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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Sorafenib in Radioactive Iodine Refractory Differentiated Thyroid Cancer: A Real-life Data with Long-term Experience

Radyoaktif İyot Dirençli Diferansiye Tiroid Kanserinde Sorafenib: Uzun Dönem Tecrübe ile Gerçek Yaşam Verisi

Emre Yekedüz[1,2], Elif Berna Köksoy[1,2], Filiz Çay Şenler[1,2], Hakan Akbulut[1,2], Ahmet Demirkazık[1,2], Yüksel Ürün[1,2], Güngör Utkan[1,2]

[1]Ankara University Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey
[2]Ankara University Cancer Research Institute, Ankara, Turkey

Abstract

Objectives: Sorafenib is one of the standard anti-cancer drugs in the treatment of radioactive iodine refractory (RR) metastatic differentiated thyroid cancer (DTC). In this study, we aimed to present a long-term real-life experience of sorafenib in the treatment of (RR) metastatic (DTC).

Materials and Methods: We retrospectively searched the patients' records for RR metastatic DTC patients treated with sorafenib in a tertiary cancer center between 01.01.2014 and 31.12.2019. Progression-free survival (PFS), overall survival (OS), response rates, and safety profile of sorafenib were assessed.

Results: A total of 19 patients were included in this study. The majority of patients had papillary thyroid cancer (80%). With a median follow-up of 18 months, the median PFS and OS were 10.9 and 41 months, respectively. The objective response rate and disease control rate were 36% and 68%, respectively. Nine patients (45%) reported any adverse events (AEs) with sorafenib.

Conclusion: This long-term real-life experience study showed that the median OS was longer than 3 years in RR metastatic DTC patients treated with sorafenib. On the other hand, AEs rates were lower in our study than in the pivotal phase III trial of sorafenib in RR DTC patients

Key Words: Thyroid, Tyrosine Kinase Inhibitor, Radioactive Iodine Refractory

Öz

Amaç: Sorafenib radyoaktif iyot (RAİ) dirençli metastatik diferansiye tiroid kanseri (DTK) hastalarındaki standart tedavilerden biridir. Bu araştırmada, sorafenibin RAİ dirençli metastatik DTK hastalarındaki uzun dönem sonuçlarının sunulması amaçlanmıştır.

Gereç ve Yöntem: 01.01.2014-31.12.2019 tarihleri arasında RAİ dirençli metastatik DTK tanısı ile takipli hastaların kayıtları geriye dönük olarak incelendi. Genel sağkalım (GSK), progresyonsuz sağkalım (PSK), yanıt oranları ve güvenlik profili analiz edildi.

Bulgular: Araştırmaya toplamda 19 hasta dahil edildi. Hastaların çoğunda (%80) papiller tiroid kanseri mevcuttu. On sekiz aylık ortanca takipte, PSK ve GSK sırasıyla 10,9 ve 41 ay olarak bulundu. Objektif yanıt oranı ve hastalık kontrol oranı sırasıyla %36 ve %68 idi. Dokuz hastada (%45) sorafenib ilişkili yan etki görüldü.

Sonuç: Bu uzun dönem gerçek yaşam deneyimi verisi, sorafenib ile tedavi edilen RAİ dirençli metastatik DTK hastalarında GSK'nin 3 yıldan daha uzun olduğunu gösterdi. Diğer taraftan, yan etki görülme oranı sorafenibin faz-3 çalışmasındakinden daha azdı.

Anahtar Kelimeler: Tiroid, Tirozin Kinaz İnhibitörü, Radyoaktif İyot Dirençli

Address for Correspondence/Yazışma Adresi: Emre Yekedüz
Ankara University Faculty of Medicine, Department of Medical Oncology; Ankara University Cancer Research Institute, Ankara, Turkey
Phone: +90 312 595 71 12 **E-mail:** emreyekeduz@gmail.com **ORCID ID:** orcid.org/0000-0001-6819-5930
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Introduction

Thyroid cancer incidence has been increasing in both sexes over the last ten years, and the estimated incidence is 6.6/100,000 in GLOBOCAN 2020 (1). Hopefully, early-stage differentiated thyroid cancer (DTC) has an excellent survival rate. However, metastatic disease is inevitable in approximately 10% of all patients (2,3). Radioactive iodine (RAI) is the mainstay of treatment in these patients. Unfortunately, during the clinical course of metastatic DTC, two out of three patients become RAI refractory (RR), and the prognosis is poor in this group of patients (2,4).

Sorafenib and lenvatinib are the two main options in the RR metastatic DTC treatment. The pivotal phase III trial of sorafenib, the DECISION trial, showed that progression-free survival (PFS) was better in the sorafenib arm than the placebo arm. On the other hand, lenvatinib had also improved PFS in the SELECT trial. However, despite the improved PFS, there was no difference between the arms in the DECISION and SELECT trials for overall survival (OS) (5,6).

Sorafenib and lenvatinib are recommended by the National Comprehensive Cancer Network (NCCN) guideline for RR metastatic DTC patients with progressive and/or symptomatic disease. On the other hand, treatment armamentarium in metastatic thyroid cancer has been expanding over the last two years. In this context, pembrolizumab for patients with high tumor mutational burden, larotrectinib/entrectinib for patients with *NTRK* gene fusion are the other options recommended in the NCCN guidelines (7).

In this study, we aimed to share six years' experience of sorafenib in the treatment of metastatic RR DTC patients from a tertiary cancer center.

Materials and Methods

This study was conducted in a tertiary cancer center in Turkey. We searched metastatic RR DTC patients diagnosed between 01.01.2014-31.12.2019 and treated with sorafenib in the metastatic setting.

Clinical and pathological data were extracted to a database from electronic and printed patient files. Patients had one of the following criteria accepted as RAI refractory: a) The total RAI dose 600 millicuries (mCi), b) Presence of metastatic lesion without RAI uptake, c) Disease progression within 16 weeks after the last RAI dose.

We assessed PFS, OS, response rates, and safety profile of sorafenib. PFS was calculated from the initial date of sorafenib to disease progression or death, OS was calculated from the initial date of sorafenib to death. Objective response rate (ORR) and disease control rate (DCR) were assessed by using "response evaluation criteria in solid tumors (RECIST) version 1.1".

Statistical Analysis

Descriptive analyses were presented by using mean ± standard deviation or median with interquartile range (IQR) for continuous variables and percentages for categorical variables. Kaplan-Meier survival estimates were used for survival analyses. A p-value of less than 0.05 was considered to show a statistically significant result. For all statistical analyses, SPSS 27.0 for Mac (IBM Corp., Armonk, NY) was used.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (approval no: I3-86-19, date: 12/09/2019).

Results

After searching the patients' records, a total of 19 patients were included in this study. The median age at the start of sorafenib was 63 years (IQR: 53-66). The majority of patients were male (63%). Fifteen patients had papillary thyroid carcinoma, and four patients had follicular thyroid carcinoma. The total median dose of RAI was 700 mCi (IQR: 450-925). Ninety percent of all patients had lung metastasis. Two patients received doxorubicin in the metastatic setting. Three patients were treated with lenvatinib after progression with sorafenib. All baseline characteristics are shown in Table 1.

At the median follow-up of 18 months, the median PFS was 10.9 months [95% confidence interval (CI): 4.4-17.5], and the median OS was 41 months (95% CI: 23.7-58.2). Kaplan-Meier estimates of PFS and OS are shown in Figure 1 and Figure 2, respectively. ORR was 36%, and DCR was 68%. Best responses, according to RECIST criteria, are shown in Table 2.

Nine patients (45%) reported sorafenib-related adverse events (AEs). The most common AEs were skin toxicities (e.g., rash or hand-foot syndrome), and one patient had a grade 4 skin rash. All sorafenib-related AEs are shown in Table 3.

Discussion

In this study, we presented a long-term real-life experience of sorafenib in RR metastatic DTC patients. The median OS was longer than three years in those patients with an acceptable toxicity profile.

The median PFS was similar to the pivotal phase III trial of sorafenib in RR DTC. In the DECISION trial, the median PFS was 10.8 months. However, although OS did not reach the median, there was no statistically significant difference between the sorafenib and placebo arms (6).

In a Korean real-life experience study, Oh et al. (8) showed that the median PFS was 13.7 months. Actually, it was slightly higher than our study. In addition, the median OS was almost the same as our study and was 41.5 months. In this real-life experience study, 33% of all patients received lenvatinib after progression. In our study, 15% of all patients were treated with lenvatinib after progression. Despite lower PFS, we revealed the same OS with the study of Oh et al. (8) It could be explained by the effect of lenvatinib after progression.

ORR was higher in our study than the DECISION trial (36% vs. 12%). Despite better ORR and DCR in our study than the DECISION trial, we did not reveal a better PFS. Conversely, with the same DCR, OS was similar in our study and the study of Oh et al. (6,8). Taken together, the best responses did not reflect the survival outcomes in thyroid cancer. DTC usually shows a slow progression. In compliance with this biological behavior, response with tyrosine kinase inhibitors is usually slow. In this context, despite higher response rates in our study, PFS was not better than the DECISION trial.

Interestingly, AEs rates were lower than the DECISION trial in our study. In the DECISION trial, higher than 90% of all patients reported any grade AEs, while this rate was 45% in our study. Similar to the DECISION trial, the most common AEs were skin toxicities. The majority of them were grade 1 or 2, and only one patient reported grade 4 skin rash. In the Korean real life-experience study, the AEs rate was 96%. This difference may be associated with the patient population. The study of Oh et al. (8) reported the results of Korean patients. Genetic variations in the drug mechanisms might affect the toxicity profile (6,8).

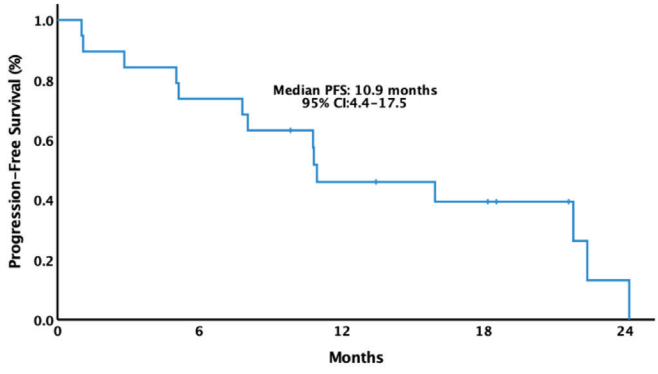

Figure 1: Kaplan-Meier estimates of progression-free survival (PFS)

CI: Confidence interval

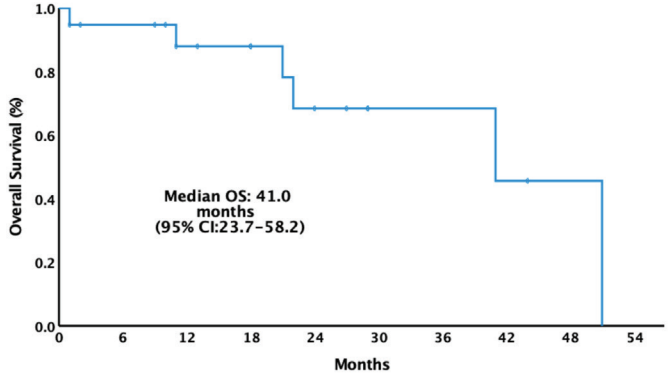

Figure 2: Kaplan-Meier estimates of overall survival (OS)

CI: Confidence interval

Study Limitations

Our study has some limitations. First, it was a retrospective data collection study. Due to its retrospective nature, we did not assess the dose adjustments after toxicity due to the lack of data. Second, RR metastatic DTC incidence is very low compared to the other common cancer types. Thus, we included a low number of patients in this study and we did not carry out a subgroup analysis.

Table 1: Baseline characteristics

	n=19 (%)	
Age-years, median (IQR)	63 (53-66)	
Total dose of RAI-mCi, median (IQR)	700 (450-925)	
Thyroglobulin-ng/mL, median (IQR)	482 (50-960)	
Anti-thyroglobulin		
Positive	5	(26)
Negative	14	(74)
Sex		
Male	12	(63)
Female	7	(37)
Histological type		
Papillary	15	(80)
Follicular	4	(20)
Distant metastasis		
Lung	17	(90)
Bone	7	(37)
Liver	5	(26)
CNS	1	(5)
Metastatic site number, median (IQR)	1 (1-2)	
Previous chemotherapy		
Yes	2	(10)
No	17	(90)

CNS: Central nervous system, IQR: Interquartile range, mCi: Millicuries, RAI: Radioactive iodine

Table 2: Best responses

	n=19	(%)
Complete response (CR)	0	(0)
Partially response (PR)	7	(36)
Stable disease (SD)	6	(32)
Progressive disease (PD)	6	(32)
ORR (CR+PR)	7	(36)
DCR (CR+PR+SD)	13	(68)

DCR: Disease control rate, ORR: Objective response rate

Table 3: Adverse events

	n=19 (%)	
	Grade 1-2	**Grade 3-4**
Skin rash	2 (10)	1 (5)
Loss of appetite	2 (10)	0 (0)
Hand-foot syndrome	1 (5)	0 (0)
Fatigue	1 (5)	0 (0)
Peripheral neuropathy	1 (5)	0 (0)
Diarrhea	1 (5)	0 (0)
Total	**8 (40)**	**1 (5)**

Conclusion

We showed that the median OS was longer than three years in RR metastatic DTC patients treated with sorafenib in this real-life experience study. RR metastatic DTC patients have a poor prognosis and sorafenib is one of the mainstays of treatment in these patients.

Ethics

Ethics Committee Approval: This study approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (approval no: I3-86-19, date: 12/09/2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.Y., E.B.K., F.Ç.Ş., H.A., A.D., Y.Ü., G.U., Design: E.Y., E.B.K., F.Ç.Ş., G.U., Data Collection or Processing: E.Y., E.B.K., Analysis or Interpretation: E.Y., E.B.K., Literature Search: E.Y., E.B.K., F.Ç.Ş., Writing: E.Y., E.B.K., F.Ç.Ş., H.A., A.D., Y.Ü., G.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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