Changes in Thyroid Functional Tests in Breast Cancer Patients under Tamoxifen Therapy

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Abstract

Background: Tamoxifen, a synthetic anti-estrogen agent, is administered as an adjuvant treatment in breast cancer. Since various studies have indicated that Tamoxifen can change some hormones and bound globolines, controversial results have been achieved using this medicine on Thyroid Functional Tests (TFT). The present study was conducted to investigate the effects of Tamoxifen on TFT in women with breast cancer referred to oncology clinic in Imam Hossein hospital between 2001 and 2002.

Method: A quasi-experimental clinical trial study was performed on 23 women with breast cancer in a single blind basis (with no control group). Patients were under Tamoxifen 20 mg P.O. daily and their serum TSH, free T4 and three Iodothyronine (T3) were assessed before treatment with Tamoxifen and after 3 months. Paired T test was used for statistical analysis.

Results: There was a significant difference in T3 before and after the treatment with Tamoxifen (p=0.02), whereas no significant differences were seen in TSH (p=0.095) and FT4 (p=0.13).

Discussion: This study showed that treatment with Tamoxifen in women suffering from breast cancer results in an increase in serum T3 but has no effect on serum TSH and FT4, therefore women under treatment with Tamoxifen remain euthyroid.

Keywords: thyroid function tests, breast cancer, tamoxifen

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IJCP 2008; 1: 91-93

Introduction

Tamoxifen is a synthetic anti-oestrogen agent, which is widely prescribed as an adjuvant treatment in breast cancer patients (1) and for all breast cancer patients with positive receptor, Tamoxifen (20mg daily) should be prescribed (2). Due to extensive use of Tamoxifen in prevention and treatment of breast cancer, there is a remarkable tendency to investigate the metabolic effects of Tamoxifen, particularly those effects that do not have remarkable clinical manifestations. Thyroid disease is common in breast cancer women; therefore, investigating thyroid function in the women on Tamoxifen therapy is clinically important (3).

Since Tamoxifen is able to change some hormones and their bound globulins, controversial results have been achieved on Thyroid Functional Tests (TFT) using this medication (4,5). The aim of this research was to study the effects of Tamoxifen on TFT in an uncontrolled group of breast cancer patients.

Method

A quasi- experimental non- randomised uncontrolled clinical trial study was performed on 23 women with breast cancer in a single blind basis (with no control group). In this study, women with breast cancer, who referred to oncology clinic in Imam Hossein hospital between 2001 and 2002 and were on Tamoxifen as adjuvant therapy formed the study population. A non-probable convenience sampling method was used. Data was collected using a questionnaire and women with a history of thyroid disease, under treatment for thyroid disease, and recent use of corticosteroid or exogenous oestrogen were excluded. From the remaining patients, blood samples were collected at the start of Tamoxifen therapy and 3 months later to measure Thyroid Stimulating Hormone (TSH), free T4 and three-Iodothyronine (T3). TSH is a glycoprotein hormone, which was measured by Enzyme Immuno Assay (EIA) in patients' serum. Free T4 and T3 were directly measured in serum using Radio Immuno Assay (RIA). All these tests were performed with one laboratory kit. Serum level changes of each hormone were

compared at the start and 3 months after medication, using paired t-test.

Results

Overall 23 patients aged between 30-68 years old were studied, of whom 12 patients were post-menopausal women. In 78% of cases, chemotherapy was terminated before Tamoxifen therapy. 15 patients had undergone supraclavicular radiotherapy, of whom TFT was tested in 11 patients in less than 3 months after radiotherapy, between 3-6 months in 3 patients and only in more than 6 months after radiotherapy in one patient.

According to the findings from TSH, free T4 and T3 at the onset of Tamoxifen (month 0= baseline) and three months after Tamoxifen therapy, it was revealed that the mean serum levels of all three variables were in normal range while after 3 months of medication, the mean level of all 3 variables increased, which was statistically significant only in T3 (p=0.025) whereas no significant differences were seen in TSH (p=0.095) and FT4 (p=0.13) (Table-1). It is worth mentioning that after 3 months of Tamoxifen therapy, serum level of TSH was higher than normal in 4 patients which led to sub-clinical hypothyroidism while just in one case, T3 level was higher than normal. However, in none of them FT4 exceeded the normal range.

Discussion

Since a limited number of breast cancer patients who referred to clinic were included in this study, no significant difference was seen in TFT three months after Tamoxifen therapy, which was probably due to technical bias in testing. Minor increase in mean levels of TSH and FT4 three months after Tamoxifen therapy, although not statistically significant, may be due to the use of this medicine. This study showed a significant rise in T3 three months after Tamoxifen therapy, which could be more valid and reliable if there was a control group.

Sixty five percent of patients in this study (n= 15) had undergone supraclavicular radiotherapy; this procedure involves only less than 50% of one lobe of thyroid if done correctly. Therefore, it is expected that supraclavicular radiotherapy interferes with TFT interpretation, however, as the literature indicates, these changes appear long time after radiotherapy (6-9). In this study, only in one patient the second TFT was performed in more than 6 months after supraclavicular radiotherapy.

Seventy eight percent of patients in this study had been under chemotherapy before the onset of Tamoxifen therapy, however, since there is no evidence of a clear complication of common chemotherapy regimens on TFT, the type of regimen and time of chemotherapy were not considered in this study.

Generally, there are two main determinants for circulating thyroid hormones. In the first type, pathologic factors affect thyroid gland and change hormone synthesis. In the second type, however, factors affect Thyroxine Binding Globulin (TBG) and hence thyroid-hypophysis axis is normal. In higher concentrations of TBG, a primary increase in total concentration of thyroid hormones is considered but there is no remarkable increase in circulating free thyroid hormones. These changes which are due to TBG change are sometimes considered as thyroid dysfunction and are therefore unnecessarily treated. Since it is important to confirm a euthyroid state in a patient with abnormal TBG, TSH and free T4 are the best available tests.

As we understand, Tamoxifen, similar to oestrogen, binds to a protein with heavier glycoside than normal TBG and therefore reduces TBG clearance which leads to an increased serum TBG level. In elder women, it is important to differentiate between significant TFT changes from those caused by Tamoxifen therapy, because clinical manifestation of hypo or hyperthyroidism could be important especially in the elderly.

Contentious results have been obtained from Tamoxifen therapy on TFT. In 1995, Momby and his colleagues on a trial on 28 breast cancer patients, of whom 14 patients received placebo, measured TBG, TSH, T-uptake and free T4 before and after Tamoxifen administration that showed an increase in T-uptake and TBG three months after Tamoxifen; however, free T4 and TSH did not change and patients remained eumetabolic. (4) These results are in line with ours; supporting this theory that Tamoxifen increases TBG through producing a protein with heavier glycoside but the patient remains euthyroid. In 1999, Zidan et al (5) measured T3, TSH, and T4 in 45 breast cancer patients on Tamoxifen (in months 0, 3 and 6 after medical therapy onset). Results revealed that Tamoxifen

Table 1: Thyroid Function Tests changes before and three months after Tamoxifen therapy in breast cancer patients

Hormones	Before Tamoxifen	After Tamoxifen	P-value
TSH	1.24± 0.85	1.88 ± 2.26	0.095
Free T4	14.7± 0.73	15.39±0.96	0.134
T3	1.46± 0.67	1.62±0.13	0.025

therapy leads to higher TSH level after 3 months which return to normal at month 6, meaning that the patient becomes a case of sub-clinical hypothyroidisim transiently. Momby realised that Tamoxifen not only affects TBG but, due to interfering with thyroid gland secretion and changing hormone synthesis, results in biological access to thyroid hormones. These results contradict our theory. Therefore by accepting the theory of Tamoxifen effect on TBG and its ineffectiveness on TSH and free T4, we may conclude that despite Tamoxifen therapy, patients remain euthyroid and changes in TFT are merely due to changes in binding proteins. Based on these essentials, the physicians should be aware of Tamoxifen's increasing effect on TBG and the subsequent T3 and total T4 elevation, and focus on TSH and free T4 to make an accurate assessment of the thyroid function in suspicious patients.

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