Redifferentiation Therapy-Induced Radioiodine Uptake in Thyroid Cancer

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Due to a dedifferentiation of tumor cells, some thyroid carcinomas lose their capability for radioiodine (RI) concentration. This phenomenon is associated with a worse prognosis and prevents effective treatment. Retinoic acid (RA) is known to induce redifferentiation in various kinds of tumors and has been used recently in thyroid cancer. **Methods:** Twelve patients (9 women, 3 men) with 6 papillary, 4 follicular and 2 mixed-cell type tumors (including 4 Hürthle cell carcinomas) were treated orally with RA (dose: 1.18 ± 0.37 mg/kg body weight) for at least 2 mo before RI therapy. None of the patients could be treated with any other modality (RI, surgery, external radiation) when RA administration was started. Initially, clinically important tumor sites did not take up significant amounts of RI. Changes of RI uptake and thyroglobulin (Tg) serum values were determined. Glucose metabolism was followed with fluorodeoxyglucose (FDG) PET imaging in 10 patients before and in 5 patients after RA treatment. **Results:** In 2 patients, a significant RI uptake was induced by RA, and in another 3 patients a faint RI uptake was achieved (responder group). In 7 patients, no change of RI uptake was observed (nonresponder group). Median Tg was increased from 105–840 μg/liter during RA therapy in the responder group, which was significantly higher than the nonresponder group (173–134 μg/liter). FDG PET was positive in all 10 patients before RA therapy. PET showed variable patterns of changes (increase/decrease/disappearance) in glucose consumption related to RA response. **Conclusion:** RA can induce RI uptake in some patients with RI negative thyroid carcinoma tumor sites. Response to RA is associated with a significantly higher increase of Tg, suggesting that a restoration of Tg synthesis can be addressed as a redifferentiation parameter in these patients.

Key Words: retinoic acid; redifferentiation; thyroglobulin; thyroid cancer; radioiodine; fluorodeoxyglucose PET

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Prognosis for differentiated thyroid cancer is related to the capability to accumulate radioiodine (RI), since this property is associated with a higher grade of differentiation and renders possible a treatment with RI (*1–4*). Besides age, the concentration of RI is one of the most significant factors that account for survival rates in patients with metastases from thyroid carcinoma (*2*). Some tumors are initially RI negative, and some tumor cells lose their RI uptake capability during the clinical course, due to a spontaneous redifferentiation or to other circumstances, e.g., effects of treatment with RI and/or external-beam radiation (*5*). Spontaneous reappearance of significant RI uptake is extremely rare and was described by Oyen et al. in 1995 (*6*). Retinoic acid (RA), a substance used earlier for redifferentiation in various other tumor types (*7,8*), has recently been applied in thyroid carcinoma (*9,10*). In the present article, we studied RA in 12 patients with thyroid cancer, in whom further RI treatment was not thought to be efficient because of insufficient uptake values in clinically important tumor tissue. Twelve consecutive patients (in varying stages of the disease)

were treated without any further selection. Therefore, there are no comparable data on history, preparation and thyroid-stimulating hormone (TSH) values for these patients.

MATERIALS AND METHODS

Data are given in Table 1. In 12 patients (9 women, 3 men; age range 52–84 yr; mean age 66 ± 10 yr) with differentiated thyroid carcinoma (6 papillary tumors, 4 follicular tumors, 2 mixed-cell type tumors; including 4 Hürthle cell carcinomas), treatment with RA was started during the clinical course when tumor tissue (local recurrence and/or metastases) could not be treated with RI, external-beam radiation or surgery. All patients had undergone several surgical procedures and RI treatments previously. In 10 of these 12 patients, initially no RI uptake could be observed. In 2 patients, RI was not concentrated in clinically significant tumor sites in amounts that could be used therapeutically. Primary tumor stage (pT) was pT1 in 1 patient, pT3 in 3 patients, pT4 in 6 patients and unknown in 2 patients. Histological grading could be obtained in 3 patients. Classification of tumor extent was done according to the International Union Against Cancer/Union Internationale Contre le Cancer (*11*) (pT1: 1 cm or less in greatest dimension; pT2: 1–4 cm; pT3: more than 4 cm; pT4: tumors of any size extending beyond the thyroid capsule). Grading was performed considering nuclear atypia, tumor necrosis and vascular invasion (*12*).

Treatment with thyroidectomy and RI was done as described previously (*13,14*). The first RI therapy was performed 4–5 wk after thyroidectomy with no replacement therapy during this time. TSH was > 30 mU/liter during the RI therapy. The first therapeutic dose was 1.85 GBq (50 mCi) or 3.7 GBq (100 mCi), depending on the RI uptake in the thyroid bed. Since iodine supplementation is low in Germany, no low-iodine diet was necessary before treatment. In our department, mean iodine excretion is about 80 ± 40 μg/g creatinine. Subsequent therapies with doses between 3.7 and 11.1 GBq (100 and 300 mCi) were performed in 3-mo intervals. Whole-body scintigraphy with therapeutically-administered RI was performed 3–4 days after each RI therapy, followed by a delayed image another 3–4 days later. Iodine excess was excluded by measurement of iodine excretion in the urine of all patients using the ceric ion-arsenious acid reaction (*15*). With only three exceptions, all RI scans were performed with therapy doses of 3.7–11.1 GBq (100–300 mCi).

Treatment with 13-cis-retinoic acid (RA; Roaccutan, Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany), dosage: 1–1.5 mg/kg body weight, was started at least 2 mo before RI therapy. In some patients the dose was reduced because of side effects (dry skin, rise of liver enzymes or triglycerides). Exact dose values are given in Table 1. The individual long-term administered dosage was 0.65–1.74 mg/kg body weight (mean: 1.18 ± 0.37).

In 10 patients, fluorodeoxyglucose (FDG) PET imaging was done before RA treatment. In 5 of these 10 patients, a second PET study was performed after the RA therapy. FDG PET imaging was done in a fasting state (>16 hr) with a Siemens/CTI ECAT Exact 921/47 PET scanner (Erlangen, Germany). FDG (185–370 MBq; 5–10 mCi) was administered intrave-

TABLE 1
Data for Redifferentiation Therapy-Induced Radioiodine Uptake in Thyroid Cancer

Patient no.	Age	Sex	Tumor type	Disease duration	pTNMG	RA dose (mg/kg)	Duration of RA therapy	Tumor tissue site	Radioiodine uptake before RA	Radioiodine uptake after RA	Initial FDG uptake	FDG uptake after RA	Response induction of radioiodine uptake
1	68	F	P	23 yr	TxN1M1Gx	0.70	10 mo	Cerv./mediast. LNM	None	Intense	All sites	Increased	+
2	55	M	F	2 yr	T4N1MxG2	1.54	2 mo	Local recurr.	None	Faint	nd	nd	+
3	84	F	P	5 yr	T3N1MxGx	0.88	2 mo	Cerv./mediast. LNM/lung M	None	Faint	All sites	nd	+
4	75	F	M	3 yr	T4N2M1Gx	0.65	3 mo	Cerv./mediast. LNM/lung M	None	Faint mediast LNM	Mediast. LNM/lung M	nd	+
5	68	F	F(H)	5 yr	T4NxM1Gx	0.90	3 mo	Mediast. LNM/lung/bone M	Faint mediast. LNM	Intense (all)	Mediast. LNM/lung/bone M[3]	All sites pos.	+
6	55	F	P	7 yr	T1NxM1Gx	1.45	3 mo	Lung M	None	None	nd	nd	−
7	59	M	M(f)	15 mo	T3N1M1Gx	1.45	3 mo	Cerv./LNM/lung M	None	None	All sites	nd	−
8	65	F	F(H)	4 yr	T4N0M1Gx	0.82	2 mo	Lung/bone/liver M	None	None	All sites	nd	−
9	74	F	P	20 yr	T3N1MxGx	1.45	3 mo	Cerv. LNM	None	None	Cerv./LNM	Cerv. LNM	−
10	52	F	P	8 yr	T4N1M1Gx	1.74	2 mo	Med. LNM/lung/bone M	Multiple[1]	Multiple[2]	All sites	All sites[4]	−
11	72	M	P	3 yr	T4N1M1G2	1.20	3 mo	Local recurr./bone M	None	None	Local recurr.	Negative	−
12	59	F	F(H)	16 yr	TxN1M1G1	1.38	9 mo	Local recurr./cerv. LNM/lung M	None	None	Local recurr./cerv. LNM	nd	−

P = papillary tumor type; F = follicular tumor type; M = mixed cell type; H = Hürthle cell tumor; RA = retinoic acid; M = metastasis; LNM = lymph node metastasis; FDG = fluorodeoxyglucose; nd = not done; x = cannot be determined.

[1] No significant uptake in largest (mediastinal) tumor mass.
[2] No significant uptake in largest (mediastinal) tumor mass (unchanged pattern).
[3] Only femur metastasis positive (rib and humerus metastases negative).
[4] Decreased uptake in several bone metastases.

nously 45 min before the start of static emission images in multiple (4–5) bed positions, starting from the base of the skull. Cross sections were generated with filtered backprojection (Hanning 0.4) and corrected by a measured attenuation matrix acquisition of a [88]Ge/[88]Ga transmission scan before or after the registration of the emission scan. Final slice width was 3.8 mm in the transaxial and 4.2 mm in both the coronal and sagittal orientations.

Tg levels were determined by an immunoradiometric assay, as described previously (16) using DYNOtest Tg (B.R.A.H.M.S Diagnostica GmbH, Berlin, Germany). Sera with Tg-specific autoantibodies or with inaccurate recovery-test results (lower than 80% or higher than 120%) were excluded from the study. For statistical evaluation, Tg changes in the responder and nonresponder groups were compared by using the unpaired Student's t-test after logarithmic transformation of the Tg ratios (values before/after RA treatment).

RESULTS

The results are summarized in Table 1. In 2 patients, a significant RI uptake, which could be considered therapeutically useful, was achieved by the RA treatment (Patients 1 and 5). In another 3 patients, we observed a faint RI uptake in tumor tissue that was initially completely RI negative (Patients 2–4). These 5 patients are addressed as "responders" for further evaluation. In 6 patients, no RI could be seen after redifferentiation therapy (Patients 6–9,11–12). In 1 female patient, multiple RI-positive metastases were known before RA treatment, and the largest (and clinically most important one) in the mediastinum was nearly RI negative (Patient 10). No alteration of the RI uptake pattern was observed following RA treatment; therefore, this patient was classified as a nonresponder.

In the responder group, there were 2 papillary tumors, 2 follicular tumors and 1 mixed-cell type tumor, including 1 patient with Hürthle cell carcinoma. In the responder group and the nonresponder group, the RA doses were 0.93 ± 0.36 (0.65–1.54) and 1.36 ± 0.28 (0.82–1.74), respectively. Minor side effects were observed in all patients but did not lead to a cessation of the treatment.

FDG PET was positive in all 10 patients in whom this examination was done before RA therapy. After RA treatment, FDG uptake was increased in all tumor sites in 1 patient (responder, Patient 1); in 1 patient FDG uptake was induced in some initially FDG-negative sites (responder, Patient 5); in 1 patient it was unchanged (nonresponder, Patient 9); in 1 patient FDG uptake was decreased in several bone metastases (nonresponder, Patient 10); and in 1 patient local recurrent tumor tissue was PET negative after RA therapy (nonresponder, Patient 11).

After RA treatment, Tg values were measured immediately after RI therapy under high-TSH values, whereas Tg values before RA treatment were lower than 30 mU/liter (with two exceptions). Median Tg was increased from 118 μg/liter (3–11,780) to 751 μg/liter (20–40,130) after RA therapy. For the responders, these values were 105 μg/liter (3–165) to 840 (27–40,130). In the nonresponder group, the values are 173 (3–11,780) to 134 (20–30, 90) (Fig. 1). The difference between the responder and the nonresponder group was statistically significant ($p < 0.05$).

DISCUSSION

The most important aim of the RA treatment in this study was to reinduce RI uptake in patients who did not have sufficient uptake values in clinically important tumor sites. In 2 of 12
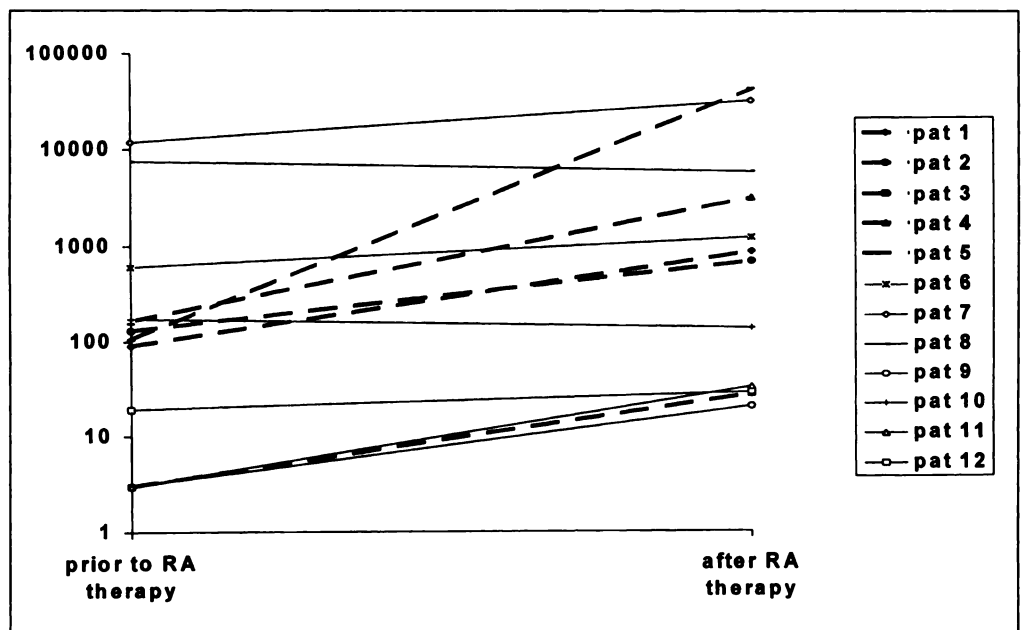
FIGURE 1. Thyroglobulin values (μg/liter) before and after redifferentiation therapy with retinoic acid. Patients 1–5 are responders, and Patients 6–12 are nonresponders as defined by induction of radioiodine uptake into tumor tissue.

patients, a markedly higher uptake was obtained after RA therapy, which could be used for further RI treatment. In another 3 patients, a faint RI uptake was observed, which was insufficient to be used therapeutically but which pointed to a partial success of the redifferentiation procedure and suggested a positive influence on tumor behavior. RA is known to bind to various nuclear retinoic acid receptors. It stimulates Type I 5'-deiodinase, which serves as a differentiation marker in thyroid carcinoma cells (17). In previous studies, 13 cis-RA has been proven to influence proliferation rate and differentiation of human follicular carcinoma cells in vitro (18). Compared with the possible therapeutic effects, side effects (dry skin, rise of liver enzymes or triglycerides) are less important. Because of known embryotoxic effects, pregnancy is an absolute contraindication against RA therapy. This was irrelevant in the patient group treated in this study.

It remains unclear which patients respond to RA treatment and which do not. All tumor types (follicular, papillary, mixed-cell type) were among the nonresponders and the responders. Even a Hürthle cell carcinoma, which can be assumed to be primarily iodine-negative, showed an RA response. The data agreed with the study of Simon et al. (9), who also found various tumor types among both groups. No tumor site could be redifferentiated preferentially. Local recurrence as well as lymph node and distant metastases were among both patient groups. The initial Tg value could not be used prognostically in this study, since there was a wide range of initial Tg values in the responder group, as well as in the nonresponder group. A lower RA dosage (reduction due to side effects in some patients) can be excluded as the cause of the nonresponse in 7 patients, because the mean dose of the responders (0.93 mg/kg) was lower than that of the nonresponders (1.36 mg/kg).

In contrast to the results obtained by Simon et al. (9) and Börner et al. (10), we found a marked increase of serum Tg in the responder group. This observation was thought to be a sign of restoration of Tg synthesis during redifferentiation, although it remains undetermined how Tg values would have developed during the clinical course without intervention. Values might have been increased in the majority of the patients related to their disease progression. Since less-differentiated carcinomas are less dependent on TSH values,

TSH can be supposed to have less influence on Tg release as in other thyroid tumors. Different TSH values before and after RA therapy also have been considered causes of the observed increase of Tg mean value. Nevertheless, the increase of Tg in the responder group was significantly higher when compared with the nonresponder group, suggesting a significant influence of RA in the metabolism of tumor cells in these patients. A cytotoxic effect of RA, causing an increased Tg release from tumor cells, has to be considered also. Börner et al. (10) observed a Tg decrease in a patient who showed up with complete remission after RA therapy and a Tg increase in a patient who did not respond to RA treatment. In our study, we observed an increase of serum Tg also in nonresponders, suggesting disease progression in addition to differences in TSH values. In the study of Simon et al. (9), no correlation was found between the RA response and Tg changes. No correlation between tumor size and response could be observed in this study.

FDG PET was positive in all patients in whom this procedure was performed, as could be expected from earlier studies (19,20). In most recurrent metastases from differentiated thyroid cancer, the sites were positive for either RI or FDG, mainly dependent on the grade of differentiation. Poorly-differentiated carcinomas are preferentially RI negative (as observed in the patients included in this study) and FDG positive (20). Primary tumor grading could be obtained in only 3 of the 12 patients studied. In 1 patient with G2 (nonresponder, Patient 11), FDG PET became normal after RA therapy. Nevertheless, no RI uptake could be obtained in this patient. In the other 2 patients with known grading, no FDG PET was performed after RA treatment. Overall, changes of glucose metabolism, measured by PET imaging, showed a wide range. Although sequential PET studies could be obtained in only 5 patients, the results suggested that RA response might be associated with an increase of glucose consumption. Since other studies showed that particularly (initially) well-differentiated tumors have low glucose consumption values (20), it was expected that FDG uptake would have decreased during successful RA treatment. Because FDG uptake in tumor cells depends also on the expression of several glucose transporter genes (GLUT), changes of glucose transport across the cell membrane have

to be taken into consideration. An increase of GLUT4 mRNA was observed after RA treatment by Sleeman et al. (*21*). Further studies are necessary to answer the question of whether redifferentiation leads to a significant change of glucose uptake in patients responding to RA treatment.

The development of thyroid carcinoma tumor tissue during the clinical course underlies complex mechanisms. In addition to spontaneous changes of differentiation grade, combined with changes of RI uptake capabilities, two influences of RI treatment have to be considered. First, radiation exposure to malignant cells (also to benign tissue) alters metabolic processes, particularly Tg synthesis and iodine metabolism. In cells not killed by radiation exposure, a loss of RI uptake capability can be expected (*1,4,22*). Nevertheless, an actual anaplastic transformation after RI therapy is uncommon (*22*). Second, initially, RI is accumulated preferentially in those cells, which are less altered in regard to iodine metabolism. Assuming different cell clones before RI therapy, a selective destruction of relatively unchanged cells has to be considered.

After several RI treatments, the remaining tumor sites often are less capable of taking up RI in amounts that can be used therapeutically. Patients whose metastases have concentrated RI have significantly higher survival rates (*2*). The impact of DNA changes encoding the Na^+/I^- symporter, which have been characterized recently (*23*), still have to be determined for the clinical course of differentiated thyroid cancer. The phenomenon of a loss of RI uptake capability is well known and has to be considered in therapy planning.

Except for a spontaneous reappearance of RI capability (*6*), which is extremely rare, a reappearance has been observed recently after chemotherapy (*24*). RA therapy seems to be an encouraging alternative for RI-negative tumors. Since RA treatment had been terminated recently or was to be continued in most patients, no sufficient evaluation in this study was possible regarding RA treatment effect on tumor mass.

CONCLUSION

The results of this study suggest that RA can be used to induce RI uptake in some patients with differentiated thyroid carcinoma. Redifferentiation therapy should be considered in patients with tumor tissue that cannot be treated by other modalities, particularly in RI-negative metastases. Tg values increased in all responders. Although a tumor progression can cause a Tg increase, a restoration of Tg synthesis can be taken as a parameter of redifferentiation in RA responders.

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