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Patients with Hypothyroidism Taking Desiccated Thyroid Extract Lost Weight As Compared with an Equivalent Dose of Levothyroxine

Jerome M. Hershman

Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MK. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. J Clin Endocrinol Metab 2013;98:1982-90. Epub March 28, 2013.

SUMMARY

Background

"1991 was the centenary of the first use of a thyroid preparation to treat successfully a previously incurable disease, myxedema " (1). Around then, thyroid hormone preparations made up over 1% of all prescriptions filled by retail pharmacies. In 1988, one fourth of all thyroid hormone prescriptions were for natural preparations, mainly thyroid USP (desiccated thyroid) in the United States, even though synthetic T_4 had gradually replaced the natural preparations for three fourths of patients during the previous 20 years (2). Now it is rare for physicians to prescribe desiccated thyroid extract (DTE) instead of levothyroxine (L-T_4). However, many patients report that they "don't feel normal" while taking L-T_4, and they want the "natural preparation" that is advertised on the Web.

The current study is a careful comparison of desiccated thyroid extract and L-T_4 in the treatment of hypothyroidism.

Methods

Patients 18 to 65 years old in the military health system with a diagnosis of hypothyroidism on a stable dose of thyroid hormone were enrolled for the double-blind, prospective, randomized, crossover study. Patients with interfering illnesses or who were taking drugs that could alter thyroxine absorption or metabolism were excluded.

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The patients were treated with either DTE (Armour) or L-T_4 (Synthroid) in coded identical capsules. After 6 weeks taking the preparation, serum TSH was checked and the dose adjusted, if necessary, to achieve a target level of 0.5 to 3.0 mU/L. When this was achieved, the patients continued on the dose for at least 12 more weeks. Then they were crossed over to the other preparation for 16 weeks.

At the start of the study, and after each period on the thyroid preparation, the patients had biochemical and psychometric evaluations. The biochemical tests included TSH, free T_4, total T_3, sex hormone–binding globulin (SHBG), T_3 resin uptake, and reverse T_3.

The primary outcomes were four psychometric tests, including memory testing using the Wechsler memory scale, Beck Depression Inventory, a thyroid symptom questionnaire, and a quality-of-life general health questionnaire. At the completion of the study, each patient was asked whether he or she preferred the first or the second treatment.

In the statistical analysis, P values <0.05 were considered significant, and there was no adjustment for multiple comparisons.

Results

A total of 70 patients completed the study (53 women and 17 men; mean age, 51 years [range, 23 to 65]). With regard to the primary outcome, the patients showed no significant difference in symptom scores, answers on general health questionnaires, or neuropsychological testing between the two thyroid replacements. There was a decrease of 2.86 lb in the weight of patients during DTE therapy as compared with L-T_4 therapy (P<0.001). With regard to drug preference, 34 patients (49%) preferred DTE, 13 (19%) preferred L-T_4, and 23 (33%) had no preference; the preference for DTE over L-T_4 was statistically significant (P<0.002).

In subgroup analysis, patients preferring DTE had an average of 4-lb weight loss during the DTE treatment as compared with the L-T_4 treatment (P<0.001), and their subjective symptoms—such as concentration, memory, sleep, happiness, and energy level—were significantly better while taking DTE; some tests of memory were objective psychometric parameters that improved significantly during the DTE treatment period, but similar improvements in memory were seen in those who preferred L-T_4 as compared with baseline.

Based on the amounts of each preparation to maintain a normal serum TSH, the mean (±SD) L-T_4 dose during the study was 119.2±38.9 µg/day (range, 75 to 225); and the DTE dose during the study was 80.6±30.0 mg/day (range, 43 to 172). Therefore, 1 mg of DTE would be approximately equivalent to 1.47 µg of L-T_4.

During the DTE therapy, the serum T_3 and TSH were significantly higher, and the T_4 and FT_4 were significantly lower than during the L-T_4 therapy.

Conclusions

Desiccated thyroid extract therapy did not result in a significant improvement in quality of life as compared with L-T_4 therapy. DTE caused modest weight loss, and nearly half of the study patients preferred it over L-T_4.

ANALYSIS AND COMMENTARY

In recent years, there have been many studies comparing combinations of L-T_4 and T_3 with L-T_4 alone. In general, these studies have not shown the improvement in psychometric parameters reported in a highly cited study written 14 years ago (3). This has led most clinicians to avoid combination therapies. In addition, supranormal T_3 levels occurring several hours after ingestion of T_3 will sometimes trigger tachycardia in susceptible patients. In the current study, the mean serum TSH was in the normal range, and indeed the level while taking DTE was very slightly, but significantly, higher than the level during L-T_4 therapy. This indicated that a higher dose was

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not the cause of the weight loss during DTE therapy. Perhaps the elevated serum T_3, compared with that during L-T_4 therapy, has a greater effect on the thyroid-hormone alpha-receptor that is mainly responsible for caloric expenditure. Celi et al. have reported that subjects with hypothyroidism who are taking T_3 alone in a dose equivalent to that of L-T_4, based on serum TSH, had reduced weight (4).

Should the present study be used as a basis for more prescriptions for DTE in patients who demand it? DTE is now standardized by its L-T_4 and L-T_3 content. The ratio of potency (micrograms of L-T_4 per milligram of DTE = 1.47) found in this study is smaller than the 1.67 ratio cited in USP drug information (5), but considerably higher than the value of 1 µg/mg calculated based on TSH suppression to 5 mU/L and to suppression of TRH-induced TSH reported in a study in 1978 (6). This could have been due to different potency or bioavailability of each preparation at that time. Based on the currently stated T_4 and T_3 content of Armour thyroid, 38 µg of T_4 and 9 of µg T_3 per 65 mg of DTE, that is equivalent to about 69.5 µg of T_4, if one assumes that T_3 is 3.5 times more potent than T_4 when given orally. The ratio of L-T_4 to DTE in micrograms per milligram (69.5/65 = 1.07), is closer to the 1 µg/mg proposed in 1978 than the 1.47 µg/mg found in this study. It requires considerable variability in absorption of the two preparations to arrive at the conclusion that 1 mg of DTE is equivalent to 1.47 µg of L-T_4. However, the comparison of potency in fact shows large individual variability, so that switching from one preparation to the other requires careful titration in each individual.

Many endocrinologists refuse to prescribe DTE under any circumstances, even telling the patient to find another doctor who may do it. I think that the present study shows that the switch is not so dangerous, as long as the serum TSH remains in the normal range with careful titration of the DTE dose. The many years of satisfactory therapy with synthetic levothyroxine make it the vastly preferred substitution therapy, but for the patient who insists on continuing or trying DTE, I think that it is no more dangerous than adding some additional L-T_3 in the hope that it will improve persistent "hypothyroid" symptoms in the patient taking L-T_4.

I am interested in receiving comments about this point of view from our readers.

References

1. Sawin CT. Who takes thyroid hormone? Thyroid 1991;1:281.
2. Kaufman SC, Gross TP, Kennedy DL. Thyroid hormone use: trends in the United States from 1960 through 1988. Thyroid 1991;1:285-91.
3. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med 1999;340:424-9.
4. Celi FS, Zemskova M, Linderman JD, et al. Metabolic effects of liothyronine therapy in hypothyroidism: a randomized, double-blind, crossover trial of liothyronine versus levothyroxine. J Clin Endocrinol Metab 2011;96:3466-74. Epub August 24, 2011.
5. United States Pharmacopeia. Drug information for the health care professional. Vol. 1. 20th ed. Greenwood Village, CO: United States Pharmacopeial Convention, 2000.
6. Sawin CT, Hershman JM, Fernandez-Garcia R, Ghazvinian S, Ganda OP, Azukizawa M. A comparison of thyroxine and desiccated thyroid in patients with primary hypothyroidism. Metabolism 1978;27:1518-25.

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Which Contributes More to the Increased Mortality in Hyperthyroidism: The Type of Therapy or Prolonged Incomplete Control of Hyperthyroidism?

Stephen W. Spaulding

Boelaert K, Maisonneuve P, Torlinska B, Franklyn JA. Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine. J Clin Endocrinol Metab 2013;98:1869-82. Epub March 29, 2013; doi: 10.1210/jc.2012-3459.

SUMMARY

Background

Several studies have indicated that patients with hyperthyroidism who are treated with ^{131}I are at increased risk of morbidity and mortality, as compared with a general population (1,2). The current paper tries to address some related questions, such as: 1) Do patients treated with antithyroid drugs (ATDs) also have an increased risk of mortality? 2) Does the length of time a patient remains hyperthyroid or subclinically hyperthyroid have an effect on mortality? 3) Do preceding comorbid conditions increase the risk of mortality? and 4) Does the increased risk occur shortly after treatment or does it persist after a long follow-up time?

Methods

The authors reviewed records on 2389 patients with hyperthyroidism who were initially evaluated between 1989 and May 31, 2003, at the Birmingham thyroid clinic and who had been followed for at least 10 years or else had died. After excluding 1353 patients for being under 40 years of age, having had been treated previously, having transient thyroiditis, having received amiodarone, having emigrated, or being lost to follow-up, 1036 were left for the study. Patients were deemed to have Graves' disease if at least two of the following had been present: a palpable diffuse goiter, a positive TPO and/or Tg antibody titer, or thyroid eye disease (345 patients). Patients with a palpable nodular goiter were deemed to have toxic nodular goiter (TNG, 285 patients). The etiology for the remaining 406 patients was deemed indeterminate, but most would have had either Graves' or toxic nodular disease. No information about thyroid imaging, TSH-receptor antibody levels or cardiovascular medications (other than the exclusion of those on amiodarone) was provided.

All patients were either given ATDs or ^{131}I. Patients with Graves' disease received ATDs 2.5 times more often than those with TNG. Of the 376 patients initially started on ATD treatment, 90% received carbimazole (maintenance dose, 5 to 10 mg/day) and 10% received propylthiouracil (PTU) (maintenance dose, 50 to 100 mg/day). Patients were seen in follow-up at least every 2 months until their hyperthyroidism was controlled (free T_4, <20 pmol/L). Of those initially given ATDs, 104 (28%), including more severe cases and elderly patients, were given ^{131}I after about 2 months of ATDs. Of those who were taking only ATDs after 12 to 18 months, 52% had gone into remission, while the remaining 20% had hyperthyroidism but continued taking ATDs. ATDs were withheld for at least a week before and after giving one or more fixed doses of ^{131}I. The fixed dose was generally 5 mCi before 1995, 10 mCi from 1995 to 2000, and 16 mCi from 2001 to 2003.

Patient-years of treatment were divided into three phases: first, the number of years a patient remained on ATD therapy or remained in remission after having taken only ATD; second, the years after taking ^{131}I that a patient went without needing to take L-T_4; and third, the number of years after taking ^{131}I that a patient received L-T_4. A patient's treatment years could have included all three phases, but death was ascribed to the last phase entered.

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Preceding comorbidities were determined by looking at patient records. A patient's cause of death was based on the International Classification of Diseases, revision 9 (ICD-9) or ICD-10 code given on the death certificate. Mortality rates were compared between the patient-years spent in the three phases, and also compared to the mortality rate in the general population in England and Wales, adjusted for sex, age, and period of study. Multiple statistical approaches were used, including multivariable Cox proportional-hazards regression models to assess the influence of different treatment groups, causes of hyperthyroidism, disease severity (initial level of free T_3 and/or T_4), disease control (serial free T_4 levels), preceding comorbidity, and period of enrollment (pre-1995, 1995 to 2000, and 2001 to 2004 [sic]).

Results

During 12,868 years of patient follow-up, 334 died—15% more than projected based on standardized mortality in the general population (P = 0.01). The risk was increased by more than 50% in those with preceding comorbidity, in those who presented with atrial fibrillation, and in current smokers. Of note, no increase in mortality was observed in the first year of follow-up, whereas increased mortality was consistently found after more than 10 years of follow-up (P<0.05). Of the "excess" deaths, half were "circulatory deaths," which is 20% more than expected (P<0.05).

During the 3325 patient-years during which patients took only ATDs or were in remission after ATD therapy, there were 88 deaths, which was 30% more than all-cause mortality in the control population (P<0.02). During the 3045 patient-years during which patients did not require L-T_4 after receiving ^{131}I, all-cause mortality was almost 25% greater than in the control population (P<0.01). During the 6498 patient-years during which patients needed L-T_4 after getting ^{131}I, however, the overall mortality was not increased as compared with the control population. When mortality in the total cohort of 1036 patients was subjected to multivariable analysis, the group that underwent ^{131}I treatment and then needed L-T_4 actually had significantly lower mortality rates than either those who only took ATDs (30%) or those who took ^{131}I but did not require L-T_4 (25%). An analysis of patients with preceding comorbidity, and an analysis of the combined subgroup of patients with Graves' and TNG, however, did not show a significant reduction in risk of mortality in those taking L-T_4 after receiving ^{131}I.

The percentage of patients who were given ^{131}I but in whom hypothyroidism did not develop rose with patient age, whereas the percentage of patients in whom hypothyroidism developed and required L-T_4 decreased with age. Patients with TNG and those with preceding comorbidities were also less likely to have hypothyroidism after ^{131}I. Supplementary graphs displaying serial free T_4 levels in all patients over 5 years of follow-up revealed that many of the 492 patents who needed to take L-T_4 had free T_4 levels substantially below 9 pmol/L over the 6-month period after receiving ^{131}I. In contrast, 20% of the 272 patients who had taken only ATDs still had a suppressed TSH at 1 year, while 12.8% of the 764 given ^{131}I still had an undetectable TSH 1 year after the first dose, indicating that subclinical hyperthyroidism persisted in a substantial fraction of those given either treatment. Mortality increased if a patient's free T_4 rose by 10 pmol/L during the serial measurements. Unfortunately, no supplementary graphs of the patients' serial TSH values were provided.

Conclusions

In the cohort of 1036 patients with hyperthyroidism who were followed for at least 10 years, 15% more died than would have been expected in the general population. A patient's risk of mortality increased by more than 50% if he or she smoked, had preceding comorbidities, or had atrial fibrillation. The authors found mortality to be increased in those treated with ATDs alone, and confirmed their previous report that mortality was increased in those who did not need to take L-T_4 after receiving ^{131}I, while in contrast, mortality was not increased in those in whom hypothyroidism developed after receiving ^{131}I but then needed to take L-T_4. Mortality in that group was 25% to 30% lower than in the other two groups.

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ANALYSIS AND COMMENTARY

The finding that patients with hyperthyroidism who had been treated only with ATDs are at increased risk of mortality is certainly provocative and should stimulate others to organize more focused prospective studies. The authors needed to combine cases seen over a 15-year period, which may have exposed their study to shifting baselines. For example, over the period of the study, the Birmingham group changed the way they used ^{131}I, using an ablative dose in the most recent period. In addition, over the period of the study, diagnostic tests (e.g., various thyroid scans, TSH, and TSI/TRAb assays), exacerbating factors (e.g., smoking), and treatments for comorbid conditions associated with hyperthyroidism also improved, and indeed death certificates citing hyperthyroidism as the cause of death, as well as those with any mention of hyperthyroidism declined in the United Kingdom, as recently discussed (3). Nonetheless, the decline in mortality assessed over the three treatment periods for the total cohort did not turn out to be significant.

Up to 1995, the Birmingham group used a fixed dose of 5 mCi of ^{131}I in hopes of reducing the incidence of hypothyroidism, but they found that 34% of patients with TNG and 56% of those with Graves' disease continued to have hyperthyroidism at 6 months (4). In the current paper, they found that the risk of mortality increased significantly (P = 0.009) if the free T_4 level rose 10 pmol/L on the serial free T_4 measurements during treatment. These findings emphasize the importance of prompt, close control of hyperthyroidism.

Another factor that may have influenced the results is that some patients were taking ATDs up to a week before of the administration of 5 mCi of ^{131}I, which Allahabadia et al. showed to be a significant predictor of failure to respond to ^{131}I (5). There is also some evidence suggesting that ATDs may affect the response of TNG glands to ^{131}I differently from the response of Graves' glands (reviewed in 6).

ATDs were used much less frequently in patients with TNG, whereas ^{131}I was used more frequently in patients with TNG than in patients with Graves' disease. The patients who did not require L-T_4 after receiving ^{131}I obviously maintained a higher level of T_4, and thus presumably were more likely to be in the group with subclinical hyperthyroidism after 1 year. The percentage of patients given ^{131}I in whom hypothyroidism did not develop rose progressively with patient age, whereas the percentage in those in whom hypothyroidism did develop and who required L-T_4 fell progressively with patient age. Furthermore, of all those given ^{131}I, more than 80% of patients with Graves' disease required L-T_4, whereas only 46% of those with TNG required L-T_4. What is more, patients with TNG and those with preceding comorbidities were also less likely to have hypothyroidism after ^{131}I therapy. All these factors could be involved in the reduced mortality observed in those in whom hypothyroidism developed and who needed L-T_4 after receiving ^{131}I.

Supplementary graphs displaying serial free T_4 levels in all patients over 5 years of follow-up showed that many of the 492 patents who needed to take L-T_4 had free T_4 levels substantially below 9 pmol/L over the 6 months after receiving ^{131}I. One might speculate that this period of hypothyroidism—although probably bad for Graves' orbitopathy—was less hazardous in terms of mortality than the persistence of subclinical hyperthyroidism in some patients who did not need L-T_4 after receiving ^{131}I, and also in some of those treated only with ATDs.

In 1998, the authors reported that ^{131}I treatment was associated with a higher mortality, as compared with the general population (2). In 2005, they first reported increased mortality in patients treated with ^{131}I who did not require L-T_4, and that excess mortality was not found in those in whom hypothyroidism developed and who required L-T_4 after ^{131}I (7); that paper studied patients enrolled from 1984

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through 2002, so presumably data from some of the same patients were also included in the current paper. In the current paper, the increased risk of mortality was most clear-cut after more than 10 years of follow-up. This is in striking contrast to the authors' earlier report that excess mortality was most prominent in the first year after ^{131}I and declined thereafter (2). Indeed, Metso et al. reported that the increased risk of cardiovascular morbidity persists for up to 35 years after ^{131}I administration (1).

Atrial fibrillation clearly is an important factor in the increased risk of mortality in Graves' disease, and it should also be noted that atrial fibrillation increases long-term mortality by 50% in the general euthyroid population as well. An interesting recent nationwide survey from Denmark found that new-onset atrial fibrillation actually is predictive of the later development of hyperthyroidism (8). The same group recently presented an abstract on a nationwide survey of overall cardiovascular mortality in individuals with a normal free T_4 who were followed for up to 10 years: there was a progressive increase in mortality in those whose TSH was <0.1 (24% increased risk), in those whose TSH was between 0.1 and 0.2 mU/L (21% increased risk), and in those whose TSH was between 0.2 and 0.4 mU/L (21% increased risk) (9).

There could be a problem with trying to apply the current findings to the average case of hyperthyroidism, because patients under 40 were excluded, thus altering the sex-distribution and etiologies seen in the general population. Nonetheless, the findings do make one possible therapeutic intervention stand out: convincing a patient with hyperthyroidism to stop smoking could reduce his or her risk of premature death. This study should prompt the development of larger time-limited prospective studies that include more advanced tests that focus on cases with well-defined etiologies of hyperthyroidism and that address specific factors suspected of being involved in the increased mortality of subgroups of patients, such as those with other autoimmune conditions (including antibodies to cardiac antigens), those with single-nucleotide polymorphisms believed to increase the risk of atrial fibrillation and of thrombosis, those taking specific cardiac medications, and other factors as well.

References

1. Metso S, Auvinen A, Salmi J, Huhtala H, Jaatinen P. Increased long-term cardiovascular morbidity among patients treated with radioactive iodine for hyperthyroidism. Clin Endocrinol (Oxf) 2008;68:450-7.
2. Franklyn JA, Maisonneuve P, Sheppard, MC, Betteridge J, Boyle P. Mortality after the treatment of hyperthyroidism with radioactive iodine. N Engl J Med 1998;338:712-8.
3. Spaulding SW. Should guidelines be developed to indicate when hyperthyroidism or hypothyroidism ought to be included on a death certificate? Clin Thyroidol 2013;25:88-91.
4. Franklyn JA, Daykin J, Holder R, Sheppard MC. Radioiodine therapy compared in patients with toxic nodular or Graves' hyperthyroidism. QJM 1995;88:175-80.
5. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine treatment of hyperthyroidism—prognostic factors for outcome. J Clin Endocrinol Metab 2001;86:3611-7.
6. Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. Endocr Rev 2012;33:920-80.

continued on next page

7. Franklyn JA, Sheppard M C, Maisonneuve P. Thyroid function and mortality in patients treated for hyperthyroidism. JAMA 2005;294:71-80.

8. Selmer C, Hansen ML, Olesen JB, Mérie C, Lindhardsen J, et al. New-onset atrial fibrillation is a predictor of subsequent hyperthyroidism: a nationwide cohort study. PLoS ONE 2013; 8(2):e57893. Epub February 28, 2013; doi:10.1371/journal.pone.0057893.

9. Selmer C, Olesen J, Madsen J, Faber J, Hansen P, et al. Subclinical hyperthyroidism and risk of cardiovascular and all-cause mortality. Eur Endocr Soc Abstracts 2013;32:OC3.6 doi:10.1530/endoabs.32.OC3.6.

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Severe Sight-Threatening Orbitopathy Is a Very Rare Event in the Natural History of Graves' Disease

Albert G. Burger

Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, Pariani N, Gallo D, Azzolini C, Ferrario M, Bartalena L. Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed Graves' hyperthyroidism seen at a single center. J Clin Endocrinol Metab 2013;98:1443-9.

SUMMARY

Background

Graves orbitopathy (GO) is a worrisome condition with an unpredictable evolution. The results of currently available medical treatments (e.g., glucocorticoids and x-ray treatment) are rather disappointing, and immunotherapy is still experimental. Some endocrinologists have a dramatic experience with the occasional patient affected by the most severe form of GO, but few endocrinologists working in a primary care center have clear-cut information about the true incidence of this dreaded complication. Indeed, only a few studies have addressed this question. The present article is a valuable addition to the available data.

Methods

From 2002 to 2010, the study enrolled 346 newly diagnosed patients with Graves' disease who presented to one clinic. At the time of diagnosis, 255 patients were free of GO, 70 had mild and inactive GO, 20 had moderate or severe eye disease, and 1 had sight-threatening GO. Of these 255 patients, 18 were lost to follow up and 237 were treated with methimazole alone. In 39 patients, the treatment could be stopped before 18 months, while it had to be continued for 18 months in198. Ocular involvement was assessed according to the guidelines of the European Group on Graves' Orbitopathy at 6, 12, and 18 months. At this time, some patients were already off methimazole.

Results

The patients were mainly women ages 18 to 84 years; 35% were smokers; 194 of the 237 patients treated with methimazole initially had no GO and 43 had mild GO. The majority of patients without initial GO remained disease-free (169 of 194 [87%]). In 20 patients (10%) mild disease developed, and only five (2.6%) presented with moderate to severe GO at the end of the study. This included soft-tissue changes and intermittent diplopia (clinical score 3 of 7) (1). One patient progressed to severe sight-threatening disease.

Among the 43 patients who initially had mild GO, 58% were free of GO after 18 months while 39% had still some mild but inactive form of GO.

Serum TSH receptor antibodies decreased in most cases but less so in those with active GO. Among the patients with initially mild GO, TSH receptor antibodies decreased more markedly in those who recovered from eye signs than in those with persistent GO. Yet the cohort was too small to identify significant differences. However, there was a significant association of the TSH-receptor antibodies between moderate to severe GO and smoking.

Conclusions

In a primary care environment ,most patients presenting with Graves' disease have no signs of orbitopathy initially. The present study indicates that

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the overwhelming majority of these patients (i.e., 81%) will never have GO; in only one patient did the orbitopathy evolve into severe sight-threatening disease. In addition, in 58 patients with mild initial GO, all signs of eye disease disappeared during the 18 months of observation. Therefore, in Graves' disease with minimal or no GO, the risk of evolution toward moderate to severe GO during methimazole therapy is minimal.

ANALYSIS AND COMMENTARY

These results are reassuring and corroborate the personal experience of most endocrinologists. The cohort of patients studied here initially included 70 individuals with mild GO. These patients need special follow-up since the eyes signs became worse during the treatment in 5 of them. These 5 patients represent, however, 25% of the 20 patients in whom mild GO was still present at the end of treatment. Since we lack reliable prognostic parameters for identifying cases of GO that may progress independently of hyperthyroidism, careful monitoring is indicated (2). Unfortunately, GO can appear many years after Graves' hyperthyroidism has been cured. Also, there is ongoing debate concerning whether ^{131}I treatment (with or without glucocorticoids) is associated with a worsening prognosis of GO. This problem is not discussed in the article.

References

1. Bartalena L, Baldeschi L, Dickinson A, Eckstein A, Kendall-Taylor P, Marcocci C, Mourits M, Perros P, Boboridis K, Boschi A, et al. Consensus statement of the European Group on Graves' Orbitopathy (EUGOGO) on management of GO. Eur J Endocrinol 2008;158:273-85.
2. Bartalena L, Tanda ML. Graves' ophthalmopathy. N Engl J Med 2009;360:994-1001.

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Early Treatment of Hypothyroidism after Radioiodine Therapy of Graves' Disease Prevents Ophthalmopathy

Jerome M. Hershman

Stan MN, Durski JM, Brito JP, Bhagra S, Thapa P, Bahn RS. Cohort study on radioactive iodine-induced hypothyroidism: implications for Graves' ophthalmopathy and optimal timing for thyroid hormone assessment. Thyroid. 2013;23:620-5. doi: 10.1089/thy.2012.0258.

SUMMARY

Background

Treatment of hyperthyroidism with radioactive iodine (RAI) has been associated with worsening of Graves' ophthalmopathy (GO). The purpose of the present study was to evaluate risk factors for GO, especially hypothyroidism, after RAI.

Methods

This was a retrospective study of a large cohort of patients treated for Graves' disease (GD) with RAI at the Mayo Clinic, using a dose of 0.2 mCi ^{131}I per gram of thyroid tissue corrected for the thyroid uptake. Patients were evaluated for the presence of GO before therapy and for worsening or onset of GO based on the development of the following features: worsening of proptosis, diplopia, soft-tissue features, or visual acuity; need for systemic or surgical GO therapy; or deterioration of the eyes as assessed by the patient. For the final analysis, patients with GO were divided into two groups: (i) new or worsened GO; and (ii) unchanged or improved GO.

Results

From January 2005 through December 2006, 291 patients with GD received RAI treatment for hyperthyroidism. Ninety-six patients were excluded from the study because of inadequate data or other factors, leaving a cohort of 195 patients, of whom 155 were followed at the Mayo Clinic and 40 were followed by mail and telephone contact. Of the 195 patients 80% were women, the mean age was 50 years, and the median duration of GD was 2 months. The prevalence of GO at baseline was 23.6% (46 of 195), with 38 patients having mild and 8 having moderate to severe GO. The prevalence of smoking was 17.4% (34 of 195).

After 1 year of follow-up, 39 patients had GO (20%), including 15 new cases and 24 preexisting cases. In the 46 patients with GO at baseline, the eye disease subsequently deteriorated in 10. In 9 (19.6%) of the 46 patients, the GO did not progress and in 27 (58.7%), it improved. Altogether, after RAI treatment, GO developed or worsened in 25 (12.8%) of 195 patients.

Hypothyroidism was present at the first follow-up visit in 102 (52.3%) of 195 patients and was strongly associated with the development or deterioration of GO (odds ratio [OR], 3.3; 95% CI, 1.3 to 8.7; P = 0.011). The time to the first visit after RAI therapy was a median of 69 days (interquartile range, 53 to 88). In a multivariate analysis, the duration to first follow-up was a predictor of hypothyroidism, with an OR of 1.05 per day increase in follow-up time (95% CI, 1.03 to 1.07). The multivariate analysis included hypothyroid status at the first follow-up, steroid prophylaxis, smoking status, FT_4 at baseline, sex, age, 24-hour RAI uptake, thyroid size, and dose of RAI. The only factors that remained independently significant were the development of hypothyroidism by the first follow-up visit after RAI therapy (OR, 3.6) and preexisting GO (OR, 2.8)

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Although more smokers had new or worse GO than nonsmokers (18% vs. 12%), the difference was not significant. Preexistent GO was associated with a higher risk for worsening as compared with patients who had no GO at baseline; 24% of patients with GO at baseline experienced worsening, but GO developed in only 11% of patients who did not have it at baseline (P = 0.021).

Conclusions

The presence of hypothyroidism at the first assessment of thyroid function after RAI administration is a strong predictor for an adverse outcome of GO, with the highest possibility in patients with preexistent GO. To prevent clinical hypothyroidism and the associated risk for GO, the optimal time for first measurement of FT_4 is prior to 6 weeks after RAI therapy.

ANALYSIS AND COMMENTARY

In other studies, hypothyroidism and smoking have been shown to predispose patients to the development of ophthalmopathy after ^{131}I therapy for GD (1,2). It is well known that RAI therapy exacerbates preexistent ophthalmopathy. Indeed, this knowledge led to the use of prednisone to prevent GO after ^{131}I therapy (3). Surprisingly, RAI was used in the current study in patients with preexistent GO, including a few with moderate GO. Although some patients received glucocorticoids, systematic data was not presented with regard to their use in the 46 patients with preexistent GO, so the effect of glucocorticoids in preventing exacerbations in this group could not be determined. The authors state that prophylactic steroids were offered only to patients deemed at high risk for deterioration.

The dose of ^{131}I was relatively large (mean, 15 mCi), resulting in a high prevalence and early onset of hypothyroidism. Forty percent of patients had hypothyroidism at 6 to 8 weeks, and about three fourths had hypothyroidism at 12 to 16 weeks, based on measurements of FT_4. It is important to note that TSH may still be suppressed at these early times after RAI therapy of hyperthyroidism, so it is not a reliable marker for hypothyroidism in this context.

Tallstedt et al. noted that early administration of levothyroxine was associated with a reduction in the development of GO (2). In another study of 72 patients with minimally active GO treated with RAI, levothyroxine was started 2 weeks after RAI; there was no deterioration of the GO, and several patients improved during the 12 months of follow-up (4).

The authors of the current study suggest that the first follow-up after RAI to detect and initiate treatment for hypothyroidism should be within 6 weeks, but it might be safer to perform routine follow-up at 4 weeks and initiate therapy for hypothyroidism, if necessary, at this time.

References

1. Bartalena L, Marcocci C, Tanda ML, Manetti L, Dell'Unto E, Bartolomei MP, Nardi M, Martino E, Pinchera A. Cigarette smoking and treatment outcomes in Graves ophthalmopathy. Ann Intern Med 1998;129:632-5.
2. Tallstedt L, Lundell G, Blomgren H, Bring J. Does early administration of thyroxine reduce the development of Graves' ophthalmopathy after radioiodine treatment? Eur J Endocrinol 1994;130:494-7.
3. Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, Bruno-Bossio G, Nardi M, Bartolomei MP, Lepri A, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 1998;338:73-8.
4. Perros P, Kendall-Taylor P, Neoh C, Frewin S, Dickinson J. A prospective study of the effects of radioiodine therapy for hyperthyroidism in patients with minimally active Graves' ophthalmopathy. J Clin Endocrinol Metab 2005;90:5321-3. Epub June 28, 2005.

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In Vitro Fertilization Outcomes Do Not Differ between Women with Adequately Treated Hypothyroidism and Women without Thyroid Disease

Elizabeth N. Pearce

Busnelli A, Somigliana E, Benaglia L, Leonardi M, Ragni G, Fedele L. In vitro fertilization outcomes in treated hypothyroidism. Thyroid. April 2, 2013 [Epub ahead of print].

SUMMARY

Background

The risk of infertility is increased among women with autoimmune thyroid disease (1). Three previous studies have examined the effects of levothyroxine (L-T_4) treatment for hypothyroidism on the outcomes of in vitro fertilization (IVF), with conflicting results (2-4).

Methods

This was a case–control study. Cases were 137 women treated with L-T_4 for overt or subclinical hypothyroidism who underwent IVF with intracytoplasmic sperm injection (IVF-ICSI) from 2009 to 2011 at the infertility unit of a single Italian institution. Controls were 274 age-matched euthyroid women with no history of L-T_4 treatment who underwent IVF-ICSI at the same institution. Women were excluded if they were 40 years of age or older or if they had a history of previous IVF-ICSI cycles; women were also excluded if they had free T_4 or free T_3 values outside the reference ranges or serum TSH ≥2.5 mIU/L. IVF-ICSI was performed according to a standard clinical protocol. Pregnancy was diagnosed by ultrasonography at 4 to 5 weeks after embryo transfer. Pregnancy outcomes were ascertained by telephone calls after delivery. The primary outcome was live birth rate per IVF cycle. Differences between cases and controls were assessed using independent-sample paired t-tests, Wilcoxon rank-sum tests, or Fisher's exact tests.

Results

Among the cases, 51% initially had overt hypothyroidism and 49% had subclinical hypothyroidism, with a median TSH before initiation of L-T_4 therapy of 4.8 mIU/L. A total of 58% of cases were antithyroid antibody–positive. The median L-T_4 dose was 75 µg daily. Smoking history, menstrual regularity and cycle length, number of previous deliveries, day 3 serum follicle-stimulating hormone, indications for IVF-ICSI, and baseline TSH (1.6 mIU/L vs. 1.5 mIU/L) did not differ between the cases and controls. The cases did have a higher body-mass index (the weight in kilograms divided by the square of the height in meters; 22.9 vs. 21.9; P = 0.013). Baseline characteristics of the antithyroid antibody–positive and antithyroid antibody–negative cases did not differ.

Among the cases, there was a higher rate of cancelled cycles for poor response (3.6% vs.0.7%, P = 0.04); the mean duration of ovarian stimulation was longer (10.9 days vs. 10.1 days, P = 0.001); and the proportion of women who did not undergo embryo transfer was higher (17% vs. 7%, P = 0.006). Pregnancies resulted in 36% of cases and 34% of controls; there were no differences in pregnancy rates per started cycle, per oocyte retrieval, or per embryo transfer. Sixteen percent of cases and 22% of controls suffered a miscarriage (P = 0.5). Live births resulted in 30% of cases and 27% of controls; live birth rates did not

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differ per started cycle, per oocyte retrieval, or per embryo transfer. Among the cases, outcomes did not differ by antithyroid antibody status. Outcomes among the patients treated for subclinical and overt hypothyroidism did not differ except that the women with a history of overt hypothyroidism had more embryos transferred (mean, 2.1 vs. 1.9; P = 0.03).

Conclusions

Although the women with hypothyroidism were more likely to have IVF cycle cancellation for poor response and had lower rates of embryo transfer, pregnancy rates resulting from IVF-ICSI did not differ between women with adequately treated hypothyroidism (TSH <2.5 mIU/L) and euthyroid women.

ANALYSIS AND COMMENTARY

These findings are discordant with those of Kilic et al. (3) and of Scoccia et al. (4), which reported reduced implantation and pregnancy rates in women with treated hypothyroidism as compared with women without thyroid dysfunction. However, mean serum TSH values of 2.2 mIU/L and 2.5 mIU/L in these previous studies suggest that treatment was not adequate in all participants. Kim and colleagues (2) previously randomly assigned 64 women with subclinical hypothyroidism who were undergoing IVF-ICSI to L-T_4 versus placebo and found lower miscarriage rates and higher live birth rates in treated women (mean TSH at the time of IVF initiation, 2.3 mIU/L) as compared with controls (mean TSH, 6.9 mIU/L). These results suggest a benefit of L-T_4 treatment for IVF outcomes in women with hypothyroidism, an outcome that could not be directly demonstrated by Busnelli and colleagues, since all of the women with hypothyroidism in their study received L-T_4.

An important limitation of this study is the lack of data regarding adequacy of thyroid hormone–replacement throughout pregnancy in the studied women. Although there were no differences in outcomes of the antithyroid antibody–positive and negative L-T_4-treated women, the antithyroid antibody status of the control women was not ascertained.

Studies to date provide suggestive, although not unequivocal, evidence that L-T_4 treatment improves IVF outcomes in women with hypothyroidism. Given the average $12,400 cost per IVF cycle in the United States (5), it seems prudent to ensure that serum TSH is <2.5 mIU/L in all women with hypothyroidism prior to IVF cycle initiation.

References

1. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev 2010;31:702-55.
2. Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD, Kang BM. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril 2011;95:1650-4.
3. Kilic S, Tasdemir N, Yilmaz N, Yuksel B, Gul A, Batioglu S. The effect of anti-thyroid antibodies on endometrial volume, embryo grade and IVF outcome. Gynecol Endocrinol 2008;24:649-55.
4. Scoccia B, Demir H, Kang Y, Fierro MA, Winston NJ. In vitro fertilization pregnancy rates in levothyroxine-treated women with hypothyroidism compared to women without thyroid dysfunction disorders. Thyroid 2012;22:631-6.
5. American Society for Reproductive Medicine. Is in vitro fertilization expensive? Accessed at http://www.asrm.org/detail.aspx?id=3023.

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Showing That a Persistently Hypothyroid Patient Has an Increase of Free T_4 Two Hours after Ingestion of 1 mg of Levothyroxine May Overcome Nonadherence

Jerome M. Hershman

Walker JN, Pallai S, Ibbotson V, Vincent A, Karavitaki N, Weetman A, Wass JA, Allahabadia A. A thyroxine absorption test followed by weekly thyroxine administration: a method to assess non-adherence to treatment. Eur J Endocrinol 2013;168:913-7.

SUMMARY

Background

Many patients taking levothyroxine (L-T_4) at a dose considered appropriate based on body weight have an elevated serum TSH, even after they have a normal serum TSH while taking the same dose of L-T_4. This may be due to ingestion of food with the dose or taking drugs that block absorption, such as iron, calcium, bile acid-sequestering resins, or phosphate binders or taking drugs that accelerate degradation of L-T_4, such as diphenylhydantoin. Patients may not absorb L-T_4 because of celiac disease, atrophic gastritis, or gastrointestinal surgery. When these causes have been eliminated, the issue of noncompliance, or nonadherence in current terminology, arises. Most patients deny this behavior. The current study used administration of a weekly dose of L-T_4 under observation to determine whether nonadherence was a probable cause of the elevated serum TSH.

Methods

At two sites in the United Kingdom, patients were identified who had a serum TSH persistently above 5.5 mU/L despite adequate daily doses of L-T_4 and no evidence of interfering drugs or diseases. The patients had baseline measurements of FT_4 and TSH; then each patient received an oral weekly dose of L-T_4 and had a measurement of FT_4 at 60, 120, 180, and 240 minutes after ingestion of the L-T_4. The patient continued on the same weekly dose of L-T_4 given under supervision for 4 weeks with serum TSH measurement 1 week after the final dose.

Results

Twenty-three patients participated in the study. The mean age was 45 years (range, 20 to 88) and the median weight 87 kg (range, 53 to 143). The mean (±SD) TSH before the study was 41±45 mU/L and the mean prestudy L-T_4 dose was 2.31±0.56 µg/kg/day. The mean weekly dose administered was 7× 1.69±0.2 µg/kg. In 19 of the 23 patients, the maximal rise in serum FT_4 occurred by 120 minutes, with almost a doubling of FT_4 at this time, increasing from 13 at baseline to 25 pmol/L at 120 minutes. The 3 patients with the most severe hypothyroidism had the lowest rise in FT_4 at 120 minutes. At the final blood test after 4 weeks of treatment, TSH was reduced in 17 of 23 patients (47±50 at baseline to 18±21 mU/L). In 6 patients, the 4-week TSH was higher than the baseline.

Conclusions

Measurement of FT_4 120 minutes after a weight-related weekly dose of L-T_4 can be used to show maximal T_4 absorption and aid in overcoming nonadherence with therapy.

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ANALYSIS AND COMMENTARY

This study addresses an important problem, namely, nonadherence with L-T_4 therapy resulting in persistent hypothyroidism, a common occurrence and a very difficult issue to deal with. The authors emphasize a principle of treatment: "adherence to medication is the key link between process and outcome in medical care and without it, the likelihood of treatment failure is high." The serum TSH provides a simple way to document nonadherence. Many years ago, my colleagues and I studied serum TSH levels in our endocrine clinic population and found that about 7% who previously had a normal TSH while taking a given dose of L-T_4 had an elevated TSH during long-term follow-up (1). When confronted with the possibility of nonadherence with the dose, less than half of the patients admitted to it. For the patients who frequently forget to take L-T_4 on a daily basis, a weekly dose can be given and is usually without side effects because of the long half-life of L-T_4 (2).

In the article reviewed here, the average patient in the study received 1030 µg of L-T_4 as the weekly dose. The weekly doses may have borne some relationship to the prescribed doses that were presumably not ingested by the patients with any regularity, but the reasons for the variations in dose were not clearly stated. The failure to normalize serum TSH in a high proportion of the patients in this study is most likely due to the fact that it can take serum TSH as long as 6 weeks to normalize on a given optimal dose of L-T_4; 4 weeks was too short a time for this to occur. In fact, 6 of the23 patients had an even higher TSH at the end of the study, indicating that the estimated weekly dose was too low for these patients.

The main conclusion is that giving the nonadherent patient a 1 mg dose of L-T_4 in the office and measuring FT_4 at baseline and at 2 hours will show that the patient can absorb the dose. Whether the nonadherent patient will become adherent after demonstrating that she can absorb L-T_4 is another issue. The authors recommend a nonjudgmental discussion about adherence. In my experience, few patients admit to being nonadherent as the basis for their elevated serum TSH, but the absorption test could help if the patient agrees to do it.

References

1. England ML, Hershman JM. Serum TSH concentration as an aid to monitoring compliance with thyroid hormone therapy in hypothyroidism. Am J Med Sci 1986;292:264-6.
2. Grebe SK, Cooke RR, Ford HC, Fagerström JN, Cordwell DP, Lever NA, Purdie GL, Feek CM. Treatment of hypothyroidism with once weekly thyroxine. J Clin Endocrinol Metab 1997;82:870-5.

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THYROID CANCER GRAND ROUNDS

Is There New Treatment for Progressive Iodine-Resistant Metastatic Differentiated Thyroid Carcinoma?

Wendy Sacks

CASE PRESENTATION

This 68-year-old woman with a history of breast cancer noticed a new neck mass 9 years ago. Ultrasound revealed an irregular-appearing lesion in the left lobe of the thyroid and FNA biopsy demonstrated papillary thyroid cancer (PTC). She underwent thyroidectomy. The tumor was adherent to the surrounding muscle, internal jugular vein, and carotid artery. The pathology demonstrated moderately differentiated classic and follicular variant (FV) PTC that was not encapsulated and essentially replaced the entire left thyroid lobe. The tumor extended into the perithyroidal soft tissue and was present at the inked margins. One central-compartment lymph node was involved without extranodal extension. In addition, there was a 7-mm focus of FV-PTC in the right lobe (pT3N1aMX, stage III). Following a thyroxine-withdrawal protocol, she received 202 mCi of radioactive iodine (RAI). A 7-day scan showed uptake in the anterior neck suggestive of a neoplastic lesion and uptake in the left parotid gland.

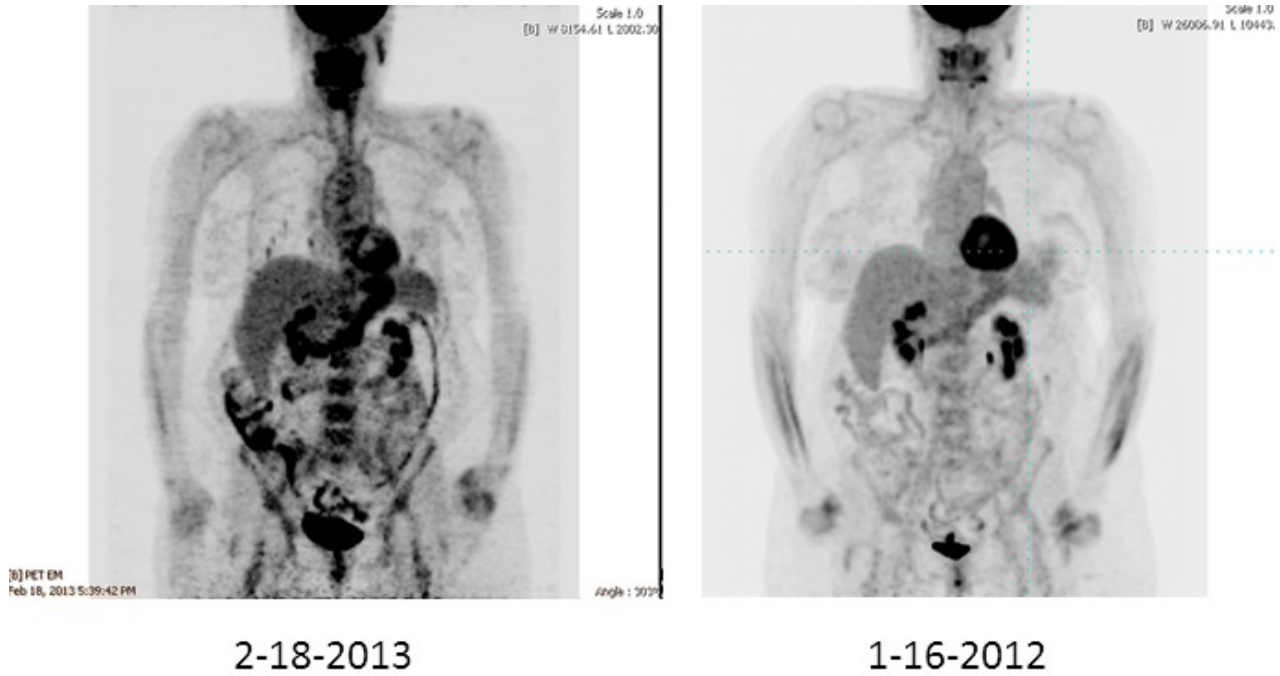

Figure 1. Figure 1. PET scan showing lung nodules in 2013 that were not visible in scan of 2012.

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THYROID CANCER GRAND ROUNDS Is There New Treatment for Progressive Iodine-Resistant Metastatic Differentiated Thyroid Carcinoma?

Wendy Sacks

For the next 5 years, recombinant human TSH (rhTSH) stimulated ^{131}I diagnostic scans showed no uptake and the thyroglobulin (Tg) level was 0.5 ng/ml on thyroid-hormone suppression. Ultrasound of the neck was not done. Five years after her initial surgery and radioactive iodine treatment, a soft-tissue mass was seen in the left neck on ultrasound and FDG uptake in the same area was seen on PET imaging. Her Tg rose from 0.5 ng/ml to 1.9 ng/ml after rhTSH stimulation. Biopsy confirmed recurrent PTC. She underwent excision of this mass. Later that year, she underwent more extensive surgery including central-compartment dissection, left modified neck dissection of levels III and IV, and a partial esophagectomy. Surgical pathology revealed metastatic PTC in the esophageal and paraesophageal soft tissue and in the soft tissue of the left lateral neck (no lymph nodes). She then completed a very complex intensity-modulated radiation therapy (IMRT) plan with 6340 cGy. IMRT uses advanced technology to manipulate beams of radiation to conform to the shape of a tumor, reducing side effects of the treatment. Seven years after the initial diagnosis, CT imaging demonstrated small lung nodules consistent with metastatic disease. On retrospective review of a prior CT scan of the chest that was done when she was first noted to have disease recurrence in the neck, multiple tiny lung nodules (the largest 3 to 4 mm) were seen. At the present time, 9 years after diagnosis of PTC, the lung nodules have increased in size, up to 1.1 cm. PET imaging has demonstrated increased intensity of FDG uptake in several of the lung nodules as compared with the prior 2 years of scans (Figure 1). Lesions less than 7 mm, even if malignant, are difficult to detect using FDG because of the partial volume effect that occurs during reconstruction of the images, making PET less sensitive than CT for detection of small lesions (1) . She is clinically asymptomatic with normal pulmonary-function tests.

ANALYSIS AND COMMENTARY

While the majority of differentiated thyroid cancers have a good prognosis, this patient had several adverse prognostic factors suggesting a poor outcome at her initial diagnosis of PTC, including age over 45 years, residual locoregional disease, and only moderately differentiated PTC histology. She had RAI treatment, and despite a seemingly disease-free period of several years with low Tg levels and a negative diagnostic whole-body scan, her cancer persisted and eventually involved the lungs. Stage IV PTC has a 10-year survival rate of approximately 30%, which falls to 10% if there is progressive disease despite conventional therapy (2). While external-beam treatment can be used to prevent locoregional progression of disease, how do we now treat this patient with dedifferentiated progressive lung metastases? Will she benefit from an empiric dose of RAI? What is the right time to use a targeted therapy?

The therapeutic utility of empiric RAI treatment has been assessed by Sabra et al. who performed a retrospective review of 27 patients with iodine-avid distant metastatic lesions after initial RAI treatment, but negative iodine uptake on follow-up diagnostic scans (3). These patients had persistent structural disease confirmed on imaging. None of the patients had regression of their disease after RAI, and while 44% had stabilization of structural metastases, 56% had progression of disease despite multiple RAI treatment doses. These results imply that the likelihood of successful treatment of our patient's distant metastases with further RAI is low.

The concept of redifferentiation, or reactivating the RAI uptake function of thyroid carcinoma, remains an ongoing area of research in RAI-refractory thyroid cancer. Several agents have been studied in the past, such as retinoids and thiazolidinedio-

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nes, but have demonstrated limited benefits (4,5). Lithium has been used as an adjunct to improve iodine retention for ablation, but the benefit is modest (6). In the February 14, 2013, issue of the New England Journal of Medicine, Ho et al. published data showing that the MEK inhibitor, selumetinib demonstrated promising results for improving uptake of RAI in patients with iodine-refractory disease (7) (reviewed in Clinical Thyroidology 2013;25:76-8). Twelve of the 20 patients (60%) treated with selumetinib had 124I uptake that was new or increased or both. All five patients with NRAS mutant tumors had increased iodine uptake, and 4 had partial responses to ^{131}I therapy after pretreatment with selumetinib.

In addition, consideration for initiation of a tyrosine kinase inhibitor (TKI) should be made. She is a good candidate for this therapy, considering the progressive disease and good overall performance status; however, since TKIs have limited duration of efficacy, starting one now may be premature.

Conclusions

Thyroid cancer lung metastases eventually developed in this well-appearing, asymptomatic woman with PTC. She may benefit from another empiric dose of RAI, after pretreatment with selumetinib. If possible, she should be enrolled in a clinical trial for treatment with selumetinib, since it is not yet available otherwise.

References

1. Hoffman EJ, Huang SC, Phelps ME. Quantitation in positron emission computed tomography: 1. Effect of object size. J Comput Assist Tomogr 1979;3:299-308.
2. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, Caillou B, Ricard M, Lumbroso JD, De Vathaire F, Schlumberger M. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab 2006;91:2892-9.
3. Sabra M, Grewal R, Tala H, Larson SM, Tuttle RM. Clinical outcomes following empiric radioiodine therapy in patients with structurally identifiable metastatic follicular cell-derived thyroid carcinoma with negative diagnostic but positive post-therapy ^{131}I whole-body scans. Thyroid 2012;22:887-83.
4. Grüning T, Tiepolt C, Zöphel K, Bredow J, Kropp J, Franke WG. Retinoic acid for redifferentiation of thyroid cancer—does it hold its promise? Eur J Endocrinol 2003;148:395-402.
5. Kebebew E, Lindsay S, Clark OH, Woeber KA, Hawkins R, Greenspan FS. Results of rosiglitazone therapy in patients with thyroglobulin-positive and radioiodine-negative advanced differentiated thyroid cancer. Thyroid 2009;19:953-6.
6. Koong S, Reynolds J, Movius E, Keenan A, Ain K, Lakshmanan M, Robbins J. Lithium as a potential adjuvant to ^{131}I therapy of metastatic, well differentiated thyroid carcinoma. J Clin Endocrinol Metab 1999;84:912-6.
7. Ho A, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, Pentlow KS, Zanzonico PB, Haque S, Gavane S, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med 2013;368:623-32.

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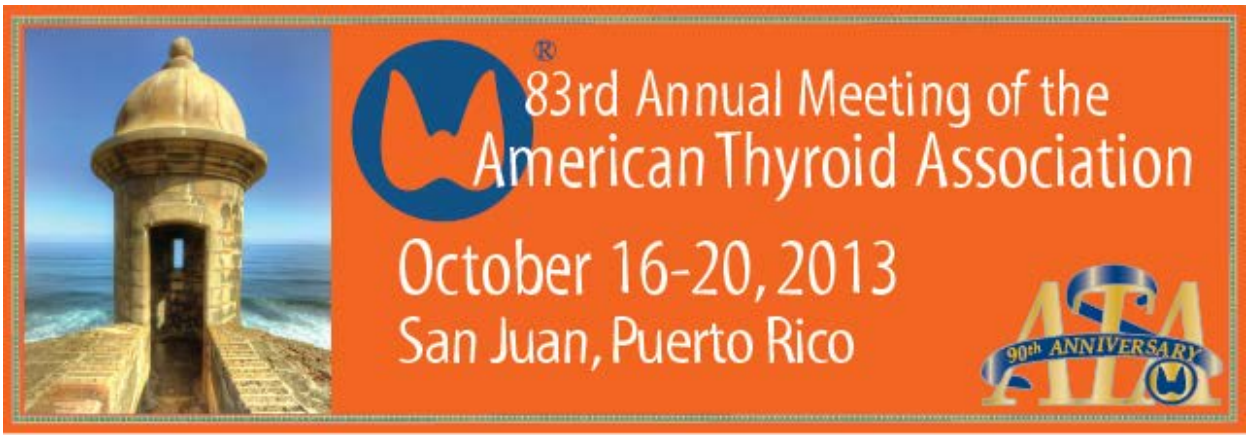

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