EMPIRIC $^{131}$I TREATMENT OF HIGH THYROGLOBULIN LEVELS IN DIFFERENTIATED THYROID CARCINOMA AFTER REMNANT ABLATION

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ABSTRACT

**Aim:** The objective of this study is to establish the efficacy of empiric $^{131}$I treatment (EIT) given for patients whose thyroglobulin (Tg) levels remained high after ablative $^{131}$I treatment (AIT).

**Methods:** Fifty-six patients (46 women, 10 men; mean age 47.4±16.8), without distant metastasis, who were treated empirically for high Tg levels after AIT in our clinic, were retrospectively studied. In all patients stimulated Tg levels before AIT (Tg I) and 6 months after AIT (Tg II) were measured. After EIT, post-therapeutic whole-body scintigraphy (PWBS) was performed to all patients. $^{18}$F-FDG PET CT was performed to patients who had negative PWBS but continued to have high Tg II levels.

**Results:** PWBS was positive in 28 patients (50%) and negative in 28 patients (50%). Twenty-eight patients did not respond to EIT (50%), and 28 patients (50%) responded to EIT at different rates. Sixteen patients (28.6%) responded to EIT completely, and 12 patients (21.4%) responded to EIT partially. Tg I was 60.7±40 ng/ml and Tg II was 31±20.4 ng/ml in responding patients, whereas Tg I was 87.6±96 ng/ml and Tg II was 114.3±106 ng/ml in unresponding ones. $^{18}$F-FDG PET CT was positive in 22 patients and negative in 6.

**Conclusion:** Our findings, suggested that the EIT is not beneficial in patients who have higher Tg II than Tg I and the cure rate is low in increasing Tg levels. The patients who have high Tg II but lower than Tg I can be treated empirically with $^{131}$I.

**Key words:** Empiric $^{131}$I treatment, High thyroglobulin levels, Ablative $^{131}$I treatment

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Introduction

The main method for the treatment of differentiated thyroid carcinoma (DTC) is total or nearly total thyroidectomy followed by $^{131}$I radiiodine treatment (RIT) and suppression of thyroid-stimulating hormone (TSH). RIT has been used for both remnant ablation and treatment of metastases in DTC.

Serum thyroglobulin (Tg) measurements are usually the best marker of residual or metastatic disease after the treatment of DTC. Stimulated Tg level obtained 6-12 months after RIT is regarded as a very good prognostic indicator and is of decisive importance for the clinical management of patients with DTC. Undetectable Tg levels with negative diagnostic whole-body scintigraphy (DWBS) results, suggest a complete remission, whereas detectable or elevated Tg levels are associated with persistent disease. Tg level after treatment of DTC above 10 ng/ml is considered pathologic by many investigators because such levels are highly predictive of residual or recurrent disease even in patients with negative DWBS. Serum Tg measurement is more sensitive than DWBS for the detection of recurrences and metastases. Deciding how to treat the patients who have high Tg levels after ablative $^{131}$I treatment (AIT) is the question that must be addressed. Empiric $^{131}$I treatment (EIT) is an important choice in these patients. In many centres including ours, the Tg cut-off value for EIT is about 10 ng/mL without thyroxin therapy.
Material and methods

Fifty-six patients (46 women, 10 men), without distant metastasis, who were treated empirically for high Tg levels after AIT, between January 2008 and December 2012, were retrospectively studied. These patients were treated by a total or near-total thyroidectomy followed by AIT, initially. Patients had no foci of uptake outside the thyroid bed on post AIT whole-body scintigraphy (WBS). Mean age was 47.4±16.8 years (range 25-82 years). Histologic examination revealed papillary thyroid carcinomas in all patients. The mean follow-up was 2.7±1.3 years (range, 1-4.8 y).

Within a few months after surgery, patients were given 75-100 mCi $^{131}$I for remnant ablation after least 4-week withdrawal of hormone therapy. Five-seven days after AIT WBS was performed to all patients. To control the AIT efficacy, DWBS was planned approximately 6 months later while the patients were off hormonal therapy. Before AIT and 6 months after AIT, stimulated Tg levels were measured. Tg was measured using immunoradiometric analyser that uses paramagnetic microparticles and chemiluminescent detection technology. All patients had a Tg level higher than expected and empirically treated with 125-175 mCi $^{131}$I without DWBS. The Tg cut-off level for EIT was accepted 10 ng/ml. WBS was performed to all patients after EIT. Post therapeutic whole-body scintigraphy (PWBS) was positive in 28 patients and negative in 28 patients. 18F-FDG PET CT was performed to PWBS negative 28 patients who had persistent high Tg II. 18F-FDG PET CT was positive in 22 patients and negative in 6 patients. 18F-FDG PET CT showed hypermetabolic lymph nodes in 20 patients and hypermetabolic recurrent thyroid tissue in two patients. These 22 patients were referred to surgery. The mean standard uptake value (SUV) was 8.1±5.2 (range 4.2-21.6). 18F-FDG PET CT positive patients were referred to surgery. The mean Tg level was 117±105.6 ng/ml (range 10-300 ng/ml) in 18F-FDG PET CT positive patients and 14.6±5.2 ng/ml (range 10.4-20.5 ng/ml) in 18F-FDG PET CT negative patients. The characteristics of PWBS negative patients are reported in Table 1.

Results

At the time of AIT thyroid remnants were present on post treatment whole-body scans in all patients and there was no foci of pathologic uptake outside the thyroid bed. No pathologic lymph node was present on ultrasonography (US). The chest computed tomography and bone scintigraphy performed before AIT were also normal in all patients. The mean Tg I was 72.4±74.6 ng/ml (range 10-300 ng/ml). To control the AIT efficacy, DWBS was planned approximately 6 months later while the patients were off hormonal therapy. Stimulated Tg levels were measured before DWBS. At the time of 6th month control, 10 patients had an elevated Tg level (Tg I, 54.8±40 ng/ml; Tg II, 164.6±85.5 ng/ml), 6 patients had a similar Tg level (Tg I, 113.6±161.5 ng/ml; Tg II, 112.6±162.3 ng/ml) and 40 patients had a decreased Tg level (Tg I, 70.6±67 ng/ml; Tg II, 41.8±54 ng/ml). All patients were empirically treated with 125-175 mCi $^{131}$I without performing DWBS. Mean Tg II level of all 56 patients was 71.3±86.6 ng/ml (range 10-300 ng/ml). PWBS was performed to all patients 7 days after EIT. PWBS was positive in 28 patients (50%) and negative in 28 patients (50%). In PWBS positive patients, pathological $^{131}$I uptake was in only thyroid bed in 20 patients and in only mediastinum in remnants 8.

18F-FDG PET CT was performed to PWBS negative 28 patients who had persistent high Tg II. 18F-FDG PET CT was positive in 22 patients and negative in 6 patients. 18F-FDG PET CT showed hypermetabolic lymph nodes in 20 patients and hypermetabolic recurrent thyroid tissue in two patients. These 22 patients were referred to surgery. The mean Tg level was 117±105.6 ng/ml (range 10-300 ng/ml) in 18F-FDG PET CT positive patients and 14.6±5.2 ng/ml (range 10.4-20.5 ng/ml) in 18F-FDG PET CT negative patients. The characteristics of PWBS negative patients are reported in Table 1.

<table>
<thead>
<tr>
<th>FDG PET CT</th>
<th>Patients (n:28)</th>
<th>Tg II level</th>
<th>SUV</th>
<th>Response to EIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>22</td>
<td>117±105.6</td>
<td>8.1±5.2</td>
<td>0</td>
</tr>
<tr>
<td>negative</td>
<td>6</td>
<td>14.6±5.2</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

Tab 1: The characteristics of PWBS negative patients.
Tg: Thyroglobulin, SUV: Standard uptake value, EIT: empiric $^{131}$I treatment

The PWBS negative patients did not respond to EIT except one and this patient who had both negative PWBS and 18F-FDG PET scan, gave partial response to EIT, because Tg level decreased from 20.5 to 15.5 on the follow up. PWBS positive patients responded to EIT in different rates except one. Six months after EIT, stimulated Tg levels were measured. DWBS was performed to 16 patients who had Tg level less than 2 ng/dl. DWBS was negative in these patients and complete remission was accepted. Mean Tg I was 54±28.4 ng/ml (range 29-101 ng/ml) and Tg II was 26.2±9.6 ng/ml (range 12-42
ng/ml) in these 16 patients. In 10 patients Tg levels decreased but still higher than expected. Mean Tg level was decreased to 31.1±28.8 ng/ml from 46.4±27.9 ng/ml. (partial response). Eight of these patients who had Tg level higher than 10 ng/dl, were treated empirically again without DWBS. Six months after EIT, DWBS was performed two patient whose Tg level was 6.7 and 7.5 ng/ml (Tg II was 42 and 38.3 ng/ml). DWBS was negative and we decided to follow up this patient. Finally, PWBS positive two patient who had mediastinal 131I uptake did not respond to EIT. The response rates of PWBS positive and PWBS negative patients are given in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>PWBS positive patients (%)</th>
<th>PWBS negative patients (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>16 (28.6%)</td>
<td>-</td>
<td>16 (28.6%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>10 (17.8%)</td>
<td>2 (3.6%)</td>
<td>12 (21.4%)</td>
</tr>
<tr>
<td>No response</td>
<td>2 (3.6%)</td>
<td>26 (46.4%)</td>
<td>28 (50%)</td>
</tr>
<tr>
<td>Total</td>
<td>28 (50%)</td>
<td>28 (50%)</td>
<td>56 (100%)</td>
</tr>
</tbody>
</table>

Tab 2: The response rates of PWBS positive and PWBS negative patients.

PWBS: Posttherapeutic whole-body scintigraphy

Twenty-eight patients did not respond to EIT (50%) and 28 patients (50%) responded to EIT at different rates. Sixteen patients (28.6%) responded to EIT completely and 12 patients (21.4%) responded to EIT partially. Mean Tg I was 60.7±40 ng/ml (range 22-146 ng/ml), mean Tg II was 31±20.4 ng/ml (range 12-93 ng/ml) and mean age was 46.7±17.3 years (range 26-82 years) in responding patients. In 2 patients Tg II was almost equal with Tg I and in 26 patients Tg II was lower than Tg I in responded patients. Mean Tg I was 87.6±96 ng/ml (range 10-300 ng/ml), mean Tg II was 114.3±106 ng/ml (range 10-300 ng/ml) and mean age was 50±17.1 years (range 25-76 years) in unresponding patients. In 10 patients Tg II was higher than Tg I, in 4 patients Tg II was almost equal with Tg I and in 14 patients Tg II was lower than Tg I in unresponded patients. Comparative Tg I and Tg II results according to treatment responses are given in Table 3.

The mean Tg level measured latest on the follow up (final Tg) was 1.5±0.45 ng/ml (range 0.6-1.9 ng/ml) in complete responded patients, 28±25.4 ng/ml (range 6.7-75 ng/ml) in partial responded patients and 114.1±105.5 ng/ml (range 10-300 ng/ml) in unresponding patients. Tg I, Tg II and final Tg levels according to treatment responses are given in Table 4.

<table>
<thead>
<tr>
<th></th>
<th>Complete responded patients (%)</th>
<th>Partial responded patients (%)</th>
<th>Unresponded patients (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tg I&gt;Tg II</td>
<td>16 (28.6%)</td>
<td>10 (17.8%)</td>
<td>14 (25%)</td>
<td>40 (71.4%)</td>
</tr>
<tr>
<td>Tg I=Tg II</td>
<td>-</td>
<td>2 (3.6%)</td>
<td>4 (7.1%)</td>
<td>6 (10.7%)</td>
</tr>
<tr>
<td>Tg I&lt;Tg II</td>
<td>10 (17.8%)</td>
<td>-</td>
<td>26 (46.4%)</td>
<td>36 (64.9%)</td>
</tr>
</tbody>
</table>

Tab 3: Comparative Tg I and Tg II results according to treatment responses.

Tg: Thyroglobulin

<table>
<thead>
<tr>
<th></th>
<th>Complete response (16 patients)</th>
<th>Partial response (12 patients)</th>
<th>No response (28 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tg I</td>
<td>54±28.4</td>
<td>73.8±50</td>
<td>87.6±96</td>
</tr>
<tr>
<td>Tg II</td>
<td>26.2±9.6</td>
<td>42±27</td>
<td>114.3±106</td>
</tr>
<tr>
<td>final Tg</td>
<td>1.5±0.45</td>
<td>28±25.4</td>
<td>114.1±105.5</td>
</tr>
</tbody>
</table>

Tab 4: Tg II and final Tg levels according to treatment responses.

Tg: Thyroglobulin

Discussion

The use of 131I has continued as a mainstay of therapy for DTC today. It has a major impact on the control and cure of thyroid carcinoma. Serum Tg levels are usually the best marker of residual or metastatic disease after the treatment of DTC. It is not rare to find patients with detectable serum Tg levels after AIT. For many investigators, total thyroid ablation seems necessary to consider the serum Tg level as a reliable tumor marker. In theory, if one could eliminate all normal thyroid cells, the remaining source of Tg production would be malignant thyroid cells. However, some studies including ours, have reported that high initial values of the postoperative Tg level could be related to initial metastases or further recurrences. The Tg level measured several months after AIT is a well-known marker of the disease course. Undetectable Tg levels under TSH stimulation are good indicators of the disease-free status, whereas elevated levels correlate with persistent disease. Serum Tg measurement is more sensitive than DWBS for the detection of recurrences and metastases. PWBS may detect new foci of tumor not seen on DWBS in up to 50% of patients with a substantial number of the newly found distant metastatic lesions. A Tg level above 10 ng/mL which measured after AIT, is considered pathologic.
by many investigators because such levels are highly predictive of recurrences\textsuperscript{5,8-10}. The Tg cut-off value for EIT is about 10 ng/ml without thyroxin therapy in many centres, including our clinic\textsuperscript{10,15-17}.

In our clinic, we empirically treat patients who have Tg II level higher than 10 ng/ml without DWBS. Because sensitivity of DWBS is low and it causes \textsuperscript{131}I treatment delay about 3 months after DWBS related to stunning effect. For such patients, we first perform a neck US. Pacini et al. found that the combination of measurement of stimulated serum Tg levels and neck US has the highest sensitivity (96\%) and negative predictive value (99\%) for monitoring patients with DTC\textsuperscript{31-33}. If the neck US examination is positive, a lymph node sample is obtained for cytology evaluation by fine-needle aspiration biopsy, and the needle washing is analysed for Tg levels\textsuperscript{25}. If either is diagnostic, surgery and \textsuperscript{131}I therapy are considered. If the US examination is negative and the Tg levels are high enough, we consider EIT. After EIT, we perform 18F-FDG PET CT scan to patients who have negative PWBS. An elevated serum Tg level (>10 ng/ml) with negative PWBS results currently is the main indication for 18F-FDG PET CT\textsuperscript{26,27}. 18F-FDG PET CT also provides prognostic information. 18F-FDG-avid metastatic DTC lesions are resistant to \textsuperscript{131}I treatment, a situation that portends a poor prognosis\textsuperscript{28}.

The findings of several studies support the use of EIT in cases with DWBS negative (DWBS-) and high serum Tg level (Tg+), because a post-treatment decrease in serum Tg was observed\textsuperscript{29,30}. On the other hand, various authors have discouraged routine use of EIT\textsuperscript{31-33}. Because some metastases may not concentrate or retain enough \textsuperscript{131}I to achieve a therapeutic benefit. Also high-dose \textsuperscript{131}I treatment is not without risk. Acute or long term side effects may occur.

Pacini et al empirically treated 42 patients with high Tg and negative DWBS\textsuperscript{29}. Thirty of patients (71\%) had positive PWBS, Tg levels decreased in 19 (45\%) patients with positive PWBS. Complete remission was seen in 33\% of patients with positive PWBS and in 17\% with negative PWBS. Pineda et al empirically treated 17 patients with high Tg and negative DWBS\textsuperscript{26}. Sixteen of patients (94\%) had positive PWBS. Tg levels decreased in 13 patients after the first EIT and in 5 patients received a second EIT. Kuang reported the results of a literature review designed to evaluate the efficacy of EIT of 310 patients with high Tg and negative DWBS\textsuperscript{34}. Kuang found that slightly more than 59\% had positive PWBS results after EIT and that serum Tg levels decreased in about 72\% of the treated patients. Kuang concluded that empiric EIT may be justified for a Tg cut-off value of 10 ng/ml.

In our study, we treated empirically 56 patients who had high Tg II levels without DWBS. Twenty-eight patients (50\%) had positive PWBS and Tg levels decreased in 28 patients (50\%). Complete remission was seen in 16 (28.6\%) patients with positive PWBS. Partial response was seen 10 patients with positive PWBS and 2 patients with negative PWBS. Mean Tg I was higher than mean Tg II in responsive patients and mean Tg II was higher than mean Tg I in unresponsive patients. Both mean Tg I and Tg II were higher in unresponsive patients than responsive ones. In 10 patients Tg II was higher than Tg I, in 4 patients Tg I was almost equal with Tg I and in 14 patients Tg II was lower than Tg I in unresponsible patients. On the other hand, Tg II was not higher than Tg I in any responded patient.

According to our findings, we concluded that the EIT is not beneficial in patients who have higher Tg II than Tg I. In these patients, performing DWBS will be a proper approach. If DWBS is negative, next step should be 18F-FDG PET scan. According to 18F-FDG PET results, other treatment options -for example surgery- may be taken into consideration. Also the cure rate is low in increasing Tg levels. The patients who have high Tg II lower than Tg I can be treated empirically with \textsuperscript{131}I without DWBS. In these patients EIT may be beneficial. Additionally, when 18F-FDG PET results are taken into consideration, we think that a detailed neck US reduces the number of unnecessary EIT.

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