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Original

Thyroid Dysfunction Following Conventional Anthracycline- and Taxane-based Chemotherapy for Breast Cancer

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Summary

Although thyroid disorders induced by immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) have attracted much attention, little research has been done on thyroid dysfunction in conventional cancer treatment containing anthracyclines and taxanes. We retrospectively studied thyroid function in 61 patients who underwent conventional chemotherapy for breast cancer. Of the 61 patients, 17 (28%) developed thyroid dysfunction, including sub-clinical and overt hypothyroidism following chemotherapy, and 9 (15%) developed overt clinical hypothyroidism. Eight of the nine patients needed thyroid hormone replacement therapy with levothyroxine (L-T4). Taxane-based regimens tended to reduce free T4 levels and increase TSH levels more markedly compared to non-taxane-based regimens. Since the present study showed, for the first time, that conventional chemotherapy, as well as ICIs and TKIs, may induce hypothyroidism, it may be appropriate to evaluate thyroid function during chemotherapy. When patients show the clinical features of hypothyroidism, thyroid hormone replacement therapy merits consideration.

Key Words: chemotherapy, hypothyroidism, breast cancer

Introduction

Chemotherapy regimens containing anthracyclines and taxanes have been the backbone of breast cancer therapy over the past two decades due to their success in improving the disease-free survival rate[1)]. Standard adjuvant or neo-adjuvant regimens include doxorubicin (Adriamycin: A) + cyclophosphamide (AC), epirubicin + cyclophosphamide (EC), as well as fluorouracil (5-FU: F), epirubicin, and cyclophosphamide (FEC). For node-positive, epidermal growth factor receptor-2 (HER2) negative breast cancer, anthracycline-based regimens with sequential docetaxel or paclitaxel treatment achieved longer disease-free survival rates[1,2)]. For HER2-positive breast cancer, anthracycline-based regimens, with sequential docetaxel and anti-HER2 agent trastuzumab for 1 year, were associated with an improving overall survival rate[3)].

Anti-cancer therapy is associated with several ad-

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verse effects, including nausea, bone marrow suppression[4], alopecia, and cardiotoxicity[5]. For the endocrine system, it has been reported that breast cancer chemotherapy may increase the risk of ovarian disfunction[6]: it induces a post-menopausal state, sometimes resulting in osteoporosis[7] as a late-phase side effect. However, whether conventional anthracycline and taxane-based breast cancer chemotherapy regimens affect thyroid function remains unclear.

Recently, it has been reported that the inhibition of programmed cell death ligand (PD-L1) antibody may reduce tumor growth, especially in breast cancers that lack estrogen and progesterone receptors and do not overexpress the HER2 protein. Some clinical studies have shown that selectively targeting PD-L1 antibody with atezolizumab plus nab-paclitaxel improves progression-free survival in metastatic breast cancer patients with PD-L1-positive triple-negative (lack of estrogen and progesterone receptors and HER2 expression) cancer[8]. In addition, more recent clinical data for pembrolizumab, one of the immune-checkpoint inhibitors (ICIs) targeting PD-L1 antibodies, show improvement of progression-free survival in triple-negative metastatic breast cancer patients[9]. The two agents (atezolizumab and pembrolizumab) share some adverse effects, such as endocrine disturbances, including thyroid dysfunction[10]. Therefore, in the case of cancer chemotherapy by these immune-checkpoint inhibitors, monitoring of endocrine system disorders, including thyroid function, is necessary.

Although thyroid disorders induced by immune checkpoint inhibitors and tyrosine kinase inhibitors (TKIs) have attracted much attention, little research has been done on thyroid dysfunction with conventional cancer treatment containing anthracyclines and taxanes. Since we sometimes had cases of thyroid dysfunction following conventional breast cancer treatment in our clinical practice, we investigated thyroid function in breast cancer patients who underwent preoperative or adjuvant conventional cancer chemotherapy.

Patients and Methods

This was a retrospective, multi-institutional, clinical observational study of 61 breast cancer patients who received preoperative or postoperative chemotherapy from 2010 to 2017. The patient background, clinical stage, hormone receptor status, HER2 expression status, and molecular subtype are shown in Table 1. The patients were treated with the sequential regimen of anthracyclines and taxanes.

Table 1 Patient characteristics

Characteristics	N = 61	%
Mean gae	57 (29-79)	
stage		
I	4	7
II	44	72
III	7	11
IV	6	10
Estrogen recptor		
Positive	46	75
Negative	15	25
Progesterone receptor		
Positive	36	59
Negative	25	40
HER-2 status		
Positive	7	11
Negative	54	89
Molecular subtype		
LuminalA	36	59
LuminalB	10	16
Her2	7	11
Basal	8	13

The clinical-stage data were as follows: 6 patients, stage IV; 7 patients, stage III; 44 patients, stage II; and 4 patients, stage I. As shown in Table 2, 27 patients were treated with only anthracycline-containing regimens, and taxane-containing regimens followed in the other 34 patients, among whom 8 were additionally treated with trastuzumab. Anthracycline regimens included AC (doxorubicin and cyclophosphamide), EC (epirubicin and cyclophosphamide), and FEC (epirubicin, cyclophosphamide, and 5FU). Taxane regimens included docetaxel (administered once every three weeks) and paclitaxel (administered once every week). All chemotherapy regimens were administered per their recommended doses. Thyroid function tests were performed before chemotherapy and following chemotherapy at 4-6 weeks, 8-12 weeks, 15-18 weeks, and 22-24 weeks, respectively. Ten patients of 61 patients underwent primary systemic therapy (PST), namely preoperative chemotherapy. In these patients, operations were done at 3 weeks after the end of chemotherapy, and thyroid function tests were also performed at 4-6

Table 2 Clinical stage and chemotherapy regimens

stage	Chemotherapy	Regimens	case	PST	total
I	Anthracycline based	AC	2		
		FEC	2		4
II	Anthracycline based	AC	14		
		FEC	9		
	Anthracycline + taxanes based	AC + D	4		
		FEC + P	4		
		AC + P	3		
		FEC + D	8	3	
	Anthracycline + taxanes + Trastuzumab	FEC + D + T	2	2	44
III	Anthracycline + taxanes based	FEC + D	3		
	Anthracycline + taxanes + Trastuzumab	FEC + D + T	4	3	7
IV	Anthracycline + taxanes based	FEC + D	4		
	Anthracycline + taxanes + Trastuzumab	FEC + D + T	2	2	6

AC: doxorubicin + cyclophosphamide; FEC: 5-FU + epirubicin + cyclophosphamide; D: docetaxel; P: paclitaxel; T: trastuzumab; PST: primary systemic therapy.

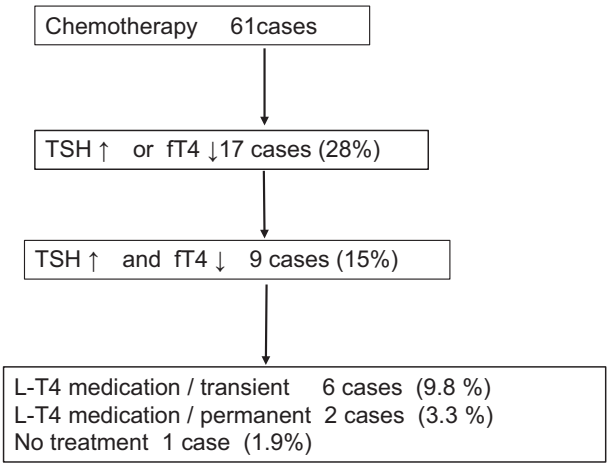

Figure 1 Frequency of subclinical hypothyroidism and clinical hypothyroidism for 61 patients who underwent chemotherapy for breast cancer.

weeks, 8-12 weeks, 15-18 weeks, and 22-24 weeks after chemotherapy. The following normal ranges were used: thyroid-stimulating hormone (TSH), 0.38-4.31 μU/mL; free thyroxin (fT4), 0.82-1.63 ng/dL; and free triiodothyronine (fT3), 2.10-3.80 pg/mL. Hypothyroidism was defined as having a TSH level above the upper limit of normal and an fT4/fT3 level below the lower limit of normal, with or without any clinical symptoms. If the TSH level was above the upper limit of normal but the fT4 level was within the normal range, we made a diagnosis of latent hypothyroidism. Patients whose levels of anti-thyroid peroxidase (TPO) antibody or anti-thyroglobulin antibody were above the normal range were excluded from the study.

This clinical study was approved by the institutional review board of Dokkyo Medical University, Saitama Medical Center No. 21056, and approved by Tokyo University Hospital for offering clinical data to our institute as cooperative research study.

Statistics

The thyroid function test parameters were compared using Student's *t*-tests or Wicoxon singed-rank test. All data were analyzed using StatView software (Version 5.0, SAS Institute, Cary, NC, USA) and statistical significance was set at $P < 0.05$.

Results

Underactive thyroid with high TSH levels or low fT4 levels was found in 17 patients after chemotherapy. Among these patients, 9 (14.8%) were diagnosed with true hypothyroidism (with high levels of TSH and low levels of fT4) and the others were diagnosed with latent hypothyroidism (Fig. 1). Fig. 2 shows the TSH levels of 17 patients who had subclinical hypothyroidism following chemotherapy. After chemotherapy, the mean TSH level was found to have elevated to above the upper limit of normal. Fig. 3 shows the fT4 levels of 17 patients who had subclinical hypothyroidism following chemotherapy. The mean fT4 level of the 17 patients was found to have decreased to below the lower limit of normal. Of the 17 patients, 9 were found to have clinical hypothyroidism as shown in Fig. 1. The clinical details of these 9 patients with hypothyroidism

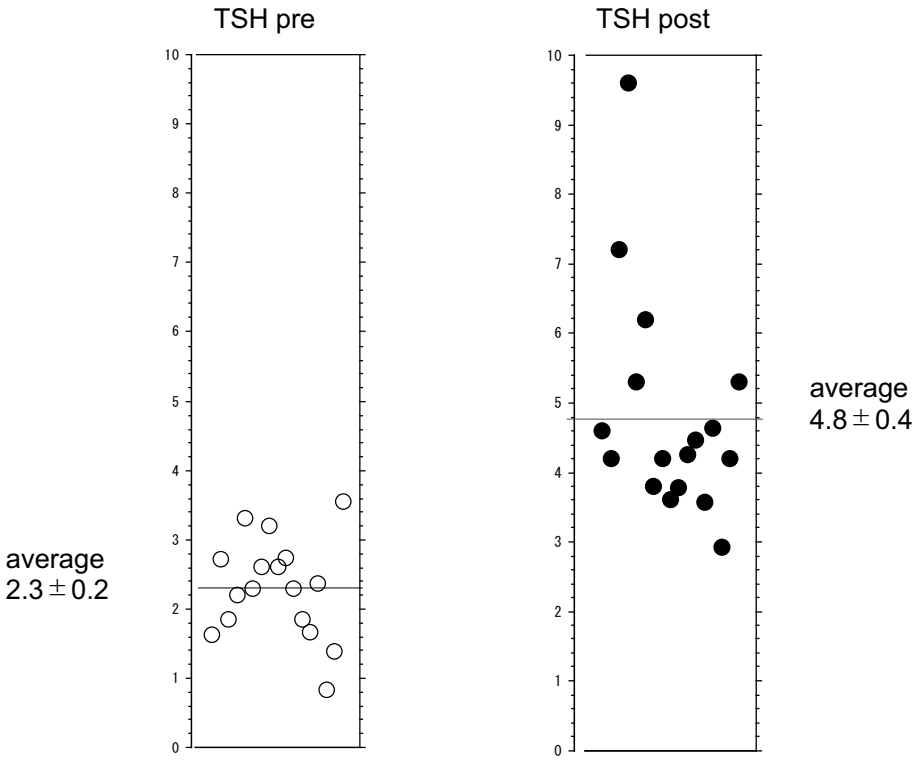

Figure 2 TSH levels before chemotherapy (○) and 2–4 weeks after chemotherapy (●) in the 17 cases that showed thyroid dysfunction after chemotherapy. Following chemotherapy, the mean TSH levels of the 17 cases was found to be elevated to above the upper limit of normal (mean 4.8 ± 0.4 μU/mL; $p < 0.01$ vs pre TSH).

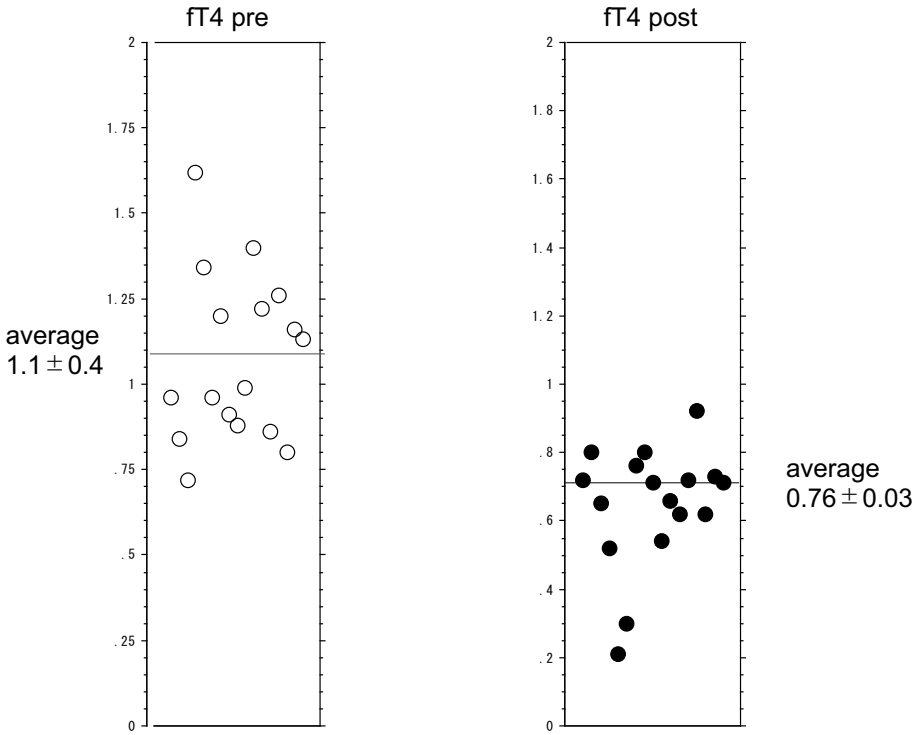

Figure 3 Free T4 levels before chemotherapy (○) and 2–4 weeks after chemotherapy (●) in the 17 cases that showed thyroid dysfunction after chemotherapy. The free T4 levels in all the 17 cases except one decreased to below the lower limit of normal (mean 0.76 ± 0.03 ng/dL; $p < 0.01$ vs pre fT4).

Table 3 Nine Patients with clinical hypothyroidism following cancer chemotherapy

case	age	regimen	fT4 (ng/dL) pre	fT4 post	TSH (μU/mL) pre	TSH post	levothyroxine (μg/day)	onset/ week	time to recover/M	medication
1	59	AC → Taxane	0.84	0.26	3.3	49	50	5		continue
2	51	FEC → Taxane	0.91	0.3	3.19	19.9	50	5		continue
3	46	AC	0.99	0.82	2.73	4.21	25	8	12	off
4	66	FEC	0.96	0.72	1.62	4.86	50	2	4	off
5	43	FEC → Taxane	0.96	0.8	2.72	5.12	25	2	4	off
6	48	FEC → Taxane	0.88	0.65	1.84	9.64	50	3	6	off
7	65	FEC → Taxane	1.62	0.52	2.2	14.4	50	3	6	off
8	53	FEC → Taxane	0.98	0.72	2.31	4.46	-	4	6	-
9	67	FEC	1.16	0.73	1.38	5.32	25	4	8	off
mean	55		1.03	0.61*	2.37	13*		4	6.6	

*$p < 0.01$ vs pre

AC: doxorubicin + cyclophosphamide; FEC: 5-FU + epirubicin + cyclophosphamide.

Table 4 17 cases of hypothyroidism following chemotherapy for breast cancer

	cases	thyroid function			
		fT4 (ng/dL) pre	fT4 post	TSH (μU/mL) pre	TSH post
A range	9	1.21 ± 0.14 (0.86-2.24)	0.79 ± 0.03 (0.62-0.93)	2.35 ± 0.25 (1.38-3.55)	4.79 ± 0.56 (3.60-8.90)
A + T range	8	1.02 ± 0.10 (0.80-1.62)	0.59 ± 0.08 (0.26-0.82)	2.33 ± 0.28 (0.84-3.30)	14.96 ± 6.14 (3.00-49.00)
p (*t*-test)		0.37	0.06	0.64	0.13

A: anthracycline based; A + T: anthracycline followed by taxane.

are shown in Table 3. Of the 9 patients, 3 were treated with an anthracycline-based regimen, and 6 were treated with sequential regimens of anthracyclines and taxanes. The interval between the last chemotherapy administration and the diagnosis of hypothyroidism was 8-24 weeks and the average was 12 weeks. Six patients had clinical symptoms, such as edema, weight gain, cryesthesia, and general fatigue. Of the 9 patients with hypothyroidism, 8 received 6 months of levothyroxine (25-50 μg/day) for thyroid hormone replacement, and it was stopped thereafter. Thyroid function was re-evaluated one month later. Of the 8 patients, 4 still had hypothyroidism, and levothyroxine was resumed for them. The thyroid function of two of the four patients recovered afterward and they stopped the medication, but the other two patients still needed a maintenance dose. Clinical symptoms improved in all patients who received thyroid hormone replacement therapy (levothyroxine).

We also evaluated the differences in the hypothyroidism according to various chemotherapy regimens. The 17 patients diagnosed with hypothyroidism included 9 patients treated with anthracycline-based regimens and 8 patients treated with sequential regimens of anthracyclines and taxanes. The fT4 and TSH levels were compared between these two groups after the completion of chemotherapy. The results are shown in Table 4. Patients treated with sequential regimens tended to have lower fT4 and higher TSH levels than those treated with anthracycline-based regimens, although the difference was not statistically significant (Student's t-test, P = 0.06, 0.13). Furthermore, we made a similar comparison among the nine patients with overt hypothyroidism. The results are shown in Table 5. The patients treated with sequential regimens of anthracyclines and taxanes tended to have higher TSH levels than those treated with anthracycline-based regimens without taxanes, al-

Table 5 9 patients of overt hypothyroidism following chemotherapy for breast cancer

	cases	thyroid function			
		fT4 (ng/dL) pre	fT4 post	TSH (μU/mL) pre	TSH post
A	3	1.04 ± 0.06	0.76 ± 0.03	1.91 ± 0.42	4.80 ± 0.32
range		(0.96-1.16)	(0.72-0.82)	(0.96-1.16)	(4.21-5.32)
A + T	6	1.03 ± 0.12	0.54 ± 0.09	2.59 ± 0.24	17.09 ± 6.81
range		(0.84-1.62)	(0.26-0.80)	(0.84-1.62)	(4.46-49.0)
p (W-test)		0.33	0.12	0.28	0.08

A: anthracycline based; A + T: anthracycline followed by taxane; W-test: Wilcoxon singed-rank test.

though the difference was not statistically significant (Wilcoxon singed-rank test, P = 0.08). These results suggest that adding taxanes to anthracycline-based regimens may worsen hypothyroidism.

Discussion

The first point that requires clarification is the definition of hypothyroidism. An expert panel defined subclinical hypothyroidism as a serum TSH level >4.5 IU/L, with a normal fT4 level[11]. On the other hand, thyroid dysfunction with a lower fT4 level, accompanied by an increase in the TSH level >4.5 IU/L, is defined as overt hypothyroidism. Most patients with overt hypothyroidism require thyroxin replacement therapy because of the associated clinical signs, such as peripheral edema, general fatigue, weight gain, hypothermia, and bradycardia, which are similar to the adverse effects of cancer chemotherapy.

Kasagi et al. established the prevalence of overt hypothyroidism in 1818 Japanese adults by evaluating serum TSH, fT4, anti-thyroglobulin antibodies (TgAb), and anti-thyroid peroxidase antibodies (TPOab), and reported that the prevalence rates of subclinical hypothyroidism and overt hypothyroidism were 105 (5.8%) and 13 (0.7%), respectively[12]. In light of this, it was found that the prevalence of overt hypothyroidism (15%) and subclinical hypothyroidism (28%) in the present data were both higher than the prevalence of these parameters in the general Japanese population. Therefore, the present study found a high prevalence of anti-cancer chemotherapy-induced hypothyroidism.

The concern with thyroid dysfunction as a side effect of cancer chemotherapy has been growing on account of the high prevalence of thyroid dysfunction following cancer treatment with TKIs and ICIs. TKIs bind competitively to the ATP binding site of tyrosine kinases, inhibiting angiogenesis or cell proliferation in cancer cells[13,14] and in the normal cells of endocrine organs. TKIs belonging to the molecular targeting anticancer drugs have recently been used for some kinds of cancers, including metastatic renal carcinomas, gastrointestinal stromal tumors (GIST), leukemias, hepatocellular carcinomas, and differential thyroid cancers refractory to iodine-131 therapy. With these cancer therapies, thyroid dysfunction, especially hypothyroidism, may occur with a prevalence of 32-85%, and transient thyrotoxicosis with a prevalence of 0-24%[15]. In light of the mechanisms of both drugs, these drugs probably induce endocrine disorders, including thyroid dysfunction. Although there are clinical studies that have investigated whether there is an association between TKIs or ICIs and hypothyroidism, there is little agreement on whether conventional anticancer drugs cause thyroid dysfunction.

The present study showed that conventional anticancer chemotherapy with anthracycline and taxanes may affect thyroid function, especially by causing hypothyroidism, with the prevalence of 14.8%, and 8 (13%) patients required thyroid hormone replacement therapy. Four of the 8 patients (6.5%) needed long-term thyroxin replacement therapy following cancer chemotherapy. It follows from this that latent subclinical hypothyroidism following conventional cancer chemotherapy may occur with a definite frequency. However, we would like to focus attention on the similarity of the clinical features of hypothyroidism and the adverse effects of anti-cancer drugs, especially taxanes.

Docetaxel is known to induce reversible peripheral edema (soft pitting edema of the lower limbs)[16,17]. The pathophysiological mechanism of fluid retention with

docetaxel treatment is thought to be related to capillary protein drainage[18,19]. Although this adverse event appears in 20-60% of the patients treated for advanced cancer, corticosteroid premedication may prevent its development[20]. Based on our findings, it is essential to distinguish the docetaxel-induced lower limb edema from general edema due to hypothyroidism. Since the present study indicates that thyroid function tended to decrease with the addition of taxanes to anthracycline-based therapy, it is important to evaluate thyroid function in patients with cancer undergoing chemotherapy, especially in those treated with docetaxel.

Recently, endocrine disorders accompanied by cancer treatment with immune-checkpoint inhibitors targeting T-lymphocyte-associated protein 4 (CTLA-4), programmed death 1 (PD-1), and its ligand PD-L1 antibody, have attracted much attention. PD-L1 ligand atezolizumab and pembrolizumab plus paclitaxel or gemcitabine-carboplatin improve progression-free survival in metastatic breast cancer patients with PD-L1 positive triple-negative cancer[21].

Since ICIs interfere with immunological self-tolerance mechanisms, immune-related adverse events (irAEs) may arise following PD-L1 ligand therapy. Hypothyroidism associated with ICIs therapy is the most frequent endocrine disorder among ICI-related irAEs[22]. The prevalence of hypothyroidism following ICI therapy has been reported to be 3.9-8.5%. As to the conventional chemotherapy, the present study shows that hypothyroidism accompanied by breast cancer chemotherapy was more prevalent with the incidence of 15%. Therefore, careful management for thyroid disfunction during conventional chemotherapy as well as ICI therapy for breast cancer should be needed.

In conclusion, the present study revealed that conventional chemotherapy, as well as TKI- and ICI-therapy, may induce thyroid dysfunction. Since, to the best of our knowledge, there is no clinical evidence for hypothyroidism induced by conventional chemotherapy, the present clinical experience is the first evidence that anthracycline-based regimens followed by taxanes may induce transient or permanent hypothyroidism and that additional taxane therapy may be associated with more frequent hypothyroidism. We should thus beware of thyroid dysfunction and evaluate thyroid function during and following conventional cancer chemotherapy.

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Conflict of interest

There are no conflicts of interest in the present study.

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