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Chapter 7

Radioiodine Therapy after Pre-treatment with Bexarotene for Metastases of Differentiated Thyroid Carcinoma

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Submitted

Abstract

Objective: To evaluate the effects of pre-treatment with the RXR agonist Bexarotene on the efficacy of radioiodine therapy of metastases of differentiated thyroid carcinoma (DTC) with limited uptake of radioiodine (I-131).

Design: Open prospective intervention study.

Methods: Eight patients with metastases of DTC, with insufficient uptake of I-131 who showed increased uptake of radioiodine after previous treatment with 300 mg Bexarotene were treated with radioiodine (7400 MBq), preceded by 6 weeks of treatment with Bexarotene 300 mg/day. Outcome parameters were serum Tg levels and dimension of metastases at CT, measured before, and 6 months after, therapy.

Tissue of the primary tumor was stained with antibodies against RAR and RXR subtypes.

Results: Bexarotene pre-treatment induced radioiodine uptake in metastases in all 8 patients, although uptake was only discernable at SPECT and had incomplete matching with the metastases visualized by CT scanning. Six months after radioiodine therapy 6 patients had progressive disease (defined as a >10% increase in serum Tg and/or a >25% increase in tumor dimensions), whereas 2 patients had stable disease. No relation was observed between retinoid receptor staining pattern and the outcome of therapy.

Conclusions: Bexarotene partially restores I-131 uptake in metastases of DTC, but this did not result in susceptibility to radioiodine therapy.

Introduction

The efficacy of radioiodine therapy in metastatic thyroid carcinoma is limited by decreased uptake of radioiodine, which is likely related to decreased expression or function of the sodium iodide symporter (NIS) in DTC during the process of dedifferentiation (1,2,3). Therefore, strategies to improve iodide uptake by DTC are mandatory.

Retinoids are derivatives of vitamin A (*i.e.* retinol). Beneficial effects of retinoids have been reported *in vitro* in thyroid carcinoma (4,5,6,7) including increased NIS mRNA expression and iodide uptake in some thyroid cancer cell lines (4). Interestingly, the promoter of the NIS gene has a retinoic acid response element (8). A limited number of human studies all performed with 13-cis retinoic acid reported variable results (9,10,11,12)(13). The only retinoid used so far in human studies in DTC is 13-cis retinoic acid. As 13-cis retinoic acid has a lower affinity for RAR than other retinoids (14) and the retinoid receptor RXR may also be important in thyroid carcinoma (15,16), we performed a prospective controlled clinical trial to investigate the efficacy of the novel ligand Bexarotene (Targretin, Ligand Pharmaceuticals, San Diego) (17,18,19), in 12 patients with metastases of DTC and decreased or absent I-131 uptake (20). We found increased uptake in metastases in 8 of these patients. Here, we report the results of high dose I-131 therapy after preparation with Bexarotene in these 8 patients.

Patients and Methods

Patients

Patients in whom 6-weeks therapy with Bexarotene 300 mg/day increased radioiodine uptake in metastases of DTC (20) were offered therapy with 7400 MBq radioiodine.

Detailed inclusion criteria and clinical data of the patients in this study are given in our previous study (20) and are summarized in Table 2. In summary, patients were selected with metastases of DTC, who had previously undergone total thyroidectomy and I-131 ablative therapy. Uptake of I-131 or effectiveness of earlier I-131 therapies had to be insufficient as indicated by progressive tumor growth despite I-131.

Exclusion criteria were pregnancy, contraindications for the application of recombinant human thyrotropin (rhTSH), contraindications for the use of Bexarotene such as hematological malignancies, leukopenia or coagulopathy, a history of pancreatic disease and severe hypertriglyceridemia (fasting triglyceride

levels > 4.5 mmol/l). Of the original 12 patients that enrolled in the first study, 8 patients were eligible for treatment with high dose radioiodine.

Protocol

Radioiodine therapy (7400 MBq, Mallinckrodt BV, Petten, The Netherlands) was given after a new 6-weeks treatment with Bexarotene (300 mg/day). A new treatment course with Bexarotene was given because it was not known how long the effects of the first course of Bexarotene would last.

Prior to radioiodine therapy, patients received i.m. injections with 0.9 mg rhTSH (Thyrogen®, Genzyme, Naarden) on 2 consecutive days before the I-131 administration. rhTSH instead of withdrawal of L-thyroxin substitution was used because Bexarotene is reported to inhibit pituitary TSH production (21). Patients were prescribed a low iodide diet from 7 days prior to the administration of I-131 (22).

Evaluation of the study objectives

The main outcome parameter of the study was the effect of treatment on the progression of metastases of DTC 6 months following I-131 therapy with pretreatment of Bexarotene.

Study objectives were evaluated with CT scans and serum thyroglobulin (Tg) measurements as assessed before Bexarotene therapy and 6 months after radioiodine treatment.

A CT scan obtained before radioiodine therapy served as anatomical reference for the number, extent and localization of metastases. The response was determined as complete response (no disease demonstrable), incomplete response (decrease in Tg $\geq 10\%$, decrease in radiological dimensions of metastases $\geq 25\%$), stable disease (difference between serum Tg levels $< 10\%$ and progression in radiological tumour dimensions $< 25\%$) or progressive disease (difference between serum Tg levels $\geq 10\%$ or progression in radiological tumour dimensions $\geq 25\%$ or the appearance of new metastatic lesions).

Outcome of radioiodine therapy was related to retinoid acid receptor expression in a subset of patients.

¹³¹I whole-body scintigraphy was performed 3.5 and 7 days after the radioiodine therapy. The run speed of the dual-head gamma camera (Toshiba GCA 7200, equipped with a high-energy collimator) was 15 cm per minute (matrix size 256×256). WBS was followed by anterior and posterior planar images of the head and neck and chest region (matrix size 256×256, preset time 10 min). Finally, single photon emission computed tomography (SPECT) of the head and neck and chest was performed (128x128 matrix, 6° step angle and 1 min. per step). Two experienced observers

visually analyzed all images. A Na¹³¹I standard was used to quantify the uptake in the area of interest at WBS.

Immunohistochemistry

Immunohistochemistry was performed on tissue blocks obtained from the primary tumors. Tissues from 2 patients, who did not respond to Bexarotene in an earlier study (20), (Pat NI-1 and Pat NI-2), were also included in the staining procedure.

Ten percent formalin-fixed, paraffin-embedded blocks routinely prepared from surgical specimens of primary thyroid tumours were selected for this study. Four µm consecutive tissue sections were cut from each arrayed paraffin block and prepared on pathological slides. The sections were deparaffinised in xylene followed by 0.3% hydrogen peroxide methanol at room temperature for 20 minutes for blocking endogenous peroxidase. After rehydration, antigen retrieval treatment was done for CK-19, HBME-1, FN-1, CITED-1, NIS and PPAR-gamma but Gal-3 immunostaining by microwave treatment in 0.01 M citrate buffer at pH 6.0. After 2 hours cooling down, endogenous avidin activity blocking was performed for NIS immunostaining by incubation with egg-white for 5 minutes followed by biotin for 15 minutes. The sections were incubated with primary antibodies against RAR and RXR (Table 1) in PBS with 1% bovine serum albumin overnight in room temperature. The negative controls were stained with the primary antibody omitted. Next, sections were incubated for 30 minutes with either the biotinylated rabbit-anti-mouse conjugate (Dako, Glostrup, Denmark, 1:200) or goat-anti-rabbit (1:400), followed by incubation for 30 minutes with the streptavidin-biotin-peroxidase conjugate (Dako, Glostrup, Denmark 1:100). This step was by a 10-minute incubation with 3,3'-diaminobenzidinetetrachloride substrate in a buffered 0.05 M Tris/HCl (pH 7.6) solution containing 0.002% hydrogen peroxide. The sections were counterstained with haematoxylin. A semi-quantitative assessment of immunohistochemical scoring was performed according to both the intensity of staining and the percentage of positive cells. Ranging from 1 – 6.

Laboratory parameters

The following laboratory parameters were assessed: plasma levels of TSH, free-T4, free-T3 and Tg were measured before both injections of rhTSH, before the administration of I-131 and during the WBS. Tg antibodies were measured before both rhTSH injections. Safety parameters were a hematological profile as well as serum levels of sodium, potassium and creatinine, lipids, renal and liver function. They were assessed every week. Urinary iodine excretion was measured to exclude iodine contamination.

Serum TSH was determined with on a Modular Analytics E-170 system (Roche Diagnostic Systems, Basle, Switzerland, intra-assay variability: 0.88-10.66%, inter-

Table 1 Antibodies against Retinoic Acid receptors

Primary antibody	Dilution	Resource	Type	Secondary Antibody	Antigen Retrieval	epitope	Ab clone
RAR α	1:3000	Gift ¹	Monoclonal	2	Na-Citrate heating	Ab9 α (F)	9 α -9A6
RAR β	1:200	Gift ¹	Monoclonal	2	Na-Citrate heating	Ab8 β (F)2	8 β -10B2
RAR γ	1:350	Gift ¹	Monoclonal	2	Na-Citrate heating	Ab4 γ (F)	4 γ -7A11
RXR α	1:1000	Gift ¹	Monoclonal	2	Na-Citrate heating	full length	4RX3A2
RXR β	1:650	Santa Cruz ²	Polyclonal	1	Na-Citrate heating	6p21.3	sc-831
RXR γ	1:500	Santa Cruz ²	Polyclonal	1	Na-Citrate heating	1q22-q23	sc-555

Secondary Antibodies

(1) Swine-anti-Rabbit, DacoCytomation, Glostrup, Denmark

(2) Rabbit-anti-Mouse, DacoCytomation, Glostrup, Denmark

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assay variability: 0.91-12.05%). Serum Tg was determined by IRMA (Tg kit, Brahms, Berlin Germany) on a Wallac (Wallac, Turku, Finland, intra-assay variability: 0.14-13.9%, inter-assay variability: 12.3-17.4 %). Serum Tg antibodies were determined with IRMA (Sorin Biomedica, Amsterdam, The Netherlands) on a Wallac (Wallac, Turku, Finland) (intra-assay variability: 3.6-4.1%, inter-assay variability: 11.6%).

Statistical Methods

Data are reported as mean \pm SD. The effects of bexarotene on outcome variables were analyzed using the two-tailed Student's *t*-test for paired data. Data without normal distribution were analyzed using the Wilcoxon test. Proportional data were analyzed using Chi-square. Differences were considered statistically significant at $P < 0.05$. The calculations were performed using SPSS 12.0 for windows (SPSS, Chicago, IL).

Results

Patients

Eight patients were included in this treatment protocol (4 males, 4 females). Their clinical characteristics are presented in Table 2. The mean age at diagnosis of DTC was 52 ± 10 years. In 2 of the patients, metastases were already present at the time of diagnosis of thyroid carcinoma, most of them pulmonary. Most patients had received extensive therapies; I-131 therapy had been administered in a median cumulative activity of 15 GBq (Table 1). Four of the 8 patients had received additional therapies during the course of their disease (surgery and/or external radiotherapy).

The patients tolerated the Bexarotene treatment well, despite temporary increases in serum triglyceride levels in 5 subjects. In 1 patient the dose of Bexarotene had to be reduced because of an episode of leucopenia.

Evaluation of the study objectives

The main outcome parameters of the study were the treatment effects 6 months following I-131 therapy after preparation with Bexarotene on the progression of metastases of DTC.

No incomplete or complete responses were observed. Six patients had an increase in serum Tg levels of $>10\%$ (Table 2). One patient had a relatively low serum Tg level (2.4 ug/L) but this level rose to 64.8 ug/L after TSH stimulation. Three patients had an increase in tumor dimensions at CT of $> 25\%$. In 2 patients, new lesions

Table 2. Patient Data

Patient Number	Gender	Age (Diagnosis)	Histology	pTNM (Diagnosis)	Relapse or Metastases	Immunohistochemistry					
						RAR α	RAR β	RAR γ	RXR α	RXR β	RXR γ
1	M	71	PTC	X-X-1	Lungs	+	-	-	+	-	-
2	F	37	FTC	4-0-0	Local, lungs	-	+	+	-	+	-
3	F	50	FTC	1-0-1	Lungs	NA	NA	NA	NA	NA	NA
4	F	61	Hürthle cell FTC	4-0-1	Lungs	+	+/-	-	+	+	+, very few
5	M	52	Hürthle cell FTC	3-0-0	Lungs	+	+	-	+	+	+, few
6	M	50	PTC	4-0-0	Lungs	+	-	+?	+	+	+
7	M	47	PTC	3-0-1	Lungs	+	+	-	+	+	-
8	F	45	PTC	2-0-0	Lungs	NA	NA	NA	NA	NA	NA

Table 3. Study Outcome 6 Months After 6400 MBq I-131

Patient	Tg (ug/L) Baseline	Tg (ug/L) After rhTSH	WBS Post Therapy	Matching	Tg (ug/L) 6 Months After Radiotherapy	CT	Outcome
1	280	530	Superior mediastinal	Incomplete	456	Progression new lesions	Progression
2	150	203	Parahilar	Incomplete	813	Progression	Progression
3	5	45.2	Pulmonary	Incomplete	5,3	Progression < 25%	Stable disease
4	312	890	Pulmonary	Incomplete	1602	Progression	Progression
5	88.7	321	Mediastinal, <i>pulmonary</i> #	Incomplete	300.5	New lesion	Progression
6	14	42,7	Neck, mediastinal discrete	Incomplete	17	Progression < 25%	Progression
7	9.7	29.4	Pulmonary	Incomplete	10.8	Progression < 25%	Stable disease
8	2.4	64.8	Pulmonary	Incomplete	3.2	Stable	Progression

Not visible at diagnostic scintigraphy post-Bexarotene

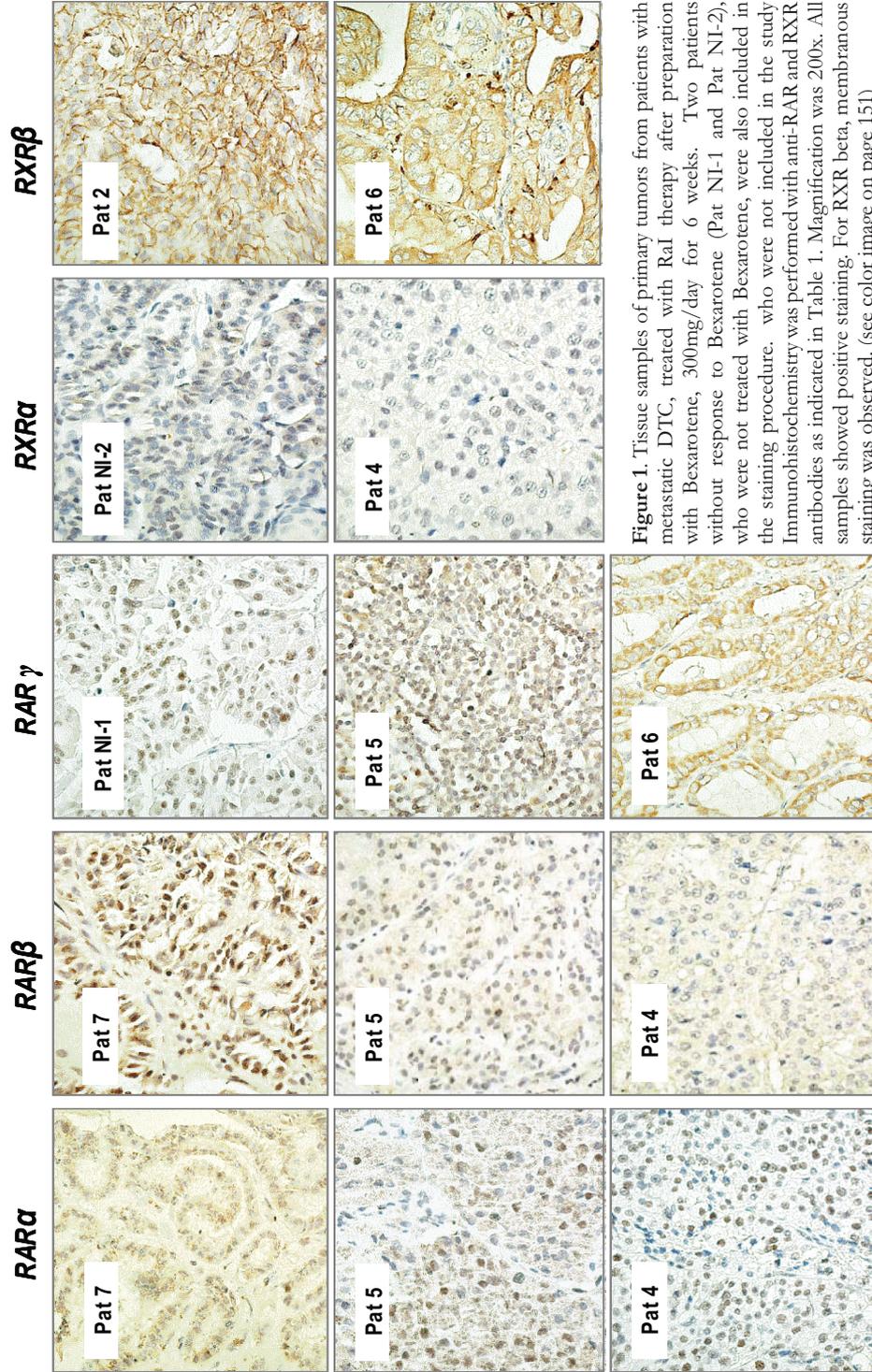


Figure 1. Tissue samples of primary tumors from patients with metastatic DTC, treated with RaI therapy after preparation with Bexarotene, 300mg/day for 6 weeks. Two patients without response to Bexarotene (Pat NI-1 and Pat NI-2), who were not treated with Bexarotene, were also included in the staining procedure. who were not included in the study Immunohistochemistry was performed with anti-RAR and RXR antibodies as indicated in Table 1. Magnification was 200x. All samples showed positive staining. For RXR beta, membranous staining was observed. (see color image on page 151)

appeared. In 3 patients, there was progression at CT but less than 25%.

All patients had received a previous course of Bexarotene to prove increased radio uptake during diagnostic scintigraphy. No differences were observed between diagnostic scintigraphy after this first Bexarotene treatment and the post-therapeutic whole body scans, and, except in one patient (nr. 5) in whom discrete pulmonary lesions became visible at SPECT after post-therapeutic WBS (Table 3). In all patients, there was an incomplete matching of lesions observed at post-therapeutic WBS with the CT scans.

Although it was attempted to quantify I-131 by calculating uptake in a region of interest using a reference I-131 source, uptake in regions of interest as visualized by SPECT were too low to allow quantification.

Immunohistochemistry

Data for immunohistochemistry are given in Table 2. Apparently there was no uniform pattern in staining for RAR and RXR subtypes (Figure 1) (see color image on page 151), and no relation was apparent with staining pattern and outcome of therapy.

Discussion

The present study investigated the effectiveness of radioiodine therapy after 6-weeks pre-treatment with the RXR agonist Bexarotene on metastases of patients with DTC with absent or insufficient uptake of I-131 during previous I-131 therapies. Although Bexarotene treatment had shown to induce I-131 uptake in these 8 patients (20), no clinically relevant response to radioiodine was observed. As the initially observed uptake of radioiodine was only discernable at SPECT and not present in all metastases as visualized by CT scanning, the clinical efficacy of Bexarotene therapy is limited.

The background of our study was that the compound used in clinical studies in DTC has been 13-cis retinoic acid (9,10,11,12,13) which had inconsistent effects. Following the observation that the RXR may be important in DTC (15,16), we decided to treat patients with an RXR agonist which also has affinity for the RAR (17,18,19,21).

The lack of success may be explained by several factors. The dose of radioiodine that is realized in a metastatic lesion is determined not only by the trapping of iodide by NIS, but also by the effective half life of the radioisotope, which may be decreased in DTC by decreased organification of iodide due to decreased thyroid peroxidase

expression as well as the loss of follicular architecture (23,3). Alternatively, the regulation of NIS may be defective at multiple transcriptional and post-transcriptional levels (24), which can apparently only be partially restored by retinoids.

An important observation was that there was only incomplete matching between the metastases identified by radiological imaging and post-therapeutic WBS. Although this is an interesting observation, illustrating the heterogeneity of DTC metastases with respect to iodide metabolism, this incomplete matching suggests that the beneficial effects of Bexarotene may be present, at best, in a subset of metastases. However, even if these metastases become susceptible to radioiodine, this does not prevent the progression of other lesions.

The question is whether patients with other characteristics might have a better response to Bexarotene. To investigate this issue, we performed RAR and RXR staining in a subset of patients. However, we did not find a relation between staining pattern and outcome of therapy. A limitation in this respect is that we only had materials of the primary tumor and it may be that the retinoid receptor expression pattern in the metastases was different.

We conclude that Bexarotene treatment partially restores I-131 uptake in some, but not all, metastases of DTC, at least in the patients selected for this study. Due to inhomogeneous effects of Bexarotene on I-131 uptake by the different metastases within each patient and the low intensity of I-131 uptake, the clinical efficacy of Bexarotene pretreatment is limited.

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