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Follow-up of patients treated with retinoic acid for the control of radioiodine non-responsive advanced thyroid carcinoma

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Abstract

During thyroid tumor progression, cellular de-differentiation may occur and it is commonly accompanied by metastatic spread and loss of iodine uptake. Retinoic acid (RA) administration might increase iodine uptake in about 40% of patients, suggesting that RA could be a promising therapeutic option for radioiodine non-responsive thyroid carcinoma, although a prospective study with a long-term follow-up has not been reported. This was a clinical prospective study assessing the value of 13-cis-RA in patients with advanced thyroid carcinoma and its impact on major outcomes such as tumor regression and cancer-related death with a long-term follow-up of patients submitted to radioiodine (¹³¹I) therapy after RA administration. Sixteen patients with inoperable disease and no significant radioiodine uptake on post-therapy scan were selected. Patients were treated orally with 13-cis-RA at a dose of 1.0 to 1.5 mg·kg⁻¹·day⁻¹ for 5 weeks and then submitted to radioiodine therapy (150 mCi) after thyroxine withdrawal. A whole body scan was obtained 5 to 7 days after the radioactive iodine therapy. RECIST criteria were used to evaluate the response. An objective partial response rate was observed in 18.8%, a stable disease rate in 25% and a progression disease rate in 56.2%. Five patients died (62.5%) in the group classified as progression of disease. Progression-free survival rate (PFS) ranged from 72 to 12 months, with a median PFS of 26.5 months. RA may be an option for advanced de-differentiated thyroid cancer, due to the low rate of side effects.

Key words: Thyroid cancer; Retinoic acid; Radioiodine therapy

Introduction

Differentiated thyroid carcinomas are slow growing and usually curable by the combination of surgery, radioiodine ablation and thyroid-stimulating hormone (TSH) suppressive therapy. However, recurrence develops in 20-40% of patients (1,2). During tumor progression, cellular de-differentiation occurs in up to 30% of cases (3) and is commonly accompanied by more aggressive growth, metastatic spread and loss of iodine uptake. The therapeutic options for de-differentiated thyroid cancer are limited and generally not efficient (4). Therefore, patients with aggressive thyroid cancer usually need multimodal adjuvant therapies such as radiotherapy and/or chemotherapy and have a less favorable outcome (5). Recently, the use of target therapy, such as tyrosine kinase inhibitors, has been reported to be effective for the control of most cases (6,7), although important

undesirable side effects sometimes occur.

Retinoic acids (RAs) are biologically active metabolites of vitamin A, which regulate the growth and the differentiation of many types of cell. The *in vitro* re-differentiating effect of RA on thyroid carcinoma cell lines has been suggested by data showing increased expression of sodium/iodide symporter mRNA, type I iodothyronine deiodinase and alkaline phosphatase (8-10), and by the increase of cellular iodine uptake and human TSH binding (11).

Some studies have evaluated the effectiveness of 13-cis retinoic acid (13-cis-RA) in thyroid cancer. Previous clinical studies have demonstrated that RA administration induces iodine uptake in about 40% of patients, suggesting that RA could be a promising therapeutic option for radioiodine non-responsive thyroid carcinoma (12-15). However, when the

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effects of RA on serum thyroglobulin (Tg) and tumor size were analyzed together with its ability to increase iodine uptake, a satisfactory response (tumoral regression or stabilization) was obtained in a minority of cases (16-18), although no prospective study with a long-term follow-up has been reported. On the basis of these considerations, we performed a clinical prospective study to assess the value of 13-cis-RA against advanced thyroid carcinoma and its impact on major outcomes such as tumor regression and cancer-related death during a 72-month follow-up of patients submitted to radioiodine (^{131}I) therapy after RA administration.

Patients and Methods

Sixteen patients (12 females and 4 males aged 28 to 79 years) with a mean age of 53 years and with advanced and progressive thyroid cancer (defined as an increase of more than 20% in the target lesion size during the last 6 months, an increase in serum Tg levels of more than 20% or the presence of a new lesion), inoperable disease (because of an extensive local tumor mass and/or metastatic spread) and no significant radioiodine uptake on post-therapy scan were selected for this prospective study. Patients were followed from 2002 to 2008. Fourteen patients (87.5%) had papillary thyroid carcinomas and 2 (12.5%) had follicular thyroid carcinomas. Exclusion criteria were pregnancy, anaplastic carcinoma and liver or renal insufficiency. Patients showed evidence of measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST). The Federal University of Rio de Janeiro Ethics Committee approved

the protocol and all patients gave written informed consent to participate in the study.

The treatment was performed with 13-cis-RA (isotretinoin) at a dose of 1.0 to 1.5 mg·kg⁻¹·day⁻¹ orally for 5 weeks and the patients were then submitted to radioiodine therapy (150 mCi) after thyroxine withdrawal. A whole body scan was carried out 5 to 7 days after administration of the therapeutic dose of radioactive iodine (^{131}I). Iodine accumulation was determined by comparison of the tumor with the background and physiological structures (such as liver). The whole body scan was performed at a gamma camera speed of 12 cm/min. Since all patients had been submitted to at least one post-therapy scan before the beginning of isotretinoin administration, comparison of the scans (before and after RA) was possible for classification of the response. Those patients who showed an increase of iodine uptake after radioiodine therapy were candidates for more than one treatment cycle before the assessment of the best response. This was done 12 months later if they had an increase in iodine uptake in the post-therapy scan.

Thyroxine treatment was discontinued and replaced with triiodothyronine up to 3 weeks prior to radioiodine therapy. Liver enzymes, blood count, lipidogram, glycemia, serum Tg, anti-Tg antibody, TSH, and free T4 measurements were determined before and during treatment in all patients. Serum Tg was quantified by an immunometric assay (Immunolite[®], Diagnostic Products Corporation, USA) with analytical sensitivity of 0.2 ng/mL, functional sensitivity of 0.9 ng/mL and interassay variation up to 8.8%.

The study end points of best objective response rate and stable disease were identified on the basis of computed tomography findings or on neck ultrasound using RECIST. All images were evaluated by the same radiologist before and after RA therapy.

Table 1. Baseline characteristics of the patients treated with retinoic acid.

Characteristic	No. of patients (N = 16)
Thyroid cancer subtype	
Papillary	14 (87.5%)
Follicular	2 (12.5%)
Previous treatment	
Surgery	16 (100%)
Radioiodine treatment	16 (100%)
Chemotherapy	3 (18.8%)
External-beam radiation	5 (31.2%)
Follow-up	
1-2 years	2 (12.5%)
2-3 years	8 (50%)
3-4 years	3 (18.8%)
>4 years	3 (18.8%)
Localization of initial disease before retinoic acid treatment	
Lung metastasis	13 (81.3%)
Bone metastasis	4 (25%)
Local recurrence	10 (62.5%)

Patients received 13-cis retinoic acid, orally, 1.0 to 1.5 mg·kg⁻¹·day⁻¹ for 5 weeks.

Results

The baseline characteristics of the patients enrolled in the study are listed in Table 1; 3 patients (18.8%) had received prior chemotherapy and 5 (31.3%) prior external-beam radiation. All patients had progressive disease evaluated by baseline scans before the initiation of treatment. All patients had been submitted to total thyroidectomy followed by ablation of remnants with radioiodine therapy. After recurrence, the patients were treated with radioiodine until the post-dose scan became negative for iodine uptake. Accumulated radioiodine doses ranged from 100 to 750 mCi (median 375 mCi). Patients had been followed for at least 12 months

after RA, and 37.5% of them had at least 36-48 months of follow-up. Three patients had been followed for 72 months after RA therapy (median follow-up of 30 months). Correlation between the initial response, defined as a positive post-therapy scan after RA therapy, and tumor shrinkage by RECIST criteria was also assessed.

In general, therapy was well tolerated and all patients completed RA treatment. However, some side effects were frequent, such as dryness of skin and mucosa and hypertriglyceridemia. One patient had a transitory rise of fasting blood glucose level and one had anemia. Elevation of triglycerides is a well-known metabolic complication of retinoid therapy, which can be explained, at least in part, by the increase in Apo C-III expression at the transcriptional level via RA interaction with the retinoid X receptor (19).

The best responses among the 16 patients were assessed 12 months after the last patient started treatment (Table 2). The objective partial response rate (defined as a 30% decrease in the sum of the longest diameter measurements by RECIST) was 18.8% (3 patients). The stable disease rate (defined as a 0 to 30% increase in the sum of the longest diameter by RECIST) was 25% (4 patients) and the progression disease rate was 56.2% (9 patients). Progression of the disease was defined as an increase in the sum of the longest diameter measurements or a finding of new lesions. Five patients died (62.5%) in the group classified as progression of disease. Responses ranged from progressive disease to a 75% decrease in target lesions by RECIST criteria (Figure 1). Progression-free survival rate (PFS) ranged from 72 to 12 months, with a median value

of 26.5 months. The Kaplan-Meier survival curve for all 16 patients is shown in Figure 2. All deaths occurred because of thyroid cancer progression, especially secondary to lung metastases. In the determination of progression disease, 44.4% (4 of 9) of the patients showed increased iodine uptake in the post-therapy scan after RA treatment, even though tumor size increased or new lesions appeared during follow-up. All patients who showed a partial response in the target lesions had a positive post-RA therapy scan at the initial evaluation, two of them received only one cycle of RA treatment and radioiodine therapy, and one received four cycles of RA. Among the patients with stable disease, two had an initial response and one did not respond (negative post-therapy scan) despite having stable disease during long-term follow-up. Two of these patients were treated

Table 2. Patient response.

Best response by RECIST	No. of patients (N = 16)
Complete response	0
Partial response	3 (18.8%)
Stable disease	4 (25%)
Disease progression	9 (56.2%)
Clinical benefit (PR + SD)	7 (43.8%)

RECIST = Response Evaluation Criteria in Solid Tumors; complete response = 100% tumor shrinkage; partial response (PR) = >30% decrease; stable disease (SD) = 0 to 30% decrease; disease progression = increase in tumor size.

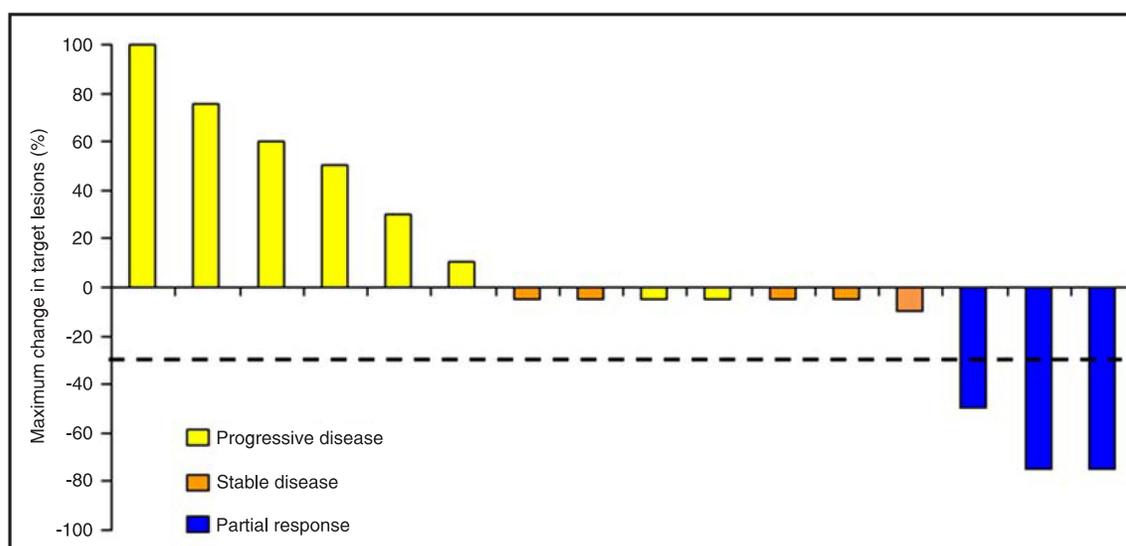


Figure 1. Best overall response regarding change in the target lesion measurement determined on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST).

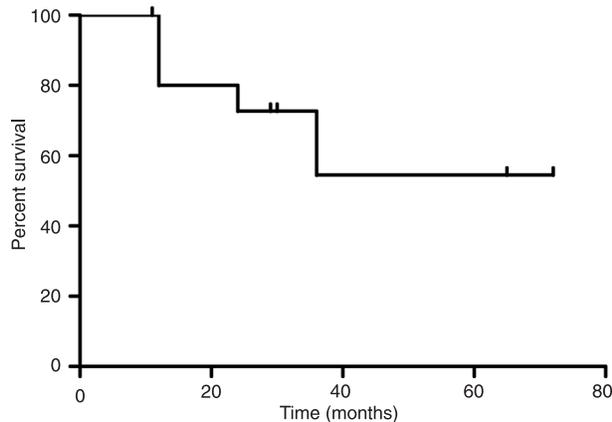


Figure 2. Kaplan-Meier curve of progression-free survival (PFS) rate for all 16 patients included in the study.

once with an RA cycle, one receiving two cycles and the other three cycles of RA.

Discussion

There are no effective therapies for advanced metastatic thyroid cancer that do not concentrate radioiodine. Recent studies with the RA isomer 13-cis-RA have shown that this drug can induce re-differentiation of thyroid carcinoma cell lines *in vitro*, as suggested by increased expression of some thyroid-specific proteins (9,10,20,21) and by the increase of cellular radioiodine uptake (22-25). In several clinical studies, RA administration was able to re-induce iodine uptake in 20 to 50% of patients (12,16,26).

In the present study, we observed a partial response rate of 18.8% and a stable disease rate of 25%, with an overall clinical benefit rate of 43.8% after 5 weeks of RA followed by a therapeutic dose of radioiodine. Previous studies (27,28) have described a shorter-term follow-up of RA-treated patients. Kim et al. (27) showed stable disease assessed by RECIST criteria in 55% of patients and none of their patients had a partial response. Zhang et al. (28) had a better outcome with a 63.6% clinical benefit (partial

response + stable disease).

In the Eastern Cooperative Oncology Group trial of doxorubicin-containing regimens, PFS time for patients with metastatic iodine non-avid differentiated thyroid cancer was estimated at 2 months for both doxorubicin alone and doxorubicin plus cisplatin, and median overall survival time was 8 months (29). In the present study, we observed a median PFS of 26.5 months, which might represent a considerably significant improvement in the outcome of these patients. Recent studies using Sorafenib (6) or Axitinib (7) have found a slightly lower partial response rate and a much lower PFS, probably because they included patients with non-differentiated thyroid carcinoma, which has a more aggressive behavior.

Despite improved iodide uptake, tumor shrinkage evaluated by RECIST criteria was less than expected (62.5% had increased radioiodide uptake vs 18.8% with a partial response). Interestingly, 44.4% of the patients who had progression of disease showed increased iodine uptake at the beginning. Recent data analyzing the role of ^{124}I -PET scan have suggested that the traditional scan using ^{131}I is not accurate enough to determine the concentration of radioiodine in tumor metastases (30). In fact, these data might explain why patients with improved iodine uptake after RA therapy do not necessarily present the expected tumor shrinkage.

There was no correlation between the number of RA cycles and the response. In fact, most of the patients who had a partial response in their target lesion had only one cycle of RA treatment associated with radioiodine therapy and also showed a good increase in iodine uptake from the beginning. These data suggest that the beneficial effect of RA does not depend on the number of drug cycles administered, but rather on the biology of the tumor.

RA might be an option for advanced de-differentiated thyroid cancer due to the low rate of side effects, especially when compared with cytotoxic drugs. However, a satisfactory response was observed in only 18.8% of our cases, similar to that reported in a previously published clinical study (28), and patients with aggressive thyroid cancer usually need adjuvant treatments such as radiotherapy and/or chemotherapy.

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