USEFULNESS OF RECOMBINANT HUMAN TSH AIDED RADIOIODINE DOSES ADMINISTERED IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

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Abstract

The published studies confirming the safety and efficacy of rhTSH for diagnostic purposes have led to an increased interest in its use for preparation for radioiodine (RI) dose administration in patients with recurrent or persistent differentiated thyroid carcinoma (DTC). In order to establish the efficacy of RI therapy after rhTSH, we have reviewed 39 rhTSH-aided radioiodine treatment in a series of 28 DTC patients. Patients were divided into two groups: GI (n=17), with previous thyroid bed uptake and undetectable thyroglobulin (Tg) levels under levothyroxine treatment and GII (n=11), with proven metastatic local or distant disease. Median follow-up after the first rhTSH-aided radioiodine treatment was 32 ± 13 months (range 8 to 54 months). Sixteen patients (94%) in GI were rendered disease free and one patient was shown to have persistent disease. In GII, the post therapy whole body scan showed pathological uptakes in all cases: in four patients in lungs, in four in mediastinum and in three in lateral neck. In two patients with mediastinum uptake, Tg levels were undetectable after rhTSH. In the follow-up, two patients with lateral neck uptake were rendered disease free, four patients died (three due to thyroid cancer) and five out of the remaining patients have persistent disease. In conclusion, rhTSH aided therapy was helpful to eliminate normal thyroid bed remnants in 16/17 (94%) patients (GI). rhTSH stimulated Tg was undetectable in two patients with mediastinal metastasis. We believe that rhTSH is a good alternative to levothyroxine withdrawal for the treatment of DTC with radioactive iodine, increasing the quality of life in these patients. Caution should be recommended in the follow-up of unselected DTC patients only with stimulated Tg levels.

Key words: cancer, thyroid, recombinant TSH, treatment, rhTSH

Differentiated thyroid carcinoma has an excellent prognosis after the initial treatment, which usually includes near-total thyroidectomy and radioiodine ablation of postsurgical thyroid remnants¹. The incidence of differentiated thyroid cancer (DTC) has increased in many places around the world over the past three decades, but this has been associated with a significant decrease in DTC mortality rates in some countries. While the best 10-year DTC survival rates are about 90%, long-term relapse rates...
remain high, in the order of 20–40%, depending upon the patient’s age and tumor stage at the time of the initial treatment.

In order to administer a radioiodine dose it is necessary to obtain an adequate $^{131}$I uptake in the metastatic focus. For this aim, a suppressive therapy with thyroid hormone must be withdrawn, during several weeks, to raise endogenous TSH to levels associated with increased iodine uptake by thyroid tissue (greater than 25 mU/l)\(^3,4\).

Levothyroxine ($\text{L-T}_4$) withdrawal, however, may be associated with signs and symptoms of severe hypothyroidism that is generally poorly tolerated. In some cases, the hypothyroid status may be fatal in patients with very poor physical conditions, advanced age, and in the presence of large metastatic foci or another concomitant illness (renal failure, heart disease, pituitary disease)\(^5,6\).

Because of the availability of recombinant human thyrotropin (rhTSH)\(^7,8\), it has been proposed to perform patient follow-up after exogenous TSH stimulation without $\text{L-T}_4$ withdrawal. Recently, it has been suggested that patients with low risk papillary thyroid carcinoma might be followed with rhTSH stimulated thyroglobulin (Tg) alone associated with ultrasonography to establish the disease free status\(^10,11\). This procedure avoids adverse effects and discomfort caused by the $\text{L-T}_4$ withdrawal-induced hypothyroidism\(^9\). These advantages would be even more important if radioiodine treatment could be indicated using rhTSH in all patients with thyroid cancer.

In the period 1997-2004, nearly 30 medical centers worldwide have reported almost 400 patients with DTC who were given rhTSH in preparation for radioiodine ablation or treatment in a series of 28 DTC patients.

Materials and Methods

Patients

A total of 39 radioiodine doses after exogenous TSH stimulation with rhTSH (Thyrogen, Genzyme Transgenics Corp., Cambridge, MA) were performed in 28 patients (24 women and 4 men; median age 58 years old, range 23 to 89 y.o.). All patients had histologically documented papillary thyroid carcinoma with primary diagnosis established between 1984 and 2002. Six out of the 28 patients were in stage IVa by TNM classification, the remaining patients were classified as follows: Stage IVa, n=1; Stage III, n=3 and Stage I, n=18. Previous treatments had included: total thyroidectomy in all but one patient who had had a lobectomy; and post-surgical radioiodine ablation in all of them. Patients were divided into 2 groups: GI (n=17), subjects with previous thyroid bed uptake and measurable stimulated Tg levels (between 1.3 and 3 ng/ml) but undetectable under $\text{L-T}_4$ suppressive therapy ($\leq 1$ ng/ml). These patients were believed to have a “normal” thyroid remnant which had not been completely ablated after the first radioiodine dose; and GII (n=11), patients with proven metastatic local or distant disease.

Some of these patients (2 in GI and 5 in GII) had also undergone previous $^{131}$I treatments, beside the post surgical ablative dose (median number of treatments, n=3; range 1 to 8) after conventional $\text{L-T}_4$ withdrawal with a mean cumulative activity of 507 ± 247 mCi (range 200 to 850 mCi).

RhTSH aided therapy was indicated due to the following reasons: advanced disease with poorly physical condition (n=9), previous hypothyroid state intolerance and/or patient denial to receive a new treatment after conventional withdrawal (n=13), depression (n=2), secondary hypothyroidism (n=1) and advanced age with other associated disorders (n=3).

The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000. Before treatment, all patients gave a written informed consent.

Methods

Before treatment, baseline serum TSH, $\text{T}_4$, $\text{T}_3$, free $\text{T}_4$, Tg and anti-thyroglobulin antibodies (Tg-Ab) levels were measured in all patients using commercially available kits. All patients were receiving $\text{L-T}_4$, at the moment of the beginning of the protocol.

Under the treatment protocol, 30 days before the radioiodine dose, $\text{L-T}_4$ was changed to $\text{T}_3$ (doses between 20 to 40 µg/day) in all patients\(^13\). One week before the $^{131}$I dose, a low iodine diet was indicated. This diet was continued until two days after the $^{131}$I dose.

All patients received an IM dose of 0.9 mg rhTSH on 2 consecutive days followed by an oral administration of $^{131}$I on day 3 (Fig. 1). The $^{131}$I administered activities ranged from 30 to 300 mCi, adjusted individually based on TNM stage, and presence of metastasis. Fifteen patients of Group I received one radioiodine dose (mean administered activity of 92 ± 41 mCi, range 30 to 150 mCi), one patient received two doses (cumulative activity of $^{131}$I=130 mCi) and one subject three doses (cumulative activity of $^{131}$I=250 mCi). In Group II, five patients had one radioiodine dose after rhTSH (mean $^{131}$I dose was 230 mCi, range 150 to 300), four received two doses (mean cumulative activity of $^{131}$I of 475 mCi, range 350 to 600 mCi) and 2 patients received three $^{131}$I doses (both subjects had a mean cumulative activity of 600 mCi). Patients with documented or suspected metastases were treated with glucocorticoids (prednisolone 40 mg/day) for 2 days before and 5 days after the radioiodine dose to prevent tumor
swelling resulting in compression of sensible structures as CNS or spine[14]. Serum Tg and Tg-Ab were measured on day 5 after the first rhTSH injection. T₃ was withdrawn and L-T₄ was restarted on the same day. Whole body scan (WBS) was performed within 5-7 days after radiiodine therapy.

Mean post therapy follow-up was 32 ± 13 months (range 8-54 months). It included regular measurement of serum Tg under L-T₄ treatment and additional WBS/Tg measurements performed after rhTSH administration. Other diagnostic procedures were performed (chest X-ray, neck ultrasonography in all patients, and chest CT in 10 patients).

**Results**

After rhTSH-aided radioiodine treatment 16/17 (94%) patients of GI were rendered disease free, with negative WBS and undetectable Tg levels. One of these patients with thyroid bed uptake and undetectable Tg levels under L-T₄, showed lateral right neck uptake after 150 mCi of ¹³¹I, with stimulated Tg levels of 9 ng/ml. An ultrasonography showed pathological lymph nodes. A fine needle aspiration biopsy demonstrated a papillary carcinoma metastasis. The patient was then re-operated on and the pathological examination revealed 4 of 15 lymph nodes with metastatic papillary carcinoma. In 1/17 patients with undetectable Tg levels after rhTSH, a lateral neck uptake was shown to be a false positive uptake caused by a laringocelec[15].

In GII, the WBS after the therapeutic dose/s showed pathological uptake/s in all cases (in 4 patients in the lungs; in 4, in the mediastinum; and in the other 3, in the lateral neck). In 2 patients with mediatistic carcinoma uptake, Tg levels were undetectable after rhTSH administration or after L-T₄ withdrawal performed 6 month previously. An MRI showed no alterations in mediastinum in any of them.

In the follow-up, two patients with lateral neck uptake were rendered disease free, four patients died (3 due to advanced thyroid cancer) and five are still having persistent disease: one patient with nodular lung metastasis increased Tg levels on L-T₄ treatment (from 17 ng/ml to 257 ng/ml) one year after 200 mCi [¹³¹I] administration. One patient with lateral neck uptake stabilized his Tg levels after two radiiodine doses. Mediastinal uptake was observed in the remaining three patients with persistent disease. In one of them the Tg level was undetectable and stabilized persistent disease was observed after two radiiodine doses in the remaining two patients (Table 1).

No adverse events were seen in this cohort of patients. Analysis of serum TSH, performed two days after the first rhTSH injection, showed sharp increases in all patients (mean serum TSH level 117 ± 34 mUI/l, range 90 to 178 mU/l).

**Discussion**

In published experiences to date, rhTSH-aided ablation has shown efficacy in a majority of cases when radioiodine doses were equal or superior to 30 mCi and especially when they were higher than 100 mCi[16-21]. Recently, Pacini et al. [22] presented the first prospective multicentric randomized study on ablation comparing results after the administration of 100 mCi in two situations: after rhTSH

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Baseline Tg levels (ng/ml)</th>
<th>Tg after the first RI dose (ng/ml)</th>
<th>Tg after the second RI dose (ng/ml)</th>
<th>Tg after the third RI dose (ng/ml)</th>
<th>Metastatic site (WBS uptake)</th>
<th>Overall outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>73</td>
<td>187</td>
<td>90</td>
<td>210</td>
<td>1287</td>
<td>Lungs</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>82</td>
<td>17</td>
<td>20</td>
<td></td>
<td></td>
<td>Lungs</td>
<td>PD</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>64</td>
<td>180</td>
<td>120</td>
<td></td>
<td></td>
<td>Brain/Lungs</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>49</td>
<td>&lt; 1*</td>
<td>&lt; 1</td>
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<td>&lt; 1</td>
<td>Lungs</td>
<td>Death</td>
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<tr>
<td>5</td>
<td>F</td>
<td>81</td>
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<td>&lt; 1</td>
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<td>Lungs</td>
<td>Death</td>
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<tr>
<td>6</td>
<td>F</td>
<td>79</td>
<td>4</td>
<td>3.5</td>
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<td>Lateral neck</td>
<td>PD</td>
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<tr>
<td>7</td>
<td>F</td>
<td>73</td>
<td>5.6</td>
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<td>PD</td>
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<tr>
<td>8</td>
<td>M</td>
<td>61</td>
<td>90</td>
<td>50</td>
<td>70</td>
<td></td>
<td>Mediastinum</td>
<td>PD</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>45</td>
<td>&lt; 1</td>
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<td></td>
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<td>Mediastinum</td>
<td>PD</td>
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<tr>
<td>10</td>
<td>M</td>
<td>89</td>
<td>&lt; 1</td>
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<td>Mediastinum</td>
<td>Death</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>72</td>
<td>6</td>
<td>5</td>
<td>5.2</td>
<td></td>
<td>Mediastinum</td>
<td>PD</td>
</tr>
</tbody>
</table>

Tg: thyroglobulin; RI: radioiodine; WBS: whole body scan; F: female; M: male; PD: persistent disease; DF: disease free.

* Undetectable Tg levels due to high Tg-Ab titles.

Tg levels were measured under L-T₄ suppressive therapy baseline and three months after each RI dose.
or after thyroid hormone withdrawal. Preliminary results showed that rates of ablation were similar in both situations.

However, Pacini et al. have shown that the 30-mCi standard dose of $^{131}$I for post-surgical ablation of thyroid remnants was less effective when patients were prepared with recombinant human TSH (54%) instead of thyroid hormone withdrawal (84%). They have attributed such a finding to an accelerated iodine clearance in the euthyroid patients, leading to the observation that their initial dose rate delivered to the residues was lower, as well as the 24-h radioiodine uptake. We think that the main reason for these findings could have a different explanation. Perhaps, the stable iodine content present in L-T$_4$ could decrease radioiodine thyroid cell uptake. By using T$_3$ instead of L-T$_4$, as we did, the competition with radioiodine would considerably decrease, leading to an increased uptake by the thyroid remnants and, perhaps, permitting a higher activity of the radioiodine dose, especially when using doses lower than 100 mCi. Recently, Barbaro et al. administered an ablative dose of 30 mCi and compared two similar groups of patients. Following the same rationale, the group that received ablation after rhTSH, discontinued L-T$_4$ from the day before the first rhTSH injection until the day after the radioiodine dose administration. Mean urinary iodine in overnight urine collected between the last rhTSH injection and the time of administration of $^{131}$I, was significantly lower than that observed in 16 other patients receiving rhTSH for diagnostic purposes that continued with L-T$_4$ treatment. At 1-year, follow-up rates of successful remnant ablation, showed by rhTSH-stimulated negative WBS were similar in both groups, a substantial difference when compared with Pacini’s study.

On the other hand, longer residence times in thyroid remnants and reduced blood doses were observed performing dosimetric studies after rhTSH-aided radioiodine administration. These results would suggest that the activity needed to ablate the remnant is not likely to be higher than that required in the hypothyroid state.

In publications to date, rhTSH has been used for a variety of reasons to aid radioiodine treatment. The majority of patients were treated under the Genzyme’s compassionate use programme. In many of these cases rhTSH-aided radioiodine therapy was indicated in elderly patients with bulky, widespread or end-stage thyroid cancer. The analysis of published outcomes of rhTSH-aided treatment showed that around 65% of patients presented clinical benefit from this modality, that is, complete or partial remission or disease stabilization.

The efficacy of the rhTSH-aided radioiodine treatment in our GII is very difficult to establish in most of the cases due to the advanced DTC status at the time performed. However, two patients with lateral neck uptake were considered disease free. Although all of our patients had a diagnosis of papillary thyroid cancer, the use of rhTSH-aided treatment could be extensive to all patients with differentiated thyroid cancer, including those with the follicular type.

The percentage of patients with low or undetectable Tg levels and positive WBS usually found in the different patient series is low. Interestingly, two of our patients of Group II presented mediastinal uptake after a 200 mCi $^{131}$I radioiodine dose associated with undetectable Tg levels.

Metastatic spread detected only by WBS with lacking of Tg rises might be explained by several reasons such as the small size of tumor, unable to release detectable amounts of Tg, or loss of the ability of secreting Tg with preserved capability of $^{131}$I trapping. Another explanation of low levels of Tg in patients with persistent disease identified by WBS can be found in structural changes of Tg. The alterations of Tg structure would occur due to a reduced iodine content and due to different quality of amino acidic residues and monosaccharides composition of Tg in papillary thyroid carcinomas in comparison with normal Tg.

Although rhTSH stimulated Tg is increasingly being recommended as the gold-standard in the follow-up of patients with DTC, it is important to bear in mind that this protocol should be only indicated in those low risk papillary thyroid cancer patients, as previously suggested.

In conclusion, in this uncontrolled retrospective analysis, rhTSH aided therapy was well tolerated in all patients. It was helpful to eliminate normal thyroid bed remnants in most of our patients of Group I. The efficacy in patients with metastatic disease is very difficult to establish in most of our cases due to the advanced DTC status at the time of this experience. However, it is well known that this kind of patients generally have the same outcome after radioiodine treatment, following the traditional L-T$_4$ withdrawal. We believe that rhTSH is a good alternative to L-T$_4$ withdrawal for the treatment of DTC with radioactive iodine. Caution is recommended when follow-up is performed only with stimulated Tg levels in unslected patients.

Conflict of interests: Fabián Pitoia is an external clinical advisor for Genzyme Corporation.

References


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Es posible que la sabiduría y la ecuanimidad del hombre no constituyan hechos extraordinarios; tal vez tampoco lo sea que se afane por criar a sus hijos, que cuide con ahínco de sus padres, que obtenga su propio sustento, que se ponga a cubierto de los peligros y que sea dueño de las dotes brindadas por la Naturaleza, porque el ser humano tiene el don máximo del lenguaje, además de contar con los favores del razonamiento, un recurso de gran utilidad. Por otra parte, también brinda respeto y veneración a las divinidades.

Claudio Eliano (c 170-c 235)


Traducción castellana de María Otero, p 11