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Prevalence and Associated Factors for Thyroid Dysfunction Among Patients On Targeted Therapy for Cancers: A Single-Center Study from Thailand

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Abstract

Objective. This study aimed to explore the prevalence and associated factors of thyroid dysfunction among cancer patients treated with tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs).

Methodology. A cross-sectional study was done in patients who received TKIs at Rajavithi Hospital in 2019. For patients treated with ICI, a retrospective chart review for patients seen in 2018 to 2019 was conducted. If there were abnormal thyroid function tests (TFT), thyroid autoantibodies were tested.

Results. There were 144 patients on TKIs with a mean age of 56.0 years. Thyroid dysfunction was found in 14.6% of patients and most had subclinical hypothyroidism (n = 16, 11.1%). Imatinib (n = 11, 10.8%) and sunitinib (n = 4, 100%) were the 2 most common TKIs given to patients with thyroid dysfunction. Thyroid dysfunction was associated with male sex, chronic kidney disease and hepatitis B virus infection but not with previous thyroid disease and presence of thyroid autoantibodies.

There were 18 patients who received ICIs. The mean age was 63.3 years. Twelve patients (66.7%) used programmed cell death protein-1 antibody (anti-PD1), mainly nivolumab. Thyroid dysfunction was found in 50%, which occurred at a median duration of 46 days. Most patients had overt hypothyroidism and 55.6% needed levothyroxine replacement.

Conclusion. Thyroid dysfunctions from TKIs were mostly asymptomatic and mild in severity. Some types of TKIs might be associated with thyroid dysfunction. On the other hand, thyroid dysfunction from ICIs usually occurs within 6 months and requires levothyroxine replacement.

Key words: thyroid dysfunction, tyrosine kinase inhibitor, immune checkpoint inhibitor, immunotherapy, malignancy

BACKGROUND

Cancer incidence increased to 23.6 million cases worldwide which led to more than 10.0 million deaths in 2019.[1] Despite advances in diagnostic techniques, surgery, radiation and chemotherapy, mortality rate in some diseases such as lung cancer have not changed significantly from 40 years ago. Nowadays, our knowledge of molecular pathogenesis allows for precision medicine. Targeted therapy is a new drug strategy designed to attack abnormal cells with altered key oncogenes or tumor suppressor genes involved in tumor promotion. Selective actions affect only cancer cells with fewer side effects compared with conventional chemotherapy.[2]

Targeted anti-cancer agents are broadly classified into small-molecule inhibitors and monoclonal antibodies with tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) as the most commonly used agents, respectively. They are reported to cause thyroid dysfunction as adverse events due to various mechanisms.

TKIs are agents that inhibit the enzyme tyrosine kinase which transfer phosphate groups on adenosine triphosphate (ATP) to the tyrosine residues of protein by phosphorylation which sends signal to regulate cell growth and differentiation.[3] There are many receptors at the cell membrane with tyrosine kinase activity e.g., epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), anaplastic lymphoma kinase (ALK), BRAF

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proto-oncogene (BRAF).[4] Increased activity of tyrosine kinase leads to uncontrolled proliferation and abnormal angiogenesis resulting in malignancies of solid organs. Over-activity of non-receptor tyrosine kinase which functions as an intracellular signal transducer, e.g., abl kinase, is responsible for pathogenesis of chronic myeloid leukemia (translocation chromosome 9, 22).[4] Indications for TKIs are non-small cell lung cancer (NSCLC), chronic myeloid leukemia (CML), renal cell carcinoma (RCC), gastrointestinal stromal tumor (GIST) and hepatocellular carcinoma (HCC).[4] TKIs available in Rajavithi Hospital, Thailand include: imatinib, sunitinib, sorafenib, gefitinib, erlotinib, afatinib, osimertinib, nilotinib, dasatinib and pazopanib. Common side effects of TKIs are gastrointestinal intolerance, anemia and folliculitis. The commonly reported TKI-related endocrinopathy is thyroid dysfunction, with a wide range of manifestations raging from asymptomatic (subclinical hypothyroid/hyperthyroid) to symptomatic patients (overt hypothyroid/ hyperthyroid). Both hypothyroidism and hyperthyroidism should be screened and treated properly to reduce complications.[5-7]

The incidence of TKIs-induced thyroid dysfunction in previous studies varied from 32-60% and depends on the type of TKI. Mechanisms of thyroid dysfunction postulated in TKI are destructive thyroiditis due to direct toxic effect as reported in sorafenib, sunitinib and axitinib.[8,9] Decreased iodine (^{123}I) scintigraphy and uptake were observed in some cases.[10] Capillary regression in thyroid gland from sunitinib,[11] increased type 3 deiodinase activity in peripheral tissue from sorafenib,[12] increased metabolism of thyroxine via potent inhibitors of CYP2C9, CYP2D6, CYP3A4/5 and increased activity of uridine diphosphate-glucuronosyl-transferase from imatinib[13] were also detected.

Immune checkpoint is the specific glycoprotein on T-cell membrane mandatory for self-recognition and controls immune response. ICI is a monoclonal antibody and binding with receptor inhibits the signal and increases anti-tumor activity. However, it can activate immune-related adverse events (irAE) such as endocrinopathies, dermatitis, colitis, hepatitis and arthritis.[14] Reported endocrinopathies are thyroid dysfunction (2.3-14.0%), hypophysitis (0.1-17.0%), insulin-dependent diabetes mellitus (0.1-0.9%) and primary adrenal insufficiency (0.5-0.9%).[15]

There are 2 pathways for immunotherapy actions. First is cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors such as ipilimumab or tremelimumab which disinhibit interleukin 2 (IL-2) production and promote cancer killing. The other drug group is involved with the programmed cell death protein-1 (PD1) pathway, namely: antibody to PD1 on T-cells (e.g., nivolumab, pembrolizumab, cemiplimab) and antibody attack PD1 ligand (anti-PD1L) on tumor cell (e.g., atezolizumab, durvalumab or avelumab) resulting in increased T-cell activity and proliferation to attack cancer cells. Indications for immunotherapy are late stage or metastatic NSCLC, RCC, malignant melanoma and other cancers from many clinical trials.[16,17]

The American Society of Clinical Oncology (ASCO) recommends monitoring of clinical symptoms and thyroid function tests (TFT) every 4-6 weeks while on immunotherapy and withdrawal of the offending drugs if grade 3 or 4 toxicity occurs. Treatment with levothyroxine for hypothyroidism or with beta blockers for thyrotoxicosis is started if persistent abnormality in TFTs is observed. A consult with an endocrinologist is likewise recommended.[18] In Thailand, there is currently no research about thyroid dysfunction associated with TKIs or ICIs use.

The objective of this study is to estimate the prevalence and associated factors for thyroid dysfunction in cancer patients who were treated with TKIs or ICI in Thailand. This will help in coming up with recommendations for best clinical care.

METHODOLOGY

This study has 2 parts: a cross-sectional study gathering data from patients who were prescribed TKIs from January to December 2019 and a retrospective chart review of cancer patients who were treated with ICIs from January 2018 to December 2019 at the hematology and oncology clinic of Rajavithi Hospital, Thailand. Baseline characteristics, history of neck surgery or radiation, underlying diseases, TKI types and duration were collected from patients and medical records. Free triiodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) were measured at recruitment. Analyses were done using Cobas e602 analyzer (Roche). The normal value for FT3 was 2.00-4.40 pg/ml (CV 1.73%), FT4 was 0.93-1.70 ng/dl (CV 2.10%) and TSH was 0.27-4.20 μIU/ml (CV 1.73%). If there were abnormal TFTs, thyroid autoantibodies which included anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO) antibodies were tested. Total enumeration was performed.

Informed consent was secured. This study was approved by Rajavithi Hospital Ethics Committee (number 62036).

Inclusion criteria

Patients more than 18 years of age treated with TKIs or ICIs who were willing to participate and have TFTs were included. Patients with previous thyroid disorders were not excluded.

Exclusion criteria

Patients who had other conditions that can alter TFTs were excluded such as: acute severe medical illness requiring admission (e.g., acute myocardial infarction, acute stroke, sepsis which can alter thyroid function tests and lead to sick euthyroid state), received other drugs known to affect hormone metabolism or interfere with assay measurement (e.g., amiodarone, lithium, ethionamide, sulfonamide, iodide, gonadotropin-releasing hormone agonist (leuprorelin), interleukin-2, granulocyte/ macrophage colony-stimulating factors and biotin). Finally,

patients who developed conditions which warrant a stop or withdrawal of TKIs or ICIs for more than 1 month before assessing TFT were excluded.

Outcome

The endpoint of this study is thyroid dysfunction defined as any abnormality in the levels of FT3, FT4 or TSH. Patients with thyroid dysfunction may be asymptomatic with abnormal TFTs such as in the case of subclinical hypothyroidism (high TSH with normal FT3 and FT4) or subclinical hyperthyroidism (low TSH but normal FT4 and FT3).

Sample size calculation

From literature review, we calculated the thyroid dysfunction from TKIs from the population proportion equation.[19] The incidence of thyroid dysfunction from TKI[20]= 34.0% at 95% statistical significance (α = 0.05) and type 2 error 20% was calculated. The computed sample size is 144 patients with 13 patients drop out, so recruitment of TKIs users of at least 157 patients is required.

For logistic regression, multivariable analyses in a previous study found 3 risk factors.[20] Calculation for sample size use G*power[21] found sample size are 237 patients with at 95% statistical significance (α = 0.05), type 2 error 20%, expected odds ratio 1.5, Pr(Y=1/X=1) = 0.34, R2 other X= 0.04 (low association).

Statistical analysis

The data was analyzed using IBM SPSS Modeler 16.0. Pearson Chi-square and Fisher exact test were applied to evaluate correlation of categorical variables. Normality test with Shapiro-Wilk test was done. Paired t-test was applied for normal distributed data. Mann-Whitney U test was used for non-normal distribution continuous data comparison. Multivariable analysis was performed by logistic regression. There were no missing data in this study.

For ICIs, data was descriptive analysis via SPSS using percentage and frequency in categorical data. In continuous data, mean with standard deviation (SD) in normal distribution and median with lowest-highest data in non-normal distribution were used.

The significance value is considered as $p<0.05$

RESULTS

Tyrosine kinase inhibitors

A total of 144 patients who received TKIs were included in this study. Baseline characteristics are as shown in Table 1. There were 73 males and 71 females and the mean age ± SD was 56.0 ± 15.6 years. All patients had no exposure to drugs that may affect TFT, except for 1 post-liver transplant patient who was given cyclosporine that may cause the rare occurrence of autoimmune thyroiditis. One patient had head and neck irradiation. Three had previous thyroid disease: non-functioning thyroid nodule (n = 1), hypothyroidism of unknown cause (n = 1) and Hashimoto's thyroiditis (n = 1). Levothyroxine was given to 2 of these patients from another hospital. Baseline TFTs were available before TKIs in 2 patients which were interpreted as euthyroid (n = 1) and sick euthyroid (n = 1). Thyroid antibodies were not done except in 1 case with previously diagnosed Hashimoto's thyroiditis. Among patients with solid malignancies, 89.5% had advanced stage (Stage 4). Among patients with CML, all had chronic phase except 1 patient with blastic phase that turned to chronic phase after chemotherapy. No patient with thyroid cancer received TKIs in our study.

Most patients (83.3%) used only 1 TKI. Eighty-eight percent received the standard dose of TKI (n = 127 patients (88.2%)) while below standard and above standard doses were given in 15 and 5 patients, respectively. Frequently prescribed TKIs were: imatinib, gefitinib and nilotinib. The median duration of treatment for all TKIs was 689.5 days or 1.89 years (range: 27 to 5642 days).

Thyroid dysfunctions were found in 21 (14.6%) patients as shown in Figure 1. The most common dysfunction was subclinical hypothyroidism (n = 16, 11.1%) with 4 patients having TSH >10 mIU/L. Overt hypothyroidism was seen in 4 patients with 2 of them diagnosed after TKI use (1.4%). Subclinical hyperthyroidism was found in 3 (2.1%) patients, 1 of them had TSH <0.01 mIU/ml. Symptoms of thyroid dysfunction were presented in 2 patients with overt hypothyroidism. Treatment with levothyroxine was initiated in 4 patients. Thyroid autoantibodies were positive in 4 (19.0%) of 21 patients: overt hypothyroidism (n = 2), subclinical hyperthyroidism (n = 1), subclinical hypothyroidism (n = 1). There was no correlation between the level of antibodies and the level of abnormal TFT. One patient with a history of head and neck irradiation did not have thyroid dysfunction.

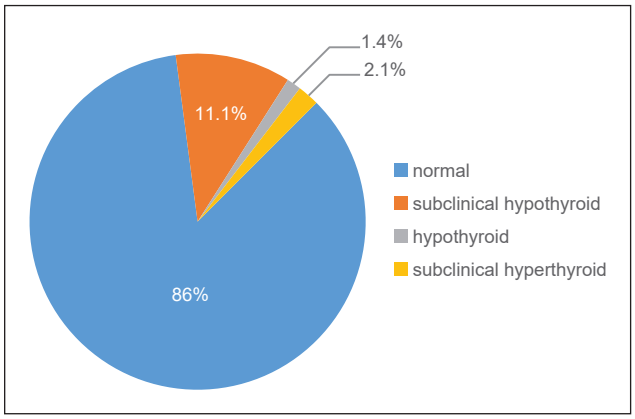

Figure 1. Type of thyroid dysfunction in TKI patients. Of the 144 users, 21 (14.6%) had thyroid dysfunction which were 16(11.1%) subclinical hypothyroid, 3 (2.1%) subclinical hyperthyroid and 2 (1.4%) hypothyroid.

The starting dose of TKIs were continued in all cases, except for 2 patients who had disease progression. Number and duration of TKI use were not significantly associated with TFT abnormality. All 4 sunitinib patients had abnormalities in TFTs including overt or subclinical hypothyroidism and treatment was indicated in 3 of these patients (Figure 2).

Male sex, comorbidity, chronic kidney disease (CKD) and hepatitis B virus (HBV) infection were associated with thyroid dysfunction. Adjusted odds ratio was still significant in male sex, CKD and HBV infection as in Table 2.

Immune checkpoint inhibitors

ICIs were given in 18 patients including 12 (66.7%) males and 6 (33.3%) females. Mean age ± SD was 63.3 ± 12.5 years old. Most patients were in the central region (n = 16, 89.0%). Five (27.8%) patients had at least 1 comorbidity which were: hypertension (n = 2), diabetes mellitus (n = 2), cerebrovascular disease (n = 1), coronary artery disease (n = 1) and cirrhosis (n = 2). Previous use of TKIs was noted in 6 patients.

The indications for ICIs were NSCLC (n = 9, 50%), RCC

Table 1. Baseline characteristics of patients who treated with TKIs

Demographic data	All (n = 144)	TFT abnormal (n = 21)	TFT normal (n = 123)	*p*
Age (mean ± SD), years	56.0 ± 15.6	58.5 ±17.2	55.6 ± 15.4	0.438
Sex (n,%)				0.040
Male	73	15, 71.4%	58, 47.2%	
Female	71	6, 28.6%	65, 52.8%	
Domicile region (n,%)				0.283
Central	118	18, 85.7%	100, 81.3%	
West	12	0, 0.0%	12, 9.7%	
Northeast	6	2, 9.5%	4, 3.3%	
East	4	0 ,0.0%	4, 3.3%	
South	3	1, 4.8%	2, 1.6%	
North	1	0, 0.0%	1, 0.8%%	
Diagnosis (n,%)				<0.001
Chronic myeloid leukemia (CML)	68	10, 47.6%	58, 47.2%	
Non-small cell lung cancer (NSCLC)	36	5, 23.8%	31, 25.2%	
Gastrointestinal stromal tumor (GIST)	35	1, 4.8%	34, 27.6%	
Renal cell carcinoma (RCC)	3	3, 14.3%	0, 0.0%	
Hepatocellular carcinoma (HCC)	2	2, 9.5%	0, 0.0%	
Staging solid tumor (n,%)	76	11	65	0.471
3	8	0, 0.0%	8,12.3%	
4	68	11, 100.0%	57, 87.7%	
Comorbid disease (n,%)				0.148
No	69	7, 33.3%	62, 50.4%	
Yes	75	14, 66.7%	61, 49.6%	
Hypertension	34	4, 19.0%	30, 24.4%	0.783
Dyslipidemia	28	3, 14.3%	25,20.3%	0.766
Diabetes mellitus	23	4, 19.0%	19, 15.4%	0.747
Chronic kidney disease	14	5, 23.8%	9, 7.3%	0.018
Coronary artery disease	4	0, 0.0%	4, 3.3%	0.528
HBV infection	4	2, 9.5%	2, 1.6%	0.102
Cerebrovascular disease	3	0, 0.0%	3, 2.4 %	1.000
Hemoglobinopathy	2	1, 4.8%	1, 0.8%	0.271
Asthma	2	1, 4.8%	1, 0.8%	0.271
HIV infection	1	0, 0.0%	1, 0.8%	1.000
Post-liver transplantation	1	1, 4.8%	0, 0.0%	0.146
Concurrent inactive cancer	3	0, 0.0%	3, 2.4%	1.000
Previous thyroid disease (n, %)	3	0, 0.0%	3, 100.0%	1.000
Thyroid nodule	1	0, 0.0%	1, 33.3%	
Hypothyroid	1	0, 0.0%	1, 33.3%	
Hashimoto's thyroiditis	1	0, 0.0%	1, 33.3%	
Number of TKI use (n, %)				0.210
1	121	16,76.2%	105, 85.4%	
2	21	4, 19.0%	17, 13.8%	
3	2	1, 4.8%	1, 0.8%	
Types of TKI use (n, %)				
Imatinib	102	11, 52.4%	91, 74.0%	0.044
Gefitinib	18	2, 9.5%	16, 13.0%	1.000
Nilotinib	16	3, 14.3%	13, 10.6%	0.705
Erlotinib	14	3, 14.3%	11, 8.9%	0.431
Sunitinib	4	4, 19.0%	0, 0.0%	0.000
Sorafenib	1	1, 4.8%	0, 0.0%	0.146
Dasatinib	6	1, 4.8%	5,4.1%	1.000
Osimertinib	2	0, 0.0%	2, 1.6%	1.000
Afatinib	4	0, 0.0%	4, 3.3%	1.000
Pazopanib	1	1, 4.8%	0, 0.0%	0.146
Duration of TKI (mean ± SD days)	1253 ± 1314	1215 ± 1332	1260 ± 1316	0.884
Dose of TKI				0.193
Standard dose	127	17, 81.0%	110, 89.4%	
Below standard dose	13	4, 19.0 %	9, 7.3%	
Above standard dose	4	0, 0.0%	4, 3.3%	

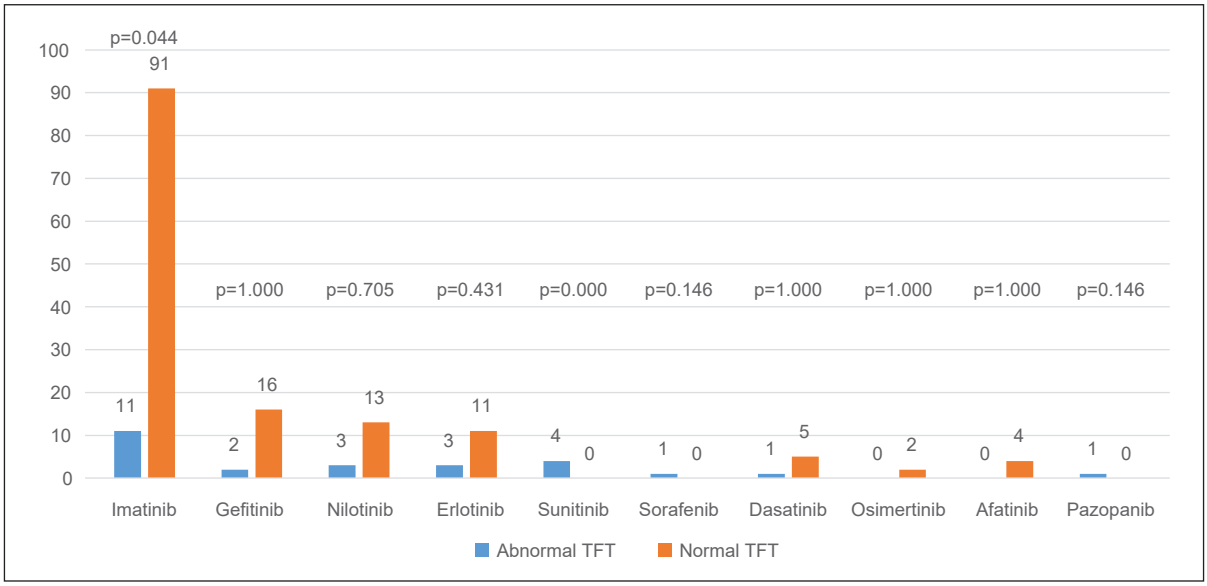

Figure 2. Thyroid dysfunctions by type of TKI.

Table 2. Risk factors associated with thyroid dysfunction from tyrosine kinase inhibitors

Variable	Crude OR (95%CI)	*p*	Adjusted OR (95%CI)	*p*
Male sex	2.802 (1.02-7.70)	0.046	3.333 (1.135-9.787)	0.028
Comorbidity	2.033 (0.768-5.382)	0.153	1.222 (0.395-3.777)	0.728
CKD	3.958 (1.178-13.301)	0.026	4.855 (1.177-20.023)	0.029
HBV infection	6.368 (0.846-47.948)	0.072	8.413 (0.917-77.187)	0.060

(n = 4, 22.2%, HCC (n = 2, 11%), malignant melanoma (n = 1, 5.6%), esophageal cancer (n = 1. 5.6%) and cecal cancer (n = 1, 5.6%). Most patients (n = 16, 88.9%) used a single drug. A combination of 2 ICIs was used in 2 patients and combination ICI with chemotherapy in 1 patient. Types of ICIs used were: nivolumab (n = 6, 33.3%), pembrolizumab (n = 4, 22.2%), durvalumab (n = 4, 22.2%), cemiplimab (n = 3, 16.7%), atezolizumab (n = 2, 11.1%) and ipilimumab (n = 1, 5.6%) as presented in Table 3.

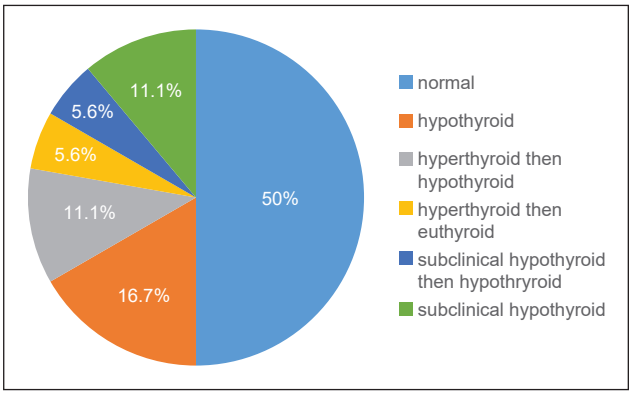

Figure 3. Types of thyroid dysfunction in ICI users. Of 18 patients, 50% had thyroid dysfunction which are 3 (16.7%) hypothyroid, 2 (11.1%) hyperthyroid then hypothyroid, 2 (11.1%) subclinical hypothyroid, 1 (5.6%) hyperthyroid then euthyroid and 1 (5.6%) subclinical hypothyroid then euthyroid. Finally, 6 (33.3%) patients had hypothyroid.

Table 3. Baseline characteristics in immune checkpoint inhibitors user

Demographic data	All ICI users
Age (mean ± SD), years	63.3 ± 12.5
Sex (%)	
Male	66.7%
Female	33.3%
Domicile region (%)	
Central	89.0%
West	5.5%
East	5.5%
Diagnosis (%)	
NSCLC	50.0%
RCC	22.2%
HCC	11.1%
Malignant melanoma	5.6%
Esophageal cancer	5.6%
Cecal cancer	5.6%
Comorbid disease (%)	27.8%
Hypertension	11.1%
Diabetes mellitus	11.1%
Cirrhosis	11.1%
Coronary artery disease	7.1%
Cerebrovascular disease	7.1%
Types of Immunotherapy use (%)	
Nivolumab	33.3%
Pembrolizumab	22.2%
Durvalumab	22.2%
Cemiplimab	16.7%
Atezolizumab	11.1%
Ipilimumab	5.6%
Combination immunotherapy	11.1%
anti-CTLA-4 + anti-PD1	5.6%
anti-PD1+ anti-PD1	5.6%
Duration of Immunotherapy before thyroid dysfunction (mean ± SD days)	61.3 ± 48.6

Baseline TFTs were unavailable in most of patients except for 2 patients with history of pazopanib use who showed sick euthyroid state with high anti-thyroid peroxidase (259 IU/ml) (n = 1) and subclinical hypothyroidism (n = 1) which resolved spontaneously before the start of immunotherapy.

Thyroid dysfunction occurred in 50% of patients. Three (16.7%) cases of hypothyroidism were found. Two (11.1%) patients initially had thyrotoxicosis followed by a state of hypothyroidism with 1 of the patients confirmed to have very low uptake in thyroid scintigraphy compatible with thyroiditis. One patient had transient hyperthyroidism then euthyroidism. Another 3 patients had subclinical hypothyroidism which turned to overt hypothyroidism (n = 1) and sick euthyroid syndrome (n = 1) on follow up (Figure 3). The mean duration of the first detected abnormal TFT was 61.3 ± 48.6 days (median 46 days, range: 14-162 days). Three of 4 patients with abnormal TFTs had positive thyroid antibodies. Conversion from hyperthyroid to hypothyroid state was in 92 and 42 days in patient numbers 3 and 10, respectively.

There was no relationship between sex, age, previous TKIs used, dose, type and duration of ICIs and thyroid dysfunction. No one had symptoms of thyroid dysfunction.

There was no interruption in ICI treatment in all patients, except 1 who received ipilimumab and cemiplimab who had hepatitis but no thyroid dysfunction.

The specific agents used were anti-PD1 for 12 patients (nivolumab, pembrolizumab and cemiplimab), anti-PD1L for 6 (atezolizumab and durvalumab), and anti-CTLA4 for 1 patient (ipilimumab). Thyroid dysfunction was found in 9 patients (6 on anti-PD1, 3 on anti-PDL1 and none from anti-CTLA4). Abnormal TFTs were observed on 50% of patients who received anti-PD1 and anti-PD1L. Hypothyroidism was observed with the combination of 2 anti-PD1 as in patient number 10 but not with the combination of ipilimumab with cemiplimab (anti-CTLA4 + anti-PD1) after 1 year follow up. Levothyroxine (LT4) replacement is needed in 55.5% of thyroid dysfunction. No other endocrinopathies such as type 1 diabetes or hypophysitis were observed in all ICI patients (Table 4).

There was no missing data in this study both in TKI and ICI group.

DISCUSSION

This is the first study to show the prevalence and associated factors of thyroid dysfunction from new anti-cancer therapies in a single tertiary center in Thailand. Assessments were done in out-patient department without other drugs affecting TFT to minimize conditions that may interfere with laboratory assays or yield sick euthyroid state. The prevalence of TKI-induced was 14.6% (n = 21) from 144 patients: subclinical hypothyroidism (11.1%), subclinical hyperthyroidism (14.5%) and overt hypothyroidism (9.5%). Most of these patients were asymptomatic or had mild clinical symptoms but did not warrant TKI interruption. Only 4 patients required LT4 treatment. Thyroid autoantibodies were positive in 4 out of 21 patients. The prevalence observed was lower than previously reported in the United States of about 40% with more overt hypothyroidism (26.8%) and subclinical hyperthyroidism (13.2%).[22] In other studies, prevalence ranged from 18-44%.[23] The differences may be due to the diagnosis and different type of TKIs used.

Table 4. Baseline characteristics and thyroid function test after immune checkpoint inhibitor use

No.	Age	Sex	Diagnosis	Previous TKI	Immunotherapy	FT4 (ng/dl)	FT3 (pg/ml)	TSH (mIU/ml)	Abnormal TFT	Onset abnormal TFT (days)	Anti-Tg (IU/ml)	Anti-TPO (IU/ml)	Treatment of Abnormal TFT	Cortisol (ug/dl)	FBS (mg/dl)	Survival
1	74	F	NSCLC	Erlotinib + Osimertinib	Atezolizumab	1.35	2.36	3.01	-	-	-	-	-	-	96	1
2	55	M	RCC	Pazopanib	Nivolumab	1.01	2.78	2.88	-	-	-	-	-	-	115	1
3	68	M	NSCLC	-	Durvalumab	2.18	5.18	0.009	Hyper-hypothyroid	46	327.50	94.82	Yes	8.20	-	1
4	83	F	HCC	Sorafenib	Nivolumab	0.73	2.99	16.21	Hypothyroid	14	-	-	-	-	-	1
5	70	M	RCC	Pazopanib	Nivolumab	0.31	1.62	>100	Hypothyroid	69	54.30	288	Yes	-	103	1
6	75	M	NSCLC	-	Atezolizumab	1.52	2.20	3.42	-	-	-	-	-	-	-	0
7	61	M	NSCLC	-	Durvalumab	1.21	2.99	0.104	Transient hyperthyroid	112	-	-	-	11.70	-	1
8	55	M	NSCLC	-	Durvalumab	1.60	3.42	2.33	-	-	-	-	-	-	-	1
9	30	F	NSCLC	-	Pembrolizumab	1.35	3.43	0.391	-	-	-	-	-	-	75	0
10	60	F	Malignant melanoma	-	Pembrolizumab + Nivolumab	1.83	4.21	<0.005	Hyper-hypothyroid	44	-	13.28	Yes	-	-	1
11	64	M	RCC	Sunitinib	Nivolumab	1.35	1.77	4.49	Sick euthyroid	-	-	-	-	-	-	0
12	61	M	Esophageal cancer	-	Nivolumab	0.99	2.27	14.30	Subclinical hypothyroid	14	<10	18.52	-	-	-	1
13	52	M	HCC	-	Durvalumab	1.39	2.74	12.18	Subclinical hypothyroid	28	-	-	-	-	97	0
14	78	F	Cecal cancer	-	Pembrolizumab	0.72	1.89	37.86	Hypothyroid	63	-	-	Yes	14.70	122*	0
15	78	F	RCC	Sunitinib	Pembrolizumab	1.32	1.61	1.66	Sick euthyroid	-	-	-	-	-	87	0
16	58	M	NSCLC	-	Ipilimumab + Cemiplimab	1.59	3.13	1.02	-	-	-	-	-	-	96	1
17	63	M	NSCLC	-	Cemiplimab	0.26	1.02	54.50	Hypothyroid	162	-	-	Yes	-	122	1
18	54	M	NSCLC	-	Cemiplimab	-	-	2.20	-	-	-	-	-	-	92	1

M = male, F = female, NSCLC = non-small cell lung cancer, RCC = renal cell carcinoma, HCC = hepatocellular carcinoma, TKI = tyrosine kinase inhibitors, FT4 = free thyroxine (normal 0.93-1.70 ng/dl), FT3 = free triiodothyronine (normal 2.00-4.40 pg/ml), TSH = thyroid stimulating hormone (normal 0.27-4.20 mIU/ml), anti-Tg = anti-thyroglobulin antibody (normal 0-115 IU/ml), anti-TPO = anti-thyroid peroxidase antibody (normal 0-34 IU/ml), TFT = thyroid function test, cortisol = morning cortisol, FBS = fasting blood sugar, survival 0 = dead, 1 = survive, * = previous type 2 diabetes

In this study, imatinib was used in 70.8% of patients mainly for CML and GIST while in other studies more usage of sunitinib, sorafenib and pazopanib for RCC or GIST were noted. The latter agents had more vascular endothelial growth factor (VEGF) inhibition resulting in more abnormal vasculature and thyroiditis from older reports. A majority of our patients were given imatinib due to government reimbursement policy and financial issues which limit the use of second or third line TKIs. The biphasic pattern of hyperthyroidism and hypothyroidism was not found in this study. However, subclinical hyperthyroidism observed in some of our patients may just be an initial manifestation of thyroid dysfunction which may subsequently convert to hypothyroidism. Hence, close follow up is needed.

The mean duration of TKI treatment in this study before TFT abnormality was 1215 ± 1332 days or 3.3 years which was longer than other previous studies of about 192-252 days. In other studies, hypothyroidism increases with more cycles of TKI used with the longest duration found at 92 weeks or 1.76 year.[24,25] We had low proportion of VEGF inhibitor use; hence, it might take more time to observe thyroid dysfunction. Ethnicity might be another factor. Most studies were done in Western countries and in Asia, the availability is limited to high VEFG inhibition drugs. Another reason was most of the dysfunctions had no or minimal clinical symptoms, hence no regular TFT monitoring was done but more cumulative exposures to TKI.

The number of TKIs used and dosing were not associated with thyroid dysfunction. Another difference was there were more males and fewer antibodies detected in patients with thyroid dysfunction suggesting a non-autoimmune process. Most of our patients live in the central region of the country and no relationship with thyroid dysfunction was seen. If iodine status were suspected to have a causal relationship, more research with patients in known iodine deficiency areas or confirmed low urinary iodine should be done.

The history of thyroid disease might not contribute to further abnormal TFTs from TKIs. One previous hypothyroid with below standard dose of imatinib use due to CKD required higher dose of LT4 (from 150 to 200 μg/day) but this may be due to poor compliance. Another patient with Hashimoto's thyroiditis and gefitinib use did not need additional LT4 dose and 1 case with thyroid nodule who received standard dose of imatinib did not have normal TFTs.

Contrast this with CKD and HBV infection which is associated with thyroid dysfunction. CKD could affect thyroid metabolism through decrease iodine excretion, decrease in thyroid binding protein, decrease peripheral conversion of thyroid hormones and increase in TSH.[24] There are no reports of chronic HBV being directly associated with thyroid dysfunction. However, in cirrhosis, there are free hormone and binding globulin changes. Some patients with interferon treatment also had more thyroid dysfunction.[26] In our study, there were no patients with decompensated cirrhosis or interferon treatment among those who have HBV infection. Thus, further study is required to confirm the association. Survival in our study was not significantly different between groups with and without thyroid dysfunction. Larger retrospective data however, showed more progression free survival, hypothesized from greater immune response, more cancer cells killed and more thyroid dysfunction.[26,27]

For ICIs, six patients had overt hypothyroidism, two of these patients had a transient thyrotoxicosis phase before hypothyroidism and another 1 had progression from subclinical to overt hypothyroidism. Transient hyperthyroidism suggests that thyroiditis might be the cause of thyroid dysfunction. One of our patients had confirmed thyroiditis by thyroid scan.

The incidence of thyroid dysfunction with ICIs in previous studies ranged from 5.9-21.0%[28,29] mainly from hypothyroidism which was lower than our study. The reported rate of overt hypothyroidism with anti-PD1 or anti-PD1L use was 6.5-7.5% which was lower than what we observed in our study with a prevalence of 50%.

The limitation of our study was the small number of patients and 66.6% of them were on anti-PD1 with more reported cases of hypothyroidism. Combination of ICIs had largest incidence of thyroid dysfunction of about 14.6% (REF). Thyroid autoantibodies, either anti-Tg and/or anti-TPO were positive in 23.0-40.0% of patients with abnormal TFTs.[30] In our study, 75% (4 out of 6 patients) had positive antibodies suggesting immune process involvement. History of TKI use before the start of ICI was not associated with thyroid dysfunction (2 patients, numbers 4 and 5). There was no previous thyroid disease identified among our ICIs population.

Baseline characteristics in patients with thyroid dysfunction were male sex (6 out of 9 patients), older (age 66.2 years, in normal TFT 60.3 years). The duration of ICI treatment to first thyroid dysfunction was 61.3 ± 48.6 days, earliest at 14 days and latest at 162 days, which were similar with prior published studies with mean duration 42 days.[31]

To our knowledge, this is the first study to collect thyroid dysfunction prevalence among cancer patients on TKIs and ICIs in single tertiary center of Thailand. There was no missing data. The limitation of our study was a cross-sectional design in TKIs and retrospective descriptive design in ICIs. There were no previous thyroid function tests at baseline before the start of TKI and ICI resulting in limitation of risk factors interpretation. The population included was below the calculated sample size, hence, the study might be underpowered. Lastly, the proportion of patients who received VEFG inhibition among TKIs was lower and anti-PD1 among ICIs were greater than in previous studies, thus, the prevalence and pattern of thyroid dysfunction might be different. Further research is therefore needed to clearly describe associations.

CONCLUSIONS

The prevalence of TKI-induced thyroid dysfunction was 14.6 %. The most common dysfunction was subclinical hypothyroidism and the majority of patients had no to mild symptoms. Treatment with levothyroxine was required in 4 patients. Prior thyroid dysfunction and thyroid autoimmunity did not show correlation. Some types of TKI were more likely to cause thyroid dysfunction but did not reach statistical significance. Male sex, CKD and HBV infection were significantly associated with thyroid dysfunction. We therefore recommend TSH monitoring for patients on TKIs with closer monitoring for patients on drugs with higher prevalence of thyroid dysfunction, e.g., sunitinib.

Thyroid dysfunction from ICIs was seen in 50% of patients which occurred at median duration of 46 days and 55.6% of them warranted levothyroxine replacement. Therefore, close monitoring in the first 6 months is recommended. No correlation between survival and thyroid dysfunction was seen. Further research is recommended to evaluate risk factors for higher thyroid dysfunction in Thailand.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
KC: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing-original draft preparation, Writing-review and editing, Visualization, Project administration, Funding acquisition; **KM:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing-original draft preparation, Writing-review and editing; **PT:** Conceptualization, Formal analysis, Investigation, Resources, Data Curation, Writing-original draft preparation, Writing-review and editing; **CD:** Conceptualization, Methodology, Validation, Formal analysis, Data Curation, Writing-original draft preparation; Writing-review and editing; Visualization, Supervision, Project administration, Funding acquisition.

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