Efficacy and Tolerability of Different Starting Doses of Sorafenib in Patients With Differentiated Thyroid Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Time to failure • Overall survival • Dose reduction • Drug interruptions • Adverse events

ABSTRACT

Background. Sorafenib has proven efficacy in advanced differentiated thyroid cancer (DTC), but many patients must reduce the dose or discontinue treatment because of toxicity. The tolerability and efficacy of lower starting doses of sorafenib for DTC remain largely unstudied.

Methods. We retrospectively examined overall survival, time to treatment failure, time to progression, discontinuation rates, and dose-reduction and interruption rates in patients with metastatic DTC treated with first-line sorafenib outside of a clinical trial. Two patient groups were compared; group 1 received the standard starting dose of 800 mg/day, and group 2 received any dose lower than 800 mg/day.

Results. We included 75 adult patients, with 51 in group 1 and 24 in group 2. Mean age at diagnosis was 54 years, and 56% were male. The most common histologies included 43%

papillary thyroid cancer of the conventional type, 15% papillary thyroid cancer of the follicular variant, and 15% Hürthle cell carcinoma. Time to treatment failure was 10 months (95% confidence interval [CI]: 5.6–14.3) in group 1 and 8 months (95% CI: 3.4–12.5) in group 2 ($p = .56$). Median overall survival was 56 months (95% CI: 30.6–81.3) in group 1 and 30 months (95% CI: 16.1–43.8) in group 2 ($p = .08$). Rates of discontinuation due to disease progression were 79% in group 1 and 91% in group 2, and 21% in group 1 and 9% in group 2 ($p = .304$) stopped treatment because of toxicity. Dose-reduction rates were 59% and 43% ($p = .29$), and interruption rates were 65% and 67% ($p = .908$) in group 1 and group 2, respectively.

Conclusion. Efficacy and tolerability of sorafenib in treatment-naïve DTC patients does not appear to be negatively influenced by lower starting daily doses. *The Oncologist* 2014;19:477–482

Implications for Practice: Sorafenib (800 mg daily) is the first oral tyrosine kinase inhibitor approved for differentiated thyroid cancer (DTC). Many patients must reduce the dose or discontinue treatment owing to toxicity. In clinical practice, outside the regimented scenario of a clinical trial, physicians sometimes choose to administer reduced doses in patients with multiple comorbidities. Our data suggest that treatment with sorafenib, when administered by experienced specialists outside of a clinical trial setting, resulted in similar efficacy and tolerability as previously reported in clinical trials. But, most importantly, we showed that the efficacy and tolerability of sorafenib in treatment-naïve DTC patients does not appear to be negatively influenced by lower starting daily doses.

INTRODUCTION

The incidence of thyroid cancer is rising annually. In 2013, an estimated 60,220 cases will be diagnosed, and despite standard treatment, 1,850 patients are expected to die of thyroid cancer [1]. Until recently, no efficacious, systemic therapies have been approved by the U.S. Food and Drug Administration for the treatment of differentiated thyroid cancer (DTC) refractory to radioactive iodine (RAI). However, the National Comprehensive Cancer Network and American Thyroid Association guidelines recommend tyrosine kinase inhibitors (TKIs) for progressive or symptomatic DTC refractory to RAI [2, 3].

Sorafenib is the TKI most studied and, therefore, the most frequently used as first-line treatment for progressive RAI-

refractory DTC. It is an orally active multi-TKI with multiple targets, including vascular endothelial growth factor receptor 2 (VEGFR2), VEGFR3, BRAF, RET, and c-KIT. Sorafenib is currently approved in the U.S. and Europe for the treatment of advanced renal cell carcinoma and unresectable hepatocellular carcinoma. In November 2013, sorafenib became the first approved targeted agent for treatment of advanced DTC. The recommended dose is 800 mg daily (400 mg twice daily) in solid tumors, but no thyroid cancer patients were included in the phase I dose-finding trials [4–8]. In all phase II trials of sorafenib in patients with advanced RAI-refractory DTC, the total daily starting dose was 800 mg, but dose reductions were

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needed in up to 79% of patients, and the drug was discontinued owing to toxicity in up to 25% [9–13]. Because of the encouraging efficacy observed in phase II trials, a phase III placebo-controlled trial was conducted in patients with DTC who had not been treated previously with TKIs [14]. Results showed a progression-free survival advantage of 5 months in the sorafenib group. Unfortunately, dose reduction was needed in 64% of patients, and drug interruption was necessary in 66% of patients. Furthermore, the rate of drug discontinuation because of toxicity was 19%. It was recently reported that sorafenib therapy may have a mild but detectable impact on health-related quality of life [15]. Patients in the sorafenib arm had lower scores at first assessment (1 month after starting treatment) compared with placebo patients, possibly related to side effects of treatment. When mild side effects occur, they are managed conservatively, but dose reduction by one dose level (400 mg daily) and drug hold is needed when they are more severe. Proactive management is important because it may help decrease symptom severity and allow patients to maintain the benefit of therapy.

It is unclear why tolerability of sorafenib in patients with thyroid cancer is so poor. In a very small study of nine patients with DTC receiving a total daily dose of 400 mg of sorafenib (200 mg twice daily), the efficacy was comparable to that reported by other trials, but none of the patients discontinued treatment because of treatment-related adverse events and no dose adjustments for toxicity were required, suggesting that sorafenib starting dose may have an impact on tolerability of sorafenib [16].

In clinical practice, outside of the regimented scenario of a clinical trial, physicians often face challenging situations when full-dose sorafenib is perceived as unsafe. These situations may include poor performance status, renal or hepatic dysfunction, high risk of bleeding or fistula formation in a previously irradiated area, and extremes of age. Consequently, we reviewed our clinical practice with sorafenib in patients who were not treated in the context of a clinical trial. Because more than half of the patients who started treatment with an 800-mg daily dose in a clinical trial required dose reductions, we sought to compare the efficacy and tolerability of the standard 800-mg starting dose with reduced starting doses in patients with advanced RAI-refractory DTC.

METHODS

Study Population

We retrospectively reviewed the records of adult patients (aged >18 years) with advanced metastatic DTC treated with sorafenib as first-line therapy outside of a clinical trial from January 2005 to July 2013 at the University of Texas MD Anderson Cancer Center. We collected the following demographic and clinicopathologic information for our analysis: age, sex, ethnicity, type of thyroid cancer, TNM stage at diagnosis, cumulative RAI activity, sites of metastases, time between diagnosis and start of treatment with sorafenib, starting dose of sorafenib, reported treatment interruptions or dose reductions and their causes, and date of death or last follow-up. We excluded patients who received an unknown starting dose of sorafenib. Patients were divided into two groups on the basis of sorafenib

total starting daily dose; group 1 received a starting dose of 800 mg/day (400 mg twice daily), and group 2 received any starting dose lower than 800 mg/day. The reasons for choosing a reduced dose of sorafenib were not evaluable in all patients, but most were related to an increased risk of bleeding (history of ischemic colitis, Crohn's disease, decompensated cirrhosis with esophageal varices, atrial fibrillation during anticoagulation treatment with warfarin, hemoptysis, or history of treated brain metastases). Other comorbidities included renal failure on hemodialysis and poor performance status. In six patients, the treating physician decided to start with a lower dose with plans for upward titration if the drug was tolerated. This was achieved in four patients.

Objectives

We compared overall survival (OS) duration, time to treatment failure (TTF), time to progression (TTP), rates of sorafenib discontinuation because of progression or toxicity, and rates of dose reductions and drug interruption between the two groups.

Definitions

TTF was calculated as the time from the start of treatment with sorafenib to discontinuation because of disease progression or unacceptable toxicity. TTP was defined as the time from the start of treatment to discontinuation because of progression, as decided by the treating physician. Patients who were still receiving sorafenib at the time of our analysis were censored at the time of last follow-up. OS was calculated as the time from the start of treatment with sorafenib to the date of death from any cause. Patients who had not died at the time of analysis were censored at the time they were last known to be alive.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics by group. Comparisons were made between groups to identify any significant imbalances in patient characteristics. An independent samples *t* test was used to compare continuous variables, and a chi-square test was used to compare categorical variables. TTF, TTP, and OS for each group were illustrated using Kaplan-Meier plots, and a log-rank test was used to compare TTF, TTP, and OS distributions between groups. A *p* value <.05 was considered statistically significant. SPSS version 17 (IBM Corp., Armonk, NY, <http://www-01.ibm.com/software/analytics/spss/>) was used for statistical analysis.

RESULTS

Study Population

Seventy-five adult patients with metastatic DTC were treated with first-line sorafenib. Group 1 (800-mg/day starting dose) included 51 patients, and group 2 (<800-mg/day starting dose) included 24 patients. In group 2, only one patient received a 200-mg/day starting dose of sorafenib; the rest received 400 mg/day. Dose escalation to 800 mg daily was subsequently achieved in four patients who initially started with a lower dose.

Patient Characteristics

Baseline characteristics of all patients and comparisons between groups are shown in Table 1. The mean age at

Table 1. Baseline demographic and clinicopathologic characteristics of all patients in the study population and comparisons between groups 1 and 2 (group 1: starting dose of 800 mg/day of sorafenib; group 2: starting dose <800 mg/day of sorafenib)

Characteristic	All patients (n = 75)	Group 1 (n = 51)	Group 2 (n = 24)	p
Age at diagnosis, mean ± SD	54 ± 10	54 ± 10	53 ± 9	.480
Sex, n (%)				.826
Male	42 (56)	29 (57)	13 (54)	
Female	33 (44)	22 (43)	11 (46)	
Ethnicity, n (%)				.826
White	57 (76)	41 (80)	16 (67)	
Hispanic	13 (17)	7 (14)	6 (25)	
Other	5 (7)	3 (6)	2 (8)	
Type of thyroid cancer, n (%)				.584
Papillary, conventional	32 (43)	23 (45)	9 (37)	
Papillary, follicular	11 (15)	7 (14)	4 (17)	
Papillary, tall cell	2 (3)	1 (2)	1 (4)	
Papillary, poorly differentiated	5 (7)	3 (6)	2 (8)	
Follicular	4 (5)	2 (4)	2 (8)	
Follicular, Hürthle	11 (15)	8 (16)	3 (13)	
Follicular, insular	5 (7)	2 (4)	3 (13)	
Poorly differentiated, not otherwise specified	5 (7)	5 (10)	0 (0)	
Tumor stage at diagnosis, n (%)				.565
T1, T2	14 (19)	11 (22)	3 (13)	
T3, T4	54 (72)	36 (71)	18 (75)	
Tx	7 (9)	4 (8)	3 (13)	
Nodal stage at diagnosis, n (%)				.405
N0, Nx	38 (51)	24 (47)	14 (58)	
N1	37 (49)	27 (53)	10 (42)	
Metastatic stage at diagnosis, n (%)				.519
M0, Mx	51 (68)	36 (71)	15 (63)	
M1	24 (32)	15 (29)	9 (37)	
Cumulative radioactive iodine activity (mCi), mean ± SD	342 ± 228	346 ± 236	343 ± 217	.963
Sites of metastases prior to starting treatment with sorafenib, n (%)				
Lung	71 (95)	50 (98)	21 (88)	.09
Bone	24 (32)	16 (31)	8 (33)	.865
Time from diagnosis (years) to starting treatment with sorafenib, mean ± SD	5.6 ± 5.7	5.4 ± 5.1	6.5 ± 6.9	.417

diagnosis was 54 years, and 42 patients (56%) were male. Most common types of DTC included the conventional type of papillary thyroid cancer (32 patients; 43%), followed by Hürthle cell carcinoma (11 patients; 15%) and follicular-variant papillary thyroid cancer (11 patients; 15%). Fifty-four patients (72%) had advanced tumors (T3 or T4), and 24 patients (32%) showed evidence of distant metastases at diagnosis. All patients had evidence of distant metastases at the time of sorafenib initiation, with the two most common sites being lung in 71 patients (95%) and bone in 24 patients (32%).

Efficacy

Time to Treatment Failure

Seventy-one patients were included in the TTF analysis; four patients (all part of group 1) were excluded because the date

of sorafenib discontinuation was unavailable. The median TTF for all patients was 9 months (95% confidence interval [CI]: 5.4–12.5). Median TTF was 10 months (95% CI: 5.6–14.3) in group 1 and 8 months (95% CI: 3.4–12.5) in group 2 ($p = .56$) (Fig. 1). TTF did not appear to be influenced by drug hold or dose reduction.

Time to Progression

Sixty-one patients were included in TTP analysis (39 patients in group 1 and 22 patients in group 2); 14 patients were excluded because they discontinued sorafenib because of toxicity or because the date of sorafenib discontinuation was unavailable. The median TTP for all patients was 10 months (95% CI: 5.1–14.8). Median TTP was 11 months in group 1 (95% CI: 6.1–15.8) and 8 months (95% CI: 5.8–10.1) in group 2 ($p = .354$).

Figure 1. Time to treatment failure in group 1 (800-mg/day starting dose of sorafenib) compared with group 2 (<800-mg/day starting dose of sorafenib).

*Four patients were excluded from group 1 because of an unknown date of sorafenib discontinuation.

Abbreviations: CI, confidence interval; TTF, time to treatment failure.

Figure 2. Overall survival in group 1 (800-mg/day starting dose of sorafenib) compared with group 2 (<800-mg/day starting dose of sorafenib).

Abbreviations: CI, confidence interval; OS, overall survival.

Overall Survival

No patients were excluded for the OS analysis. The median OS duration of all patients was 39 months (95% CI: 17.9–60.0). Median OS was 56 months (95% CI: 30.6–81.3) in group 1 and 30 months (95% CI: 16.1–43.8) in group 2 ($p = .08$) (Fig. 2). The median follow-up time was 25 months in group 1 and 27.5 months in group 2.

Tolerability Profile

Reason for Sorafenib Discontinuation

Forty-two of 51 patients discontinued sorafenib in group 1, and 22 of 24 patients discontinued sorafenib in group 2. Nine patients in group 1 and two patients in group 2 are still receiving sorafenib at the time of this analysis. Sorafenib was discontinued because of disease progression in 33 patients

Table 2. Tolerability of sorafenib in group 1 (800-mg/day starting dose) compared with group 2 (<800-mg/day starting dose)

Variable	Group 1	Group 2	<i>p</i>
Sorafenib discontinuation			
No. of patients in analysis	42	22	
Progression, <i>n</i> (%)	33 (79)	20 (91)	.304
Toxicity, <i>n</i> (%)	9 (21)	2 (9)	
Sorafenib dose reduction			
No. of patients in analysis	46	21	
Yes, <i>n</i> (%)	27 (59)	9 (43)	.290
No, <i>n</i> (%)	19 (41)	13 (57)	
Sorafenib interruptions			
No. of patients in analysis	46	21	
Yes, <i>n</i> (%)	30 (65)	14 (67)	.908
No, <i>n</i> (%)	16 (35)	7 (33)	

(79%) in group 1 and in 20 patients (91%) in group 2 and because of toxicity in 9 patients (21%) in group 1 and 2 patients (9%) in group 2 ($p = .304$) (Table 2). Toxic effects leading to sorafenib discontinuation included weight loss, anorexia, rash, squamous cell skin carcinoma, mucositis, diverticulitis, hand-foot syndrome, and altered mental status.

Dose Reductions and Drug Interruptions

Dose reductions and drug interruptions occurred in 46 of 51 patients in group 1 and 21 of 24 patients in group 2. Dose reduction was required in 27 patients (59%) in group 1 and 9 patients (43%) in group 2 ($p = .29$). Drug interruptions were necessary in 30 patients (65%) in group 1 and 14 patients (67%) in group 2 ($p = .908$) (Table 2).

DISCUSSION

Sorafenib has shown efficacy in patients with advanced RAI-refractory DTC and, therefore, was recently approved for this disease. In phase II and III trials of sorafenib in patients with DTC, the starting daily dose was 800 mg. This was based on previous experience from phase I studies and from phase III studies in renal and hepatocellular carcinoma. Unfortunately, many patients with DTC receiving sorafenib 800 mg as starting daily dose require dose reduction or drug interruption; therefore, the maximum tolerated dose resulting in optimal efficacy should be considered. The only study to evaluate the effect of reduced starting doses was a very small prospective study of nine patients with DTC receiving a total daily dose of 400 mg [16]. Results of this study showed that the efficacy of the 400-mg/day dose was similar to that reported in the other trials, but none of these patients discontinued treatment because of treatment-related adverse events and no dose adjustments for toxicity were required.

Our study included a large number of patients with treatment-naïve DTC who were treated with sorafenib outside a clinical trial, and we compared outcomes of patients who started with a daily dose of 800 mg with those

who started at a lower dose. Our results for group 1 (800 mg/day) were very similar to those of the phase III clinical trial of sorafenib for patients with DTC receiving the same sorafenib starting dose [14]. Efficacy as measured by median TTP was 11 months for those patients receiving 800 mg/day in our study. Although not directly comparable, TTP in our study population is similar to the median progression-free survival rate of 10.8 months in the sorafenib group reported in the phase III clinical trial. An important finding of our study was that the median TTP was not statistically different between the two groups (11 months and 8 months), suggesting that efficacy may not be influenced by the sorafenib starting daily dose. In clinical practice, outside of the regimented scenario of a clinical trial, physicians often face challenging situations when full-dose sorafenib is perceived as unsafe because of comorbidities or relative contraindications to therapy. In this cohort of patients, treatment with a lower starting dose of sorafenib may still offer clinical benefit, as suggested by a median TTP of 8 months.

Surprisingly, the lower starting dose of sorafenib was associated with similar high rates of discontinuation, dose reduction, and drug interruption when compared with the standard 800 mg dose. Because of a clinical benefit and similar toxicity profile, a lower dose of sorafenib may be started in challenging cases when full-dose sorafenib is perceived as unsafe. If tolerable, the dose may be subsequently increased. The discontinuation, drug-hold, and dose-reduction rates reported in the phase III trial in DTC (19%, 64%, and 66%, respectively) are very similar to the results we found in our study. Interestingly, in phase III trials of sorafenib in patients with renal and hepatocellular carcinoma, the discontinuation, dose-reduction, and drug-interruption rates (10%, 13%, and 21%, respectively, in patients with renal cell carcinoma and 11%, 26%, and 44%, respectively, in patients with hepatocellular carcinoma) were much lower than those observed in patients with thyroid cancer [17, 18]. It is unclear why patients with thyroid cancer have a different tolerability profile than patients with other cancers. One possible explanation is that patients with thyroid cancer continue treatment with sorafenib for a longer duration than patients with other cancers, and this increases the cumulative dose regardless of the starting dose. The median treatment durations noted for patients in phase III studies for DTC, renal cell carcinoma, and hepatocellular carcinoma were 46 weeks, 23 weeks, and 21 weeks, respectively [14, 17, 18]. Moreover, there are inherent differences in patients with DTC, including the presence of postoperative hypothyroidism, prior treatment with RAI, and the possibility of comorbidities such as hypoparathyroidism. A standardized approach related to prescribing commercially available tyrosine kinase inhibitors outside of a clinical trial for patients with advanced thyroid cancer was recently published [19]. This represents an effort to improve patient safety and monitoring and to prolong duration of therapy as long as it remains effective.

In our study, the median OS duration for all DTC patients receiving first-line sorafenib was 39 months; the median OS was 56 months in group 1 (800-mg/day starting dose) compared with 30 months in group 2 (<800-mg/day starting dose).

However, the difference was not statistically significant, possibly because of small sample size. Differences in median OS may be related to the dose effect itself, but this needs further study to be determined. Another hypothesis for the difference in OS is that the group of patients receiving a lower starting dose was selected because of worse performance status or medical comorbidities (as described under Methods).

Our study contains several limitations. The retrospective nature of the study resulted in missing information regarding duration of treatment with various sorafenib starting daily doses before dose escalation and de-escalation, and this may have resulted in inhomogeneity between the two groups. There is also lack of information regarding patient performance status, evidence of disease progression before sorafenib initiation, radiographic assessment for evaluation of response rate and progression-free survival, and the type and grade of adverse events noted. Analysis of the effects of these variables on tolerability and outcomes is beyond the scope of this study.

CONCLUSION

Our data suggest that treatment with sorafenib, when administered by experienced specialists outside of a clinical trial setting, resulted in efficacy and tolerability similar to that previously reported in clinical trials. In clinical practice, physicians sometimes choose to administer reduced starting daily doses in patients with multiple comorbidities. Our results indicate that the efficacy of sorafenib in treatment-naïve patients with DTC does not appear to be negatively influenced by starting the treatment at a reduced daily dose. Interestingly, we did not find that reduced starting doses led to better tolerability; however, a prospective clinical trial randomizing patients with advanced DTC to receive different sorafenib starting doses would best address this question. Future studies analyzing the influence of dose intensity and total cumulative dose on outcomes and tolerability are also warranted.

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DISCLOSURES

Steven I. Sherman: Bayer (C/A); **Naifa L. Busaidy:** Bayer-Onyx (C/A); Bayer (RF). The other authors indicated no financial relationships. (C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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For Further Reading:

Taofeek K. Owonikoko, Rajasree P. Chowdry, Zhengjia Chen et al. Clinical Efficacy of Targeted Biologic Agents as Second-Line Therapy of Advanced Thyroid Cancer. *The Oncologist* 2013;18:1262–1269.

Implications for Practice:

Significant benefit can be achieved in patients with iodine-refractory thyroid cancer treated with targeted agents in the first-line setting. It is currently unknown whether additional benefit would be obtained with the use of different biologic agents to treat patients after failing first-line therapy. This study reports the authors' experience using biologic agents as second-line treatment for advanced thyroid cancer and shows that patients derived additional benefit, albeit modest, in comparison to the front-line treatment. These findings are relevant for the clinical management of patients and for future studies of second-line targeted therapy of thyroid cancer.