Efficacy of sorafenib in advanced differentiated and medullary thyroid cancer: experience in a Turkish population

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Background: Antivascular endothelial growth factor tyrosine kinase inhibitors have been used recently in the treatment of advanced differentiated thyroid cancer (DTC) and medullary thyroid cancer (MTC). Off-label sorafenib is used in Turkey with special permission by the Ministry of Health for this indication.

Patients and methods: Patients with advanced DTC and MTC were retrospectively identified from the Turkish Ministry of Health database. Data on these patients were prospectively collected before permission was granted to use sorafenib.

Results: Thirty patients with complete data were analyzed: 14 DTC (papillary number \(n\) = 10; follicular \(n\) = 4) and 16 MTC. The median age of the patients was 57 years (range: 28–79 years), and there were 18 males and 12 females. All DTC patients were iodine refractory and had received a median three doses of radioactive iodine (range: 1–7 doses). Sorafenib was used for a median of 12 months (range: 1–49 months). The overall response rate was 20%, all partial responses, with no complete response. The overall response rate was 14% in DTC and 25% in MTC patients. The median progression-free survival (PFS) was 17.1 months (95% confidence interval [CI]: 7.3–26.8) and overall survival (OS) was not reached. The 2-year PFS and OS were 39% and 68%, respectively. DTC and MTC patients had similar survival outcomes: median PFS of 21.3 months (95% CI: 5.8–36.7) versus 14.5 months (95% CI: 3.7–25.2), respectively (\(p\) = 0.36), with the median OS not reached in either group (\(p\) = 0.17). Tumor marker levels did not have any prognostic or predictive role. The toxicity profile was similar to that of other sorafenib trials.

Conclusion: Sorafenib is an effective and well-tolerated treatment in advanced thyroid cancers.

Keywords: advanced thyroid cancer, sorafenib, overall survival

Introduction

Thyroid cancer is the most common endocrine cancer; it is the ninth most common cancer in the United States and the seventh most common cancer in Turkey.\(^1,2\) The main histopathologic types are differentiated thyroid cancer (DTC) (including papillary, follicular, and Hurthle), medullary thyroid cancer (MTC), and anaplastic thyroid cancer. Advanced thyroid cancer is a lethal disease with no effective systemic therapy. Novel therapies are needed for radioiodine (RAI)-refractory DTC and advanced MTC.

Thyroid cancers are vascular tumors that overexpress vascular endothelial growth factor (VEGF).\(^3,4\) The definition of molecular pathogenesis and the role of downstream mitogenic signal transduction pathways, including mitogen-activated protein kinase in thyroid cancers, has led to the introduction of multikinase inhibitors that block tyrosine kinases in the treatment of metastatic DTC and MTC.\(^5\) In this context, several tyrosine kinase inhibitors (TKIs) have been used with various results.\(^6,19\)
Sorafenib is an orally active multikinase inhibitor of the tyrosine kinases including BRAF, rearranged during transfection (RET), FLT-3, KIT, VEGFR-1, VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor-β.\textsuperscript{20} Sorafenib is one of the most commonly utilized agents for this indication.\textsuperscript{10–19} Several Phase II studies\textsuperscript{10–15} and retrospective observations\textsuperscript{16–13} proved its efficacy and have led to the design of the Phase III DECISION trial.\textsuperscript{19} The DECISION trial showed that sorafenib is a viable therapeutic option in advanced thyroid cancers. Sorafenib has been used in Turkey with special permission from the Ministry of Health for this off-label indication in the treatment of these patients. We report herein the Turkish experience with off-label sorafenib in patients with metastatic DTC and MTC.

Patients and methods

Study design

Patients with advanced DTC and MTC were retrospectively identified from the Turkish Ministry of Health database. Off-label uses of all medications are only possible with special permission from the Turkish Ministry of Health. Data on these patients were prospectively collected before permission is granted to use the drugs. Therefore, it was possible to reach all of the patients using a specific drug for a specific indication from the database. Sorafenib has been used in the treatment of metastatic thyroid cancer in this context, and basic clinical information about the patients could be obtained retrospectively through this system. Ethics committee approval was obtained prior to the study.

Advanced thyroid cancer patients had the following inclusion criteria: iodine-refractory disease in differentiated cancers; measurable disease by the Response Evaluation Criteria in Solid Tumors (RECIST); and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Patients who did not meet these criteria were not evaluated and were excluded from the analysis.

Sorafenib was given per the discretion of attending physicians. The usual starting dose of 400 mg twice daily (bid) was most commonly applied. Clinical information, including efficacy and toxicity data, were obtained retrospectively from individual medical records. Toxicity was graded according to Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0).

Statistics

The primary objective was to assess the overall response rate (ORR) using RECIST. Additional endpoints were progression-free survival (PFS), overall survival (OS), and adverse events (AEs). PFS was assessed as the time the study drug was started until documented progression or death, whichever came first. OS was defined as the period from the first day of treatment until the date of the last follow-up or death. The probabilities of PFS and OS were estimated using the Kaplan–Meier method and were compared by log-rank test. $P<0.05$ was considered statistically significant.

Results

Patients

A total of 42 Caucasian patients were obtained from the database. Twelve of them were not included in the analysis because of the refusal by the treating physicians to participate in the study (number [n] = 5), missing medical records (n = 5), or the patients not using sorafenib after approval (n = 2).

Thirty patients were appropriately analyzed. Demographics and baseline characteristics of these patients are given in Table 1. Of these, 14 had DTC (papillary, n = 10; follicular, n = 4) and 16 had MTC (one patient tested positive for the RET proto-oncogene). The median age of the patients was

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<td>Baseline ECOG performance status</td>
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<td>Other</td>
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<td>Number of metastatic sites</td>
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<td>1</td>
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Abbreviations: n, number; DTC, differentiated thyroid cancer; MTC, medullary thyroid cancer; ECOG, Eastern Cooperative Oncology Group; M, male; F, female.
57 years (range: 28–79 years). Eighteen patients were males (60%) and 12 were females (40%). All DTC patients were iodine refractory and had received a median of three doses of RAI (range: 1–7). Twenty-three patients (77%) had had surgery and most patients (70%) had received radiotherapy to the neck (33%) and metastatic sites for palliation. Most of the patients had received chemotherapy (n=24; 80%) – most commonly, cisplatin and doxorubicin/epirubicin alone or in combination with cisplatin (n=19; 79%). Only six patients (20%) had received two or more lines of chemotherapy.

Sorafenib was started at a 400 mg bid dose in 24 patients (80%). The median sorafenib dose was 800 mg per day (range: 400–800 doses). Seven patients required a dose reduction for AEs, and the dose was increased to 400 mg bid in one patient. Sorafenib was used for a median of 12 months (range: 1–49 months). The median duration of sorafenib therapy in DTC and MTC patients was 15 months (range: 2–49 months) and 9 months (range: 1–27 months), respectively.

Efficacy
In the entire study population, the ORR was 20%; all were partial responses with no complete response. An additional ten patients (33%) had stable disease (SD) with a clinical benefit rate (clinical benefit rate = ORR + SD) of 53%. The ORR was 14% in DTC and 25% in MTC patients. SD was observed in six DTC patients and four MTC patients.

In the survival analysis, the median PFS was 17.1 months (95% confidence interval [CI]: 7.3–26.8) and the OS was not reached. The 2-year PFS and OS were 39% and 68%, respectively. The median PFS in the DTC and MTC groups was similar (21.3 months [95% CI: 5.8–36.7] versus 14.5 months [95% CI: 3.7–25.2], respectively; P=0.36) (Figure 1). The median OS was not reached in either group (P=0.17) (Figure 2).

Calcitonin and thyroglobulin levels were obtained in some patients at both baseline and at one time point after sorafenib administration. Of 14 DTC patients, eight had thyroglobulin measurements and only three of them had a decrease in thyroglobulin levels. These three patients had SD as a tumor response. Similarly, of the 16 MTC patients, 12 had calcitonin measurements. Nine of these had an increase or no change in calcitonin levels, whereas only three patients had a decrease. Of these three patients, one had a partial response, one had SD and one had PD. There was no correlation of tumor marker levels with sorafenib efficacy.

Adverse events
The toxicity profile was similar to those of other sorafenib trials. Grade 1–2 AEs might have been overlooked because of the retrospective nature of the data collection. The most common grade 3–4 toxicities are summarized in Table 2. One patient discontinued therapy because of fatigue and hand–foot syndrome. In addition, the sorafenib dose was reduced in seven patients (23%) because of AEs.

Discussion
Treatment of advanced thyroid cancers is challenging once they are RAI refractory in DTC or unresectable with curative
It seems that sorafenib is as effective as vandetanib or cabozantinib, with available Phase III data and consequent US FDA approval.12–14 Nevertheless, all grade 3/4 severe reactions were precisely recorded. Likewise, the survival outcomes achieved in our study are within the range of other published results in comparable patient populations. Our report reflects actual clinical experience and is free of innate trial problems, such as patient selection bias and closer follow-up, resulting in better clinical outcomes. Most importantly, this article includes real-life results of consecutive patients with advanced thyroid cancer who used off-label sorafenib in a given time period.

**Conclusion**

In summary, we demonstrated that sorafenib is an active agent with a tolerable toxicity profile in the treatment of patients with advanced DTC and MTC. These results showed that its efficacy in this indication is reproducible in real life. The equal efficacy of sorafenib both in DTC and MTC patients is an important observation that demands further exploration of its activity in advanced MTC.
Acknowledgments
Turkish Thyroid Cancer Study Group Collaborators (in alphabetical order according to last name): Dilsen Colak (Diskapi Education and Research Hospital); Turkan Evrensel (Uludag University); Guzin Gonullu (19 Mayis University); Saadettin Kiliçkap (Cumnuruyet University); Seref Komurcu (Bayindir Hospital); Fatih Kose (Baskent University Adana Hospital); Bulent Orhan (Acibadem Bursa Hospital); and Mustafa Ozguroglu (Cerrahpasa University).

Disclosure
The authors report no conflicts of interest in this work.

References