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Transient early increase in thyroglobulin levels post-radioiodine ablation in patients with differentiated thyroid cancer

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ABSTRACT

Objectives: Treatment of differentiated thyroid cancer (DTC) includes surgical thyroidectomy and, in most cases, radioactive iodine (RAI) ablation. Measurement of serum thyroglobulin (Tg) levels is used for assessing disease burden and identifying persistent–recurrent DTC. This prospective study determined the Tg profile before and after RAI-ablation in patients with DTC.

Design and methods: Fifty-five DTC patients with complete resection received RAI-ablation and were assessed for Tg at baseline (non-stimulated), pre-ablation (stimulated), 7 days post-ablation (stimulated) and at 6 months (stimulated). Stimulation of Tg was achieved by thyroid hormone withdrawal to achieve serum thyroid stimulating hormone (TSH) ≥30 mU/L. Thyroid remnant size was estimated from whole body scintigraphy. Similar protocols were implemented for nine patients with incomplete resection/metastatic disease for comparison.

Results: Mean stimulated Tg levels for DTC patients with complete resection at 7 days post-RAI increased 13-fold from 13.7 to 175.5 μg/L ($p < 0.0001$), and the Tg levels reduced to 2.3 μg/L ($p < 0.0001$ versus post-RAI) by follow-up. None of the patients had recurrence of disease. For the nine patients with incomplete resection/metastases, Tg levels were higher throughout compared to the patients with complete resection. There was no increase in Tg between pre- and post-RAI. We did not observe a significant correlation between the remnant size and Tg increase.

Conclusions: This study confirms a prominent transient early increase in Tg post-RAI ablation in DTC patients with complete resection, with the Tg levels falling below baseline by 6 months. This is presumed to reflect RAI-induced thyroid tissue destruction/inflammation with subsequent release of Tg from the thyroid remnant. Recognizing this transient phenomenon is important for post-ablation Tg interpretation and patient management.

Introduction

The incidence of thyroid cancer in the general population has been increasing steadily, with a greater prevalence observed in the female population, particularly in the past decade [1]. The five- and ten-year relative survival rate for affected individuals is 90–95%, which can, in part, be attributed to advances in detection and treatment [2,3]. Differentiated thyroid cancer (DTC), which consists of papillary and follicular histologies, is the most common endocrine malignancy [4]. The recurrence rate of DTC has been reported to be as high as 35% in patients who were followed for four decades [4], and up to 79% in high risk groups within two years of initial treatment [5], thus highlighting the need for long-term follow-up.

The initial treatment of majority of DTC patients is with total thyroidectomy, and in most cases, administration of radioactive iodine (RAI) for ablation of remnant tissue. The efficacy of RAI ablation is directly related to tissue uptake and retention, characteristics observed with most DTCs [6]. On the contrary, poorly-differentiated thyroid malignancies, such as Hürthle cell histology or anaplastic thyroid cancer, rarely concentrate RAI, which makes this treatment option ineffective in most cases. Administration of RAI after surgery in DTC patients facilitates follow-up by destroying normal thyroid remnants, which enables serum thyroglobulin (Tg) to be a specific tumor marker for detecting recurrence of disease [7]. A previous study has demonstrated that Tg levels after a median follow-up of 5 years (range: 2.5–22) were <0.1 μg/L in 274 out of 290 (95%) non-ablated patients and 492 out of 495 (99%) ablated patients, thus confirming the utility of Tg measurement at follow-up [8].

Low pre-ablation serum Tg levels (<10 μg/L) have been shown to be a favorable prognostic biomarker [9,10]. Moreover, one study showed

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that a stimulated serum Tg cut-off of 10 μg/L at 6 months post initial surgical therapy had 100% sensitivity and 93% specificity for persistent tumor [9]. Thus, the Tg levels guide the management of these patients. However, a previous study has shown that Tg levels are elevated 6 days after RAI-ablation [11]. This may suggest that inappropriately timed blood sampling may show elevated and misleading Tg levels, which may be misinterpreted as more extensive and/or recurrence of disease. This is particularly important for patients being stimulated with human recombinant thyroid stimulating hormone (hrTSH), because the Tg levels are assessed up to 72 h after final hrTSH injection and RAI ablation. Thus, the purpose of this prospective, single center study was to determine the serum Tg profile in patients with DTC before RAI-ablation, one week after ablation, and at 6 months follow-up.

Methods

Subjects

This study has been approved by the Institutional Ethics Review Board. Sixty-four consecutive DTC patients treated between 2012 and 2013 were included in this study. Each patient had undergone complete thyroidectomy for the removal of the primary tumor, followed by ablation of remnant tissue with RAI. Thyroid remnant size and I-131 uptake for all patients were estimated from whole body scintigraphy performed after RAI-ablation. The subjects were separated in to two groups, complete resection ($n = 55$) or incomplete resection/metastasis ($n = 9$) post-thyroidectomy, based upon surgical pathology findings, preoperative imaging, intraoperative findings, and post-operative investigations. Those with incomplete resection had invasive tumor intraoperatively that was not amenable to curative resection, and gross residual disease was left behind.

Sample collection

Serum specimens were collected for all individuals at baseline (non-stimulated), pre-RAI ablation (stimulated), 7 days post-RAI ablation (stimulated) and 6 months follow-up (stimulated). The pre-ablation Tg was taken 2–3 days before administration of the RAI. The follow-up 6 month Tg values were only available for 39 patients in the complete resection group and 8 in the incomplete resection/metastatic group. The pre- and post-ablation Tg measurements for all patients were performed following brief (3 weeks) thyroid hormone withdrawal to achieve serum thyroid stimulating hormone (TSH) levels of ≥30 mU/L. The patients were then restarted on thyroid hormone replacement therapy 2 days post RAI ablation at double the usual dose for the first week. One patient received human recombinant thyroid stimulating hormone (hrTSH; Thyrogen, Genzyme) for preparation due to an inadequate elevation of serum TSH from thyroid hormone withdrawal.

Serum Tg, anti-Tg and TSH measurements

Serum Tg was measured by the Roche–Cobas TG-I electrochemiluminescent (ECL) assay (lower functional sensitivity = 0.8 μg/L). Serum anti-Tg antibodies were measured by the Roche–Cobas anti-Tg ECL assay (lower functional sensitivity = 10 IU/mL), and all patients had undetectable levels of anti-Tg. Serum TSH was measured by the Roche–Cobas TSH ECL assay (lower functional sensitivity = 0.005 mU/L).

Statistics

A paired t-test was used to analyze the Tg levels before and after RAI ablation. Deming regression analysis was used for correlating the Tg levels and thyroid bed uptake. A $p < 0.05$ was considered to be statistically significant.

Results

Patient characteristics

Patient characteristics with the appropriate TNM staging are found in Table 1. The proportion of females is higher in both groups, representing approximately two thirds of the patient number. The mean age for both groups is comparable. The incomplete resection/metastatic group received a higher treatment dose of RAI, which is consistent with severity of disease.

Tg levels in DTC patients with complete resection

The Tg profile in the 55 patients with complete resection is shown in Fig. 1. The mean non-stimulated Tg levels at baseline was 5.1 μg/L and increased to 13.7 μg/L (stimulated) just prior to RAI ablation. Seven days after ablation, the average serum Tg levels increased by approximately 13-fold to 175.5 μg/L ($p < 0.0001$, relative to pre-ablation). Six months after ablation, the levels fell to below baseline at 2.3 μg/L ($p < 0.0001$, relative to post-RAI treatment). At follow-up, 69% of patients had stimulated Tg levels below <0.8 μg/L, which is a larger proportion compared to pre (13%, $p < 0.05$) and post (2%, $p < 0.001$) values. None of the patients in this group had recurrence of disease at time of follow-up, as determined by diagnostic imaging and clinical assessment. There was no significant correlation between thyroid remnant size and absolute ($p = 0.8$) or relative ($p = 0.85$) Tg increase.

Tg levels in DTC patients with incomplete resection/metastases

The Tg profile for the 9 patients with incomplete resection/metastatic disease is found in Fig. 2 for comparison. The Tg levels for all sampling time points were much higher in these patients compared to those from the group with complete resection. At baseline, the average serum Tg was 115.5 μg/L and increased by approximately 4-fold to 431.6 μg/L pre-RAI ablation ($p = 0.08$). There was no significant difference in Tg levels between pre-RAI and post-RAI measurements (431.6 versus 509.5 μg/L, respectively ($p = 0.1$)). The Tg levels had decreased to 57.4 μg/L by 6 months follow-up ($p < 0.01$, relative to post-RAI ablation). There was no correlation between thyroid remnant size and Tg increase ($p = 0.23$).

Table 1
Patient characteristics.

Parameter	Complete resection	Incomplete resection/metastatic
Male N (%)	20 (36%)	3 (33%)
Female N (%)	35 (64%)	6 (67%)
Age (years)	Mean = 51.7 (20–91)	Mean = 52.9 (24–81)
RAI dose (GBq)	Median = 2.0 (IQR: 1.1–3.7)	Median = 5.5 (IQR: 5.2–7.4)
TSH level (mU/L)	Median = 51.1 (IQR: 41.9–65)	Median = 61.7 (IQR: 51.8–77.5)
TNM staging		
T stage:		
T1	12	2
T2	8	0
T3	33	5
T4	2	2
N stage:		
N0 or NX	31	1
N1a	10	5
N1b	14	3
M stage:		
M0 or MX	55	5
M1	0	4

IQR = interquartile range.

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