Stimulated thyroglobulin level at ablation in differentiated thyroid cancer: the impact of treatment preparation modalities and tumor burden

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Abstract

Objective: In patients with differentiated thyroid cancer (DTC), the stimulated serum thyroglobulin (Tg) level at radioiodine ablation is a known predictive factor of persistent disease. This prognostic value is based on data obtained after thyroid hormone withdrawal (THW), but little is known about this prognostic value after recombinant human TSH (rhTSH) stimulation and about the relationship between the stimulated Tg level and the burden of persistent tumor. We aimed to assess the impact of both radioiodine preparation modalities and persistent tumor burden on stimulated Tg levels.

Design and methods: The stimulated Tg level was measured at radioablation in 308 consecutive DTC patients without serum Tg antibodies. Of these, 123 (40%) were prepared with rhTSH and 185 with THW. Post-ablation scintigraphy included total-body scan and neck and thorax single photon emission computed tomography with computed tomography (SPECT-CT). During a mean follow-up of 43 months, persistent/recurrent disease (PRD) was found in 56 patients (18%). PRD was considered structural in the presence of lesions > 1 cm and nonstructural otherwise.

Results: Nonstructural PRD was more frequent in the rhTSH group than in the THW group (64 vs 26%, $P=0.01$). Stimulated Tg levels were lower after rhTSH than after THW in patients with (13.5 vs 99.5 ng/ml, $P<0.01$) and without (1.2 vs 3.2 ng/ml, $P<0.001$) PRD. Also, Tg levels were lower in nonstructural disease than in structural disease in both rhTSH (3.8 vs 127.0 ng/ml, $P<0.01$) and THW (13.0 vs 143.5 ng/ml, $P<0.0001$) patients. The best Tg cutoff to predict PRD was 2.8 in rhTSH and 28 ng/ml in THW patients.

Conclusion: Both radioiodine preparation modalities and the burden of persistent tumor affect the stimulated Tg level at ablation.

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Introduction

In patients with differentiated thyroid cancer (DTC), the stimulated serum thyroglobulin (Tg) level measured at radioiodine ablation has a good prognostic value for persistent/recurrent disease (PRD). A low Tg level has a high negative predictive value (NPV) (1), whereas a high Tg level is frequently associated with persistent disease (2, 3). Several factors including the thyroid-stimulating

hormone (TSH) stimulation modalities (4), the burden of residual tumor disease, and the volume of the thyroid remnants potentially influence the stimulated serum Tg level. Stimulated Tg level cutoffs have been mainly established after thyroid hormone withdrawal (THW) (2, 5), whereas data on stimulated Tg level after recombinant human TSH (rhTSH) stimulation are very limited (6).

As rhTSH has recently emerged as the most widely used method for radioiodine ablation preparation, especially in low-risk patients (7, 8), there is a need to assess the Tg response after rhTSH and to compare it with that obtained after THW. The production of Tg by well-differentiated tumor cells generally correlates with the tumor burden. Little is known, however, about the influence of the volume of residual disease on the stimulated Tg-level after rhTSH or THW preparation.

We aimed to assess the impact of both radioiodine preparation modalities and persistent tumor burden on stimulated Tg levels and to correlate these data with patients' outcomes.

Materials and methods

Patients

The records of 363 consecutive patients with DTC who were referred to our institution for radioiodine ablation between January 2006 and January 2012 were reviewed. Fifty-five patients (15%) with Tg antibodies (TgAb) were excluded from the data analysis. The study group thus included 308 patients.

Radioiodine ablation and preparation modalities

Radioiodine ablation was administered after either THW or rhTSH. In patients who were given levothyroxine (L-T₄) after surgery, THW consisted of stopping L-T₄ 35 days before the radioiodine treatment and replacing it with levotriiodothyronine (L-T₃) during the first 23 days. In patients who were given L-T₃ after surgery, L-T₃ was withdrawn 12 days before the radioiodine treatment. The rhTSH stimulation consisted of two i.m. injections of 0.9 mg of rhTSH (Thyrogen, Genzyme Corp., Cambridge, MA, USA), one on each of the 2 days before the radioiodine treatment. In all patients, the TSH level was above 30 mUI/l on the day of radioiodine treatment. The radioiodine activity (1.1 or 3.7 GBq) and the preparation modalities were determined at the local multidisciplinary thyroid meeting, except for the 42 low-risk patients enrolled in the ESTIMABL trial (7). A post-ablation ¹³¹I total-body scan with neck and thorax SPECT-CT was performed 2 or 5 days following 1.1 or 3.7 GBq, respectively, as previously described (9).

Tg assay

For stimulated serum Tg measurements, blood samples were collected immediately before the radioiodine

treatment and stored at −20 °C. For the purpose of this study, all serum Tg levels were measured using Roche Cobas 6000 Tg (Roche Diagnostics) with a lower detection limit of 0.1 ng/ml and a functional sensitivity of 1.0 ng/ml.

Definition of PRD

PRD was defined as evidence of tumor in the thyroid bed, lymph-node metastases, or distant metastases after completion of the initial treatment (surgery and radioiodine ablation), that is from ablation to last follow-up visit. Confirmation was obtained either by histology or by complementary imaging modalities and follow-up. Otherwise, patients were considered disease free.

In an attempt to assess the tumor burden, PRD was classified into two categories, that is structural or non-structural lesions. Structural disease was defined by large (>1 cm) lesions, clearly evidenced by conventional radiology, disregarding the presence or absence of scintigraphic abnormalities. Conversely, nonstructural disease was defined either by the presence of clearly abnormal foci on post-ablative radioiodine scintigraphy or identified on 18-Fluorodeoxyglucose- positron emission tomography (FDG-PET) scan without obvious lesions on conventional modalities (neck ultrasound (US), CT scan, and magnetic resonance imaging), or small-volume (<1 cm) radiological lesions, whatever their scintigraphic profile.

Clinical outcome assessment

As previously described (9), patients with a normal post-ablation ¹³¹I scan were observed at 3 months by serum TSH, Tg, and TgAb assays on L-T₄ treatment. When the Tg level was <1 ng/ml in the absence of TgAb, the disease status was assessed at 9 months by serum rhTSH-stimulated Tg assay and neck US. When the evaluation at 9 months was normal (i.e. stimulated-Tg level ≤1 ng/ml and normal US), patients were followed up on an annual basis. Otherwise, imaging modalities such as CT of the neck and thorax or FDG-PET scan were performed.

Statistical analysis

Patients' characteristics were compared using Fisher's exact test, the Wilcoxon's test, or the Kruskal-Wallis test, as appropriate. Sensitivity, specificity, positive predictive value (PPV), and NPV are presented with exact CIs. Statistical significance was defined as *P*<0.05. All tests were two-sided. SAS 9.3 Statistical Software (SAS Institute, Inc., Cary, NC, USA) was used to analyze the data.

Table 1 Characteristics of patients.

	rhTSH (n=123)	THW (n=185)	P value
Women	102 (83%)	124 (67%)	<0.01
Age (years)	51 ± 16	49 ± 18	0.12
TNM classification, 7th edn			
T status			<0.0001
T1a+T1b	44+38 (66%)	30+41 (38%)	
T2	25 (21%)	61 (33%)	
T3	15 (12%)	47 (26%)	
T4a	1 (1%)	6 (3%)	
N status			<0.0001
Nx	75 (61%)	71 (38%)	
N0	35 (28%)	46 (25%)	
N1a+N1b	11+2 (11%)	36+32 (37%)	
M status ^a			0.02
M0	119 (97%)	166 (90%)	
M1	4 (3%)	19 (10%)	
Pathology			0.03
PTC	112 (90%)	154 (83%)	
FTC	11 (10%)	23 (13%)	
PDTC	0	8 (4%)	

PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; PDTC, poorly differentiated thyroid cancer.

^aM status determined after post-ablation radioiodine scintigraphy.

Results

Characteristics of patients

Patients' characteristics are summarized in Table 1. The study group included 266 papillary thyroid cancers, 34 follicular thyroid cancers, and eight poorly DTC. There were 226 women (73%) and 82 men. The mean age was 50 ± 17 years.

For radioiodine ablation, 123 patients (40%) were prepared with rhTSH and 185 patients (60%) with THW. The rhTSH group included a higher proportion of T1 tumors (66 vs 38%, $P<0.0001$), a lower proportion of N1 patients (11 vs 37%, $P<0.0001$), and a lower proportion of M1 patients (3 vs 10%, $P=0.02$). The rhTSH and THW groups also differed for sex ($P<0.01$) and pathology ($P=0.03$) (Table 1).

The mean follow-up period was 43 months. PRD was found in 56 patients, including 29 with nodal disease, 16 with distant metastases (lung, 10; bone, 4; and both, 2), six with both nodal and distant metastases, and five with residual tumor in the thyroid bed (including one with lung and one with bone metastases). Of these 56 patients, 42 had been prepared using THW and 14 using rhTSH stimulation. Twenty of the 56 patients with PRD were considered to have nonstructural lesions and 36 to have structural lesions. Nonstructural PRD was more frequent in the rhTSH group than in the THW group (nine out of 14, 64% vs 11 out of 42, 26%, $P=0.01$).

Stimulated serum Tg values at ablation

The median stimulated Tg value was lower after rhTSH than after THW in patients who remained disease free (1.2 (0.1–209) vs 3.2 (0.1–88) ng/ml, $P<0.001$) and in those who presented PRD (13.5 (1.1–439) vs 99.5 (6.3–58 690) ng/ml, $P<0.01$).

The stimulated Tg value at ablation was also lower in patients without PRD than in patients with nonstructural disease in both the rhTSH group (1.2 (0.1–209) vs 3.8 (1.1–55) ng/ml, $P<0.03$) and the THW group (3.2 (0.1–88) vs 13.0 (6.3–117) ng/ml, $P=0.0001$). Moreover, the stimulated Tg value was lower in patients with nonstructural than structural PRD after both rhTSH (3.8 (1.1–55) vs 127.0 (31–439) ng/ml, $P<0.01$) and THW (13.0 (6.3–117) vs 143.5 (16.1–58 690) ng/ml, $P<0.0001$) (Fig. 1).

In the group of patients with nonstructural PRD, stimulated Tg levels were lower in rhTSH patients than that in THW patients (3.8 (1.1–55) vs 13.0 (6.3–117) ng/ml, $P<0.03$; Fig. 1). No such statistical difference was observed in the structural group (127.0 (31–439) vs 143.5 (16.1–58 690) ng/ml, $P=0.31$).

Receiver operating characteristics analysis

In the THW patients, the receiver operating characteristics (ROC) study showed that the optimal cutoff for the

Figure 1

Stimulated serum thyroglobulin (Tg) levels at ablation according to tumor burden (nonstructural or structural persistent/recurrent disease) and preparation modality (rhTSH stimulation or thyroid hormone withdrawal (THW)).

stimulated serum Tg level to predict PRD was 28 ng/ml. This cutoff yielded sensitivity of 83% (95% CI, 68–93%), specificity of 94% (95% CI, 88–97%), PPV of 80% (95% CI, 65–91%), and NPV of 95% (95% CI, 90–98%). Similarly, the optimal cutoff in the rhTSH patients was found to be ten times lower at 2.8 ng/ml with sensitivity of 86% (95% CI, 57–98%), specificity of 64% (95% CI, 55–73%), PPV of 24% (95% CI, 13–37%), and NPV of 97% (95% CI, 90–100%).

Discussion

The present data show the impact of both the treatment preparation modalities and the tumor burden on the stimulated serum Tg level measured at radioiodine ablation. These results were obtained in 308 consecutive nonselected DTC patients using the same Tg assay, all of whom had been treated in the same way with surgery and radioiodine ablation, and all of whom had undergone sensitive post-ablation scintigraphy combining total-body scan and neck and thorax SPECT–CT.

In France, rhTSH has been commercially available for radioablation since 2005, first with authorization limited to low-risk DTC patients, and since 2010, to all DTC patients except those with known distant metastases. Therefore, most radioiodine treatments are now administered after rhTSH and the assessment of stimulated Tg after this preparation has become mandatory. Until now, studies on the stimulated serum Tg level at ablation have been performed almost exclusively in patients prepared with THW (2, 3, 5, 10, 11, 12). We found lower stimulated Tg levels in patients prepared with rhTSH than in those prepared with THW (4). There were few data regarding stimulated Tg levels in the two recent randomized trials that compared low- and high-dose radioiodine after THW or rhTSH (7, 8). In the ESTIMABL study, which included low-risk patients of whom more than 90% achieved complete ablation, the proportion of patients with a Tg level ≤ 1 ng/ml was higher in patients prepared with rhTSH (59%) than in those prepared with THW (38%) (7). Such a difference was not reported in the HILO trial, in which the proportion of patients with a Tg level < 2 ng/ml was 25% in both the rhTSH and THW groups (8). Nevertheless, specific data on stimulated Tg levels in patients who showed or did not show PRD were not reported in either study.

Several factors may account for lower stimulated Tg levels in patients prepared with rhTSH than in those prepared with THW. First, rhTSH stimulates less Tg production than does THW (4). This was demonstrated

in the patients of our study who never showed PRD and in whom the Tg level was exclusively related to normal thyroid remnants. Second, stimulated Tg was measured 2 days after the first rhTSH injection, immediately before the radioiodine treatment, thus resulting in lower Tg values than those expected at 4 days (13, 14). The main advantage of assessing rhTSH-stimulated Tg before radioiodine ablation is to overcome the serum Tg increase due to the effects of radiation on thyroid remnants (15). Third, the present data strongly suggest that the stimulated Tg level is related to the burden of PRD. Indeed, we consistently found lower Tg values in nonstructural (microscopic) than that in structural (macroscopic) residual disease, whatever the radioiodine preparation modality used. The lower stimulated Tg value in the rhTSH group than that in the THW group was also related to a higher proportion of nonstructural PRD in the rhTSH subgroup, which was probably the consequence of a selection bias due to regulations concerning the use of rhTSH between 2006 and 2012. Patients prepared with rhTSH had better prognostic characteristics than those prepared with THW. A correlation between tumor burden and stimulated Tg levels after THW had already been reported in patients with lymph node disease (16).

In previous studies, reported Tg cutoffs for predicting PRD after THW were highly variable, ranging from 10 to 58 ng/ml depending on the Tg assay used, on the TNM status of the patients studied, on the methods used to determine the Tg threshold (ROC analysis or selection of an empirical cutoff), and on the methods used to detect PRD. We found a Tg cutoff of 28 ng/ml in the THW group and a ten times lower Tg cutoff of 2.8 ng/ml in the rhTSH group. In a recent meta-analysis involving 3947 patients, Webb *et al.* (1) found that a 10 ng/ml cutoff after THW was associated with the optimal sensitivity and specificity. If the 10 ng/ml cutoff had been applied in the patients of our series, it would have yielded high sensitivity (90%) in the THW group but poor sensitivity (57%) in the rhTSH group. Recently, Melo *et al.* (6) have reported a Tg cutoff at 7.2 ng/ml after rhTSH, a higher threshold than ours (2.8 ng/ml), which would also have provided low sensitivity (57%) in our rhTSH patients. Several explanations are possible. First, the Tg level was measured 3 days after radioiodine treatment in the study by Melo *et al.* (6) and before treatment in ours. Second, the group of patients prepared with rhTSH was at a higher risk of PRD in the study by Melo *et al.* (6) than in ours, with a higher proportion of T3/T4 tumors (44 vs 13%) and of N1 patients (21 vs 11%). Finally, our patients systematically underwent neck and thorax SPECT/CT in addition to total-body

scan. Therefore, nonstructural PRD was more likely to be detected in patients with small (<1 cm) neck lymph nodes and/or microscopic distant metastases as previously shown (3, 9). As the Tg cutoff at 2.8 ng/ml after rhTSH provided a sensitivity of 86%, it means that 14% of patients with PRD had a very low stimulated Tg value (i.e. below 2.8). Previous studies have shown that PRD is very unlikely when stimulated Tg levels (17, 18), or even unstimulated Tg levels using highly sensitive Tg assays (19), are undetectable. In few patients, however, PRD can be observed in the presence of very low Tg levels after rhTSH (1.1 ng/ml in our study). These results are in accordance with previous studies (17, 20) and suggest that the value of stimulated Tg should not be the only factor to select patients for radioablation.

Conclusion

In conclusion, our data clearly showed that the stimulated serum Tg level is related to the burden of persistent/recurrent tumor and highlighted the impact of the radioiodine preparation modality (rhTSH or THW) on the stimulated serum Tg level at ablation. In practice, therefore, the preparation modality used and the tumor burden should be taken into account when interpreting the stimulated Tg level. For a similar tumor burden, the stimulated serum Tg level after rhTSH stimulation should be expected to be lower than that after THW.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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