Recombinant Human Thyroid-Stimulating Hormone-Aided Remnant Ablation Achieves a Response to Treatment Comparable to That with Thyroid Hormone Withdrawal in Patients with Clinically Relevant Lymph Node Metastases

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Key Words

Thyroid cancer · Lymph node metastases · Recombinant human thyroid-stimulating hormone · Thyroid hormone withdrawal · Remnant ablation

Abstract

It has already been shown that remnant ablation in patients with thyroid cancer and lymph node (LN) metastases has similar results when patients are prepared after recombinant human thyroid-stimulating hormone (rhTSH) therapy or thyroid hormone withdrawal (THW). Due to the current changes in the risk-of-recurrence classifications, we decided to evaluate the initial response to treatment and the outcome at medium-term follow-up in 40 consecutive patients with clinically relevant lymph nodes who received radioiodine remnant ablation after rhTSH therapy (n = 20) or THW (n = 20). Each patient received either 100 or 150 mCi ¹³¹I for ablation based on TNM status, and the mean amounts of ¹³¹I used in the 2 groups were not significantly different. An excellent response to treatment was observed in 45% of the patients prepared after rhTSH therapy compared to 20% of those prepared after THW (p = 0.08). Three patients (2 in the THW group and 1 in the rhTSH group) who had N1a

in the initial surgery presented with structural persistence as an initial response to treatment. One patient in the THW group had a follow-up of the persistent disease with no surgical treatment, and 2 others received a lateral LN dissection. When the status at final follow-up was considered (median follow-up 3.3 years, range 3–4.2), 60% of the patients ablated after rhTSH therapy were considered with no evidence of disease, compared to 30% of those who underwent THW. The frequency of structural persistence (metastatic LN) was similar in the 2 groups (15 vs. 25%), and the distribution of the responses at final follow-up was not statistically significantly different (p = 0.12). We conclude that preparation after rhTSH therapy seems to be as effective as after THW for patients with clinically relevant LN metastases.

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Introduction

Remnant ablation is a traditional procedure that is usually performed after total thyroidectomy in patients with differentiated thyroid cancer (DTC) tumors >1 cm

in diameter [1, 2]. Numerous studies have confirmed that administration of radioiodine for remnant ablation after recombinant human thyroid-stimulating hormone (rhTSH) therapy achieves results that are good and by no means inferior to the traditional way of preparing patients, i.e. by thyroid hormone withdrawal (THW) [3–11]. For this reason, most national and society guidelines do not distinguish between rhTSH or THW for the preparation of DTC patients for ablation, except for those with proven distant metastatic disease [2, 12, 13].

Therapy with rhTSH presents less risk of hypothyroid morbidity, improving the quality of life of patients [3, 9, 10, 14–16]. It has also been shown that rhTSH-aided ablation decreases exposure to extrathyroidal radiation [17, 18]. Fewer adverse events are observed in patients ablated after rhTSH therapy [5, 9, 10, 17, 18]. It has been used for the preparation for ablation in intermediate- and high-risk patients with results comparable to those of THW [4, 19, 20]. In 1 study, rhTSH in preparation for thyroid remnant ablation in patients with T4 primary tumors achieved a rate of ablation success that was not inferior to the rate after THW [21]. In a previous publication, we showed that rhTSH stimulation was associated with outcomes that were as good as with THW in high-risk DTC patients [19]. However, what was considered at that time to be a high risk of recurrence has changed in the last 5 years [12, 13]. In a previously published investigation, we included patients with T3 tumors (minimal extrathyroidal extension) classified as having a high risk of recurrence according to our regional guidelines [12]. With the current changes observed worldwide in the classification of the risk of recurrence in patients with DTC, we aimed to recategorize patients according to the new data that appeared after the validation of the American Thyroid Association (ATA) classification in several cohorts of patients [22–25]. According to the analysis of these and other data, patients with low-risk DTC comprise a larger group than previously considered [26]. Several studies have shown that the presence of a T3 tumor with minimal extrathyroidal extension, <5 metastatic lymph nodes (LN) and/or micrometastasis (<2 mm), independently of the number of affected LN, makes for a probability of recurrence not greater than 5–7%, which thus includes this group of patients as being at a low risk of recurrence [26–36].

Therefore, we decided to retrospectively compare the initial response to treatment and the outcome at the medium-term follow-up post-remnant ablation in 40 con-

secutive patients after preparation with rhTSH therapy or THW with only 1 dose of radioiodine, according to this new classification of risk of recurrence.

Subjects and Methods

We retrospectively reviewed a group of 40 consecutive patients from our database who were ablated and followed up in the Hospital de Clínicas, University of Buenos Aires, from January 2009 to January 2014 after preparation with rhTSH or THW. The election of the preparation method was according to the preference of the patients, and according to the reimbursement of the costs of rhTSH therapy by health medical insurances in Argentina. The response to treatment at the final follow-up was evaluated after rhTSH therapy in all but 1 patient.

This cohort initially had a T stage with N1a or N1b (with >5 LN presenting metastatic disease)/M0 staging according to TNM staging (7th ed.) [37]. All these patients were classified as being at an intermediate or high risk of recurrence.

For inclusion, patients had to present a diagnosis of papillary thyroid cancer (PTC), be older than 18 years and have an undetectable level of antithyroglobulin antibodies (TgAb) measured by ultrasensitive assay at the time of ablation. Patients had to be followed up over at least 36 months. M0 status was initially evaluated with chest CT scan in high-risk patients and then confirmed by postablation whole-body scintigraphy (WBS) in all patients.

Treatment and Follow-Up Protocol

All patients received a total thyroidectomy in a specialized center with subsequent radioiodine remnant ablation. The median follow-up in the cohort was 3.3 years (range 3–4.2 years). Baseline characteristics of included patients can be observed in table 1.

LN dissections were performed in all 40 patients. All had confirmed nodal involvement: N1a alone with >5 affected LN in 23 patients and N1a + N1b with >5 affected LN in 18 (table 1).

All patients received remnant ablation. Our traditional ablation protocol uses fixed radioiodine action based on the extent of the initial disease. We administered 3.70 GBq (100 mCi) ¹³¹I-iodine when there was an intermediate risk of recurrence, i.e. when any T (except T4) and N1a or N1b were observed, and 5.55 GBq ¹³¹I-iodine (150 mCi) for high-risk disease according to ATA criteria (patients with T4 and N1). A low-iodine diet was prescribed, from 1 week before radioiodine administration until 2 days afterwards. Within the rhTSH group, 17 patients received 100 mCi and 3 patients received 150 mCi, while within the THW group these patient numbers were 18 and 2, respectively. The mean activities of ¹³¹I given in the two groups were 107.5 mCi for the rhTSH group and 105 mCi for the THW group (p=0.8).

THW and Preparation. THW comprised at least 3 weeks without TH, starting from the thyroidectomy. Following this interval, radioiodine was administered to all cases with TSH levels >50 mIU/L.

rhTSH Therapy and Preparation. rhTSH was given as 2 consecutive 0.9-mg intramuscular injections daily, with the ablative activity applied 24 h after the second injection. The rhTSH was given while patients were euthyroid with suppressed TSH and receiving levothyroxine, except that this hormone was briefly withdrawn (2 days before radioiodine therapy until 2 days afterwards)

Table 1. Baseline characteristics of 40 patients with PTC included in the study

	rhTSH (n = 20)	THW (n = 20)	p
Gender			
Female	90	80	0.66 ^b
Male	10	20	
Age			
<45 years	40	55	0.41 ^a
≥45 years	60	45	
Histology			
Papillary	100	95	0.51 ^b
Hürthle cell	–	5	
Variant of PTC			
Classic	95	80	0.41 ^a
Follicular	5	15	
Tall cell	–	5	
TNM stage			
T1b N1a M0	15	10	0.83 ^a
T1b N1b M0	5	–	
T2 N1a M0	5	–	
T2 N1b M0	15	20	
T3 N1a M0	25	30	
T3 N1b M0	20	30	
T4a N1a M0	15	10	
Lymph nodes			
N1a	60	50	0.88 ^a
N1b	40	50	
Gross extrathyroidal extension	15	10	0.81 ^a

All values are percentages. ^a χ^2 test. ^b Fisher exact test.

to reduce the risk of iodine interference [38]. Radioiodine was administered on day 3. Post-therapy WBS was performed 5–7 days after the therapeutic administration of radioiodine.

No additional doses of radioiodine were administered to any of the patients. After ablation, all patients were kept on a suppressed TSH (target TSH: <0.1 mIU/l) [12].

The primary end point of the study was the best response to the initial therapy (surgery + radioiodine ablation) usually assessed at the follow-up visits in the first 12–18 months (mean 14 ± 3 months) based on stimulated thyroglobulin (Tg) values and neck ultrasound in all patients, diagnostic WBS in 10 subjects and additional risk-appropriate functional and cross-sectional imaging [22–25]. Measurements of Tg levels for assessment of initial response to treatment were performed after rhTSH therapy in all, except 1 patient. An excellent response to therapy was defined as a stimulated Tg <1 ng/ml in the absence of TgAb, with a normal postoperative neck ultrasound scan. Patients demonstrating a Tg level <1 ng/ml and a stimulated Tg value of between 1 and 10 ng/ml with unspecific findings (small LN) were classified as having an indeterminate response to treatment. Patients with a stimulated Tg >10 ng/ml without structural evidence of disease were classified as having a biochemical in-

Table 2. Initial response to treatment and outcome at the end of follow-up in 40 patients with thyroid cancer ablated after rhTSH or THW

	rhTSH (n = 20)	THW (n = 20)	p value
Initial response to treatment, %			
Excellent response	45	20	0.08 ^a
Indeterminate response	40	25	
Biochemical incomplete response	10	45	
Structural incomplete response	5	10	
Outcome at end of follow-up, %			
NED	60	30	0.12 ^a
Indeterminate response	20	30	
Biochemical incomplete response	5	15	
Structural incomplete response	15	25	
Follow-up, months			
Median	38	39	0.67 ^b
Range	36–51	37–49	

^a χ^2 test. ^b Mann-Whitney U test. NED = No evidence of disease.

complete response. Patients with structural evidence of disease (with or without abnormal Tg values) were classified as having a structural incomplete response.

The second end point of the study was a patient's clinical status at the final follow-up [22–25]. Patients were classified as having 'no evidence of disease' (NED) if the suppressed and stimulated Tg levels were <1 ng/ml, TgAb were negative, neck ultrasound scan was free of suspicious signs and no pathological findings were detected on any other imaging studies (performed for clinically indicated reasons, e.g. WBS, radiography, CT, FDG-PET or any other modality) or in any biopsy specimen.

Patients with persistent disease or an indeterminate response at the final follow-up were classified according to the same definitions used in the evaluation of response to initial therapy. Those with structural or biochemical evidence of disease identified following a period of NED were classified as having recurrent disease. Disease sites were classified as local (the thyroid bed), LN (metastasis confirmed by fine-needle aspiration biopsy with positive cytology) and/or distant (metastasis confirmed by biopsy and/or imaging).

Tg/TgAb Measurement

Levels of Tg and TgAb were assessed in a reference laboratory in Argentina using a commercial immunometric assay. The Tg assay comprised the Elecsys Tg electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany), which has a 0.5-ng/ml functional sensitivity. The TgAb assays used were the Elecsys anti-Tg electrochemiluminescence immunoassay (RSR Ltd., Cardiff, UK). A value of >20 IU/ml was considered to be positive and rendered the Tg measurements invalid. All procedures were applied in agreement with the ethical guidelines of our institutions. Written consent was obtained for all subjects.

Table 3. Correlative final outcomes in both groups of patients according to the initial response to treatment

Initial response	Groups	Final outcomes				p value
		NED	indeterminate response	biochemical incomplete response	structural incomplete response	
Excellent response	rhTSH (n = 9)	9	–	–	–	–
	THW (n = 4)	4	–	–	–	
Indeterminate response	rhTSH (n = 8)	2	4	1	1	0.67
	THW (n = 5)	2	3	0	0	
Biochemical incomplete response	rhTSH (n = 2)	1	–	–	1	0.02
	THW (n = 9)	–	3	3	3	
Structural incomplete response	rhTSH (n = 1)	–	–	–	1	0.71
	THW (n = 2)	–	–	–	2	

Table 4. Explanatory variables of the status of patients at the end of follow-up

	Response at the end of follow-up				p
	NED (n = 18)	indeterminate response (n = 10)	biochemical incomplete response (n = 4)	structural incomplete response (n = 8)	
Group, %					
rhTSH	67	40	25	38	0.41 ^a
THW	33	60	75	62	
Gender, %					
Female	89	70	75	100	0.23 ^a
Male	11	30	25	–	
Age, %					
<45 years	28	60	50	75	0.21 ^a
≥45 years	72	40	50	25	
DTC histology, %					
Classic PTC	78	80	100	100	0.71 ^a
Follicular variant PTC	17	10	–	–	
Tall cell PTC	5	–	–	–	
Hürthle cell	–	10	–	–	
Affected LN, %					
N1a	40	60	50	75	0.52 ^a
N1b	60	40	50	25	
Initial response, %					
Excellent response	72	–	–	–	0.0001 ^a
Indeterminate response	22	70	25	12.5	
Biochemical incomplete response	6	30	75	50	
Structural incomplete response	–	–	–	37.5	
Follow-up, months					
Median	42.5	39.6	48	45	0.45 ^b
Range	38–44	37–45	39–52	37–52	

^a χ^2 test. ^b Kruskal-Wallis test.

Fig. 1. Disease-free survival for patients with DTC comparing patients ablated after rhTSH or THW.

Statistical Analysis

Data are expressed as median (range) unless otherwise noted. Categorical comparisons were made using the χ^2 test and the Fisher exact test when appropriate. The Mann-Whitney U test was used to compare the follow-up of patients in the 2 groups (rhTSH/THW). The Kruskal-Wallis test was used to compare the initial response to treatment and clinical status at the time of the final follow-up. Cumulative disease-free survival plots were constructed using the Kaplan-Meier method, and 95% confidence interval (CI) and p value were reported. Analysis was performed using SPSS software (v15.0.0; SPSS, Inc., Chicago, Ill., USA). $p \leq 0.05$ was considered to be statistically significant.

Results

Table 2 provides key data regarding the initial response to treatment and the status at the final follow-up for both groups of patients. An excellent response to treatment was observed in 45% of the patients prepared after rhTSH therapy compared to 20% of those prepared after THW ($p = 0.08$). There were more patients with a biochemical incomplete response in the group ablated after THW (45 vs. 10%). All patients with biochemical persistence had undetectable serum Tg levels under TH suppressive therapy, which became detectable after stimulation with rhTSH.

Three patients (2 in the THW group and 1 in the rhTSH group) who had N1a in the initial surgery presented with a structural incomplete response as their initial response to treatment, diagnosed in the LN in all 3 cases. There were no cases of local or distant metastatic persistent disease. One patient in the THW group had persistent disease with

no surgical treatment at follow-up and 2 patients (1 from each group) received a lateral LN dissection.

When the clinical status at the final follow-up was considered (median follow-up 3.3 years, range 3–4.2 years), 60% of the patients ablated after rhTSH were considered to have NED compared to 30% of those ablated after THW ($p = 0.12$).

According to the initial response to treatment, we evaluated the respective correlative final outcomes in both groups of patients (table 3). All patients with an initial excellent response to treatment ($n = 13$) had NED at the end of follow-up, independent of the methodology used for the preparation of ablation (rhTSH or THW).

The frequency of a structural incomplete response at the final follow-up (metastatic LN) was comparable between the 2 groups (15 vs. 25%); the distribution of the responses was not statistically significantly different ($p = 0.12$; table 3). No patients had biochemical or structural recurrent disease during the long-term follow-up.

Taking a patient's status at the end of follow-up as a dependent variable, we analyzed the explanatory variables of this outcome (table 4). The initial response to treatment, as expected, was the only variable significantly associated with the status at the final follow-up ($p = 0.0001$).

Considering the time between surgery and the diagnosis of structurally persistent disease, the Kaplan-Meier analysis suggested that the probability of a 5-year disease-free survival rate was similar in the 2 groups: 85% (95% CI 64.8–98.2) after rhTSH therapy and 75% (95% CI 61.3–93.7) after THW (fig. 1).

Discussion

This retrospective analysis of DTC patients with clinically relevant LN metastases (without M1) showed that rhTSH therapy was equally effective when the initial response to treatment was considered. Similar medium-term disease outcomes, i.e. the same probability of having NED status and the same frequency of structurally persistent disease, were found at the end of the follow-up.

Our findings confirm those of previous retrospective studies [4, 20, 39, 40], showing the rates of ablation success and disease outcome associated with rhTSH therapy to be statistically similar or even superior to the rates achieved with THW before ablation in DTC patients who had initially had an intermediate or high risk of recurrence.

With regard to the success of ablation, Rosario et al. [4] noted respective rates of 80 and 79% (68 and 67% in pa-

tients with Tg >1 ng/ml at ablation) in the rhTSH (n = 77) and THW subgroups (n = 198) of what we now call a low-risk-of-recurrence cohort (T3/N0–N1, but no T4 patients). Their study can be compared to the one we had already published, i.e. considering T3 with minimal extrathyroidal invasion as a feature of a high risk of recurrence [19]. Several studies have already been published that show the lack of deleterious prognostic value of T3 tumors with a minimal extrathyroidal invasion for PTC [32–36]. So we decided to perform this new analysis including only those patients with any T stage and relevant LN metastasis. It was shown that massive invasion (T4a or T4b) is one of the high-risk factors for disease-free survival in patients aged ≥50 years [41, 42].

Hugo et al. [20] reported respective rates of 16 and 9% for an ‘excellent’ response to initial therapy and 13 and 7% for an ‘acceptable’ response (now called an ‘indeterminate’ response) in their rhTSH (n = 69) and THW subgroups (n = 92) of patients with an initial ATA classification of high risk; these rates did not differ significantly.

Our initial excellent response to treatment was 45% for those patients prepared after rhTSH and 20% for the THW group. Although the response seems to be better after rhTSH-aided ablation, the statistical analysis showed that the distribution of the initial response to treatment was not significantly different between the 2 groups. This situation can probably be related to the number of patients.

After a longer follow-up [median not reported for the initial ATA high-risk patients, but at 9 years for the overall cohort (n = 586)], Hugo et al. [20] noted that the disease outcomes for rhTSH and THW patients with ATA intermediate and high risk-of-recurrence status were not statistically different; this is similar to our findings. We included intermediate- and high-risk patients in our analysis. The difference in response at the final follow-up (median 3.3 years) was not statistically significant, but better than that in the study by Hugo et al. [20] (54 and 36% in the rhTSH and THW groups, respectively). We also found a higher frequency of a biochemical incomplete response in the group of patients ablated after THW. This situation could be related to a higher rate of successful normal thyroid tissue remnant ablation when rhTSH was used or else it is coincidental due to the low number of patients analyzed.

It was previously shown that, whatever the risk of recurrence is, approximately 20–30% of patients who are clinically NED and have undetectable Tg under TH will present with Tg levels >2 ng/ml after rhTSH or THW stimulation [43–49]. Structural persistence may be iden-

tified on imaging studies in about one third of these patients [43–49]. The clinical significance of minimally detectable serum Tg levels is still unclear, especially when this situation occurs after TSH stimulation [22–25]. In a recent investigation, we concluded that clinical outcomes in patients with an indeterminate response or a biochemical incomplete response after initial treatment are very good; only 16% developed structurally identifiable disease during the first 4 years of follow-up [50]. This is very similar to our current findings, in which 11 of 40 patients (27%) had a biochemical persistence and only 4 (36%) presented with structural persistence, which can be expected because of the inclusion of the intermediate- and high-risk patients.

In our study cohort, only a few patients had T4 tumors with N1a (n = 5). They showed similar responses when compared according to the preparation methodology for remnant ablation by using 150 mCi of ¹³¹-iodine. In a retrospective chart-review protocol at 9 centers in Europe, it was shown that, in 144 eligible patients with T4 tumors who underwent ¹³¹-iodine remnant ablation, successful ablation (judged by WBS) was achieved in 93 and in 91% of the rhTSH and THW patients, respectively. The authors of that study concluded that the use of rhTSH as a preparation for thyroid remnant ablation in patients with T4 primary tumors achieved an ablation success rate similar to that seen after THW [21].

However, we think that a multicenter, randomized, prospective trial would more accurately address these issues. The retrospective studies presented until now show that preparation with rhTSH seems to be as effective as THW, at least in those patients with low and intermediate risk of recurrence.

Disclosure Statement

Fabián Pitoia is a consultant for Genzyme-Sanofi. The other authors have nothing to declare.

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