

ACTA ONCOLOGICA LECTURE

Present status of the use of recombinant human TSH in thyroid cancer management

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A large majority of thyroid carcinomas derive from the follicular epithelium and retain, albeit to a markedly reduced degree, important biological characteristics of normal thyroid tissue. One of these characteristics is the expression of the so-called sodium iodide symporter (NIS), the key cellular feature for specific uptake of iodine. Another such characteristic is the ability to increase the synthesis of NIS and thyroglobulin (Tg) in response to exposure to thyroid-stimulating hormone (TSH). Tg is the storage protein for thyroid hormones and, in the absence of healthy thyroid tissue, a specific tumor marker.

Tumors retaining basic characteristics of healthy thyroid tissue are referred to as differentiated thyroid carcinoma (DTC) and when adequately initially treated, generally have an excellent prognosis: <3% of DTC patients will die of their disease within the 5 years after initial diagnosis, while the 40-year mortality rate is estimated at around 10% [1]. Adequate initial treatment of a thyroid nodule which, after appropriate diagnostic work-up (including clinical examination, neck ultrasonography and cytological examination after a fine-needle biopsy), is known or suspected to be malignant should always be surgical excision, namely total thyroidectomy. The surgery should routinely include a systematic dissection of the central lymph node compartment, and in the presence of clinically, sonographically or cytologically suspicious neck lymph nodes, lateral dissection as well [2].

In addition, initial management of DTC should comprise application shortly after surgery of a large activity of radioiodine, specifically, iodine 131 (^{131}I),

as adjuvant therapy against any occult tumor [3]. This so-called radioiodine ablation also is intended to destroy healthy thyroid remnant tissue that could impair the sensitivity of follow-up monitoring for persistent or recurrent disease. Radioiodine ablation also allows for the detection of persistent thyroid remnants and of previously unsuspected metastases on a post-ablation scan (see below).

Some controversy exists as to which patient groups can be adequately initially treated with less intensive regimens than that described above, and, in particular, without radioiodine ablation. However, it is generally agreed that the papillary micro-carcinoma (stage T1N0M0) with a tumor radius of ≤ 1 cm can be treated sufficiently by a hemi-thyroidectomy, without systematic lymph node dissection or radioiodine ablation.

Following thyroidectomy, patients are placed on thyroid hormone to restore a clinically euthyroid state. Thyroid hormone generally is given at a supra-normal dose, with the additional goal of suppressing TSH levels to <0.1 mU/l and thereby avoiding or minimizing growth stimulation of any occult DTC cells.

Although DTC patients generally have a long survival, they also have relatively high rates of tumor recurrence: 10–30% [4]. Timely detection and treatment of recurrent tumor is critical to decrease morbidity and mortality associated with such disease. Therefore performance of – and patient adherence to – periodic and sensitive long-term follow-up monitoring is vital in DTC management.

Apart from clinical examination and neck ultrasonography, two mainstays of such management are

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testing for serum Tg as a tumor marker and, albeit to a decreasing extent, “diagnostic” whole-body scanning (dxWBS) with small activities of radioiodine. Radioiodine – in large activities – also is a valuable tool in the treatment of inoperable DTC, including distant metastatic disease found at DTC diagnosis. A precondition to the optimal application of Tg testing or radioiodine administration is elevation of serum TSH to levels (>25 or 30 mU/l) ensuring ample Tg production and radioiodine uptake and storage by thyroid tumor cells.

Serum TSH elevation can be obtained endogenously, through thyroid hormone withdrawal (THW). Such elevation also can be obtained exogenously, allowing patients to remain on thyroid hormone therapy and maintain metabolic homeostasis. However, use of bovine TSH for exogenous TSH stimulation proved inadequate because of frequent severe allergic reactions and development of anti-TSH antibodies, while use of “natural” cadaveric human TSH became obsolete because of the risk of Creutzfeldt-Jakob disease.

Since 1998 in the United States and 2000 in Europe, though, another means of providing exogenous TSH has seen increasing use: administration of recombinant human thyroid-stimulating hormone (rhTSH, Thyrogen[®], Genzyme Therapeutics, Cambridge, MA, USA), highly purified synthetic human TSH produced in a genetically modified Chinese hamster ovary cell line. Worldwide, rhTSH has been administered some 250 000 times to date, with an increase of approximately 5 000 applications per year. The approved rhTSH regimen is 0.9 mg, given by intramuscular (IM) injection every 24 h for two doses. Radioiodine is given one day after the second rhTSH injection, while serum Tg testing takes place 3 days after that rhTSH injection. If performed, dxWBS takes place 48 to 72 h, or post-therapy WBS, 3–7 days after the second rhTSH injection.

The present article seeks to provide an overview of the current status of rhTSH in DTC management. It begins with a discussion of the rationale for the use of rhTSH, and then describes that use in the approved indications of serum Tg testing, dxWBS, and, most recently, radioiodine ablation of healthy thyroid remnant. Next, the article examines rhTSH application in various experimental indications. The article closes by discussing rhTSH safety and pharmacoeconomics.

Rationale for rhTSH use

Avoidance of clinical hypothyroidism

In view of the long survival of individuals with DTC and their need to adhere to long-term monitoring

protocols to optimize aftercare, patient quality of life (QOL) considerations have become increasingly important in the management of this malignancy. The principal rationale for rhTSH use is the avoidance of the phase of clinical hypothyroidism that typically accompanies each THW: to attain serum TSH elevation >25 or 30 mU/l, it traditionally has been considered necessary to discontinue levothyroxine (LT4) for approximately 4 weeks and to replace LT4 with triiodothyronine (T3) for only the first 2 of those weeks, so that the patient receives no thyroid hormone whatsoever in the last 2 of the weeks.

The morbidity and deleterious effects of clinical hypothyroidism on patient QOL, the ability of rhTSH administration to avoid these problems, or both have been documented by a variety of studies in which hypothyroid symptoms and QOL were rated by patients using diverse symptom- or disease-specific or generic instruments [5–12]. These instruments frequently have included the Billewicz score that is based on a list of potential hypothyroid symptoms [13], the Short Form-36 (SF-36) QOL questionnaire that has been used across numerous diseases and the “profile of mood states” (POMS) that assesses depression and anxiety [14].

For example, we recently published results of a pilot survey of 131 patients undergoing THW for dxWBS at the University of Würzburg from 1992–2001 [15]. Ninety-two percent of these patients reported symptomatic and 85%, multisymptomatic hypothyroidism during withdrawal; 25% of patients had six or more of the nine hypothyroid symptoms listed in the questionnaire. The most commonly reported hypothyroid symptoms were fatigue (87% incidence), difficulty concentrating (52%) and intolerance of cold (51%); the survey did not query whether patients experienced increased depression during THW. Hypothyroidism was reported to restrict or prevent the performance of activities of daily living in nearly two-thirds of respondents to the relevant question ($n = 115$).

In another recent publication [16], Schroeder et al. re-analyzed QOL data from the pivotal Phase 3 study of rhTSH in the diagnostic follow-up of DTC, comparing SF-36 QOL scores in 228 thyroidectomized DTC patients when on and off thyroid hormone with the scores of the US general population or the scores of patients with several disease states. These authors found that on thyroid hormone therapy, the DTC patients had SF-36 QOL scores at or above the US general population norms in six of eight domains addressed, namely, physical functioning, role physical, bodily pain, vitality, social functioning, and role emotional. After THW, however, the DTC patients had SF-36 QOL scores signifi-

cantly lower than these norms in all eight domains (the previously listed domains plus general health and mental health). Surprisingly, after THW, the DTC patients had significantly lower SF-36 QOL scores than did even patients with heart failure or migraine in six of eight domains, or patients with chronic clinical depression in three of eight domains.

The unpleasantness of clinical hypothyroidism may decrease patient adherence to follow-up monitoring regimens. Almost 15% of one Israeli series ($n=48$) cited hypothyroid symptoms as the reason for their non-participation in such testing [17].

Besides avoiding the morbidity and QOL impairment of clinical hypothyroidism itself, obviation of THW prevents hypothyroid exacerbation of sometimes debilitating or even life-threatening morbidity associated with co-existing conditions such as ischemic heart or brain disease, renal or pulmonary insufficiency, depression, psychological instability, serious gastritis, general weakness or severe headache [18–26]. In addition, avoidance of the prolonged high serum TSH levels associated with THW – since rhTSH administration results in days – rather than weeks-long TSH elevation – theoretically could decrease the risk of tumor growth stimulation that can occur rapidly in some patients [18,27–29], or of inflammatory tumor expansion. This is an especially important consideration in patients with metastases affecting confined anatomical spaces in the central nervous system, lungs, and bones. The literature contains some anecdotal suggestions that patients with a history of rapid tumor growth under THW may be spared such growth by rhTSH administration [30,31]; however, isolated cases of tumor expansion and perhaps tumor growth have been reported after rhTSH use [24,27,32]. Therefore steroid co-administration and clinical caution are advised when giving rhTSH to patients with known or suspected tumor in confined anatomical spaces, as they are when subjecting such patients to THW.

Another at least theoretical safety benefit of rhTSH use is its potential to decrease the risk of automobile or other accidents that potentially could result from the fatigue and inability to concentrate secondary to THW. Suggesting that such a benefit might be appreciable is the surprising finding of our 131-patient pilot survey [15] that approximately one-third of respondents drove automobiles during THW despite medical advice to the contrary.

Supplying TSH stimulation in patients with insufficient or slow capacity to raise TSH endogenously

Patients who have received long-term TSH suppressive therapy, who are on glucocorticoids, or

who have any of a large thyroid remnant, functioning metastases, radiation-induced thyroiditis, pituitary or hypothalamic disorders, or damage from radiotherapy of brain metastases may be unable or excessively slow to raise TSH levels endogenously [22,26,27,33–38]. In such patients, rhTSH administration is the only way to attain sufficient, timely TSH stimulation.

Extra-thyroidal radiation reduction

There is a substantially higher renal clearance of radioiodine under euthyroidism than under hypothyroidism [39], which, in a recent randomized trial of rhTSH- versus THW-aided ablation with an ^{131}I activity of 3.7 GBq, was documented to result in a significantly lower radiation dose to the blood (0.109 ± 0.028 vs. 0.167 ± 0.061 mGy/MBq of administered radioiodine, $p < 0.0001$) [40]. A trade-off for the lower radiation exposure to extra-thyroidal tissues could well be a lower pool of circulating radioiodine available for target healthy or cancerous thyroid tissue, resulting in lower re-uptake of radioiodine in such tissue [40]. However, the rapid decrease of serum TSH levels after rhTSH administration may, by quickly reducing iodine efflux from thyroid tissue, prolong radioiodine residence time in such tissue [40]. This phenomenon would rapidly offset the effects of the increased renal radioiodine clearance rate under euthyroidism, eliminating any clinically material difference with conditions under THW.

Indeed, in the diagnostic follow-up and ablation settings, randomized, controlled studies have shown rhTSH-aided diagnostic scanning to have equivalent, high sensitivity, and rhTSH-aided ablation to have equivalent, high efficacy, compared to the same procedures aided by THW [9,10]. If decreased re-uptake under euthyroidism is of any concern, it would mainly be in the radioiodine treatment of late-stage DTC, where the tumor tends to have especially deficient radioiodine uptake even under THW.

Other rationale for rhTSH administration

Use of rhTSH allows more predictable timing and more rapid TSH elevation than does THW, and hence potentially more convenient scheduling of diagnostic or ablative procedures. In particular, rhTSH administration may allow ablation to be performed sooner after surgery, permitting patients to complete initial therapy of DTC and move on with their lives weeks more quickly than they would were THW employed.

Serum Tg testing and diagnostic radioiodine scanning

rhTSH was first approved as an aid to serum Tg testing, dxWBS, or both in the diagnostic follow-up of patients after primary treatment of DTC. The approval was based on a multicenter, multinational, prospective pivotal Phase 3 study [9] involving 229 patients who had been totally or near-totally thyroidectomized ($n=228$), 83% of whom had received radioiodine ablation. The patients served as their own controls, undergoing serum Tg testing while on LT4 therapy, and Tg testing plus dxWBS after rhTSH administration and then after THW. The rhTSH phase of the trial preceded the THW phase because the investigators felt that it would be more ethical and practical not to have patients undergo two separate THWs should the diagnostic follow-up findings necessitate radioiodine treatment of persistent or recurrent disease. The study also included a randomized comparison of two rhTSH regimens, 0.9 mg by IM injection every 24 h $\times$ 2 doses or every 72 h $\times$ 3 doses, but noted no statistical differences in any safety, efficacy or QOL variable between the regimens. Hence when comparing rhTSH versus THW, the pivotal Phase 3 study combined the results under both rhTSH regimens. Also, because the regimens produced equivalent results but the 2-dose regimen was more convenient and had been investigated more extensively than the 3-dose regimen, the 2-dose regimen became the approved dosage scheme.

The pivotal Phase 3 study found that using a radioimmunoassay with an analytical sensitivity of 0.2 ng/ml and a functional sensitivity of 0.5 ng/ml, and using a 2.0 ng/ml threshold for positivity, rhTSH-aided or THW-aided serum Tg testing both identified 100% of anti-Tg-antibody- (TgAb-) negative patients with metastatic disease. Unstimulated Tg testing on LT4 therapy, however, missed approximately 20% of these patients. Metastatic disease was defined as a dxWBS or post-therapy WBS positive for uptake outside the thyroid bed ($n=39$ of 194 TgAb-negative patients), or a THW-aided Tg of ≥ 10 ng/ml ($n=10/194$).

The pivotal Phase 3 study also found that rhTSH administration and THW resulted in statistically equivalent dxWBS results: in patients with evaluable scans ($n=220$), scanning under the two modalities was concordant in 89%, superior after rhTSH in 4%, and superior after THW in 8% ($p=0.108$, sign test and continually adjusted 95% confidence interval). The trial used a fixed radioiodine activity of $148 \pm 10\%$ MBq of ^{131}I 24 h after the last rhTSH injection or after THW was found to have produced serum TSH levels ≥ 25 mU/l. The study also used a

standard diagnostic imaging technique, with dxWBS taken 48 h after ^{131}I administration and with minimum scanning time of 30 min or 140 000 counts for whole-body images. For spot images, minimum scanning time was 10–15 min or 60 000 counts for a large field of view camera or 30 000 counts for a small field of view camera. In current everyday clinical practice, smaller diagnostic radioiodine activities (e.g., 1.75–3.7 MBq) [41] often are applied to calculate the radioiodine uptake in the neck in order to avoid “stunning” by the higher activities needed for whole-body scintigraphy. However, the pivotal Phase 3 trial’s scanning techniques have become the standard when rhTSH-aided dxWBS is used [42]. It also is recommended to use a large field of view camera with thick crystals and high-energy collimators, and to include spot imaging of the neck when performing dxWBS [42]. Some clinicians may have the misconception that rhTSH-aided dxWBS is less sensitive than THW-aided dxWBS, because of the results of an earlier, smaller Phase 3 study [8] that found a statistically significant advantage for THW. However, this earlier study did not employ standardized radioiodine activities or scanning techniques or systematic Tg testing, and the advantage of THW generally lay in the detection of thyroid bed uptake in isolation, which typically is of little clinical relevance: for example, a retrospective comparative analysis [43] at Memorial Sloan Kettering Cancer Center, New York, NY that included 161 patients receiving THW-aided dxWBS and 128 patients receiving rhTSH-aided dxWBS found that after some 2–3 years’ follow-up, only 13% of patients with thyroid bed uptake in isolation eventually had metastatic disease by methods other than dxWBS and serum Tg testing; and since this analysis was conducted at a tertiary referral center, given the inherent selection bias for higher-risk patients in such a setting, even this percentage is probably higher than that seen in everyday practice.

A large number of subsequent studies have confirmed the pivotal Phase 3 study’s findings of equivalent accuracy of rhTSH-aided versus THW-based serum Tg testing or dxWBS, and because of the QOL and safety rationale discussed above, rhTSH administration has become the “gold standard” for TSH stimulation in DTC diagnostic monitoring [41,42,44,45]. The recommended technique for rhTSH-serum Tg testing is use of an immunometric assay with a functional sensitivity of <0.5 – 1.0 ng/ml, performed by a laboratory experienced in Tg determination [41]. Whenever Tg testing is used, serial Tg measurement should be conducted using the same laboratory, because differences in laboratory standards and techniques may bias comparison of Tg results from different institu-

tions. Also, in a given patient, clinicians should not compare Tg results obtained with rhTSH stimulation versus those obtained with THW on a one-to-one basis, since generally, rhTSH stimulation results in 2–3-fold Tg elevations, while THW results in 5–10-fold elevations [41].

Due to the results of a number of recent, well-conducted, large, and mostly prospective studies, the algorithm for initial diagnostic follow-up of DTC has come to rely substantially on serum Tg testing plus neck ultrasonography performed by an experienced operator [42,44]. For example, a group of European experts recently recommended use of these two modalities, plus serum TgAb testing, at the 6–12-month post-ablation exam to help classify patients' risk status and hence determine the nature of subsequent follow-up and LT4 therapy [41,42]. These investigators define low-risk patients as those who have undergone complete thyroid surgery, and who lack distant metastases, extensive neck disease (pT4) or poorly differentiated histotypes at the time of primary treatment and clinical or biochemical evidence of disease in the 6–12 months afterwards [41,42]. When such patients are TgAb-negative, the investigators recommend yearly rhTSH-aided Tg testing for patients found to have Tg levels that are detectable but below the institutional cut-off mandating further investigation, and use of neck ultrasonography in all patients in every follow-up exam. Hence presently, the role of dxWBS in diagnostic follow-up lies largely as a substitute for Tg testing when monitoring TgAb-positive patients, or to localize disease outside the thyroid bed.

Radioiodine ablation

rhTSH was in 2005 approved in Europe to stimulate radioiodine uptake for thyroid remnant ablation. The approval was for use with 3.7 GBq of ^{131}I and was based on a multinational, multicenter, prospective, randomized, controlled study [10] comparing rhTSH versus hypothyroidism as preparation for such ablative radioiodine therapy in DTC patients without confirmed distant metastases. In that study, 100% of both the rhTSH group ($n=24$ evaluable patients) and the hypothyroid group ($n=21$ evaluable patients) met the primary ablation success endpoint of no visible or $<0.1\%$ visible thyroid bed uptake on an rhTSH-aided dxWBS with 150 MBq of ^{131}I taken 8 months after ablation. Among TgAb-negative patients, 96% of the rhTSH group and 86% of the hypothyroid group were considered successfully ablated according to the criterion of an rhTSH-stimulated serum Tg level <2 ng/ml 8 months after ablation. When that criterion was defined as an 8-month serum Tg <1 ng/ml, 83% of the rhTSH

group and 86% of the hypothyroid group were considered successfully ablated. Earlier literature suggested that rhTSH-aided ablation with radioiodine activities ≥ 3.3 GBq had a high success rate and one comparable with that of hypothyroid ablation (reviewed in [46]). A retrospective, single-center study by Robbins et al. [47] found ablation success rates of 84% in an rhTSH group ($n=45$) given a mean 4.1 ± 2.5 GBq of ^{131}I , versus 81% in a hypothyroid group given a mean 4.8 ± 2.7 GBq. In this study, ablation success was defined as lack of visible thyroid bed uptake on dxWBS taken a mean 10.8 ± 3.2 months post-procedure in the rhTSH group and a mean 11.2 ± 2.5 months post-procedure in the hypothyroid group; the dxWBS was rhTSH-aided in every case but five, all in the hypothyroid group. In addition, in one series [23], three of three patients given rhTSH-aided ablation with 4 GBq ^{131}I had ablation success, based on remnant uptake $\leq 0.1\%$ on a post-ablation scan and 6-month Tg ≤ 1.9 ng/ml, while in another series [26], three of four patients given rhTSH-aided ablation with 3.3–4.0 GBq had ablation success, according to unspecified criteria.

Based on a pair of studies, results may be more mixed with rhTSH-aided ablation using 1.11 GBq activities. In a prospective, single-center trial [48] with randomization by consecutive blocs, ablation success rates were 84% in a hypothyroidism group ($n=50$), 80% in a hypothyroidism+rhTSH group ($n=42$), and 54% in an rhTSH group (rhTSH versus other groups, $p<0.01$, Mann-Whitney U test and Kruksal-Wallis test) when ablation success was defined as absence of visible thyroid bed uptake on an THW-aided dxWBS performed 6–10 months post-procedure. If ablation success had been defined as negative thyroid bed uptake or an undetectable serum Tg at the time of the dxWBS, the success rates would have been 88% in the hypothyroidism group, 95% in the hypothyroidism+rhTSH group and 74% in the rhTSH group. Due to dosimetry-related study design features, in this trial, the ablative radioiodine was given 48 h after the last rhTSH injection in the rhTSH group, and 72 h after the last rhTSH injection in the hypothyroid+rhTSH group, versus 24 h after the last rhTSH injection in all other published papers and in the approved product labeling; this timing of ^{131}I administration may have accounted at least in part for the less favorable results of this study.

In a non-randomized, single-center study by Barbaro et al. [49] using matched groups of consecutive patients, ablation with 1.11 GBq ^{131}I had a success rate of 88% in the rhTSH group ($n=16$) versus 75% in the hypothyroid group ($n=24$), based on a dxWBS with negative thyroid bed uptake one

year after the procedure; the success rates were 81% in the rhTSH group versus 75% in the withdrawal group when the additional criterion of undetectable serum Tg at the same time was included. In this study, the rhTSH patients underwent a thyroid hormone "mini-withdrawal," consisting of LT4 discontinuation for 4 days: from the day before the first rhTSH injection to the day after ^{131}I administration.

The mini-withdrawal was employed with the rationale of precluding potential interference with radioiodine uptake by the stable iodine in thyroid hormone, an issue that had been previously raised by others [50,51]. Barbaro et al. [49] noted mean urinary iodine concentrations, measured with high-pressure liquid chromatography combined with electrochemical detection in overnight urine collected between the last rhTSH injection and ^{131}I administration, of 47.2 ± 4.0 $\mu\text{g/l}$ in the rhTSH + mini-withdrawal group versus 38.6 ± 4.0 $\mu\text{g/l}$ in the hypothyroid group and 76.4 ± 9.3 $\mu\text{g/l}$ in 16 additional patients receiving rhTSH for diagnostic reasons (rhTSH + mini-withdrawal vs. withdrawal, $p = 0.21$, rhTSH + mini-withdrawal vs. rhTSH without mini-withdrawal, $p = 0.019$, Student's *t*-test).

However, the multicenter ablation trial found statistically similar urinary iodine levels in the group receiving rhTSH *without* thyroid hormone interruption versus in the hypothyroid group [10]. Using a colorimetric method on urine collected within 2 days before the first rhTSH injection in the rhTSH group or 2 days before radioiodine administration in the hypothyroid group, the multicenter investigators noted mean urinary iodine levels of 12.1 ± 8.9 $\mu\text{g/dl}$ (median 9.8, range 1.2–40.8 $\mu\text{g/dl}$) in the rhTSH group ($n = 31$) and 9.0 ± 7.5 $\mu\text{g/dl}$ (median 6.8, range 1.4–31.4 $\mu\text{g/dl}$) in the hypothyroid group ($n = 30$) ($p = 0.157$, Student *t*-test and Wilcoxon rank sum test). The multicenter investigators noted that at the time of ablation, the mean and median urinary iodine levels in the rhTSH patients were substantially beneath the 25 $\mu\text{g/dl}$ level conventionally, if arbitrarily, considered to indicate potential interference with radioiodine uptake. In addition, at 8 months post-ablation, the two groups, now both on thyroid hormone, again, and unsurprisingly, had similar mean urinary iodine levels: 15.2 ± 17.0 $\mu\text{g/dl}$ (median 12.3, range 2.7–91.7 $\mu\text{g/dl}$) in the former rhTSH group ($n = 33$) and 14.5 ± 8.1 $\mu\text{g/dl}$ (median 12.2, range 3.4–32.7 $\mu\text{g/dl}$) in the former hypothyroid group ($n = 29$) ($p = 0.837$, Student *t*-test and Wilcoxon rank sum test).

In summary, rhTSH now is well-established as preparation for radioiodine ablation with activities around 3.7 GBq. Further study is required to confirm the efficacy of rhTSH-aided ablation with smaller activities. Whether the iodine intake from the

continued thyroid hormone therapy made possible by rhTSH use has any clinical relevance also warrants additional investigation.

Experimental indications

Radioiodine treatment

An appreciable amount of experience has accumulated with rhTSH as an adjunct to treatment of distant metastatic, or to a lesser extent, locally aggressive DTC, with large ^{131}I activities (reviewed in Luster et al. [46]). However, no prospective trial of rhTSH-aided treatment yet has been conducted, and much of the published experience has consisted of individual cases or of relatively small case series (other than one 54-patient clinical study [30] and another 64-patient dosimetric trial [25], $n = \leq 12$ for reports published through August, 2004). Due to the lack of scientific data and the existence of a potentially curative treatment, THW-aided radioiodine, for earlier-stage cases of a life-threatening disease, rhTSH-aided radioiodine to date has been applied almost exclusively in the palliative setting, for bulky, disseminated, late- or end-stage disease, rather than against pulmonary micrometastases. Indeed, the main indications for rhTSH use in metastatic disease have included (and continue to include) patients who would not otherwise be able to receive radioiodine treatment: those who have insufficient or unusually slow endogenous TSH production or a history of symptomatic or rapidly progressive DTC under THW, who are at risk for exacerbation of concomitant illness or are elderly or frail, or who refuse THW.

As of August, 2004, the published experience with rhTSH-aided treatment of metastatic or locally aggressive disease included at least 266 courses of therapy (1–6 courses/patient) in a total of 216 patients, with individual radioiodine activities ranging from 1.0–19.055 GBq [46]. Of the 216 published patients, 108 were female, 90 were male, and the sex was unreported or not clearly reported in the remaining individuals. Patient age ranged from 14 to 87 years and at least 40% of patients for whom age was reported (59/149) were ≥ 65 years old. DTC histology was papillary in 68 instances, follicular in 64, Hürthle cell in one and unreported or not clearly reported in 83, while 75% of patients for whom disease status was reported (112/149) had distant metastases.

rhTSH appeared to promote radioiodine uptake by tumor tissue in nearly all patients with functioning lesions [46]. Isolated cases have been noted [52,53] in which lesions took up ^{131}I after THW but not rhTSH; conversely, some investigators reported

better uptake after rhTSH than THW in some patients [30,31]. Such experience is difficult to interpret, given the frequently months-long intervals between radioiodine treatments and the potential influence of tumor de-differentiation during those times and of variation in therapeutic conditions, e.g., dietary iodine intake, at the times of the different treatments.

Assessment of the published outcomes of rhTSH-aided treatment is complicated by the late- or end-stage disease status of most patients, by heterogeneity in the patient characteristics, the natural history of the disease in different individuals, the study center response criteria and the scope of the data reported, and by the retrospective and frequently anecdotal nature of the reports. Nonetheless, it appears that a considerable proportion of published patients derived some clinical benefit from rhTSH-aided radioiodine treatment [46]. Of 115 patients for whom outcome had been reported by August, 2004, the clinical benefit rate was 65% (74/115), including a complete response in 2% (2/115), a partial response in 36% (41/115), and disease stabilization in 27% (31/115) of patients. Responses were defined according to radiological or biochemical (Tg) criteria, or both. Thirteen patients died of thyroid cancer ($n=12$) or were discharged to hospice ($n=1$) 40 days to ~ 36 months after the rhTSH-aided treatment, including two former partial responders, in one of whom rhTSH-aided radioiodine treatment.

The role of rhTSH-aided radioiodine treatment of DTC, especially in the curative treatment of earlier-stage patients, such as those with lung "miliary" micrometastases, must be defined by further studies. This investigation preferably would include a prospective, randomized pilot dosimetry study comparing rhTSH- and THW-aided radioiodine kinetics that could confirm "proof of concept" and provide guidance in radioiodine dosing with rhTSH, followed by a multicenter, randomized, prospective study comparing the two stimulation methods in as homogeneous as possible a patient population. In the meanwhile, a multicenter, multinational, retrospective study involving some 400 patients, in which statistical analysis is ongoing as of this writing, should provide additional useful information on rhTSH-aided ^{131}I treatment.

Positron emission tomography (PET) scanning

rhTSH has been suggested to stimulate uptake of 18-fluorodeoxyglucose (18-FDG) by DTC lesions in PET scanning during thyroid hormone therapy in a prospective study by Petrich et al. [54] involving 30 DTC patients who had elevated or borderline

elevated Tg levels and negative or equivocal results on ^{131}I or morphological imaging. The study population had a mean age of 55 years, and had undergone primary treatment a mean 4.9 years (range 0.1–12.1 years) previously. The patients received thyroid hormone throughout the study and underwent unstimulated scans at the start of the trial and then rhTSH-aided scans a mean 9.3 ± 8.8 weeks later. The scans under TSH suppression detected 45 foci and 22 tumor-like lesions in nine subjects, while the rhTSH-aided scans detected 82 foci and 78 tumor-like lesions in 19 patients. Both methods of measurement used to quantify FDG uptake, the tumor-to-background ratio (TBR; count density in the suspected lesion/count density in a reference area consisting of neck muscle) and the standardized uptake values (SUV) were significantly higher with scanning that was rhTSH-aided versus unstimulated: the mean TBR of regions showing positive FDG uptake under either type of scanning was 5.51 ± 2.99 after rhTSH administration compared to 2.54 ± 1.89 without rhTSH ($p < 0.0001$, paired t-test), while the respective corresponding mean SUV were 2.77 ± 1.58 versus 2.05 ± 1.45 ($p < 0.001$, paired t-test). Suggesting specificity of rhTSH-aided PET was the observation that in four foci found by histological analysis ($n=3$) or observation and Tg testing ($n=1$) to be inflammatory, TBR and SUV, were only marginally, and non-significantly, increased by rhTSH administration.

A subsequent, small, prospective, randomized study [55] involving seven DTC patients with biochemical signs of residual disease but negative dxWBS provided additional evidence that rhTSH improves 18-FDG PET scanning. In this study, patients were randomized to receive two 18-FDG-computed tomography fusion scans, one after rhTSH administration and one on thyroid hormone suppression therapy (THST) alone, in the two possible sequences. Image interpretation was performed by two examiners blinded to the rhTSH status of the scan. The rhTSH scans identified all lesions seen on the THST scans, four additional lesions, and one patient who was negative on the THST scan. Additionally, mean and maximum TBR were significantly higher in the rhTSH scans ($p = 0.02$ for both comparisons, Wilcoxon signed rank test). However, the mean and maximum SUV of the five lesions seen on both the rhTSH and the suppression scan were numerically, but not statistically significantly higher, for the rhTSH scans ($p = 0.06$ and $p = 0.3$, respectively, Wilcoxon signed rank test).

The findings of these studies need to be confirmed by additional trials, and the role of rhTSH in iodine

124 PET scanning also merits, and indeed is under investigation.

Pediatric use

rhTSH is indicated in patients age 18 years and older, and due in large part to the rarity of pediatric DTC, limited study of rhTSH use has been carried out in younger patients. Jarzab et al. [56] discussed their preliminary experience with 11 rhTSH-aided radioiodine therapies in six children ages 6–16 years (mean: 13 years). One patient received five courses and another patient, two courses of rhTSH-aided radioiodine, and the remainder of the children, one course each. The rhTSH dose was not adjusted for body weight or body surface area. After rhTSH administration, peak serum TSH was a mean 200 ± 66 mU/l (range 128–289 mU/l) and free T₃ and free LT₄ levels remained stable under continuous LT₄ intake. The only side effect noted was a mild, transient skin rash after the second rhTSH course in one girl. In one of two children given rhTSH primarily to aid thyroid remnant ablation, post-ablation scanning detected a previously unsuspected mediastinal focus leading to a THW-aided radioiodine treatment resulting in apparent remission. Of four children given rhTSH to aid ¹³¹I treatment of pulmonary metastases (and in one case, also a mediastinal lymph node lesion), two had partial tumor regression, one, who also had been given retinoids, had stable disease, and one was considered to have had confirmation by post-therapy scanning of complete remission attributable to prior THW-aided treatment.

Iorcansky et al. also have published data on pediatric rhTSH use [57]. Their results suggested that serum TSH levels are similar in children and adults, notwithstanding earlier work by other investigators that suggested an inverse correlation between post-rhTSH serum TSH peaks and body surface area [58] or lean body mass [59]. Mean serum TSH in the Iorcansky et al. series of children given rhTSH ($n = 19$) was 134 ± 44 mU/l 24 h after the second rhTSH injection. At the time of radioiodine administration ~24 h after the second injection, the mean serum TSH level in the children was 134 ± 75 mU/l, versus 105 ± 43 mIU/l in one adult rhTSH series ($n = 45$) [47] and 124 ± 59 mU/l in another adult rhTSH series ($n = 117$) [9].

Recently, Hoe and coworkers published their retrospective experience with 11 standard courses of two consecutive daily intramuscular injections of 0.9 mg rhTSH to aid serum Tg testing with or without dxWBS in seven pediatric patients (ages 8–17 years, 5 female, histology papillary in 6 and follicular in 1) seen at the Children's Hospital of

Philadelphia from 2000–2004 [60]. In this series, serum TSH levels were 224 ± 29 mU/l the day of the second rhTSH injection, and 13 ± 5 mU/l 3 days after that. In this study, rhTSH was demonstrated to stimulate Tg secretion and radioiodine uptake in children, and no patient reported any adverse effect of rhTSH.

A multicenter retrospective database including a relatively large number of patients age ≤ 18 years is currently being collected in a collaboration among our center, the University of Perugia, and participating investigators, to more fully characterize safety and dosing issues related to rhTSH use in the pediatric population. Clinicians who have used rhTSH in patients age ≤ 18 years are invited to contact the author if they have an interest in participating in this study.

Other experimental uses

At least three other experimental uses of rhTSH in DTC have been investigated. First, rhTSH has been studied as an adjunct to iodine 123 (¹²³I) WBS [61]. Although it currently is more expensive than ¹³¹I, ¹²³I may achieve superior images, avoid “stunning” effects impairing the efficacy of subsequent radioiodine ablation or treatment, and require fewer radiation precautions. A retrospective analysis of 101 consecutive whole-body scans with each radio-nuclide showed that rhTSH-aided 123I and 131I scans had similar rates of concordance with serum Tg measurement (90% vs. 84%) and detected similar numbers of disease foci (9 in 6 patients vs. 10 in 9 patients) [61]. Second, Taieb and coworkers [62] studied subcutaneous (SC) instead of the standard IM administration of the approved rhTSH regimen of two consecutive daily injections of 0.9 mg to aid serum Tg testing and dxWBS in five consecutive patients, ages 41–73 years, on oral anticoagulants. The study was performed in an effort to minimize the risk of injection site hematoma in such individuals. SC administration produced a rapid, sharp increase in serum TSH levels in all patients. The mean peak TSH level was 246 ± 68 mU/l and a retrospective comparison with the center's data on IM injection preliminarily and anecdotally suggested that SC administration might produce a higher peak level. Serum Tg rose rapidly and markedly, and dxWBS showed thyroid bed uptake, in one patient with a large thyroid remnant; in the other four patients, undetectable Tg and negative dxWBS were considered to confirm previously suspected disease-free status. No side effects of SC rhTSH were observed.

Lastly, a small ($n = 16$) pilot trial [63] tested rhTSH or thyroid hormone dose reduction as

potential chemo-sensitization strategies in diffuse lung metastases of poorly-differentiated thyroid carcinoma. The rationale was that TSH elevation might transiently stimulate metabolism of poorly-differentiated thyroid cancer cells that retain TSH receptors, making these cells more sensitive to chemotherapy that targets rapidly-dividing cells, in this study, carboplatinum+epirubicin. There were one complete and five partial responses (37% objective response rate) and seven cases of disease stabilization (44%), and in the 14 patients completing treatment, median survival was 21 months (range: 15–34 months) from the start of chemotherapy.

Safety

rhTSH typically is well tolerated, with short-lived and generally mild nausea (~10% incidence), headache (~7% incidence) and asthenia (~3% incidence) the most common side effects [64]. Transient and usually mild chills, fever, flu-like symptoms, vomiting with or without nausea, dizziness or paresthesia occur in 1–2% of patients each. Our anecdotal impression, based on a limited number of patients, is that vomiting and nausea may be more frequent rhTSH side effects in pediatric than in adult patients.

Hypersensitivity reactions, consisting of one or more of urticaria, rash, pruritus, flushing or respiratory difficulties, are rare. As alluded to earlier, however, due to the possibility of tumor expansion, caution is warranted, and glucocorticoid premedication indicated, when rhTSH is given to patients with known or suspected metastases – especially bulky ones – or large thyroid remnants. Such expansion, also a concern under THW, may potentially cause compression symptoms in confined anatomical spaces or aggravation of preexisting impaired function (e.g. in the neck, lungs, central nervous system or bones). For example, pain from bone metastases has been documented to transiently and in some cases sharply increase after rhTSH administration, although in most instances, patients reported that the increase was shorter-lived, milder, or both after rhTSH than under THW [23,30,31]. Some ten cases of neck edema, often accompanied by a choking sensation or dyspnea, have appeared in the literature [23,24,27,32,65]; these cases either resolved spontaneously or responded to steroid treatment. Rare reports exist of neurological symptoms ranging from mild extremity paresthesia to paraparesis in patients with metastases in or around the brain or spinal cord [27,30]. Isolated cases involving patients with late-stage DTC have been published of pathological fracture, clinical thyrotoxicosis, or

pneumonia possibly or probably related to rhTSH administration [18,30].

Pharmacoeconomics

The main drawback to rhTSH use is the relatively high acquisition cost of the drug. However, in addition to the QOL, safety and convenience benefits of rhTSH, its acquisition costs must be weighed against the high societal costs of THW. Our 131-patient pilot survey [15] found a 9-day median absence from salaried work per THW for dxWBS over and above the 2-day absence necessary for the procedure regardless of TSH stimulation method. In addition, of 59 patients in our series who were employed outside the home, 42, or 71%, reported moderately to severely decreased productivity during times that they were able to work. These findings agree with those of an earlier French study (J. Leclère, Satellite Symposium Presentation at the European Association of Nuclear Medicine Congress, Paris, France, 3 September 2000), which found a mean 13.7 missed workdays per THW, including time for procedures, in 69 patients, and with those of an earlier, 25-patient Dutch study [66], in which respondents reported an inability to work for a mean 45%, or unproductiveness in work for a mean 14% of their normal working hours during THW.

We recently used the observations from our pilot survey to retrospectively construct a societal cost model comparing THW versus rhTSH administration in the dxWBS setting in Germany [15]. We also performed a sensitivity analysis by increasing the conservatism of eight assumptions about THW costs. In our societal cost model, the total cost per dxWBS was some €1 648 for THW versus some €1321 for rhTSH, i.e., approximately €326, or ~25% greater, for withdrawal relative to rhTSH. In our sensitivity analysis, societal costs of rhTSH exceeded those of THW by approximately €307, or ~30%. Taken together, the results of our models suggested a roughly equivalent societal cost for the two forms of TSH stimulation.

In both our pharmacoeconomic model and our sensitivity analysis, the primary driver of THW costs was missed or unproductive workdays, which in Germany have to be covered by the individual employer, whereas the drug acquisition expenses are reimbursed by the patient's insurance. However, our study revealed a medical expense of THW that could be a more important cost driver, for example, in the USA than it is in Germany: health care resource use to treat hypothyroid symptoms. Thirty-eight percent of patients answering the relevant question on our survey (n=101) required at least one primary physician visit, and 20%, multiple

such visits, to treat hypothyroid symptoms, while 31% of patients answering the relevant survey question ($n=95$) needed at least one specialist physician visit, and 12%, multiple such visits. An earlier, 25-patient Dutch study [66] in a younger patient population than ours (mean age 41 years versus median age 52 years), however, found only a 16% incidence of primary care physician use to treat hypothyroid symptoms.

Additional studies are needed to better elucidate the pharmacoeconomics of both THW and rhTSH administration in different countries; prospective studies of course will be optimal for that purpose.

Conclusion

A number of important rationales exist for using rhTSH instead of THW for TSH stimulation in thyroidectomized patients with DTC. First, rhTSH use avoids clinical hypothyroidism and hence, decreases morbidity and enhances QOL in all such patients, and improves safety in those with concomitant illnesses that could be exacerbated under hypothyroid conditions. Second, with its relatively short-lived elevation of serum TSH levels, rhTSH administration at least theoretically diminishes the risk of tumor growth or compressive symptoms in patients with a history of rapid progression during a protracted period of TSH elevation. Third, because rhTSH administration preserves euthyroidism and hence, kidney function, renal radioiodine clearance is more rapid and extra-thyroidal radioactivity exposure lower than under hypothyroidism secondary to THW. However, at the same time, because TSH elevation is shorter-lived after rhTSH than after THW, so is stimulation of iodine efflux by thyroid cells and this phenomenon may result in equivalent thyroidal radiation exposure under the two stimulation modalities. Fourth, rhTSH is the only means of providing TSH stimulation in patients with absent, insufficient or unusually slow endogenous TSH production. Lastly, the predictable timing of TSH elevation with rhTSH administration may offer convenience advantages over THW, especially in the ablation setting, where it could expedite the completion of primary treatment.

Because of these rationales and the abundant documentation in clinical studies of equivalent efficacy with that of THW, rhTSH use is the "gold standard" for TSH elevation whenever serum Tg testing or dxWBS are performed. Following a randomized, prospective, multicenter, multinational study that established non-inferiority to THW, rhTSH administration recently has been approved

in Europe to aid radioiodine ablation with 3.7 MBq of ^{131}I in low risk patients. Additional investigation is underway of rhTSH use as an adjunct to ablation with lower radioiodine activities. The most-studied experimental use of rhTSH is stimulation of radioiodine treatment of locally aggressive or distant metastatic DTC, especially the latter. Albeit anecdotally, a considerable literature suggests that rhTSH administration may have equivalent efficacy to that of THW as an adjunct to (essentially palliative) radioiodine treatment of late-stage disease. Indeed, rhTSH is the only means of making such treatment available to certain patients, e.g., those who are unable to tolerate clinical hypothyroidism, or at risk of serious morbidity under hypothyroid conditions. Other experimental indications for rhTSH include stimulation of FDG or iodine 124 uptake in PET scanning or of ^{123}I WBS, use in children, SC injection, and use as a chemosensitization agent.

rhTSH is generally well-tolerated, with transient, often mild nausea, headache or vomiting the most common side effects. As with THW, caution and steroid premedication are warranted when using rhTSH in patients known or suspected to have bulky thyroid remnants or to have tumor in confined anatomical spaces, e.g., the central nervous system, airways, or bones.

The main disadvantage of rhTSH is its relatively high acquisition cost. However, studies have suggested that from a societal perspective, this cost may be offset by improved work productivity and fewer missed workdays, as well as decreased medical resource consumption when hypothyroid symptoms are absent.

The introduction of rhTSH has had an important impact on a variety of dimensions of DTC follow-up and care. Ongoing investigation is likely to extend the applications for this drug and to further improve patient QOL and treatment.

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