Sorafenib and sunitinib are effective in patients with widely progressive metastatic DTC

Cabanillas ME, Waguespack SG, Bronstein Y, Williams MD, Feng L, Hernandez M, Lopez A, Sherman SI, Busaidy NL. Treatment with tyrosine kinase inhibitors for patients with differentiated thyroid cancer: the M. D. Anderson experience. J Clin Endocrinol Metab 2010. jc.2009-1923 [pii];10.1210/jc.2009-1923 [doi]

SUMMARY

BACKGROUND

Patients with progressive differentiated thyroid cancer (DTC) that is refractory to standard therapy, including surgery, radioiodine, and external-beam radiotherapy (EBRT) , now have the option of being treated with novel therapies such as tyrosine kinase inhibitors (TKIs) that may be especially useful for patients with radioactive iodine-resistant tumors. In this study, patients with progressive DTC were treated with sorafenib and sunitinib because they were either unable or unwilling to participate in clinical trials or the trials were not feasible for the patient for various reasons.

METHODS

All patients with refractory metastatic DTC who were treated with TKI outside a clinical trial were entered into a retrospective database from 2006 through 2008. Adult patients were treated with a single agent, sorafenib, with or without sunitinib. Patients who had a baseline and at least one follow-up imaging study to assess the response to therapy after 3 months were included in the study. Excluded from the study were patients with medullary thyroid cancer or anaplastic thyroid cancer.

Abbreviations of Outcomes OS = overall survival; PD = progressive disease; PFS = progression-free survival; PFT = progression-free time; PR = partial response; SD = stable disease; TL = target lesion.

Study Objectives

The objective of this study was to determine the response and PFS in patients with DTC treated with sorafenib or sunitinib. Secondary objectives were to determine whether a tissue-specific response occurred and to assess the correlation between response and serum thyroglobulin (Tg) levels over time.

Laboratory Assessments

Thyrotropin-suppressed serum Tg levels at each scan date were collected on all patients without serum Tg antibodies. BRAF mutation analysis was performed on DNA extracted from formalin-fixed paraffin-embedded tumor tissue in patients with papillary thyroid carcinoma (PTC) that was evaluated for V600E BRAF mutation.

Radiographic Assessments

Computed tomographic (CT) scans and neck ultrasonography were used to determine the rate of tumor change before and after treatment with sorafenib or sunitinib. Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 is a set of published rules that define patients with cancer who improve with at least a 20% response in the total size of TLs, or stay the same (stabilize) or worsen (progression) during treatment.

Therapy

All patients but one were treated twice daily with 400 mg of sorafenib. Dose reductions were common as a result of drug toxicity, with the exception of one patient who was started at 200 mg twice daily because of age and comorbidities. The

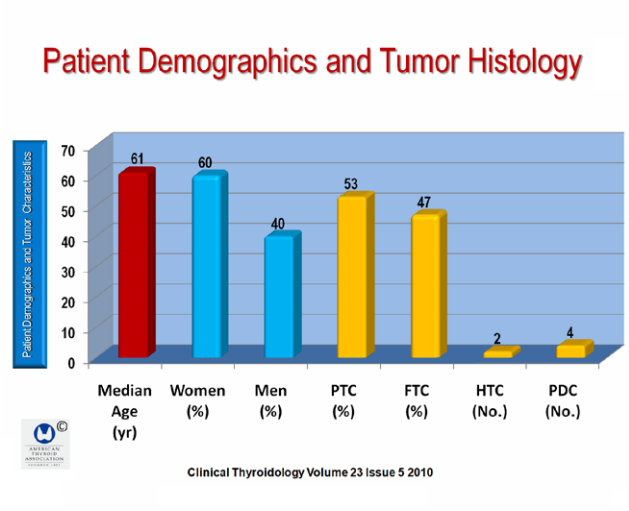

Figure 1A. This figure shows the patient demographics and tumor histology in the study cohort. HTC = Hürthle cell cancer; PDC =poorly differentiated cancer.

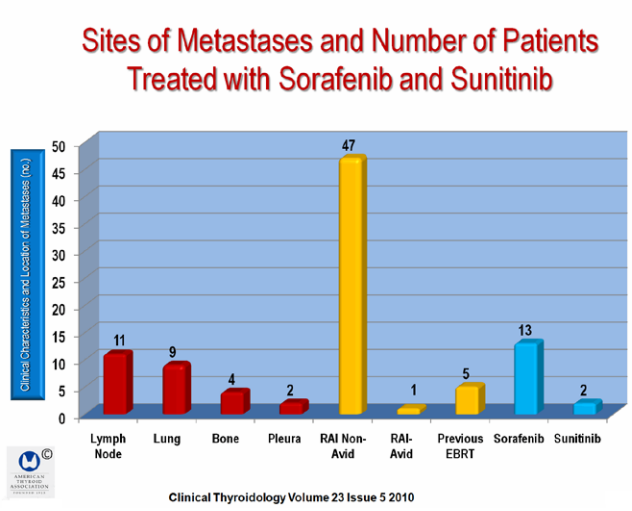

Figure 1B. This figure shows the sites of metastases and the number of patients treated with sorafenib and sunitinib. EBRT = external-beam radiotherapy; RAI = radioactive iodine.

patients treated with sunitinib with either 50 mg by mouth once daily for 4 weeks, followed by 2 weeks off drug, or 50 mg daily for 2 weeks followed by 1 week off drug.

Clinical Characteristics of the Patients (Figure 1A and 1B)

A total of 15 patients, 9 women (60%) and 6 men (40%), met the inclusion criteria for the study. The median age was 61 years, 8 (53%) had PTC, 7 (47%) had follicular thyroid cancer, 2 of whom had Hürthle-cell subtypes, and 5 had poorly differentiated tumors. The most common location of metastases (73%) were in the lung, followed by bone (27%) and pleura (13%), and most had more than one tumor location (Figure 1).

Tumor Assessments

Two patients with bone metastases and two with lung metastases had received EBRT; they were not included in the response assessments. Fourteen patients had nonavid ^{131}I tumors; however, one had tumor that retained ^{131}I avidity but had been treated with over 1000 mCi of ^{131}I and was accordingly considered to have nonavid tumor. Fourteen of these 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. Another patient had a malignant pleural effusion before therapy and was considered to have PD. All 15 patients initially were treated with sorafenib, 2 of whom discontinued the drug and resumed sunitinib therapy. One patient had been treated previously but discontinued sorafenib due to PD, and another had a grade 3 hand–foot skin reaction from sorafenib and elected to discontinue the drug.

Radiographic Responses

CT scans and neck ultrasounds were used to determine the pace of change before and after treatment with sorafenib or sunitinib. RECIST was used to determine the responses. TLs were defined as soft-tissue lesions that could be accurately measured in at lease one dimension with the longest diameter of at least 1 cm. Non-TLs were soft-tissue lesions that could not be accurately measured in at least one dimension. Patients with new lesions were considered to have PD and were assigned a value of a 20% increase in tumor measurement.

RESULTS

From November 2006 through June 2008, a total of 33 patients were treated with targeted therapy for their advanced DTC; 18 were excluded from the study for a variety of reasons: 4 had no follow-up or had outside follow-up radiographs in the electronic medical record, and 11 were on combination therapy or on a TKI other than sorafenib or sunitinib. Two were pediatric patients, and one had medullary thyroid carcinoma. Within the first 3 months of therapy, no patients were excluded from the study because of death or PD.

Radiographic Responses (Figures 2, 3, and 4)

Waterfall plots were constructed for the best response in TLs (Figure 2). PR was seen in of 3 of 15 patients (20%), SD in 9 of 15 patients (60%), and PD in 3 of 15 patients (20%). There were no complete responses. Durable responses were seen in 10 of 15 patients (60%), and PD in 3 of 15 patients (20%). In all, clinical benefit was seen in 80% of the patients. The response

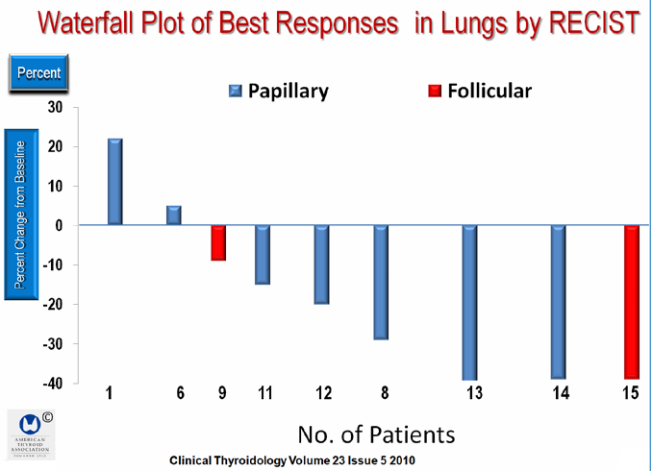

Figure 3. This figure shows the best responses in lung metastases by RECIST criteria.

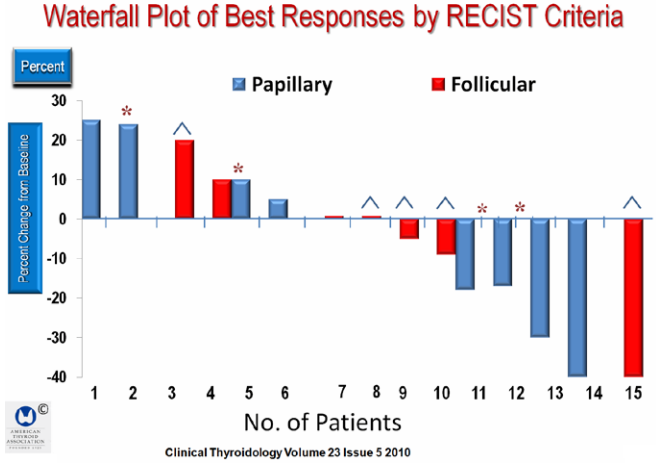

Figure 2. This waterfall plot shows the best responses by RECIST criteria.

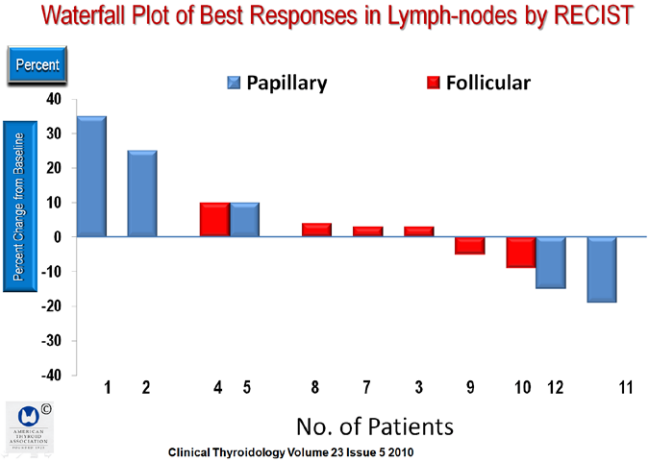

Figure 4. This figure shows the best responses in lymph-node metastases by RECIST criteria.

was similar in all histologic types, including Hürthle-cell and poorly differentiated tumors. The patient who had PD on a phase 2 sorafenib trial had a PR with a decrease of 39% in TLs. Waterfall plots were constructed for response in TLs by organ site.

Lung responses (–22%; range, –38 to 21%) were more robust than those in lymph-node metastases (median change, 0%; range, -18 to 33%) (Figure 3). Two patients with nonirradiated bone metastases had rapidly progressive disease and died from thyroid cancer. A dramatic response to lymph-node metastases occurred in one of these patients, with an average of 72 to 13 Hounsfield units on CT, with minimal change in lymph-node size. Two patients who were treated with EBRT had SD in those lesions, and two had new, progressive bony metastases while on treatment. Another had new liver metastases while on sorafenib, and both patients with pleural metastases had PD in the pleura. Eight patients with a radiographic response of stable disease after treatment with a TKI were plotted (Figure 4). The change of tumor size was 0.44 cm/mo before treatment and approximately 0.48 cm/mo after treatment (P = 0.035), which suggests that stabilization of tumor in these patients is a clinically valid end point.

BRAF Mutation Analysis

Seven of the 8 patients with PTC had BRAF testing; 4 (57%) had a V600E mutation, 3 had SD, and 1 had PD as the best response. Among the 5 patients who did not have BRAF mutations, 2 had a PR, 2 had SD, and 1 had PD as their best response.

Survival Rates

PFS after starting sorafenib or sunitinib was plotted on a Kaplan–Meier curve. The median PFT was 19 months. The mean (±SD) ratio of PFT (before treatment was started) was approximately 3.0±2.2, demonstrating that, on average, patients experienced a PFT that was three times longer (95% confidence interval, 1.7 to 4.2 after treatment). Although the median OS was not reached, 2-year follow-up OS was 67%.

Correlation of Tg with Tumor Measurements

The log Tg correlated significantly with the radiographic response (P = 0.005)

Adverse Events (Figures 5 and 6)

The most common adverse events were diarrhea (53%), hypertension (33%), and weight loss/anorexia (20%). The most common dermatologic complication was hand–foot–skin syndrome (60%), followed by maculopapular skin rash (33%) and 4 of 15 patients had squamous-cell carcinoma of the skin, all after sorafenib therapy. The nondermatologic and dermatologic adverse events are shown in Figures 5 and 6.

CONCLUSIONS

Sorafenib and sunitinib are effective in patients with widely progressive metastatic DTC. Most patients achieved stable disease or a partial response, despite having progressive disease at baseline before TKI therapy.

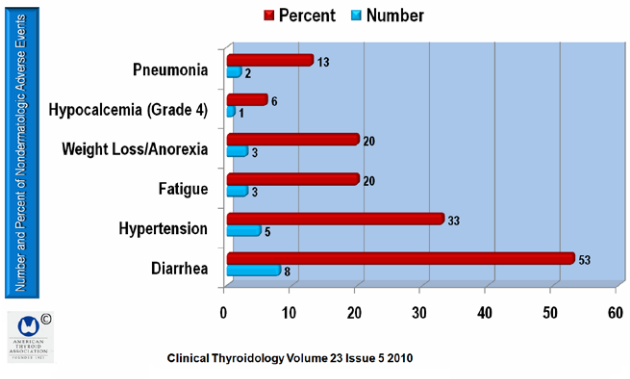

Figure 5. This figure shows the nondermatologic adverse events.

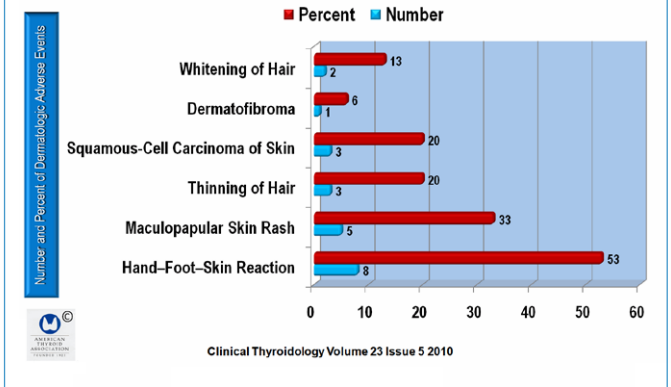

Figure 6. This figure shows the dermatologic adverse events.

COMMENTARY

This is an important study that describes the off-label use of sorafenib and sunitinib for patients with progressive metastatic DTC not amenable to radioiodine or other therapy. Sorafenib and sunitinib are approved by the Food and Drug Administration for use in advanced renal-cell carcinoma, hepatocellular carcinoma (sorafenib), and gastrointestinal stromal tumor (sunitinib). Both are TKIs, that inhibit vascular endothelial growth factor (VEGF) receptors 2 and 3, platelet-derived growth factor, Flt-3 c-kit, and RET. Sorafenib also inhibits wild-type and mutant BRAF V600E, which are the most frequent genetic alterations found in PTC, affecting approximately 45 to 70% of these tumors in adults (1). In addition, overexpression of VEGF and other growth factors is often found in thyroid tumors, particularly BRAF mutations. The authors mention that these findings provide the rationale for using sorafenib and sunitinib in patients with metastatic non–radioiodine ^{131}I-avid thyroid cancer.

Two phase II studies, one by Gupta-Abramson (2) and the other by Kloos et al. (3) have shown efficacy in treating metastatic thyroid cancer. The Ohio State study by Kloos et al. had 46 evaluable patients with PTC , in whom 78% had a diagnosis of PTC. The response rates were 13% PR and 74% SD, and the median PFS was approximately 15 months. The study by Gupta-Abramson found a PR rate of 32%, SD rate of 68%, and no PD, with a median PFS of 21 months in patients with DTC.

The study by Cabanillas et al. found a PR rate of 20%, a durable response rate of 66%, and a clinical benefit rate of 80%, which is similar to the Gupta-Abramson and Kloos studies.

Although there were only 15 patients in the Cabanillas study, the authors point out what seems to be a differential response of metastases to the same drug in the same patients in different tumor tissues. One of the other important observations by Cabanillas was that patients had a clinical response to sunitinib despite progression on sorafenib, suggesting that treatment failure with one TKI should not exclude the use of another TKI.

The adverse events encountered in this study are consistent with previous reports for sorafenib and sunitinib (2,4,5). Skin cancers, weight loss, hypertension, and diarrhea were some of the important adverse events with sorafenib and sunitinib in this study. One woman with primary hypoparathyroidism had a novel complication from sorafenib; grade 4 hypocalcemia developed despite treatment with calcitriol and calcium supplements, which seems to be a new observation. Also, 3 patients had squamous-cell skin cancer after sorafenib, which has been described in a small number of patients (6). Still, among the small Cabanillas cohort, 20% had squamous-cell skin cancer, suggesting that this might be more common than described. The authors of this study concluded that despite the number of adverse events, their patients seemed to accept these problems.

The authors suggest that there are several limitations to this study, including its retrospective nature, and the small sample size, and since some of the patients were treated by their local physicians, less information was available to the authors.

Nonetheless, this study demonstrates that sorafenib and sunitinib are useful agents in patients with advanced progressive disease, and the toxicity profiles of the drugs were reasonably well tolerated by the patients. Sorafenib prolonged the PFS in this cohort, even the patients in whom SD developed as their best response. Still, the authors point out that the development of skin cancers with the long-term use of sorafenib and sunitinib are potential limitations to the use of TKIs. Moreover, the authors provide the caveat that physicians need to be well versed in the management of the toxicities of these drugs to provide optimal care.

— Ernest L. Mazzaferri, MD, MACP

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