Response to sorafenib treatment in advanced metastatic thyroid cancer

Resposta ao tratamento com sorafenibe em pacientes com carcinoma metastático de tireoide

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ABSTRACT

Objective: To investigate the efficacy of sorafenib in progressive radioiodine resistant metastatic thyroid carcinoma. **Subjects and methods:** Off-label observational study. Sorafenib 400 mg twice daily was evaluated. Therapy duration was 12 ± 3 months (range 6-16 months). **Results:** Eight patients were included (seven papillary, one insular variant). The eight patients meeting study criteria received sorafenib 400 mg orally twice a day until disease progression or unacceptable toxicity developed. One patient showed a partial response with tumor regression of -35%, six months after the beginning of the treatment; five patients exhibited stable disease and two patients had progressive disease and died. Thyroglobulin decreased within 4 weeks in all patients by 50% ± 23%. Adverse events: one patient had heart failure, and recovered after sorafenib withdrawal. However, she died five months later of sudden death. **Conclusion:** These data suggest a possible role for sorafenib in the treatment of progressive metastatic DTC. Adverse event are usually manageable, but severe ones may appear and these patients should be strictly controlled. Arq Bras Endocrinol Metab. 2014;58(1):37-41

Keywords

Metastasis; sorafenib; thyroid; cancer

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RESUMO

Objetivo: Investigar a eficácia do sorafenibe no carcinoma de tireoide metastático progressivo e refratário à iodoterapia. **Sujeitos e métodos:** Estudo observacional do efeito do sorafenibe *off-label* administrado 400 mg duas vezes ao dia. A duração da terapia foi de 12 ± 3 meses (variação de 6-16 meses). **Resultados:** Oito pacientes foram incluídos (sete com variante papilífera e um com variante insular). Os oito pacientes que preencheram os critérios do estudo receberam o sorafenibe 400 mg por via oral duas vezes por dia até progressão da doença ou toxicidade inaceitável. Um paciente apresentou uma resposta parcial com regressão tumoral da lesão alvo de 35% seis meses após o início do tratamento; cinco pacientes apresentaram doença estável e dois pacientes progrediram e morreram. A tireoglobulina diminuiu 50% ± 23% em 4 semanas em todos os pacientes. Eventos adversos: um paciente teve insuficiência cardíaca e morreu por morte súbita cinco meses após a retirada do sorafenibe. **Conclusão:** Esses dados sugerem um possível papel para sorafenibe para o tratamento do CDT metastático progressivo. Arq Bras Endocrinol Metab. 2014;58(1):37-41

Descritores

Metastático; sorafenibe; tireoide; câncer

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INTRODUCTION

Differentiated thyroid cancer (DTC) accounts for more than 90% of all thyroid cancers and includes the papillary, follicular, and poorly differentiated histological types. The incidence of the disease continues to rise rapidly worldwide, especially in women (1), long-term survival is excellent, and most patients die of other causes. A good overall prognosis generally applies to patients aged < 60 years with no extension beyond the thyroid capsule, and no local or distant metastases (2). These patients can experience 10-year survival rates as high as 85% (2,3). Unfortunately, local or distant metastases can occur, and 25%-66% of patients with locally advanced or metastatic disease will become refractory to treatment with radioiodine (RAI) (4,5). Patients with advanced RAI-refractory DTC are rare, representing < 5% of patients with clinical thyroid cancer. This subgroup of patients has a poor overall prognosis, with 10-year survival rates of only 10% and a median survival from the discovery of metastases of only 3 to 5 years (4-6).

The American Thyroid Association and the Latin American Thyroid Society, among others societies in the world, currently provide recommendations to include patients with advanced, RAI-refractory DTC in clinical trials or considering treatment with *off-label* small-molecule kinase inhibitor (*e.g.*, sorafenib, sunitinib, pazopanib etc.) if trials are not available (7,8), but the practical details of managing these patients often vary between physicians and countries (9).

To optimize care, it is important to reach a common definition of ^{131}I refractory disease, both for clinical trials and in community practice. At least ^{131}I refractory disease should be defined as the presence of a lesion that does not uptake ^{131}I detected at imaging, or clinical evidence that ^{131}I is no longer beneficial despite visible uptake or, for example, cumulative activity > 600 mCi (4,10,11). In the latter case, tumor progression should also be confirmed by imaging performed every 6 to 14 months according to Response Evaluation Criteria in Solid Tumors (12). As tumor markers, such as thyroglobulin (Tg) reflect risk, not tumor burden, increasing concentrations of these markers should be considered suspicious, but not diagnostic, of progressive disease, as should the results of 18-fluorodeoxyglucose (FDG) PET/computerized tomography (9,11). RAI-resistance might be complicated to define when mixed response is present.

The objective of this study was to investigate the efficacy of *off-label* compassionate use of sorafenib in progressive radioiodine resistant metastatic thyroid carcinoma.

SUBJECTS AND METHODS

Eligible patients to receive sorafenib treatment after confirmation of RAI-resistant metastatic thyroid cancer were > 18 years old with histologically confirmed thyroid carcinoma (papillary & follicular subtypes) for which no curative or standard palliative therapies were available. Patients had evidence of disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) in the 12 months before entering the study, and all patients had measurable disease according to RECIST criteria. Previous therapies such as radioiodine therapy (n = 8), radiotherapy (n = 4), radiofrequency ablation and percutaneous ethanol injection (n = 2) had been performed in these patients. Other inclusion criteria were Eastern Cooperative Oncology Group performance status (ECOG) = 2 with preserved renal, hepatic, and bone marrow function. All patients provided written informed consent and the protocol was reviewed and approved by an external ethics committee. Mean radiodiodine cumulative dose before considering RAI resistance was 810 ± 312 mCi ^{131}I.

Study design

Off-label compassionate use observational study. Sorafenib 400 mg twice daily was evaluated. The primary endpoint was the objective RECIST score assessed on day 30 and every 12 weeks thereafter. Additional endpoints were duration of tumor response and changes in tumor marker (Tg) measured initially, at 4 weeks, and then every 4 weeks. Clinical benefit was defined as partial response, PR (at least a 30% decrease in the sum of diameters of target lesions) or stable disease, SD (neither sufficient increase nor decrease in the size of target lesions considered to be meaningful). Patients were withdrawn from the study after radiological confirmation of tumor disease progression, PD (a 20% or greater increase in the sum of diameters of the target lesions) according to RECIST criteria. Mean therapy duration was 12 ± 3 months (range 6 to 16 months).

RESULTS

Between May 2010 and January 2013, eight patients were included (7 papillary, 1 insular variant), whose baseline characteristics are summarized in table 1. At baseline, all patients had previously undergone total thyroidectomy and RAI therapy (mean cumulative activity 830 ± 312 mCi), four patients (50%) had received radiotherapy (2 for neck, and 2 for bone metastasis) and two patients with bone and soft tissue metastases were treated with radiofrequency ablation and percutaneous ethanol injections. In all cases there was progressive disease confirmed by RECIST criteria.

Efficacy

One patient showed a partial response with tumor regression of -35% three months after the beginning of the treatment. This patient kept this response after 16 months of full dosage of sorafenib treatment (Figure 1); 5 patients exhibited stable disease after a mean follow-up of 8 ± 3 months, and 2 patients had stable disease for 8 and 12 months, respectively, and then exhibited progressive disease and died (Table 2). Marker correlation: In figure 2, the mean decrease in serum Tg after sorafenib treatment can be observed (50 ± 23%).

Other pictures better illustrate some of the responses to sorafenib treatment (Figure 1 and Figure 3).

Table 1. Baseline characteristics, mean radioiodine cumulative received dose before sorafenib treatment and follow-up of included subjects

	n = 8 patients
Sex	
M/F	4 (50%)/4 (50%)
Mean age (range)	61 ± 12 (48-73)
Papillary thyroid cancer	7 (88%)
Insular thyroid cancer	1 (12%)
TNM stage	
IV	8 (100%)
ATA risk of recurrence	
High	8 (100%)
Metastatic site	
Lymph nodes and lungs	2 (25%)
Lungs and bones	4 (50%)
Lungs	2 (25%)
Mean cumulative radioiodine dose before sorafenib treatment (mCi)	810 ± 312
Follow-up after sorafenib prescription in months (range)	12 ± 3 (6-16)

Table 2. Tumor response to sorafenib treatment

Tumor response	n (%)
Partial response (PR)	1 (12.5)
Stable disease (SD)	5 (62.5)
Progressive disease (PD)	2 (25)

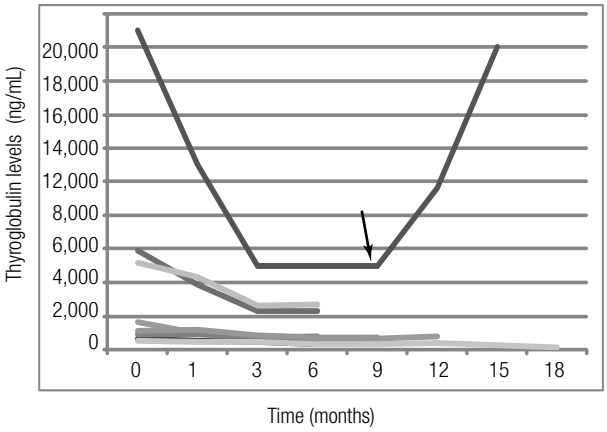

Figure 2. Results of serum Tg levels in 8 patients with advanced DTC treated with sorafenib. The black arrow indicates sorafenib withdrawal in patient number 1 due to a severe adverse event (heart failure, *see text*).

Adverse events

One patient suffered heart failure probably related to sorafenib, which led to the withdrawal of the drug 9 months after starting the treatment. She died 5 months later after sorafenib withdrawal, from sudden death. The initial ejection fraction (EF) before sorafenib prescription was 67%, which decreased to 25% when heart failure developed. One month after sorafenib withdrawal EF increased to 55% after additional cardiovascular medications.

Other adverse events were: fatigue (n = 3), diarrhea (n = 3), hand-foot syndrome (n = 1), mucositis (n = 1), rash (n = 1), and hair loss (n = 1). Hypertension was not observed. In two patients, sorafenib dose was reduced 400 mg/d, and in two to 600 mg/d due to these adverse events. Two other patients are still on the full dose (800 mg/d), one patient after 16 months of treatment.

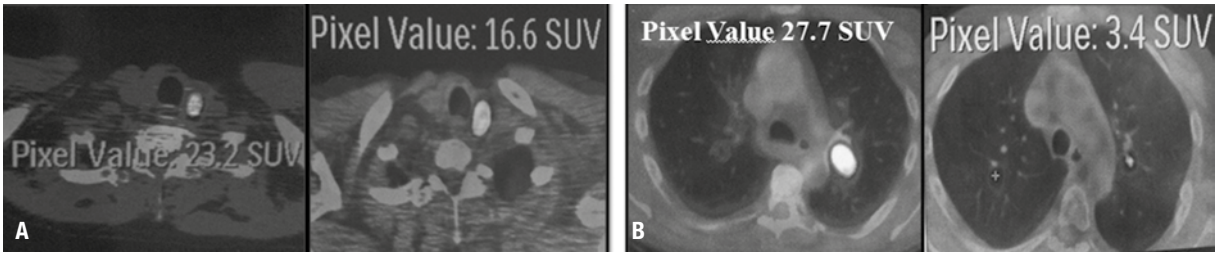

Figure 1. 69-year-old male patient with dedifferentiated papillary thyroid carcinoma. After 12 years of follow-up and a cumulative radioiodine activity of 700 mCi, progressive lung and cervical neck metastases were observed. He denied receiving cervical surgery. This figure shows two 18-FDG PET-CT performed with an interval of 6 months. A decrease in 18-FDG uptake (SUV) in the cervical mass after 6 months of 800 mg b/d of sorafenib treatment (**A**) and a decrease in size and 18-FDG uptake (SUV) in lung metastasis were observed (**B**). There was a Partial Response in metastatic lung disease and Stable Disease in cervical lymph node metastasis.

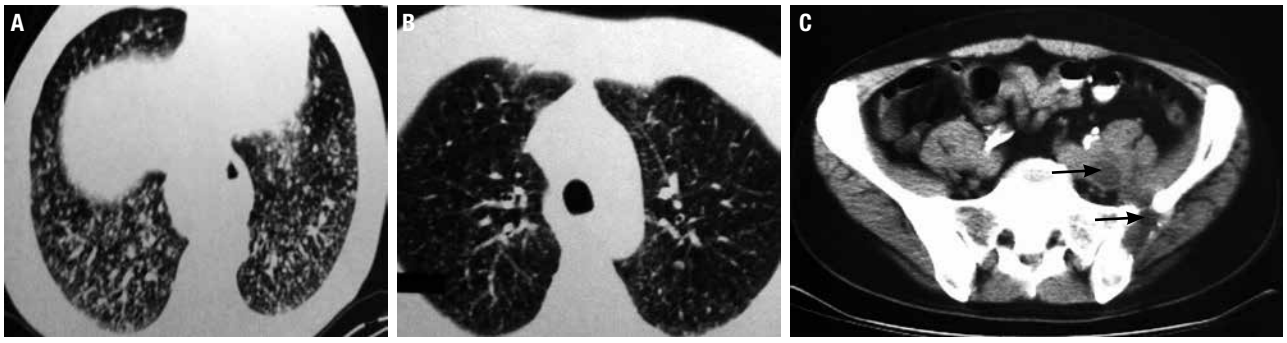

Figure 3. 53-year-old male patient with dedifferentiated papillary thyroid carcinoma metastatic to lung and bones. There was a symptomatic and imaging response in lung metastasis: (**A**) baseline; (**B**) after 5 months of 800 mg/d sorafenib treatment (no RECIST criteria), and (**C**) stable disease in lytic and soft tissue pelvic metastasis.

DISCUSSION

Sorafenib is a multiple tyrosine kinase inhibitor (TKI), targeting CRAF, BRAF, VEGF receptor (VEGFR)-1, -2, -3, PDGF receptor (PDGFR)-β, RET, c-kit and Flt-3 (13). As a multifunctional inhibitor, sorafenib inhibits tumor growth, progression, metastasis and angiogenesis, as well as downregulating mechanisms that protect tumors from apoptosis. These findings have suggested that sorafenib may significantly improve outcomes in patients with DTC.

Several Phase II trials have assessed the effects of sorafenib monotherapy in over 200 patients with thyroid cancer, most with DTC, with other patients having medullary and anaplastic carcinomas (14-20). The median progression-free survival (PFS) ranged from 14 to 24 months, with PR rates as high as 38%, and disease control rates (defined as SD plus PR) of 59%-100%. Median overall survival was reported to be as long as 35 months. In approximately 62% of these series (50% in ours), patients required dose reductions due to adverse events (AEs) that were mostly grade 1 or 2. Similar to what it was seen in these 8 patients, the most common AEs have been hand–foot skin reactions and other skin toxicities, fatigue, weight loss, and diarrhea.

A less common but serious adverse event associated with TKIs is systolic and diastolic congestive heart failure (20). Patients may present with very dramatic symptoms of heart failure, as it occurred with one of our patients. Others demonstrate mild symptoms which may be difficult to differentiate from fatigue due to the TKI or the tumor itself (20). This toxicity is not completely understood, but platelet-derived growth factor receptor-β (PDGFR-β) inhibition has been implicated as playing a role in the response to pressure overload-induced stress (21).

The encouraging results of these trials and the need for improvement in the treatment of ^{131}I refractory DTC have led to the designing of a double-blind, multicenter, multinational, randomized Phase III trial of sorafenib in 380 patients with locally advanced or metastatic I-131 refractory DTC (DECISION) (19).

The results of this trial were recently presented (22). Finally, a total of 417 patients were randomized (207 to sorafenib and 210 to placebo); median age 63 yrs., 52% female. Tumor histology by independent assessment was 57% papillary, 25% follicular, and 10% poorly differentiated. Ninety-six percent of patients had metastatic disease; the most common target lesions were lungs (71%), lymph nodes (40%), and bones (14%). Sorafenib significantly extended PFS, the primary endpoint of the study, compared to placebo. The median PFS was 10.8 months among patients treated with sorafenib, compared to 5.8 months among patients receiving placebo (HR = 0.587 [95% CI, 0.454-0.758]; $p < 0.0001$). Safety and tolerability in the study were generally consistent with the known profile of sorafenib. The Phase 3 DECISION data will probably form the basis for regulatory submissions of sorafenib for the treatment of RAI-refractory differentiated thyroid cancer. However, there was no statistically significant difference in overall survival between the treatment arms (HR = 0.802 [95% CI, 0.539-1.194]; $p = 0.138$), a secondary endpoint of the trial, this was due to that median overall survival has not yet been reached in either arm (22).

In this investigation, the efficacy and toxicity profile of *off-label* compassionate use of sorafenib for the treatment of advanced and refractory thyroid cancer in an unselected population representative of routine clinical practice was reported. The observed efficacy

data are comparable with other published studies with sorafenib in DTC patients. With the fase III Decision Study already finished, it is expected that sorafenib (and probably, in the near future, other drugs of this type) will soon be available to improve survival of RAI-refractory advanced thyroid cancer patients.

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REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.
2. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer. 1998;83(12):2638-48.
3. Eustatia-Rutten CF, Corssmit EP, Biermasz NR, Pereira AM, Romijn JA, Smit JW. Survival and death causes in differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2006;91(1):313-9.
4. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006;91(8):2892-9.
5. Hodak SP, Carty SE. Radioiodine-resistant differentiated thyroid cancer: hope for the future. Oncology. 2009;23(9):775-6.
6. Robbins RJ, Wan Q, Grewal RK, Reibke R, Gonen M, Strauss HW, et al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxyd-glucose-positron emission tomography scanning. J Clin Endocrinol Metab. 2006;91(2):498-505.
7. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-214.
8. Pitoia F, Ward L, Wohllk N, Friguglietti C, Tomimori E, Gauna A, et al. Recommendations of the Latin American Thyroid Society on diagnosis and management of differentiated thyroid cancer. Arq Bras Endocrinol Metabol. 2009;53(7):884-7.
9. Brose MS, Smit J, Capdevila J, Elisei R, Nutting C, Pitoia F, et al. Approach to the patient with advanced differentiated thyroid cancer. Expert Rev Anticancer Ther. 2012;12(9):1137-47.
10. Pacini F, Ito Y, Luster M, Pitoia F, Robinson B, Wirth L. Radioactive iodine-refractory differentiated thyroid cancer: unmet needs and future directions. Expert Rev Endocrinol Metab. 2012;7(5):541-54.
11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
12. Kim A, Balis FM, Widemann BC. Sorafenib and sunitinib. Oncologist. 2009;14(8):800-5.
13. Gupta-Abramson V, Troxel AB, Nellore A, Puttaswamy K, Redlinger M, Ransone K, et al. Phase II trial of sorafenib in advanced thyroid cancer. J Clin Oncol. 2008;26(29):4714-9.
14. Keefe SM, Troxel AB, Rhee S. Phase II trial of sorafenib in patients with advanced thyroid cancer. J Clin Oncol. 2011;29(Suppl. 15), abstract 5562.
15. Kloos RT, Ringel MD, Knopp MV, Hall NC, King M, Stevens R, et al. Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Oncol. 2009;27(10):1675-84.
16. Ahmed M, Barbachano Y, Riddell A, Hickey J, Newbold KL, Viros A, et al. Analysis of the efficacy and toxicity of sorafenib in thyroid cancer: a phase II study in a UK based population. Eur J Endocrinol. 2011;165(2):315-22.
17. Hoftijzer H, Heemstra KA, Morreau H, Stokkel MP, Corssmit EP, Gelderblom H, et al. Beneficial effects of sorafenib on tumor progression, but not on radioiodine uptake, in patients with differentiated thyroid carcinoma. Eur J Endocrinol. 2009;161(6):923-31.
18. Capdevila J, Iglesias L, Halperin I, Segura A, Martínez-Trufero J, Vaz MA, et al. Sorafenib in metastatic thyroid cancer. Endocr Relat Cancer. 2012;19(2):209-16.
19. Brose MS, Nutting CM, Sherman SI, Shong YK, Smit JW, Reike G, et al. Rationale and design of decision: a double-blind, randomized, placebo controlled phase III trial evaluating the efficacy and safety of sorafenib in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory, differentiated thyroid cancer. BMC Cancer. 2011;11:349.
20. Cabanillas ME, Hu MI, Durand JB, Busaidy NL. Challenges associated with tyrosine kinase inhibitor therapy for metastatic thyroid cancer. J Thyroid Res. 2011;2011:985780. doi: 10.4061/2011/985780.
21. Chintalgattu V, Ai D, Langley RR, Zhang J, Bankson JA, Shih TL, et al. Cardiomyocyte PDGFR-beta signaling is an essential component of the mouse cardiac response to load-induced stress. J Clin Invest. 2010;120(2):472-84.
22. Brose M, Nutting C, Jarzab B, Elisei R, Siena S, Bastholt L, et al. J Clin Oncol 2013;31 (suppl; abstr 4) Presented June 2, 2013, at the 49th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, IL at 3:20pm CDT (Abstract #4).