Tertiary Care Experience of Sorafenib in the Treatment of Progressive Radioiodine-Refractory Differentiated Thyroid Carcinoma: A Korean Multicenter Study

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Background: Sorafenib, a multi-kinase inhibitor, is approved for the treatment of patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC). This study evaluated the efficacy and safety of sorafenib in real-world clinical practice and compared the results to those of the DECISION trial. The clinical features associated with better clinical outcomes after sorafenib treatment were also evaluated.

Methods: This multicenter, retrospective cohort study evaluated 98 patients with progressive RAI-refractory DTC who were treated with sorafenib in six tertiary hospitals in Korea. The primary objective was the progression-free survival (PFS) according to Response Evaluation Criteria In Solid Tumors v1.1. Overall survival, response rate (defined as the best objective response according to Response Evaluation Criteria In Solid Tumors v1.1), and safety were also evaluated.

Results: The median PFS was 9.7 months; median overall survival was not reached during follow-up. Partial responses and stable disease were achieved in 25 (25%) and 64 (65%) patients, respectively. Stable disease of >6 months was achieved in 41 (42%) patients. Subgroup analyses identified several prognostic indicators of a better PFS: absence of disease-related symptoms (hazard ratio [HR]=0.5; $p=0.041$), lung-only metastasis (HR=0.4; $p=0.048$), a daily maintenance dose ≥ 600 mg (HR=0.3; $p=0.005$), and a thyroglobulin reduction $\geq 60\%$ (HR=0.4; $p=0.012$). The mean daily dose of sorafenib was 666 ± 114 mg, and drug withdrawals due to adverse events (AEs) occurred in 13% of patients. AEs and serious AEs were reported in 93 (95%) and 40 (41%) patients, respectively. The most frequent AE was hand-foot skin reaction (76%).

Conclusions: The PFS of progressive RAI-refractory DTC patients treated with sorafenib was consistent with the findings of the DECISION trial. Disease-related symptoms, lung-only metastasis, a daily maintenance dose, and thyroglobulin reduction were significantly associated with PFS. These results suggest that sorafenib is an effective treatment option for patients with progressive RAI-refractory DTC.

Keywords: thyroid neoplasm, sorafenib, progression-free survival, radioactive iodine refractory, real-world clinical practice

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Introduction

DIFFERENTIATED THYROID CANCER (DTC), which is classified histologically as papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC; including Hürthle cell), or poorly differentiated thyroid carcinoma (PDTC), is generally associated with good prognosis and can be treated effectively with surgery, radioactive iodine (RAI), and L-thyroxine suppression therapy (1–3). Distant metastasis occurs in 4–9% of patients with DTC and is the main cause of cancer-related death (4–7). Two-thirds of locally advanced or distant metastases of DTC have low avidity for iodine and become refractory to RAI therapy (8). Until recently, patients with RAI-refractory DTC had limited therapeutic options, and their 10-year survival rate is only about 10% (6–9).

Sorafenib and lenvatinib are currently approved by the U.S. Food and Drug Administration for the treatment of progressive RAI-refractory DTC. Sorafenib is a multikinase inhibitor that targets both tumorigenic and angiogenic molecules, including *RET*, *vascular endothelial growth factor receptors 1–3*, *Flt3*, *c-KIT*, and *BRAF* (10). In the DECISION trial, sorafenib significantly improved progression-free survival (PFS) compared to placebo in patients with progressive RAI-refractory DTC (11). Despite the efficacy and safety of sorafenib shown in a Phase III clinical trial, there are limited studies about sorafenib treatment in the real-world, routine clinical setting (12,13). As of yet, there is no study focusing on the prognostic factors predicting the clinical benefits of sorafenib in patients with progressive RAI-refractory DTC.

Real-world studies determine how new drugs perform outside the clinical trial setting because life does not always mirror the idealized world of a clinical trial (14). In general, randomized clinical trials (RCTs) use a standard therapy in a select group of patients and are typically restricted to evaluating specific discrete interventions one at a time (15). Patients often have characteristics, experiences, and treatment protocols that differ from the controlled environment of RCTs, and therefore the information gained from the RCTs might not be “generalized” to a broader group of patients (14). Real-world studies can provide important health information on patients in the social context of their day-to-day lives (14).

This multicenter retrospective cohort study aimed to evaluate the efficacy and safety of sorafenib for patients with progressive RAI-refractory DTC in real clinical practice. The clinical features associated with better clinical outcomes after sorafenib treatment were also evaluated.

Materials and Methods

Study design

This multicenter, retrospective cohort study evaluated 98 patients with progressive RAI-refractory DTC from six tertiary hospitals who were treated with sorafenib from April 1, 2011, to December 31, 2016, in Korea. Eligible patients were aged ≥ 18 years and had pathologically confirmed DTC (including PTC, FTC including Hürthle cell carcinoma, and PDTC), and evidence of RAI-refractory disease. Inclusion criteria also included at least one measurable lesion, confirmed by axial imaging modality, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, and adequate hematologic and end-organ function defined by the following laboratory results: white blood-cell count

$>2500/\mu\text{L}$, absolute neutrophil count ≥ 1500 cells/ μL , platelet count $\geq 100,000/\mu\text{L}$, hemoglobin ≥ 9.0 g/dL, aspartate aminotransferase and alanine aminotransferase ≤ 2.5 times upper limit of normal (ULN), and serum creatinine ≤ 1.25 times ULN or creatinine clearance ≥ 60 mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation. RAI-refractory DTC was defined as the presence of at least one target lesion without iodine uptake, patients whose tumors had iodine uptake and either progressed after one RAI treatment within the past 14 months, or patients who had progressive disease after receiving cumulative RAI activity of at least 22.3 GBq (600 mCi). Patients who had previously received targeted therapy, enrolled in the DECISION trial, or without target lesions due to curative surgery or radiotherapy were excluded. Twenty-three patients were excluded for the following reasons: absent evidence of RAI-refractory disease ($n=1$), absent measurable lesion ($n=5$), ECOG performance status score 3–4 ($n=7$), previous history of target therapy ($n=7$), and prior enrollment in trials ($n=3$). The study protocol was reviewed and approved by the Institutional Review Board of each participating institution.

Evaluation of efficacy

The primary objective was to evaluate the PFS, which was defined as the time from sorafenib administration to the first documentation of disease progression according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. Overall survival (OS), response rate (defined as the best objective response according to RECIST), disease control rate (complete response [CR] plus partial response [PR] plus stable disease [SD] for six months or more), disease control duration (duration of CR, PR, or SD), time to response, and tumor burden (defined as the percentage change from baseline in the sum of target lesion diameters) were evaluated. OS was defined as the time from the first dose sorafenib to death from any cause. Progression and objective response were assessed by repeated axial images obtained from computed tomography or magnetic resonance imaging of the neck, chest, abdomen, pelvis, spine, and all other known sites of disease according to RECIST every two to three months.

Safety and adverse effects

Safety and tolerability were also monitored. In general, follow-up intervals after starting sorafenib were one to two weeks for one month and every month when the patients were clinically stable. Adverse event (AE) severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. If a causal relation between AEs and sorafenib could not be ruled out, events were classified as treatment-related AEs.

Thyroglobulin and antithyroglobulin antibody measurement

All patients were treated with L-thyroxine to suppress thyrotropin (TSH). Serum thyroglobulin (Tg) and anti-Tg antibody (TgAb) levels were measured during L-thyroxine administration. Serum Tg levels were measured using a Tg-plus RIA kit (Brahms AG, Henningsdorf, Germany) with a functional sensitivity (20% inter-assay variation coefficient) of 0.2 ng/mL and an analytical sensitivity of 0.08 ng/mL.

(16,17). Serum TgAb levels were measured with an anti-Tg RIA kit (Brahms AG, Henningsdorf, Germany) with a functional sensitivity (20% inter-assay variation coefficient) of 0.07 ng/mL. The status of TgAb was defined as positive when its level was >60 IU/mL (16,17).

Statistics

Statistical analyses were performed using R v3.10 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org). Continuous variables are presented as medians with interquartile ranges (IQRs) or mean with standard deviation. Categorical variables are presented as numbers with percentages. Survival curves were plotted using the Kaplan–Meier method, and the log-rank test was used to determine significance. Subgroup analyses were performed according to the best objective response, age (<65 years vs. ≥65 years), sex, pathologic subtypes, presence of disease-related symptom at the time of sorafenib administration, metastatic site, sum of largest diameter of target lesions, maximal diameter of target lesions, and maintenance dose of sorafenib. The maintenance dose was determined by the most frequently administered dose of sorafenib in each patient. A Cox proportional hazard model was used to analyze prognostic factor associations with PFS. The relative risk for PFS is presented as the hazard ratio (HR), confidence interval (CI), and *p*-value. All *p*-values were two-sided, and *p*-values <0.05 were considered statistically significant.

Results

Patients

The baseline clinicopathologic characteristics of the 98 patients with progressive RAI-refractory DTC are summarized in Table 1. The median age was 65.6 years (IQR 57.7–72.2 years), and 30 (31%) patients were male. In addition, 67 (68%), 18 (18%), and 12 (12%) patients had PTC, FTC, and PDTC, respectively. One patient had both PTC and FTC. All patients had distant metastasis, most frequently in the lungs (98%), lymph nodes (55%), and bone (37%). The median duration between DTC diagnosis and sorafenib administration was 9.1 years (IQR 4.7–14.2 years). All patients underwent RAI therapy, and the median cumulative RAI dose was 14.8 GBq (IQR 7.7–22.2 GBq). Six (6%) patients underwent radiofrequency ablation therapy in neck and cervical lymph nodes, three (3%) patients underwent systemic chemotherapy, and 26 (27%) patients underwent excisional surgery for metastatic tumors before treatment with sorafenib. According to the definition of RAI-refractoriness, 74% (*n* = 73) of patients had at least one target lesion without RAI uptake, and 33% (*n* = 32) of patients showed disease progression, even after RAI therapy within the past 14 months (*n* = 4) or a cumulative RAI dose that was >22.3 GBq (*n* = 28). The median follow-up duration from sorafenib administration to censoring or death was 12.3 months (IQR 6.1–24.3 months).

Efficacy of sorafenib

The median PFS was 9.7 months (IQR 4.5–16.7 months) after sorafenib treatment (Fig. 1A). Tumor burden according to the sum of the largest diameter of target lesions decreased in 85 (87%) patients (Fig. 1B). The median OS was not reached at the time of data cutoff of April 30, 2017 (Supplementary Fig. S1;

TABLE 1. BASELINE CLINICOPATHOLOGIC CHARACTERISTICS OF THE PATIENTS TREATED WITH SORAFENIB FOR PROGRESSIVE RAI-REFRACTORY DTC (*N* = 98)

	Median (IQR) or <i>N</i> (%)
Age (years)	65.6 (57.7–72.2)
≥65	52 (53%)
Sex (male)	30 (31%)
Pathology	
PTC	67 (68%)
FTC	18 (18%)
PDTC	12 (12%)
PTC and FTC	1 (1%)
Distant metastases	98 (100%)
Time from diagnosis (years)	9.1 (4.7–14.2)
Previous treatment	
RAI therapy	98 (100%)
External beam radiation therapy	37 (38)
Radiofrequency ablation	6 (6%)
Systemic chemotherapy	3 (3%)
Resection of metastatic tumor	26 (27%)
Cumulative RAI dose (GBq)	14.8 (7.7–22.2)
Metastatic lesion sites	
Lung	96 (98%)
LN	54 (55%)
Bone	36 (37%)
Pleura	14 (14%)
Liver	2 (2%)
Head and neck	24 (24%)
Others (adrenal, kidney, pancreas, soft tissue)	7 (7%)
Target lesions	
Lung	75 (77%)
Bone	11 (11%)
LN	12 (12%)
Head and neck	10 (10%)
Others (adrenal, kidney, pancreas)	5 (5%)
Definition of RAI refractoriness	
At least one target lesion without RAI uptake	73 (74%)
RAI uptake, but progressive target lesions	11 (11%)
Disease progression even with RAI therapy or cumulative RAI ≥22.3 GBq	32 (33%)

Data are presented as median (IQR) or *n* (%) unless indicated otherwise.

RAI, radioactive iodine; IQR, interquartile range; DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; PDTC, poorly differentiated thyroid cancer; LN, lymph node.

Supplementary Data are available online at www.liebertpub.com/thy. No patient achieved a CR. A PR was achieved in 25 (25%) patients after a median duration of treatment with sorafenib of 7.7 months (IQR 3.7–15.3 months; Table 2). The median duration of the PR was 4.4 months (IQR 0.6–34.4 months). Sixty-four (65%) patients had SD, and 41 (42%) patients were in SD for six months or longer (Table 2). The disease control rate (PR plus SD for six months or longer) was 67%.

The proportion of patients according to disease control duration (duration of PR or SD) is listed in Table 2 (lower

panel). Thirty-seven (38%) patients had disease progression within six months. Disease control duration was ≥ 18 months in 23 (23%) patients. When the characteristics of these two subgroups were compared, patients with a longer disease control duration (≥ 18 months) were more likely to show a Tg reduction $\geq 60\%$ than those with progressive disease within six months ($p=0.044$; Supplementary Table S1).

At the end of the follow-up, 45 (46%) patients had progressive disease; 23/45 (51%) patients had disease progression in target lesions, and 22 (49%) patients had disease progression in nontarget lesions without progression in the

target lesion. New metastatic lesions in nontarget lesions developed in 17 (38%) patients, including the lung ($n=3$), bone ($n=4$), liver ($n=1$), lymph nodes ($n=2$), pleura ($n=2$), brain ($n=2$), muscle ($n=2$), and operation bed ($n=1$).

The median serum Tg concentration decreased initially after sorafenib, regardless of the best objective treatment response (Fig. 1C). Serum Tg levels subsequently increased after the nadir in two months, and there was no significant difference according to the best response to sorafenib therapy.

FIG. 1. Therapeutic response to sorafenib in patients with progressive RAI-refractory DTC. (A) Progression-free survival (PFS). (B) Best change in size of the largest diameter of target lesions from baseline. (C) Changes in serum thyroglobulin concentrations (median, interquartile range) according to response rate (defined as the best objective response according to Response Evaluation Criteria In Solid Tumors v1.1.). RAI, radioactive iodine; DTC, differentiated thyroid cancer; PR, partial response; SD, stable disease; PD, progressive disease. *No change in target lesion size.

TABLE 2. TREATMENT EFFICACY IN PATIENTS TREATED WITH SORAFENIB FOR PROGRESSIVE RAI-REFRACTORY DTC

	N (%)
<i>Disease response</i>	
CR	0
PR	25 (25%)
SD ≥6 months	41 (42%)
Disease control rate ^a	66 (67%)
<i>Disease control duration^b</i>	
<6 months	37 (38%)
6–12 months	24 (25%)
12–18 months	14 (14%)
18–24 months	5 (5%)
≥24 months	18 (18%)
Disease control (PR or SD) ≥6 months	61 (62%)

Tumor responses were assessed with the use of Response Evaluation Criteria In Solid Tumors (RECIST) v1.1.

^aDisease control rate was calculated as CR + PR + SD ≥6 months.

^bDisease control duration was calculated as duration of partial or stable disease.

CR, complete response; PR, partial response; SD, stable disease.

Clinical characteristics associated with better clinical outcomes

Subgroup analysis was performed to identify prognostic indicators in patients treated with sorafenib. There was no significant difference in PFS according to the age, sex, and pathological subtypes (data not shown). There was no significant difference in PFS between patients who achieved PR and those with SD (Fig. 2A). Patients without disease-related symptoms who had no complaints about symptoms related to RAI-refractory DTC prior to the administration of sorafenib had better PFS than those with disease-related symptoms (HR=0.5 [CI 0.3–0.9], $p=0.041$; Fig. 2B). Patients with lung metastasis alone had better PFS than other patients (HR=0.4 [CI 0.2–0.9], $p=0.048$; Fig. 2C). However, there was no significant difference in PFS according to the presence or absence of bone metastasis (data not shown). A daily maintenance dose ≥600 mg was significantly associated with better PFS (HR=0.3 [CI 0.2–0.7], $p=0.005$; Fig. 2D). The sum of the largest diameters of target lesions, and the maximal diameter of target lesions were not associated with PFS (data not shown). Serum TgAb levels were negative in 72 patients. The baseline serum Tg concentration (median 111.5 ng/dL) was not associated with PFS (Fig. 2E). The serum Tg level decreased >60% in 42/72 (58%) patients. However, a Tg decrease ≥60% was significantly associated with a prolonged PFS (HR=0.4 [CI 0.2–0.8], $p=0.012$; Fig. 2F).

In multivariate analysis, a daily maintenance dose ≥600 mg (HR=0.3 [CI 0.1–0.9], $p=0.037$) was found to be significantly associated with an improved PFS (Supplementary Table S2).

Safety and adverse effects

AEs were reported in 93 (95%) patients receiving sorafenib (Table 3). These events were mainly grades 1 or 2, and serious AEs occurred in 40 (41%) patients. The mean daily dose of sorafenib was 666 ± 114 mg. Drug interruptions, reductions, and withdrawals due to AEs occurred in 19 (19%),

38 (39%), and 13 (13%) patients, respectively. The most frequent AE was hand-foot skin reaction (76%). Diarrhea (47%), rash or desquamation (33%), hypertension (32%), alopecia (31%), general weakness (30%), and mucositis (27%) were also common AEs. Severe neutropenia, tracheoesophageal fistula, empyema, acute pancreatitis, and severe hepatitis occurred in one patient each. Secondary malignancies occurred in two patients (squamous-cell carcinoma of the lung and skin, respectively). A 71-year-old male patient who had RAI-refractory lung metastatic DTC died, probably of therapy-associated toxic hepatitis.

Discussion

This study evaluated the efficacy and safety of sorafenib outside of clinical trials in patients with progressive RAI-refractory DTC. The median PFS of 9.7 months and disease control rate of 67% are consistent with the findings of the DECISION trial (median PFS = 10.8 months; disease control rate = 54%) (11). Tumor burden decreased in 87% of patients, and PR was achieved in 25% of patients in this study. About 42% of patients had SD for six months or longer. RAI-refractory DTCs with absence of disease-related symptoms, lung-only metastasis, a daily maintenance dose ≥600 mg, and a Tg reduction ≥60% were significantly associated with better PFS. The mean daily dose of sorafenib was 666 ± 114 mg, and drug withdrawal due to AEs occurred in 13% of patients. Serious AEs were reported in 41% of patients, and most of the AEs were less frequently reported than in the DECISION trial (11). The AEs were generally consistent with the known safety profile of sorafenib (11,18,19), except for hemoptysis, neutropenia, tracheoesophageal fistula, empyema, and acute pancreatitis.

Subgroup analyses identified several prognostic indicators predicting better PFS after sorafenib treatment: absence of disease-related symptoms, lung-only metastasis, a daily maintenance dose ≥600 mg, and a Tg reduction ≥60%. In the DECISION trial, the clinical benefits of sorafenib in terms of PFS were observed in all subgroups, split by region, age, histology, metastatic organ, fluoro-D-glucose uptake, number of target or nontarget lesions, target lesion size, sex, and cumulative RAI dose (11). However, the results of the DECISION trial did not identify prognostic indicators in patients with sorafenib treatment because a comparative analysis was made mainly between sorafenib and placebo groups. One of the strengths of the present study consists in the identification of several prognostic indicators in patients treated with sorafenib.

The pattern of disease progression was also analyzed in 45 patients after sorafenib treatment. About 51% of the patients were classified as having disease progression at the end of follow-up due to a significant increase in target lesion size. However, 38% of these patients were defined as having disease progression due to new lesions in nontarget organs during follow-up. The escape phenomenon and growth of some lesions, or the appearance of new lesions, is a common limitation of tyrosine kinase inhibitor (TKI) therapy, and the mechanisms underlying this phenomenon are still undefined (20). In the present series, new metastatic lesions were found in various organs, including the lung, bone, liver, neck, pleura, and muscle. If the initial evaluation does not include those areas with metastatic lesions, it is difficult to distinguish

FIG. 2. Subgroup analyses to evaluate prognostic factors associated with better PFS. (A) PFS in patients who achieved PR and those with SD. (B) PFS according to the presence of disease-related symptoms. (C) PFS in patients with lung-only metastasis and those with metastases to other organs. (D) PFS according to the daily maintenance dose of sorafenib. PFS according to the baseline serum Tg concentration (E) and a decrease in serum Tg levels ($\geq 60\%$) (F). Tg, thyroglobulin.

the actual occurrence of new lesions from simple disclosure of previously unknown lesions. Therefore, it is important to evaluate other organs besides target lesions before initiating treatment with sorafenib in the real clinical situation.

The value of serum Tg as a prognostic indicator in patients with metastatic DTC has not been established, although it is well recognized that detectable amounts of Tg in serum after total thyroidectomy frequently indicates the presence of metastatic foci (21,22). In addition, monitoring of serum Tg levels does not predict structural tumor progression according to RECIST, and the implications of Tg changes occurring during TKI administration are unclear (11,23). In the current study, serum Tg levels decreased in most patients after sorafenib administration but then gradually increased, even in patients who achieved PR. There was no significant difference in the change of serum Tg levels after sorafenib treatment within subgroups of

patients according to the disease response (PR, SD, or progressive disease). Baseline serum Tg levels were not associated with PFS. However, the best change in serum Tg levels $\geq 60\%$ was significantly associated with prolonged PFS and longer disease control duration. Further studies are needed to determine whether Tg monitoring could predict the time of structural disease progression. Long-term follow-up studies will be helpful to identify the prognostic value of Tg doubling time after treatment of TKIs in refractory DTC patients.

The frequency of dose interruptions, reductions, and withdrawals was lower in the current series than in the DECISION trial (11). In particular, the frequency of dose interruptions was much lower in the real clinical setting (19% vs. 66%) (11). These findings suggest that AEs of sorafenib were mostly mild and manageable with standard clinical interventions or dose modifications. This could

TABLE 3. ADVERSE EVENTS OCCURRING IN PATIENTS TREATED WITH SORAFENIB

Adverse events	Any grade, n (%)	Grade 3–4, n (%)	Withdrawal, n (%)
Any treatment-related adverse effect	93 (95)	40 (41)	13 (13)
Hand-foot skin reaction	74 (76)	20 (20)	3 (3)
Diarrhea	46 (47)	1 (1)	0
Alopecia	30 (31)	0	0
Rash or desquamation	32 (33)	3 (3)	0
Mucositis	26 (27)	3 (3)	0
Hypertension	31 (32)	2 (2)	0
Abdominal pain	2 (2)	0	0
Hemoptysis	3 (3)	1 (1)	1 (1)
General weakness	29 (30)	7 (7)	2 (2)
Headache	2 (2)	0	0
Neutropenia	3 (3)	1 (1)	1 (1)
Tracheoesophageal fistula	1 (1)	1 (1)	1 (1)
Empyema	1 (1)	1 (1)	1 (1)
Anorexia/nausea	7 (7)	1 (1)	0
Secondary malignancy	2 (2)	2 (2)	2 (2)
Constipation	1 (1)	0	0
Dyspnea	2 (2)	0	0
Dizziness	1 (1)	0	0
Decreased weight	1 (1)	0	0
Acute pancreatitis	1 (1)	1 (1)	1 (1)
Increased aspartate aminotransferase	2 (2)	2 (2)	1 (1)

Adverse events were classified with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

also be an important factor to explain differences in the response rate and duration compared to the DECISION trial (11). Because sorafenib is a cytostatic agent, it should be considered that cancer cells start to grow more rapidly when sorafenib is withdrawn (20,24). For this reason, patients should be evaluated more frequently in the early period to avoid severe AEs because it is preferable to reduce the daily dose of the drug than to interrupt or withdraw it before AEs worsen (20). Importantly, the PFS in the study patients was significantly poorer when the maintenance dose of sorafenib was <600 mg/day. Therefore, proper management of AEs plays an important role to maximize the clinical benefits of sorafenib in patients with progressive RAI-refractory DTC.

This study has several limitations. First, it is a retrospective analysis, and the possibility of a selection bias cannot be completely ruled out. Second, the median OS was not reached during follow-up because the follow-up period was relatively short. The effects of sorafenib on OS in the real clinical setting should be explored in further studies. Third, information on the mutational profiles of metastatic disease was available only in a limited number of patients ($n=16$). The association between PFS and mutational status could not be evaluated. Fourth, the clinical characteristics of the study subjects were similar to those of the DECISION trial. Therefore, the results might not fully reflect the real-life clinical

setting of all patients. Despite these limitations, the present study is a relative large multicenter study evaluating efficacy and predictive prognostic factors of sorafenib in a real clinical setting, outside of clinical trials, in patients with progressive RAI-refractory DTC.

In summary, the PFS of progressive RAI-refractory DTC patients who were treated with sorafenib is consistent with the results of the DECISION trial. The absence of disease-related symptoms, lung-only metastasis, a daily maintenance dose ≥ 600 mg, and a Tg reduction $\geq 60\%$ were found to be significantly associated with an improved PFS. Sorafenib is an effective treatment option with significant efficacy and manageable AEs in patients with progressive RAI-refractory DTC.

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The investigators in Korean Thyroid Cancer Study Group (KTCSG) are listed in the Appendix. An abstract (Poster 143) covering a part of this article was presented at the 87th Annual Meeting of the American Thyroid Association, October 18–22, 2017, Victoria, Canada.

Author Disclosure Statement

The authors have nothing to disclose.

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