0021-972X/03/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 88(9):4110–4115

doi: 10.1210/jc.2003-030298

Radioiodine Treatment with 30 mCi after Recombinant Human Thyrotropin Stimulation in Thyroid Cancer: Effectiveness for Postsurgical Remnants Ablation and Possible Role of Iodine Content in L-Thyroxine in the Outcome of Ablation

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The main steps in the management of differentiated thyroid cancer are thyroidectomy, treatment with iodine-131 (^{131}I), and follow-up with whole-body scanning (WBS) and serum thyroglobulin (Tg) determination. Both ^{131}I treatment and follow-up require maximum stimulation of normal or pathological thyroid remnants by TSH. The use of recombinant human TSH (rhTSH) has been shown to be useful for follow-up, whereas previous reports are not univocal regarding the use of ^{131}I postsurgical ablation of thyroid remnants, at least when low doses (30 mCi) of ^{131}I are administered. A possible explanation for the diminished effectiveness of ^{131}I treatment after rhTSH may be the interference of iodine content of L-thyroxine (L-T4) therapy during the protocol of administration of rhTSH. We have evaluated the effectiveness of stimulation by rhTSH for radioiodine ablation of postsurgical remnants, stopping L-T4 the day before the first injection of rhTSH and restarting L-T4 the day after ^{131}I. The study included two groups of patients: group 1 included 16 patients with differentiated thyroid cancer (15 papillary cancers and 1 follicular cancer, stages I and II), who were treated with 30 mCi ^{131}I with the aid of rhTSH, using the standard protocol but stopping L-T4 as stated previously; and group 2 included 24 patients with the same features (histology and stage) of disease treated with 30 mCi in the hypothyroid state after L-T4 withdrawal. In both groups, serum TSH reached a very good stimulation level [76–210 U/liter (mean, 112 ± 11 SE) and 38–82 U/liter (mean, 51 ± 3 SE), respectively]. At the first WBS (after ^{131}I treatment), all patients showed thyroid remnants. Furthermore, two patients of the first group and three patients of the second group showed lymph node metastases. After 1 yr, all patients were studied again and underwent WBS with a tracer dose of ^{131}I and serum Tg measurement using rhTSH with the same protocol in both groups. The percentage of ablation (undetectable Tg and a negative WBS) was higher, although not reaching statistical significance, in patients treated with rhTSH: 81.2% in patients treated by rhTSH withdrawal and 75.0% in patients treated by L-T4 withdrawal, respectively. No patient experienced symptoms of hypothyroidism during the 4 d of L-T4 interruption, and serum T4 remained in the normal range. Urinary iodine was analyzed in both groups and compared with a control group of patients who received, for diagnostic purposes, rhTSH without stopping L-T4. In the first group, urinary iodine was 47.2 ± 4.0 μg/liter (mean ± SE; $P = 0.21$ *vs.* the second group, $P = 0.019$ *vs.* control group). In the second group, urinary iodine was 38.6 ± 4.0 μg/liter (mean ± SE; $P < 0.001$ *vs.* control group); urinary iodine in the control group was 76.4 ± 9.3 μg/liter (mean ± SE).

Our data show that rhTSH, as administered in the protocol stated previously, allows at least the same rate of ablation of thyroid remnants when low doses (30 mCi) of ^{131}I are used. The possible role of interference of iodine content in L-T4 is not surprising if we consider that the amount of iodine in 30 mCi is negligible (5 μg) compared with the amount of iodine content in a daily dose of T_4 (~50 μg). The cost of rhTSH seems modest compared with the high cost of complex therapeutic regimens in other areas of oncology and in consideration of the well-being of patients and of the high level of effectiveness of the treatment. (*J Clin Endocrinol Metab* 88: 4110–4115, 2003)

DIFFERENTIATED THYROID CANCER (DTC) is a neoplasm with a relatively indolent course in which long-term survival is usually good. However, tumor recurrence is common, affecting up to 20% of patients, sometimes decades after the initial therapy (1, 2). Despite some controversies for tumors smaller than 1 cm and for minimally invasive follicular cancer, there is general agreement that total thyroidectomy should be performed. Another debated question regards the use of thyroid remnants ablation by iodine-131 (^{131}I). Nevertheless, routine administration of ^{131}I after thyroidectomy, although its beneficial effects are not confirmed by some studies (3–5), is usually performed. Total thyroidectomy and ablation of thyroid remnants with ^{131}I are then followed by L-thyroxine (L-T4) TSH-suppressive therapy (6, 7). Periodic follow-up with whole-body scanning (WBS) with a tracing dose of ^{131}I and serum thyroglobulin (Tg) measurement is then performed. Radioiodine treatment and follow-up, as stated previously, requires the stimulation of normal or pathological thyroid residual tissue. Maximum

Abbreviations: DTC, Differentiated thyroid cancer; FT3, free T_3; FT4, free T_4; ^{131}I, iodine-131; L-T4, L-thyroxine; rhTSH, recombinant human TSH; Tg, thyroglobulin; WBS, whole-body scanning.

stimulation can be achieved by L-T4 withdrawal or by administration of recombinant human TSH (rhTSH) (8), now widely available, without the need of stopping L-T4 therapy. rhTSH has been shown to be useful in the follow-up of DTC. The use of rhTSH for radioiodine treatment is indicated in patients who cannot tolerate L-T4 withdrawal and in patients who cannot generate endogenous TSH (9–13). In contrast, there is no widespread experience regarding the use of rhTSH for the initial treatment (14, 15). Moreover, some data would suggest that rhTSH is not as effective for ablation of postsurgical thyroid remnants when low-dose (30 mCi) ^{131}I is used (16). Possible explanations for these data are the enhanced clearance of ^{131}I in the euthyroid state and interference of the iodine derived from the metabolism of T_4.

We evaluated the effectiveness of rhTSH for ablation of postsurgical thyroid remnants by low-dose ^{131}I (30 mCi), and, to avoid a possible role of iodine interference, we stopped L-T4 the day before rhTSH and restarted this treatment the day after the dose of ^{131}I.

Patients and Methods

The rate of ablation was compared in two groups of consecutively enrolled patients. Group 1 was represented by 16 patients (age, 22–71 yr; 10 females and six males) who were, after their written consent, consecutively enrolled in the study as soon as rhTSH was made available in Italy. All patients had papillary cancer or minimally invasive follicular cancer and could be considered patients at low risk of recurrence (stages I and II). All patients underwent total thyroidectomy and lymphectomy of the central compartment of the neck. Patients in whom we found positive laterocervical lymph nodes at fine-needle aspiration before surgery also underwent modified hypsolateral laterocervical lymphectomy. After surgery, all these patients began treatment with a TSH-suppressive dose of L-T4. After at least 30 d, TSH and free thyroid hormones were checked and, if necessary, the dose of L-T4 was modified. Subsequently, patients received ^{131}I treatment using rhTSH as reported below. Group 2 was represented by 24 patients (age, 24–69 yr; 18 females and six males) with the same features (histology and stage) of disease who were treated the year before the availability of rhTSH. These patients underwent L-T4 withdrawal, and ^{131}I treatment was performed in the hypothyroid state, the patients having adhered to a low-iodine diet 2 wk before. The time between thyroidectomy and ^{131}I treatment was 42–57 d, depending on the availability of ^{131}I for treatment.

Table 1 summarizes pathological tumor node metastasis stage and histology of the cancers in both groups of patients.

Control group for data of urinary iodine

The data of urinary iodine in both groups were compared with a control group of 16 patients (age, 20–66 yr; nine females and seven males) who underwent standard protocol (without L-T4 interruption) with rhTSH for diagnostic purposes. These patients were comparable for stage of disease (stages I and II), and the dose of L-T4 ranged between 800 and 1450 μg weekly.

TABLE 1. Histology and clinical stage of both groups of patients studied

	pT1–2, Nx	pT1–2, N1	CVPC	FVPC	FC
Group 1					
<45 yr	3	4	4	3	
>45 yr	9		7	2	
Group 2					
<45 yr	4	5	6	2	1
>45 yr	15		11	3	1

CVPC, Classical variant of papillary cancer; FVPC, follicular variant of papillary cancer; FC, follicular cancer.

Hormone, Tg, and urinary iodine measurements

TSH, free T_4 (FT4), free T_3 (FT3), Tg, and anti-Tg and antithyroid peroxidase antibodies were measured by Immulite 2000 (Diagnostic Products, Los Angeles, CA). The functional sensitivity of Tg was 0.5 ng/ml. The determination of urinary iodine was performed on the overnight urine (17) the day after the last injection of rhTSH and just before ^{131}I administration and was performed by HPLC combined with electrochemical detection. After one-step sample clean-up (C18 columns), iodide was separated by ion-pair reversed phase HPLC and detected electrochemically with a silver electrode (Coulochem II; ESA, Inc., Bedford, MA).

Protocol for rhTSH administration (Fig. 1)

The protocol for rhTSH administration, both for therapeutic and diagnostic purposes, was the same as reported below. After adhering to a low-iodine diet for 2 wk, patients underwent stimulation with rhTSH (Thyrogen; Genzyme Corp., Cambridge, MA. rhTSH was administered (0.9 mg, im) for two consecutive days, L-T4 was stopped the day before the first administration of rhTSH, and L-T4 was then given again the day after administration of ^{131}I. Serum samples of TSH, FT4, FT3, Tg, and anti-Tg antibodies were taken the day before the first administration of rhTSH and the day after the second administration of rhTSH. Serum samples for Tg were also taken 2 and 3 d after the last administration of rhTSH.

^{131}I administration and WBS

Thirty-eight to 45 d after surgery, 30 mCi (1.11 Gbq) ^{131}I were administered for therapeutic purposes, the day after the last injection of rhTSH. A posttherapy WBS was acquired after 4–6 d. Twelve months after therapy, a diagnostic ^{131}I WBS was performed according to the same protocol of stimulation by rhTSH. Images were obtained 48 h after oral administration of 5 mCi (185 MBq) ^{131}I with a double-head gamma camera (Millenium MG; GE Medical System, Milwaukee, WI) using a 3/8-inch-thick crystal and a high-energy, general all-purpose collimator. WBS with anterior and posterior views were acquired after scanning for a minimum of 30 min. Anterior neck/chest spot views with and without markers (technetium-99m) on the suprasternal notch and chin were acquired after scanning a minimum of 15 min or after obtaining 150,000 counts.

Thyroid bed uptake was diagnosed on whole-body or spot view images that showed only visible uptake between the suprasternal notch and thyroid cartilage.

Follow-up

In all patients, serum levels of TSH, FT4, FT3, Tg, and anti-Tg antibodies were periodically assessed. All patients had undetectable levels of Tg during TSH- suppressive treatment. Patients who had positivity of anti-Tg antibodies were excluded from the study.

After 1 yr, the outcome of thyroid ablation was assessed in both groups by conventional ^{131}I scan and serum Tg measurements using rhTSH as in the protocol stated previously.

Statistical analysis

Results are expressed as mean ± SE for laboratory data and as percentage for the groups of subjects. Student's *t* test was used to compare laboratory data. The χ^2 test was used to detect differences in the proportion of cases.

Results

Serum TSH in patients who underwent ^{131}I treatment in the two groups was 76–210 mU/liter (112 ± 11) in the first group the day after the second injection of rhTSH and 38–82 mU/liter (51 ± 3) in the second group (hypothyroid patients). At that time, Tg was 1.2–21.1 ng/ml in patients treated with rhTSH stimulation (less than 0.5–2.3 ng/ml before rhTSH) and less than 0.5–16.0 ng/ml in hypothyroid

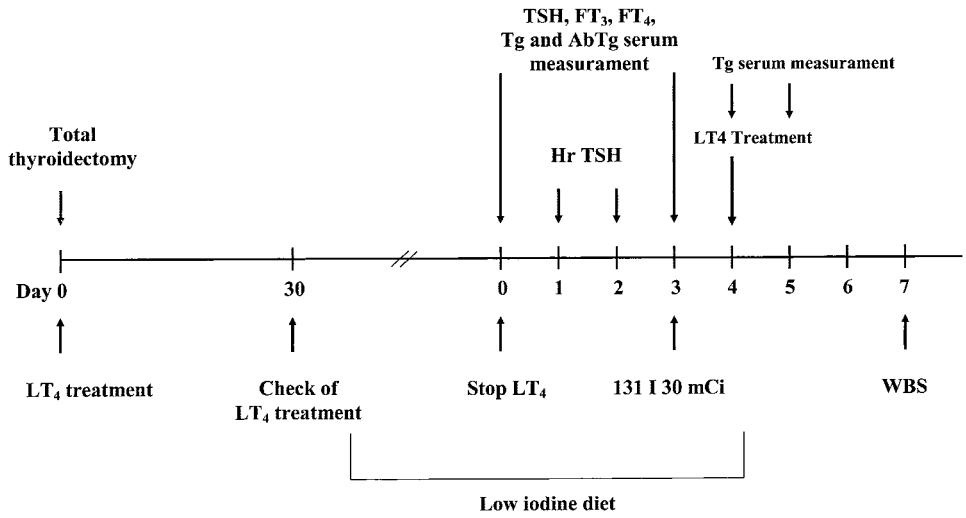

FIG. 1. Protocol for rhTSH administration.

TABLE 2. TSH, free thyroid hormones, and Tg before the treatment with ^{131}I

	TSH	FT4	FT3	Tg
Group 1	112 ± 11 (76–210) mU/liter; before rhTSH, 0.11 ± 0.03 (<0.01–0.3)	1.76 ± 0.04 (1.61–1.91) ng/dl	4.04 ± 0.27 (3.1–4.8) pg/ml	After stimulation, 9.42 ± 1.60 (1.2–21.1); before rhTSH, 1.25 ± 0.33 (0.5–4.3) ng/ml
Group 2	51 ± 3 (38–82) mU/liter	0.24 ± 0.01 (<0.20–0.31) ng/dl	1.29 ± 0.08 (<1.0–1.6) pg/ml	5.48 ± 1.14 (<0.5–16.0) ng/ml

Conversion factor for T_3, pg/ml × 1.536 = pmol/liter; conversion factor for T_4, ng/dl × 12.87 = pmol/liter. Serum values of Tg are the peak values.

patients. TSH, free thyroid hormones, and Tg data before ^{131}I treatment are reported in Table 2.

After surgery, both patients treated with ^{131}I after rhTSH and patients in the hypothyroid state showed residual thyroid tissue in the thyroid bed at the posttreatment scan. Also, two patients treated with rhTSH showed minor abnormal areas of uptake in the neck, and three hypothyroid patients showed a similar minor abnormal uptake in the neck (Fig. 2).

At the 1-yr follow-up, 14 patients (87.6%) treated with ^{131}I after rhTSH showed a negative WBS. In one case, there was minor uptake in the thyroid bed, and in another case, WBS was clearly positive for a residual uptake in the thyroid bed. In hypothyroid patients treated with ^{131}I, WBS was negative in 18 patients (75.0%). In one case, there was a minor uptake in the thyroid bed, and in the other cases, WBS was clearly positive for residual uptake in the thyroid bed. Values of Tg in both groups were not completely in agreement with the results of diagnostic WBS. In the group of patients treated by rhTSH, Tg was less than 0.5 ng/ml in 14 patients (87.6%; 13 patients with a negative WBS, and one patient with minor uptake in the thyroid bed). Tg was 1.1 ng/ml in the one patient with a negative WBS, whereas in the last patient (with a positive WBS) Tg was 6.1 ng/ml. In the group of hypothyroid patients, Tg was less than 0.5 ng/ml in 19 patients (79.1%): all 18 patients with a negative WBS and one patient with minor uptake in the thyroid bed. In the other patients, with a positive WBS, Tg was 2.9–4.6 ng/ml. In Fig. 3, data of WBS and serum Tg in both groups of patients are reported. Data about TSH and free thyroid hormones, at that time, were similar to those before treatment with ^{131}I and are not reported.

Comparison of urinary iodine showed the following results. In the first group (patients treated with rhTSH as in the protocol used in this study), urinary iodine was 47.2 ± 4.0 μg/liter ($P = 0.21$ *vs.* the second group, $P = 0.019$ *vs.* control group). In the second group (patients treated in hypothyroidism), urinary iodine was 38.6 ± 4.0 μg/liter ($P < 0.001$ *vs.* control group), and in the control group (patients treated with rhTSH with standard protocol), urinary iodine was 76.4 ± 9.3 μg/liter.

After administration of rhTSH, no patient had any significant side effects. No symptoms, even mild, of hypothyroidism were reported by patients during the 4 d of L-T4 withdrawal.

Discussion

Thyroid cancer represents no more than 2% of all cancers. Approximately 95% of thyroid cancers originate in follicular cells, and the majority of cases are DTC: papillary cancer and a minority of follicular cancer (18). DTC maintains the capability of trapping iodine and synthesizing Tg, and these two features represent the crucial points of DTC management (18, 19). The capability of trapping iodine allows ablation of postsurgical normal and neoplastic remnants with ^{131}I and allows for the discovery of pathological tissue with WBS. Moreover, Tg represents an exceptionally useful marker that can be even more sensitive than WBS with a

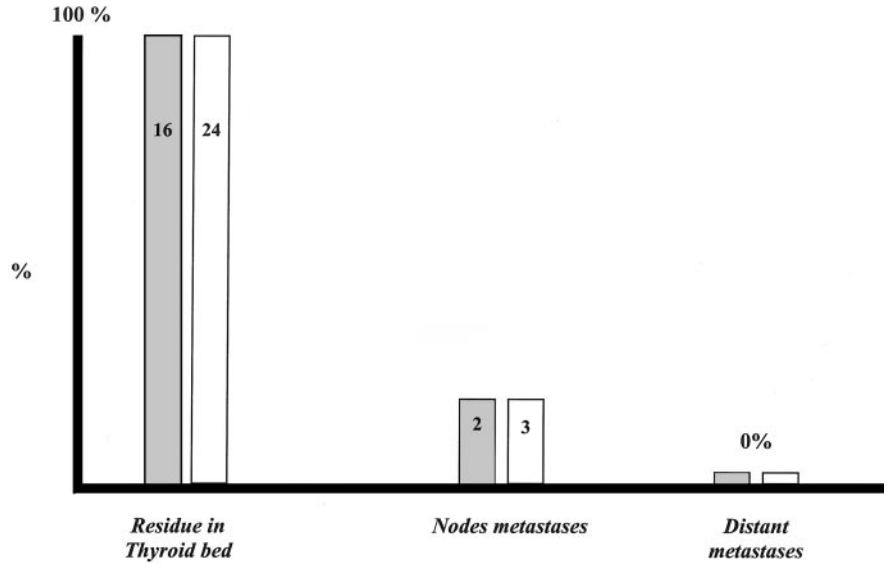

FIG. 2. WBS after a therapeutic dose of ^{131}I. ▨, Patients treated by rhTSH stimulation; □, patients treated in hypothyroidism. The number of patients is indicated inside the *columns*.

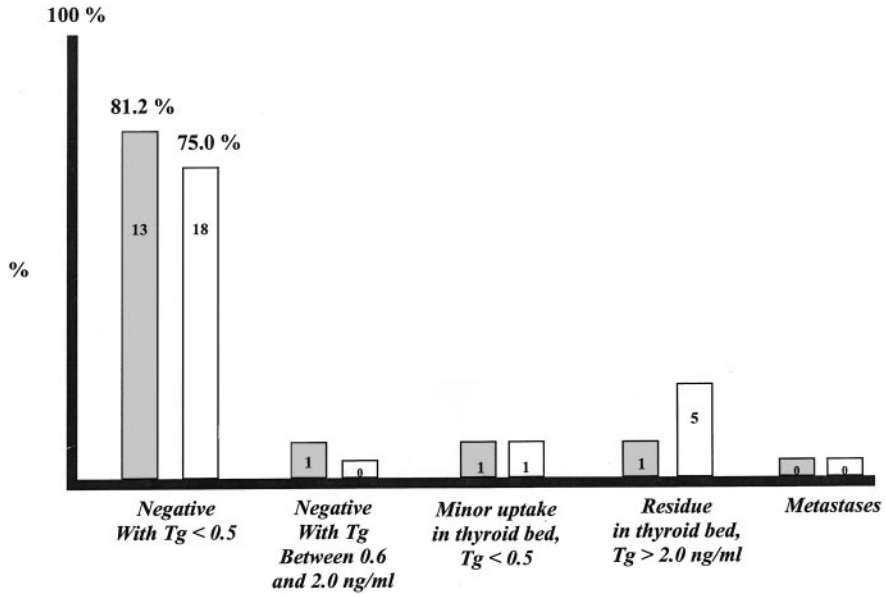

FIG. 3. WBS with a tracer dose of ^{131}I and serum Tg values after 1 yr from the therapeutic dose of ^{131}I. ▨, Patients stimulated by rhTSH; □, patients in treated in hypothyroidism. The number of patients is indicated inside the *columns*.

tracer dose of ^{131}I (20, 21). However, some controversies exist. One regards the necessity of total thyroidectomy for small papillary cancer and for minimally invasive follicular cancer. Papillary cancer may be multicentric, and microscopic papillary cancer may give lymph node metastases. For these reasons, there is general agreement that radical treatment is advisable at least for this cancer. Another controversy concerns the necessity and, above all, the amount of ^{131}I dose to ablate postsurgical remnants. Regarding the second point, the standard doses of ^{131}I commonly used range from 30 mCi to 100 mCi (18). However, follow-up is easier, and long-term survival for DTC is better, when total thyroidectomy and ablation of postsurgical thyroid remnants are performed (22).

Both administration of ^{131}I for therapeutic or diagnostic purposes and serum Tg measurements need maximum stimulation by TSH. For many years, L-T4 withdrawal and the hypothyroid state has represented the way to achieve high levels of endogenous TSH. Today, the availability of rhTSH gives further options in the management of DTC (23). Previous studies have shown that rhTSH represents an improvement in the follow-up of DTC, because Tg measurements after stimulation with rhTSH seem to have even more sensitivity than after L-T4 withdrawal, whereas, in contrast, WBS after rhTSH may be a little less sensitive than after L-T4 withdrawal (21, 23).

Other previous reports about rhTSH for therapeutic purposes are not of univocal interpretation because the great majority of these patients could not tolerate L-T4 withdrawal for their advanced disease, and high doses of ^{131}I, at least 100 mCi, had been used (9–13). In these studies, rhTSH had been shown to be capable of bringing about an amelioration of the disease. Vice versa, there is not a widespread experience regarding rhTSH for the ablation of postsurgical remnants after using a low dose of ^{131}I (14, 15, 24), and a recent study would suggest that it is not as effective as L-T4 withdrawal, at least when 30 mCi were used (16). However, in this study,

a 24-h uptake with a tracer dose of ^{131}I (50 mCi) was measured and, for this reason, the time of administration of the therapeutic dose of ^{131}I was delayed by 24 h. At that time, the peak of rhTSH was lower, but, in contrast, *in vitro* studies of sodium iodide symporter have shown that its expression is delayed with respect to TSH stimulation. To date, the relative importance of these two points is unknown.

Therefore, rhTSH seems to be a very potent stimulator of Tg synthesis, but it does not appear potent enough to induce ^{131}I uptake for diagnostic and therapeutic purposes when small doses of ^{131}I are administered. Possible explanations for the reduced ^{131}I uptake may be an interference of the administration of T_4, or, as suggested in the previous study (16), the accelerated iodine clearance observed in euthyroid patients.

The easiest interpretation for the interference of T_4 on iodine uptake is that it is due to interference by iodine coming from L-T4 metabolism. In fact, the role of the amount of the iodine intake in the uptake of both tracer and therapeutic dose of ^{131}I has been clearly shown (19, 25). Our results using a protocol in which L-T4 has been interrupted for a few days, from the day before rhTSH until iodine administration, seem to emphasize the interference of iodine content of T_4 on the effectiveness of radiometabolic treatment. In our study, the percentage of ablation of postsurgical thyroid remnants was higher than the percentage of ablation reported previously and, in our experience, also higher than ablation after L-T4 withdrawal, although the difference did not reach statistical significance. These data are not surprising if we consider that rhTSH has shown a high biological activity *in vitro* and *in vivo* (8), that it produces a short, but high, peak, and that it is stronger in Tg synthesis than L-T4 withdrawal and its consequent hypothyroid state. Tg synthesis represents the way by which iodine is stored after it has been organified, and, therefore, Tg synthesis represents one of the means by which ^{131}I causes its destroying action. If we decrease the iodine pool as much as possible, we can have a sufficient stimulation for uptake of iodine and, therefore, a better therapeutic action. The comparison of the urinary iodine in patients treated with rhTSH in the standard protocol and in the group treated with rhTSH by our modified protocol has shown a decrease of urinary iodine in our subjects. These two groups were comparable for stage of diseases, and, of course, all patients were euthyroid. For these reasons, our data confirm that the short interruption of T_4 administration, as reported, can actually decrease the iodine pool.

The other potential problem in the use of rhTSH for radiometabolic treatment may be related to the clearance of iodine, which is enhanced in the euthyroid state, and could, therefore, determine, as stated previously, a high clearance of ^{131}I.

The therapeutic action of ^{131}I is based on complex mechanisms and depends on the amount of ^{131}I uptake and on the amount of ^{131}I stored inside the cells and follicles. For these reasons, additional studies on the kinetics of iodine and about absolute ^{131}I uptake will be necessary to understand the relative importance of the interference of iodine content of L-T4 and of the enhanced clearance of iodine on ^{131}I uptake, and to clarify the amount of ^{131}I urinary iodine stored after acute stimulation with rhTSH and during the hypothyroid state.

In point of fact, our data about ioduria confirm that the interruption of L-T4, as reported in our protocol, can decrease the size of the iodine pool and that stimulation of rhTSH in this condition allows a rate of ablation of thyroid remnants that is at least the same as in the hypothyroid state.

All the considerations about interference of iodine content of L-T4 seem to be of particular importance if we consider the relative proportion between the amount of iodine derived from thyroid hormone metabolism and the amount of iodine contained in 30 mCi ^{131}I. The former is at least of 50–60 μg daily, and the second is no more than 5 μg. Additional consideration should be given to iodine metabolism and body iodine pool. Most body iodine (~90%) is present in its organic form, both in the thyroid and in a smaller proportion in the thyroid hormone pool. An even smaller proportion (~250 μg during a normal intake of dietary iodine) is in the extracellular peripheral pool. This represents the inorganic element that is in equilibrium with intake of iodine, iodine coming from metabolism of thyroid hormones, and urinary excretion (4). Therefore, the amount of iodine coming from the daily dose of thyroid hormones may really represent an important source of interference.

In addition to the issues discussed previously, one other major advantage of rhTSH is in the avoidance of symptoms of thyroid failure. A report that analyzed the economic impact of hypothyroidism due to L-T4 withdrawal showed a cost of 1027 euros for each working person (26). Apart from a mere economic analysis, we have to consider the quality of life of the patient; moreover, 500 euros, which is the cost of rhTSH, seems modest when compared with the expenditure on complex therapeutic regimens for other neoplastic diseases. For these reasons, an important consideration regards the well-being of the patients who have interrupted treatment with L-T4 even for a few days. All patients were treated with L-T4 in a TSH-suppressive dose, and considering that the half-life of T_4 is about 7 d, the decrease in serum T_4 was negligible, obviously never in the range of hypothyroidism, and all the patients experienced a sense of well-being.

In conclusion, the use of rhTSH allows for the ablation of postsurgical thyroid remnants with a low dose of ^{131}I. This is not surprising if we consider that rhTSH is a potent stimulator of Tg synthesis, which represents the main way of storing iodine. However, a crucial point appears to be the avoidance, at least partially, of the interference of iodine coming from the metabolism of L-T4. The use of a modified protocol of rhTSH administration, with a short interruption of L-T4, can ameliorate the efficacy of radiometabolic treatment, with a perfect sense of well-being on the part of the patients. In our experience, we had an even higher percentage of ablation than with L-T4 withdrawal. Given these advantages, we think that the cost of the use of rhTSH seems negligible, considering that its use for the ablation of thyroid remnants will be performed only once in the majority of cases.

Acknowledgments

Received February 21, 2003. Accepted May 18, 2003.

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