2 weeks) was significantly greater ($\chi^2 = 100.6$, $p < 0.01$) than the median duration of therapy for patients who did not respond.

DISCUSSION

A comparative clinical trial was conducted by members of the cooperative Breast Cancer Group to investigate the relative clinical efficacy and dose-response of two androgens, one at two dose levels, and one at three dose levels. The primary criterion of clinical efficacy was considered to be presence or absence of objective tumor regression; evaluations made of each of the 500 patients were subjected to review by two independent investigators. The study was double-blind, and all patients were required to have demonstrated metastatic carcinoma of the breast, which was

progressive at the time the patient was entered on-study.

Two potent androgens were studied. One, dromostanolone propionate, was studied at dosage levels of 100 mg and 200 mg three times per week, and was found to have an average regression rate of 19%. No significant differential effect of dosage was detected at the dose levels included in this study.

The second androgen, 7α-methyl-19-nortestosterone acetate, was studied at three dosage levels: 10 mg, 33 mg, and 100 mg three times weekly; this drug produced regression rates that were progressively larger at successively higher doses. The relationship between regression rate and the logarithm of the dose level was statistically significant, and was essentially linear. The proportion regressing (28 %), which was obtained at the highest dose of 7α-methyl-19-nortestosterone acetate, was the largest proportion of regressions obtained among the five dosage-agent treatment combinations studied.

Androgens have been used empirically in the management of advanced breast cancer for three decades, and it has been difficult to define the exact mechanism of action. No controlled and evaluated dose-response has previously been reported, partly because of difficulties inherent in giving large doses of the previously available androgens. The solubility characteristics of 7α-methyl-19-nortestosterone permitted a full log increase of the lowest dose vs. the highest dose, and still permitted the study to be carried out in a double-blind technique. This study does confirm a preliminary study of O'Bryan and Talley[5] which suggested that an increased dose of 7α-methyl-19-nortestosterone acetate is associated with an increased response rate. Further dose-response studies with other androgens and estrogens have been undertaken by the Cooperative Breast Cancer Group and should yield important information as to optimal dosage schedules.

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