Endocrine Status of Premenopausal Node-positive Breast Cancer Patients following Adjuvant Chemotherapy and Long-Term Tamoxifen

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ABSTRACT

The endocrine status of 49 premenopausal women taking tamoxifen after completion of adjuvant chemotherapy for breast cancer was determined by radioimmunoassay from serial blood samples. Of these 49 women, 7 had regular menses, 14 had irregular menses, 23 were amenorrheic, and 5 had undergone hysterectomies. A group of 12 premenopausal women who had no history of breast cancer and were not taking tamoxifen served as a control group. Evidence of ovarian function (estradiol levels >100 pg/ml) was seen in 7 of 7, 9 of 14, 2 of 23, and 1 of 5 women with a clinical history of regular menses, irregular menses, amenorrhea, and hysterectomy, respectively. Supraphysiological levels of estradiol (>350 pg/ml) were noted in 13 of 19 women with endocrine evidence of ovarian function. Supraphysiological progesterone levels (>20 ng/ml) were also seen in 5 of 7 of the regularly menstruating women taking tamoxifen. Supraphysiological levels of estradiol were associated with elevated follicle-stimulating hormone levels, but there was no mean change from baseline luteinizing hormone levels. Minimum and maximum serum follicle-stimulating hormone levels were 1.9 and 9.0 mIU/ml in the 12 normal women and 5.2 and 24.3 mIU/ml in the 13 women with supraphysiological estradiol levels. Our findings demonstrate that the majority of women who continue to menstruate while taking continuous tamoxifen following cytotoxic chemotherapy have supraphysiological estradiol levels. This is a potential mechanism for failure of tamoxifen therapy in these premenopausal women.

INTRODUCTION

The endocrine status of women with hormonally dependent breast cancer is of particular importance. Treatment strategies have been based on the use of antiestrogens or manipulations to perturb the hormonal milieu. Indeed some of the therapeutic efficacy of cytotoxic adjuvant chemotherapy in premenopausal women may be due to treatment-induced amenorrhea (1), although this has not been clearly demonstrated in all clinical trials (2). Not all premenopausal women develop treatment-induced amenorrhea. Women who are less than 40 yr of age (3) and those treated with 6 or less treatment cycles often complete adjuvant chemotherapy with intact ovarian function (4, 5). This is of particular significance in women who are then treated with continuous tamoxifen. In premenopausal women tamoxifen has been reported to induce supraphysiological 17β-estradiol levels (6–9). These supraphysiological 17β-estradiol levels may interfere with the therapeutic efficacy of tamoxifen, a drug which is a competitive inhibitor of 17β-estradiol binding to the estrogen receptor (10).

We have examined the endocrine status of women who were taking long-term tamoxifen following adjuvant chemotherapy for breast cancer that was resected when the patient was premenopausal. Our objectives were to measure the endocrine status of a sufficiently large group of such patients to examine the correlation between the clinical status and actual endocrine status, and to define and to describe the range of endocrine states present in these women.

RESULTS

Evidence of ovarian function (17β-estradiol levels of >100 pg/ml) was seen in 7 of 7 patients with regular menses, 9 of 14 with irregular menses, 2 of 23 who were amenorrheic, and 1 of 5 after hysterectomy. Fig. 1 shows the relationship between peak 17β-estradiol levels and age in the 4 groups of patients taking continuous tamoxifen as well as the 12 normal women. The figure shows that women taking tamoxifen who had ovarian function following adjuvant chemotherapy usually had supraphysiological levels of 17β-estradiol. The maximum 17β-estradiol level seen in the 12 control women was 326 pg/ml. This level was exceeded in 13 of 19 of the patients taking tamoxifen who had evidence of ovarian function.

Fig. 1 also shows the importance of age in the post-adjuvant chemotherapy endocrine status, with 83% (11 of 13) of the patients <40 yr of age showing evidence of ovarian function but only 22% (8 of 36) of the patients >40 showing evidence of ovarian function. The number of treatment cycles of adjuvant therapy was also an important determinant of eventual endo-

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The abbreviations used are: LH, luteinizing hormone; FSH, follicle-stimulating hormone; PROG, progesterone.
ever. Maximum and minimum LH levels were 25.3 (SD ± 10.2) and 4.0 (SD ± 1.8) mIU/ml in the 7 regularly menstruating patients. These data for the cycles are shown in Fig. 3.

In order to define in detail the endocrine status of the 7 menstruating patients, blood was drawn 3 times a wk over a menstrual cycle from these women as well as from the 12 normal women. The variation in 17β-estradiol levels throughout the menstrual cycle is shown in Fig. 4. As previously stated 6 of 7 of the patients developed 17β-estradiol levels greater than the maximum 17β-estradiol levels seen in the normal women (the range of values for these women during the cycle lies within the cross-hatched area). In most of the patients the monthly pattern of serum 17β-estradiol levels is an exaggeration of the normal pattern. Fig. 5 shows the total estrogen levels in the 7 menstruating patients and the 12 control women. Again it shows elevations in these levels in the menstruating patients with all of them (7 of 7) achieving levels above those seen in the control group at some time during the menstrual cycle. The monthly patterns in the majority of the patients are an exaggeration of the normal pattern. All of the patients studied ovulated and had elevated PROG levels (Fig. 6). Fig. 7 shows the FSH levels in the control and tamoxifen-treated groups. In 6 of 7 of the menstruating patients maximum levels of FSH were seen that were greater than the maximum level seen in the control women.

DISCUSSION

The aim of this study was to describe the endocrine status of women undergoing continuous tamoxifen treatment following adjuvant chemotherapy. This study was undertaken because many premenopausal patients have evidence of ovarian function following the completion of adjuvant chemotherapy (particularly those receiving <6 cycles), and tamoxifen has been shown to cause hyperestrogenemia in normal premenopausal women (8) and premenopausal women while receiving chemotherapy before onset of amenorrhea (5, 9). We have previously reported the hyperestrogenemia seen in 3 premenopausal breast cancer patients on continuous tamoxifen following adjuvant chemotherapy (5). In this study we expand this study group to 49 patients.

We found that the patients' reported clinical menstrual status correlated well, but not perfectly, with evidence of ovarian function. All patients who stated that they were menstruating regularly had ovarian function, and the majority of these women had both hyperestrogenemia and also high PROG levels. Of the 14 patients who reported irregular menses, some evidence of ovarian production of 17β-estradiol was seen in 9, and 6 had supraphysiological levels of estrogen. The lack of evidence of ovarian function in 5 of the patients may be because the ovaries were quiescent during the 10-wk observation period, or there was a transition to a postmenopausal state by the time of observation. In the 23 patients reporting no menstrual activity during the year before endocrine testing we found 17β-estradiol levels of >100 pg/ml in only 2. Neither of these 2 patients achieved normal PROG levels which may explain the amenorrhea in these two women.

The results show supraphysiological 17β-estradiol levels to be common (12 of 21) in patients reporting any recent menstrual activity while on tamoxifen following adjuvant chemotherapy. Thus these patients might be candidates for analysis of whether supraphysiological 17β-estradiol levels can interfere with tamoxifen's therapeutic efficacy in premenopausal women. These women might also be evaluated for risk of medical...
This table shows the endocrine status as determined by radioimmunoassay of the 12 normal women in the control group as compared to the 49 women who were taking tamoxifen following completion of cytotoxic chemotherapy. The tamoxifen-treated women were stratified both according to their clinical menstrual status as reported by the patient and by whether they had any evidence of ovarian function with the determinant being an estradiol at some point of greater than 100 g/ml.

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>17β-estradiol (pg/ml)</th>
<th>17β-estradiol &gt; 350 (pg/ml)</th>
<th>PROG (ng/ml)</th>
<th>Maximum FSH (mIU/ml)</th>
<th>Minimum FSH (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (control group)</td>
<td>12</td>
<td>225 ± 69*</td>
<td>0/12</td>
<td>12.7 ± 4.5</td>
<td>9.0 ± 1.9</td>
<td>2.1 ± 0.7</td>
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<tr>
<td>Clinical stratification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(by patient history)</td>
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<td></td>
</tr>
<tr>
<td>Regular menses</td>
<td>7</td>
<td>824 ± 319</td>
<td>6/7*</td>
<td>32.0 ± 13.5</td>
<td>30.7 ± 18.7</td>
<td>4.8 ± 3.0</td>
</tr>
<tr>
<td>Irregular menses</td>
<td>14</td>
<td>400 ± 428</td>
<td>6/14</td>
<td>9.3 ± 8.2</td>
<td>19.8 ± 11.9</td>
<td>8.2 ± 4.4</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>5</td>
<td>158 ± 290</td>
<td>1/5</td>
<td>8.1 ± 15.9</td>
<td>36.2 ± 17.7</td>
<td>27.6 ± 16.4</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>23</td>
<td>29 ± 58</td>
<td>0/23</td>
<td>0.2 ± 0.2</td>
<td>29.3 ± 12.0</td>
<td>22.6 ± 9.9</td>
</tr>
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<td>Endocrinological stratification</td>
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<tr>
<td>(an 17β-estradiol &gt; 100 pg/ml)</td>
<td></td>
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</tr>
<tr>
<td>Ovarian function</td>
<td>19</td>
<td>656 ± 80</td>
<td>13/19</td>
<td>20.7 ± 14.5</td>
<td>25.9 ± 14.5</td>
<td>7.3 ± 5.5</td>
</tr>
<tr>
<td>No ovarian function</td>
<td>30</td>
<td>13 ± 10</td>
<td>0/30</td>
<td>0.2 ± 0.1</td>
<td>28.3 ± 14.6</td>
<td>22.2 ± 11.9</td>
</tr>
</tbody>
</table>

* Mean ± SD.
* Different from control group values at P = 0.004.
* Different from control group values at P ≤ 0.02.

Fig. 3. LH levels in 7 menstruating patients (individual patients plotted as same symbol) compared to the 12 controls (all values within hatched area). One volunteer (31 yr) has an LH value of 19.9 mIU/ml on Day 7 that is not included in the graph.

Fig. 5. Total estrogen levels in 7 menstruating patients (individual patients plotted as same symbol) compared to the 12 controls (all values within hatched area). One volunteer (41 yr) has a total estrogen value of 941 pg/ml on Day 5 that is not included in the graph.

Fig. 6. PROG levels in 7 menstruating patients (individual patients plotted as same symbol) compared to the 12 controls (all values within hatched area).

problems that are associated with hyperestrogenemia, such as thrombotic events (11, 12) and cancer of the endometrium (13). Whether tamoxifen-induced supraphysiological levels of 17β-estradiol do in fact interfere with the efficacy of tamoxifen is not clear. Clinical trials of tamoxifen as a single agent in premenopausal patients show it to be efficacious (14), and the Nolvadex Adjuvant Treatment Organization's adjuvant tamoxifen trial reported a significant improvement in both relapse-free survival and survival in favor of tamoxifen-treated women over control women in both premenopausal and postmenopausal groups (15). The fact that oophorectomy (16) or radiation-induced ablation (17) often produces clinical responses in premenopausal women who eventually failed tamoxifen suggests that, in some premenopausal women, tamoxifen cannot suppress the effects supraphysiological levels of 17β-estradiol.

The exact event that causes hyperestrogenemia in tamoxifen-
treated women is unclear. Some authors have reported an increase in FSH and LH secretion (7), but in other studies this was not found (6, 8, 18, 19). To some degree these differences may be due to sampling frequency, with studies with samples once a month being unlikely to detect the peak LH and FSH values. Also the antisera used in the immunoassay may be important. Differences have been noted in the changes in FSH (20) and LH (21) levels as measured by bioassay and radio-immunoassay. Our results agree most closely with those of Sherman et al. (7) in that we found no effect on LH levels but an increase in FSH levels, although we found a more striking increase in FSH levels with both maximum and minimum cycle FSH levels increased >100% compared to normal women. The feedback control mechanisms for FSH and LH secretion are known to differ, but tamoxifen can clearly effect secretion of both the hormones, as in postmenopausal patients treated with tamoxifen (5). The drug probably acts as a partial agonist at the level of the pituitary, because there is a partial decrease in both LH and FSH levels.

The elevated levels of sex steroids apparently are caused by tamoxifen interfering with normal negative feedback mechanisms within the pituitary with resultant increases in FSH driving ovarian steroidogenesis, but additional mechanisms exist including a direct interaction of tamoxifen with granulosa cells enhancing the FSH-driven production of 17β-estradiol (22) and modifying LH receptor expression (23). Overall, antiestrogens should be most effective in a low-estrogen environment. The effectiveness of tamoxifen may, however, be compromised in some cases by the elevated levels of 17β-estradiol and PROG. We have found supraphysiological levels of 17β-estradiol to be common in women taking long-term tamoxifen who continue to menstruate following adjuvant chemotherapy. Investigations to look for the possible negative effects of the elevated sex steroid levels in these women seem warranted.

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