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Thyroid functions consequences following adjuvant chemotherapy for breast cancer after mastectomy

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SUMMARY

The goal: It is to evaluate the effect of adjuvant chemotherapy on thyroid function in women with diagnosed breast cancer after radical mastectomy and prior to radiotherapy.

Patients and interventions: Forty Egyptian women with age ranging from 18 to 60 years who adminstered 5-flourouracil, epirubicin and cyclophosphamide as adjuvant therapy for breast cancer after mastectomy and prior to radiotherapy. Free T3, Free T4, TSH, anti-thyroglobulin antibody and thyroid peroxidase antibody were evaluated prior and after 6 cycles of treatment with chemotherapy.

Results: There were highly statistically significant difference in TSH p=0.005 being higher after chemotherapy, also in free T4 values P=0.025 being lower after chemotherapy. There was no statistically significant difference in free T3 P=0.051, Concerning both anti-thyroglobulin and anti-peroxidase there was no change in values before and after chemotherapy

Conclusion: Adjuvant chemotherapy in women with breast cancer led to a rise of TSH and lower fT4 levels which although still being in normal, it may grounds for longer follow up to detect overt hypothyroidism later in life.

Key words: mastectomy, breast cancer, adjuvant chemotherapy

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INTRODUCTION

Breast cancer is the most frequent malignancy and theleading cause of death from malignancies amongwomen [1,2]. It was reported that incidence of this cancerin developed countries is more than that in developing countries. Treatment modalities for thiscancer include surgery, radiation therapy, chemotherapy, and hormone therapy [3].

Chemotherapy can be applied asadjuvant or neoadjuvant treatment. Adjuvant che- motherapy is considered as a gold standard therapy for many patients with breast cancer at high risk early stage [4,5]. Thyroid hormones, which act in cell development,growth, differentiation, and metabolism, are adjusted by hypothalamic-pituitary axis. It seems thatin patients with cancer, thyroid function is found to bevulnerable to chemotherapeutic drugs, as hypothalamic-pituitary axis is active and this treatment modality is asystemic therapy for the patients [6].

Cytotoxic agents may render the thyroid gland sensitive to the effects of concomitant radiation therapy, increasing the risk of primary hypothyroidism due to radiation, Some agents such as mitotane, 5-fluorouracil, estrogens, tamoxifen, podophyllin, and L-asparaginase alter levels of thyroid hormone-binding proteins without clinical significance [7]. Several epidemiological studies show a positive association between plasma thyroid hormones (TH)-triiodothyronine (T3) and the prohormonethyroxine (T4)-levels and breast cancer risk, which supports the notion that THpromote tumor growth [8]. Definitely, in patients with hypothyroidism, breast cancer is diagnosed at an older age and in earlier stage, suggesting that hypothyroidism protects against breast cancer and is associated with more indolent disease [9].

GOAL OF THE STUDY

To evaluate the effect of adjuvant chemotherapy on thyroid functions in women with breast cancer after radical mastectomy and prior to radiotherapy.

MATERIAL AND INTERVENTIONS

Our prospective interventional study was performedin the period from March to September 2019 on forty Egyptian women 18-60 years old who administerted 5-flourouracil, epirubicin and cyclophosphamide for a dianosed breast cancer after radical mastectomy and prior to radiotherapy selected from oncology out-patient clinic at Ain Shams University Hospital.

Our study was approved by a Ain Shams University, Faculty of medicine Research Ethics Committee FWA 000017858 independent ethical committee.

Exclusion criteria

Patients with thyroid functions abnormalities prior to treatment, Patients received previous neck irradiation, Patients with sick euthyroid illness prior to treatment.

All patients were subjected to the following

Full history taking. Thorough clinical examination emphasizing on pulse, blood pressure weight, neck examination, Laboratory investigations including: Free T3, Free T4, TSH Prior to treatment and after the last cycle after 6 months, thyroid peroxidase antibody and antithyroglobulin antibody before and after treatment.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution foundparametric.The comparison between two paired groups with quantitative data and parametric distribution were done by using Paired t-test.

RESULTS

It was found a high significant increase in TSH p=0.005, significant decrease in free T4 values p=0.025 with no statistically significant difference in free T3 value p=0.051 as shown in Tables 1-3. Regarding both antithyroglobulin and antiperoxidase antibodies there was no statistically significant difference in values before and after chemotherapy.

According to our study we found that there was high significant difference between TSH values before and after chemotherapy (p=0.005) being higher after the adjuvant therapy with statistically significant decrease in unbound T4 values ($p \leq 0.05$) and decrease in free T3 value which was of no statistical significance (p=0.051).

This was constant with Desai et al. who found that cyclophosphamide caused hypothyroidism in thirty six percent of patients. Twenty percent of patients had clinically significant thyroid impairment as documented by elevated serum TSH concentration. Their data suggest that the incidence of hypothyroidism increases with the duration of cyclophosphamide therapy. This may explain the higher incidence of hypothyroidism in their study compared with the 4% to 7% occurrence cited in earlier reports in which this agent was used for shorter periods [12].

Also Mannavola et al. in their study on cyclophosphamide showed similar results as ours with decreased free T3 and T4 and increased TSH. Hypothyroidism was documented in 46% of patients and a transient elevation of TSH levels in another 25% of cases. Thus, the overall prevalence of elevated TSH levels after cyclophosphamide was 71%, in accordance with recent reports [13].

Several potential mechanisms of cyclophosphamide induced thyroid dysfunction have been proposed. Desai et al. suggested destructive thyroiditis because of the high incidence of transient thyrotoxicosis prior to developing hypothyroidism [12].

The increase of TSH value observed in our study (2.42 mU/L before chemotherapy vs. 2.87 mU/L after chemotherapy) could also be explained in the context of recovery of ''Non Thyroidal Illness'' (NTI), an adaptive response to (chemotherapy- induced) cellular damage. In critically ill patients, the hypothalamus-pituitary-thyroid axis down-regulates as an adaptation to adverse physical conditions [14].

Tab.1. Comparison between TSH values for studied group before and after chemotherapy

TSH (mU/L)	Before No= 40	After No. =40	Test value	P value
Mean±SD	2.42±1.00	2.87±0.88	-2.992	0.005
Range	0.7-4.2	1.2 – 4.2		

Tab.2. Comparison between fT3 values for studied group before and after chemotherapy

Free T3 (pg/ml)	Before No = 40	After No =40	Test value	p value
Mean ± SD	2.68 ± 1.01	2.58 ± 0.93	2.01	0.051
Range	1-4.4	1-4.3		

Tab.3. Comparison between fT4 values for studied group before and after chemotherapy

Free T4 (ng/dl)	Before No= 40	After No=40	Test value	P value
Mean±SD	1.32 ± 0.50	1.23 ± 0.46	2.326	0.025
Range	0.2-2.5	0.2-2.5		

DISCUSSION

Endocrine disorders are among the most commonly reported long-term complications of cancer treatment [10].
Thyroid disorders include a broad variety of pathophysiological mechanisms; it may be subtle in presentation, sometimes hardly identified, and even more difficult to relate to a specific chemotherapeutic regimen due to the little specific wide clinical trials [11].

According to our study, there was decline of fT4 (p=0.025) and this was constant with Khalili, et al. who found that the large reduction of circulating fT4 is associated with less side effects of treatment, but can lead to clinical symptoms of hypothyroidism and rarely life threatening complications [15].
The effect of thyroid hormones on chemotherapeutic efficacy rarely researched before, and whether adding thyroid hormones during chemotherapy is suitable for breast cancer patients is still

unknown. Some researchers found hypothyroidism may be the protective element for cancers, as hypothyroidism can inhibit tumor growth [5].

SUMMARY AND CONCLUSION

So, from our study we can conclude that cytotoxic drugs that are still widely used as adjuvant chemotherapy in multiple types of cancer patientscan cause alterations in thyroid function by different mechanisms. In our study these alterations didn't reach the value of overt hypothyroidism, so, longer duration of follow up is needed to detect these changes early to avoid adverse outcomes. Also, follow up of thyroid functions before and after chemotherapy is recommended.

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