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Clinical Research Article

Significance of Thyroglobulin Autoantibodies in Patients With Thyroid Cancer Treated With Lenvatinib

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Abstract

Context: Serum thyroglobulin (Tg) is a highly sensitive and specific tumor marker, employed in post-operative management of patients with differentiated thyroid carcinomas. Tumor shrinkage of radioiodine-refractory thyroid cancer (RAIR-DTC) treated with multitarget kinase inhibitors as lenvatinib, expressed according to the Response Evaluation Criteria in Solid Tumors (RECIST), is also associated with a drastic reduction of Tg levels. However, interference caused by circulating thyroglobulin autoantibodies (TgAb) represents the main limitation in the clinical use of Tg.

Objective: To evaluate if in RAIR-DTC TgAb could be considered a surrogate marker of Tg in monitoring response to treatment with lenvatinib.

Design: We retrospectively evaluated patients who had started lenvatinib and correlated serum Tg and TgAb with the radiological response across visits.

Setting: University of Pisa, Italy.

Patients: We selected 9/97 RAIR-DTC patients with detectable TgAb.

Intervention: None.

Main Outcome Measure(s): None.

Results: Tg values correlated neither with TgAb title nor with radiological response across visits. Greater decreases in TgAb titer correlated with favorable radiological response to lenvatinib after 1 month (Spearman's correlation = 0.74, $P = .021$) and 6 months (correlation = 0.61, $P = .079$). According to RECIST, patients with partial response showed a ~10-fold greater decrease in TgAb compared to those with stable disease at 1 month (median TgAb decrease: −142 vs −14 IU/mL, $P = .01$) and those with progressive disease at 6 months (median TgAb decrease: −264 vs−24 IU/mL, $P = .04$).

Conclusion: TgAb evaluation may represent a reliable surrogate marker for Tg trend in evaluating response of RAIR-DTC to treatment with lenvatinib. A multicentric study would be useful to confirm our results.

Key Words: differentiated thyroid carcinoma, radioiodine-refractory differentiated thyroid cancer, thyroglobulin autoantibodies, lenvatinib

Serum thyroglobulin (Tg) is a highly sensitive and specific tumor marker employed in the post-operative management of patients with differentiated thyroid carcinomas (DTC) [1]. There is a close correlation between Tg levels and tumor burden before and after TSH stimulation [2, 3]. After total thyroid ablation for DTC, detectable values of Tg are typically associated with the recurrence or persistence of neoplastic disease [4]. Interference caused by circulating thyroglobulin autoantibodies (TgAb) represents the main limitation in the clinical use of Tg measurement, inducing falsely negative or positive results [1, 4, 5]. Indeed, the presence of TgAb makes Tg measurements unreliable because it either underestimates Tg levels when common Tg-immunometric assays are used or overestimates Tg levels when less common Tg-radioimmunoassay methods are employed [6–9]. Indeed, the current guidelines for the management of DTC patients strongly recommend the measurement of TgAb with every measurement of Tg, ideally in the same laboratory and using the same assay [1, 10, 11]. TgAb are detected in approximately 7.5% to 25% of DTC patients [10, 12, 13] and in only 10% of the general population [14]. In patients who are in complete remission after total thyroid ablation and in absence of any further treatment, serum TgAb gradually decline and disappear after a median time of 3 years [13]. Particularly, TgAb decline approximately by 50% in the first 6 month after thyroidectomy (due to the reduction of circulating thyroid antigens and the half-life of pre-existing TgAb) while they increase in the first 6 months after administration of radioactive iodine therapy because of the release of Tg antigens following tissue destruction [15–17]. Persistence, increase, or reappearance of TgAb during follow-up is highly suspicious for recurrence or persistence of thyroid disease [18]. Thus, TgAb

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should be quantitatively assessed when Tg is measured [1, 11, 19]. In patients with DTC refractory to RAI (RAIR-DTC) and treated with new multitarget kinase inhibitors (TKI) such as sorafenib, lenvatinb, and cabozantinib, response to therapy in terms of radiological tumor shrinkage is associated with a drastic reduction in Tg value while the progression of disease correlates with higher Tg levels [20–24]. No data about TgAb trend in these patients are available. The aim of this study was to evaluate if TgAb trend could be useful as a surrogate marker for Tg in monitoring response to TKI therapy for patients affected by RAIR-DTC.

Table 1. Epidemiological and pathological features of study cohort (n = 9)

Cohort Features	
Sex (%)	
Male	3
Female	6
Age at diagnosis (%)	
< 55 years	1
≥ 55 years	8
Beginning of treatment (%)	
< 55 years	0
≥ 55 years	9
Histological Features	
Tumor size (T)	
T1-2	0
T3-4	9
Node	
N0	2
N1	7
Metastasis	
M0	5
M1	4
Site of metastasis	
Nodes	6
Lungs	6
Liver	1
Brain	1
Bones	5
Local recurrence	6
Histological Features of Tumors	
Papillary	
Classic variant	1
Follicular variant	1
Tall cell variant	2
Follicular	2
Poorly differentiated	3
Treatment	
131-I mCi (%)	
< 100	3
≥ 100	5
≥ 300	1
Outcome	
Alive	4
Dead	5

Patients and Methods

Selected Study Group

We carried out a retrospective observational study by analyzing 97 metastatic RAIR-DTC patients since the beginning of therapy with lenvatinib because of progression of the disease, followed at the Endocrine Unit of University of Pisa, Italy, from January 2012 to December 2020. RAIR-DTC were defined according to American Thyroid Association guidelines [1]. In 13 (13.4%) patients, serum TgAb were detectable at the beginning of target therapy with lenvatinib. Of these, we excluded 2 patients because of very high levels of Tg (>5.000 ng/mL) and 2 because they had been previously treated with other additional systemic therapies (other kinase inhibitors than lenvatinib like sorafenib or conventional chemotherapy such as carboplatin plus epirubicin). Of the 9 selected patients, we evaluated the biochemical and the radiological response to lenvatinib therapy across visits. General features of our cohort are reported in Table 1. All patients, as per our hospital policy, signed an informed consent for the use of their clinical and biochemical data for research purposes. The study has been approved by the local ethical committee.

Biochemical Measurement

Serum Tg was measured with a highly sensitive chemiluminescent assay (Beckman Coulter, Fullerton, CA, USA) with a functional sensitivity of 0.1 ng/mL. Quantitative determination of TgAb in human serum was performed by immunofluorometric assay using the 2-step immune-enzymometric assay AIA-PACK Tg-Ab system and the TOSOH AIA System Analyzers (Tosoh Biosciences, catalog no. 0020291, RRID:AB_2920885) (normal range: 0-30 U/mL). Due to the potential interference with serum Tg determination, we have considered negative patients with a TgAb title lower than 8 U/mL, which was demonstrated to not interfere with Tg measurement [25].

Radiological Evaluation

Patients underwent whole-body computerized tomography (CT) scan with contrast medium at the baseline and 1 and 6 months from the beginning of the systemic therapy with lenvatinib. All CT studies were performed using multidetector equipment (Revolution Evo GE 64 slices, General Electric Medical System, USA), with scans at baseline and after intravenous administration of 120 mL nonionic iodinated contrast material (Iomeron 400, Bracco, Milan, Italy) at a varying flow rate from to 3 to 4 mL/sec. The scan protocol was: 2.5 mm slice thickness; 2.5 mm reconstruction, 0.7 second rotation time, 100 KVp, and sampling field of view (20 cm) for exploration of neck and mediastinum. All native axial images were transferred to a dedicated workstation (Advantage Windows 7.0, General Electric Medical System) where multiplanar reconstruction studies were performed. A single thyroid cancer expert radiologist (P.R.) analyzed all CT scan imaging, and the radiological therapeutic response during the follow-up was expressed according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [26] (1) stable disease (SD); (2) partial response (PR); (3) complete response; (4) progressive disease (PD). Moreover, for the statistical analysis, radiological response was also expressed as the variation (reduction or increase) of the sum of the target lesions diameter compared to baseline imaging.

Statistical Analysis

Statistical data analyses were performed using SPSS (Version 22.0., IBM Corp., Armonk, NY, USA). Data are presented as median with interquartile range. The Friedman non-parametric test was used to evaluate within-patient changes in TgAb, Tg, and target lesions diameter across visits. The Spearman's index was used to quantify correlation among changes TgAb, Tg, lenvatinib dosage, and target lesions diameter at each follow-up visit compared to baseline. The Mann-Whitney U test was used to evaluate differences in TgAb and Tg changes at each follow-up visit between patients with a PR and those with SD/PD according to RECIST 1.1. Due to the relatively small sample size, a P-value $\leq .10$ was considered statistically significant.

Results

Tg and TgAb Evaluation

Among the 9 patients under investigations, Tg was negative in 4 (44.4%) and Tg median values were 2.11 mcg/L (range 0.00-4608.00 mcg/L) at baseline, 1.63 mcg/L (range 0.00-1292.00 mcg/L) at 1 month, and 1.69 mcg/L (range 0-782.67 mcg/L) at 6 months of follow-up. Overall, there was no change in Tg across visits ($P = .12$). TgAb median values were 196 IU/mL (range 36-1059 IU/mL) at baseline, 146 IU/mL (range 22-709 IU/mL) at 1 month, and 39 IU/mL (range 12-352 IU/mL) at 6 months, indicating a substantial reduction in TgAb across visits ($P < .001$). No significant correlations between serum Tg and TgAb levels were found at any visit ($P = .32$ at 1 month; $P = .86$ at 6 months).

Radiological Evaluation

According to RECIST 1.1, all patients were in PD at the beginning of treatment with TKI. Median diameter of target lesions was 103 mm (range 44-123 mm) at baseline. Of the 9 selected patients, 5 (55.6%) had a PR and 4 (44.4%) a SD, and no one had new lesions at 1 month of follow-up; median diameter of target lesions was 75 mm (range 28-133 mm). At 6 months, 7 (77.8%) patients had a PR and 2 (22.2%) had PD, and no one had new lesions; median diameter of target lesions was 68 mm (range 22-225 mm). Two PD patients, at 6 months, had a limited radiological response to lenvatinib at 1 month (SD according to RECIST 1.1). Overall, there was a reduction in target lesions diameter across visits ($P = .03$).

Correlation of Tg and TgAb Levels With Radiological Response to Lenvatinib

Variation of serum Tg did not correlate with concomitant radiological response either at 1 month ($P = .74$) or at 6 months ($P = .31$) of follow-up. On the other hand, significant correlations between variation of TgAb titers and modification of diameter of target lesions were observed during therapy with lenvatinib, such that greater decreases in TgAb levels correlated with favorable radiological response to lenvatinib after 1 month (Spearman's correlation = 0.74, $P = .021$) and 6 months (correlation = 0.61, $P = .079$) (Fig. 1) At variance, we did not find any correlation between change in TgAb levels and the worsening of the disease in the 2 cases showing PD at 6 months (Fig. 2). According to RECIST 1.1, patients with PR showed a ~10-fold greater decrease in TgAb levels compared to those with SD at 1 month (median TgAb decrease: −142.0 vs −14.0 IU/mL, respectively, $P = .01$) (Fig 3A) and those with PD at 6 months (median TgAb decrease: −264.0 vs −24.0 IU/mL, respectively, $P = .04$) (Fig 3B) while Tg levels did not changes both at 1 and 6 months ($P > .45$).

Discussion

Progression rate of RAIR-DTC can be suspected by the doubling time of serum Tg and confirmed by total-body CT scan [27, 28]. However, Tg measurement is not useful in patients with detectable TgAb because they affect the reliability of Tg values. In these cases, surveillance is usually performed only through morphofunctional imaging every 3 to 6 months at the beginning and, in absence of documented progression, at an interval of 6 to 12 months [28, 29]. Radiological interpretation is made according to RECIST 1.1 based on the assessment of target lesions diameter and the development of new metastatic disease or local recurrence [26]. Although we analyzed a selected group of patients with thyroid cancer (ie, advanced and RAIR-DTC treated with lenvatinib), the percentage of cases with detectable TgAb levels was similar to that reported in larger and unselected series [10, 12, 13]. This result might indicate that the presence/absence of circulating TgAb, likely expression of a concomitant thyroiditis, does not predict the possibility that the disease will become radiorefractory and progressive. Tg levels were extremely variable and correlated with neither TgAb titer nor radiological response of RAIR-DTC to therapy. This result could be due to the interference of immunometric assays currently used for TgAb and the low or absent ability to produce Tg by dedifferentiated tumors [29–31]. Conversely, in our patients, both TgAb levels and radiological variation of target lesions diameter in response to lenvatinib significantly declined over time. Moreover, we observed a direct correlation between TgAb decrease and a radiological reduction of target lesions during the follow-up. Particularly when we considered the tumoral response to lenvatinib according to RECIST, TgAb titer drastically and significantly declined in patients with PR and SD. A similar finding has been also found in DTC treated with total thyroidectomy plus/minus radioiodine therapy, in agreement with the concept that TgAb could be considered a Tg surrogate [9, 13, 32–35]- These results are in line with the concept that persistent antibody production is dependent on antigen exposure [36, 37], thus tumor shrinkage might reduce the immune stimulus causing a reduction in TgAb production.

Although a reduction of serum TgAb was also observed in the 2 PD patients, the variation across time of TgAb levels was significantly lower in PD than in PR patients (around 10-fold lower). This finding is in favor of a greater role of the percentage of TgAb reduction (ie, >50% in 6 months) in predicting a good response to therapy. Although Kim et al already reported that a TgAb reduction >50% could be considered a good prognostic factor in the management of thyroid cancer patients [18], so far no data have been reported regarding RAIR-DTC patients under lenvatinib. Several limitations of this study should be considered. First, retrospective data evaluation was associated with an unavoidable selection bias and a limited clinical observation over time. Second, the sample size was too small to obtain a statistical cut-off of TgAb variation over time that could be clinically useful to differentiate PD from PR patients. Although our cohort of patients treated with lenvatinib is one of the largest reported

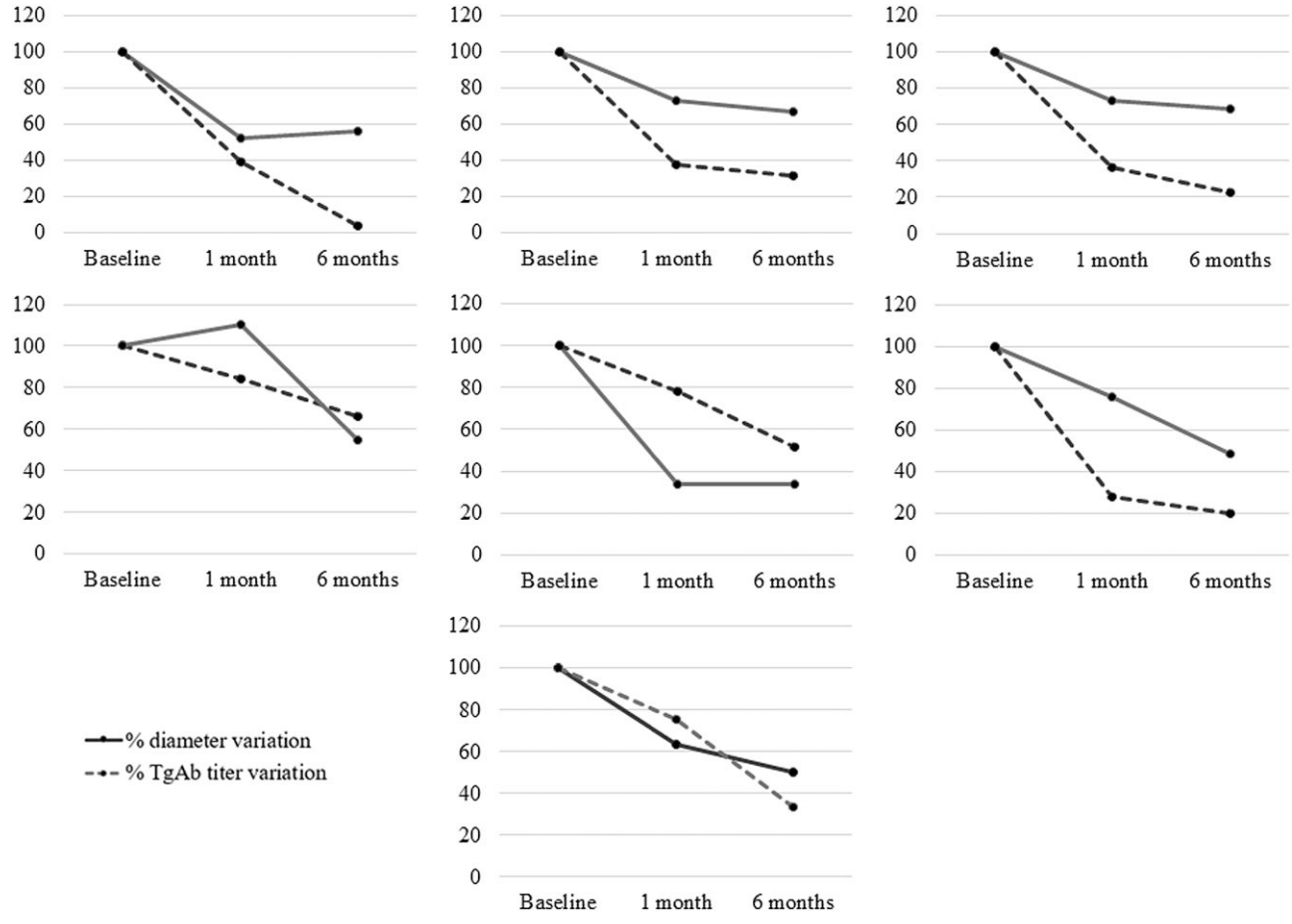

Figure 1. Modifications over time of TgAb titer (continuous line) and of the target lesions diameter (dashed line) both expressed as percentage variation of 7 patients who showed a partial response after 6 months of therapy with lenvatinib.
Abbreviations: TgAb, thyroglobulin autoantibodies.

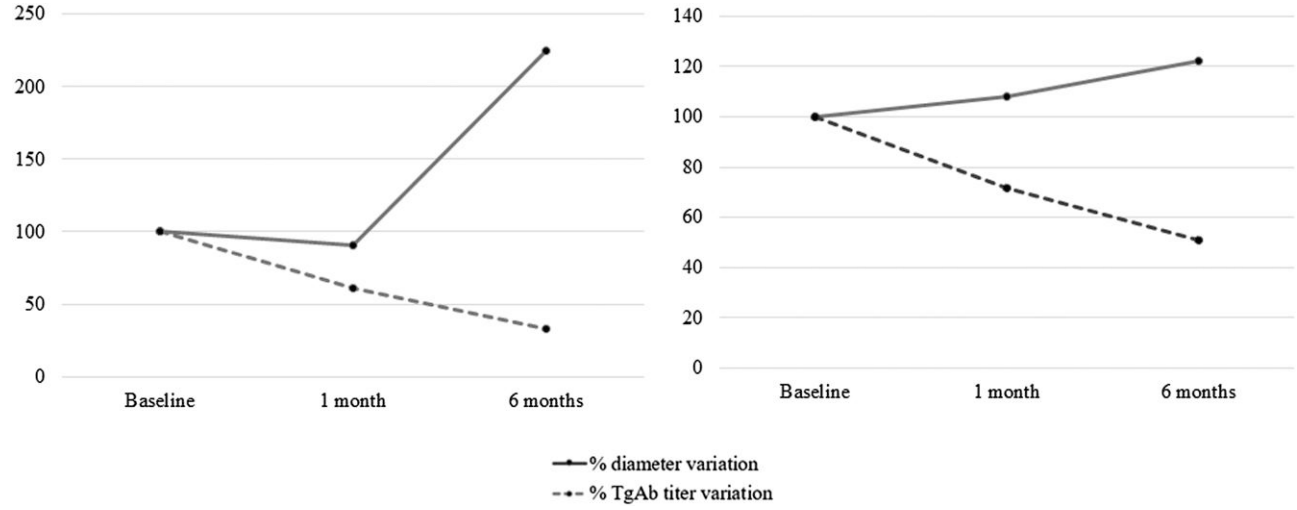

Figure 2. Modifications over time of TgAb titer (continuous line) and of the target lesions diameter (dashed line) both expressed as percentage variation of 2 patients who showed a progressive disease after 6 months of therapy with lenvatinib.
Abbreviations: TgAb, thyroglobulin autoantibodies.

so far, only a few of them had positive TgAb, consistent with the percentage of DTC TgAb positive patients. For this reason, only a multicentric study might overcome this limit.

Finally, this study did not evaluate TgAb variations in patients treated with other systemic therapies, and we cannot say if this is a specific response to lenvatinib or, more likely,

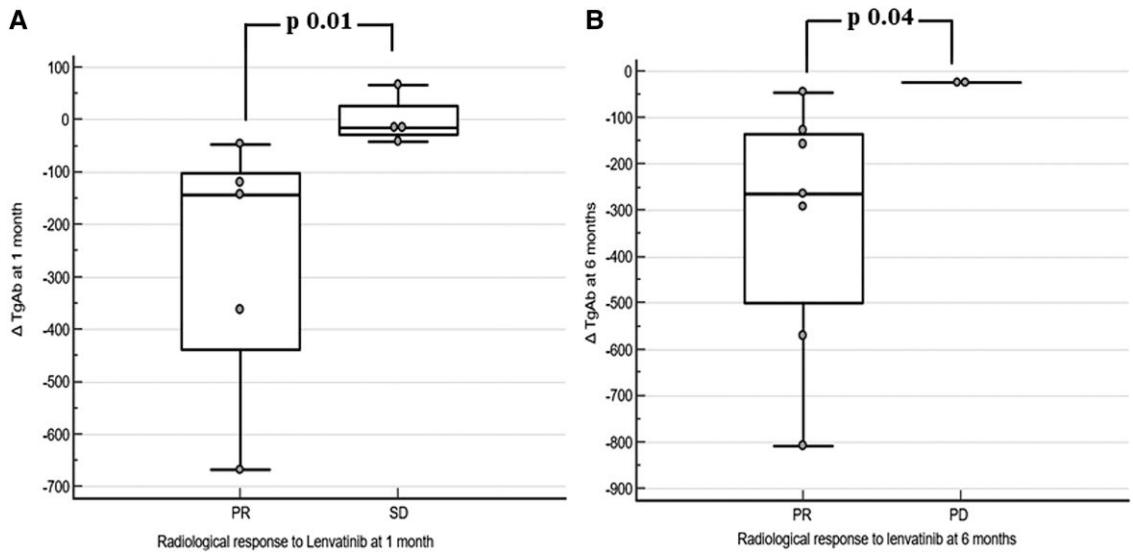

Figure 3. Variations of serum TgAb in patients with advanced and progressive RAIR-DTC during the treatment with lenvatinib. (A) Patients with PR showed a ~10-fold greater decrease in TgAb titer compared to those with SD after 1 month of therapy; (B) patients with PR showed a ~10-fold greater decrease in TgAb titer compared to those with PD after 6 months of therapy.
Abbreviations: PD, progressive disease; PR, partial response; RAIR-DTC, radioiodine-refractory thyroid cancer; SD, stable disease; TgAb, thyroglobulin autoantibodies.

a more general behavior due to the reduction of the tumoral burden.

In conclusion, when serum Tg values cannot be reliably interpreted because of the presence of TgAb, the measurement of the latter during follow-up may represent a useful additional tool in evaluating the response of RAIR-DTC to treatment with lenvatinib. To our knowledge, this is the first study demonstrating that TgAb can be used as a Tg surrogate marker also in these patients during lenvatinib treatment. A multicentric study investigating a large cohort of patients with RAIR-DTC TgAb positive would be useful to confirm our results.

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Author Contributions

D.S., L.A., and R.E. planned the study. D.S., L.A., F.L. P.R., and R.E wrote the manuscript. P.P. performed the statistical analysis. All authors discussed the results of the study.

Disclosures

The authors declare no potential conflicts of interest.

Data Availability

Data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

Authorship Criteria

The work submitted is original and has not been published other than as an abstract or preprint in any language or format and has not been submitted elsewhere for print or electronic publication consideration.

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