Response of Thyroglobulin to Radioiodine Therapy in Thyroglobulin-elevated Negative Iodine Scintigraphy (TENIS) Syndrome*

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Abstract. *Background: While radioiodine (131-I) is widely used in the treatment of differentiated thyroid cancer, its role remains less certain when abnormal 131-I uptake cannot be demonstrated in a pre-therapy diagnostic scan. Documentation of abnormal 131-I uptake in a post-therapy scan in such cases helps to justify the radioiodine therapy, but the post-therapy scan can remain persistently negative. Aim: To evaluate (i) whether 131-I therapy had any measurable effect on thyroglobulin (Tg) levels in patients who were scan negative prior to radioiodine therapy and remained scan negative after therapy, and (ii) whether the magnitude of the effect on Tg depended on the pre-therapy Tg level. Patients and Methods: Retrospective analysis of 78 patients. All patients had pre-therapy and post-therapy Tg levels measured under stimulation with thyroid stimulating hormone. Hospital data until date of last contact were analyzed to assess for recurrent disease. Results: Tg levels decreased by 55% in those having Tg 10 μg/l or higher; and by 41% in those with less than 10 μg/l. In patients with detectable Tg antibodies, there were no statistically significant decreases demonstrated for either Tg or Tg antibody levels. Conclusion: Radioiodine therapy can reduce Tg levels, independently of the pre-therapy level, even when the pre-therapy level is low and the pre-therapy, as well as the post-therapy, radioiodine scan remains negative.*

Thyroid cancer incidence rates have shown a rapid rise in the past several years, particularly, the incidence of papillary thyroid cancer in females (1). Not uncommonly, during the course of thyroid cancer management, a situation arises where there is no radiologically or clinically evident disease, but thyroglobulin (Tg) levels remain detectable or even significantly elevated. This situation has been referred to as TENIS syndrome (thyroglobulin elevated negative iodine scintigraphy) (2). This leads to biochemical evidence of persistent or recurrent thyroid cancer as evidenced by the Tg levels but no obvious disease to treat with 131-I. A Tg level of 10 μg/l has been recommended as a cut-off point, with patients with higher Tg levels and negative 131-I whole body scans (WBS) being considered for 131-I therapy (3, 4). Often, a scan following the administration of a therapeutic dose of 131-I demonstrates iodine avid disease in such situations (5-8) which has been explained by the higher sensitivity of detection resultant upon the usage of the much higher therapeutic dose as compared to the pre-therapy scan dose. Less commonly, the post-therapy scan continues to be negative and no iodine-avid malignancy is demonstrated. The only evidence of successful therapy is then the Tg level. We have attempted to retrospectively look at post-therapy Tg levels in patients in whom the post-therapy scan continues to be negative.

Patients and Methods

A retrospective chart review of patients with differentiated thyroid cancer treated with 131-I at our hospital over an 80-month period was performed after obtaining approval from the Institutional Review Board. Patients were included for this analysis if they met all of the following criteria: (i) prior therapeutic 131-I administration for ablation or therapy; (ii) a follow-up diagnostic 131-I WBS performed 24 and 48 hours following the oral administration of 185 MBq (5 mCi) was negative (iii) Tg measured on the day of 131-I administration for follow-up WBS was available; (iv) a therapeutic dose of 131-I was administered when the diagnostic WBS was negative; and (v) post-therapy WBS performed 48 hours following the therapy continued to be negative. A total of 78 patients met these criteria. For each patient, a follow-up Tg level was recorded, as first measured under thyroid hormone withdrawal or Thyrogen® (Genzyme, Cambridge, MA, USA)

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stimulation following the 131-I therapy. Tg level was measured by standard laboratory technique (Beckman-Coulter, Fullerton, CA, USA). Additionally, levels of Tg antibodies (TgAb) were recorded on the date of the 131-I therapy and follow-up Tg level. Clinical charts were also analyzed until last contact at the hospital to assess for radiologic or laboratory evidence of recurrent disease.

The identified patients were divided into three groups: (i) group A consisted of patients with Tg level of 10 μg/l or more and with no detectable Tg antibody; (ii) group B consisted of patients with Tg level less than 10 μg/l and with no detectable Tg antibody; and (iii) group C consisted of patients with detectable Tg antibody, independent of Tg levels.

Results

A total of 78 patients were identified, who received 79 therapies. Radioiodine dose ranged from 3.7 GBq – 4.6 GBq (100-125 mCi) in 3 therapies and 5.6 GBq – 22 GBq (150-594 mCi) in 76 therapies.

There were 18 patients in group A (13 female and 5 male), who received 19 therapies. Histopathologic distribution was papillary thyroid cancer in 14, tall cell variant of papillary thyroid cancer in 2, Hürthle cell thyroid cancer in 1, and follicular thyroid cancer in 1. The mean pre-therapy Tg level was 223 μg/l (range 11.7 μg/l to 1669.9 μg/l, standard deviation 429.4 μg/l). Post-therapy thyroglobulin as measured after a mean 326 day period showed a mean Tg level of 148 μg/l (range 0.1 μg/l to 1637.7 μg/l, standard deviation 380.8 μg/l). Pre- and post- therapy Tg levels were found to be significantly different ($p<0.04$) (Figure 1). Of the 19 therapies administered, there was a reduction in Tg levels after 17 therapies. These 17 therapies were administered to 16 patients. One patient was treated twice after having a negative 131-I WBS, and both treatments resulted in negative post-therapy WBS and reductions in Tg levels. The mean Tg level reduction among all patients was 55% and among the responders 65%. Of the two patients who did not show a post-therapy reduction in Tg level, one had papillary cell and the other, Hürthle cell cancer. There were 5 patients among the 17 responders who showed radiologic progression of disease as evidenced by ultrasonography, 18-fluorodeoxyglucose PET/CT, or CT scans, over a mean follow-up period of 1,594 days; all five had papillary thyroid cancer.

Group B had 50 patients (39 female and 11 male), who received 50 therapies. Histopathologic distribution was papillary thyroid cancer in 34, tall call variant of papillary thyroid cancer in 5, follicular variant of papillary thyroid cancer in 7, Hürthle cell variant of papillary thyroid cancer in 1, Hürthle cell thyroid cancer in 1 and follicular thyroid cancer in 2. The mean pretherapy Tg level was 2.4 μg/l (range 0.1 μg/l to 9.5 μg/l, standard deviation 2.5 μg/l). Post-therapy thyroglobulin as measured after a mean 455-day period showed an interval reduction to a mean level of 0.8 μg/l (range 0.1 μg/l to 4.0 μg/l, standard deviation 1.0 μg/l) ($p<0.001$) (Figure 2). Treatment resulted in decrease of Tg levels in 42 out of the 50 patients. Among the eight patients who failed to show reduction in their post-therapy Tg levels, five had papillary cell cancer, one had tall cell variant papillary cancer, one had follicular cell variant papillary cancer and one follicular thyroid cancer. The mean Tg level reduction was 41% among all patients, and 72% among the 42 responders. Of the 42 responders, only a single patient with follicular variant of papillary thyroid cancer showed radiologic progression of disease over a mean follow-up period of 1461 days.

Group C had 10 patients (6 female, 4 male). Histopathologic distribution was papillary thyroid cancer in 6, tall cell variant of papillary thyroid cancer in 1, Hürthle cell variant of papillary thyroid cancer in 1, Hürthle and tall cell variant of papillary thyroid cancer in 1, and follicular thyroid cancer in 1. The mean pre-therapy Tg antibody level was 310 IU/ml (standard deviation 670 IU/ml) and Tg level was 8.5 μg/l, (standard deviation 25.4 μg/l). After a mean follow-up period of 1,043 days, the Tg antibody level was 205 IU/ml (standard deviation 417 IU/ml) and Tg level 0.1 μg/l (standard deviation 0.2 μg/l). However, these decreases were not found to be statistically significant ($p<0.2$ for Tg antibody and $p<0.17$ for Tg). Eight out of the ten patients demonstrated a reduction in their Tg antibody level after therapy. Six patients showed a reduction in their Tg levels after therapy, the other four did not show any change in their Tg levels and all remained disease-free by laboratory and radiologic criteria after a mean follow-up of 1,803 days.

Discussion

The role of 131-I therapy in thyroid cancer which is scan negative but with elevated Tg levels has been well discussed in the literature (5-8). It is generally agreed that radioiodine therapy can be administered even when diagnostic radioiodine scans are negative, provided the Tg level obtained under thyroid hormone withdrawal is higher than 10 μg/l (3,4). Typically, post-therapy scans in about 60% of such patients have been shown to demonstrate evidence of iodine avid disease not detected in the pre-therapy diagnostic scan (9). Pacini *et al*., by retrospective analysis of patients with detectable Tg and negative 131-I WBS, have suggested that patients with pulmonary metastases, and to some extent patients with lymph node metastases are the most suitable candidates for 131-I therapy (10). Kabasakal *et al*. in their study of patients with negative 131-I WBS and Tg of at least 20 μg/l reported therapeutic benefit in patients with micrometastases but not macrometastases (11). However, this approach of empiric radioiodine therapy in scan-negative individuals is not universally accepted (12, 13). Less is known about radioiodine therapy in scan-negative individuals with Tg levels less than 10 μg/l.

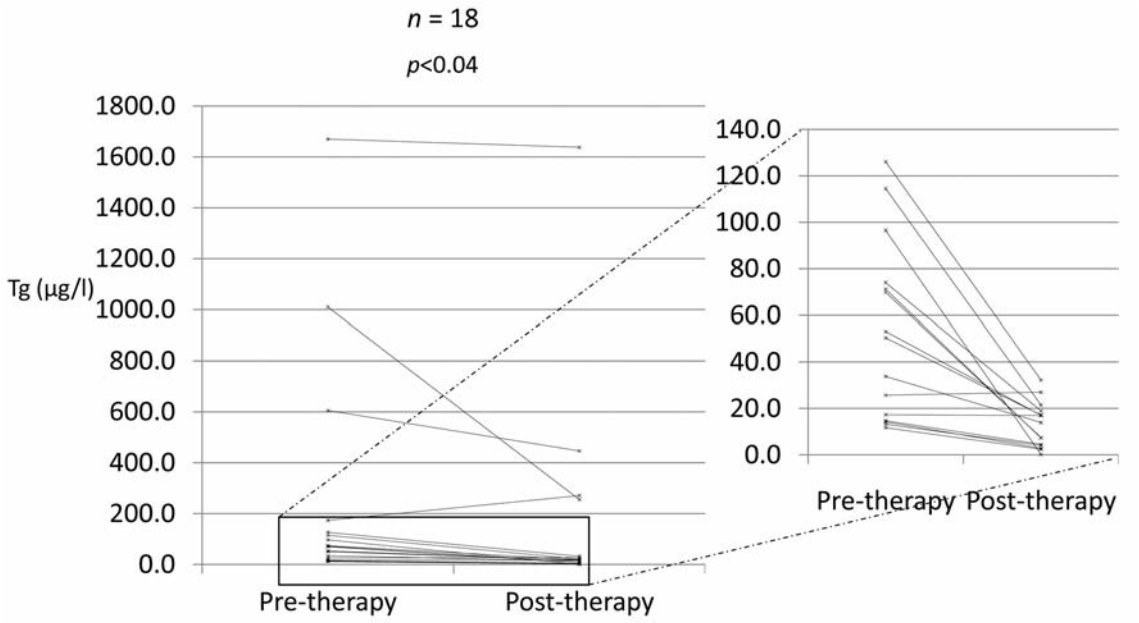

Figure 1. *In group A patients (pre-therapy Tg level of 10 µg/l or more), Tg levels as measured under TSH stimulation after a mean of 326 days following radioiodine therapy show a mean reduction of 55% (p<0.04). Data from patients with a pre-therapy Tg level less than 140 µg/l are magnified in the inset for better clarity.*

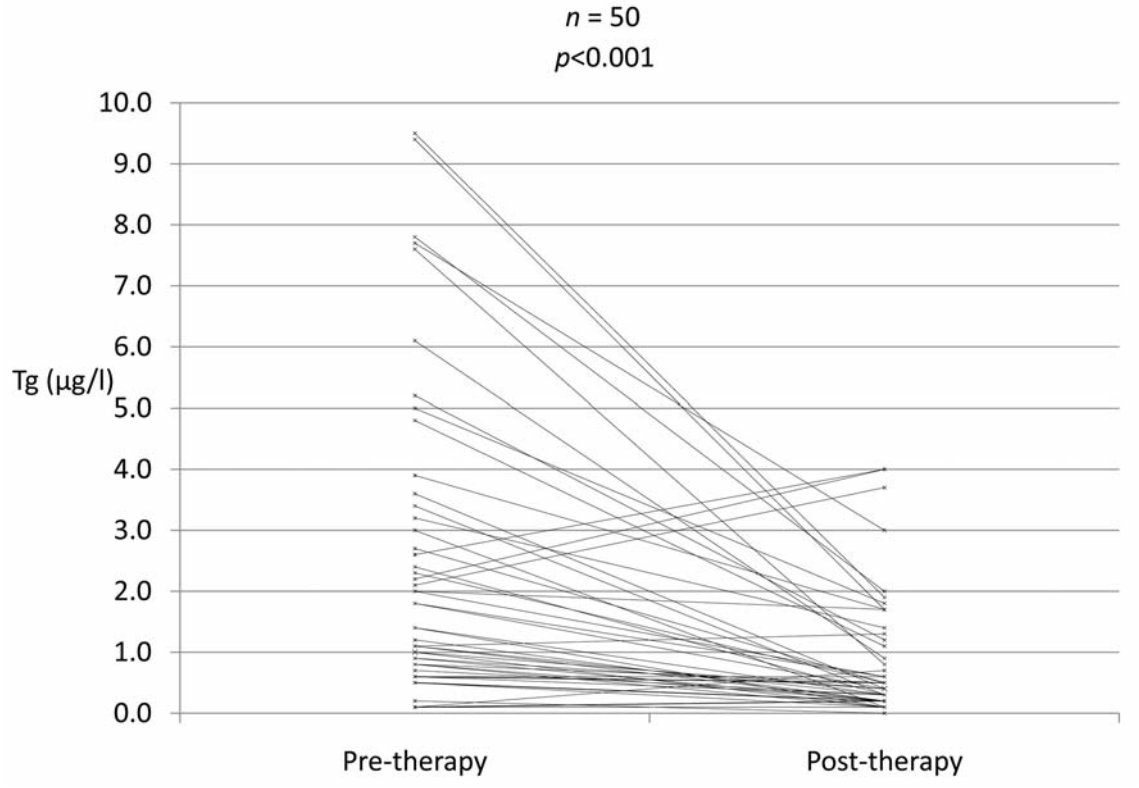

Figure 2. *In group B patients (pre-therapy Tg level less than 10 µg/l), Tg levels as measured under TSH stimulation after a mean of 455 days following radioiodine therapy show a mean reduction of 41% (p<0.001).*

Our data are confined to only those patients who continued to be scan-negative in the post-therapy scan. The Tg response rate in Group A (Tg ≥10 μg/l) with a 55% mean reduction, is similar to that reported by other workers (9). Interestingly, the Tg response in group B (Tg less than 10 μg/l) showed a 41% mean reduction, only slightly lower than that of group A. This observation shows that at least for those patients who continue to be scan negative in the post-therapy scans, radioiodine therapy produces a similar Tg response in the two groups.

Group C patients had detectable Tg antibodies. A review of the charts showed that these patients received radioiodine therapy following negative WBS for a variety of reasons. Indications included the presence of high Tg antibody levels, as has been suggested by others (14, 15), lack of complete documentation of prior therapies in the case of patients being treated at our institution for the first time, and simply the patients' desire to have their Tg antibody and Tg levels reduced to undetectable levels. Eight out of the ten patients (80%) demonstrated an interval reduction of their Tg antibody levels and six out of the 10 patients (60%) also had a reduction in their Tg levels. The significance of this therapeutic response in these ten patients is not clear, given that within the mean follow-up period of 1,803 days, no patient, even those not showing a therapeutic response, had clinical or radiologic evidence of recurrent thyroid cancer.

Conclusion

We have demonstrated that 131-I therapy can reduce Tg levels in the face of negative 131-I WBS, even when Tg levels are low. The Tg response rate in the negative post-therapy scan group appears to be the same whether Tg was above or below 10 μg/l. The value of 131-I therapy in those patients with Tg antibodies remains less certain, as in our study, a statistically significant decline could not be demonstrated either for Tg antibody or Tg levels following 131-I therapy and none of the ten patients with Tg antibodies had radiologic or clinical evidence of recurrent thyroid cancer after a mean follow-up period of 1,803 days.

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