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Sorafenib treatment of radioiodine refractory advanced thyroid cancer in daily clinical practice: a cohort-study from a single centre

Running head: Sorafenib in advanced thyroid cancer


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Key words: thyroid cancer, sorafenib, tyrosine kinase inhibitors, targeted therapy, quality of life

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Abstract

Purpose Treatment options for recurrent or metastatic differentiated thyroid cancer (DTC) refractory to radioactive iodine (RAI) are inadequate. Multitargeted kinase inhibitors have recently shown promising results in phase 2-3 studies. This retrospective study aimed to document our clinical experience on the effects of sorafenib in the setting of daily clinical practice.

Methods Retrospective study evaluating the efficacy and safety of sorafenib in a cohort of patients consecutively treated with sorafenib at a single centre. Twenty patients with advanced RAI-refractory thyroid carcinoma were enrolled (March 2011-March 2014). Patients generally started with sorafenib 400 mg twice daily, tapering the dose in case of side effects. Radiological response and toxicity were measured during follow-up, together with safety parameters. CT scans were performed by a single experienced radiologist every 3-4 months.

Results Five patients stopped sorafenib within 90 days for severe toxicities. Median progression free survival was 248 days. Five patients had a partial response (PR), achieved in all cases within 3 months, whereas 5 had stable disease (SD) at twelve months. Durable response rate (PR plus SD) for at least 6 months was 50%, among those who received sorafenib for at least 3 months. Commonest adverse events included skin toxicity, gastrointestinal and constitutional symptoms.

Conclusions In our cohort of patients with advanced RAI-refractory thyroid carcinoma, sorafenib confirmed antitumor activity leading to SD or PR in the majority of cases, at the expense of clinically relevant side effects. More effective and tolerable agents are still needed in the treatment of RAI-refractory DTC.
Introduction

Thyroid carcinoma is the most frequent endocrine cancer, despite accounting for approximately 2% of all tumours [1]. According to the American Cancer Society, it is the sixth most frequently diagnosed cancer in female subjects and the eighth in men [2]. Its annual incidence has been steadily increasing, doubling in the last 30 years. In 2013, over 60,000 new cases of thyroid cancers were expected to develop in the United States [3, 4]. Although this cancer is generally regarded an indolent disease, the total annual mortality rate for thyroid cancer is about 3% in the United States. These deaths have been reported to be more than those for Hodgkin’s lymphoma, osteosarcoma, and testicular cancer [5].

Differentiated thyroid carcinomas (DTCs) consist of papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), with their different histological subtypes. They constitute the vast majority of thyroid cancers: PTC accounts for over 85% of all cases while FTC accounts for 5-10%. Poorly differentiated thyroid carcinoma (PDTC) is rarer and it has recently been acknowledged as an autonomous entity, characterized by clinical and histological aspects that place them in an intermediate position between DTC and anaplastic thyroid carcinoma [6-8].

Generally, thyroid carcinomas are slow growing and highly curable by a combination of surgery, radioactive iodine (RAI) ablation, and TSH-suppressive doses of L-thyroxine. However, 10-20% of patients show progressive disease, and half of them become refractory to RAI; this event is associated with a high relapse rate and shorter survival [9-12]. Treatment options for thyroid cancers no longer responsive to standard therapy and that are characterized by progressive de-differentiation are currently limited. Traditional chemotherapeutic agents generally provide disappointing results, along with considerable side effects [3, 13]. Even external beam radiation therapy (EBRT) does not show effectiveness in advanced thyroid carcinomas, being used only for palliation [3]. In order to develop new therapeutic strategies, in recent years pre-clinical and
clinical studies have been conducted in particular on tyrosine kinase inhibitors (TKIs)[14, 15]. Among these, sorafenib, an oral multikinase inhibitor with antiproliferative and antiangiogenic effects acting at the level of the signal transduction pathways of RAS and BRAF/MEK/ERK, of the RET/PTC receptors, of VEGF receptors 1-3, and of PDGF receptor β, showed encouraging results [16-18].

Sorafenib was originally approved for the treatment of advanced kidney cancer and of unresectable hepatocellular carcinoma [19]. Preliminary trials and phase 2 studies showed clinically relevant anti-tumour activity also in patients with metastatic, iodine-refractory thyroid cancer, with a partial response rate ranging from 15 to 33% and a stable disease rate of 41-82% [18, 20-26], together with an overall acceptable safety profile. The recently published DECISION trial was the first phase 3 randomized study in RAI-refractory DTC showing significantly improved (by 5 months) median progression-free survival with sorafenib versus placebo (10.8 vs 5.8 months, respectively)[27]. This data led the US Food and Drug Administration to approve sorafenib for the treatment of well-differentiated RAI-resistant metastatic thyroid cancer, in November 2013.

Starting from 2011, we began treating patients with advanced thyroid cancer no longer responsive to conventional therapy with sorafenib, as an off-label drug. The purpose of this retrospective study is to document our Centre experience (in terms of efficacy and safety) in a cohort of patients consecutively treated with sorafenib, in the setting of a daily clinical practice.
Patients and methods

Patients

In March 2011, the Ethics Committee of our Institution approved the use of sorafenib for the treatment of patients with advanced iodine-refractory DTC/PDTC, after the publication of phase 2 studies showing promising results in the induction of stable disease and occasional partial response in this setting. Advanced DTC was defined as progressive and/or metastatic DTC with no further indication for RAI therapy because of: 1) a lack of RAI uptake (partial or complete, assessed by I-131 whole-body scan); 2) having received cumulative RAI activity higher than 22.2 GBq (600 mCi); 3) disease progression during conventional therapy. Patients provided written informed consent both for treatment with sorafenib and for entering data in our database. The local Ethical Committee of the University Hospital “Città della Salute e della Scienza” of Turin approved our retrospective analysis.

Patients were enrolled if they met the following inclusion criteria:

- age 18 years or older (females were excluded if pregnant or lactating);
- locally advanced or metastatic RAI-refractory DTC or PDTC (at outset, according to the Turin proposal)[8] that had progressed within the past 12 months prior to signing informed consent, according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1;
- at least one measurable lesion by computed tomography (CT) or magnetic resonance imaging (MRI) according to RECIST at enrolment;
- Eastern Cooperative Oncology Group (ECOG) performance status of 0–2;
- adequate bone marrow, blood coagulation, liver, and renal function;
- adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP < 150/90 mmHg;
Patients were excluded if they had significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) class II, unstable angina, myocardial infarction or stroke within 6 months, cardiac arrhythmia requiring medical treatment, or prolongation of QTc. Patients who had previously been treated with traditional chemotherapy or with EBRT were not excluded.

*Therapy with sorafenib*

Eligible patients started treatment with sorafenib 800 mg/day (2x200 mg tablets twice daily) or with 600 mg/day in case of relevant comorbidities, maintaining TSH-suppressive doses of L-thyroxine. The follow-up was generally carried out on a monthly basis to coincide with the renewal of the prescription of sorafenib, or more frequently according to the clinical situation. Furthermore, each patient had the opportunity to contact us via phone or email at any time of the study. The drug dose was sequentially reduced or interrupted in case of important side effects, according to previous recommendations [28]. Treatment continued until disease progression or unacceptable toxicity.

*Laboratory parameters and imaging restaging*

Serum TSH, free-thyroxine (T4), thyroglobulin (Tg), and Tg antibody levels were measured at all visits, together with safety parameters. These included blood cell count, serum levels of sodium, potassium, lipids, creatin kinase (CK), N-terminal pro-brain natriuretic peptide (NT-proBNP), blood coagulation, liver, and renal function.
Restaging of disease with CT scan was performed at month 3 from the start of treatment in patients who had taken the drug for at least 30 days. Patients in long-term therapy were also restaged by CT scan every 3-4 months. All CT images were evaluated by a single radiologist.

**Outcomes**

The study outcomes were efficacy and safety of sorafenib in patients with advanced iodine-refractory DTC/PDTC. In order to evaluate efficacy, we considered as endpoints the overall and progression free survival, and the objective response rate (complete or partial response).

The radiologic response to therapy with sorafenib was classified according to the RECIST 1.1 criteria as complete remission of disease (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

Safety was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. In order to evaluate safety, we considered occurrence of any adverse event and of severe adverse event (grade 3-4), and time to treatment discontinuation.

**Statistical analysis**

The distribution of patient characteristics was summarized using percentiles for continuous variables, and percentages and frequencies for categorical variables.

Overall survival (OS) was defined as the elapsed time between the date of the first sorafenib treatment and either the date of death or the last follow-up (if death was not observed during the follow-up period). Progression free survival (PFS) was defined as the elapsed time between the first sorafenib treatment and disease progression (or death), or the last follow-up (if progression was not observed during the follow-up). Patients without any CT evaluation were considered as censored at 90 days after the first sorafenib dose, in PFS analysis. OS and PFS were estimated
using the Kaplan-Meier estimator.

Time to treatment discontinuation was defined as the elapsed time between the date of the first sorafenib treatment and the date of sorafenib discontinuation. The cumulative incidence of treatment discontinuation was estimated using Kaplan-Mayer estimator.

Statistical analyses were performed using Stata v.11.2 (StataCorp, College Station, TX, USA).
**Results**

**Patients**

From March 2011 to March 2014, twenty eligible patients were consecutively enrolled and started on treatment with sorafenib. Detailed demographic and clinical characteristics are reported in **Table 1**. Most of patients were female and the median age was 56.5 years (range 37-76).

Seven out of the 20 enrolled patients had a histological diagnosis of PDTC, 9 of FTC/Hürthle cell carcinoma, and 4 of PTC. Time from diagnosis exceeded 5 years in 65% of patients, and distant metastases were present in 17 of them (70% to the lung). Tg antibodies were positive in 25% of the patients. All of the patients had undergone total thyroidectomy followed by remnant ablation with I-131 and by therapy with TSH-suppressive doses of L-thyroxine. Thirteen patients had been re-operated at least once (65%) for locoregional recurrences or distant disease. Three patients had been previously treated with chemotherapy, 7 with EBRT. Before starting sorafenib, patients had an ECOG score of 0 (40%), 1 (55%), and 2 (5%). Patients generally started treatment with sorafenib 400 mg twice daily, tapering the dose in case of side effects. The median cumulative dose was 94,800 mg (interquartile range 21,400-181,200 mg). Mean daily dose was 601.73 mg.

**Efficacy**

During follow-up, 6 deaths were recorded (5 within 12 months). Radiologic responses to sorafenib are shown in detail in the flow chart (**Figure 1**). OS at 6 and 12 months was 89.06% (95% CI 62.66; 97.17) and 65.77% (95% CI 35.15; 84.54), respectively (**Figure 2**). The median survival time was 28.38 months. Five patients discontinued sorafenib due to severe toxicity (grade 3-4) before the first CT scan, four of which within the first month. PFS at 6 and 12 months was 81.43% (95% CI 52.26; 93.70) and 48.86% (95% CI 20.97; 72.01), respectively (**Figure 3**). The median PFS time was 8.25 months. Durable response rate (PR plus SD) for at least 6 months was 50%, among those who received sorafenib for at least 3 months.
Although median Tg levels showed a trend toward changing accordingly to the radiological response (reduction, stabilization, or progression), no significant association was observed after exclusion of patients with Tg antibodies positivity (data not shown).

**Tolerability**

Most common adverse events included constitutional symptoms (fatigue, weight loss, and anorexia), skin toxicity (hand-foot syndrome, rash/desquamation, and alopecia), gastrointestinal symptoms (diarrhoea, oral mucositis), and hypertension (Table 2). These side effects were mainly grades 1-2 toxicity according to CTCAE. Serious adverse events included severe gastrointestinal toxicity (2 cases), myocardial infarction, intra-tracheal bleeding, and anaphylactic reaction (1 case each). Neither bone marrow toxicity nor secondary malignancies occurred in our cohort, during the observation period. All deaths (6/20) were attributable to underlying disease progression. None of the QTc prolongations observed (4/20) exceeded the upper normal limit (450 ms). NT-proBNP, CK, and liver transaminases increased in 55%, 10%, and 35% of patients, respectively. Dose adjustments of L-thyroxine due to change in TSH levels (mostly increased) were needed for 5/20 patients.

The median duration of treatment with sorafenib was 5.75 months (CI 95% 0.99-8.02). All patients who started with the maximal sorafenib dose (400 mg twice daily) required either dose reduction and/or transient drug interruption to control adverse events. At the end of our observation, three patients were still on therapy with sorafenib without discontinuation (Figure 4).
Discussion

Major existing guidelines suggest novel therapies with orally available anti-angiogenic TKIs for patients with significantly progressive, macroscopic RAI-refractory DTC, preferentially in the setting of experimental trials [3, 30]. New targeted therapies are thus regarded with increasing interest by both endocrinologists and oncologists [29, 31]. After the publication of the DECISION trial, sorafenib—the first drug approved for this indication—represents the first-line systemic approach in this setting [26, 27]. However, treatment with sorafenib is, at best, effective in stabilizing patients with progressive disease, with a PR rate ranging from 12 to 22% [32].

Our data add to the growing evidence that sorafenib can slow down tumour progression in patients with advanced thyroid carcinomas, at least temporarily. The results of our study are broadly consistent with previous ones [18, 20, 21, 26, 33]. In particular, the disease control rate (PR plus SD for ≥6 months) of our cohort was quite similar to the rate of the DECISION trial (50.0% vs 54.1%, respectively)[27]. In our study, however, progression free survival was lower than generally reported, with a median time of 8.25 months vs. 10-19 months [18, 20-24, 27, 34], but similar to other retrospective studies [25]. In our study, all of the patients treated with sorafenib had advanced, progressive, and aggressive thyroid cancer with high disease burden that was refractory to RAI. Furthermore, the cohort included some patients with PDTC. Therefore, it is possible that the tumour burden of our patients was higher than that of other studies. As an alternative hypothesis, it must be considered that the mean daily dose in our study was slightly lower than previous phase 2-3 clinical trials [24, 27].

Similarly to previous studies, also in our cohort median Tg levels changed accordingly to radiological response, even if no significant association was observed (likely due to the small number of patients). At present, if serum Tg determination can be used on an individual basis to monitor treatment with anti-angiogenic agents remains to be established [18, 24, 27]. During
tumour progression, cellular dedifferentiation occurs in up to 5% of cases, leading to poorly differentiated pathological features. These characteristics may include the loss of the ability to produce Tg [31].

Adverse events were generally consistent with the known safety profile of sorafenib [26, 27]. A substantial percentage of our patients discontinued treatment because of side-effects within 3 months. In particular, constitutional symptoms and skin toxicity were extremely common. In addition, hand–foot syndrome and diarrhoea significantly affected the quality of life of those who remained on sorafenib. Skin reactions are sometimes difficult to control and can strongly limit daily routine activities. The importance of monitoring and of taking care of the skin should always be emphasized, when starting sorafenib treatment, also taking into account the possibility of development of skin squamous cell carcinomas [27]. Dose adjustments of L-thyroxine due to change in TSH levels were rather common in our cohort. Indeed, TSH levels should be monitored frequently during treatment with sorafenib, adjusting L-thyroxine dose accordingly [28]. Conversely, in our experience, QTc prolongation seldom represents an adverse effect of sorafenib treatment. Moreover, deaths were always related to underlying disease, in our cohort.

In our cohort, most patients required either dose reduction and/or (temporary or definitive) drug interruption of sorafenib for adverse events, especially those who started with the maximal sorafenib dose. This scenario is well known in everyday clinical practice and confirmed by the existing meta-analysis [26, 28], but it has been the subject of few reports in the literature.

According to previous reports, sorafenib may be better tolerated in patients with renal cell carcinoma than in advanced hepatocellular or thyroid carcinoma, but the reasons for this difference are still unclear [35]. This excess of toxicity is somewhat unexpected, because patients with thyroid cancer usually have a better renal function. Recently, it has been suggested that it could be linked to a high prevalence of sarcopenia in this population, secondary to long-term
thyroxine suppressive therapy leading to muscle loss [36].

It has to be highlighted that often patients place unrealistic expectations on the effectiveness of targeted therapies, and erroneously believe that these treatments are not burdened with significant side effects, unlike traditional chemotherapy. Actually, treatment with sorafenib present difficulties in daily clinical practice. Thus, a detailed discussion and obtaining written informed consent from the patient before initiation of TKI therapy are fundamental aspects [28].

Our observational study has the advantage of describing sorafenib effects in patients belonging to our daily clinical practice, instead of those recruited by strictly defined enrollment criteria in the setting of a sponsored (or not) clinical trial. Yet, all CT images were evaluated by a single radiologist with longstanding experience in radiological assessment of oncological diseases.

This study also contains several limitations, such as its retrospective design and the relatively small sample size, which makes impossible to draw any subgroup analysis according to patient characteristics or tumour histology, which was quite heterogeneous and included a third of patients with PDTC.

Besides, information regarding patient quality of life during treatment with sorafenib were not systematically collected (e.g. with questionnaires to be completed at baseline and at regular intervals thereafter).

Another limitation is that we did not perform any mutational analyses on tumour tissues. **BRAF** and **RAS** mutations have been associated with poor outcomes in patients with DTC [37, 38], even if their potential prognostic or predictive value in patients with advanced, RAI-refractory thyroid cancer has not been extensively evaluated. However, in the DECISION trial, sorafenib improved progression-free survival irrespective of **BRAF** or **RAS** mutation status, thus suggesting that these mutations are neither independently prognostic nor predictive of sorafenib efficacy [27].

Our retrospective study, showing the experience of a single centre, did not include a control
group, so it is not possible to argue if the outcomes observed with sorafenib were really effective and clinically relevant. Furthermore, some heterogeneity in drug dose was present among patients. Certainly, our patients showed progression of the disease during conventional therapy within the past 12 months, and it is likely that they would have further progressed if left untreated. Anyhow, target lesions shrank in over 35% of the patients who were given sorafenib and were restaged by CT scan at least once.

Similarly to previous studies, the radiologic response to sorafenib was classified according to the RECIST criteria, even if they do not properly evaluate all the real benefits of targeted therapies in solid tumours [32]. However, in the absence of alternative validated criteria, RECIST is the mainstays of response evaluation for antitumor agents, at the moment.

In conclusion, also in the setting of everyday clinical practice, sorafenib confirmed antitumor activity leading to durable response in the majority of a cohort of patients with significantly progressive, advanced RAI-refractory DTC/PDTC. However, our findings showing a median PFS of about 8 months and a high incidence of serious adverse events, together with a high rate of dose reductions, add to the growing evidence that more effective agents with less toxicity and possibly costs are still needed in the treatment of RAI-refractory DTC [26, 32]. Furthermore, responses with sorafenib are often not durable, and salvage target therapies after sorafenib failure have not been extensively evaluated yet [39]. Sunitinib may represent a feasible option in this setting, even if few studies have been performed so far [40]. Promising results with another TKI, lenvatinib, in the setting of a phase-III trial, have been reported at the recent 2014 ASCO meeting [41]. According to preliminary findings, lenvatinib seems more effective than sorafenib in both improving PFS and obtaining an objective tumour response. Moreover, the role of TKIs in this setting may be revolutionised by the recent findings according to which selumetinib may restore iodine uptake and clinical response to RAI [29]. These and other recent findings have been extensively discussed
by Marotta et al. in a recent review [42].

Physicians well-versed in the management of advanced thyroid cancers should carefully evaluate, on an individual basis, if starting or not systemic therapy with TKIs, as the risks of therapy can often outweigh potential benefits. Indeed, watchful waiting may still be appropriate for many cases with stable or slowly progressive asymptomatic disease, especially with patients of advanced age, with severe comorbidities, or scarcely motivated to tolerate unpleasant side effects.
References


with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 91, 2892–2899 (2006)


21 Kloos, R.T., Ringel, M.D., Knopp, M.V., Hall, N.C., King, M., Stevens, R., Liang, J., Wakely, P.E. Jr, Vasko, V.V., Saji, M., Rittenberry, J., Wei, L., Arbogast, D., Collamore, M., Wright, J.J., Grever,


30 National Comprehensive Cancer Network.: NCCN Clinical Practice Guidelines in Oncology:


40 Marotta, V., Di Somma, C., Rubino, M., Sciammarella, C., Modica, R., Camera, L., Del Prete, M., Marciello, F., Ramundo, V., Circelli, L., Buonomano, P., Colao, A., Faggiano, A.: Second-line sunitinib as a feasible approach for iodine-refractory differentiated thyroid cancer after the
failure of first-line sorafenib. Endocrine (2014) [Epub ahead of print]
Figure legends

**Figure 1** Flow chart

**Figure 2** Overall survival (OS) from the date of the first sorafenib dose (N=20).

**Figure 3** Progression free survival (PFS) from the date of the first sorafenib dose (N=20).

**Figure 4** Cumulative incidence of treatment discontinuation

Table legends

**Table 1** Main baseline demographic and clinical features of patients treated with sorafenib

**Table 2** Adverse events
Tab. 1 Main baseline demographic and clinical features of patients treated with sorafenib

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N, number; %, proportion.
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N, number; %, proportion.
20 patients started sorafenib treatment

1 patient died within 3 months from treatment start

19 patients were followed at least 3 months after treatment start

5 patients were not assessed by CT at 3 months because of sorafenib discontinuation within 3 months

14 patients were assessed by CT at 3 months

1 PD at 3 months

8 SD at 3 months:
- 3 SD at 6 months
- 3 PD at 6 months
- 2 deaths at 6 months

5 PR at 3 months:
- 1 PR at 6 months
- 3 SD at 6 months
- 1 PD at 6 months
Figure 3

[Graph showing progression-free survival over months from the first treatment, with number at risk indicated at each time point: 20, 19, 12, 10, 7, 6, 5]
Figure 4

Cumulative incidence of treatment discontinuation

Number at risk
20 12 10 8 5 4 3

Months from the first treatment