Redifferentiation Therapy with 13-cis Retinoic Acids in Radioiodine-Resistant Thyroid Cancer

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Abstract. Radioiodine (I-131) therapy is of proven efficacy for treatment of differentiated thyroid carcinoma (DTC). However, loss of differentiation in recurrent or metastatic DTC which decrease I-131 uptake may decrease the efficacy of I-131 therapy. Therefore, strategies to improve I-131 uptake are mandatory. This study is an open label clinical study to evaluate the effectiveness of 13-cis retinoic acid (13-cis RA) for improving I-131 uptake in recurrent or metastatic of DTC with defective I-131 uptake. Eleven patients (Age 27–66 years, M : F=4 : 7) were given 13-cis RA (1.5 mg/kg daily for 5 weeks), followed by 200 mCi (7.4 GBq) I-131 treatment. The differences of serum thyroglobulin (Tg) level and I-131 uptake on the post-treatment whole body scan (RxWBS) were compared before and after 13-cis RA therapy. Six out of 11 patients showed significantly increased (above 50%) Tg levels just after RA therapy. However, Tg levels a year after I-131 therapy were increased, stable and decreased in 7, 2 and 1 patients, respectively. Iodine uptake on RxWBS showed marginal improvement in only 2 patients and their Tg levels after one year follow-up increased. Most frequent adverse events were dry skin and lips. 13-cis RA partially restores I-131 uptake in few patients with recurrent or metastatic DTC. The use of 13-cis RA in current protocol has only limited usefulness and is not routinely recommended as currently used protocol.

Key words: Thyroid cancer, 13-cis Retinoic acid, Radioiodine therapy, Redifferenciation, Thyrogolobulin

DIFFERENTIATED thyroid cancer (DTC) is slow growing and well treatable disease with favorable prognosis. However, about 10–15% of patients with DTC have recurrent disease, and about 5% have distant metastases at presentation [1, 2]. Until recently, treatment of recurrent and metastatic disease has consisted of thyroid stimulating hormone (TSH) suppressive therapy with levothyroxine (T4), surgery (when feasible), and radioiodine (I-131) treatment when radioiodine (RI) uptake is present in neoplastic foci. Previous study reported that about 30% of these recurrent or metastatic DTC showed dedifferentiation of malignant cells with morphological and functional changes [3]. Loss of differentiation with reduced thyroidal sodium/iodide symporter (NIS) expression eventually leads to decreased iodine uptake and decreases the efficacy of I-131 therapy [4].

Retinoic acids (RA) are biologically active metabolites of vitamin A that play important roles in the cell differentiation and proliferation. Differentiation effects of RA had been demonstrated in many types of tumor cells [5–9] and RA therapy achieved up to 90% remission in promyelocytic leukaemia [10, 11]. RA receptors are also expressed in human thyroid carcinomas in varying degrees [12]. Experimental studies have shown that RAs may increase the expression of NIS, type I 5'-deiodinase, intercellular adhesion mole-
cule-1 (ICAM-1) and thyroglobulin (Tg) which were known to be decreased or even lost in thyroid cancer cells [13–17]. The results of a few early clinical pilot trials demonstrated that RA may restore RI uptake and decreases tumor size [18–21]. However, the clinical outcomes of 13-cis RA in subsequent studies were disappointing, as only 0–20% of patients showed I-131 uptake after RA pre-treatment [22, 23].

In the present study, we aimed to evaluate the effectiveness of 13-cis RA therapy in approving efficacy of high dose I-131 therapy in Korean subject with radioiodine negative recurrent or metastatic DTC.

Subjects and Methods

Subjects

Eleven DTC patients with persistent disease after surgery and high does I-131 therapy were enrolled from November 2002 to November 2005 at Asan Medical Center, Seoul, Korea. Eligible criteria were as followed: WHO performance status <2, age >18 and <70, locally invasive cervical or mediastinal tumor or distant metastasis documented by computerized tomography (CT) or 18 Fluoro-dexoyglucose (FDG) positron emission tomography (PET), and primary failure of RI uptake or decrease/or loss of RI uptake. Exclusion criteria were as follows: anaplastic carcinoma or Hurthle cell or insular cell type, pregnancy, patients with elevated liver enzyme or triglyceride level and other contraindication of RA treatment. This study was approved by local ethics committee (IRB No. 2002-121). Detailed explanation was given to all the patients and informed consents were obtained from every patient.

13-cis RA treatment

Treatment with 13-cis RA (Roaccutan, Roche®) was administered with once daily dosage of 1.5 mg/kg for 5 weeks prior to high dose I-131 therapy. All patients were monitored clinically and biologically before commencing treatment and 2 weeks after RA administration. Side effects were evaluated according to National Cancer Institute (NCI) Common Toxicity Criteria version 3.0 by interview of symptoms, complete blood cell counts, glucose, cholesterol, triglycerides and liver enzymes. Levothyroxine (T4) supplementation was discontinued for the duration of RA treatment.

I-131 therapy and whole-body scan (WBS)

After 4 weeks of T4 withdrawal, 111 MBq of I-131 was administered and WBS was obtained 48–72 h later using a dual-head γ-camera (BiadXL24, Tronix, Ohio, USA) equipped with a high-energy collimator. Scan speed was 12 cm/min, with a total count of at least 100,000 cpn. After completion of 13-cis RA therapy, 7.4 GBq of I-131 was administrated to all subjects. Post-treatment WBS (RxWBS) was obtained 7 days after I-131 administration. All patients had serum TSH concentrations of 30 μIU/ml or more at the time of I-131 therapy. To evaluate the efficacy of 13-cis RA, post-treatment WBS was compared with previous post I-131 therapy scan. A semi-quantitative visual analysis was performed. The RI uptake was classified as no uptake, faint uptake and increased uptake. RI scans were reviewed by one experienced nuclear physician (JS.Ryu).

Measurements of serum Tg and serum anti-Tg antibody

Serum Tg measurements and anti-Tg antibody (Ab) assays were performed at intervals of 4–6 months after thyroidectomy, and at the time of administration of therapeutic doses of I-131. Serum Tg, anti-Tg Ab, and TSH assays were performed as previously described [24]. An elevated Tg level was defined as Tg >10.0 ng/ml while hypothyroid (if serum TSH level = 30 μIU/ml, stimulated Tg; sTg) or >2.0 ng/ml during TSH suppression (non-stimulated Tg; nsTg). The changes of Tg level were available in 10 patients except one patient with persistently high level of anti-Tg Ab.

Serum sTg levels were measured just-before 13-cis RA administration (sTg0), just after 13-cis RA (sTgRA) and 1 year later (sTg1). Serum nsTg levels were also measured at less than 3 months prior to the administration of 13-cis RA (nsTg0) and 1 year after I-131 therapy (nsTg1). If the changes in nsTg level and sTg level were discrepant in a patient, the change of sTg was used. The changes of sTg levels between before and after 13-cis RA were available in 6 patients and nsTg levels were available in 10 patients, respectively.
Statistics

Categorical variables are presented as numbers and percentages, and were compared using chi-square or Fisher’s exact test. Continuous variables are presented as median (range). The Mann-Whitney $U$-test was used for comparisons of the parametric variables between groups. $P$ values are two sided throughout, and $P$ less than 0.05 were considered significant. Data were analyzed using SPSS 12.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Clinical characteristics of patients

Eleven patients (7 women and 4 men) were included according to eligible criteria. Their median age was 51 years (range 27–66 years). Histopathological types were distributed as follows: 9 papillary carcinoma (PTC), 1 follicular carcinoma (FTC), and 1 follicular variant of papillary carcinoma (FV-PTC). Baseline radiologic assessments of I-131 resistant lesion were available in all subjects (eligible criterion). Details of staging and previous treatment of each patient were described in Table 1.

Change of RxWBS uptake after 13-cis RA followed by high dose I-131 therapy

Comparison of RxWBSs between pre- and post RA therapy was done in all subjects. I-131 uptake was significantly improved in only 2 patients (18%) and there was no significant increased uptake in 9 patients (Table 2). Patient 6, 51 year-old woman, underwent right lobectomy and completion thyroidectomy due to follicular thyroid carcinoma. She received 3 times of high dose I-131 therapy because of metastatic disease in left lung and left iliac bone. RxWBS after the third therapy showed no RI uptake in iliac bone (Fig. 1A). RxWBS after RA trial showed faint RI uptake in her left iliac bone (Fig. 1B). Patient 9, 55 year-old man with papillary thyroid carcinoma, underwent total thyroidectomy and modified radical neck dissection followed by remnant ablation. RxWBS showed diffuse RI uptake in both lung. He received repeated high dose I-131 therapy due to persistently elevated Tg levels during the follow up periods. RxWBS showed only minimal uptake in oropharyngeal area after the second high dose I-131 (Fig. 2A). RxWBS after the first RA trial showed increased uptake in mediastinal lymph nodes and left upper lung field (Fig. 2B). RxWBS after second RA therapy showed increased RI uptake in diffuse lung field as shown Fig. 2C.

Change of tumor size after 13-cis RA followed by high dose I-131 therapy

The change of tumor size after RA was assessable by CT scan or MRI according to the Response Evaluation Criteria in Solid Tumors (RECIST). In 5 patients (45%), disease progression was evident and in 6 patients (55%) tumor size was stable. There was no

Table 1. Baseline characteristics of patients included in 13-cis retinoic acid redifferentiation trial.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Tumor</th>
<th>Previous treatment</th>
<th>Retinoic acid treatment</th>
<th>Disease sites</th>
<th>Other image modality</th>
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<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>F</td>
<td>PTC</td>
<td>1</td>
<td>3</td>
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<td>5</td>
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<tr>
<td>2</td>
<td>30</td>
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<td>PTC</td>
<td>4</td>
<td>2</td>
<td>150</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>PTC</td>
<td>3</td>
<td>1</td>
<td>200</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>F</td>
<td>PTC</td>
<td>2</td>
<td>1</td>
<td>150</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>F</td>
<td>FTC</td>
<td>2</td>
<td>1</td>
<td>150</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>F</td>
<td>FTC</td>
<td>2</td>
<td>1</td>
<td>600</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>F</td>
<td>FTC</td>
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<td>3</td>
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</tr>
<tr>
<td>8</td>
<td>46</td>
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<td>9</td>
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<tr>
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<td>1</td>
</tr>
<tr>
<td>11</td>
<td>61</td>
<td>M</td>
<td>FTC</td>
<td>2</td>
<td>1</td>
<td>150</td>
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PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; FV-PTC, follicular variant papillary carcinoma; LN, lymph nodes
partial response in study subjects as shown in Table 2.

Change of Tg just after 13-cis RA

We compared percent increase (RA-Tg change) in Tg levels between sTg0 and sTg-RA. Significant increase was defined above 50%.

RA-Tg change was assessable in 10 patients and calculated as follows: RA-Tg increase = (sTg-RA – sTg0)/sTg0 × 100.

Significant increased was found in 8 patients. There was no significant relationship between RA-Tg change and increased I-131 uptake (p = 0.53).

Table 2. The results of post-treatment whole body scan before and after retinoic acid (RA) treatment and response in tumor size after RA therapy followed by high dose radioactive iodine treatment.

<table>
<thead>
<tr>
<th>No.</th>
<th>Post-treatment WBS uptake</th>
<th>Response in tumor size</th>
<th>Tg0</th>
<th>Tg1</th>
<th>Survival status</th>
<th>Survival duration (years)</th>
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<td>Post</td>
<td>Response</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>None</td>
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<td>126</td>
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<td>None</td>
<td>None</td>
<td>SD</td>
<td>156</td>
<td>119</td>
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<td>3</td>
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<td>None</td>
<td>SD</td>
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<td>3.6</td>
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<td>&lt;1</td>
<td>&lt;1</td>
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<td>None</td>
<td>None</td>
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<td>PD</td>
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<td>1.3</td>
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<td>Thyroid bed</td>
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<td>PD</td>
<td>37.4</td>
<td>151</td>
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</table>

WBS, whole body scan; RA, retinoic acid; PD, progressive disease; SD, stable disease; Response in tumor size, according to RECIST criteria; Tg0, serum thyroglobulin level measured just before 13-cis RA; Tg1, serum thyroglobulin level measured at 1 year after high dose I-131 therapy; Survival duration, calculated after 13-cis retinoic acid treatment.
Change of Tg one year after 13-cis RA followed by high dose I-131 therapy

We also compared percent change in Tg levels before and one year after 13-cis RA. ‘Tg change’ was calculated as follows: (Tg1 − Tg0)/Tg0 × 100. Tg levels a year after I-131 therapy were significantly (above 50%) decreased or stable only 1 and 2 patients, respectively (Table 2). But, 7 out of 10 patients showed significant (above 50%) increased Tg level despite of 13-cis induced I-131 therapy.

Adverse effects

There was no serious adverse event and all subjects completed 5 weeks 13-cis RA therapy. All patients experienced mild (Grade 1–2) adverse effects such as dry lips, mucosa and skin. Serum triglyceride levels were elevated after RA therapy in 3 patients (Grade 1) and returned to normal range after follow up. There were no significant changes in liver enzymes, electrolytes, calcium level, and blood cell counts in all subjects.

Discussion

This study evaluated the effectiveness of 13-cis RA in improving I-131 uptake in recurrent or metastatic DTC with defective I-131 uptake. sTg level just after 13-cis RA were increased in most of the study subjects. However, 13-cis RA partially restored I-131 uptake in few patients with recurrent or metastatic DTC and could not achieve any response in reduction of tumor size.

The naturally occurring retinoids including all-trans-RA (ATRA), 9-cis-RA and 13-cis-RA are interconverted in vivo, and have similar effects and toxicities. RAs display their effects by binding to specific receptors. There are two families: the retinoic acid receptors (RAR) and the retinoic acid X receptors (RXR), and each family again divides into various subtypes and isoforms (RAR α/β/γ and RXR α/β/γ, RAR α1/2/3/4, and so on). Normal human thyroid cells express RAR-α and RXR-γ and expression of RAR-α is reduced in thyroid carcinomas. RA receptors act as ligand-dependent transcription factor and modulate the expression of RA-regulated genes. In vitro studies have shown that RA leads to not only growth inhibition but also redifferentiating effects. ATRA partly redifferentiates follicular carcinoma cell lines, as shown by stimulation of type I 5'-deiodinase, alkaline phosphatase and increased ICAM-1 level [15, 16]. 13-cis RA also reduces clonogenic survival in follicular carcinoma cell lines and increases cellular I-131 uptake [13]. Increased iodine uptake in thyroid cancer cell lines may be related with the expression of NIS [14].

13-cis RA was first used in clinical study on redifferentiation therapy of thyroid cancer in the late 1990s.
Since then a few pilot studies reported encouraging results. Simon et al. showed RI uptake increased in 8 (50%) of 16 evaluable DTC patients with locally invasive or metastatic disease after 5 weeks therapy with 1–1.5 mg/kg [18]. However, tumor size decreased in only one of 15 patients who could be evaluated, and increased in 9 and unchanged in 5 patients. Grünwald et al. showed RI uptake was improved in 5 (42%) of 12 patients after 2 months of pre-RA administration [21]. Largest pooled study from multiple German center, including those from previous two studies have been published [20]. They enrolled 75 patients, but excluded one third of patients because of different protocols for the RI scan. RI uptake increased in 21 patients (42%), with mild increase in 8 patients. Tumor size was decreased in only 6 (12%) of 37 evaluable patients. They reported overall clinical outcome defined by combined tumor size, Tg response and RI uptake and reported that response in 10 (20%) patients, stable disease in 9 (18%) and disease progression in 31 (62%) patients.

However, the clinical outcomes of 13-cis RA in the subsequent clinical trials were somewhat disappointing. Grüning et al. reported that increased RI uptake was noted in 5 (20%) of 25 patients including minor improvement in 2 patients after 3 months RA administration (1 mg/kg) [22]. Phase II clinical study using 13-cis RA (1.5 mg/kg for 8 weeks) showed limited value with increased RI uptake in only one of 16 patients. But, this study evaluated RA effect only by comparing diagnostic WBS [25]. Courbon et al. recently demonstrated defective efficacy of RA therapy with 1.5 mg/kg over 8 weeks in prospective study [23]. Only one of the 11 patients showed increased uptake. Five patients died of their thyroid carcinoma, 5 had a progressive disease and one was considered stable after follow up of 2 years. This study was also stopped after inclusion of 11 patients due to lack of efficacy. In the present study, we could demonstrate only two (18%) of 11 patient had marginally increased RI uptake and no shrinkage of tumor after I-131 therapy accompanied by 13-cis RA pre-treatment. One of the patients (No. 9) with 13-cis RA therapy induced iodine uptake died of his thyroid cancer. The other showed stable disease after high dose I-131 therapy but his serum Tg level progressively increased during follow up. Actual tumor size increased during the follow up in every patients and 6 (55%) were classified as stable disease, 5 (45%) were classified as progressive disease.

Serum sTg levels just after RA administration increased in most of patients in the present study. Theoretically, increase in serum Tg level could be regarded as a marker of re-differentiation and most previous studies showed RA therapy increased serum Tg level. However, serum Tg level could reflect tumor burden and is generally used as a marker of tumor recurrence. In addition, increase in the serum sTg values just after RA therapy may be explained by longer period of TSH stimulation than the sample taken before RA administration. It is not easy to delineate whether increased serum Tg means redifferentiation effect of RA therapy or it reflects disease progression. In present study, elevated sTg-RA were not associated with increased I-131 uptake and most of patients showed elevated sTg1 or nsTg1 value one year after this trial. Therefore, change in Tg level just after RA therapy would not be a suitable maker of re-differentiation.

Recently reported re-differentiation therapy with different regimens did not show any significant improvement of RI uptake. Induction with ATRA before high dose I-131 therapy resulted in effective response only in 2 of 8 patients [26]. Study with RXR agonist, bexarotene, to improve the efficacy of I-131 therapy for metastasis also showed no restoration of RI uptake in 8 patients [27]. Further studies would utilize alternative approach with different doses or duration of treatment or a combination regimen to improve the effectiveness of RA.

In summary, 13-cis RA marginally restored I-131 uptake in 18% of patients with recurrent or metastatic DTC and could not achieve any response in reduction of tumor size. We conclude that the use of 13-cis RA in current protocol has only limited usefulness and is not routinely recommended.

Acknowledgments

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