Effect of Tamoxifen on Plasma Insulin-like Growth Factor I in Patients with Breast Cancer


Departments of Pediatrics [R. B. C., K. C. C.] and Medicine [J. D. R., J. T. D.], University of Vermont College of Medicine, Burlington, Vermont 05405

ABSTRACT

Human breast cancer cells secrete and have membrane receptors for insulin-like growth factor I (IGF-I), a growth hormone-dependent peptide that stimulates cell replication. However, little is known about plasma concentrations of IGF-I in breast cancer patients. Plasma IGF-I levels are decreased in malnutrition, decline with advancing age, and are influenced by estrogen. We evaluated the effect of the antiestrogen agent tamoxifen on plasma IGF-I in 32 ambulatory breast cancer patients. Treatment with tamoxifen was associated with lower concentrations of plasma IGF-I (0.48 ± 0.3 unit/ml in treated versus 1.03 ± 0.6 units/ml in nontreated patients, P < 0.01). However, patients treated with tamoxifen did not differ from nontreated patients in age, menopause, duration since diagnosis, metastatic disease, recent weight loss, or measures of nutritional status. We conclude that tamoxifen therapy results in a reduction of plasma IGF-I concentration. We speculate that the antitumor action of tamoxifen in breast cancer is due in part to suppression of IGF-I.

INTRODUCTION

IGF-I in vitro has a variety of insulin-like effects, including stimulation of protein synthesis, incorporation of thymidine into DNA, and cell replication (1). The plasma concentration of IGF-I primarily reflects GH activity but is also sensitive to nutritional status (2, 3). It decreases in acute starvation and is low in chronic malnutrition. Nutritional repletion restores plasma IGF-I levels to normal, and plasma IGF-I is a reliable indicator of acute directional change in nitrogen balance. Plasma IGF-I is also affected by age, sex, and estrogen. Plasma IGF-I in adulthood declines gradually with aging (4) and is slightly higher in females (5). The effect of estrogen is variable, with plasma IGF-I decreased in some conditions but increased in others (6).

The biological effects of IGF-I, although similar to those of insulin, are mediated by distinct receptors. Some human breast cancer cells secrete and have membrane receptors for IGF-I, suggesting that mitogenesis, cell proliferation, and tumor growth may result from an autocrine effect of IGF-I (7). IGF-I receptors are more numerous in tumor tissues than in adjacent normal tissues, are present in metastases as well as primary breast cancer cells, and are related to estrogen receptor content (8). Studies of human lung tumors indicate that IGF-I may be an autocrine growth factor in carcinoma and small cell cancer as well (9, 10). In one study IGF-I content in lung tumor was higher than in normal lung tissue (11). Plasma concentrations of IGF-I in the same patients were lower than in age-matched controls, but the patients were not matched for body weight or nutritional status.

Tamoxifen, a tumorstatic antiestrogen agent, binds to estrogen receptors (12) and, when administered long-term in premenopausal breast cancer patients, increases serum levels of estrogen (13). We evaluated the effect of tamoxifen on plasma IGF-I levels in breast cancer patients.

MATERIALS AND METHODS

Between September 1985 and February 1986, 99 ambulatory patients with a diagnosis of cancer attending the medical oncology clinic at the University Health Center, Burlington, VT, were evaluated and have been reported previously (14). The current study consists of the 32 subjects with a diagnosis of breast cancer from that larger group of patients. All subjects with breast cancer attending the clinic during that time were offered enrollment and >90% accepted. At a single clinic visit height (cm), weight (kg), midarm circumference (cm), and TSF (mm) were measured. TSF was measured using a Lange caliper. Blood was obtained for measurement of IGF-I, albumin, transferrin, and thyroxine-binding prealbumin.

Charts were reviewed for diagnoses, duration of illness, physical abnormalities, usual weight, and recent weight loss. Diabetes mellitus; other endocrine, liver, renal, and cardiac disorders; and pregnancy were noted if present. Anorexia, vomiting, diarrhea, edema, ascites, malignant effusion, and severe dehydration were noted if present. Medications, including oral contraceptive agents and insulin, and the time since the last dose of tamoxifen or chemotherapy, if any, were recorded. Patients were categorized as treated with tamoxifen or chemotherapy if they had received treatment during the previous 30 days. The dose of tamoxifen was 20 mg daily. Menopause was defined as absence of menses by history. Patients were classified as having either metastatic disease or no evidence of disease.

Plasma IGF-I levels were measured by double antibody radioimmunoassay (6, 15). The assay has a sensitivity of 0.008 unit/ml with intra- and interassay coefficients of variation of 4 and 13%, respectively. One unit is equivalent to approximately 150 ng of the recombinant DNA-derived THR-59 analogue of IGF-I (AMGEN). Serum albumin, transferrin, and thyroxine-binding prealbumin were measured by quantitative radial immunodiffusion (16).

Standard weight for height by sex was defined as 50th percentile based on medium frame (17). Standard MAMA and TSF were defined as 50th percentile for age and sex (18). Body mass index equals weight (kg) divided by height (m) squared. Results are expressed as the mean ± SD. Statistical significance was defined as P < 0.05.

Univariate and regression models were performed to determine associations of IGF-I with age, measures of body mass, and serum proteins. The Pearson product-moment correlation coefficient was used as a measure of strength of the linear association between two indices. Patients treated with tamoxifen were compared to nontreated patients by Wilcoxon rank sum test for independent samples. Premenopausal and postmenopausal patients were also compared by Wilcoxon rank sum test. Proportions of patients treated with chemotherapy were compared by Fisher's exact test.

A stepwise regression was performed to evaluate the effect of tamoxifen on IGF-I. Partial correlation coefficients provided a measure of strength of independent association after removing the effect of another variable or variables in the regression model. The square of the correlation was interpreted as the proportion of the variance of IGF-I explained by the predictor index. This study was approved by the Committee on Human Research of the University of Vermont.

RESULTS

There were 32 females, mean age 54.0 ± 14 years (range, 27-77), with a mean duration since diagnosis of 31.7 ± 34 months.
(range, 1–155). Metastatic disease was present in 14 patients (44%). There were 14 patients treated with tamoxifen for a mean of 13.1 months (range, 1–43); only 2 were treated for less than 5 months. Eleven patients received combination chemotherapy with cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, vinblastine, and/or mitomycin C. Two patients treated with tamoxifen received combination chemotherapy (cyclophosphamide-methotrexate-5-fluorouracil or cyclophosphamide-doxorubicin-5-fluorouracil). Nine patients not treated with tamoxifen received chemotherapy (cyclophosphamide-methotrexate-5-fluorouracil, cyclophosphamide-doxorubicin, cyclophosphamide-doxorubicin-5-fluorouracil, doxorubicin-vinblastine, mitomycin C-vinblastine, or methotrexate-5-fluorouracil); one received aminogluthethimide.

Obesity was common; 47% of patients were >120% of standard weight, but only 3% were <80% of standard weight. The mean percentage of standard weight was 117; of standard MAMA 102; and of standard TSF 123. Mean IGF-I was 0.79 ± 0.6 unit/ml (range, 0.12–2.87). Log IGF-I correlated negatively with percentage of standard weight, MAMA, and body mass index but not TSF or serum albumin, transferrin, or thyroxine-binding prealbumin (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Correlation coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.05</td>
</tr>
<tr>
<td>% of standard:</td>
<td>0.78</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>MAMA</td>
<td>-0.42</td>
</tr>
<tr>
<td>TSF</td>
<td>-0.54</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.003</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>-0.04</td>
</tr>
<tr>
<td>Serum transferrin</td>
<td>0.85</td>
</tr>
<tr>
<td>Serum prealbumin</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Treatment with tamoxifen was associated with lower concentrations of plasma IGF-I (Table 2). However, patients treated with tamoxifen did not differ from nontreated patients in age, menopause, duration since diagnosis, metastatic disease, recent weight loss, or measures of body mass. Although not statistically significant, patients treated with tamoxifen were less likely to also be treated with chemotherapy (2 of 14 versus 9 of 18, P = 0.06). When chemotherapy-treated patients were excluded, tamoxifen treatment was still associated with lower concentrations of plasma IGF-I (0.50 versus 0.83 unit/ml, P < 0.01). Stepwise regression indicated that tamoxifen treatment had the strongest association with IGF-I (r = 0.48, P = 0.02). After removal of the linear dependence on tamoxifen treatment, the partial correlations of other variables with IGF-I were not significant. Tamoxifen treatment accounted for 23% of the variance.

Nine patients were premenopausal and 23 were postmenopausal. Postmenopausal patients differed from premenopausal patients in age as expected (59.0 ± 13 versus 41.2 ± 6 years, P < 0.01), but not in plasma levels of IGF-I, measures of obesity, or proportion of patients treated with tamoxifen (12 of 23 versus 2 of 9) or chemotherapy (6 of 23 versus 5 of 9). When the 23 postmenopausal patients were considered separately, the 12 treated with tamoxifen had lower plasma IGF-I levels than those not treated (0.50 ± 0.4 versus 1.18 ± 0.7 units/ml, P = 0.01). Excluding patients treated with tamoxifen, plasma IGF-I was 0.80 ± 0.4 in premenopausal patients (n = 7) and 1.18 ± 0.7 units/ml in postmenopausal patients (n = 11, P > 0.1).

DISCUSSION

We recently reported that obesity was far more common than malnutrition in 99 ambulatory patients with a diagnosis of cancer (14). These observations are confirmed in the present study of the subgroup of patients with breast cancer. They are consistent with studies suggesting that excessive intake of dietary fat or calories may predispose to the development of cancer (19).

In addition, as previously demonstrated in both cancer patients (14) and normal adult males, plasma IGF-I levels correlated negatively with percentage of standard weight and other measures of body mass. Whether low plasma IGF-I levels in obese subjects reflect suppression of GH secretion by obesity per se (20) or represent a primary defect in GH secretion or both is unknown.

Although estrogen treatment is known to influence plasma IGF-I (6), the effect of menopause on IGF-I has not been reported previously. In the current study plasma IGF-I was 48% higher in the postmenopausal than the premenopausal patients, but the difference was not statistically significant. Estradiol administered to patients with prostate cancer (21) and normal postmenopausal women (22) increases GH secretion but decreases plasma IGF-I. The mechanism of the estrogen-induced reduction of IGF-I is unknown (11), although a direct inhibitory effect of estrogen on IGF-I production seems likely in view of the simultaneous increase in GH secretion.

The nonsteroidal antiestrogen tamoxifen competitively inhibits estrogen action in breast tumor cells by blocking the binding of estradiol to the tumor estrogen receptor (12). Tamoxifen causes a blockade in the G1 phase of the breast cancer cell cycle in vitro, an effect reversible by estrogen. Yet tamoxifen has numerous estrogen-like effects (12, 23, 24). It increases sex hormone-binding globulin, lowers antithrombin III, prevents bone resorption, and has an estrogen effect on vaginal cytology. In premenopausal patients tamoxifen causes an early striking increase in production of ovarian estrogens and, when ovarian failure eventually occurs from chemotherapy, tamoxifen inhibits rises of luteinizing hormone and follicle-stimulating hormone to postmenopausal levels (13). In postmenopausal breast cancer patients receiving adjuvant combined chemotherapy, tamoxifen causes a reduction in luteinizing hormone and follicle-stimulating hormone similar to that seen with estrogen treatment. However, tamoxifen treatment of postmenopausal women also has been associated with a reduction in GH secretion, an effect opposite to that typically observed with estrogen treatment (25).

The current study demonstrates for the first time that the antiestrogen agent tamoxifen, when administered to breast cancer patients, is associated with lower plasma IGF-I. This

effect is independent of age, nutritional status, menopause, and chemotherapy. The mechanism by which tamoxifen results in a reduction of plasma IGF-I is unknown. This effect may be mediated in part by higher serum estrogen levels; however, since it also occurs in postmenopausal subjects it is likely that other mechanisms are involved. Although the role of plasma IGF-I in the growth and treatment of breast cancer is currently unknown, we speculate that the antitumor action of tamoxifen in breast cancer is due in part to suppression of IGF-I.

ACKNOWLEDGMENTS

We are grateful to the staff of the medical oncology clinic of the University Health Center; T. McAuliffe, Ph.D., Clinical Research Center (USPHS-GCRC-RR109), for assistance with statistical analysis by CLINFO; P. Kelleher, M. D., N. Roff, R. N., C. G. C, and M. DeSouza for technical assistance; and S. A. Victory for assistance in preparation of the manuscript.

REFERENCES

Effect of Tamoxifen on Plasma Insulin-like Growth Factor I in Patients with Breast Cancer


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/49/7/1882

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.