

# Clinical Profile of Non-thyroidal Cancer Patients with Tyrosine Kinase Inhibitor-induced Thyroid Dysfunction in the University of Santo Tomas Hospital, Philippines: A 5-Year Single-center Retrospective Study

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## Abstract

**Objectives.** This study aimed to determine the clinical profile of non-thyroidal cancer patients with thyroid dysfunction associated with tyrosine kinase inhibitor (TKI) therapy at the University of Santo Tomas Hospital (USTH), Philippines.

**Methodology.** This is a retrospective observational study of TKI-initiated adult non-thyroidal cancer patients with thyroid function testing from 2013 to 2018.

**Results.** Forty percent (95% CI: 26.2% - 58.61%) of the sixty individuals who had thyroid function tests (TFT) had incident thyroid dysfunction. Thirty percent had hypothyroidism (i.e., 25% overt [mean TSH 16.64 uIU/mL]; 5% subclinical [mean TSH 6.62 uIU/mL]). The median time at risk was 8 and 16 months for overt and subclinical hypothyroidism, respectively. Fifty-six percent had persistent hypothyroidism (median TSH 16.75,  $p = 0.009$ ). The average time to recovery of transient hypothyroidism was 39 months. Ten percent had hyperthyroidism with a median time at risk of 1.5 months. Non-small cell lung cancer and renal cell carcinoma were possible associated risk factors of thyroid dysfunction.

**Conclusion.** TKI-induced thyroid dysfunctions are common. Screening and monitoring for thyroid abnormalities during TKI therapy is important.

**Key words:** tyrosine kinase inhibitors, hypothyroidism, hyperthyroidism

## INTRODUCTION

Tyrosine kinase inhibitors (TKI) belong to a class of molecular multi-targeted anti-cancer therapy which target active sites of kinases. This mechanism prevents phosphorylation and subsequently inhibits cell proliferation and angiogenesis.<sup>1</sup> There have been numerous accounts of TKI-induced thyroid dysfunction (i.e., hypothyroidism or hyperthyroidism) with incidence varying from 3.1 to 100% depending on the drug, dose and monitoring protocol.<sup>2</sup>

Hypothyroidism occurred most frequently with sunitinib, one of the earliest TKIs, with a reported incidence of 36-46% in prospective studies. The median time to development of thyroid dysfunction was 4 weeks.<sup>3</sup> In patients treated with sorafenib, the incidence of hypothyroidism is about 18%.<sup>4</sup> Most of the incidence studies focused on a single class of TKI: sunitinib (53-85%), sorafenib (20-36%), imatinib (90-100%) among patients who underwent total

thyroidectomy, and axatinib (83-92%).<sup>3</sup> The incidence of hyperthyroidism with sunitinib reached up to 40%.<sup>5</sup> Meanwhile, subclinical and transitory hyperthyroidism has been reported with sunitinib, sorafenib and axatinib.

The possible mechanisms of TKI-induced thyroid dysfunction were studied mostly with sunitinib.<sup>2</sup> Sunitinib likely triggers thyroid dysfunction more frequently because of its broad-spectrum characteristic (i.e., inhibition of VEGF-1, PDGF and VEGF-2) suggesting its important role in the angiogenesis of the thyroid gland.<sup>6</sup> Thyroiditis is believed to be due to TKI-induced cell lysis and devascularization. Other probable mechanisms include reversible reduction of iodine uptake, inhibition of thyroid peroxidase activity and progressive depletion of thyroid functional reserve.<sup>3,4</sup>

The predisposing risk factors for thyroid dysfunction have not been fully determined.<sup>5</sup> According to the study by Lechner and colleagues, patients who developed hypo-

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thyroidism had greater odds of being female as compared to those who remained euthyroid throughout.<sup>7</sup> On the contrary, cumulative TKI exposure duration, greater number of TKI received and the type of cancer do not seem to modify the risk.<sup>2</sup>

In the Philippines, TKIs have been used in various aggressive cancers. Currently, newer classes of TKIs are available which could lead to an increase in TKI-induced thyroid dysfunction. There is no local data on TKI-induced thyroid dysfunction that has been published to date.

Hence, the study aimed to determine the clinical profile of non-thyroidal cancer patients who developed TKI-induced thyroid dysfunction (i.e., thyroiditis-induced thyrotoxicosis, hypothyroidism, worsening of thyroid function/ recurrent hypothyroidism) in USTH from January 2013 to December 2018. This study also aimed to assess the timing of thyroid dysfunction with cumulative TKI exposure.

## METHODOLOGY

### Study design

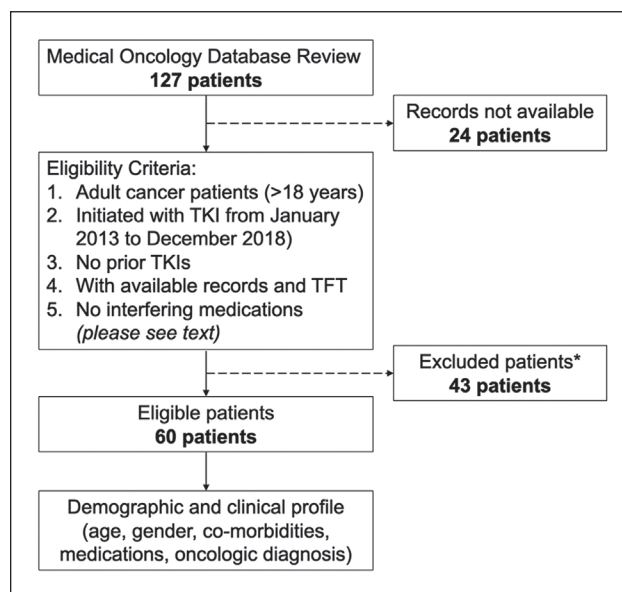
This is a retrospective observational study of adult non-thyroidal cancer patients treated with TKI in USTH, Manila, Philippines approved by the Research Ethics Committee.

### Study participants

All patients who were on TKIs were screened for eligibility criteria which included the following: (1) non-thyroidal cancer patients >18 years old; (2) initiation of TKI between January 2013 and December 2018 at the USTH; (3) with serial TFT; (4) not on any medications that could alter thyroid function test (e.g., systemic steroids, amiodarone, iodinated contrasts, dopamine, octreotide, metoclopramide). The patients with any of the following were excluded: (a) absent TFT; (b) had previous immune checkpoint inhibitor therapy (ICI); (c) admission for critical conditions and/ or infections (Figure 1).

### Sample size

The sample size included all identified eligible patients from the medical oncology residents' database and the individual clinic data of the affiliated oncologists. The total number of patients may be underestimated because no department database included all the patients initiated with TKI. A minimum number of 35 patients was needed to achieve a 95% confidence interval and 10% margin of error based on the highest reported incidence of sunitinib (85%).<sup>2</sup> Sunitinib was used for the sample size computation since it is the most widely studied TKI. Because of the retrospective design of the study and since testing of thyroid function is not routinely done by all specialists, only 60 patients were included in the study. The unavailability of TFT is the most common reason for exclusion from the study.



**Figure 1.** Study Flowchart. Sixty patients satisfied the eligibility criteria.

\*Excluded because of lack of TFT monitoring

### Study procedure

The patients who received their first dose of TKI treatment between January 2013 to December 2018 with a minimum follow-up period of 2 years after the initiation were included in the study. Data collection included the following: demographic profile, family history of thyroid disorders, cancer diagnosis and stage, comorbidities and the Eastern Cooperative Oncology Group (ECOG) status. Monitoring and treatment of thyroid dysfunction were noted.

### Definition of thyroid dysfunction

Thyroid dysfunction was defined based on clinical and biochemical evidence of thyroid disorder. Thyroid Stimulating Hormone (TSH) levels were reported in uIU/mL.

**Overt Hyperthyroidism** – biochemical evidence of suppressed TSH level, elevated free T4 (FT4) or free T3 (FT3) based on laboratory-specific reference range, clinically hyperthyroid or those requiring anti-thyroid medications

**Subclinical hyperthyroidism** – asymptomatic patient with suppressed TSH level and normal FT4 or FT3 based on a laboratory-specific reference range

**Overt hypothyroidism** – biochemical evidence of elevated TSH level, low FT4 based on laboratory-specific reference range, clinically hypothyroid or those requiring thyroid hormone replacement

**Subclinical hypothyroidism** – TSH 5-10 uIU/mL or higher if FT4 is normal

### Study outcomes

The primary outcome is the clinical profile of patients with TKI-induced thyroid dysfunctions. Thyroid dysfunction was stratified according to the class of TKI. The timing of

occurrence of the thyroid dysfunction with cumulative exposure to TKI was also determined.

### Statistical analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Mean and SD were used for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables and frequency and proportion for categorical variables. Mann-Whitney U test was used to determine the difference between persistent hypothyroid patients versus those non-persistent. Wilcoxon-Signed rank test was used to determine the difference from the baseline to the next time point. One-way ANOVA and Kruskal-Wallis test were used to determine the difference across diagnoses, namely euthyroid, hyperthyroidism, and hypothyroidism. The chi-square test or Fisher's Exact test was used to compare proportions. Crude odds ratios and corresponding 95% confidence intervals from binary logistic regression analysis were computed to assess the possible association of demographic and clinical characteristics with thyroid dysfunction. Null hypotheses were rejected at 0.05  $\alpha$ -level of significance. STATA 13.1 was used for the data analysis.

## RESULTS

Of the 127 patients initially identified, only 60 patients satisfied the eligibility criteria. Incident thyroid dysfunction occurred in 40% (95% CI: 26.2% - 58.61%) of the patients. Hypothyroidism occurred in 30% of the patients [25% overt hypothyroidism (mean TSH 16.64 uIU/mL, SD 10.22) and 5% subclinical hypothyroidism (mean TSH 6.21 uIU/mL, SD 3.49)]. Ten percent had hyperthyroidism [3.3% overt hyperthyroidism (mean TSH 0.20 uIU/mL, SD 0.14) and

6.7% subclinical hyperthyroidism (mean TSH 0.20 uIU/mL, SD 0.20)].

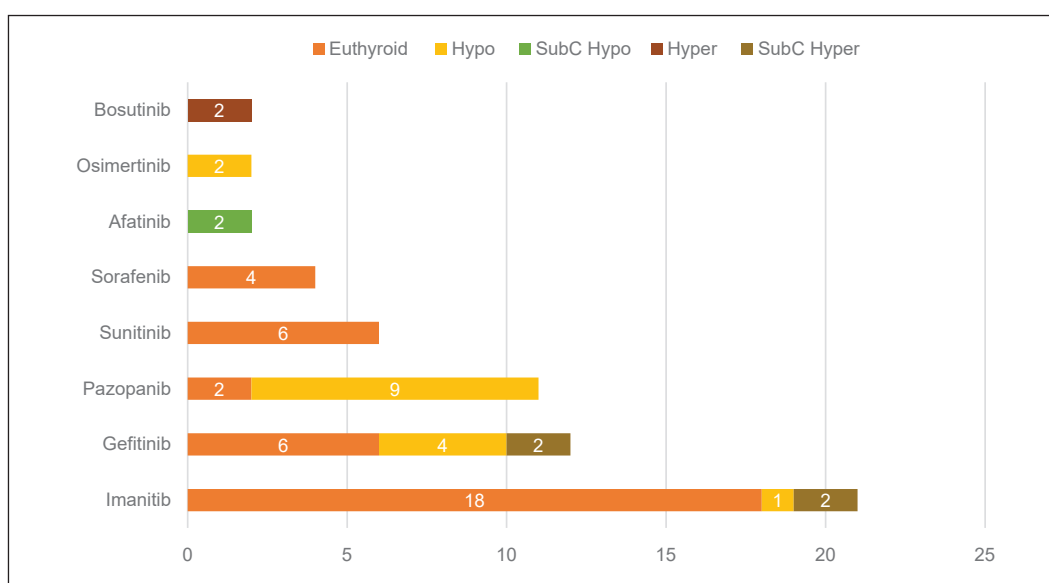
The comparison of demographic characteristics among the groups is shown in Table 1. The incidence of thyroid dysfunction differs significantly among cancer types. A greater proportion of patients with non-small cell lung carcinoma (NSCLC) [ $p = 0.028$ ] and renal cell carcinoma (RCC) [ $p = 0.008$ ] had overt hypothyroidism. Forty-five percent of patients with diabetes were able to maintain a euthyroid status ( $p = 0.015$ ). There were no differences in terms of age, gender, ECOG status and cancer stage.

### TKI exposure and thyroid dysfunction

The distribution of thyroid dysfunction according to TKI is shown in Figure 2. The majority of the patients received imatinib (21/60, 35%). Eighty-two percent of the pazopanib group developed overt hypothyroidism. Aside from pazopanib, overt hypothyroidism occurred in gefitinib (4/12, 33%) and osimertinib (2/2, 100%). Hyperthyroidism developed in both patients treated with bosutinib. Subclinical hypothyroidism occurred in imatinib (1/21, 5%) and afatinib (2/2, 100%) while subclinical hyperthyroidism occurred in imatinib (2/18, 11%) and gefitinib (2/12, 17%). No thyroid dysfunction developed in the sunitinib and sorafenib group. There were no significant differences in thyroid dysfunction between a single TKI and two subsequent TKIs ( $p = 1.000$ ).

### Clinical course of TKI-induced thyroid dysfunction

All patients were biochemically euthyroid (mean TSH 1.25 uIU/mL) at baseline with no significant difference between the initial levels of TFT. The majority remained euthyroid during treatment (59%). Among the hypothyroid group,



**Figure 2.** The distribution of patients with thyroid dysfunction\* stratified according to TKI ( $p < 0.001$ ).

\*Hypo – Overt Hypothyroidism, SubC Hypo – Subclinical hypothyroidism, Hyper – Overt Hyperthyroidism, SubC Hyper – Subclinical hyperthyroidism

the median level of TSH increased to 10.58 uIU/mL on the first follow-up (IQR: 8.57-18.5) from 0.85 uIU/mL (IQR: 0.72-0.98). The median time at risk (i.e., the median time of TKI exposure from initiation to thyroid dysfunction) for overt hypothyroidism was eight months (mean TSH 16.64; IQR: 4.5-12). The median time at risk for subclinical hypothyroidism was 16 months (mean TSH 7.75; IQR: 15.75-27.00). The median TSH level in the hyperthyroid group changed from 1.27 uIU/mL to 0.21 uIU/mL upon the first follow-up. The median time at risk for overt and subclinical hyperthyroidism were 1.5 and 16 months, respectively.

The highest recorded TSH level was 44.01 uIU/mL in an asymptomatic patient two months after pazopanib initiation. This was the shortest time to develop hypothyroidism. The longest time at risk for overt hypothyroidism was 24 months (osimertinib). The maximum median TSH was 14.15 uIU/mL (IQR: 10-19) for overt and 7.75 uIU/mL (IQR: 5.5-10) for subclinical hypothyroidism.

Discontinuation of TKI was made in 93% of overt hypothyroid patients. Sixty-seven percent of the cases were referred to the service of endocrinology. The median TSH of patients referred to endocrinology was 14.65 uIU/mL. Levothyroxine was initiated in 57% of the cases with doses ranging from 50-100 mcg/day.

**Persistent hypothyroidism**

Seventy-one percent had persistent hypothyroidism (i.e., patients who were maintained on thyroid hormone therapy for at least two years). Table 2 shows the clinical course of patients with persistent hypothyroidism. The median maximum TSH level was significantly higher in the persistent hypothyroid group (16.8 versus 8.9 uIU/mL). All patients with overt hypothyroidism were given thyroid hormone therapy (p = 0.023) and were all referred to an endocrinologist (p = 0.002). TKIs were resumed after achieving biochemical euthyroidism. In 88% of patients who had transient hypothyroidism, the average time to recovery was 40 months without thyroid hormone replacement.

**Table 1.** Demographic characteristics of the patients stratified with thyroid dysfunctions

	Diagnosis				P-value*
	Total (n = 60)	Euthyroid (n = 36, 60%)	Hyperthyroidism (n = 6, 10%)	Hypothyroidism (n = 18, 30%)	
	<b>Frequency (%); Mean ± SD</b>				
<b>Age</b>	60.58 ± 12.64	59.19 ± 13.7	55.83 ± 16.27	64.94 ± 7.61	0.182
<b>Gender</b>					0.591
Male	30 (50)	16 (44.44)	4 (66.67)	10 (55.56)	
Female	30 (50)	20 (55.56)	2 (33.33)	8 (44.44)	
<b>ECOG</b>					0.060
0	46 (76.67)	30 (83.33)	6 (100)	10 (55.56)	
1	12 (20)	6 (16.67)	0	6 (33.33)	
2	2 (3.33)	0	0	2 (11.11)	
<b>Cancer</b>					
NSCLC	19 (31.67)	7 (19.44)	4 (66.67)	8 (44.44)	0.028
CML	14 (23.33)	12 (33.33)	2 (33.33)	0	0.009
RCC	14 (23.33)	5 (13.89)	0	9 (50)	0.008
Others	13 (21.67)	12 (33.33)	0	1 (5.56)	0.035
<b>Stage (n = 18)</b>					
IIIB	2 (11.11)	2 (16.67)	0	0	1.000
IV	16 (88.89)	10 (83.33)	2 (100)	4 (100)	
<b>Comorbidities</b>					
Hypertension	24 (40)	12 (33.33)	2 (33.33)	10 (55.56)	0.278
Diabetes Mellitus	11 (18.33)	5 (13.89)	4 (66.67)	2 (11.11)	0.015

ECOG – Eastern Cooperative Oncology Group, NSCLC – Non-small cell lung carcinoma, CML – Chronic Myelogenous Leukemia, RCC – Renal Cell Carcinoma  
\*p-value less than 0.05 is considered to be statistically significant

**Table 2.** Clinical course of patients with persistent hypothyroidism

	Total (n = 18)	Persistent (n = 10)	Not persistent (n = 8)	P-value*
	Frequency (%); Median (IQR)			
<b>Time to dysfunction (in months)</b>	10 (6 to 16)	10 (2 to 12)	11.5 (7 to 26)	0.264
<b>TSH levels during therapy</b>				
Maximum	11.7 (8.3 to 16.75)	16.75 (12.29 to 22.77)	8.89 (5.61 to 11.45)	0.009
<b>Diagnosis</b>				0.023
Hypothyroidism	14 (77.78)	10 (100)	4 (50)	
Subclinical Hypothyroidism	4 (22.22)	0	4 (50)	
<b>Initial TKI management</b>				1.000
Stopped	16 (88.89)	9 (90)	7 (87.5)	
Maintained	2 (11.11)	1 (10)	1 (12.5)	
<b>Referred to Endocrinologist</b>	12 (66.67)	10 (100)	2 (25)	0.002
<b>LT4 (n=9)</b>				1.000
50-100 ug/day	3 (33.33)	2 (28.57)	1 (50)	
100 ug/day	6 (66.67)	5 (71.43)	1 (50)	
<b>Time to resolution (n=10)</b>	37 (12 to 40)	19 (12 to 26)	39 (24 to 42)	0.237

\*p-value less than 0.05 is considered to be statistically significant



**Table 3.** Binary logistic regression analysis of the clinical profile of TKI-induced thyroid dysfunction\*

Parameters	Crude OR	95% CI	P-value
<b>Cancer</b>			
NSCLC	4.1429	1.3123 to 13.078	0.015
CML	0.1818	0.0365 to 0.9049	0.037
RCC	3.7200	1.0604 to 13.050	0.040
<b>TSH on follow-up</b>	1.4806	0.9954 to 2.2024	0.053
<b>Age</b>	1.0234	0.9798 to 1.0689	0.298
<b>Male</b>	1.7500	0.6158 to 4.9728	0.294
<b>ECOG</b>			
0	(reference)	-	-
1	1.8750	0.5192 to 6.7706	0.337
2	-	-	-
<b>Comorbidities</b>			
Hypertension	2.0000	0.6940 to 5.7641	0.199
Diabetes Mellitus	2.0667	0.5514 to 7.7466	0.282

ECOG – Eastern Cooperative Oncology Group, NSCLC – Non-small cell lung carcinoma, CML – Chronic Myelogenous Leukemia, RCC – Renal Cell Carcinoma, OR – Odds Ratio  
\*p-value less than 0.05 is considered to be statistically significant

None of the patients who developed hyperthyroidism were given anti-thyroid medications. TKIs were temporarily discontinued in all cases of overt hyperthyroidism. The respective median times to recovery of subclinical and overt hyperthyroidism were 17 and 1.5 months.

### Clinical profile of thyroid dysfunction

There was a crude association between cancer and thyroid dysfunction as shown in Table 3. Patients with NSCLC or RCC were more likely to have thyroid dysfunction and CML patients were less likely to have such. No other clinical parameters were significant.

## DISCUSSION

Tyrosine kinase inhibitors may induce thyroid dysfunction, more commonly, hypothyroidism. Overall, our study showed an incident thyroid dysfunction (i.e., hyper- and hypothyroidism) of 40% among the patients with thyroid function monitoring. Incident hypothyroidism occurred more frequently. Similar to previous reports, there were only limited reports of TKI-induced thyrotoxicosis and thyroiditis. In a review of the literature by Amahdieh and Salti, isolated hyperthyroidism occurred only in a small percentage of patients given sunitinib (10%), sorafenib (2.6-5%), and axitinib (16%).<sup>3</sup>

Among the TKIs, 47% of hypothyroidism occurred in pazopanib. Pazopanib is a multi-tyrosine kinase inhibitor, targeting VEGFR 1, 2 and 3, c-kit and PDGF receptor.<sup>3</sup> The median TSH level among this group was 16 uIU/mL with the highest recorded at 44 uIU/mL. The median time to occurrence of pazopanib-induced hypothyroidism was six months. Limited reports are available on the occurrence of thyroid dysfunction with pazopanib. In contrast with the present results, hypothyroidism occurred only in less than ten percent of patients in a randomized phase III trial of pazopanib.<sup>8</sup> In a study of 578 patients who received pazopanib from three trials, the incidence of overt hypothyroidism was 6%.<sup>3,9</sup>

Overt hypothyroidism also occurred with osimertinib and gefitinib. Both were not among the TKIs known to develop hypothyroidism in the study by Amahdieh and Salti.<sup>3</sup> Osimertinib is a third-generation TKI recommended as a third- or later-line treatment for NSCLC.<sup>10</sup> It has a great affinity for mutant EGFR and irreversibly binds various intracellular tyrosine kinase domains.<sup>11</sup> In a multicenter study of advanced NSCLC treated with osimertinib, there were no accounts of thyroid dysfunction.<sup>10,11</sup> Gefitinib inhibits numerous tyrosine kinases including EGFR and is extensively studied in NSCLC. In a prospective observational study, gefitinib was among the TKIs that caused a 4% incident hypothyroidism and subclinical hyperthyroidism in NSCLC patients.<sup>12</sup> Gefitinib, likewise, induced overt hypothyroidism and subclinical hyperthyroidism in this present study.

Thyroid dysfunction was most commonly studied among patients given sunitinib and sorafenib. Most studies on the mechanism and clinical course of TKI-induced hypothyroidism were based on sunitinib. The incidence of sunitinib-induced hypothyroidism ranged between 53 and 85%. Less common than sunitinib, the incidence of thyroid dysfunction in patients on sorafenib ranged between 20 and 36%.<sup>3</sup> This present study showed that none of the patients initiated with both TKIs developed thyroid dysfunction. This may be due to the small number of patients who were on these two medications.

While the majority of patients received imatinib, 82% of these patients maintained euthyroidism throughout. Imatinib was shown to increase the dose of thyroid hormone replacement among post-thyroidectomy patients. In the study by de Groot, all advanced medullary thyroid cancer patients who had previous total thyroidectomy had increased hormone requirement while on imatinib while those who had not undergone thyroidectomy remained euthyroid.<sup>13</sup> None of the patients who received imatinib had previous thyroidectomy or RAI which could explain why no overt hypothyroidism was observed despite the large proportion of patients.

Both patients started on bosutinib therapy developed hyperthyroidism. Bosutinib is a dual Src and ABL1 TKI reserved for resistant CML patients.<sup>14</sup> In one study, 88% of patients on bosutinib developed hypothyroidism and none had hyperthyroidism. Notably, hyperthyroidism preceded hypothyroidism in one of these patients.<sup>15</sup>

The main mechanisms of TKI-induced hypothyroidism include the following: (a) drug-induced thyroid atrophy through inhibition of vascularization; (b) drug-induced thyroiditis; (c) reduction in the synthesis of thyroid hormones; and (d) inhibition of thyroid uptake of iodine.<sup>4,16</sup> The TKI-induced hyperthyroidism is probably secondary to the destructive thyroiditis due to the vascular damage which leads to thyroid atrophy and permanent hypothyroidism which shows the need to monitor patients serially for thyroid dysfunction.<sup>2</sup> This continuum was not observed in

any patients who developed hyperthyroidism in our study. The patients who developed subclinical hyperthyroidism subsequently had normal thyroid function tests after repeat TFT after two weeks. However, controlled serial monitoring of TSH was limited by the retrospective nature of the study.

Overall, the median time at risk for overt hypothyroidism from TKI exposure was eight months (4.5 to 12 months) while for subclinical hypothyroidism was 26 months (16 to 36 months). On the other hand, the median time exposure to the development of overt and subclinical hyperthyroidism was 1.5 and 16 months, respectively. This was comparable to a prospective study by Wolter et al. in which the median time to abnormal TSH was 1 month (0.5 to 11 months).<sup>17</sup> After 36 months, no further thyroid dysfunctions were observed. Hence, beyond which, TFT monitoring may be decreased. The longest evidence of euthyroidism was observed in an imatinib-treated patient for 182 months. In the study by Wong et al., among patients on sunitinib, elevated TSH occurred after a median exposure of five months.<sup>18</sup> The median level of TSH rose to 10.58 (14.15 for overt) uIU/mL from 0.85 uIU/mL on the first follow-up. On the other hand, the median TSH level in the hyperthyroid group was 0.21 uIU/mL upon the first follow-up, from a baseline level of 1.27 uIU/mL. The increasing TSH levels on follow-up were associated with lower odds of maintaining euthyroidism. This emphasizes the need for serial TFT.

Initial management was temporary discontinuation of TKIs in 93% of overtly hypothyroid patients. Patients with higher TSH levels were referred to endocrinology (median 14.65 uIU/mL). Among these patients, levothyroxine was initiated in 57% with doses ranging from 50-100 mcg/day. Guidelines would recommend starting treatment if the TSH level is above 10 uIU/mL,<sup>17</sup> similar to the major thyroid societies. Some suggest initiating supportive treatment at a TSH level between 5 and 10 uIU/mL if symptomatic.<sup>2</sup> After achieving biochemical euthyroidism with levothyroxine, TKIs may be resumed. In 88% of patients who had transient hypothyroidism, the average time to recovery was 40 months off TKI without thyroid hormone replacement. All of the patients who had transient hypothyroidism only had subclinical dysfunction. In a similar study, serum TSH levels returned to normal within 60 days after permanently discontinuing sunitinib.<sup>16</sup> However, since the majority of the patients would be maintained on TKI due to advanced cancer, levothyroxine therapy and serial TFT monitoring were continued. In comparison with the study of Mannavola et al., 46% of patients on sunitinib had permanent and 25% had transient hypothyroidism. The class of TKIs used and the time exposure at risk did not differ between transient and persistent hypothyroidism. The study showed that the degree of TSH elevation increased in subsequent treatment cycles.<sup>16</sup>

Patients with solid tumors such as non-small cell lung cancer and renal cell carcinoma had a high incidence of hypothyroidism. In the study of Lechner et al., of 538 patients, those who developed hypothyroidism had higher

odds of being female. Similarly, a greater number of TKI received was not associated with thyroid dysfunction.<sup>7</sup> In contrast, there were no significant differences found among all the groups and age, ECOG status and cancer stage in our study. The patients who had prior thyroid dysfunction had worsening of their thyroid dysfunction.

In Southeast Asia, a recent study in Thailand was published regarding thyroid dysfunctions among cancer patients who received targeted therapies. Incident thyroid dysfunction with TKI was 14.6% with subclinical hypothyroidism being the most common.<sup>19</sup>

It has been previously recommended to check for TSH levels at each cycle more importantly on the first four cycles<sup>3</sup> and, if with normal results, may be done every three cycles. With our findings, we similarly recommend baseline TSH determination and prior to each treatment cycle. Our present study showed less likelihood of occurrence of thyroid dysfunction beyond 36 months, therefore, monitoring may be decreased thereafter. Observation of patients with subclinical hypothyroidism without thyroid hormone therapy should be done serially as recovery was observed to occur at 40 months. Treatment with levothyroxine should be initiated whenever TSH levels exceed 10 uIU/mL.<sup>3,4,9</sup> Referral to endocrinology should be done among patients with higher TSH levels and in whom levothyroxine replacement should be deemed necessary. Once euthyroidism is achieved with thyroid hormone therapy, TKIs may be resumed and TSH should be serially monitored.

## CONCLUSION

Thyroid dysfunction is common among TKI-treated non-thyroidal cancer patients occurring more frequently among NSCLC and RCC. In this study, hypothyroidism is the most common TKI-induced thyroid dysfunction. Serial monitoring of thyroid function is important during TKI therapy.

## Limitations

The study has potential limitations. First is the small sample size due to the single-center nature of the study which could affect its applicability in the general population. Analysis for identification of possible associated risk factors for thyroid dysfunction was not made due to the limited sample size. Secondly, thyroid function testing and monitoring were non-uniform and non-standardized owing to the retrospective design of the study. With this study design, the time in months to first follow-up varied among the patients and the time exposures to TKI were based on the timing of repeat TSH determination. We recommend a prospective design to obtain baseline thyroid function testing and controlled serial follow-up determinations in relation to the treatment cycles. A prospective study design could also eliminate possible selection bias brought about by symptom-triggered TSH determinations. Furthermore,

we recommend a larger sample size to confirm the possible association between cancer and thyroid dysfunction and identify other associated risk factors. Lastly, we recommend a multi-center study to increase the generalizability of the study.

#### Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

#### CRedit Author Statement

**NAL:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **JQ:** Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration, Funding acquisition; **EM:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Funding acquisition; **SK:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Funding acquisition; **PC:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Supervision, Funding acquisition.

#### Author Disclosure

The authors declared no conflict of interest.

#### Data Availability Statement

Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

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None.

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