CLINICAL STUDY

Bexarotene increases uptake of radioiodide in metastases of differentiated thyroid carcinoma

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Abstract

Objective: Treatment options for metastases of differentiated thyroid carcinoma (DTC) are limited due to decreased uptake of radioiodide (I-131). Therefore, strategies to improve I-131 uptake are mandatory. It has been suggested that retinoids have beneficial effects on iodide uptake *in vitro* and in humans. However, to date, only studies with 13-*cis*-retinoic acid have been performed in humans. We therefore decided to study the effects of 6 weeks of treatment with the retinoid X receptor activator bexarotene on I-131 uptake in patients with metastatic DTC.

Design: Open prospective intervention study.

Methods: Twelve patients with metastases of DTC, with insufficient uptake of I-131, received 6 weeks of treatment with 300 mg bexarotene/day. Prior to, and after this intervention, I-131 uptake was measured by whole-body scintigraphy and single photon emission tomography (SPECT) 3 days after 185 MBq I-131. Diagnostic imaging was preceded by two consecutive injections of recombinant human TSH.

Results: Bexarotene treatment induced I-131 uptake in metastases of 8 out of 11 patients (one patient died for reasons not related to the study). However, uptake was only discernable at SPECT and had incomplete matching with metastases as visualized by CT scanning.

Conclusions: Bexarotene partially restores I-131 uptake in metastases of DTC. The clinical relevance of this observation may be limited due to the differential responses of the different metastases within each patient and the low intensity of I-131 uptake.

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Introduction

Differentiated thyroid carcinoma (DTC) in general has a favorable prognosis due to the effectivity of combined treatment with surgery and radioactive iodide (I-131) and the biological behavior of the tumor (1, 2). However, about 50% of patients with distant metastases of DTC die within 10 years of diagnosis (3). Although the role of I-131 in recurrent or metastatic thyroid cancer is beyond dispute (4–6), the efficacy of this therapy is hampered by the decreased expression and/or function of the sodium iodide symporter (NIS) in DTC during the process of dedifferentiation (7–9). 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 promyelocytic leukemia and several types of carcinoma (10–12). *In vitro* studies have reported that retinoids

have beneficial effects in thyroid carcinoma (13–16) including increased NIS mRNA expression and iodide uptake in some thyroid cancer cell lines (13). Interestingly, the promoter of the NIS gene has a retinoic acid response element (17). A limited number of human studies have been performed on the effects of retinoids on I-131 uptake. In four publications, three from the same group, 13-*cis*-retinoic acid therapy increased I-131 uptake in 26–40% of patients (18–21), but failed to do so in another study (22). The only retinoid used so far in human studies in DTC is 13-*cis*-retinoic acid. This compound is a ligand for the retinoic acid receptor (RAR). However, 13-*cis*-retinoic acid has a lower affinity for RAR than other retinoids such as retinoic acid and all-*trans*-retinoic acid (23). In addition, recent studies indicated a differential expression of both RAR and the retinoid X receptor (RXR) in thyroid carcinoma cell lines and tissues (24, 25) which corresponded to the responsiveness to

ligands for these receptors. The importance of RXR expression with respect to responsiveness to retinoid treatment was demonstrated in the latter study (25). We therefore decided to perform a prospective controlled clinical trial to investigate the efficacy of the novel ligand bexarotene (Targretin; Ligand Pharmaceuticals, San Diego, CA, USA) in 12 patients with metastases of DTC and decreased or absent I-131 uptake. Bexarotene is an RXR agonist, which also induces RAR by transcriptional activation. The anti-neoplastic potential has been demonstrated in cutaneous T-cell lymphoma, but also in other malignant tumors (26–28).

Patients and methods

Design

The study was a 6 week open study with 12 patients. Patients underwent diagnostic I-131 whole-body scintigraphy (WBS) before and after 6 weeks of treatment with bexarotene 300 mg/day. An open study design was chosen, because the study parameters can be assessed by objective criteria. Each patient served as his/her own control. An interval of 6 weeks between the two observations was chosen to allow normalization of serum thyrotropin (TSH) concentrations after the first application of recombinant human TSH (rhTSH) and to enable complete disappearance of the first I-131 dose from the tumor. The objective of this study was to investigate if addition of bexarotene has beneficial effects on radioiodine uptake in metastatic lesions of patients with DTC.

Patients

The Leiden University Medical Center is a large referral center for DTC in The Netherlands. With the exception of unifocal T-1,N-0,M-0 tumors, initial therapy consists of near-total thyroidectomy followed by routine I-131 ablative therapy with 3700 MBq I-131. Follow-up is performed according a standard protocol, involving serum thyroglobulin (Tg) measurements, both during thyroxine (T4) suppressive therapy and after T4 withdrawal, as well as I-131 scintigraphy after T4 withdrawal. In the case of recurrent disease or metastases, surgery will be attempted if the lesion is solitary and accessible, followed by additional radioiodide therapy (7400 MBq).

For the present study, 12 consecutive patients were selected with metastases of DTC as proven by measurable serum Tg levels and the presence of metastases or recurrent disease at post-therapeutic WBS, X-ray, CT or MRI. A CT scan performed <3 months prior to the study served as anatomical reference for the number, extent and localization of metastases. Patients who were selected had to have 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 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).

The institutional review board approved the study, and all patients gave written informed consent.

Protocol

A CT scan performed <3 months prior to the study served as anatomical reference for the number, extent and localization of metastases. After inclusion, the patients underwent a first diagnostic scintigraphy 3 days after i.v. administration of 185 MBq I-131. Patients were prescribed a low-iodide diet from 7 days prior to the administration of I-131 (29). The patients received i.m. injections of 0.9 mg rhTSH (Thyrogen; Genzyme, Naarden, The Netherlands) on 2 consecutive days before the I-131 administration. rhTSH instead of T4 withdrawal was used to avoid the methodological and clinical disadvantages of persistent high TSH levels during a long withdrawal period.

The day after the first WBS, patients started treatment with bexarotene 300 mg/day at the evening meal to prevent interference with T4 absorption.

Six weeks after initiation of bexarotene therapy, the I-131 imaging study was repeated. bexarotene was continued until the WBS was performed. Patients visited the hospital every week for a physical examination and assessment of laboratory safety parameters. When the intervention was successful (see below), patients were offered high dose I-131 therapy, again preceded by 6 weeks of bexarotene therapy.

Evaluation of the study objectives

The main outcome parameter of the study is the effect of bexarotene therapy on I-131 uptake in metastases at WBS. Uptake was investigated as follows: a quantitative assessment of I-131 uptake was performed by calculating uptake in a region of interest using a reference I-131 source (see below). In addition, uptake was compared between the first and the second WBS in comparable regions and expressed as 'increased', 'stable', 'decreased' or 'mixed'. 'Mixed' was used when lesions with a mix of increased, stable or decreased uptake were present. It was studied also if there was a complete or incomplete matching of areas with I-131 uptake at WBS and metastatic locations as visualized by CT scanning.

A 'complete response' was defined as increased I-131 uptake in all lesions visible on CT. A 'partial response' was defined as increased I-131 uptake as compared with the first WBS, but not in all lesions visible at CT.

'No response' was defined as absent or similar I-131 uptake in both WBS. The study was defined as successful when at least 50% of the patients had at least a partial response.

WBS with 185 MBq I-131

I-131 WBS was performed 3 days after the oral administration of 185 MBq of ^{131}I (Mallinckrodt BV, Petten, The Netherlands). The run speed of the dual-head gamma camera (Toshiba GCA 7200, equipped with a high-energy collimator) was 15 cm/min (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 (128×128 matrix, 6° step angle and 1 min/step). Two experienced observers visually analyzed all images. A Na^{131}I standard was used to quantify the uptake in the area of interest at WBS.

Laboratory parameters

The following laboratory parameters were assessed: TSH, free T4, free triiodothyronine (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 a Modular Analytics E-170 system (Roche Diagnostic Systems, Basle, Switzerland), intra-assay variability: 0.88–10.66%, inter-assay variability: 0.91–12.05%. Serum Tg was determined with IRMA (Tg kit; Brahms, Berlin,

Germany) on a Wallac gamma-counter (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 gamma-counter, intra-assay variability: 3.6–4.1%, inter-assay variability: 11.6%.

Statistical methods

Data are reported as means $\pm$ s.d. 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, USA).

Results

Patients

Twelve patients were included in the protocol (five males, seven females). Their clinical characteristics are presented in Table 1.

The mean age at diagnosis of DTC was 49 ± 11 years. Most patients had papillary thyroid carcinoma. In three 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 16 GBq (Table 1). Seven of the 12 patients had received additional therapies during the course of their disease (surgery and/or external radiotherapy).

One patient (no. 3) died during the study. She was admitted to the hospital and underwent acute surgery for intestinal volvulus. This event was considered to have no relationship to the study. The other patients

Table 1 Patient data.

Patient number	Gender	Age (diagnosis)	Histology	pTNM (diagnosis)	Cumulative activity I-131 (MBq)	Additional therapy	Disease-free interval (years)	Relapse or metastases
1	M	71	PTC	X-X-1	5640	RT	0	Lungs
2	F	37	FTC	4-0-0	22 560	RT, surgery	6	Local, lungs
3	F	36	PTC	1-0-0	57 600	Neck surgery	24	Lungs
4	F	50	FTC	1-0-1	15 416		17	Lungs
5	F	61	Hürthle cell FTC	4-0-1	9738	RT, thoracic surgery	0	Lungs
6	M	52	Hürthle cell FTC	3-0-0	13 893	RT, thoracic and neck surgery	4	Lungs
7	M	50	PTC	4-0-0	16 500		0	Lungs
8	F	32	FTC	3-0-0	41 000	RT, neck surgery	0	Lungs
9	F	51	FTC	4-0-1	27 372	RT	0	Lungs
10	M	47	PTC	3-0-1	13 160	Neck surgery	7	Lungs
11	F	45	PTC	2-0-0	27 000		10	Lungs
12	M	59	Hürthle cell FTC	3-3-0	14 100	Neck surgery	0	Lungs

PTC, papillary thyroid carcinoma; RT, radiotherapy; FTC follicular thyroid carcinoma.

tolerated the bexarotene treatment well. However, in two patients (nos 6 and 9), the dose had to be reduced because of hypertriglyceridemia that stabilized after dose reduction. One patient (no. 2), experienced an episode of leukopenia, which also led to a dose reduction of bexarotene.

Biochemical parameters

No differences in TSH levels without and after rhTSH stimulation were observed before and after 6 weeks of bexarotene treatment (Table 2). There was a remarkable decrease in serum free T4 and serum free T3 levels after 6 weeks of bexarotene treatment. Serum Tg levels before and after rhTSH were not different before and after bexarotene therapy. No iodine contamination was observed according to urinary iodine measurements.

Evaluation of the study objectives

The main outcome parameter of the study is the effect of bexarotene therapy on I-131 uptake in metastases at WBS. No patients with a complete response were observed (Table 3). A partial response was observed in eight patients. In seven of these patients, increased uptake was only visible at SPECT, indicating that the accumulation of iodide was low. Scans of two of these patients (nos 5 and 6) are depicted in Fig. 1. The number of lesions with increased or visible I-131 uptake was lower than visible at the reference CT scan. In one patient, pulmonary metastases were visible at the baseline WBS. Because the matching of these metastases was incomplete, it was decided to include her in the study. After 6 weeks of bexarotene, WBS revealed uptake in additional lesions that were not visible before (Fig. 1, patient no. 8).

Although we 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.

Discussion

The present study investigated the effectiveness of 6 weeks of bexarotene treatment in re-inducing I-131 uptake in metastases of patients with DTC with absent or insufficient uptake of I-131 during earlier I-131 therapies. Bexarotene treatment induced I-131 uptake in the majority of the patients (8/11), but the uptake was only discernable at SPECT and not present in all metastases, visualized by CT scanning. Therefore, the clinical relevance of these findings remains to be determined.

All clinical studies performed so far with retinoids in DTC used 13-*cis*-retinoic acid (18–22). The study with the best design (22), however, failed to demonstrate any positive effect. Because 13-*cis*-retinoic acid has a limited specificity and affinity for the RAR (23) and the importance of RAR subtypes and RXR have been demonstrated in recent studies (24, 25), we hypothesized that a ligand with RXR affinity and also affinity for RAR may have beneficial effects (26–28, 30).

Several factors may be involved in the partial success of the intervention. I-131 accumulation is not only determined by the trapping of iodide by NIS, but also by the effective half-life. The effective half-life of I-131 is diminished in DTC by several factors including decreased organification of iodide due to decreased thyroid peroxidase expression as well as the loss of follicular architecture (9, 31). Therefore, enhancing NIS expression may not be adequate to reach sufficient radiation exposure to I-131, even if we used a low iodide diet (29) to increase the specific activity of the I-131 administered. Alternatively, the regulation of NIS may be defective at multiple transcriptional and post-transcriptional levels (32), which can only be partially restored by retinoids.

Table 2 Biochemical data.

	Before intervention	After intervention	P
Before rhTSH			
Free thyroxine (pmol/l)	25.7±6.5	13.2±3.4	<0.001
Free T3 (pmol/l)	3.6±1.3	2.1±1.0	0.016
Thyrotropin (mU/l)	0.025 (<0.005–2.18)	0.024 (<0.005–1.06)	0.652
Thyroglobulin (µg/l)	108 (2.4–880)	158 (3.7–1145)	0.892
After rhTSH			
Free thyroxine 24 h (pmol/l)	25.7±5.6	13.6±3.3	
Thyrotropin 24 h (mU/l)	190.5 (89.2–324)	165.6 (100–312)	0.561
Thyrotropin 72 h (mU/l)	17.7 (10.2–44.3)	19.6 (12.0–56.1)	0.538
Thyroglobulin 24 h (µg/l)	112 (14.7–1390)	163 (20.9–1905)	0.704
Thyroglobulin 72 h (µg/l)	123 (25.7–2650)	165 (45.2–1558)	0.747
Cholesterol (mmol/l)	5.4±1.0	7.8±1.2	<0.001
Triglycerides (mmol/l)	1.6±0.7	3.7±1.5	<0.001

Table 3 Diagnostic whole body scintigraphy (WBS) 3 days after 185 MBq I-131.

Patient number	Before intervention			After intervention			Outcome
	WBS	SPECT	Matching	WBS	SPECT	Matching	
1	No uptake	No uptake	—	No uptake	Superior mediastinal	Incomplete	Partial response
2	No uptake	No uptake	—	No uptake	Parahilar	Incomplete	Partial response
3	No uptake	Mediastinal discrete	Incomplete	#	—	—	—
4	No uptake	Pulmonary discrete	Incomplete	No uptake	Pulmonary, increased intensity	Incomplete	Partial response
5	No uptake	Pulmonary discrete	Incomplete	No uptake	Pulmonary, increased intensity	Incomplete	Partial response
6	No uptake	No uptake	—	No uptake	Mediastinal	Incomplete	Partial response
7	No uptake	Neck, mediastinal discrete	Incomplete	No uptake	Neck, mediastinal discrete (unaltered)	Incomplete	No response
8	Pulmonary	Pulmonary	Incomplete	Pulmonary	Pulmonary, new locations	Incomplete	Partial response
9	No uptake	No uptake	—	No uptake	No uptake	—	No response
10	No uptake	No uptake	—	No uptake	Pulmonary	Incomplete	Partial response
11	No uptake	No uptake	—	No uptake	Pulmonary	Incomplete	Partial response
12	No uptake	No uptake	—	No uptake	No uptake	—	No response

Patient died.

Figure 1 I-131 uptake before and after 6 weeks of treatment with 300 mg/day bexarotene in three patients with pulmonary metastases of DTC. In all patients, a subtle increase in I-131 uptake was observed after bexarotene therapy on SPECT imaging, 3 days after 185 MBq I-131. The protocol for image processing is described in the Methods. In patient no. 8, new lesions (boxes) became apparent after bexarotene therapy.

An interesting observation was that in one patient (no. 8), a new lesion became apparent after bexarotene, which did not accumulate iodide earlier. This is an interesting illustration of the heterogeneity in DTC metastases with respect to iodide metabolism.

Free serum T4 and T3 levels decreased markedly in all patients without an increase in TSH levels. Although the effects of bexarotene on TSH have been well established (33), the fact that bexarotene decreases thyroid hormone levels in patients in whom thyroid hormone levels are TSH-independent suggests an effect on thyroid hormone metabolism. We do not believe that the differences in thyroid hormone levels after bexarotene have affected the study results, as TSH induction after rhTSH was comparable before and after bexarotene.

We conclude that bexarotene treatment may partially restore I-131 uptake in some, but not all, metastases of DTC. The clinical importance of this observation remains to be demonstrated but may be limited by the incomplete matching and the low intensity of I-131.

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