Effects of Endocrine Regulation of Growth of a Mouse Mammary Tumor on Its Sensitivity to Chemotherapy

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ABSTRACT

Mice bearing the androgen-responsive Shionogi mammary carcinoma SC115 were treated with different concentrations of testosterone to determine if regulation of growth by testosterone would affect the susceptibility of the tumor to eradication by drugs. Following s.c. injection of $2 \times 10^6$ cells, tumors grew to 3 g by $21 \pm 2.1$ days in males ($n = 7$) and $30 \pm 2.4$ days in females administered testosterone ($n = 10$). If androgen was withdrawn, tumors weighing 1 g regressed temporarily but resumed growing after a delay of 19 ± 1.7 days in males and 6 ± 3.2 days in females. A combination of cyclophosphamide (100 mg/kg) and Adriamycin (6.5 mg/kg), three i.p. injections 7 days apart, caused a tumor growth delay (TGD) of 5 ± 3.8 days in males and 26 ± 3.2 days in females. The combination of endocrine therapy and chemotherapy was superior to either treatment alone in males. Androgen withdrawal plus chemotherapy was additive; a submaximal dose of testosterone for tumor growth plus drugs was more effective, causing a TGD of 40 ± 2.7 days. There were no significant differences in TGD in females receiving treatments singly or in combination, possibly due to the fact that tumors in females were more sensitive to drugs alone and less sensitive to testosterone alone than were tumors in males. To ascertain if combination therapy would be effective in females in an adjuvant situation, the same treatment regimens were administered 1 day after injection of $10^6$ tumor cells. Under these conditions, hormonal manipulations combined with chemotherapy resulted in a longer TGD than either modality alone. Furthermore, submaximal doses of testosterone for growth plus chemotherapy induced a longer disease-free interval (no palpable tumors by 120 days in 12 of 12 mice) than did complete androgen withdrawal plus drugs (palpable tumors in 4 of 5 mice by 104 ± 2.7 days). The results demonstrate that endocrine regulation of SC115 mammary tumor growth can alter responsiveness of the tumor to chemotherapy.

INTRODUCTION

Breast cancers are commonly composed of both hormone- and drug-sensitive and hormone- and drug-resistant cells (14, 16). Due to this heterogeneity, endocrine therapy and chemotherapy used in the treatment of breast cancer are rarely curative (13). In fact, there is evidence to suggest that the types of hormone therapy used to cause tumor regression encourage autonomous growth (9, 24). Since the growth of subpopulations of cells within a tumor is influenced by the presence of other subpopulations (12, 14), it is plausible that a decrease in the cells affected by therapy can stimulate the growth of unresponsive cells. Similarly, the sensitivities to chemotherapeutic agents of subpopulations within a neoplasm are influenced by the presence of other subpopulations (21). Therefore, chemotherapeutic regimens which decrease or eliminate responsive cells may also quicken the emergence of drug-resistant cells.

Considering that hormones and drugs act independently on cells (3, 4), simultaneous or sequential administration of these agents should be superior to either modality alone. Combination therapy of mammary tumors does increase the disease-free interval in some patients (15, 18) and some animal model systems (8, 28, 29) and retards the growth of the human mammary tumor cell line, MCF-7 (1, 32). However, the effects of combination therapy may be enhanced by utilizing hormonal regulation of mammary tumor growth to increase the sensitivity of tumors to cytotoxic agents. The rationale for chemotherapy is based on tumor cell kinetics; drugs are most effective on cycling populations of cells (27). When a tumor regresses upon withdrawal of the stimulating hormone, presumably the dividing population of responsive neoplastic cells is being eliminated. It has been demonstrated that a submaximal dose of estrogen for growth of mammary carcinomas in rats reduces the extent of tumor regression achieved with complete estrogen withdrawal but stabilizes tumor weight and delays or prevents autonomous change (24). A slow-growing tumor may be more controllable with drugs if it remains in the susceptible growth phase either with (19) or without (30) the aid of hormone therapy. Hormonal manipulations directed toward regulating cell growth, rather than producing cell death, combined with chemotherapy should be more effective in increasing cure rates in mammary carcinomas.

This study was designed to determine if regulation of growth by androgens of the androgen-responsive Shionogi mouse mammary carcinoma SC115 would render the tumor more susceptible to eradication by drugs. The tumor originated spontaneously in a female mouse of the DD/S strain. After 19 passages in male mice, an androgen-responsive variant was isolated which continued to grow in females, but at a slower rate and after a longer lag period than in males (17, 22). This mouse mammary tumor is similar to some human breast cancers in its sensitivity to different classes of steroid hormones, including androgens (17), estrogens (25), and glucocorticoids (31). Our research shows that hormonal regulation of growth of this tumor can alter its sensitivity to chemotherapy.

MATERIALS AND METHODS

Animals and Tumors

Sufficient mice of the DD/S strain to start a colony were received as a gift from Dr. N. Bruchovsky of the Cancer Control Agency of British Columbia. The SC115 mammary carcinoma, maintained by serial trans-
planted in the DD/S mouse strain, was also received from Dr. Bruchovsky. The subline used in these experiments was the androgen-responsive tumor classified as Class 1 by Bruchovsky and Rennie (2). The tumor was maintained in male mice and transplanted to intact males, castrated males, and intact females for the experiments.

Tumor Transplantation

Tumors weighing approximately 2 g were dissected free of s.c. tissue and finely minced. The pieces were transferred to a flask containing 0.05% trypsin (1:250) and 0.025% EDTA (Sigma Chemical Co., St. Louis, MO) in Ca²⁺- and Mg²⁺-free Saline A, pH 7.3 (20). The flask was shaken at 37°C for two 15-min periods. At the end of each period, the supernatant was decanted and centrifuged at 80 × g for 4 min. The pellets were resuspended in Dulbecco's modified Eagle's medium (Terry Fox Laboratory, Vancouver, BC), combined, and then passed through 150 µm Nitex followed by 48 µm Nitex (Tetko, Inc., Elmford, NY) to collect single cells or small groups of cells. Viable cells, determined by trypan blue exclusion, were counted on a hemacytometer. Suspensions of 2 × 10⁶ cells in 0.2 ml of Dulbecco's modified Eagle's medium were injected s.c. into the interscapular region of intact male, castrated male, and intact female mice 2 to 4 months old. Male mice were castrated through an abdominal incision either 2 weeks prior to tumor cell injection or when tumors reached a weight of 1 g, depending on the experiment. Caliper measurements of tumors were taken 2 times/week. Tumor weights were calculated according to the formula

\[ \text{Weight (g)} = \frac{\text{Length (cm)} \times \text{[width (cm)]}^2}{2} \]

A minimum of 7 to 10 mice was used for each experimental group. The mice were distributed to the various treatment groups immediately following tumor cell injection.

Testosterone Injections

Testosterone (4-androsten-17-ol-3-one; Steraloids, Inc., Pawling, NY) was suspended in an aqueous solution containing 0.9% NaCl solution, 0.4% Polysorbate 80, 0.5% carboxymethylcellulose, and 0.9% benzyl alcohol (31). To induce tumor growth in castrated male and intact female mice comparable to growth of androgen-responsive tumors in intact males, 0.4 mg of testosterone in 0.2 ml of vehicle was injected s.c. in the dorsal region of the hind limbs 3 times/week beginning 2 weeks prior to tumor cell injection and continuing until the animal was terminated. Administration of reduced concentrations of testosterone to maintain tumor weight was initiated when tumors weighed 1 g. The dosages and scheduling of testosterone for determining the effects of early and late endocrine and/or drug therapy on the growth of SC115 tumors are outlined below.

Drug Injections

CY² (Procytome; Horner, Montreal, Que.) at 100 mg/kg and AD (Adria Laboratories of Canada, Ltd., Mississauga, Ont.) at 6.5 mg/kg were each injected i.p. in 0.2 ml of distilled H₂O singly or in combination, 3 times, 7 days apart. The scheduling of drugs for determining the effects of early and late endocrine and/or drug therapy on SC115 tumors is described below.

Statistics

Statistical analysis of the data was carried out with the Student t test.

²The abbreviations used are: CY, cyclophosphamide; AD, Adriamycin; TGD, tumor growth delay.
Hormone-Drug Interactions in Mammary Tumor Therapy

Group C: Female Mice Receiving No Testosterone to Stimulate Tumor Growth

Subgroup C1. Controls (Testosterone and Drug Vehicles).

Subgroup C2. Testosterone Vehicle, Chemotherapy.

Testosterone, 0.4, 0.2, or 0.1 mg, was administered 3 times/week for 2 weeks, the length of time for chemotherapy to be completed. The chemotherapy regimen was a combination of CY, 100 mg/kg, and AD, 6.5 mg/kg, 3 i.p. injections, 7 days apart.

There were 2 additional subgroups in Group A, castrated males receiving 0.4 mg of testosterone 3 times/week until death, with or without 3 injections of drugs. These groups are not included in this report as the tumors behaved the same as those in Subgroups A1 and A2.

Effects of Early Hormone and/or Drug Therapy on Growth of SC115 Tumors

In a second experiment, suspensions of $10^6$ tumor cells from androgen-responsive tumors were injected into 2 groups of mice: Group A, intact males; and Group B, intact females which had received 0.4 mg of testosterone 3 times/week for 2 weeks prior to tumor cell injection to prime the mice. Mice were subdivided into groups, and treatment was initiated 1 day following tumor cell injection as follows.

Group A: Male Mice

Subgroups A1 and A2.
Same as Subgroups A1 and A2 in Protocol 1.

Group B: Female Mice

Subgroups B1 to B10.
Same as Subgroups B1 to B10 in Protocol 1.

Testosterone, 0.4, 0.2, or 0.1 mg, was administered 3 times/week for 2 weeks. Chemotherapy included the combination of CY and AD, 3 i.p. injections on Days 1, 8, and 15 following tumor cell injection.

The end point used to assess the effectiveness of the hormone and drug treatments was the TGD, i.e., the time required for tumors in the treated groups to reach 3 g minus the time required for the tumors in the control groups to reach 3 g. A number of mice receiving CY and AD died prior to their tumors reaching a weight of 3 g. Death was assumed to be caused by drug toxicity; therefore, these animals were excluded from the data.

RESULTS

Tumor Response to Testosterone. Androgen-responsive tumors weighing approximately 2 g were transplanted as single-cell suspensions of $2 \times 10^6$ cells/mouse. Tumors were palpable 10 days after tumor cell injection into intact males and into castrated males and intact females receiving testosterone. There was 100% tumor incidence by 30 to 40 days. In castrated males and intact females not receiving testosterone, palpable tumors (androgen independent) were detected 30 days after tumor cell injection, and tumor incidence reached 85% by 60 days. Tumor weights increased rapidly in mice receiving testosterone, reaching 3 g by 20 to 25 days in intact males and by 30 to 35 days in castrated males and intact females. Growth rates of androgen-independent tumors were much slower; by 60 days, tumor weights were approximately 1 g.

The androgen-responsive and autonomous nature of these tumors was confirmed by subsequent transplantation experiments. Tumors from mice receiving androgens appeared sooner and grew more rapidly in intact males than in untreated castrated males and intact females. Tumors arising in androgen-deprived mice appeared at the same time and grew equally well in all hosts.

The weights of androgen-responsive tumors could be modulated by varying the concentration of circulating androgens. The weights of tumors in intact males were compared with those in males which were castrated when tumors reached 1 g and received either no exogenous testosterone or a submaximal dose of testosterone for tumor growth, 0.1 mg of testosterone, 3 times/week (Chart 2). Following castration, tumors regressed but resumed growing approximately 21 days later in androgen-deprived males. The administration of the submaximal dose of testosterone did not permit tumor regression but arrested tumor growth for 14 days. The weights of tumors grown in males, which had been castrated 2 weeks prior to tumor cell injection, and in intact females, all of which received testosterone injections for maximum growth of tumors, were compared to those in mice which had their dosages of testosterone discontinued or reduced when the tumors reached 1 g. Since the responses of tumors to testosterone for growth under these experimental conditions were the same in both castrated males and intact females, the results are combined in Chart 3. After androgen withdrawal, the tumors regressed but resumed growing in approximately 10 days. The submaximal dose of testosterone for tumor growth maintained tumor weights constant for 10 days.

Tumor Response to Drugs. CY and AD were the choice of drugs as they are effective in improving survival of patients with breast cancer (18) and in causing tumor growth delay in mammary carcinomas in rodents (6). Either drug alone had little effect on retarding growth of androgen-responsive tumors, but, administered simultaneously, the drugs postponed tumor growth by 10 days in intact males (Chart 4) and by 16 days in castrated males and intact females (Chart 5). The CY:AD combination was used in the experiments described below.
Effects of late hormone and/or drug therapy on s.c. growth of androgen-responsive SC115 tumors in male mice

Treatments were initiated when tumors weighed ~1 g. Mice were castrated and then received no exogenous testosterone or 0.4, 0.2, or 0.1 mg testosterone 3 times/week for 2 weeks (until chemotherapy was finished). Chemotherapy included the combination of CY, 100 mg/kg, and AD, 6.5 mg/kg, 3 injections, 7 days apart.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of mice</th>
<th>Treatment</th>
<th>Days from tumor cell injection to tumor wt ~3 g</th>
<th>TGD (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>7</td>
<td>None</td>
<td>21 ± 2.1*</td>
<td>4</td>
</tr>
<tr>
<td>A2</td>
<td>7</td>
<td>Chemotherapy</td>
<td>26 ± 3.8</td>
<td>5</td>
</tr>
<tr>
<td>A3</td>
<td>7</td>
<td>Castration</td>
<td>40 ± 1.7</td>
<td>19</td>
</tr>
<tr>
<td>A4</td>
<td>7</td>
<td>Castration, chemotherapy</td>
<td>50 ± 3.4</td>
<td>29</td>
</tr>
<tr>
<td>A5</td>
<td>7</td>
<td>Castration, 0.4 mg testosterone</td>
<td>21 ± 1.9</td>
<td>0</td>
</tr>
<tr>
<td>A6</td>
<td>7</td>
<td>Castration, 0.4 mg testosterone, chemotherapy</td>
<td>23 ± 1.2</td>
<td>2</td>
</tr>
<tr>
<td>A7</td>
<td>7</td>
<td>Castration, 0.2 mg testosterone</td>
<td>26 ± 0.4</td>
<td>5</td>
</tr>
<tr>
<td>A8</td>
<td>7</td>
<td>Castration, 0.2 mg testosterone, chemotherapy</td>
<td>32 ± 6.9</td>
<td>11</td>
</tr>
<tr>
<td>A9</td>
<td>7</td>
<td>Castration, 0.1 mg testosterone</td>
<td>36 ± 1.0</td>
<td>15</td>
</tr>
<tr>
<td>A10</td>
<td>7</td>
<td>Castration, 0.1 mg testosterone, chemotherapy</td>
<td>61 ± 2.7</td>
<td>40</td>
</tr>
</tbody>
</table>

*Mean ± S.E.

Effects of late hormone and/or drug therapy on s.c. growth of androgen-responsive SC115 tumors in female mice

Treatments were initiated when tumors weighed ~1 g. Mice received no exogenous testosterone or 0.4, 0.2, or 0.1 mg testosterone 3 times/week for 2 weeks (until chemotherapy was finished). Chemotherapy included the combination of CY, 100 mg/kg, and AD, 6.5 mg/kg, 3 injections, 7 days apart. Females were administered 0.4 mg testosterone 3 times/week beginning 2 weeks prior to tumor cell injection to stimulate tumor growth.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of mice</th>
<th>Treatment</th>
<th>Days from tumor cell injection to tumor wt ~3 g</th>
<th>TGD (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>10</td>
<td>None</td>
<td>30 ± 2.4*</td>
<td>4</td>
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<td>B2</td>
<td>10</td>
<td>Chemotherapy</td>
<td>56 ± 3.2</td>
<td>26</td>
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<tr>
<td>B3</td>
<td>10</td>
<td>–Testosterone</td>
<td>36 ± 3.2</td>
<td>6</td>
</tr>
<tr>
<td>B4</td>
<td>10</td>
<td>–Testosterone, chemotherapy</td>
<td>63 ± 3.1</td>
<td>33</td>
</tr>
<tr>
<td>B5</td>
<td>10</td>
<td>0.4 mg testosterone</td>
<td>28 ± 3.7</td>
<td>0</td>
</tr>
<tr>
<td>B6</td>
<td>10</td>
<td>0.4 mg testosterone, chemotherapy</td>
<td>54 ± 4.3</td>
<td>24</td>
</tr>
<tr>
<td>B7</td>
<td>10</td>
<td>0.2 mg testosterone</td>
<td>32 ± 0.8</td>
<td>2</td>
</tr>
<tr>
<td>B8</td>
<td>10</td>
<td>0.2 mg testosterone, chemotherapy</td>
<td>57 ± 2.2</td>
<td>27</td>
</tr>
<tr>
<td>B9</td>
<td>10</td>
<td>0.1 mg testosterone</td>
<td>41 ± 4.0</td>
<td>11</td>
</tr>
<tr>
<td>B10</td>
<td>10</td>
<td>0.1 mg testosterone, chemotherapy</td>
<td>58 ± 2.9</td>
<td>28</td>
</tr>
</tbody>
</table>

*Mean ± S.E.

Since the tumors behaved similarly in castrated males and intact females in their responses to hormones and drugs, the experiments involving combination endocrine therapy and chemotherapy were limited to intact males and females.

Effects of Late Hormone and/or Drug Therapy on Growth of SC115. The effects of hormonal regulation of tumor growth on the sensitivity of visible SC115 tumors to chemotherapy were investigated. The results of experiments on male mice are presented in Table 1. The time from tumor cell injection to a tumor weight of 3 g was approximately 20 days for the controls, which included intact male mice and male mice which were castrated when tumors reached 1 g and then received exogenous testosterone, 0.4 mg 3 times/week, until death. Castrated males receiving the same dosage of testosterone for only 2 weeks, the length of time required to complete chemotherapy in other experimental groups, had the same tumor growth rate as did the controls. Chemotherapy alone slightly retarded tumor growth. Mice treated by androgen withdrawal (castration) had a statistically longer TGD than both hormone therapy (p < 0.001) and chemotherapy alone (p < 0.005).

The submaximal dose of testosterone for tumor growth, 0.1 mg of testosterone administered 3 times/week for 2 weeks after the tumor weights approximated 1 g, maintained tumor weights for 2 weeks but was no more effective in causing TGD than was total androgen withdrawal. However, statistical analysis revealed that the reduced testosterone dose plus coincident administra-
females receiving chemotherapy and no testosterone and those receiving chemotherapy plus different concentrations of testosterone. Thus, the androgen-responsive tumors reacted differently to hormone and drug therapy in males and females. Furthermore, in female mice bearing androgen-responsive tumors, androgen regulation of tumor growth did not alter the sensitivity of tumors to chemotherapy.

Tumors that arose in female mice that had never received exogenous testosterone to stimulate tumor growth (androgen-independent tumors) reached a weight of 3 g by 72 days after tumor cell injection. Administration of the chemotherapeutic agents postponed growth of tumors weighing 1 g by 29 ± 2.0 days, causing the same TGD as in stimulated female mice with androgen-responsive tumors.

Effects of Early Hormone and/or Drug Therapy on Growth of SC115 in Female Mice. We investigated the possibility that hormone-drug combination therapy administered under conditions simulating an adjuvant situation would be superior to either treatment alone in female mice. Mice received 0.4 mg of testosterone 3 times/week for 2 weeks prior to tumor cell injection to prime the animals. Treatments were initiated 1 day after s.c. injection of 10⁶ cells from androgen-responsive tumors.

The data from this experiment are presented in Table 3. The controls included intact males, and intact females receiving 0.4 mg of testosterone 3 times/week until death. Tumors were palpable in control mice within 3 weeks. Administration of CY and AD on Days 1, 8, and 15 following tumor cell injection significantly postponed tumor growth by 6 weeks in males and by 9 weeks in females (p < 0.001). Complete androgen withdrawal following tumor cell injection had no effect on the time until palpable tumors appeared in female mice, while reducing the dosage of testosterone following tumor cell injection slightly increased the delay in appearance of palpable tumors. However, there was a statistically significant increase in disease-free interval following androgen withdrawal plus simultaneous administration of chemotherapy, compared to chemotherapy alone (p < 0.05). In addition, administration of submaximal doses of testosterone (0.2 and 0.1 mg) plus chemotherapy significantly inhibited growth of tumor cells compared to total androgen withdrawal plus chemotherapy (p < 0.001).

DISCUSSION

We have demonstrated that regulation of SC115 tumor growth by modulating androgen levels can modify treatment by chemotherapy. It is realized that the data represent results from a single drug regimen and that other drug combinations and schedulings may give different results. Nevertheless, in this study, hormone therapy involving removal of the stimulating hormone plus chemotherapy is superior to either modality alone in causing TGD. Combining cytotoxic agents with a reduced level of hormone, rather than with total hormone withdrawal, is even more effective in retarding tumor growth. In this case, presumably, the hormone level is sufficient to maintain a dividing population of cells which is susceptible to drugs without causing a rapid increase in tumor burden.

Hormonal manipulations do not augment the therapeutic efficacy of drugs in female mice bearing visible tumors as they do in males. A plausible explanation is that these tumors are more sensitive to chemotherapy alone and less sensitive to hormone therapy alone when grown in hormone-stimulated castrated males and intact females than in intact males. There has been much controversy as to whether hormone-responsive tumors are more or less sensitive to chemotherapeutic agents than hormone-independent tumors (5). In this study, cells from the same androgen-responsive tumors show different responses to chemotherapeutic agents when grown in males and females despite similar growth rates in response to androgens. On the other hand, cytotoxic drugs produce the same TGD in androgen-responsive and androgen-independent tumors when grown in females. A complex of interacting factors in the environment must influence the response of tumors to therapy as well as the tumor cells themselves.

Endocrine therapy plus chemotherapy administered simultaneously to female mice immediately following injection of cells from androgen-responsive SC115 carcinomas is better than either treatment alone in delaying the appearance of tumors. Furthermore, combining a submaximal dose of testosterone for growth and chemotherapy is even more effective in increasing the disease-free interval. The small tumor burden is probably a major variable responsible for the effectiveness of combination hormone and drug therapy in females under adjuvant conditions. These observations support those reported recently by Mulder et al. (23) which demonstrated that responses of large tumors to therapy are not predictive for the successful use of the same therapy in the adjuvant situation.

It is possible that so called "hormone-independent" tumors will respond to adjuvant therapy consisting of a submaximal dose of stimulating hormone combined with chemotherapy. Hormonal effects on cell replication in hormone-independent tumors have been demonstrated (7, 10, 28). An overt response of a tumor to hormones may not be necessary for effective combination ther-

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of mice</th>
<th>Treatment</th>
<th>No. of mice with tumors by 120 days/No. of surviving mice</th>
<th>Time until tumors palpable (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>10</td>
<td>Male, none</td>
<td>10/10</td>
<td>17 ± 3.3a</td>
</tr>
<tr>
<td>A2</td>
<td>10</td>
<td>Chemotherapy</td>
<td>8/8</td>
<td>65 ± 6.4</td>
</tr>
<tr>
<td>B1</td>
<td>10</td>
<td>Female, none</td>
<td>10/10</td>
<td>21 ± 1.3</td>
</tr>
<tr>
<td>B2</td>
<td>10</td>
<td>Chemotherapy</td>
<td>4/6</td>
<td>85 ± 7.7</td>
</tr>
<tr>
<td>B3</td>
<td>10</td>
<td>Testosterone</td>
<td>10/10</td>
<td>21 ± 2.0</td>
</tr>
<tr>
<td>B4</td>
<td>10</td>
<td>Testosterone, chemotherapy</td>
<td>4/5</td>
<td>104 ± 2.7</td>
</tr>
<tr>
<td>B5</td>
<td>10</td>
<td>0.4 mg testosterone</td>
<td>9/10</td>
<td>22 ± 4.2</td>
</tr>
<tr>
<td>B6</td>
<td>10</td>
<td>0.4 mg testosterone, chemotherapy</td>
<td>8/8</td>
<td>80 ± 5.1</td>
</tr>
<tr>
<td>B7</td>
<td>10</td>
<td>0.2 mg testosterone</td>
<td>10/10</td>
<td>30 ± 1.8</td>
</tr>
<tr>
<td>B8</td>
<td>10</td>
<td>0.2 mg testosterone, chemotherapy</td>
<td>0/6</td>
<td>NPb</td>
</tr>
<tr>
<td>B9</td>
<td>10</td>
<td>0.1 mg testosterone</td>
<td>10/10</td>
<td>29 ± 2.9</td>
</tr>
<tr>
<td>B10</td>
<td>10</td>
<td>0.1 mg testosterone, chemotherapy</td>
<td>0/6</td>
<td>NP</td>
</tr>
</tbody>
</table>

* Mean ± S.E.
* NP, nonpalpable.
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apy. Using a computerized model, Goldie et al. (11) proposed that even a small hormone response not recognized clinically should increase the probability of achieving a cure if hormones and drugs are administered at the same time.

Our results demonstrate that hormonal regulation of growth of a hormone-responsive mammary tumor can alter the sensitivity of the tumor to chemotherapy. It seems apparent that we can more effectively combine endocrine therapy and chemotherapy to be beneficial to the clinical management of breast cancer and other endocrine-sensitive neoplasms.

ACKNOWLEDGMENTS

We thank Dr. N. Brucnovsky for his helpful discussions and advice during the course of this work.

REFERENCES


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