rhTSH-aided radioiodine ablation and treatment of differentiated thyroid carcinoma: a comprehensive review

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Abstract

Traditionally, withdrawal of thyroid hormone has been used to attain the increase in serum TSH concentrations that are believed to optimize the trapping and retention of radioiodine for diagnostic procedures, thyroid remnant ablation and treatment of patients with differentiated thyroid cancer (DTC). However, withdrawal frequently causes clinical hypothyroidism, with resultant cognitive impairment, emotional dysfunction, physical discomfort, health risks in patients who are elderly, frail or have concomitant illness, and impaired quality of life and ability to work. Recombinant human TSH (rhTSH) was developed to provide TSH stimulation without withdrawal of thyroid hormone and the associated morbidity. rhTSH has been approved as an adjunct for diagnostic procedures in patients with DTC, but is currently an experimental aid in thyroid remnant ablation and the treatment of thyroid tumours.

In the period 1997–2004, nearly 30 medical centres worldwide have reported on almost 400 patients with DTC who were given rhTSH in preparation for radioiodine ablation of thyroid remnants or treatment of local tumours of metastatic disease. We have analysed and summarized the findings reported in this literature. Ablation aided by the standard course of rhTSH, two consecutive daily injections of 0.9 mg, had success rates better than 84% in 90 patients given radioiodine activities in excess of 4000 MBq. However, when 1110 MBq was administered, success rates were 81.2% in 16 patients given the standard course of rhTSH and 4-day withdrawal of thyroid hormone around the time of radioiodine administration in one study, but 54% in 70 patients in another study. rhTSH-aided treatment of persistent or recurrent local or metastatic cancer, or both, with from one to six courses of radioiodine 1000–19055 MBq, achieved 2% complete remission, 36% partial response and 27% disease stabilization rates, for a 65% clinical benefit rate, in 115 primarily elderly, late-stage patients for whom responses were reported. Twelve of these patients died as a result of progressive disease or were discharged from hospital into hospice care.

Generally, rhTSH was very well tolerated. However, in a minority of patients with central nervous system, spinal or bone metastases, or bulky thyroid remnant or neck lesions with or without poor pulmonary reserve, administration of rhTSH, like thyroid hormone withdrawal, was found to stimulate expansion of the tumour, with ensuing compression of key anatomical structures and neurological, respiratory or other clinical complications. The rapid onset, response to glucocorticoids and radiological findings of peritumoural oedema or, less commonly, haemorrhage in the published cases, strongly suggest that the tumour expansion was the result of swelling rather than growth. As in the case of thyroid hormone withdrawal, special attention and glucocorticoid premedication are thus warranted when rhTSH is given to patients known or suspected to have the above characteristics.
Dosimetric data suggest that whole-body and whole-blood radioiodine clearance may be faster in euthyroid patients after administration of rhTSH. In theory, the faster clearance could allow, or demand, increased radioiodine activities when rhTSH is used, but clinical data to date suggest that this may be unnecessary. The faster clearance also might result in safety or convenience benefits with the use of rhTSH, such as decreased exposure of extrathyroid areas to radiation, and shorter hospital stays.

In conclusion, in preliminary results from open-label studies, both rhTSH-aided tumour ablation and treatment have been well tolerated and have shown efficacy in substantial proportions of patients. rhTSH-aided ablation merits further study. rhTSH-aided treatment may be preferred in patients who are at greater risk of hypothyroid complications from withdrawal of thyroid hormone or are unable to produce sufficient endogenous TSH, and warrants additional investigation in younger patients at earlier stages of thyroid cancer.

Endocrine-Related Cancer (2005) 12 49–64

Introduction

For more than five decades, along with surgical resection and thyroid hormone suppressive therapy (THST) with levothyroxine (lT4), treatment with iodine-131 (131I) has been a mainstay in the management of differentiated thyroid carcinoma (DTC) (Reiners & Farahati 1999, Schlumberger & Pacini 2003). 131I activities of at least 925 MBq are administered for two main purposes: ablation of healthy thyroid tissue remaining after thyroidectomy and of any microscopic cancer deposits, or curative or palliative treatment of inoperable functioning tumour. Administration of such radioiodine activities also permits ‘post-therapy’ whole-body scanning (WBS), which may detect lesions not visualized on diagnostic WBS (dxWBS) or other imaging modalities, and thereby may influence disease management (Schlumberger & Pacini 2003).

The trapping and retention of radioiodine by functioning thyroid tissue are believed to be optimized when serum concentrations of thyroid-stimulating hormone (TSH) are high (30–50 μIU/ml or more; McDougall & Weigel 2001). Historically, increased serum TSH has been achieved by the withdrawal of lT4 for 4 weeks or more. However, during and often beyond this time, withdrawal of THST frequently results in clinical hypothyroidism. Symptoms including cognitive impairment, emotional dysfunction and physical discomfort may significantly disrupt patients’ lives, especially as a large proportion of patients are young or middle-aged, in good general health and therefore more active (Dow et al. 1997, Mazzaferri & Kloos 2000, Brans et al. 2001, M Luster, R Felbinger, M Dietlen & C Reiners, unpublished observation). In the elderly, muscle weakness and cerebellar ataxia as a result of hypothyroidism can impair ambulation, increasing the risk of trauma (Brans et al. 2001).

Withdrawal of THST also may pose a danger of cardiac, cerebrovascular, pulmonary or neurological complications, especially in patients with co-existing disorders or metastatic involvement of these organ systems, or in frail or elderly individuals. A documented potential risk of withdrawal of THST for all patients is stimulation of cancer progression in tumours generally exposed to increased TSH concentrations for several weeks, both during the withdrawal of lT4 and while TSH concentrations return to baseline after the resumption of THST (Rudavsky & Freeman 1998, Vargas et al. 1999, Jarzab et al. 2000a, Robbins et al. 2001). Indeed, contraindication to the withdrawal of THST because of risks of tumour complications or progression has precluded the use of radioiodine therapy in some patients with greatest need for such treatment (Berg et al. 2002). As a general rule, the actual or potential consequences of hypothyroidism render the majority of patients with DTC unwilling or unable to undergo one withdrawal of THST per year (Mazzaferri & Kloos 2000).

In addition, withdrawal is not always effective. Even after weeks of withdrawal, TSH concentrations may not increase sufficiently in cases of persistent thyroid hormone production by large thyroid remnants or functionally active metastases, of hypothalamic or pituitary dysfunction, of long-term steroid administration as prophylaxis against tumour compression of key anatomical structures, or of unusually slow response, particularly in the elderly (Adler et al. 1998, Perros 1999, Luster et al. 2000a, Jarzab et al. 2003). Exogenous stimulation with bovine TSH was introduced as an alternative to withdrawal of THST, but because of frequent adverse reactions and the development of neutralizing antibodies, has fallen into disuse (Schlumberger & Pacini 2003).

Recombinant human TSH (rhTSH; Thyrogen, Genzyme Therapeutics, Cambridge, MA, USA) was
developed to provide TSH stimulation without the requirement for THST withdrawal and the resultant metabolic disturbance, and without the drawbacks associated with the use of bovine TSH. Three clinical studies have demonstrated the safety and efficacy of rhTSH in stimulating uptake of diagnostic activities (≤163 MBq) of $^{131}$I and the release of thyroglobulin by thyroid remnant tissue and metastatic lesions of DTC (Meier et al. 1994, Ladenson et al. 1997, Haugen et al. 1999). As a result, rhTSH gained regulatory approval as a diagnostic adjunct in North America and Europe.

rhTSH is not licensed as an adjunct to radioiodine remnant ablation or treatment. However, since 1995, it has been administered for these purposes, to several hundred patients around the world (Schlumberger et al. 2000). Much therapeutic administration has taken place within the manufacturer’s compassionate use programme, in patients likely to develop life-threatening conditions or unable to generate sufficient endogenous TSH under THST withdrawal, for whom other treatments are unavailable. However, some administration also has taken place ‘off-label’ in everyday practice (Adler et al. 1998, Mariani et al. 2000, Robbins et al. 2002).


Here, we provide a comprehensive review of this published experience. Throughout the text, ‘ablation’ refers to treatment with the primary goal of destroying thyroid remnants, and ‘treatment’ refers to therapy with the primary goal of destroying thyroid tumour.

**rhTSH-aided thyroid remnant ablation**

Currently, radioiodine ablation is widely used after thyroidectomy in patients with DTC. Four main reasons explain the popularity of the technique: (1) some studies have shown it to reduce disease recurrence and mortality rates (DeGroot et al. 1994, Mazzaferi 1997); (2) it enables sensitive ‘post-therapy’ WBS and, by removing healthy thyroid tissue, which is more iodine-avid than cancerous thyroid tissue, increases the sensitivity of subsequent dxWBS and measurements of thyroglobulin; (3) it is therefore perceived to confer ‘peace of mind’; (4) generally, it is safe (Robbins et al. 2001, Schlumberger & Pacini 2003).

Ablation is the standard of care in patients with ‘high-risk’ factors such as: age <16 or >45 years; papillary tall-cell, columnar cell or diffuse sclerosing, follicular widely invasive or poorly-differentiated histology; tumour size >1.0–1.5 cm in diameter or extension beyond the thyroid capsule; large, multiple or bilateral lymph node metastases; distant metastases; increased serum thyroglobulin concentrations more than 3 months after thyroidectomy (Schlumberger & Pacini 2003). Conversely, the consensus is that the procedure should not be applied to patients with papillary thyroid cancer stage pT1N0M0 (tumour diameter ≤1 cm), with unmistakable medullary or anaplastic histology, or to those who, after administration of an $^{131}$I test activity, lack thyroid bed uptake or have uptake indicating a remnant large enough to warrant further surgery (Reiners & Farahati 1999). Disagreement exists as to the use of radioiodine ablation in other patients.

Disagreement also exists regarding the optimal $^{131}$I activities for ablation. Nonetheless, activities between 1110 and 3700 MBq commonly are used, in an attempt to deliver doses of at least 300 Gy to the remnant (Maxon et al. 1992, Reiners & Farahati 1999, Robbins et al. 2001, Schlumberger & Pacini 2003).

A major drawback to ablation has been the need for withdrawal of THST and consequent hypothyroidism (Robbins et al. 2001). Most candidates for ablation comprise the healthiest thyroid cancer patients, for whom hypothyroid morbidity is most disruptive.
Moreover, patients are forced to wait 3–6 weeks after surgery before endogenous TSH concentrations are sufficiently increased to allow ablation to be performed. In contrast, the procedure can take place a few days after surgery when rhTSH is administered, allowing patients to move on with their lives (Reiners & Farahati 1999, Schlumberger & Pacini 2003). Use of rhTSH to aid radioablation, then, would appear potentially to provide patients with important advantages in safety, comfort and convenience.

In published experience to date, rhTSH-aided ablation has shown efficacy in a majority of cases with administered radioiodine activities of 1110 MBq were used, and especially when radioiodine activities ≥4000 MBq were used. The findings of these studies show the feasibility of rhTSH-aided ablation, but additional investigation is needed to optimize the procedures, and publication is awaited of the results of a randomized trial that compared the efficacy of this approach with that of withdrawal-aided ablation.

A total of 180 patients (124 women and 56 men; 163 with papillary, 9 with follicular, 1 with poorly differentiated and 7 with unreported histology; reported ages 17–77 years) have been reported to have received rhTSH-aided ablation (Table 1), 138 while differentiated and 7 with unreported histology; with papillary, 9 with follicular, 1 with poorly hypothyroid state (Park et al. 1996, Haugen et al. 1999), the Pisa investigators suggested increasing the radioiodine activity as one potential means of improving the ablation rate in euthyroid patients.

Indeed, a report of rhTSH-aided ablation with mean activities of at least 4 GBq in euthyroid patients demonstrated a much greater success rate. This retrospective review of 87 patients who underwent thyroid tumour ablation in everyday practice at Memorial-Sloan Kettering Cancer Center, New York, NY, USA in 1999 or 2000 showed an 84% complete ablation rate in 45 euthyroid patients given rhTSH, compared with an 81% rate in 42 patients hypothyroid after withdrawal of THST (Robbins et al. 2002). In that study, successful ablation was defined as negative thyroid bed uptake or undetectable serum thyroglobulin, the success rates would have been 88% in the THST withdrawal group, 95% in the THST withdrawal + rhTSH group and 74% in the rhTSH group.

The 24-hour delay in the administration of radioiodine may help to explain the lower ablation rate for the rhTSH group in the Pisa study. In addition, in light of the more rapid excretion of radioiodine that has been documented in the euthyroid compared with the hypothyroid state (Park et al. 1996, Haugen et al. 1999), the Pisa investigators suggested increasing the radioiodine activity as one potential means of improving the ablation rate in euthyroid patients.
Table 1  rhTSH ablation studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arm</th>
<th>No. of patients</th>
<th>Ablation success rate by dxWBSa (%)</th>
<th>Ablation success rate by dxWBS and/or undetectable thyroglobulin (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacini et al. 2002</td>
<td>Withdrawal + 1110 MBq 131I</td>
<td>50</td>
<td>84.0</td>
<td>88.0</td>
<td>Randomized prospective single-centre study with randomization by consecutive blocs. Withdrawal + rhTSH and rhTSH groups received 131I for 72 and 48 h respectively after last rhTSH injection, vs 24 h in the standard procedure. Urinary iodine excretion was &lt;200 μg/l in all patients.</td>
</tr>
<tr>
<td></td>
<td>Withdrawal + rhTSH + 1110 MBq 131I</td>
<td>42</td>
<td>78.5</td>
<td>95.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rhTSH + 1110 MBq 131I</td>
<td>70</td>
<td>54c</td>
<td>74.1</td>
<td></td>
</tr>
<tr>
<td>Robbins et al. 2002</td>
<td>Withdrawal + mean 4769 ± 2738 MBq 131I</td>
<td>42</td>
<td>80.9</td>
<td>Not reported</td>
<td>Retrospective, single-centre review. Treatment arm was a result of patient choice. rhTSH group was statistically older and likelier to have N0 status at initial diagnosis.</td>
</tr>
<tr>
<td></td>
<td>rhTSH + mean 4084 ± 2405 MBq 131I</td>
<td>45</td>
<td>84.4</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Barbaro et al. 2003</td>
<td>Withdrawal + 1110 MBq 131I</td>
<td>24</td>
<td>75.0</td>
<td>75.0c</td>
<td>Non-randomized, single-centre study using matched groups of consecutive patients.</td>
</tr>
<tr>
<td></td>
<td>rhTSH + ‘mini-withdrawal’ + 1110 MBq 131I</td>
<td>16</td>
<td>87.6</td>
<td>81.2</td>
<td>‘Mini-withdrawal’ in rhTSH group took place from day before first rhTSH injection until day after 131I administration (4 days total). Patients followed low-iodine diet for 2 weeks pre-ablation. Mean urinary iodine excretion was 38.6 ± 4.0 μg/l in withdrawal group, 47.2 ± 4.0 μg/l in rhTSH group (NS).</td>
</tr>
<tr>
<td>Kovatcheva et al. 2004</td>
<td>rhTSH + 131I activities unreported except as between 3300 and 4400 MBq</td>
<td>4</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Open-label, non-randomized prospective single-centre study. Ablation success rate stated to be 75%, based on unreported criteria.</td>
</tr>
<tr>
<td>Berg et al. 2002</td>
<td>rhTSH + 4000 MBq 131I</td>
<td>3</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Open-label, non-randomized prospective single-centre study. Ablation success rate was 100% based on remnant uptake of 0.002–0.1% on post-therapy scan and thyroglobulin of 0.19–1.9 ng/ml at 6 months.</td>
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</table>

131I, iodine-131; dxWBS, diagnostic whole-body scan; rhTSH, recombinant human thyroid-stimulating hormone. aAblation success on dxWBS was defined as absent thyroid bed uptake. DxWBS was performed a mean 8.4, 7.8 and 8.1 months after ablation in the Pacini et al. study (withdrawal, withdrawal + rhTSH, rhTSH groups, respectively), a mean 11.2 ± 2.5 and 10.8 ± 3.2 months after ablation in the Robbins et al. study (withdrawal and rhTSH groups respectively) and 1 year after ablation in the Barbaro et al. study. bIn all studies, rhTSH was given in two consecutive i.m. injections of 0.9 mg each. cP < 0.0001 compared with withdrawal and P < 0.01 compared with withdrawal + rhTSH group. dAbsent visible thyroid bed uptake on dxWBS plus undetectable thyroglobulin in the Barbaro et al. study.
THST was withdrawn exhibited stimulated serum thyroglobulin ≤2 ng/ml, the institutional cut-off value on an immunoradiometric assay with a functional sensitivity of 0.3 ng/ml. Some 9% of those in the rhTSH group and 17% of the withdrawal group had been found to have metastatic disease on post-ablation WBS.

The patients of the Memorial Sloan-Kettering Cancer Center underwent dosimetric assessments with a diagnostic activity of 37–185 MBq during the week before ablation, and the rhTSH group received significantly greater mean diagnostic activities (90.7 ± 62.9 MBq) than did the withdrawal group (72.2 ± 92.5 MBq, P = 0.01, t-test). The rhTSH group underwent tumour ablation with a lower mean activity (4085 ± 2405 MBq) than was given to the withdrawal group (4769 ± 2738 MBq), but this difference was not significant. The authors noted that theirs was a retrospective analysis of groups selected by patient choice, not a prospective study, but believed that their findings supported the design of a randomized trial comparing success rates of rhTSH-stimulated and withdrawal-stimulated ablation techniques.

A recent Italian study using an ablative activity of 1110 MBq compared two similar groups of consecutively enrolled patients: 16 received the standard rhTSH regimen but discontinued LT4 from the day before the first rhTSH injection until the day after radioiodine administration (4 days), and 24 underwent conventional withdrawal of THST (Barbaro et al. 2003). The rationale for the brief withdrawal of LT4 in the rhTSH group was that it had the potential to decrease interference with 131I uptake by the stable iodine in the thyroid hormone, the subject of earlier speculation (de Keizer et al. 2003, Löffler et al. 2003). Mean urinary iodine, measured with high-pressure liquid chromatography combined with electrochemical detection in overnight urine collected between the last rhTSH injection and the time of administration of 131I, was 47.2 ± 4.0 μg/l in the rhTSH + brief withdrawal group, compared with 38.6 ± 4.0 μg/l in the withdrawal group, and 76.4 ± 9.3 μg/l in 16 other patients receiving rhTSH for diagnostic purposes. The difference in urinary iodine concentrations between the rhTSH + brief withdrawal and rhTSH groups was significant (P = 0.019, Student’s t-test). At 1-year follow-up, 81.2% of the rhTSH + brief withdrawal patients and 75.0% of the withdrawal patients had their remnants successfully ablated, defined by a negative rhTSH-stimulated dxWBS and undetectable thyroglobulin. Several factors complicate interpretation of the clinical relevance of this study, for example its small size and its lack of a control group receiving rhTSH for ablation without any withdrawal of LT4.

rhTSH-aided treatment

Curative or palliative radioiodine treatment is indicated when unresectable functioning tumour is present or suspected on the basis of increased thyroglobulin (Pacini et al. 1994, Reiners & Farahati 1999, Pacini et al. 2001). An additional, experimental indication is in clinical trials of re-differentiation therapy with drugs such as retinoic acid (Jarzab et al. 2003). Pregnancy is the sole contraindication, and breast-feeding must be stopped when 131I therapy is planned.

The effect of radioiodine treatment correlates inversely with tumour mass and extent, and younger age is predictive of a favourable response (Reiners & Farahati 1999, Schlumberger & Pacini 2003). Quantitative data on the efficacy of withdrawal-aided radioiodine treatment of metastatic disease are relatively limited (Robbins et al. 2000). However, according to published experience, complete responses are achieved in from about 33% to 50% of patients with distant metastases, but may take up to 5 years of repeated treatments in about 33% of cases (Schlumberger & Pacini 2003). Criteria for partial response vary between medical centres, but include (all without lesion growth at non-responding sites or appearance of new lesions): decreases in tumour volume clinically or by non-131I WBS imaging modalities in tandem with decreases in 131I-WBS uptake; declines in serum thyroglobulin concentrations; improvement in performance status.

Table 2 Published indication for use of rhTSH in radioiodine therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>References</th>
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<tr>
<td>Insufficient or unusually slow endogenous TSH production after THST withdrawal as a result of:</td>
<td>Adler et al. 1998</td>
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<td>• Long-term THST</td>
<td>Colleran &amp; Burge 1999</td>
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<td>• Large thyroid remnant and/or functioning metastases</td>
<td>Masukiewicz et al. 1999</td>
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<td>• Glucocorticoid therapy</td>
<td>Vargas et al. 1999</td>
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<td>• Radiation-induced thyroiditis</td>
<td>Luster et al. 2000b</td>
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<tr>
<td>• Pituitary or hypothalamic disorders or damage from radiotherapy of brain metastases</td>
<td>Roman-Pikielny et al. 2000</td>
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<tr>
<td>Risk of progressive disease or potentiation of tumour compression symptoms with prolonged exposure to increased TSH, especially in patients with:</td>
<td>Checrallah et al. 2001</td>
</tr>
<tr>
<td>• Bone metastases</td>
<td>Pellegritti et al. 2001</td>
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<tr>
<td>• Lung metastases</td>
<td>Kovatcheva et al. 2004</td>
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<td>• Lymph node metastases</td>
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<td>• Brain or spinal cord metastases</td>
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<td>Risk of life-threatening or debilitating exacerbation or appearance of concomitant illness:</td>
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<td>• Ischaemic heart disease</td>
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<td>• Renal insufficiency</td>
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<tr>
<td>• Hypoxia and/or dyspnoea</td>
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<tr>
<td>• Ischaemic brain disease</td>
<td></td>
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<td>• Depression and/or psychological instability</td>
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<tr>
<td>• Serious gastritis</td>
<td></td>
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<td>• General weakness</td>
<td></td>
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<td>• Severe headache</td>
<td></td>
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<tr>
<td>Risk of aggravation, by THST withdrawal of hyperlipidaemia caused by clinical trial of retinoic acid re-differentiation therapy</td>
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<tr>
<td>In patients needing very frequent treatment, avoidance of quality-of-life impairment of nearly unremitting hypothyroidism secondary to withdrawals</td>
<td>Driedger &amp; Kotowycz 2004</td>
</tr>
<tr>
<td>Patient refusal of THST withdrawal</td>
<td>Mazzaferri &amp; Kloos 2000</td>
</tr>
<tr>
<td></td>
<td>Jarzab et al. 2003</td>
</tr>
</tbody>
</table>

THST, thyroid suppressive therapy; TSH, thyroid-stimulating hormone.

The majority of patients were treated under the manufacturer’s compassionate use programme. Hence they comprised individuals with bulky, widespread, late- or end-stage cancer, many of whom were elderly: 75% (113/150) of patients in whom disease status was reported had metastases and at least 39% (59/150) were aged at least 65 years. More than 80% of published patients belonged to seven series of 8–54 consecutive patients each or to a 64-patient dosimetric report; the balance appeared in case reports.

rhTSH-aided therapy appeared to promote the uptake of radioiodine by tumour tissue in nearly all patients with functioning lesions. One hundred and three (75%) of 138 patients for whom post-therapy WBS results were published exhibited radioiodine uptake; among those lacking uptake, 19 represented non-responders to a trial of re-differentiation treatment; in four, the negative rhTSH-aided post-therapy WBS confirmed a suspected complete response to prior withdrawal-aided treatment or confirmed suspected disease-free status; in three, metastases apparently lost avidity for iodine because of disease progression; two had small pulmonary metastases that were non-functional on a prior or subsequent withdrawal-aided post-therapy scan; one had iodine excess from recent administration of a computed tomography contrast medium; and no explanation was published in the case of four others. Two of the patients lacking therapeutic radioiodine uptake after rhTSH administration, and an additional patient who lost rhTSH-aided therapeutic radioiodine uptake after five treatments, did demonstrate uptake after later withdrawal-aided treatment. The authors reporting two of these cases (Driedger & Kotowycz 2004) speculated that their observations might be explained by disparities in the ability of some individuals’ TSH receptors to take up recombinant and endogenous TSH, which differ in sialylation.

Analysis of published outcomes of rhTSH-aided treatment (Table 3) shows that 74 of 115 patients (65%) for whom this parameter was reported derived clinical benefit from this modality – that is, complete or partial remission or disease stabilization. There were only a single confirmed complete remission and one other possible complete response (in a patient who may have had only tumour remnant to begin with), but 41 partial responses, for an objective response rate of 38% (2% complete response rate plus 36% partial response rate). In addition, 31 patients (27%) had disease stabilization. In this sometimes late- or end-stage
Table 3  Responses to rhTSH-aided radioiodine treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>No. evaluable patients</th>
<th>Duration of follow-up</th>
<th>$^{131}$I single activities (MBq)</th>
<th>Number of patients with:</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR*</td>
<td>SD</td>
</tr>
<tr>
<td>Jarzab et al. 2004</td>
<td>27 (functional metastases at baseline)</td>
<td>Median 12.5 months (range 6–33 months)</td>
<td>3400–7400</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>20 (non-functional metastases at baseline)</td>
<td></td>
<td></td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Lippi et al. 2001</td>
<td>12</td>
<td>3–12 months</td>
<td>3700–9250</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Luster et al. 2000a</td>
<td>11</td>
<td>Mean 4.3 months (range 2–10 months)</td>
<td>1000–7400</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>de Keizer et al. 2003</td>
<td>10</td>
<td>3 months</td>
<td>7400</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Berg et al. 2002</td>
<td>8</td>
<td>3–6 months</td>
<td>4000</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pellegritti et al. 2001</td>
<td>6</td>
<td>13–73 months</td>
<td>3700</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Kovatcheva et al. 2004</td>
<td>6</td>
<td>6–18 months</td>
<td>Mean 3900 ± 300 (range 3300–4300)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1 or 2-patient case reports: Adler et al. 1998</td>
<td>14</td>
<td>0–24 months where reported</td>
<td>2400–19055</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

$^{131}$I, iodine-131; OR, objective response (complete + partial responses); PD, progressive disease; SD, stable disease.

*Best response. Criteria for response varied but included decreases in tumour volume clinically and/or by non-WBS imaging modalities in tandem with decreases in WBS uptake, declines in serum thyroglobulin concentrations and/or improvement in performance status (all without lesion growth or development of new lesions). All responses were partial except for one complete response in Jarzab et al. 2003 and a possible complete response in Perros 1999.
population, 9 non-responders died of apparent or possible progressive disease 40 days to 22 months after the first (and in most cases, only) rhTSH treatment. Another patient with a partial response of decreased periorbital oedema died 2 months after treatment, and a second patient with a partial response including good quality of life died at about 3 years of follow-up. A further patient was discharged from hospital into hospice care.

When published results of rhTSH-aided treatment are being evaluated, data must be interpreted cautiously, because standardized response criteria were used in only about 50% of the patients, and many papers did not give data for one or more parameters such as follow-up WBS, thyroglobulin measurement or clinical response. Moreover, randomized studies have not been published and, indeed, are unlikely to be performed, because of the relative rarity and great heterogeneity of metastatic DTC and the challenging ethical issues in this setting (Sherman 2003). The dearth of randomized studies, of course, increases the possibility of selection biases affecting reported results. However, any bias might lead to an understatement of efficacy, given the advanced disease stage and associated grim prognosis — exemplified by the 10-year survival rate in the literature of approximately 11% for patients with several metastatic sites — of most of the published patient population (Reiners & Farahati 1999, Schlumberger & Pacini 2003). Despite the limitations of the published experience, there undoubtedly have been some patients in whom rhTSH-aided treatment achieved important clinical palliation such as restoration of ambulation, ability to work and socialize, or both, and diminution or resolution of bone pain (Adler et al. 1998, Rudavsky & Freeman 1998, Robbins et al. 2002, Berg et al. 2002, Jarzab et al. 2003).

Two studies have revealed that the efficacy of rhTSH-aided treatment compares favourably with that of prior withdrawal-aided treatment. In a 54-patient, single-centre trial, Jarzab and co-workers (2003) made a qualitative comparison between post-therapy WBS after rhTSH and post-therapy scans obtained after the most recent withdrawal of THST. Two experienced clinicians evaluated the location and number of foci of uptake, with scans considered concordant if all visible foci in one scan were also present in the other. The possible impact of disease regression or progression on changes between scans was assessed in the light of clinical, laboratory and other radiological findings. Among 27 evaluable patients with functional metastases at baseline, median time between scans was 6 months (range 3–12 months), 18 (67%) scan pairs were concordant, 4 (15%) were discordant in favour of rhTSH, and 5 (19%) were discordant in favour of THST withdrawal. Among 23 evaluable patients with non-functional metastases at baseline, 19 (83%) scan pairs were concordant, and 4 (17%) were discordant in favour of rhTSH. All discordant scans appeared to be explicable on clinical grounds. The scans discordant in favour of rhTSH were attributed to disease progression causing additional foci of uptake or to success of re-differentiation therapy with retinoic acid in restoring uptake in the rhTSH-aided scan compared with the withdrawal-aided scan. The scans discordant in favour of withdrawal were explained by tumour de-differentiation or by complete response to the most recent withdrawal-aided treatment.

In an earlier study, Lippi et al. (2001) had performed a retrospective comparison of rhTSH-aided and withdrawal-aided post-therapy WBS, using methodology similar that of Jarzab and co-workers (2003). They found concordance in six of nine evaluable pairs of scans, and additional sites of uptake in three pairs of rhTSH-aided scans. The latter finding was attributable to tumour progression between scans.

Jarzab and colleagues (2003) also compared the clinical and biochemical response to one to four courses of rhTSH-aided therapy with those to two to eight previous courses of withdrawal-aided therapy in 44 evaluable patients. They used standard criteria of objective response, disease stabilization and progressive disease. Twenty-three patients (52%) had similar responses to the two modalities, 12 (27%) had a superior response to rhTSH-aided treatment, 2 others (5%) had a superior response to rhTSH-aided treatment, attributed to response to retinoic acid re-differentiation therapy, and 7 patients (16%) had a superior response to withdrawal-aided treatment.

**Immediate biochemical effects of rhTSH**

In the 11 largest studies of rhTSH-aided therapy published to date (Lippi et al. 2001, Luster et al. 2000a, Mariani et al. 2000, Pellegritti et al. 2001, Berg et al. 2002, Robbins et al. 2002, Barbaro et al. 2003, Jarzab et al. 2003, de Keizer et al. 2003, Pacini et al. 2002, Kovatcheva et al. 2004), peak serum TSH concentrations after the administration of rhTSH ranged from 42 to 400 mU/ml in euthyroid patients and from 124 to 582 mU/ml in hypothyroid patients. One study observed that serum TSH generally remained increased 48 h beyond its peak (Lippi et al. 2000). This agrees with the observations of others that the standard two-dose rhTSH regimen results in 3–4 days of increased
serum TSH concentration, compared with 6–10 weeks after withdrawal of THST (Robbins et al. 2001).

Limited reports show generally minimal effect of the administration of rhTSH on serum free tri-iodothyronine and free $\mathrm{LT}_4$ concentrations in patients with DTC and total thyroidectomy (Luster et al. 2000a, Jarzab et al. 2003). Administration of rhTSH stimulated an increase in serum thyroglobulin concentrations in at least 67% of patients for whom data were reported.

**Safety of rhTSH**

Despite the frequently late-stage, elderly or frail nature of the 393 patients for whom data have been published, rhTSH-aided therapy generally was well tolerated, with most patients experiencing no, or only minor and transient, unwanted effects. The adverse events profile generally has been similar to that observed in the diagnostic phase III studies (Ladenson et al. 1997, Haugen et al. 1999), which included few patients with metastatic disease. However, as in the case of withdrawal of THST, an important safety consideration in relation to the administration of rhTSH involves potential TSH stimulation of thyroid expansion, with ensuing compression of key anatomical structures and neurological, respiratory or other clinical complications. This possibility warrants special attention in patients with known or suspected central nervous system or spinal metastases. It also warrants special attention in patients with bulky neck lesions or tumour remnants, or both, especially if they have poor lung reserve as a result of pulmonary fibrosis from having received high cumulative activities of prior radioiodine, or other causes (Goffman et al. 2003).

In their 54-patient study, for example, Jarzab et al. (2003) reported mild extremity paraesthesia in two of 21 rhTSH-aided courses given to patients with spinal and brain metastases. They also reported radiologically confirmed pathological spine fracture accompanied by paraparesis the night after the administration of radioiodine, in a 53-year-old woman with a large vertebral metastasis. In addition, neck tumour oedema developed, starting on the second day of application of rhTSH, in three of 20 patients with massive neck infiltrates; the oedema was accompanied by a choking sensation in two of the patients, and by dyspnoea in the other. A half dozen or so similar cases have been reported elsewhere (Vargas et al. 1999, Robbins et al. 2000, Braga et al. 2001, Berg et al. 2002, Goffman et al. 2003).

Transient, moderate-to-severe exacerbation of bone pain in patients with bone metastases also has been observed after the administration of rhTSH in three studies (Lippi et al. 2001, Berg et al. 2002, Jarzab et al. 2003). Such exacerbation occurred in 25% (8/32) of courses given to patients with bone metastases in the largest of these studies (Jarzab et al. 2003). Of interest, in most cases, patients stated that the increased bone pain was shorter-lived, milder, or both, after the administration of rhTSH than under prior withdrawal of THST, and in no case was it said to be longer-lived or more severe.

Three points should be noted about tumour enlargement after the administration of rhTSH. Firstly, its rapid onset, its response to glucocorticoid administration and the radiological findings of peritumoural oedema or, less commonly, haemorrhage, in the published cases, strongly suggest that the enlargement is attributable to tumour swelling rather than to growth (Vargas et al. 1999, Robbins et al. 2000, Braga et al. 2001, Berg et al. 2002, Jarzab et al. 2003). However, there may be rare instances in which stimulation of tumour growth by rhTSH cannot be ruled out (Jarzab et al. 2003). Secondly, rhTSH product labelling now recommends glucocorticoid premedication of, and caution with, patients with known or suspected lesions in confined spaces, as is recommended for patients subjected to withdrawal of THST. Thirdly, in studies to date, premedication with dexamethasone, prednisone or hydrocortisone, or combinations thereof, has avoided complications of tumour swelling in a number of high-risk patients, but not in all individuals (Luster et al. 2000a, Pellegritti et al. 2001, Berg et al. 2002). Meticulosus clinical attention should be the rule when patients with known or suspected lesions in confined spaces are exposed to increases in TSH, whether withdrawal- or rhTSH-stimulated.

Among the 394 patients described in the literature on rhTSH-aided therapy, a single case of clinical thyrotoxicosis, in which cardiac symptoms were easily relieved by $\beta$-blockers, has been reported in an individual with massive functional skeletal and soft-tissues masses (Jarzab et al. 2003). One case also has been reported of a patient who had pneumonia after rhTSH-aided treatment; the investigators did not state whether the pneumonia had any relationship to the intervention in this desperately ill patient (Rudavsky & Freeman 1998).

$^{131}$I dosimetry under rhTSH stimulation

The selective avidity of thyroid tissue for radioiodine and the short range of $^{131}$I $\beta$-radiation mean that doses of radiation delivered to extrathyroidal tissues are about...
1/1000–1/10000 less than those delivered to thyroid tissue. Therefore in many cases, standard or empirical activities of $^{131}$I may be used for radioiodine ablation or treatment. However, pre-therapeutic measurement of whole-blood, whole-body, remnant or lesion kinetics of radioactivity in an individual after administration of a tracer activity of $^{131}$I is sometimes used to ‘customize’ the activity to be used for a given therapeutic procedure.

The objective of whole-blood and whole-body dosimetry is to determine the maximum radioiodine activity that can be given in a procedure without serious risk of bone marrow depression or pulmonary fibrosis. Traditionally, a dose of 2 Gy of radiation to the blood (a surrogate for bone marrow) has been considered the safe limit to minimize the risk of bone marrow depression. An activity of 3 GBq in the lung at 24 h has been considered the safe limit to avoid pulmonary fibrosis in patients with extensive lung involvement (Benua et al. 1962, Leeper 1973).

The objective of remnant or lesion dosimetry is to determine the radioiodine activity that delivers the recommended minimum dose of radiation to ablate the thyroid remnant or to treat metastatic disease. The doses are traditionally considered to be 300 and 80 Gy respectively (Maxon et al. 1992). In contrast to these pre-therapeutic dosimetric procedures, the radiation dose delivered by the $^{131}$I therapeutic activity itself to the thyroid remnant or to lesions also may be measured after the therapy, to attempt to correlate this dose with clinical results.

In practice, patient-specific dosimetry has several limitations: estimations of the volume of tissue concentrating $^{131}$I may be imprecise, for example when micrometastases are too small for visualization; uptake can be heterogeneous, even within a particular lesion; and biological half-lives can vary according to the individual, lesion or time of measurement (Schlumberger & Pacini 2003, Sgouros et al. 2004). In addition, poor physical condition may preclude an additional administration of $^{131}$I (i.e. of a test activity) in some candidates for radioiodine therapy (Luster et al. 2000a). Furthermore, with rhTSH-aided therapy, measurement of a test activity would entail the cost of additional injections of rhTSH required to replicate the conditions of the actual therapy.

Nonetheless, some clinicians have advocated dosimetric studies before use of rhTSH-aided therapy, because experience of $^{131}$I dosing gained in relation to THST withdrawal may not be wholly relevant when the patient is euthyroid (Mazzaferrri & Kloos 2000). Initial reports in the diagnostic setting, presumably from patients with minimal thyroid remnant or tumour, suggested that renal clearance of radioiodine generally was approximately 50% more rapid in the euthyroid than in the hypothyroid state (Park et al. 1996, Ladenson et al. 1997). More recently, a three-centre pilot German-American dosimetry study comparing biokinetics of diagnostic radioiodine administration after rhTSH administration and THST withdrawal (Luster et al. 2003) found that clearance of radioactivity from the blood was faster after the administration of rhTSH in all nine patients studied; the mean effective half-life of radioactivity after the standard course of two injections of 0.9 mg rhTSH was $0.75 \pm 0.07$ times that after withdrawal. This study involved low-risk patients without evidence of disease after complete thyroidectomy, who were scheduled to receive remnant ablation after completion of the dosimetric study. All patients received 74 MBq $^{131}$I test activity under THST after stimulation by two-day ($n=4$) or three-day courses ($n=5$) of rhTSH and then 4–6 weeks later under hypothyroid conditions ($n=9$) after withdrawal of THST.

In the treatment setting, Robbins et al. (2000) found, in four dosimetric studies performed in a patient undergoing rhTSH-aided treatment, that whole-body radioiodine clearance was more rapid but, surprisingly, blood clearance was consistently less rapid in the euthyroid state than in the hypothyroid state (Robbins et al. 2000). Menzel et al. (2003) found that, despite considerable overlap in values between the groups, the mean effective whole-body half-life of radioiodine was significantly lower in consecutive patients receiving rhTSH stimulation than in other consecutive patients given withdrawal stimulation: $0.43 \pm 0.11$ days ($n=64$) compared with $0.54 \pm 0.11$ days ($n=163$) ($P<0.001$, unpaired t-test). The significant difference persisted in subgroup analyses designed to factor-out possible effects of tumour burden and thyroid tissue volume.

In contrast, a recent report by de Keizer et al. (2003) on 16 evaluable patients given 19 courses of rhTSH-aided treatment with a radioiodine activity of 7400 MBq noted median biological and effective half-lives of radioiodine of 4.1 days (range 0.6–34.7 days) and 2.7 days (range 0.5–6.5 days) respectively, in tumour. These half-lives were comparable to data obtained after withdrawal-aided therapy, suggesting similar iodine kinetics in thyroid cancer tissue after both forms of TSH stimulation.

In theory, a more rapid clearance of radioiodine in euthyroidism might result in delivery of a lower dose to the thyroid remnant or tumour after administration of rhTSH than after withdrawal of THST. The lower dose presumably would be attributable at least in part to decreased $^{131}$I re-uptake by thyroid tissue of previously
secreted radioiodine, as a result of the reduced radioiodine pool in the bloodstream over time. Decreased radioiodine availability for re-uptake would be expected to be more relevant in treatment than in ablation, because of the diminished uptake and organization of radioiodine in metastases compared with that in healthy thyroid tissue (Schlesinger et al. 1989).

The recent University of Pisa ablation study (Pacini et al. 2002) found that the rhTSH group had significantly lower mean 24-hour thyroid uptake of a test activity of radioiodine than did the THST withdrawal or THST withdrawal + rhTSH groups: 2.5 ± 4.3% (range 0.1–32%) compared with 5.8 ± 5.7% (range 0.2–21%) and 5.4% ± 5.7% (range 0.2–26%) respectively (P < 0.0001). The Pisa investigators found that the mean initial dose rate, a value proportional to the 24-hour 131I uptake divided by the remnant mass (determined by ultrasound), also was significantly lower for the rhTSH group than for the THST withdrawal or THST withdrawal + rhTSH groups: 10.7 ± 12.6 Gy/h compared with 27.1 ± 42.5 Gy/h (P = 0.01) and 48.5 ± 43.0 Gy/h (P < 0.001) respectively. However, in that study, therapeutic radioiodine was administered 24 or 48 h later (rhTSH and withdrawal + rhTSH respectively) than in other ablation or treatment series. Furthermore, the method used to measure the dose delivered to tumour remnant did not give the cumulative absorbed dose, and is validated by only one previous study (Samuel & Rajashekharrao 1994).

In contrast to the observations in the Pisa study, the German-American dosimetry study found that the remnant dose was greater after rhTSH than after withdrawal in eight of nine patients; overall, residence time was 5.7 ± 6.3 times longer after rhTSH. However, the investigators noted that these results may have been influenced by a sequencing effect of ‘stunning’ of the thyroid remnant by the first, rhTSH-aided test dose. In the treatment setting, de Keizer et al. (2003) found that the dose absorbed by the tumour was a median 26.3 Gy (range 1.3–368.4 Gy), and exceeded 80 Gy in only five of 25 tumours.

In theory, delivery of a lower dose to remnant or lesions in euthyroidism might affect the efficacy of rhTSH-aided therapy. However, in studies reported to date, the correlation between dose absorbed by the remnant or tumour and the clinical or biochemical response has been unclear. In the University of Pisa ablation study, although ablation was successful in all patients in whom the initial dose rate was greater than 50 Gy/h, the initial dose rate overlapped extensively between those in whom ablation was and was not achieved. In the treatment study performed by de Keizer et al. (2003), several patients with tumour absorbed doses below the 80 Gy threshold nonetheless exhibited a partial thyroglobulin response or shrinkage of several metastatic lesions confirmed by chest X-ray.

On the basis of the dosimetric and clinical results of their ablation study, the University of Pisa investigators speculated that increased radioiodine activities could improve the efficacy of rhTSH-aided procedures (Pacini et al. 2002). In their 12-patient study of rhTSH-aided treatment (Lippi et al. 2001), the Pisa team empirically increased their treatment activity from 52–74 MBq/kg of body weight (their standard range under THST withdrawal), to 100–111 MBq/kg, with some successful clinical outcomes and no apparent radioiodine toxicity. However, other reported studies (e.g. Luster et al. 2000a, Robbins et al. 2001, 2002, Berg et al. 2002, Jarzab et al. 2003) seem to have administered customary institutional activities of 131I in conditions of THST withdrawal, with no apparent diminution of ablation or treatment efficacy.

Were an increased therapeutic activity necessary with the use of rhTSH, the possibility of adverse effects of the larger activities on the bone marrow or lungs presumably would be mitigated by the faster whole-body radioiodine clearance and resultant decreased exposure of extrathyroid tissues to radiation in euthyroid patients. Were an increased therapeutic activity unnecessary, the faster clearance associated with the administration of rhTSH might decrease the whole-body and whole-blood retention of radioiodine, with attendant safety benefits, decreased hospital stays, or both. In fact, in one 11-patient study of rhTSH-aided therapy that successfully used activities similar to those administered after withdrawal, the investigators reported an anecdotal impression that patients generally were able to leave the radioprotection ward 1–2 days sooner after rhTSH-aided than after past withdrawal-aided procedures (Berg et al. 2002).

de Keizer et al. (2003) speculated that the lower doses of radiation delivered to the tumour in their study with rhTSH, compared with those associated with withdrawal of THST, might be attributable to interference with radioiodine uptake by iodine derived from the continuing thyroid hormone treatment in patients given rhTSH. As noted earlier, in a small study, Barbaro et al. (2003) found that rhTSH-aided ablation with 1110 MBq radioiodine and a 4-day ‘mini-withdrawal’ around the time of administration of radioiodine resulted in numerically greater success rates than those attained with conventional THST withdrawal; however, in the absence of a study arm in which rhTSH was given without a ‘mini-withdrawal,’ the 7-day half-life of LT4 calls into question whether the ‘mini-withdrawal’ really had any impact.
In summary, to date, dosimetric findings have been published in widely varying levels of detail in 259 patients given rhTSH-aided therapy (Luster et al. 2000b, 2003, Mazaferri & Kloos 2000, Robbins et al. 2000, 2001, 2002, Rotman-Pikielny et al. 2000, Pacini et al. 2002, de Keizer et al. 2003, Menzel et al. 2003). Despite the relatively large number of publications and population of patients reported, questions of methodology, bias and clinical relevance surround the data accrued, so that knowledge of the kinetics of radioiodine after the administration of rhTSH and their efficacy and safety impact must still be considered as preliminary, and further investigation desirable.

rhTSH-aided ablation and treatment: current status, future directions

Radioiodine ablation of thyroid remnants would seem to be a logical setting for the administration of rhTSH, because of the desirability of avoiding hypothyroidism in the generally younger, healthier and more active population of patients undergoing this procedure. In such patients, economic savings from preserving the ability to work and, in some instances, from obviating the need to return for radioiodine ablation weeks or months after thyroidectomy, should offset the cost of rhTSH in some cases at least (M Luster, R Felbinger, M Dietlein & C Reiners). Published experience to date has shown the safety and, especially when radioiodine activities of at least 4000 MBq are used, the efficacy of rhTSH in aiding ablation (Robbins et al. 2001, 2002, Berg et al. 2002, Pacini et al. 2002, Barbaro et al. 2003, Kovatcheva et al. 2004). These benefits may be further established when results are reported from a recently completed randomized pilot clinical study comparing rhTSH and THST withdrawal as adjuncts to ablation. This study at eight locations in five countries involved a total of approximately 60 adults with well differentiated papillary or follicular thyroid carcinoma and used a fixed 131I activity of 3700 MBq.

Regarding rhTSH as an aid to treatment, the published international experience in 217 patients, most with advanced disease, suggests that rhTSH safely and effectively stimulates the uptake of radioiodine in local and metastatic lesions of well differentiated thyroid cancer, and that it may achieve clinical benefit in a substantial percentage of patients, even those in whom the cancer is late-stage. The results also suggest that rhTSH-aided treatment may have an efficacy at least equivalent to that of withdrawal-aided treatment, even though in most cases, the 131I activities given in the rhTSH-aided treatment were not adjusted to compensate for the faster clearance of radioiodine in the euthyroid state. rhTSH stimulation may become the modality of choice in most, if not all, the categories of patients listed in Table 1, and certainly merits additional investigation, preferably in randomized studies, including in younger patients with less advanced disease.

Acknowledgements

The authors thank Robert J Marlowe for editorial assistance on this paper, provided under an unrestricted grant by Genzyme Europe BV, Naarden, The Netherlands.

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