

Judicious use of recombinant TSH in the management of differentiated thyroid carcinoma

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Abstract

Objective To evaluate the feasibility of using recombinant human TSH (rhTSH) in conjunction with ^{131}I to treat patients with differentiated thyroid carcinoma.

Methods Between July 2003 and April 2009, 14 patients [mean age, 39.1 years (range 14–71 years)], of whom seven were treated for remnant ablation and seven for irresectable or metastatic disease, received rhTSH-aided ^{131}I therapy. None had an adequate rise in TSH. The mean ^{131}I dosage administered was 5206.3 MBq. Baseline thyroglobulin/anti-thyroglobulin (Tg/anti-Tg) and TSH levels were documented. rhTSH (0.9 mg) was given intramuscularly on days 1 and 2, and TSH levels were recorded. ^{131}I was given when the TSH level rose to >30 $\mu\text{IU/ml}$. Tg/anti-Tg levels were measured at 3-month intervals. A ^{131}I whole-body scan (^{131}I scan) was performed 6 or 12 months after treatment.

Results The baseline median valid Tg and TSH levels were 76.2 ng/ml (range 14.1 to >30000) and 3.63 $\mu\text{IU/ml}$ (range 1.36–11.0), respectively. The rise in TSH level was 34.8–96.9 $\mu\text{IU/ml}$ after the first rhTSH injection and 33.1 to >75 $\mu\text{IU/ml}$ after the second injection. The post-therapy ^{131}I scan showed uptake at disease sites in all patients, indicating the initial empirical adequacy of treatment. Follow-up ^{131}I scan was positive for four patients, but

negative for three of these patients after subsequent therapy. Complete resolution of disease was seen in eight patients and partial resolution in four after 3 months of therapy; one had stable disease; and in one patient with progressive disease, complete resolution was achieved after repeated ^{131}I doses with thyroxine withdrawal. After a median follow-up of 39.2 months, all patients were alive and no disease recurrence was observed. The overall response rate at 3 months was 86% and had improved to 93% at the time of this review. The final ablation rate in seven patients was 100%. Apart from notable neck swelling in four patients, which was responsive to medication, and headache in two patients, no significant short-term side-effects of therapy were seen.

Conclusion In our setting, the use of rhTSH-aided ^{131}I ablation and treatment was safe and effective.

Keywords Recombinant human TSH · Differentiated thyroid carcinoma · Radioactive iodine ablation · rhTSH-aided radioactive iodine treatment

Introduction

Bovine TSH was first used for patients with thyroid cancer at Montefiore Hospital and Memorial Sloan Kettering Cancer Center in the USA five decades ago [1, 2]; however, hypersensitivity and neutralizing antibodies precluded its regular use. In 1993, with the evolution of recombinant DNA technology, rhTSH was produced in engineered ovary cell lines. The production process has since been modified and scaled up, and the compound was approved for use by the US FDA in December 1998 [3]. Approval for its clinical use in Europe was granted in 2001 [4]. This drug is also now approved elsewhere for use

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in adults with differentiated thyroid carcinoma (DTC), as preparation for serum thyroglobulin (Tg) testing, diagnostic ^{131}I scan and ^{131}I ablation [5].

The efficacy of ^{131}I therapy depends on a sufficiently high level of TSH in the patient's serum. A TSH level of ≥ 30 $\mu\text{IU/L}$ is presumed to amplify sodium iodide symporter expression and thus to optimize ^{131}I uptake [6]. Such levels of TSH occur only at least 3–4 weeks after thyroidectomy or 4–5 weeks after discontinuation of treatment with levothyroxine. rhTSH provides an alternative way to raise the TSH level exogenously.

rhTSH is used to enhance ^{131}I uptake by cancer cells in certain groups of patients: (1) those in whom levothyroxine withdrawal might be hazardous as it would allow TSH stimulation of the tumor mass; (2) those in whom there are hypothalamic-pituitary alterations and reduced pituitary reserve; (3) those in whom hypothyroidism is intolerable, especially older and frail patients; and (4) those in whom there is continued thyroxine production by metastatic tissue, resulting in an inadequate rise in endogenous TSH [5, 7, 8]. Other uses for rhTSH proposed recently include treatment of nodular goiters, enhancement of PET scanning, uptake of chemotherapy and differential diagnosis of hypothyroidism [9].

Use of rhTSH has rapidly increased over the past decade, and it has been termed “one of the most exciting innovations” in the management of DTC [4]. The recent guidelines of the European Association of Nuclear Medicine envisage its clinical use in detail and recommend its use in management of DTC [5]. Although it is an effective alternative to levothyroxine withdrawal, its clinical use in developing countries must be well thought out owing to its expense. The great majority of the world's population (more than 80%) still has suboptimal health care [10]. In such situations, rhTSH should be used only for specific patients.

Few reports from developing countries on the use of rhTSH-aided ^{131}I ablation or treatment in DTC patients have been published. We present our experience over 5 years and a recent literature review on the use of rhTSH in a tertiary care charity-based cancer center in Pakistan.

Methods

Patients and setting

The study population comprised 14 patients with DTC who gave informed consent and underwent either rhTSH-aided ^{131}I ablation or treatment between July 2003 and April 2009. The TSH levels of these patients had not risen adequately either secondary to reduced pituitary reserve or due to continued thyroxine production by locally advanced or metastatic tissue even 3 months after initial surgery or external

beam radiation to the neck. All patients were managed from diagnosis and treatment to follow-up in a multidisciplinary setting. The mean age was 39.1 years (range 14–71 years), including two young patients aged <18 years at the time of presentation. Table 1 gives their characteristics.

Initial evaluation

DTC was diagnosed and patients managed according to the guidelines of the European Association of Nuclear Medicine and the American Association of Clinical Endocrinologists [5, 11]. Patients were evaluated initially in the Thyroid Clinic in the Nuclear Medicine department, where baseline diagnostic and staging work-up were undertaken, including biochemical thyroid profile and imaging (thyroid scan, chest X-ray, ultrasound or neck MRI, non-contrast CT where indicated). The management plan was formulated by a multidisciplinary team which comprised a surgical oncologist, a nuclear medicine physician, and a radiation oncologist with experience in treating patients with DTC.

Stage, clinical and biochemical status, resectability, nodal status and local or distant spread at presentation were recorded. Baseline TSH levels (institutional normal reference range: 0.4–4.0 $\mu\text{IU/ml}$) and serum Tg and anti-Tg levels were also recorded. The institutional serum thyroglobulin normal reference range was 0.83–68 ng/ml, and anti-thyroglobulin levels were measured at the same time as serum thyroglobulin levels.

rhTSH protocol and ^{131}I administration

rhTSH was given at a dose of 0.9 mg intramuscularly on days 1 and 2, and TSH levels were documented 24 h after every rhTSH injection. Patients were given ^{131}I within 24–48 h of the second rhTSH injection if their TSH level rose to >30 $\mu\text{IU/ml}$. The stimulated Tg/anti-Tg levels were measured 72 h after the first rhTSH injection. The dose of ^{131}I was 3700–6290 MBq (mean, 5206.3 MBq). Any short-term side-effects were documented and treated with non-steroidal anti-inflammatory drugs or steroids where indicated.

Follow-up

Patients were seen every 3 months as outpatients, when they were evaluated clinically for Tg/anti-Tg levels and subsequent ^{131}I -scan.

Definitions

Complete resolution (CR) of disease was considered to have been achieved when the valid Tg levels on follow-up after

Table 1 Baseline clinical characteristics, indications, ¹³¹I dosage, baseline TSH levels, TSH levels after rhTSH injections, baseline and follow-up thyroglobulin levels for 14 consecutive patients with differentiated thyroid carcinoma

Age (years)	Sex	Histopathology	Stage	Indication (RRA/Rx)	Site of metastases	¹³¹ I-dose (MBq)	Baseline TSH (μIU/ml)	TSH after first rhTSH injection	TSH after second rhTSH injection	Baseline Tg levels (ng/ml)	Follow-up Tg levels (ng/ml)
30	F	Papillary	II	Irresectable/metastases (Rx)	Lungs	3700	2.18	71.6	>75	81.9	2.6
14	F	Papillary	I	RRA (Ab)	-	5550	7.40	96.9	33.1	570	88.4
55	M	Papillary	IV	Metastases (Rx)	Bone	6290	3.01	68.4	>75	300	510
18	F	Follicular	I	RRA (Ab)	-	5550	3.98	>75	>75	39.7	0.2
39	F	Papillary	II	Metastases (Rx)	Lungs	5550	2.00	34.8	48.8	17.9	0.7
22	M	Papillary	I	RRA (Ab)	-	5550	3.27	>75	>75	14.1	0.5
49	M	Follicular	III	Irresectable (Rx)	-	5550	2.90	74.3	>75	353	225
30	F	Papillary	I	RRA (Ab)	-	5550	8.48	51	59.5	70.4	0.2
68	F	Follicular	IV	Irresectable/metastases (Rx)	Lungs	5550	6.68	>75	>75	30000	29804
20	F	Papillary	I	RRA (Ab)	-	4440	10.80	>75	>75	69.9	0.2
29	F	Papillary	I	RRA (Ab)	-	4440	8.24	>75	>75	39.5	1.6
54	F	Papillary	III	RRA (Ab)	-	5550	11.00	>75	>75	27.1	2.5
49	M	Papillary	IV	Irresectable/metastases (Rx)	Lungs	4810	3.14	>75	>75	131	36.9
71	F	Papillary	III	Irresectable (Rx)	-	4810	1.36	>75	>75	242	298

RRA residual remnant ablation, Rx treatment, Ab ablation

rhTSH-aided ¹³¹I ablation or treatment were negligible (less than 10 ng/ml). Partial resolution (PR) was considered to have occurred when the valid Tg levels dropped after treatment but not to negligible levels. If no significant drop was seen, the disease was regarded as stable, and if the valid Tg levels were found to have increased on follow-up, the disease was deemed to be progressive. A subsequent ¹³¹I-scan was performed at 6 or 12 months after rhTSH-aided ¹³¹I ablation or treatment, depending on the trend in Tg levels. If a patient was positive for ¹³¹I-avid disease on ¹³¹I-scan or had not achieved CR, another course of ¹³¹I therapy was given after levothyroxine withdrawal. Two patients with raised anti-Tg were followed primarily by ¹³¹I-scan, ultrasonography and chest X-rays or non-contrast CT. All patients were started on incremental TSH-suppressive doses of thyroxine on discharge.

Results

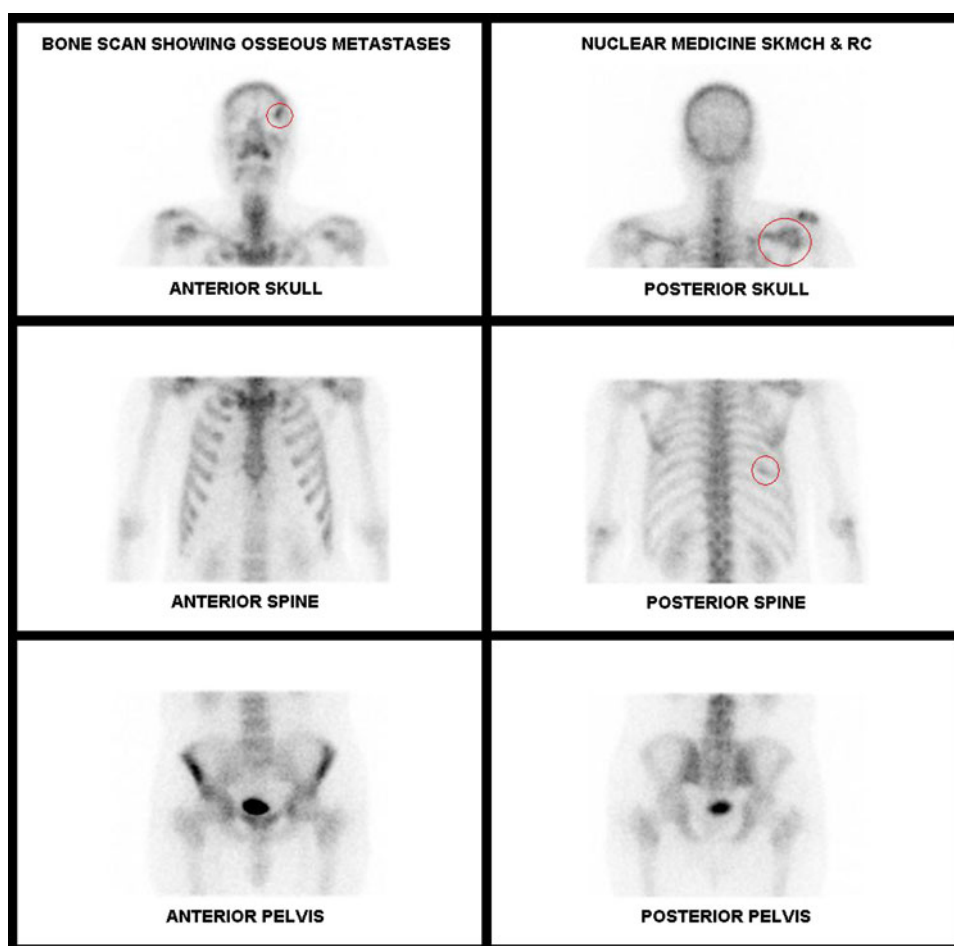
The baseline median valid Tg level was 76.2 ng/ml (range 14.1 to >30000), and the baseline median TSH level was 3.63 μIU/ml (range 1.36–11.0). The TSH level rose to 34.8–96.9 μIU/ml after administration of the first rhTSH injection and to 33.1 to >75 μIU/ml after the second. The TSH level in all patients was >30 μIU/ml after the rhTSH administration, which was adequate for administration of ¹³¹I. All these patients were given ¹³¹I with therapeutic intention, and no pre-therapy ¹³¹I-scan was performed, in order to save a dose of rhTSH. After treatment, all patients underwent an ¹³¹I-scan prior to discharge, which showed ¹³¹I uptake in the neck or thyroid remnant and at diseased sites in all cases, indicating the empirical adequacy of the therapy.

The follow-up ¹³¹I-scans with levothyroxine withdrawal at 6 or 12 months were positive in four patients but became negative in three of these patients after subsequent ¹³¹I therapy with levothyroxine withdrawal. By 3 months after treatment, CR was achieved in eight patients, PR in four, stable disease in one and disease progression in one. The patient with progressive disease had osseous metastases at presentation (Figs. 1, 2) but achieved CR after repeated doses of ¹³¹I with levothyroxine withdrawal.

The overall response rate at 3 months, therefore, was 86%. By April 2009, it had increased to 93%, with only one patient with stable disease. Six patients who had residual remnant ablation achieved CR at 3 months, and one patient with PR at 3 months achieved CR after the next dose of ¹³¹I with levothyroxine withdrawal. In these patients, the ablation rate was 100%.

Recurrence of disease was not seen in any of the patients. After a median follow-up of 39.2 months (minimum 8; maximum 63), all the patients are alive.

Fig. 1 Male patient with T3N1M1 papillary carcinoma. Bone scintigraphy with Tc-99m methylene diphosphonate showing osseous metastases



OSSEOUS METASTASES IN THE LEFT SKULL, RIGHT SCAPULA AND 8TH RIGHT RIB POSTERIORLY

No significant short-term side-effects were noted: 4/14 (28.6%) patients with locally advanced disease at presentation complained of significant neck swelling after therapy, possibly secondary to tumor enlargement, which was managed with non-steroidal anti-inflammatory drugs initially. Three of these four patients needed a short course of steroids. Two patients complained of headache after the second rhTSH injection, which subsided after 24 h after administration of routine analgesics.

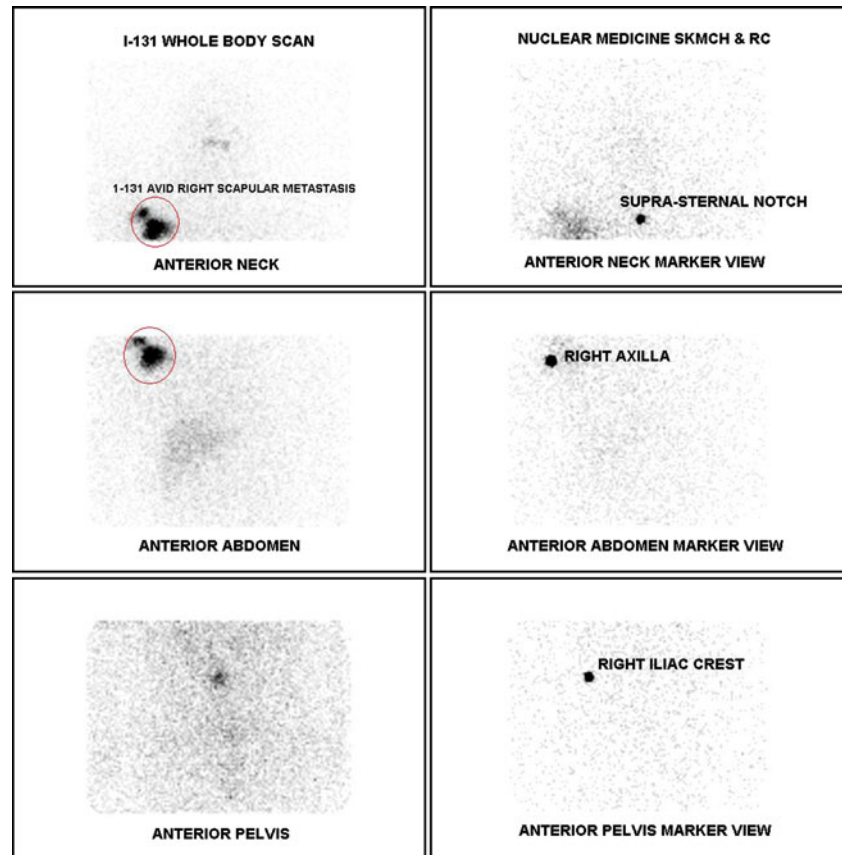
Discussion

Our preliminary experience with rhTSH shows that it is effective, with impressive response rates and an ablation rate of 100%. Our use of a significant decline or negligible valid Tg levels for assessing disease status or resolution brings our study into line with current standards for following-up DTC patients. We used ^{131}I at high doses empirically, depending on the disease burden.

Successful rhTSH-assisted thyroid residual remnant ablation was reported previously by Robbins et al. [12].

A favorable response to rhTSH-stimulated ^{131}I therapy was reported for the first time in a patient with widespread DTC metastases by Rudavsky and Freeman [13]. Robbins et al. [14] also reported use of rhTSH-assisted ^{131}I therapy in a patient with follicular carcinoma of the thyroid, who was unable to produce TSH secondary to radiotherapy to the hypothalamus. rhTSH-stimulated ^{131}I therapy has also been used in patients with brain metastases [15]. Although none of these studies involved large numbers of patients, they do highlight the significance of using rhTSH. In the study by Robbins et al. [12], 50% patients had stage I disease and the remainder had more advanced stage III or IV disease; nevertheless, 100% ablation was seen when complete absence of uptake was found on ^{131}I -scan. Pacini et al. [16] treated 162 patients for residual remnant ablation with a low dose of 1110 MBq of ^{131}I after a delay of 24 h (^{131}I given 48 h after rhTSH injection) to allow ^{131}I uptake measurements. In this study, unlike others, the percentage ablation was lowest in patients treated with rhTSH in a euthyroid state, when the criterion for ablation was a standard ^{131}I -scan with 148 MBq performed after levothyroxine withdrawal. In a study by Berg et al. [17],

Fig. 2 ^{131}I whole-body scan after rhTSH-aided ^{131}I therapy showing dose delivery to remnant in neck and also to the right scapular metastasis seen on bone scan in Fig. 1



patients were treated with >3700 MBq of ^{131}I , resulting in 100% ablation. The difference in the results of Pacini et al. [16] and Berg et al. [17] might have been due to interference from thyroid hormone metabolism [4]. The studies thus suggest that a high rate of ablation occurs when high doses of ^{131}I are used. In another study, Pacini et al. [18] used a multi-center setting to evaluate 60 patients and confirmed that use of 3700 MBq of ^{131}I for ablation was effective (100% ablation) and comparable with the use of either levothyroxine withdrawal or rhTSH. With regard to ^{131}I kinetics, the fractional uptake of ^{131}I was lower in the group treated with rhTSH, but the effective half-life in remnant tissue was reduced in the group with levothyroxine withdrawal. Therefore, the reduced uptake in the rhTSH-aided treatment arm was compensated by an increased half-life of ^{131}I in thyroid cells, significantly reducing the radiation burden to the rest of the body, especially the bone marrow. These findings were later confirmed by Hanscheid et al. [19]. More recently, Barbaro et al. [20] also confirmed the effectiveness of rhTSH-aided ^{131}I ablation, with comparable results for rhTSH and levothyroxine withdrawal.

All our patients who underwent rhTSH-aided treatment were also given high doses of ^{131}I . In retrospective reviews of metastatic DTC, the percentage remission achieved has been 33–50% in cases of levothyroxine withdrawal and

only 2% in rhTSH-assisted ablation [8, 21]. In our study, 2/7 patients with metastatic DTC initially had CR, which increased to 5/7 at the time of data analysis. This could be due to the fact that in other studies rhTSH was often used on a compassionate basis in patients who were frailer or had more advanced disease. Repeated ^{131}I therapy should be considered for such patients.

With regard to the use of rhTSH-aided ^{131}I treatment for locally advanced or metastatic disease, the literature is even more diverse. Owing to the heterogeneity of cases of metastatic DTC, it is unlikely that the efficacy of rhTSH and of levothyroxine withdrawal could be compared in a randomized trial [8, 22]. Nevertheless, many studies have shown that rhTSH can enhance ^{131}I uptake in metastatic lesions [21]. In a study of the residence time of ^{131}I , Potzi et al. [23] showed that ^{131}I uptake is also reduced in metastatic tissue, and the median half-life of ^{131}I was shorter with rhTSH than with levothyroxine withdrawal (21.9 vs. 39.8 h). The authors concluded that, for metastatic tumors, higher doses of ^{131}I are required when using rhTSH to achieve the same therapeutic effect as with levothyroxine withdrawal.

In our study, two patients under 18 years of age had CR of disease with rhTSH-assisted ^{131}I therapy, indicating that it is both safe and effective. Although the use of rhTSH in juvenile DTC has not been approved, Luster et al. [24]

included a few juvenile DTC patients in his study, and rhTSH-aided ^{131}I ablation was used in seven children in a more recent study [25], with safe and effective results.

The optimal dose of rhTSH has been debated. In a comparison of doses of 0.1, 0.3 and 0.9 mg of rhTSH in patients with goiter, it was concluded that a dose of 0.1 mg was sufficient, in order to avoid dose-dependent acute effects of rhTSH on thyroid size or function [26]. Similarly, Pitoia et al. [27] advocated use of one kit instead of two for diagnostic ^{131}I -scan, followed by another kit for therapy. We therefore used a single kit (two injections) in order to decrease the total cost of ^{131}I therapy, which appeared to be judicious in our setting.

Minimal side-effects have been reported with rhTSH [4]. Nevertheless, tumor enlargement after administration of rhTSH can occur. Its rapid onset, its responsiveness to glucocorticoid therapy, and the radiological finding of peritumoral edema or, less commonly, hemorrhage suggest that the enlargement is attributable to tumor swelling rather than growth [14, 28]. Furthermore, caution should be exercised in treating lesions in confined spaces. Even a short course of prophylactic steroid therapy prevents or removes tumor swelling, and prophylactic use of a short course of oral steroids is effective. We observed that intravenous steroid therapy was more effective for patients who developed tumor enlargement with pressure symptoms. rhTSH-aided ^{131}I ablation and treatment is thus safe and effective and results in a better quality of life for DTC patients. Its use in most if not all patients is therefore recommended [29, 30].

In conclusion, the perspective from a developing country is different from that of developed countries, as the standard of care has major financial implications. For developing countries and charity-based hospital settings, we would recommend judicious use of rhTSH only for specific indications, such as when endogenous TSH cannot be raised either due to pituitary problems or continued production of thyroid hormones by metastatic tissue.

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Conflict of interest The authors have no conflict of interest to disclose.

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