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ORIGINAL

Tumor doubling time predicts response to sorafenib in radioactive iodine-refractory differentiated thyroid cancer

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Abstract. Sorafenib has emerged as an effective therapeutic option for radioactive iodine (RAI)-refractory, locally advanced or metastatic differentiated thyroid cancer (DTC). We investigated the efficacy and safety of sorafenib treatment in a real-world setting and unveil predictive markers of responsiveness to sorafenib. The treatment response, progression-free survival (PFS), overall survival, and adverse events (AEs) of sorafenib-treated RAI-refractory, locally advanced or metastatic DTC patients at three institutes were retrospectively reviewed, and their tumor doubling time was calculated by three investigators. Total eighty-five patients were treated with sorafenib, and seven patients discontinued sorafenib due to AEs before the first tumor assessment. The median PFS was 14.4 months, and the objective response rate was 10.3% in 78 patients who were able to evaluate the tumor response. Age, sex, histologic type, tumor location, RAI avidity, or the presence of FDG-PET uptake did not affect PFS. However, smaller tumor size (≤1.5 cm) of the target lesions in lung showed better PFS (hazard ratio [HR] 0.39, $p = 0.01$), and tumors with the shortest doubling time (≤6 months) had worse outcome (HR 2.70, $p < 0.01$). Because of AEs, dose reductions or drug interruptions were required in 64% of patients, and eventually, 23% of patients discontinued sorafenib permanently. The most common AE was hand-foot skin reaction (HFSR). Patients with severe HFSR showed better PFS, but there were no statistical significance (HR 0.65, $p = 0.05$). In conclusion, small tumor size and long doubling time of each target lesion can be a prognostic marker to predict the responsiveness to sorafenib in RAI-refractory DTC patients.

Key words: Efficacy, Sorafenib, Thyroid cancer, Thyroid neoplasm, Tumor doubling time

DIFFERENTIATED THYROID CANCER (DTC) has an excellent prognosis because the tumor grows indolently, and the treatment method including surgery and radioactive iodine (RAI) is very effective. However, patients with locally advanced or metastatic thyroid cancer showed a poor outcome [1]; the 10-year survival rate of patients with distant metastasis has been reported to range from 42% to 85% [1-3]. Among them, patients with RAI-refractory metastatic DTC have shown a much worse prognosis than those responsive to RAI [1]. Several chemotherapies have been attempted but disappointing results have lead to patients with RAI-refractory metastatic DTC being followed without further treatment until the development of tyrosine kinase inhibitors (TKIs) [4]. However, current guidelines including the American Thyroid Association and National Comprehensive Cancer Network recently included TKI therapy as a promising treatment modality [5, 6].

Sorafenib is the first TKI drug approved for RAI-refractory DTC. It inhibits multiple kinase targets including rearranged during transfection (*RET*), vascular endothelial growth factor receptor (*VEGFR*), platelet-derived growth factor receptor (*PDGFR*), *c-KIT*, and *BRAF*. In the DECISION trial, the progression-free survival (PFS) of 10.8 months in the sorafenib group was significantly longer than that of 5.8 months in the placebo group with 41% reduction in the risk of progression

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[7]. However, which patients will benefit from sorafenib remains uncertain. Even *BRAF* or *RAS* mutations, the two representative genetic alterations occurred in DTC, did not predict the treatment outcome as well. Recently, Sabra *et al.* suggested that the average tumor doubling time of two dominant lung metastatic lesions can predict the response of TKI treatment [8]. However, metastatic lesons other than lung were not included in their analysis. We tried to verify the results of the clinical trial by comparing the results of the clinical trial and actual treatment through a comprehensive review of adverse reactions and tumor response of each target lesion [9].

In this study, we aimed to investigate the efficacy and safety of sorafenib in patients with RAI-refractory locally advanced or metastatic DTC and attempted to unveil predictive markers of responsiveness to sorafenib.

Materials and Methods

Patients

All the study subjects with locally advanced or metastatic RAI-refractory DTC were treated with sorafenib at Gangnam Severance Hospital, National Cancer Center, and Seoul National University Hospital from September 2009 to May 2017. In these hospitals, patients with one or more tumor lesions showing progression or the appearance of new lesions within 14 months by radiologic assessment usually used sorafenib. After subjects who enrolled in the DECISION trial, subjects with anaplastic thyroid cancer (ATC), and subjects without a measurable target lesions were excluded, 85 patients were finally included in this study. The medical records of patients were reviewed retrospectively to collect data including age, sex, time from diagnosis, initial histological diagnosis, distant metastasis, and detailed information of radiologic images and RAI treatment. We also reviewed the dose and duration of sorafenib use and the severity and time to adverse events (AEs). The study protocol was approved by the Institutional Review Board of Gangnam Severance Hospital (3-2017-0093), National Cancer Center (NCC2017-0162), and Seoul National University Hospital (H-1702-134-834).

Study outcomes

The primary outcome was PFS, defined as the time from the initiation of sorafenib and date of progression, death, or date of the last follow-up if the tumor has not progressed. Target lesions were defined as measurable lesions by computed tomography (CT) or magnetic resonance imaging (MRI) with at least a longest diameter of 1.0 cm in non-lymph node organs and a short diameter of 1.5 cm in lymph nodes. The location, size, and RAI avidity of all target lesions were reviewed by three investigators (K. S., L.E.K. and K.M.J.). To assess the growth rate of each tumor, the doubling time (DT) of tumor volume was calculated [8]. The tumor volume was calculated as follow: $\pi/6 \times$ longest diameter $\times$ smallest diameter^2. After then, assuming that changes in tumor volume are exponential, a regression line, $\log y = \log a + bx$ (x: years after the baseline radiologic image, y: tumor volume), was calculated by nonlinear square regression. The DT of tumor volume was defined as (log2)/b. DT was calculated from the baseline image and historical image which was performed before. The median time interval between the baseline image and historical image was 7.2 months. The target lesion response was evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 [10]. According to RECIST criteria, tumor responses were categorized into four groups: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate includes CR and PR. Secondary outcomes were overall survival, tumor response rate, and AEs.

Statistical analyses

The results are expressed as median (range). The PFS and overall survival were represented using Kaplan-Meier curves. The best change in the target lesion size was plotted using a waterfall plot. To identify clinical factors that affect PFS, a Cox proportional hazard model was performed and the relative risk for PFS was presented as the hazard ratio (HR) and 95% confidence interval (CI). The PFS depending on tumor size, DT, the dosage of sorafenib, and the presence of hand-foot skin reaction (HFSR) was plotted using Kaplan-Meier curves and compared using the log-rank test. All statistical analyses were performed by SPSS version 22.0 software for Windows (SPSS, Chicago, IL, USA).

Results

Baseline characteristics of patients

Eighty five patients treated with sorafenib were included in the present study. The baseline characteristics of those patients were summarized in Table 1. The median age of the patients was 55 years, and 33 men were included. The median time from the initial diagnosis of cancer to sorafenib use was 9.9 years (range: 0–36.4 years). Papillary thyroid carcinoma (PTC) was the most common initial histological diagnosis. Most patients (96%) had distant metastases, most commonly to the lung and bone, and the median time from diagnosis of distant metastasis to sorafenib use was 3.8 years (range: 0–16.3 years).

Table 1 Baseline characteristics of patients

Variable	This study (n = 85)
Age (yr)	55 (22–81)
Sex, men	33 (39%)
Time from diagnosis (yr)	9.9 (0–36.4)
Histology	
Papillary	60 (71%)
Follicular	17 (20%)
Poorly differentiated	8 (9%)
Previous RAI	84 (99%)
Cumulative RAI dose (mCi)	615 (150–1,650)
Previous tyrosine kinase inhibitor	5 (6%)
Distant metastasis	82 (96%)
Time from diagnosis to metastasis (yr)	3.6 (0–36.5)
Time from metastasis to sorafenib (yr)	3.8 (0–16.3)
Metastatic lesions	
Lung	74 (87%)
Bone	30 (35%)
Brain	10 (12%)
Sum of target lesion size (cm)	4.0 (1.2–12.8)
Follow-up period (months)	19.1 (1.8–92.2)

Data was presented as median (range).
RAI, radioactive iodine.

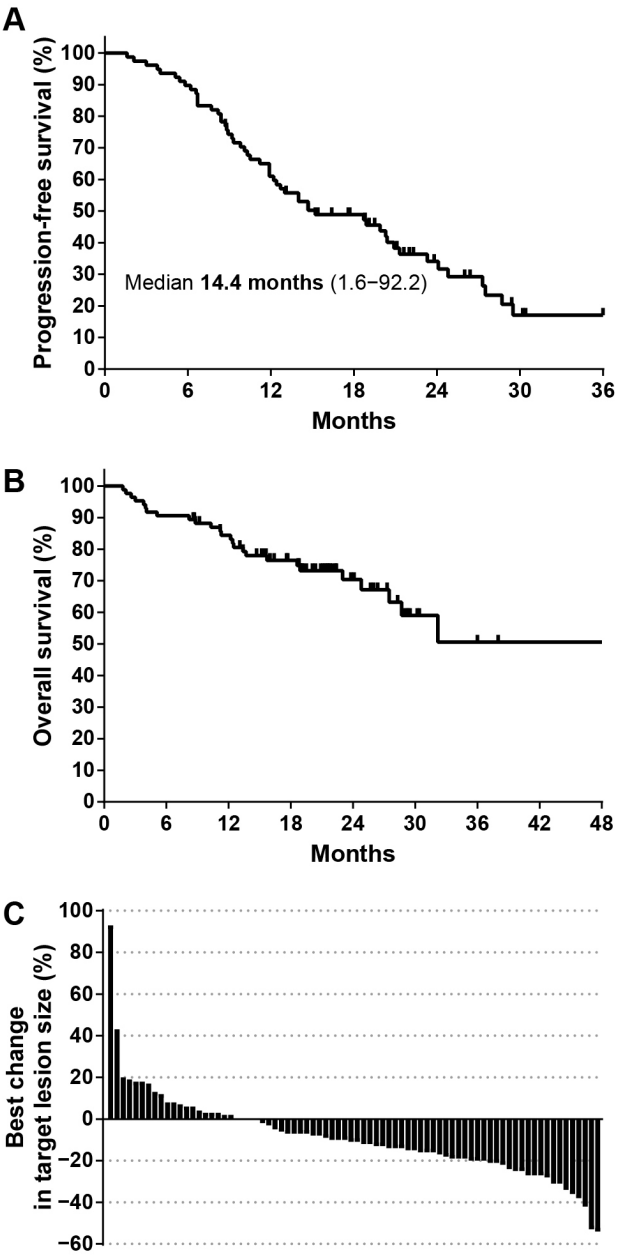

Fig. 1 Progression-free survival (PFS), overall survival, and best tumor response in sorafenib-treated patients
(A) Kaplan-Meier curves of PFS (n = 78).
(B) Kaplan-Meier curves of overall survival (n = 85).
(C) Best tumor response. Waterfall plot showing the best change in the sum of target lesions (n = 78).

Efficacy

Of 85 patients, 7 patients discontinued sorafenib due to AEs before any radiological evaluation for the tumor response. Therefore, the efficacy of sorafenib was analyzed in 78 patients. The median PFS was 14.4 months (range: 1.6–92.2 months) (Fig. 1A). Overall survival of 85 patients was plotted (Fig. 1B), but the median overall survival was not yet reached; 26 patients (30%) had died until now. In patients who died, the median time interval between starting sorafenib and death was 11.8 months (range: 1.8–32.3 months).

Waterfall plot illustrated the best change in target lesion size (Fig. 1C). Sorafenib treatment reduced the sum of target lesions in 69.2% of patients compared to baseline, which was similar with that (73%) in the DECISION trial. An objective response was obtained in 10.3% (8/78) of patients, and SD for 6 months or longer in 66.7% (52/78). They all achieved a PR and there was no CR. The median time from sorafenib treatment to an objective response was 4.2 months, lasting for median 7.0 months (range: 3.0–25.8 months).

Prognostic markers to predict the responsiveness to sorafenib

Among the proposed prognostic factors, age at the time of sorafenib treatment, sex, histologic type of thyroid cancer, or lung metastasis alone did not affect PFS (data not shown). To assess the biological features of each tumor and apply for the prediction of responsiveness to sorafenib, lesion-based response assessment was attempted. Total 164 target lesions in 78 patients were analyzed for previously proposed prognostic markers such as the metastasized organ, size, RAI avidity, or PET uptake of target lesions. The target lesions were located

Table 2 Relative risk of PFS according to several clinical factors

	Total target lesions (n = 164)		Target lesions in lung (n = 112)	
	n	HR (95% CI)	n	HR (95% CI)
Location				
Lung	112	1 (Reference)		
Lymph node	23	0.94 (0.44–1.99)		
Bone	23	0.36 (0.13–1.02)		
Others	6	1.53 (0.47–4.98)		
Size				
≤1.5 cm	54	0.97 (0.48–1.94)	48	0.39 (0.18–0.82)*
1.6–3.0 cm	70	1.52 (0.79–2.93)	39	0.86 (0.42–1.75)
>3.0 cm	40	1 (Reference)	25	1 (Reference)
RAI avidity				
Non-Avid	79	1 (Reference)	49	1 (Reference)
Avid	68	0.71 (0.43–1.17)	49	0.72 (0.41–1.27)
PET				
No uptake	29	0.69 (0.37–1.29)	29	0.51 (0.26–0.97)*
Uptake	111	1 (Reference)	65	1 (Reference)
Doubling time				
≤6 months	36	2.70 (1.33–5.45)*	21	2.50 (1.05–5.97)*
6 months–1yr	24	2.06 (0.92–4.63)	20	1.63 (0.62–4.25)
1–5 yrs	53	1.35 (0.69–2.63)	42	1.36 (0.61–3.03)
>5 yrs	46	1 (Reference)	25	1 (Reference)

*$p < 0.05$

HR, hazard ratio; CI, confidence interval; RAI, radioactive iodine

in the lung (n = 112, 68%), lymph nodes (n = 23, 14%), bone (n = 23, 14%), and others (n = 6, 4%), and their location did not affect PFS (Table 2). Because most of the target lesions were located in lung, pulmonary lesions were analyzed separately in the subsequent analysis.

The median size of the target lesions was 2.1 cm (range: 1.0–7.8 cm) in this study. After dividing the target lesions into three groups of ≤1.5 cm, 1.6–3.0 cm, and >3.0 cm, no difference in PFS was found among the groups (Fig. 2A). However, in a subgroup analysis with lung metastasis, PFS was significantly improved in small lesions (≤1.5 cm) compared to largest ones (HR 0.39, 95% CI 0.18–0.82, p = 0.01; Fig. 2B). The analysis of whole-body scan or ^{18}F-FDG PET images were available in 145 and 101 target lesions, respectively. The loss of RAI avidity and the absence of FDG uptake did not affect PFS (Table 2).

To determine the tumor growth rate, the tumor DT was calculated based on the concept that the increase in tumor size follows the exponential growth curve [11]. The median DT of the target lesions was 1.7 years. When the target lesions were grouped according to the DT (≤6 months, 6 months–1 year, 1–5 years, and >5 years), those with the shortest DT (≤6 months) had an increased risk of progression compared with those with the longest one (>5 years) (HR 2.70, 95% CI 1.33–5.45, $p < 0.01$; Fig. 2C). In a subgroup analysis with lung metastasis, the shortest DT (≤6 months) was associated with worse PFS (HR 2.50, 95% CI 1.05–5.97, p = 0.03; Fig. 2D). However, the average DT for each patient using the average of the calculated DTs of target lesions was not associated PFS (data not shown).

Safety and adverse events

In this study, the mean dosage of sorafenib was significantly lower than those of DECISION trial (602 mg in this study *vs.* 651 mg in DECISION trial, p = 0.02). Dose reduction or interruption occurred in 49% and 26% of patients, respectively. These dose modifications were less frequent (64% in this study *vs.* 78% in DECISION trial, $p < 0.01$), but dose modification happened earlier (0.9 months in this study *vs.* 2 months in DECISION

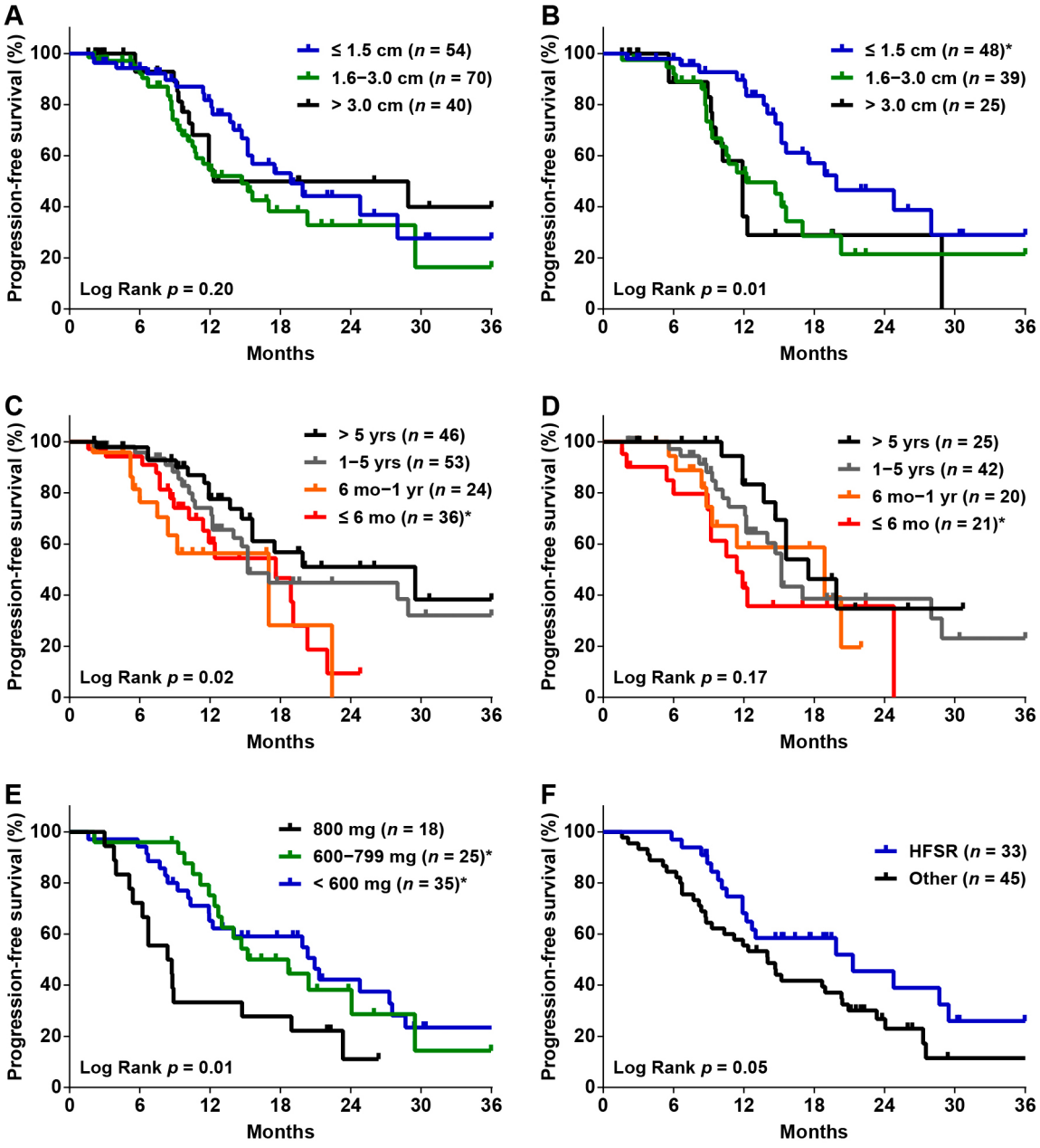

Fig. 2 Kaplan-Meier curves of PFS

(A) PFS according to the size for each target lesion

(B) PFS according to the size for each target lesion in lung. *$p < 0.05$ compared to target lesions of >3.0 cm.

(C) PFS according to the tumor doubling time for each target lesion. *$p < 0.05$ compared to target lesions with the doubling time >5 yrs.

(D) PFS according to the tumor doubling time for each target lesion in lung. *$p < 0.05$ compared to target lesions with the doubling time >5 yrs.

(E) PFS according to the mean dosage of sorafenib. *$p < 0.05$ compared to patients with 800 mg.

(F) PFS according to the presence of severe HFSR.

trial). It may be due to the proactive monitoring and proper management for AEs available in real world. Patients with a full dose (800 mg) had shorter PFS compared to patients taking less than 800 mg of sorafenib ($p < 0.01$; Fig. 2E), unlike the expectation that a larger mean dose of sorafenib would further delay the progression of thyroid cancer. However, there was no difference in PFS according to the dosage of sorafenib in patients who used sorafenib for more than 6 months. Taken together, it suggests that dose modification does not seem to affect disease progression.

Severe AEs requiring dose reductions or drug inter-

Table 3 Grade 3 or 4 adverse events and the time to first occurrence

	n (%)	Median time to first onset (weeks)
Hand-foot skin reaction	34 (40%)	3.5 (0.3–137.4)
Anorexia	5 (6%)	6.0 (0.3–29.9)
Oral mucositis	5 (6%)	12.7 (8.9–22.4)
Diarrhea	3 (4%)	16.0 (0.7–41.4)
Fatigue	3 (4%)	51.9 (31.9–68.6)
Hypertension	3 (4%)	73.0 (3.1–217.7)
Rash or desquamation	2 (2%)	2.6 (2.1–3.1)
Proteinuria	1 (1%)	2.1
Weight loss	1 (1%)	15

ruption occurred in 54 (64%) patients. The most common AEs were HFSR (40%), oral mucositis (6%), and anorexia (6%) (Table 3). Patients with severe HFSR showed better PFS with marginal statistical significance (HR 0.65, 95% CI 0.31– 1.01, $p = 0.05$; Fig. 2F).

Among all patients, 20 (23%) patients discontinued sorafenib permanently and the median time to discontinuation was 0.9 months. Compared with the DECISION trials, dose modification was less frequent in this study ($p = 0.01$), but drug discontinuation was similar ($p = 0.37$). The most common treatment-related cause of permanent discontinuation was oral mucositis (4 patients), HFSR (3 patients), and hypertension (3 patients). Two patients discontinued the drug due to AEs not related to sorafenib: intracranial hemorrhage and toxic hepatitis by herb medication.

Discussion

This study demonstrated that sorafenib is effective for RAI-refractory locally advanced or metastatic DTC in the real-world with an objective response rate of 10.3% and a median PFS of 14.4 months. It was comparable to those in previous non-investigational studies; the median PFS ranged from 6.7 to 21.3 months [12-16], and the objective response rate ranged between 14% and 29% [13-17]. Small (≤1.5 cm) lung metastasis and tumors with a long DT showed better PFS, suggesting that the tumor size and DT can be a predictor for the responsiveness to sorafenib.

A large tumor burden is suggested as a key factor to decide TKI initiation [18, 19]. The DECISION trial showed that sorafenib was more beneficial in patients with a larger sum of the target lesion size (≥7.1 cm) and more lesions (≥5). In this study, the sum of the target lesion size (median 4.0 cm) was relatively smaller than that in the DECISION trial (median 7.1 cm) and did not affect PFS (data not shown). Since the meanings of the individual tumor sizes may differ from the sum of the target lesions (tumor burden), this study evaluated the response to sorafenib on the basis of each lesion. The lesion-based analysis demonstrated that the smaller size (≤1.5 cm) of target lesions in lung showed better response and PFS. To the contrary, a subgroup analysis of the DECISION clinical trial showed that the effect of sorafenib was greater for patients with a maximum target tumor size of 1.5 cm or greater, though no published article was available for further analysis [20]. There was another study reported that the effect of sorafenib was not associated with the tumor size [16]. Therefore, further studies regarding the tumor size is needed.

A rapid tumor growth rate is another important determinant to TKI initiation [18, 19]. Majority of thyroid cancers progress very slowly, and the tumor DT was about 1.5 years in patients with pulmonary metastasis [8]. However, because long-standing DTC can dedifferentiate or transform to ATC, resulting in an increase in the tumor growth rate, rapid growing tumors with shorter tumor DT had a poor prognosis [8]. DECISION trial enrolled patients with an increase of ≥20% in the sum of the target lesion size over 14 months [7], and initiation of TKI is generally considered when tumor shows progression defined by RECIST criteria over at least 12~14 months [19]. A 20% increase in diameter over 12~14 months would approximate a DT of 1.3~4.4 years [11]. In this study, the median DT of target lesions were 1.7 years as well. Among them, 22% of target lesions had a less than 6 months of DT, and they significantly progressed faster (9.2 months *vs.* 12.3 months) despite of sorafenib treatment. From this finding, sorafenib treatment should be initiated before the DT accelerates to 6 months or less. To our knowledge, this is the first analysis of the relationship between tumor DT and sorafenib responsiveness.

However, care should be taken to exclude the possibility of ATC before using sorafanib, because tumor with short DT might be transformed into ATC and sorafenib has little effect in that case. In addition, other targeted therapy such as lenvatinib, dabrafenib plus trametinib, and vemurafenib or conventional chemotherapy are usually recommended for patients with target lesions with short DT less than 6 months [21]. Calculating the tumor volume DT is rather cumbersome. However, once the tumor size is measured in all tumor evaluations, DT can be easily derived with a web-based calculator.

Other prognostic factors such as age, sex, histologic type, and metastatic location of thyroid cancer were also analyzed in this article, but there was no significant difference. Patients with no disease-related symptoms recently showed better clinical outcomes than patients

with disease-related symptoms [16, 22]. However, we did not include the analysis in this article the symptoms because the frequency of disease-related symptoms recorded on a medical chart was not sufficient to analyze and the method of description of the symptoms was heterogeneous among the participating institutions.

Another interesting finding in this study was that PFS tends to be better in patients with HFSR. HFSR is one of the most commen AEs and occured in 40% of our patients, which was higher than that in the DECISION trial or previous data in real-world settings (20%–28%) [13, 14, 23]. The occurrence of HFSR may be associated with multiple blockade of VEGFR, PDGFR, and/or c-KIT in skin [24], the same signaling pathways that exert the effect of sorafenib. Such mechanism-based toxicities can be a predictive marker of efficacy of TKIs [25]. The association between the occurrence of HFSR and treatment outcome has been reported in other cancers [26, 27]. A recent meta-analysis of clinical studies with sorafenib-treated hepatocellular carcinoma patients showed that the occurrence of sorafenib-related AEs including HFSR was associated with a better overall survival [26]. Our study first suggests that HFSR may also be used as a predictive marker in thyroid cancers.

Frequent AE is one of the major obstacles to initiate and maintain TKI treatment in patients with RAI-refractory DTC [28]. Furthermore, AEs and treatment-related mortality rates of sorafenib in patients with DTCs were reported more frequently than in other cancer patients, due to the lack of tumor-related symptoms and long exposure periods [29, 30]. In this study, 64% of patients experienced severe AEs requiring the dose reduction or interruption, and 23% of patients discontinued sorafenib permanently due to AEs. Most of AEs also appeared early in the treatment of sorafenib. In the DECISION trial, dose modification or discontinuations were highest during the first 2 months and decreased thereafter, reaching a plateau in the drug dose [23]. Therefore, it is important to monitor and manage the AEs in the early phase of sorafenib treatment. The prevalence of hypertension in this study was significantly lower than in the DECISION trial (4% *vs.* 10%). This is because the antihypertensive drug was actively prescribed even if a slight rise of blood pressure was detected. It suggested that when sorafenib related AEs are monitored and managed more proactively, they can be reduced or alleviated.

Due to the coexistence of clinical effects and AEs of sorafenib treatment [31-33], the time to initiate sorafenib should be carefully determined. This study suggests that sorafenib is more effective when the size of the tumor is less than 1.5 cm and the DT is more than 6 months. In conclusion, the tumor size and tumor growth rate should be monitored regularly in RAI-refractory DTC patients who are candidates for treatment with sorafenib.

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