CLINICAL STUDY

Radioiodine treatment of metastatic differentiated thyroid cancer in patients on L-thyroxine, using recombinant human TSH

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Abstract

Objective: This study tested the hypothesis that administration of human recombinant thyroid-stimulating hormone (rhTSH: Thyrogen, thyrotropin alpha) could promote iodine-131 (^{131}I) uptake in the therapy for metastatic or locally invasive differentiated thyroid cancer (DTC), obviating L-thyroxine suppressive therapy (L-T4) withdrawal and hypothyroidism in patients with advanced disease.

Methods: Twelve totally (or almost completely) thyroidectomized adults, nine of whom had received earlier therapy after L-T4 withdrawal, underwent ^{131}I treatment while euthyroid on L-T4, after rhTSH administration. Nine underwent diagnostic whole-body scanning (WBS) after two consecutive daily i.m. injections (0.9 mg) of rhTSH. They then received an identical second course of rhTSH to promote therapeutic ^{131}I uptake. Post-therapy WBS was performed one week later. Three patients received only rhTSH ^{131}I therapy.

Results: Administration of rhTSH promoted ^{131}I uptake in all patients, as demonstrated by post-therapy WBS. Administration of rhTSH also promoted a significant increase in serum thyroglobulin (Tg) concentrations. According to the most recent measurements, 3–12 months after therapy, serum Tg levels fell in four, and stabilized in two out of eleven patients. Upon additional rhTSH-WBS 8 months post-study, a reduction in one metastatic site was noted in one patient. The rhTSH was well tolerated, with mild, transient fever and/or nausea occurring in only a minority of patients. Individuals with bone metastases experienced degrees of peritumoral pain and swelling that were similar (though more short-lived) to those seen in the same or other patients after L-T4 withdrawal. **Conclusions:** Administration of rhTSH is a safe, successful tool for inducing ^{131}I uptake in local and metastatic DTC lesions, and avoids L-T4 withdrawal, preserving metabolic homeostasis and preventing the debilitating effects of hypothyroidism.

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Introduction

Radioiodine treatment of patients with metastatic differentiated thyroid cancer (DTC) currently requires protracted withdrawal of L-thyroxine suppression therapy (L-T4). Such withdrawal is needed to raise the endogenous thyroid-stimulating hormone (TSH) above an arbitrary level (such as 30 $\mu\text{U}/\text{ml}$) and thereby to maximize selective radioiodine uptake by neoplastic cells.

L-T4 withdrawal also results in a lengthy period of hypothyroidism of variable, but often marked, severity (1). This metabolic impairment may lead to adverse clinical consequences such as occasional cases of ischaemic heart disease or dementia, and, particularly when bone metastases are present, compressive symptoms due to tumour growth stimulation (2).

Recent randomized multicentre trials in the diagnostic follow-up setting demonstrate that administration of recombinant human TSH (rhTSH: Thyrogen, thyrotropin alpha; Genzyme Corporation, Cambridge, MA, USA) induces ^{131}I uptake in both local and metastatic lesions of DTC, obviating L-T4 withdrawal and the signs and symptoms of hypothyroidism (3, 4). Thus, we hypothesized that rhTSH administration also could promote the incorporation of adequate doses of radioiodine in a therapeutic setting in which avoidance of L-T4 withdrawal and hypothyroidism would be of particular interest, because of the frequently ill and fragile state of the patient population.

To test this hypothesis, we treated a number of patients with metastatic, or, in two cases, locally invasive, DTC, using rhTSH and ^{131}I on L-T4. Here we report the results of this regimen in the first twelve

of these patients, and show that rhTSH successfully promoted local and metastatic uptake of ^{131}I in this group.

Materials and methods

Patients

The twelve patients in this study comprised six females and six males, aged 48–75 years, with follicular ($n = 10$) or papillary ($n = 2$) DTC. Ten patients had metastatic disease, affecting the lungs, bones, lymph nodes, adrenal glands and/or kidneys, whereas two patients each had a locally invasive tumour (patient nos 4 and 7). All patients underwent total or near-total thyroidectomy, and nine had previously received at least one course of high-dose ^{131}I after L-T4 withdrawal (a mean cumulative dose of $17\,464 \pm 2738$ MBq (472 ± 74 mCi); the maximum number of prior treatments was 6 (one case)). In three patients, two with distant metastases and one with a computed tomography (CT)-confirmed persistent local tumour infiltrating the oesophagus, the rhTSH-stimulated high-dose ^{131}I was the initial radioiodine treatment.

Most of the patients were suffering from advanced disease with a high tumour burden, some were particularly ill, and one had terminal disease. All patients met the criteria for, and were given rhTSH under, the manufacturer's 'compassionate use program'. The criteria for the programme included the potential to develop life-threatening conditions under L-T4 withdrawal or an inability to generate sufficient endogenous TSH in the context of non-eligibility for surgery, external radiation or alternative methods of TSH stimulation. Under the 'compassionate use program', the patient's treating physician applies to the manufacturer to enrol the patient and the application must be approved by the manufacturer's medical affairs department.

All patients granted informed consent to participation in this study, which was also approved by the Ministry of Health Ethical Committee.

Treatment protocol

For L-T4 suppressive therapy in the twelve patients, nine received two consecutive daily i.m. injections (0.9 mg) of rhTSH, the regimen studied in the diagnostic follow-up clinical trials (3–5). Twenty-four hours after the last rhTSH injection, 148 MBq (4 mCi) ^{131}I were administered orally. Forty-eight hours after ^{131}I administration, a diagnostic whole-body scan (WBS) was obtained using a gamma camera (Apex SPX-4, one head; Elscint-Italia, Milan, Italy) with a high-energy collimator. Whenever possible, the scanning protocol matched that of the confirmatory Phase III diagnostic follow-up trial (5).

Twenty-four hours after the diagnostic WBS, patients were given a second course of two consecutive, daily, i.m. injections (0.9 mg) of rhTSH. A therapeutic activity of ^{131}I was administered orally 24 h after the last rhTSH injection. The dosimetric data for radioiodine administration under rhTSH stimulation are not yet available. Therefore, for this study, to adjust for the ~50% greater renal clearance of ^{131}I when patients are euthyroid rather than hypothyroid (6), in all but two cases (patient nos 1 and 7) we increased our usual therapeutic dose of 52–74 MBq (1.4–2.0 mCi)/kg body weight to 100–111 MBq (2.7–3.0 mCi)/kg. A post-therapy WBS was performed 7 days after the administration of ^{131}I , using the same model of gamma camera as that employed in the diagnostic WBS. Three patients were not subjected to the diagnostic procedure, but instead proceeded to rhTSH-stimulated ^{131}I treatment.

Serum TSH and thyroglobulin assays

Serum TSH was measured by an immunochemoluminescent assay (Immulite; Diagnostic Products Corporation, Los Angeles, CA, USA) and thyroglobulin (Tg) concentrations by an immunoradiometric (IRMA) assay with a sensitivity of 1.5 ng/ml (HTGK-2-DIA; Sorin, Saluggia, Italy). Serum TSH and Tg were monitored daily during the study period, and Tg was also measured 3 months post- ^{131}I therapy in ten patients (6/12 months later in five cases). Serum anti-Tg antibodies were measured at baseline (IRMA method; ICN Pharmaceuticals Inc., Diagnostic Division, Costamesa, CA, USA).

Results

Serum TSH and Tg after rhTSH administration

As shown in Fig. 1, in nine patients subjected to both diagnostic and therapeutic phases, the serum TSH rose after each course of rhTSH, peaking 24 h after the last injection at levels ranging from 100–325 $\mu\text{U}/\text{ml}$. The administration of diagnostic and therapeutic activities of ^{131}I coincided with the serum TSH peaks. The serum TSH generally remained elevated throughout the 48 h following each peak. Serum TSH behaviour was similar after the first and second courses of rhTSH.

As shown in Table 1, after the first course of rhTSH, all patients had a high increase in serum Tg concentrations, confirming rhTSH stimulation of thyroid tissue. Serum Tg concentrations peaked 2–4 days after the last injection of rhTSH. The second course of rhTSH appears to maintain this increase in serum Tg concentrations, rather than producing higher peaks.

Figure 1 Serum TSH response to rhTSH administration in the nine patients who underwent both diagnostic whole-body scanning and ^{131}I therapy. The arrows indicate each injection of rhTSH.

Diagnostic and post-therapy WBS

As shown in Table 2, post-therapy WBS confirmed the rhTSH stimulation of therapeutic radioiodine uptake in local and/or metastatic sites in all twelve patients. In four of the nine patients subjected to both diagnostic and post-therapy rhTSH-WBS, rhTSH-stimulated diagnostic and post-therapy WBSs were similar. Three patients (nos 6, 7 and 10) had positive diagnostic scans but their post-therapy scans showed additional sites of uptake. Two patients (nos 1 and 2) had negative diagnostic WBSs but positive post-therapy WBSs after rhTSH stimulation; these same patients had negative diagnostic scans but positive post-therapy scans after L-T4 withdrawal, in their most recent imaging before this study.

In six of the nine patients (nos 2, 3, 6, 8, 11 and 12) for whom comparable scans were available, diagnostic

WBSs after rhTSH stimulation confirmed the results of the most recent diagnostic WBSs after L-T4 withdrawal. In the other three patients (nos 1, 7 and 9) for whom comparable scans were available, post-therapy WBSs after rhTSH stimulation extended the findings obtained in the most recent post-therapy WBSs after L-T4 withdrawal, disclosing additional sites of ^{131}I uptake.

Efficacy of rhTSH-stimulated radioiodine treatment

In a short-term follow-up, rhTSH-stimulated radioiodine treatment showed possible signs of efficacy in some members of this late-stage patient population. As shown in Table 3, at the latest available measurement, four out of ten patients (nos 3, 4, 5 and 11) showed a reduction in Tg with respect to baseline levels. The Tg levels essentially remained stable in two additional patients (nos 6 and 12), whereas they increased in the remaining four patients (nos 2, 7, 8 and 9).

In one patient, a locally invasive bone lesion showed reduced ^{131}I -activity in rhTSH-stimulated diagnostic and post-therapy WBSs performed 8 months after the study (Fig. 2). Four patients (nos 3, 4, 7 and 8) received a second course of rhTSH-stimulated treatment in the 6 months after the study. In one of these four patients, a dramatic decrease in the size of a left supraclavicular tumoral mass was observed in a CT scan 3 months after the second treatment (Fig. 3). No substantial changes were observed after the second rhTSH-stimulated treatment in the other three patients.

Safety and mortality

The rhTSH and radioiodine therapy were generally well tolerated. Two patients (nos 3 and 8) experienced transient swelling and pain in bone lesions. In one of these patients, who had a very large metastatic

Table 1 Time course of serum Tg concentrations (ng/ml) after rhTSH treatment (diagnostic phase, days 1 and 2; therapeutic phase, days 5 and 6).

Patient	Tg (ng/ml)							
	Day 1 rhTSH	Day 2 rhTSH	Day 3	Day 4	Day 5 rhTSH	Day 6 rhTSH	Day 7	Day 15
1	1750	1800	1900	2220	2650	2910	1800	1400
2	854	735	1020	2310	2000	18 900	11 600	8800
3	n.d.	n.d.	n.d.	n.d.	33 200	36 200	48 500	62 100
4	66	192	288	696	950	912	849	846
5	746	995	12 700	19 900	15 100	9750	6510	4690
6	127	728	3650	3110	2670	2040	1630	1240
7	13	30	80	110	96	131	154	182
8	74	81	119	201	288	331	317	350
9	n.d.	n.d.	n.d.	n.d.	2940	2720	2570	2640
10	8250	12 900	17 100	49 800	79 000	76 800	59 700	41 000
11	638	876	4710	6450	5060	3730	3840	4120
12	n.d.	n.d.	n.d.	n.d.	30	58	341	87

n.d., not done.

Table 2 Overview of diagnostic and post-therapy ^{131}I WBSs: most recent scans of patients off L-T4 versus scans of patients on L-T4 and rhTSH.

Patient	Last WBS off L-T4 ^a			rhTSH-WBS on L-T4		
	Diagnostic: results	Post-therapy: results	Post-therapy: activity (MBq)	Diagnostic: results	Post-therapy: results	Post-therapy: activity (MBq)
1	Negative	Lungs, nodes	5550	Negative	Lungs, nodes, kidneys, bones	5550
2	Negative	Lungs, nodes	4810	Negative	Lungs, bones	6475
3	Bone	Bone	4810	n.d.	Bone	9250
4	n.d. ^b	n.d.		Local tumour	Local tumour	7400
5	n.d.	n.d.		Residue, bones	Residue, bones	5550
6	Local tumour	Local tumour, lungs	3700	Local tumour	Local tumour, lungs	6734
7	Local tumour	Local tumour	3700	Residue	Residue, nodes	3700
8	Bone	Bone	3700	Bone	Bone	6290
9	Residue	Residue	3700	n.d.	Residue, lungs	6290
10	n.d.	n.d.	3700	Residue	Residue, lungs	4810
11	Lungs	Lungs	3700	Lungs	Lungs	7030
12	Lungs	Lungs	3700	n.d.	Lungs	6364

^a These scans were performed approximately one year before our study.

^b n.d., not done.

invasion of the pelvis from bone metastases, bone-lesion pain was very severe and required major analgesic drugs. In both patients, bone pain was of at least comparable severity but shorter in duration after rhTSH than it had been after L-T4 withdrawal.

Three patients had mild, transient fever, whereas two patients experienced mild, transient nausea after rhTSH administration. One individual with diffuse metastatic involvement died of tumour cachexia 40 days after treatment.

Discussion

This study in the therapeutic setting confirms the ability of rhTSH to promote ^{131}I uptake by normal thyroid residues and local lesions and/or metastatic foci of DTC in euthyroid patients undergoing L-T4 suppression therapy. This ability was demonstrated previously by three randomized, multicentre studies in the diagnostic setting, including a Phase I/II trial involving

19 patients (3) and two large Phase III trials (involving a total of 356 patients) in the United States, France, Italy and Germany (4, 5). In our study, ^{131}I uptake was demonstrated by positive post-therapy WBSs in all twelve patients, even in two individuals for whom the diagnostic scan was negative. The rhTSH stimulation of thyroid tissue was demonstrated by significant increases in serum Tg levels in every case.

A short follow-up study yielded possible evidence of the efficacy of rhTSH-stimulated radioiodine treatment in some patients. At 3 months after treatment, serum Tg concentrations had decreased in five out of ten patients. However, because of the extremely advanced stage of disease, decreases in serum Tg concentrations were not always clinically relevant, as overall status remained poor in three patients with such decreases. One patient showed a significant reduction in ^{131}I activity in a bone lesion in diagnostic and post-therapy rhTSH-WBSs performed 8 months after the study.

Table 3 Serum Tg concentrations before and 3 (in ten patients) and 6/12 months (in five patients) after rhTSH ^{131}I therapy.

Patient	Basal Serum Tg (ng/ml)	Serum Tg 3 months after rhTSH-stimulated ^{131}I therapy (ng/ml)	Serum Tg 6/12 months post-therapy (ng/ml)
1	n.a. ^a	n.a.	n.a.
2	854	857	9960
3	39 000	30 000	n.a.
4	66	27	8.2
5	746	30	108
6	127	138	n.a.
7	13	274	n.a.
8	89	59	294
9	1790	2460	n.a.
10	n.a.	n.a.	n.a.
11	638	542	n.a.
12	22	87	21

^a n.a., not available.

Figure 2 A representative example of a diagnostic and post-therapy WBS after rhTSH in one patient subjected to two courses of therapy. The arrows highlight a rib lesion (A, B) that had undergone evident reduction by the time of a second treatment, 8 months later (C, D). By that time, however, other metastatic lesions in the mediastinal region had become more evident.

These relatively limited signs of the efficacy of rhTSH-stimulated radioiodine treatment are not surprising. Our study was performed under the aegis of a 'compassionate use programme' for which the inability to tolerate L-T4 withdrawal was an entry requirement; thus, it included only a late-stage, poor-prognosis population. In such patients, it is difficult to assess the real usefulness and efficacy of ^{131}I therapy.

Despite the critical condition of the population in this study, rhTSH was generally well tolerated. Constitutional side-effects were limited to mild, transient fever and/or nausea in a minority of patients. Patients with bone lesions experienced transient pain and swelling at these sites. The pain was at least similar in magnitude to that observed in the same and other patients during L-T4 withdrawal. Notably, however, the pain lasted for a shorter time (3–4 days) after rhTSH stimulation than it did after L-T4 withdrawal in the same and other patients. Swelling, probably attributable, as in the cases of our patients, to peritumoral oedema, has also been noted in central nervous system (CNS) lesions in a few individuals (7). Because swelling of CNS lesions has resulted in hemiplegia in rare cases, caution should be exercised when administering rhTSH to patients with CNS involvement, as it should when withdrawing them from L-T4.

To the authors' knowledge, ours is the largest reported series, to date, of patients with rhTSH-stimulated radioiodine treatment, and contains the most detailed data on serum TSH and Tg responses to rhTSH in this setting. At least twelve other similarly treated patients have been presented or published in case reports (8–11). Our findings of rhTSH efficacy in promoting therapeutic ^{131}I uptake, and of rhTSH-stimulated therapeutic ^{131}I in (possibly) reducing serum Tg concentration and/or lesion size, resemble those from these earlier cases.

Our observation of negative diagnostic, but positive post-therapy, WBSs after rhTSH stimulation in a few patients echoes a number of reports in patients withdrawn from L-T4. Several investigators have reported the occurrence of negative diagnostic WBSs in patients with elevated serum Tg concentrations, which became positive in post-therapy WBSs (12–14). Indeed, both patients with negative diagnostic but positive post-therapy scans in this study experienced the same phenomenon in their most recent scans after L-T4 withdrawal.

Compared with L-T4 withdrawal, rhTSH stimulation of ^{131}I therapy has the advantage of avoiding hypothyroidism, which markedly reduces patient

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