Treatment with Tyrosine Kinase Inhibitors for Patients with Differentiated Thyroid Cancer: the M. D. Anderson Experience

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Objectives: Until recently, treatment options for patients with progressive, radioactive iodine-resistant differentiated thyroid cancer (DTC) have been limited. In our clinical practice, we have begun to use sorafenib and sunitinib for patients with progressive DTC who are not able or willing to participate in clinical trials. In this paper, we describe the University of Texas M. D. Anderson Cancer Center's experience with the off-label use of these tyrosine kinase inhibitors for DTC.

Methods: Adult patients were included if they had a diagnosis of radioactive iodine-refractory DTC, were treated with single agent sorafenib or sunitinib, and had both baseline and at least one follow-up scan for restaging purposes. All imaging data were collected, as well as the TSH-suppressed thyroglobulin (Tg) levels corresponding to each scan date. The primary endpoints were radiographic response and progression-free survival (PFS). Secondary objectives were tissue-specific radiographic responses and correlation of Tg with overall response.

Results: We identified 33 patients from our clinical database. Fifteen patients (nine women, six men) met inclusion criteria, with a median age of 61 yr (range, 38–83 yr). Eight patients had papillary and seven had follicular thyroid carcinoma. Sorafenib was used in 13 and sunitinib in two, including one patient who failed prior sorafenib therapy. All patients had evidence of progressive disease (PD) before start of therapy, with a median PFS of only 4 months. Best response in target lesions was: partial response (PR) in three (20%), stable disease (SD) in nine (60%), and PD in three (20%). Clinical benefit (PR+SD) was 80%. The sunitinib patient previously refractory to sorafenib had a 38% reduction in tumor size. The most noticeable organ-specific response was observed in lung (median change, −22%) compared to lymph nodes (median change, 0%). Pleural disease and nonirradiated bone metastases demonstrated PD. All histological subtypes had similar responses. The median PFS was 19 months. The median overall survival has not yet been reached, but at 2 yr of follow-up, overall survival is 67%. Log Tg correlated with radiographic response ($P = 0.0005$).

Conclusions: Sorafenib and sunitinib appear to be effective in patients with widely metastatic, progressive DTC, with most patients achieving SD or PR, despite having PD at baseline. The most noticeable responses occurred in the lungs in contrast with minimal changes in nodal metastases and PD in pleural and nonirradiated bone metastases, suggesting a tissue-specific response to therapy. Log Tg significantly correlated with response to treatment and therefore may have value as a surrogate marker of response. **(*J Clin Endocrinol Metab* 95: 2588–2595, 2010)**

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Abbreviations: CT, Computed tomography; DTC, differentiated thyroid cancer; HU, Hounsfield units; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFT, progression-free time; PR, partial response; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; SD, stable disease; Tg, thyroglobulin; TKI, tyrosine kinase inhibitor; TL, target lesion; VEGF, vascular endothelial growth factor.

Although the prognosis for differentiated thyroid cancer (DTC) is usually good, approximately 5% of tumors will become dedifferentiated, resulting in a more aggressive behavior such as metastasis and loss of the ability to capture iodine (1). About 10–20% of patients with DTC will develop distant metastases (2), at least half of which will not respond to conventional therapy such as radioactive iodine (RAI) and TSH suppression. Although relative survival is good for those diagnosed under age 45 with distant metastases (stage II), survival steadily declines with diagnosis after age 45 (stage IV). Long-term survival for patients presenting with stage IV thyroid cancer is about 43%, compared with 86% in those with stage I disease (3–5). In patients with RAI-resistant disease, the long-term overall survival (OS) drops to 10% (6). Conventional chemotherapy response rates are typically 25% or less, at the expense of marked toxicity (7). Until recently, the standard of care for patients with progressive, unresectable disease that is unresponsive to RAI was limited. However, the recent explosion of knowledge in tumor biology and the identification of potential biological targets, such as vascular endothelial growth factor (VEGF) (8–10) and BRAF (11–13), have led to several clinical trials with targeted therapy using various targeted agents (14–21). Two phase II trials using sorafenib for metastatic thyroid cancer, a drug that is Food and Drug Administration (FDA)-approved for hepatocellular and renal cell carcinoma, were recently published (17, 18). The promising preliminary results of these studies led us to begin using the commercially available multi-kinase inhibitors, sorafenib and sunitinib, in patients with progressive, metastatic DTC refractory to RAI, for whom clinical trials were neither available nor feasible. In fact, these drugs are now included in the practice guidelines for metastatic thyroid cancer (22). This paper discusses the University of Texas M.D. Anderson Cancer Center's experience with the off-label use of sorafenib and sunitinib in patients with metastatic DTC.

Patients and Methods

Study population and data collection

With institutional review board approval, all patients with metastatic DTC treated outside of a clinical trial with a tyrosine kinase inhibitor (TKI) from 2006 to 2008 were entered into a retrospective database. Adult patients with a diagnosis of DTC, treated with single agent sorafenib and/or sunitinib, and those who had a baseline and at least one follow-up imaging study to assess response after 3 months of therapy were included in this series. Patients with medullary and anaplastic thyroid carcinoma were excluded.

Therapy

All patients but one were treated with sorafenib 400 mg by mouth twice daily, and dose reductions were common due to toxicity. The exception was a patient who was started at 200 mg by mouth twice daily due to age and comorbidities. Of the patients treated with sunitinib, the dosing was either 50 mg by mouth once daily for 4 wk followed by 2 wk off drug, or 50 mg daily for 2 wk followed by 1 wk off drug.

Study objectives

The primary objective was to determine response and progression-free survival (PFS) in patients with DTC treated with sorafenib or sunitinib. Secondary objectives included determining whether a tissue-specific response occurred and assessing the correlation between response and thyroglobulin (Tg) levels over time.

Laboratory studies

TSH-suppressed Tg levels corresponding to each scan date were collected on all patients. Only Tg levels with corresponding negative Tg antibodies were included. Serum TSH was determined with a two-site sandwich immunoassay using direct chemiluminometric technology (ADVIA Centaur TSH-3 kit, Siemens Healthcare). Serum Tg and Tg antibodies were determined by chemiluminescent immunometric assays (Immulite 2500 Tg and Anti-Tg kits, Siemens Healthcare). *BRAF* mutation analysis was performed on patients with papillary thyroid carcinoma (PTC). DNA was extracted from formalin-fixed, paraffin-embedded tumor tissue enriched for tumor (>80% of each sample). The DNA was amplified by PCR using standard primers for *BRAF* exon 15 region. Amplified PCR products were sequenced using either pyrosequencing or dye terminator sequencing techniques evaluating for the V600E mutation.

Radiographic assessments

Computed tomography (CT) scans and neck ultrasounds were used to determine pace of change before and after treatment with sorafenib or sunitinib. RECIST 1.0 was used to determine responses (23). Target lesions (TLs) were defined as soft tissue lesions that could be accurately measured in at least one dimension with the longest diameter of at least 1 cm. As per RECIST, lesions less than 1 cm, bone lesions, leptomeningeal disease, ascites, and pleural/pericardial effusion are nonmeasureable and therefore are non-TLs. Patients with new lesions were considered to have progressive disease (PD) and were automatically assigned a value of 20% increase in overall tumor measurements. Previously irradiated tumors were not considered TLs.

Definitions

Response was defined per RECIST version 1.0 as follows: Progressive disease (PD) - at least 20% increase in sum of the total size of TLs or presence of new metastatic lesion; partial response (PR) - at least 30% decrease in sum of the total size of TLs; stable disease (SD) - any percent change between + 19% and −29% in sum of the total size of TLs; durable response - SD or PR for at least 6 months; and clinical benefit - SD plus PR.

OS was defined as the percentage of patients who were alive after they were treated with sorafenib or sunitinib. PFS was defined as the length of time during and after treatment in which a patient was living and without PD. Progression-free time (PFT) was characterized by the time interval before the imaging date immediately before the start of a TKI, in which a patient was

without PD. The term PFT was used rather than PFS, which incorporates death as an endpoint, because patients who died before they were able to start treatment would not have been included in this analysis.

Statistical considerations and definitions

Patient demographic data were summarized using descriptive statistics. The best tumor responses for individual patients, calculated as a percentage change in TLs compared with baseline, were plotted graphically ("waterfall plot"). Eight patients with SD as their best response each provided at least three measures for tumor size over the course of their disease experience. Time in months was recorded as positive or negative depending on when a patient's tumor size was measured relative to start of treatment. On the day of treatment, patients were imaged before the actual initiation of the treatment agent. Patients had their first scan within 1–2 months after starting treatment. Because a scan is not given instantaneously after receiving treatment, we assumed that tumor size does not change until at least half of the first month has elapsed; therefore, the tumor size on the day of treatment was also recorded as the first posttreatment tumor size measurement at half a month after treatment. Response profiles for each patient were provided, where a linear growth curve is used to summarize the relationship between tumor size and time, with different slopes occurring before and after treatment. A linear mixed effects model was used to compare the rate of change in tumor size (*i.e.* slopes of linear models) in centimeters per month before and after treatment.

The method of Kaplan-Meier was used to describe both OS and PFS after therapy and to provide estimates for the median time to event at respective time points. To assess patient benefit from being on therapy, the ratio of PFT before treatment to PFS was computed independently for each patient. Subsequently, a mean of the ratios was computed along with its corresponding 95% confidence interval. A ratio greater than 1 was an indication that progression-free periods were longer after therapy had been initiated.

Graphical methods (*i.e.* BLiP plots) were used to summarize the distribution of the biomarker, Tg (24). Logarithmic transformation was performed on the TSH and Tg scores. Individual response profiles for each patient were used to demonstrate graphically the correlation between radiographic response and Tg over time. Linear mixed effects models were also used to assess the effect of Tg and time on radiographic responses. All tests are two-sided. *P* values were compared with significance level of 0.05.

Results

From November 2006 to June 2008, 33 patients in the Endocrine Neoplasia Department at M. D. Anderson Cancer Center were treated with targeted therapy for their advanced DTC. Eighteen patients were excluded from the study for the following reasons: four patients had no follow-up at the M. D. Anderson Cancer Center or had no outside follow-up radiographs uploaded into the electronic medical record; 11 patients were on combination therapy or on a TKI other than sorafenib or sunitinib; two were pediatric patients; and one patient had medullary thyroid carcinoma. No patients were excluded due to death or progression within the first 3 months of therapy.

Clinical characteristics

Fifteen patients were included in this series (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). The median age was 61 yr, and 60% of patients were women. Eight of 15 patients (53%) had a diagnosis of PTC, compared with seven of 15 (47%) with follicular thyroid carcinoma. Of the patients with follicular thyroid carcinoma, two had Hurthle cell (oxyphilic) subtypes. Five patients had poorly differentiated tumors. Lymph nodes (neck and hilar nodes) were the most common location of metastasis (73%), followed by lung parenchyma (66%), bone (27%), and pleura (13%). Most patients had more than one location of metastatic disease. Two of the patients with bone metastases and two with lung metastases had received external beam radiation, and therefore these lesions were not included for response assessments. All patients had information available regarding RAI avidity. Fourteen of these had nonavid disease. One patient's disease retained RAI avidity, but the patient had received over 1000 mCi of RAI and was thus considered refractory to this therapy. Fourteen of 15 patients had an increase in tumor size of at least 20% before starting on sorafenib or sunitinib and were considered to have PD per RECIST. One patient did not have pretreatment imaging available, but she had developed a malignant pleural effusion before therapy and therefore was considered to have PD. Sorafenib was given to all 15 patients initially. Two patients discontinued sorafenib and resumed therapy with sunitinib. One of the patients had previously been treated on a phase II clinical trial with sorafenib but discontinued sorafenib due to PD. Another patient had a grade 3 hand-foot skin reaction from sorafenib and preferred to discontinue the drug.

Reasons for off-label therapy

Four patients were treated off trial by a local oncologist due to the patients' inability to travel to the M. D. Anderson Cancer Center or a clinical trial site closer to their home. Three patients did not qualify for a phase I trial that was available at the time: one due to progression on sorafenib, one due to problems with insurance coverage, and another due to locally metastatic disease (patient refused surgery for neck adenopathy). One patient refused to participate in a clinical trial, and in seven other cases, the reason for off-label treatment was not specified in the medical records.

Radiographic responses

Waterfall plots were constructed for best response in TLs (Fig. 1A). PR was seen in three of 15 patients (20%), SD in nine of 15 (60%), and PD in three of 15 (20%). There were no complete responses. Durable responses were seen in 10 of 15 (66%). Clinical benefit was seen in 80% of patients. All

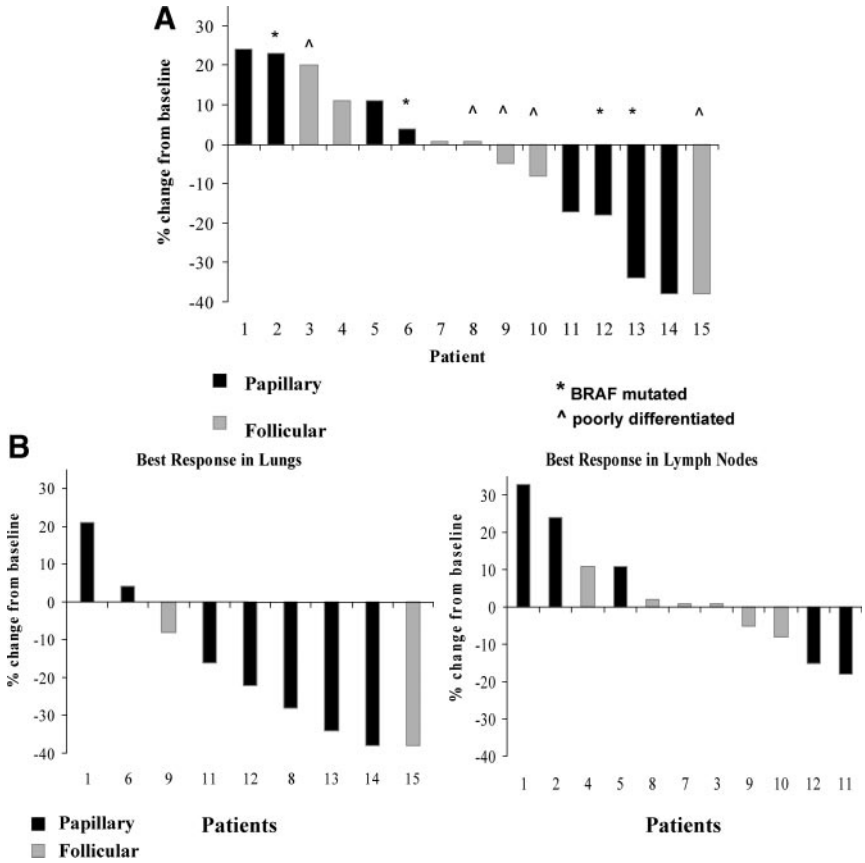

FIG. 1. A, Waterfall plot of best responses by RECIST. All patients had progression before starting on drug. Best response was PR of three of 15 (20%), SD of nine of 15 (60%), and PD of three of 15 (20%); clinical benefit (PR+SD) = 80%. Durable responses (≥6 months SD or PR) were seen in 10 of 15 (66%). All histological types had similar responses. Seven of eight patients with PTC had BRAF testing (tissue not available on patient 13). Four patients, indicated by *asterisks* (*) on graph, had a V600E mutation. Five patients had poorly differentiated tumors. B, Waterfall plots for best response by RECIST in lung parenchyma *vs.* lymph nodes (neck, hilar, and medistinal nodes) TLs. There was a median decrease in size of lung lesions of 16% *vs.* a median increase in size of 3% in the lymph nodes.

histological types had similar responses, including Hurthle cell and poorly differentiated tumors. The patient who progressed on a phase II sorafenib trial had a PR (decrease of 38% in TLs) on sunitinib (patient 14 on Fig. 1A).

Waterfall plots were then constructed for response in TLs by organ site. Responses in the lungs (median change, −22%; range, −38 to 21%) were more robust than in lymph nodes (median change, 0%; range, −18 to 33%; Fig. 1B; Wilcoxon rank sum test P value = 0.02). Two patients with nonirradiated bone metastases had rapidly progressive disease in those lesions and ultimately died from thyroid cancer (patients 3 and 10 on Fig. 1A). However, both patients had SD in TLs (lymph nodes). One of these patients also had a dramatic decrease in the lymph node enhancement as measured by Hounsfield units (HU) on CT (Fig. 2). This patient had a decrease from an average of 72 to 13 HU, with minimal change in lymph node size. Two patients who received radiation to bone metastases had SD in those lesions. In addition, two patients developed new, progressive bony metastases while on treatment. Another patient developed a new liver metastasis while on sorafenib. Both patients with pleural metastases had PD in the pleura.

All tumor measurements (before and after therapy) of eight patients with a radiographic response of SD after treatment with a TKI were plotted (Fig. 3). The trend line (*bold dashed line*) represents the average tumor measurements of these patients. The slope or the average change in tumor size before treatment was 0.44 cm/month, and after treatment, it was −0.04 cm/month. The difference between slopes before and after treatment of approximately 0.48 cm/month was statistically significant (P = 0.035), suggesting that stabilization of disease in these patients is a clinically valid endpoint.

BRAF mutation analysis

Seven of the eight patients with PTC had BRAF testing performed (tissue not available on patient 13). Of these seven patients, four patients (57%, indicated on Fig. 1A) had a V600E mutation detected. Of the patients with *BRAF* V600E mutations, three had SD and one had PD as their best response. Of those without *BRAF* mutations, one had PR, two had SD, and one had PD as their best response.

Survival

PFS after starting sorafenib or sunitinib was plotted on a Kaplan-Meier curve (Fig. 4, *blue line*). The median PFS was 19 months. The mean ratio of PFT (before treatment was started) to PFS (after treatment was started) was approximately 3.0 ± 2.2 SD, indicating that on average patients experienced a PFT that was three times longer (95% confidence interval, 1.7 to 4.2) after treatment.

OS is shown on Fig. 4 (*red line*). The median OS has not been reached, but at 2 yr of follow-up, OS is 67%.

Correlation of log Tg with tumor measurements

BLiP plots were generated for baseline and all follow-up logarithmic Tg levels and plotted with tumor measurements over time for each patient (data not shown). Log Tg significantly correlated with radiographic response (Supplemental Fig. 1) (P = 0.0005).

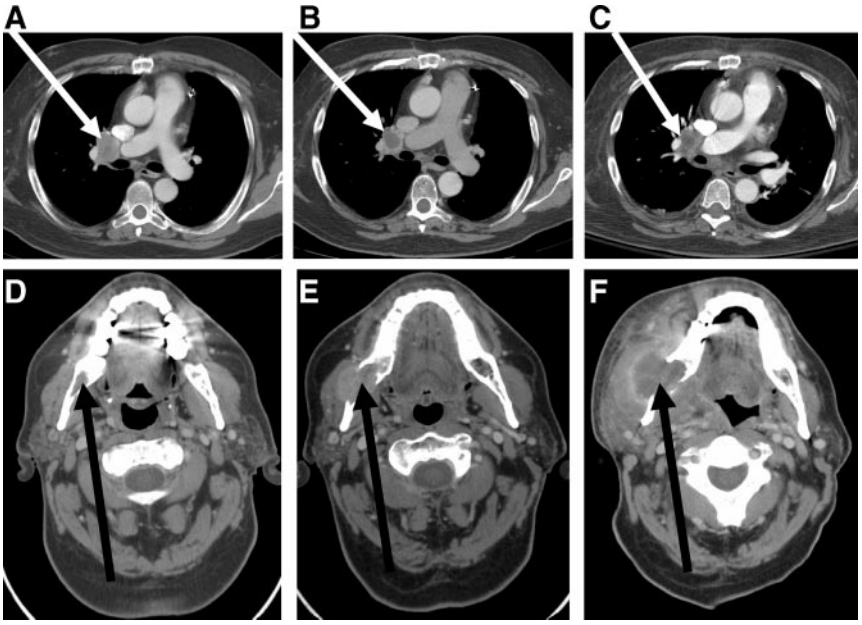

FIG. 2. A, CT scan of the chest showing a 3.8-cm metastatic disease in a hilar lymph node (indicated by *white arrow*) at baseline (before treatment with sorafenib). B, CT scan of the chest of the same patient showing necrosis of the hilar lymph node (indicated by *white arrow*) after 2 months of treatment with sorafenib. The node now measures 3.4 cm, and the HU decreased from an average of 72 HU at baseline to 13 HU after treatment. C, CT scan of the chest with a 3.7 cm hilar node (indicated by *white arrow*) after 5 months of therapy. D, CT scan of the neck showing a small metastasis to the right mandible (indicated by *black arrow*) at baseline. E and F, CT scan of the neck showing progression of the mandibular metastasis (indicated by *black arrow*) after 2 months of treatment with sorafenib (E) and after 5 months of sorafenib (F).

Adverse events

The most common adverse event was diarrhea (53%), followed by hypertension (33%), fatigue (20%), and weight loss/anorexia (20%). Two patients (13%) developed pneumonia, and one patient experienced a grade 4 hypocalcemic event (Supplemental Table 1). This patient had a history of primary hypoparathyroidism due to surgery but had stable calcium levels on calcitriol and calcium supplements before starting sorafenib. The patient also had diarrhea and weight loss while on sorafenib, suggesting that malabsorption of her calcitriol and calcium may have led to the hypocalcemia.

Several dermatological changes were seen in our series of patients (Supplemental Table 1). Hand-foot skin reaction was the most common dermatological adverse event (60%), followed by maculopapular skin rash (33%). Four of the 15 patients (27%) developed squamous cell carcinoma of the skin, of which two were the keratoacanthoma type. All of these patients had received sorafenib.

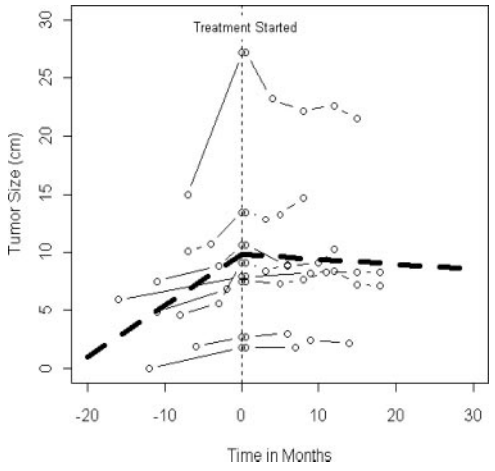

FIG. 3. The pretreatment and posttreatment tumor measurements of eight patients with SD as the best response was plotted for each patient. One patient did not have pretreatment imaging available for exact measurements and therefore is not included in this analysis. The *open circles* represent the size and timing of the patient's imaging. The trend line in *black* is a moving average of tumor sizes with a window of 10 months before and after treatment. The slope of the trend line significantly flattened after treatment with sorafenib or sunitinib ($P = 0.035$).

Discussion

Sorafenib and sunitinib are FDA-approved drugs for gastrointestinal stromal tumor (sunitinib), unresectable hepatocellular carcinoma (sorafenib), and advanced renal cell carcinoma (sorafenib and sunitinib). Both are multi-kinase inhibitors that inhibit VEGF receptors 2 and 3, platelet-derived growth factor receptor, Flt-3, c-kit, and RET. In addition, sorafenib inhibits wild-type and mutant BRAF V600E. Gain-of-function mutations in the BRAF oncogene are the most frequent genetic alterations found in PTC, occurring in

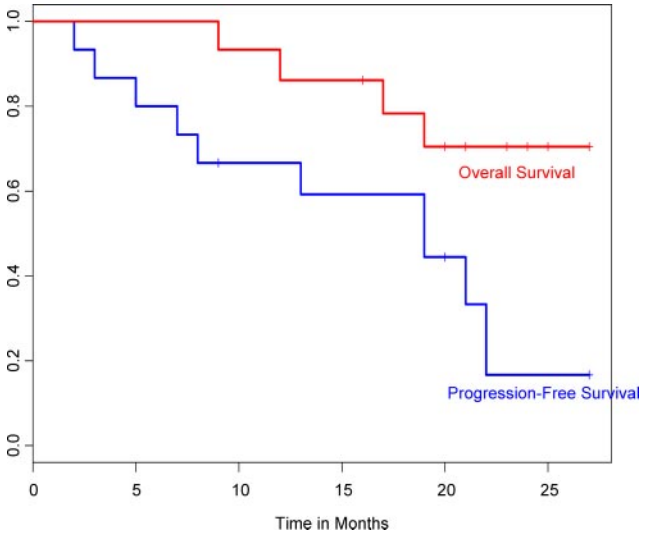

FIG. 4. Kaplan-Meier analysis of PFS (*blue line*) and OS (*red line*). The median PFS was 19 months. The median OS has not been reached, but at 24 months, OS was 67%.

approximately 45–70% of these tumors in adults (11, 12, 25). Also, overexpression of VEGF and other growth factors is commonly found in tumors of thyroid origin, particularly those bearing *BRAF* mutations (8–10, 26). These findings provided the rationale for using sorafenib and sunitinib in patients with metastatic, non-RAI-avid thyroid cancer.

Two phase II clinical trials with sorafenib have been reported and have shown efficacy in metastatic thyroid cancer (17, 18). Gupta-Abramson *et al.* (17) found a PR rate of 32%, SD rate of 68%, and no PD, with a median PFS of 21 months in patients with DTC. In that trial, 22 patients had DTC and of those, 68% had a diagnosis of PTC. In the study from Ohio State by Kloos *et al.* (18), there were 46 evaluable patients with DTC, of which 78% had a diagnosis of PTC. Response rates were 13% PR, 74% SD, and 13% PD. Median PFS was approximately 15 months for patients with PTC. Two phase II sunitinib trials have been reported at national meetings, but only one reported response rate in DTC separately. Of 31 patients who completed two cycles, 13% had PR, 68% SD, 10% PD, and 13% were not evaluable. PFS was not reported (27).

Our study describes the treatment of metastatic, progressive DTC with the TKIs sunitinib and sorafenib at the M. D. Anderson Cancer Center. The results found here with a partial remission rate of 20%, durable response rate of 66%, and a clinical benefit rate of 80% are similar to that in the published phase II trials evaluating sorafenib and sunitinib in thyroid cancer. Based on the observation that patients had a clinical response to sunitinib despite progression on sorafenib, progression during therapy with one TKI should not exclude use of another TKI. This paper also raises important questions about what appears to be a differential response of metastases in different tissues to the same drug in the same patient. Metastases in lung tend to respond better to this therapy. Lymph nodes respond, but less robustly. One of the most interesting findings was the refractory nature of the bony metastases. Although small in number, the patients who had irradiated bony metastases before initiation of targeted therapy had SD in bone, and those who did not had rapid progression despite concomitant good response in their lung metastases. This would perhaps suggest that in patients with progressing bony lesions, external beam radiation should be considered before treatment with TKIs. Pleural metastases also tended to progress while on TKIs. This variability of response by tissue site seen in these patients needs to be validated in larger studies. Whether these differences in response are seen due to differential expressions and different inhibitions of various VEGF receptors or whether this is due to a non-VEGF-mediated mechanism, such as differences in drug levels in tissues, remains to be determined. A randomized trial with the *a priori* hypothesis of the differential effects on various tissue responses may need to be done to answer this.

Although not a randomized prospective clinical trial, our study is the first to show that, by using each patient as his own control, targeted therapy with sorafenib or sunitinib appears to prolong PFT. This is a significant and important finding considering that nearly half of the patients had aggressive histologies such as Hurthle cell and poorly DTC. Sixty percent of the patients developed SD, a clinically relevant endpoint considering that all patients had progressed before receiving the drug. We further showed that, in those patients in whom SD was their best response, the rate of the slope of change in progression is statistically significant, indicating that the disease is truly slowing down in this subset of patients.

Limitations to this study include its retrospective nature and the small sample size. Given that some patients were treated by their local physicians, less information was available to us. For example, performance status and grading of adverse events were not always reported. Our observations regarding pretreatment PFT and posttreatment PFS are also limited by the lack of standardized frequency of response assessment. However, despite these limitations, our PFS is similar to what has been reported in clinical trials and substantiate the value of these treatments in routine care.

We observed the expected adverse events reported for sorafenib and sunitinib (28, 29). However, it is interesting to note that one patient had a grade 4 hypocalcemic event on sorafenib despite taking her usual calcitriol and calcium supplements for primary hypoparathyroidism. The patient also had diarrhea and weight loss while on sorafenib, suggesting that malabsorption of her calcitriol and calcium may have led to the hypocalcemia. Treatment with sorafenib and sunitinib is fairly well tolerated in patients with progressive metastatic nonradioiodine-avid DTC. Although these drugs have a similar PR rate to some cytotoxic chemotherapies, their adverse event rate is lower, they are more convenient (due to the oral route of administration), and they seem to be accepted well by patients.

Other interesting observations seen here include the development of squamous cell carcinomas after sorafenib therapy. Although this is a small sample size, frequency seen here may be higher than that described in other tumor types treated with sorafenib and with other drugs that inhibit the BRAF pathway (15, 21, 30–34). Further studies will be needed to elucidate whether the development of these skin lesions is due to BRAF inhibition, immune mechanisms, or other unknown mechanisms. The development of a new primary cancer after therapy raises the

need for appropriate skin cancer screening therapy before and during treatment with these agents.

In summary, sorafenib and sunitinib appear to be useful agents in patients with advanced, progressive DTC and demonstrate a fairly well-tolerated toxicity profile. These drugs appear to prolong the PFS, even in those who develop SD as their best response. The differential response in various metastatic sites (lungs, bones, lymph nodes, and pleura) will need to be further elucidated.

The development of skin cancers together with the long-term use of these drugs with their associated chronic adverse events are potential limitations to the use of TKIs. As with any biological agents or chemotherapeutic agents, the prescribers of these drugs need to be well versed in the management of these toxicities. However, better agents or combinations of agents are needed to decrease tumor burden, improve survival, and not adversely affect patients' quality of life.

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References

1. **Antonelli A, Fallahi P, Ferrari SM, Carpi A, Berti P, Materazzi G, Minuto M, Guastalli M, Miccoli P** 2008 Dedifferentiated thyroid cancer: a therapeutic challenge. Biomed Pharmacother 62:559–563
2. **Shaha AR, Shah JP, Loree TR** 1996 Patterns of nodal and distant metastasis based on histologic varieties in differentiated carcinoma of the thyroid. Am J Surg 172:692–694
3. **Jonklaas J, Sarlis NJ, Litofsky D, Ain KB, Bigos ST, Brierley JD, Cooper DS, Haugen BR, Ladenson PW, Magner J, Robbins J, Ross DS, Skarulis M, Maxon HR, Sherman SI** 2006 Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 16:1229–1242
4. **Sampson E, Brierley JD, Le LW, Rotstein L, Tsang RW** 2007 Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. Cancer 110:1451–1456
5. **Shaha AR, Shah JP, Loree TR** 1997 Differentiated thyroid cancer presenting initially with distant metastasis. Am J Surg 174:474–476
6. **Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, Caillou B, Ricard M, Lumbroso JD, De Vathaire F, Schlumberger M** 2006 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 91:2892–2899
7. **Sherman SI** 2008 Early clinical studies of novel therapies for thyroid cancers. Endocrinol Metab Clin North Am 37:511–524, xi
8. **Lin JD, Chao TC** 2005 Vascular endothelial growth factor in thyroid cancers. Cancer Biother Radiopharm 20:648–661
9. **Tuttle RM, Fleisher M, Francis GL, Robbins RJ** 2002 Serum vascular endothelial growth factor levels are elevated in metastatic differentiated thyroid cancer but not increased by short-term TSH stimulation. J Clin Endocrinol Metab 87:1737–1742
10. **Vieira JM, Santos SC, Espadinha C, Correia I, Vag T, Casalou C, Cavaco BM, Catarino AL, Dias S, Leite V** 2005 Expression of vascular endothelial growth factor (VEGF) and its receptors in thyroid carcinomas of follicular origin: a potential autocrine loop. Eur J Endocrinol 153:701–709
11. **Cohen Y, Xing M, Mambo E, Guo Z, Wu G, Trink B, Beller U, Westra WH, Ladenson PW, Sidransky D** 2003 BRAF mutation in papillary thyroid carcinoma. J Natl Cancer Inst 95:625–627
12. **Henderson YC, Shellenberger TD, Williams MD, El-Naggar AK, Fredrick MJ, Cieply KM, Clayman GL** 2009 High rate of BRAF and RET/PTC dual mutations associated with recurrent papillary thyroid carcinoma. Clin Cancer Res 15:485–491
13. **Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE, Fagin JA** 2003 High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. Cancer Res 63:1454–1457
14. **Cohen EE, Rosen LS, Vokes EE, Kies MS, Forastiere AA, Worden FP, Kane MA, Sherman E, Kim S, Bycott P, Tortorici M, Shalinsky DR, Liau KF, Cohen RB** 2008 Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. J Clin Oncol 26:4708–4713
15. **Schwartz GK, Robertson S, Shen A, Wang E, Pace L, Dials H, Mendelson D, Shannon P, Gordon M** 2009 A phase I study of XL281, a selective oral RAF kinase inhibitor, in patients (Pts) with advanced solid tumors. J Clin Oncol Vol. 27, no. 15S, Abstract 3513
16. **Dawson SJ, Conus NM, Toner GC, Raleigh JM, Hicks RJ, McArthur G, Rischin D** 2008 Sustained clinical responses to tyrosine kinase inhibitor sunitinib in thyroid carcinoma. Anticancer Drugs 19:547–552
17. **Gupta-Abramson V, Troxel AB, Nellore A, Puttaswamy K, Redlinger M, Ransone K, Mandel SJ, Flaherty KT, Loevner LA, O'Dwyer PJ, Brose MS** 2008 Phase II trial of sorafenib in advanced thyroid cancer. J Clin Oncol 26:4714–4719
18. **Kloos RT, Ringel MD, Knopp MV, Hall NC, King M, Stevens R, Liang J, Wakely Jr PE, Vasko VV, Saji M, Rittenberry J, Wei L, Arbogast D, Collamore M, Wright JJ, Grever M, Shah MH** 2009 Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Oncol 27:1675–1684
19. **Sherman SI, Wirth LJ, Droz JP, Hofmann M, Bastholt L, Martins RG, Licitra L, Eschenberg MJ, Sun YN, Juan T, Stepan DE, Schlumberger MJ** 2008 Motesanib diphosphate in progressive differentiated thyroid cancer. N Engl J Med 359:31–42
20. **Wakeling AE, Guy SP, Woodburn JR, Ashton SE, Curry BJ, Barker AJ, Gibson KH** 2002 ZD1839 (Iressa): an orally active inhibitor of epidermal growth factor signaling with potential for cancer therapy. Cancer Res 62:5749–5754
21. **Flaherty K, Puzanov I, Sosman J, Kim K, Ribas A, McArthur G, Lee RJ, Grippo JF, Nolop K, Chapman P** 2009 Phase I study of PLX4032: proof of concept for V600E BRAF mutation as a therapeutic target in human cancer. J Clin Oncol Vol. 27, no. 15S, Abstract 9000
22. **Sherman SI, Tuttle RM, Ball DW, Byrd D, Clark OH, Daniels GH, Dilawari RA, Doherty GM, Ehya H, Farrar WB, Haddad RI, Kandeel F, Kloos RT, Kopp P, Lamonica DM, Loree TR, Lydiatt WM, McCaffrey J, Olson JA, Parks L, Ridge JA, Shah JP, Sturgeon C, Waguespack SG, Wang TN, Wirth LJ** 2009 NCCN practice guidelines in oncology: thyroid carcinoma. J Natl Compr Canc Netw 1.2009
23. **Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS,**

Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG 2000 New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216

24. **Lee JJ, Tu ZN** 1997 A versatile one-dimensional distribution plot: the BLiP plot. The American Statistician 51:353–358
25. **Riesco-Eizaguirre G, Gutiérrez-Martínez P, García-Cabezas MA, Nistal M, Santisteban P** 2006 The oncogene BRAF V600E is associated with a high risk of recurrence and less differentiated papillary thyroid carcinoma due to the impairment of Na+/I− targeting to the membrane. Endocr Relat Cancer 13:257–269
26. **Jo YS, Li S, Song JH, Kwon KH, Lee JC, Rha SY, Lee HJ, Sul JY, Kweon GR, Ro HK, Kim JM, Shong M** 2006 Influence of the BRAF V600E mutation on expression of vascular endothelial growth factor in papillary thyroid cancer. J Clin Endocrinol Metab 91:3667–3670
27. **Cohen EE, Needle BM, Cullen KJ, Wong SJ, Wade JL, Ivy SP, Villaflor VM, Seiwert TY, Nichols K, Vokes EE** 2008 Phase 2 study of sunitinib in refractory thyroid cancer. J Clin Oncol Vol. 26, no. 15S, Abstract 6025
28. **Package insert** 2010 Sunitinib (Sutent). New York: Pfizer Inc.
29. **Package insert** 2009 Sorafenib (Nexavar). Emeryville, CA: Bayer HealthCare and Onyx Pharmaceuticals Inc.
30. **Arnault JP, Wechsler J, Escudier B, Spatz A, Tomasic G, Sibaud V, Aractingi S, Grange JD, Poirier-Colame V, Malka D, Soria JC, Mateus C, Robert C** 2009 Keratoacanthomas and squamous cell carcinomas in patients receiving sorafenib. J Clin Oncol 27:e59–61
31. **Dubauskas Z, Kunishige J, Prieto VG, Jonasch E, Hwu P, Tannir NM** 2009 Cutaneous squamous cell carcinoma and inflammation of actinic keratoses associated with sorafenib. Clin Genitourin Cancer 7:20–23
32. **Hong DS, Reddy SB, Prieto VG, Wright JJ, Tannir NM, Cohen PR, Diwan AH, Evans HL, Kurzrock R** 2008 Multiple squamous cell carcinomas of the skin after therapy with sorafenib combined with tipifarnib. Arch Dermatol 144:779–782
33. **Kong HH, Turner ML** 2009 Array of cutaneous adverse effects associated with sorafenib. J Am Acad Dermatol 61:360–361
34. **Kong HH, Cowen EW, Azad NS, Dahut W, Gutierrez M, Turner ML** 2007 Keratoacanthomas associated with sorafenib therapy. J Am Acad Dermatol 56:171–172