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Efficacy of radioiodine therapy in the treatment of elevated serum thyroglobulin in patients with differentiated thyroid carcinoma and negative whole-body iodine scan

Mohsen Saghari, Ali Gholamrezanezhad, Sahar Mirpour, Mohammad Eftekhari, Abbas Takavar, Armaghan Fard-Esfahani, Babak Fallahi and Davood Beiki

Introduction In the management of patients with differentiated thyroid carcinoma, serum thyroglobulin levels are often well correlated with whole-body radioiodine scanning (WBS) results. However, occasionally, a mismatched result – increased thyroglobulin with negative WBS – is observed. Radioiodine therapy has been suggested as a therapeutic choice with controversial results.

Method We studied 32 differentiated thyroid carcinoma patients with elevated thyroglobulin level and negative WBS who had been treated with high-dose radioiodine. With a mean follow-up of 25.6 months (all follow-ups >11 months), thyroglobulin and thyroid-stimulating hormone levels, WBS, clinical, radiographic and pathological findings following treatment were recorded.

Results The mean pre-therapy off-treatment thyroglobulin was $152 \pm 119.0 \text{ ng ml}^{-1}$. Although there was a mild trend towards an increase in thyroglobulin in the first post-treatment year, the difference was not significant. At the end of the follow-ups, 22 patients (68.7%) were categorized as non-responders to radioiodine therapy (any change or elevation of thyroglobulin or radiological and pathological evidences of progression), four patients (12.5%) as partial responders (transient reduction but not a normalization of thyroglobulin) and six patients (18.7%) as responders (normalization of thyroglobulin with no

evidence of remnant disease). In nine of 10 partial and complete responders, reduction or normalization of thyroglobulin had occurred in the first post-treatment year.

Conclusion We recommend that in differentiated thyroid carcinoma patients with elevated thyroglobulin and negative WBS, at least one course of radioiodine therapy should be undertaken and if reduction or normalization of serum thyroglobulin is not achieved, repeated courses of radioiodine therapy are not logical and other therapeutic methods should be applied. *Nucl Med Commun* 27:567–572 © 2006 Lippincott Williams & Wilkins.

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Introduction

The diagnostic follow-up of patients with differentiated thyroid carcinoma (DTC) is routinely performed by means of serum thyroglobulin (Tg) measurement and diagnostic whole-body radio-iodine scanning (WBS) [1–5]. Serum Tg represents a sensitive tool for detection of possible residual/recurrent disease and for early identification of DTC metastases, particularly after the initial radioiodine (RAI) thyroid ablation following total thyroidectomy [1,2,5]. Diagnostic whole-body radioiodine scans are also performed periodically to detect possible residual/recurrent disease or metastases in the follow-up course of DTC patients [1,2,5].

With this widely accepted management protocol, serum Tg levels are often well correlated with WBS results

[3,4,6]. Generally, undetectable Tg levels accompany negative WBSs, suggesting complete remission, whereas detectable or elevated Tg concentrations are associated with the presence of one or more foci of abnormal ^{131}I uptake, as a marker of residual/recurrent disease or local or distant metastases [3,4,6]. However, occasionally, a mismatched result – detectable serum Tg levels associated with a negative WBS – is observed. This pattern has been widely studied [7–20] and a few explanations have been suggested [21]. However, the proper and logical therapeutic approach in these settings has not yet been defined exactly. Chemotherapy is generally ineffective in these relatively slow-growing tumours. Surgical intervention and radiotherapy can not be attempted because the exact site of residual/remnant disease or metastatic involvement is not identifiable. Therefore,

several researchers have suggested that in these patients empirical treatment with high doses of RAI should be considered as a therapeutic choice [19], but its therapeutic effect is controversial.

The aim of the present study was to evaluate the efficacy of therapeutic doses of ^{131}I in the treatment of DTC patients with elevated thyroglobulin level but negative diagnostic WBS.

Patients and methods

We performed a large retrospective review on medical records of patients who were assessed, followed and treated for DTC (papillary, follicular or Hürtle cell thyroid carcinomas) in our nuclear medicine ward between 1995 and 2005. The study only included those patients who had history of total thyroidectomy and RAI ablation therapy for DTC and subsequently during their course of follow-up developed high levels of Tg with negative WBS. Hence, these patients had another session of hospitalization in order to treat this elevated serum thyroglobulin and negative WBS state. Hospitalization for RAI ablation therapy after thyroidectomy was called the 'first hospitalization', and the session of hospitalization for treatment of elevated Tg and negative WBS was called the 'target hospitalization'. Moreover, of this limited group of patients only those were selected who had at least 11 months complete follow-up (with measurement of Tg and WBS every 6 months) after target hospitalization. Those who had discontinued their follow-up after discharge from target hospitalization were excluded. No patient was lost to the study because of death from thyroid cancer. Finally, 32 patients (12 men and 20 women) with a mean age of 42.3 ± 17.4 years (range, 10–71 years) entered the study. Twenty-five patients had papillary, six follicular, and one Hürtle cell cancer.

Patients' records were reviewed for initial surgical and pathological findings; the time and sequence of subsequent RAI treatments; related pathological findings; serum Tg, anti-Tg and thyroid-stimulating hormone (TSH) levels and WBS results during the follow-up period; subsequent clinical findings and surgery for possible recurrences or metastases; and also, in a few cases, the radiographic results obtained throughout the follow-up period. Treatment with thyroxine had been stopped for 4–6 weeks before measurement of Tg and diagnostic whole-body scanning, and these two diagnostic tests were performed 2 weeks after discontinuing a 2-week course of liothyronine. All patients had been advised to have a low-iodine diet and to avoid pharmacological iodine during the period of preparation for the diagnostic scan. Pre-treatment scans were performed 48 h after oral administration of 185 MBq ^{131}I . The pre-therapy and post-therapy WBSs were reviewed by nuclear medicine specialists blinded to other clinical data. The

presence of areas with definite or possible abnormal RAI uptake was identified and all patients with either definite or possible abnormal RAI uptake in pre-therapy WBSs were excluded from the study. All WBSs were acquired using a planar gamma camera (Scintronix, UK) equipped with a high-energy collimator, energy setting of 364 keV and a 15% window.

The serum levels of TSH (normal value, 0.3–4 mIU·l⁻¹) and anti-Tg antibody (normal value, less than 100) were measured by IRMA (RADIM, Italy) and Tg was measured by a radioimmunoassay method (CIS Bio International, France). A serum Tg level of more than 1 ng·ml⁻¹ was considered positive [9,11]. Tests for Tg antibodies were negative in all patients except a 62-year-old lady with an anti-Tg of 212. As noted by Fatourechi *et al.* [17], this is not surprising as positive anti-Tg antibodies, because of interference with the assay, result in falsely low or undetectable values, and by definition these patients might have been excluded from the study.

Statistical analysis

SPSS for Windows software package (Release 11.5.0, SPSS Inc., Chicago, Illinois) was used for statistical analysis. Tg levels before and after ^{131}I therapy were compared by using the Wilcoxon test for all patients. When more than one post-therapy result for Tg was available, the lowest value was used. Both pre-therapy and post-therapy Tg levels were obtained when the patients were off thyroxine suppression. A *P* value of 0.05 or less was considered significant. All *P* values were two-tailed.

Results

The mean time interval between the first hospitalization and the target hospitalization was 23.5 ± 17.1 months. In the 6-month follow-up visits after the first hospitalization, nine patients had a history of positive WBS remnant/recurrence or metastatic disease before transformation of the disease to the WBS negative form, and they had one or more sessions of hospitalization for its treatment. In seven of these patients, there was only one pre-target hospitalization course of RAI therapy between the first hospitalization and the target hospitalization. Of these seven patients, two had a history of pulmonary metastases and were treated with 7400 MBq radioiodine and the remaining five patients had only thyroid bed remnants and were treated with 3700–5500 MBq radioiodine (mean dose of 5180 MBq). In one patient this hospitalization for treatment of WBS positive disease was repeated three times before target hospitalization (because there was remnant thyroid tissue in the thyroid bed the patient was treated twice with 3700 MBq ^{131}I and once with 4625 MBq) and in another patient it was repeated five times with 6475 MBq ^{131}I (each time because of disseminated pulmonary metastasis, with or without

thyroid bed remnant and supraclavicular ^{131}I uptake in pre-treatment scans).

At the time of the diagnostic WBS and measurement of the serum Tg level, the mean serum TSH was $46.8 \text{ mIU}\cdot\text{l}^{-1}$, and all patients had a serum TSH levels above $30 \text{ mIU}\cdot\text{l}^{-1}$. The mean pre-target hospitalization serum Tg with the patients off-treatment was $152 \pm 119.0 \text{ ng}\cdot\text{ml}^{-1}$ (range, 11–500 $\text{ng}\cdot\text{ml}^{-1}$). All pre-therapy scans showed no evidence of functioning thyroid tissue throughout the body. The mean therapeutic ^{131}I dose in target hospitalization was 5661 MBq (range, 3700–7400 MBq).

Post-treatment diagnostic whole-body scans

Post-therapy scans were available for 26 patients and were done 6–10 days after radioiodine administration. No abnormal radioiodine uptake was noted in 12 patients (46%). Faint uptake was noted in the thyroid bed in four patients, in cervical lymph nodes in two, in lung fields in two, in cervical lymph nodes and lung fields in four, in lung fields and skull in one, and in the mediastinum in one patient.

The first-year follow-up after target hospitalization

After approximately 6 months (5–7 months), 25 patients were visited again for the first post-target hospitalization follow-up. All of these patients were withdrawn from thyroxine therapy for diagnostic WBS and Tg measurement: 14 of them had an increase in serum Tg (all of them underwent another course of RAI therapy), and five had a reduction (but not normalization) of serum Tg. In three patients the serum Tg in the first post-target hospitalization follow-up (6 months) was completely negative (no further RAI treatment was recommended). In the remaining three patients in the 6–7 months post-target hospitalization, clinical evidence of regional recurrence was present and, subsequently, patients underwent surgery again. In two cases the pathology report indicated cervical lymph node involvement with papillary carcinoma of thyroid (these findings were confirmed by elevation of the serum Tg level compared to the baseline pre-target hospitalization level) and in the third case it was consistent with a recurrence of the disease which involved soft tissue of the neck and cervical and supraclavicular lymph nodes. Despite these findings in the latter case, the serum Tg level was decreased compared to the pre-target hospitalization level. In general, 17/25 patients (68%) showed no therapeutic benefit, 5/25 (20%) partial benefit (some degree of reduction, but not normalization of the serum Tg), and 3/25 (12%) of patients showed complete improvement.

The mean 6-month post-treatment serum Tg level was $161.7 \pm 129.2 \text{ ng}\cdot\text{ml}^{-1}$ (range, 1.0–560.0 $\text{ng}\cdot\text{ml}^{-1}$); Although there was a mild trend toward the increase in serum Tg

level comparing to the pre-target hospitalization Tg level, the difference did not reach statistical significance ($P > 0.5$).

The second post-target hospitalization follow-up was performed approximately 12 months afterwards (11–13 months) and sufficient data for 22 patients were available. All of these patients were withdrawn from thyroxine therapy for Tg measurement: 16 of these patients (72.7%) had a significant increase, three (13.6%) had a reduction of serum Tg (compared with the baseline pre-target hospitalization level) and two (9%) had normal serum Tg tests. Magnetic resonance imaging of one patient showed cervical lymph node involvement, while X-ray examination and a bone scan showed evidence of metastatic involvement of both humeri. The pathological analysis showed metastatic papillary carcinoma. Of those five patients who had shown a reduction of Tg level in the first post-target hospitalization follow-up and therefore no further radioiodine treatment, two patients did not show any significant change of Tg level in the second visit and two patients had a negative serum Tg tests on the second follow-up (no RAI treatment was recommended). Data for the remaining patient were not available. In general, 17/22 patients (77.2%) showed no therapeutic benefit, 3/22 (13.6%) showed partial benefit (some degree of reduction but not normalization of the serum Tg level), and 2/22 (9%) of patients showed complete improvement.

The mean 6-month post-treatment serum Tg level was $159.3 \pm 132.5 \text{ ng}\cdot\text{ml}^{-1}$ (range, 1.0–620.0 $\text{ng}\cdot\text{ml}^{-1}$); Although there was a mild trend towards an increase in serum Tg level, the difference did not reach statistical significance ($P > 0.5$).

Follow-up diagnostic whole-body scan

In the first-year follow-up of patients (5–13 months), all patients were withdrawn from thyroxine therapy for at least one diagnostic WBS. All the follow-up scans were negative, except in the only patient with Hürtle cell carcinoma whose WBS showed faint uptake in the region of thyroid bed and lungs and two patients with faint uptake in the neck (both had pathological evidence of cervical lymph node involvement after resection). All these three patients were recommended for another course of RAI therapy, the follow-up outcome of which was not available.

In general, all 32 patients had at least one post-target hospitalization follow-up visit during the first year. According to the serological, scintigraphic and pathological evidence mentioned above, there were 27 patients (84.3%) categorized as having recurrent/remnant disease. Of these, 23 were non-responders (any change or elevation of the serum Tg level or radiological and pathological evidence of progression, 71.8%) and three

patients were partial responders (reduction of serum Tg, but not a normal Tg level, 12.5%) to the first radioiodine treatment) and re-hospitalization for RAI therapy was recommended. Of these 27 patients, three refused further hospitalization. In five patients (15.6%) there was no serological or scintigraphic evidence of the disease and these patients were categorized as responders (normalization of serum Tg with no other evidence of remnant disease) and no subsequent therapy was given.

Subsequent follow-ups after the first post-treatment year

The mean follow-up of our patients after target hospitalization was 25.6 ± 7.6 months (range, 11–66 months) and a total of 21 patients have been visited for the second to fifth year follow-ups (14 patients who had been categorized as non-responders at the end of the first year, three partial responders and four responders). During 2–4 years of their follow-up, none of responders showed recurrence of the disease. Two of three partial responders (with 1.5 and 2.5 years of follow-up) showed serological evidence of remnant/recurrent disease as an increase in serum Tg level, while only one of them had negative serum Tg tests and normalization of the serum Tg level during the 2.5 years of follow-up. Twelve of 14 non-responders showed scintigraphic, pathological and serological evidence of disease progression and the presence of remnant/recurrent disease (10 patients with increased serum Tg level, three with regional recurrence in cervical lymph nodes, and one with a pathological fracture in the ribs secondary to a metastatic papillary carcinoma), while in two patients the disease remained stable with no significant changes in serum Tg levels. Of the two groups of non-responders and partial responders (16 patients), 15 underwent re-hospitalization (one to three times) with no evidence of reduction in serum Tg level, but two patients refused to be hospitalized again and had no further follow-up. As mentioned above only one partial responder showed regression of the disease and normalization of serum Tg level.

At the end of the follow-ups, and based on the serological, scintigraphic and pathological evidence mentioned above, 22 patients (68.7%) were categorized as non-responders, four as partial responders (12.5%) and six patients (18.7%) as responders to RAI therapy.

Discussion

In current practice, it is not unusual to encounter cases of negative WBS and elevated TSH-stimulated or non-stimulated serum Tg levels [6]. In these cases the causes of false negative scans, such as inadequate TSH elevation and iodine contamination, must be excluded initially [21]. If these explanations are not clinically relevant, a true state of Tg positive, WBS negative DTC is present, which may result from a disturbance of the iodine-

concentrating mechanism and dissociation between Tg synthesis and the iodine-trapping mechanism [19,21]. Another possible explanation is that micro-metastases which have dispersed or are too small to be visualized by diagnostic doses of ^{131}I result in elevation of serum Tg level without visualization in WBSs [19,21]. In these cases micro-metastases may be seen with higher therapeutic doses of radioiodine. Accordingly, several researchers have shown that in such cases administration of high ^{131}I activity (3700 MBq or more) increases the sensitivity of a post-therapy diagnostic ^{131}I whole-body scan performed a few days later and allows the detection of neoplastic foci not seen with diagnostic doses of ^{131}I . This fact was confirmed in our study as 53.8% (14/26) of patients had foci of radiotracer uptake in the post-treatment scan, which were not detected in the pre-treatment images. Also, it is possible that these foci of abnormal radiotracer uptake become visualized in diagnostic scans after a few months (as was observed in three patients in our study), which could be explained by bulky enlargement of the tumoral mass. In fact, it could be concluded that, in the first scan, the volume of the tumoral mass was so small that it could not be detected by the limited resolution of the imaging system [19,21]. After a few months of tumour growth, the tumoral mass reaches the minimum volume required for detection by the gamma camera. Similar findings were noted in a review by Ma *et al.* [6] who noted that 62% positive post-therapy scans indicated that a therapeutic dose of ^{131}I could reveal approximately one half of previously undiagnosed lesions in some patients. Also, the similar rate in the study by de Keizer *et al.* [15] was reported to be 59%.

On the other hand, despite of the fact that RAI therapy has so far not been considered harmful [10] (although this assumption can be questioned, as the obligatory rise in serum TSH levels necessary for RAI therapy may have disadvantageous effects on tumour behaviour [10]) TSH receptor expression is retained even in advanced stages of thyroid carcinoma, which may exert proliferative effects on tumour cells. With this assumption it is not logical to impose the risk of tumour growth enhancement without any confirmed beneficial effect of this presumptive treatment. This fact is well documented in our study, as only less than on third of patients have some degree of response to radioiodine treatment.

Previous results are also somewhat controversial and it has not yet been determined that this approach is effective or not. Fatourechi and Hay [19] emphasized that, based on presently available information, a generalized recommendation for RAI therapy of Tg-positive, diagnostic scan-negative patients should await further studies. Meanwhile, in some high-risk patients, in the absence of alternative therapies, empirical RAI therapy is justified [19]. On the other hand, the need for treatment of these

patients has been questioned, as there are some reports indicating that Tg levels may remain stable, decline, or even disappear over time without treatment [22].

In the study by Koh *et al.* [14], 60 DTC patients with elevated serum Tg levels but negative WBSs were divided into two groups. Twenty-eight patients were treated with RAI and 32 were untreated. In a mean follow-up of 23.8 ± 19.6 months, the percentage decrease in Tg level of the treated group was significantly higher than that of the untreated group and in four cases serum Tg levels became negative. It was concluded that therapeutic doses of RAI have a therapeutic effect, at least for palliation in short-term observation, considering the serum Tg level as an index of tumour burden [14].

In a recent review by Ma *et al.* [6], the results of 10 serial observations and three non-randomized controlled trials were assessed. The authors mentioned that, on the basis of data from recent studies, ^{131}I therapy should be individualized according to clinical characteristics. In their meta-analysis, a decrease in Tg levels was achieved in 63% of DTC patients with elevated Tg and negative WBSs, suggesting that ^{131}I therapy does have a therapeutic effect when the Tg level is considered an index of tumour burden. Therefore, ^{131}I therapy may be justified in patients with elevated Tg levels and negative WBSs and who are at high risk of any recurrence [6]. However, in our opinion the major drawback of their conclusion is that Tg level could not always be considered as a reliable indicator of treatment efficacy. This fact is clear from the results obtained from one of our patients, in whom the serum Tg level was decreased in comparison to the pretreatment level, although clinical and pathological evidence of locoregional recurrence was apparent. The same drawback is present in the conclusion of de Keizer *et al.* [15], who stated that blind therapeutic doses result in a decrease in Tg levels in the majority of patients with suspected recurrence or metastases.

However, as mentioned previously the results are controversial [23] and similar benefits were not observed in other studies. For example, Schaap *et al.* [10] did not observe a beneficial effect and they did not advise the continuation of radioiodine therapy in patients with negative post-therapeutic whole-body scintigraphy, unless a positive response is observed in individual cases. Accordingly, in our study more than two thirds of patients showed no benefit of treatment, which was consistent with the results obtained by Kamel *et al.* [24]. These latter authors showed normalization of Tg levels in only 6/38 patients while off thyroxine therapy and concluded that the effect of ^{131}I therapy on long-term survival is not obvious [24].

In general, our findings are in agreement with those of Rosario *et al.* [25], who had previously concluded that, if

the post-therapy scan is negative or reveals discrete uptake in the thyroid bed, other methods (e.g., fluorodeoxyglucose positron emission tomography) can be performed, and the physician should not insist on radioiodine therapy [25]. If WBSs detect lymph node metastases, surgery is indicated [25,26], while in cases of diffuse lung metastases radioiodine is indicated until the occurrence of a negative WBS or normalization of stimulated Tg levels. These authors have found that patients with a positive post-therapy scan may show a significant reduction in Tg, with even complete remission in some cases after radioiodine, but they emphasized that the impact of this treatment on mortality remains controversial [25].

In our opinion one of the most important findings of our study which is not mentioned in previous reports is that in nine of 10 partial and complete responders, the reduction or normalization of serum Tg occurred in the first post-treatment year. Therefore, in conclusion we recommend that in DTC patients with elevated Tg and negative WBS, at least one course of RAI therapy should be given and if a satisfactory response (reduction or normalization of serum Tg) is not achieved, additional courses of RAI therapy are not logical and other therapeutic methods should be applied. As more than half of these patients will have positive post-treatment scans, this approach can have the advantage of localizing the remnant disease for other possible therapeutic modalities, such as surgical resection of involved cervical lymph nodes.

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