ORIGINAL RESEARCH

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Our Experience with Abiraterone and Enzalutamide in the Treatment of Metastatic Castration-Resistant Prostate Cancer: Retrospective Real-Life Data

Özlem Nuray SEVER[a], Aykut BAHÇECİ[b], Havva YEŞİL ÇINKIR[a], Mustafa YILDIRIM[c]

[a]Department of Medical Oncology, Gaziantep University Faculty of Medicine, Gaziantep, Türkiye
[b]Clinic of Medical Oncology, Gaziantep Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Türkiye
[c]Department of Medical Oncology, SANKO University Faculty of Medicine, Gaziantep, Türkiye

ABSTRACT Objective: In recent years, agents targeting the androgen signaling pathway, such as abiraterone and enzalutamide, have become increasingly crucial in the treatment of metastatic castration-resistant prostate cancer (mCRPC). This study aimed to compare the effectiveness of both agents retrospectively. **Material and Methods:** Patients with the diagnosis of mCRPC who received abiraterone (ABI group) or enzalutamide (ENZA group) and who were followed up and treated in our clinics were analyzed retrospectively. **Results:** A total of 59 patients, 23 receiving abiraterone and 36 enzalutamide, were included in the study. Moreover, the prostate-specific antigen (PSA) level reduced by more than 50% in 33 (14 in the ABI group and 19 in the ENZA group) patients. The median progression-free survival (PFS) and overall survival-2 (OS-2) were 7.46±2.08 months and 13.60±6.19 months in the ABI group and 8.80±4.21 months and 21.03±3.84 months in the ENZA group (p=0.448; p=0.571), respectively. When the Cox regression analysis was performed, PSA reduction of more than 50% was statistically significant for OS-2 but not for PFS (p=0.023). **Conclusion:** Both abiraterone and enzalutamide are effective treatment agents for mCRPC. The decrease in the PSA value is a crucial predictive marker in evaluating the effectiveness of the treatment.

Keywords: Prostate cancer; abiraterone; enzalutamide; overall survival

Prostate cancer is the second most frequent cancer diagnosed in men and the fifth leading cause of death worldwide.[1] Although localized prostate cancer has an excellent prognosis, castration-resistant prostate cancer (CRPC) has a survival time of approximately 1-3 years.[2,3] Castration resistance is defined as a condition that occurs with clinical, biochemical, or radiographic progression, although serum testosterone level is at the castration level. In recent years, androgen receptor signaling pathway-targeted therapeutic agents such as abiraterone and enzalutamide have changed the clinical management of metastatic CRPC (mCRPC).

As several treatment options exist in the management of mCRPC, optimizing the order of application of these treatments is necessary. Abiraterone and enzalutamide were initially approved for use after docetaxel (postdocetaxel); however, they were soon approved to be used before docetaxel (predocetaxel). Abiraterone and enzalutamide are frequently used in the treatment of mCRPC on the basis of oncologist experience and toxicity profile, given their favorable side effect profiles and outpatient comfort compared with taxanes. To date, no direct prospective study has compared the efficacy of abiraterone and enzalutamide in patients with mCRPC; only a few centers have reported their own experience as a retrospective analysis.

Therefore, it is necessary to investigate whether these 2 agents used in mCRPC treatment have any effect on survival. In this study, real-life data of our patients with a diagnosis of mCRPC who received

Correspondence: Özlem Nuray SEVER
Department of Medical Oncology, Gaziantep University Faculty of Medicine, Gaziantep, Türkiye
E-mail: ozlem.sever@hotmail.com

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abiraterone or enzalutamide were analyzed retrospectively.

MATERIAL AND METHODS

PATIENTS SELECTIONS

Patients with the diagnosis of mCRPC receiving abiraterone or enzalutamide who were followed up and treated in the Gaziantep University Faculty of Medicine, Gaziantep, Dr. Ersin Arslan Training and Research Hospital, and SANKO University Medical Faculty medical oncology clinics were analyzed retrospectively. Pathological features at diagnosis, European Cooperative Oncology Group (ECOG) performance score (PS), presence and localization of metastases at diagnosis, number of metastatic foci, prostate-specific antigen (PSA) level before and after abiraterone/enzalutamide, treatment history before abiraterone/enzalutamide, and best achieved response with abiraterone/enzalutamide were obtained from patient files and hospital automation records. The treatment response status of all patients included in the study was obtained from the evaluations made in their own centers according to the standard imaging response criteria.

This study was approved by the Clinical Research Ethics Committee of Gaziantep University on 14.04.2021 (study number 2021/136) and conducted in accordance with the Declaration of Helsinki Principles. An informed consent form was obtained from the patients included in the study.

STATISTICAL ANALYSES

t-test or analysis of variance was used to compare independent groups. Categorical measurements were analyzed using the chi-square test. The Kaplan-Meier method was used to estimate the mean-median overall survival (OS) and progression-free survival (PFS) rates. The log-rank test was used to compare the survival distributions between groups. The Cox proportional regression model was used to estimate the hazard ratios. The results were reported as mean±standard deviation (SD), median, number (n), and percentage (%). p values less than 0.05 were considered significant in all tests. Data were expressed as means±SDs for continuous variables and as number (n) and percentage (%) for categorical variables. The analyses were performed using the statistical package SPSS v22.0 software (IBM Inc. Armonk, NY, USA).

OS for all patients included in the study was calculated using 2 different periods: OS-1 was calculated as the time from metastatic to death from any cause and OS-2 as the time from the initiation of abiraterone/enzalutamide to death from any cause. PFS was calculated as the time from the date of abiraterone/enzalutamide initiation to the date of radiological or clinical progression.

RESULTS

A total of 59 patients, 23 receiving abiraterone and 36 enzalutamide, were included in the study. The median age of the patients was 69.0 [interquartile range (IQR): 45-89] years: 74.0 (IQR: 55-89) years for abiraterone group (ABI) and 68.5 (IQR: 45-81) years for enzalutamide group (ENZA). The median baseline PSA level was 39.0 (2.3-1,500) ng/mL: 28.8 (2.3-1,500) ng/mL for ABI and 62.8 (3.0-1,430) ng/mL for ENZA. The median Gleason score was 9 (6-10): 9 (6-10) for ABI and 9 (7-10) for ENZA. The ECOG performance status was 0 in 4 patients in the ABI group, ECOG PS 1 in 15 patients, and ECOG PS 2 in 4 patients, whereas in the ENZA group, ECOG PS 1 in 34 patients and ECOG PS 2 in 2 patients.

Abiraterone was used as first-line treatment in 3 patients in the ABI group, second-line treatment in 19 patients, and third-line treatment in one patient. In the ENZA group, enzalutamide was used in 5 patients as first-line, in 28 patients as second-line, in 2 patients as third-line, and in one patient as fourth-line treatment.

Isolated bone metastasis was observed in 28 patients, isolated visceral metastasis in 3 patients, and bone+visceral metastasis in 28 patients. When the metastasis regions were examined in both groups, 15 patients had isolated bone metastasis, 2 had isolated visceral metastasis, and 6 had bone+visceral metastasis in the ABI group, whereas 13 patients in the ENZA group had isolated bone metastases, one had isolated visceral metastasis, and 22 had bone+visceral metastasis. The total number of oligometastatic pa-

tients was 5, 1 in the ABI group and 4 in the ENZA group.

PSA response (more than 50% reduction in PSA level at the 3rd month) was observed in 33 patients in total, 14 in the ABI group and 19 in the ENZA group.

In terms of response to the treatment, 5 patients in the ABI group had partial response, 12 had stable disease, and 6 had progression, whereas in the ENZA group, 1 patient had complete response, 10 had partial response, 16 had stable disease, and 9 had progression.

Progression was observed in 44 patients at the end of the follow-up, 18 patients in the ABI group and 26 patients in the ENZA group.

At the last control, 38 (16 in the ABI group and 22 in the ENZA group) patients were dead and 21 (7 in the ABI group and 14 in the ENZA group) were alive.

Baseline demographic and clinical characteristics of the patients included in the study and end-of-treatment situations are shown in Table 1.

Median OS-1 was 45.93±10.98 months: 45.93±10.08 months in the ABI group and 44.73±19.55 months in the ENZA group (p=0.448). Median OS-2 was 21.03±4.01 months: 13.60±6.19 months in the ABI group and 21.03±3.84 months in the ENZA group (p=0.571). PFS was 7.46±1.85 months: 7.46±2.08 for ABI and 8.80±4.21 months for ENZA groups (p=0.448; Table 2, Figure 1, Figure 2, Figure 3).

When Cox regression analysis was performed for PFS and OS-2, no difference was observed in terms of age, ECOG, metastasis site, number of metastatic foci, treatment (abiraterone or enzalutamide), and Gleason score; however, a statistically significant difference was noted in PSA response for OS-2, but not for PFS (p=0.023; Table 3).

OS-2 was 23.33±1.61 months for 14 patients in the ABI group and 28.43±3.27 months (p=0.649) for 19 patients in the ENZA group with a PSA response. Nine patients in the ABI group had no PSA response, with OS-2 of 12.03±0.44 months, and 13 patients in the ENZA group had no PSA response, with OS-2 of 9.63±3.47 months (p=0.900) (Table 4; Figure 4, Figure 5).

When patients receiving abiraterone/enzalutamide as first-line therapy were evaluated, PFS was 1.06±0.02 months for ABI and 11.36±4.81 months for ENZA (p<0.0001). OS-2 was 12.03±3.64 months for ABI and 17.33±8.98 months for ENZA (p=0.544). When the patients receiving abiraterone/enzalutamide as second-line therapy were evaluated, PFS was 7.93±0.96 months for ABI and 10.23±3.35 months for ENZA (p=0.702), and OS-2 was 13.60±8.70 months for ABI and 23.46±4.01 months for ENZA (p=0.433) (Table 5).

Among the patients included in the study, Grade 2 hypertension and Grade 2 fatigue were observed in 1 patient in the ABI group, whereas 2 patients in the ENZA group had Grade 2 nausea and 4 patients had Grade 2 fatigue. Grade 3 or higher side effects were not observed in any patient.

DISCUSSION

In this retrospective study where real-life data were evaluated, abiraterone and enzalutamide had similar efficacy in the treatment of patients with mCRPC. Although not statistically significant, PFS and OS were longer in the ENZA group than the ABI group (PFS: 7.46 versus 8.80 months, p=0.448 and OS-2: 13.6 months versus 21.03 months, p=0.571). In the Cox regression analysis, the patients were evaluated according to the use of abiraterone or enzalutamide, but no statistically significant difference was found.

Although no randomized controlled prospective study has compared both agents head-to-head in the literature, various meta-analyses and retrospective studies are available. One of these meta-analyses is the trial-level meta-analysis by Fang et al.[4] The researchers have found that receiving enzalutamide in the predocetaxel setting increased PFS by 8.3 months (p<0.001) and OS by 5.9 months (p<0.001) compared with abiraterone, although enzalutamide in the post-dosetaxel setting increased OS by 2.2 months. However, this was not statistically significant. In our country, enzalutamide and abiraterone can be used in mCRPC treatment after docetaxel use. In cases where only docetaxel use is not suitable (ECOG performance score >1, bone marrow reserve is extremely insufficient, creatinine clearance <45 mL/min, and liver

TABLE 1: Baseline characteristics and treatment results of patients.

	All	ABI group	ENZA group
Numbers (n)	59	23	36
Age (years)	69 (45-89)	74 (55-89)	68.5 (45-81)
Performance status (ECOG)			
0	4	4	0
1	49	15	34
2	6	4	2
Initial PSA (ng/mL)	39 (2.3-1,500)	28.8 (2.3-1,500)	62.8 (3.0-1,430)
Gleason score	9 (6-10)	9 (6-10)	9 (7-10)
Metastasis			
Bone only	28	15	13
Visceral only	3	2	1
Bone+visceral	28	6	22
Oligometastasis	5	1	4
Treatment lines			
First line	8	3	5
Second line	47	19	28
Third line	3	1	2
Fourth line	1	0	1
PSA response[a](n)	33	14	19
Best response			
Complete response	1	0	1
Partial response	15	5	10
Stabil disease	28	12	16
Progression	15	6	9
Last status			
Progression	44	18	26
Exitus	38	16	22
Alive	21	7	14

[a]PSA response was defined as patients with more than 50% PSA reduction at the 3rd month control; ABI group: Abiraterone acetate; ENZA group: Enzalutamide; PSA: Prostate-specific antigen; ECOG: European Cooperative Oncology Group (performance score).

TABLE 2: Survival analysis of patients.

	All	**ABI group**	**ENZA group**	**p value**
OS-1 (months)	45.93±10.98	45.93±10.08	44.73±19.55	0.448
OS-2 (months)	21.03±4.01	13.60±6.19	21.03±3.84	0.571
PFS (months)	7.46±1.85	7.46±2.08	8.80±4.21	0.448

OS-1: The time from metastatic to death from any cause; OS-2: The time from the initiation of abiraterone/enzalutamide to death from any cause; PFS: The time from the date of abiraterone/enzalutamide initiation to the date of radiological or clinical progression; ABI: Abiraterone; ENZA: Enzalutamide; OS: Overall survival; PFS: Progression-free survival.

reserve is insufficient), it can be used in predocetaxel setting by obtaining off-label approval. Therefore, the number of patients in the predocetaxel setting is limited for both agents as observed in our study.

In the COU-AA-301 study investigating the effectiveness of abiraterone use in the postdocetaxel setting, PFS was 10.2 months and OS was 14.8 months, whereas the response rate was 38%.[5] In this study, PFS was 7.93±0.96 months and OS-2 was

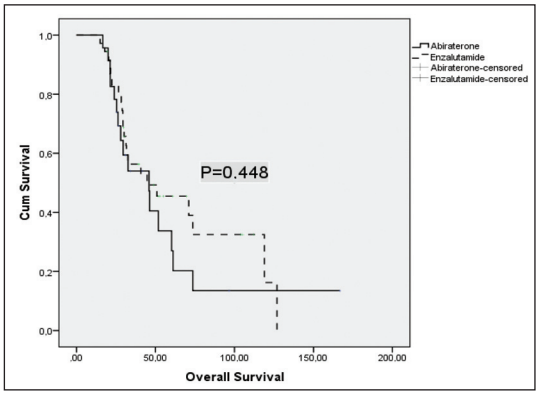

FIGURE 1: Overall survival-1.

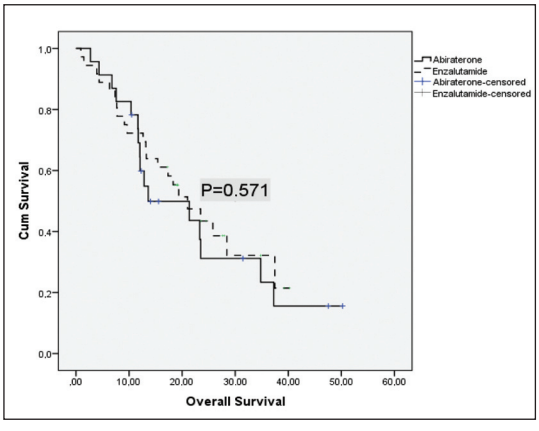

FIGURE 2: Overall survival-2.

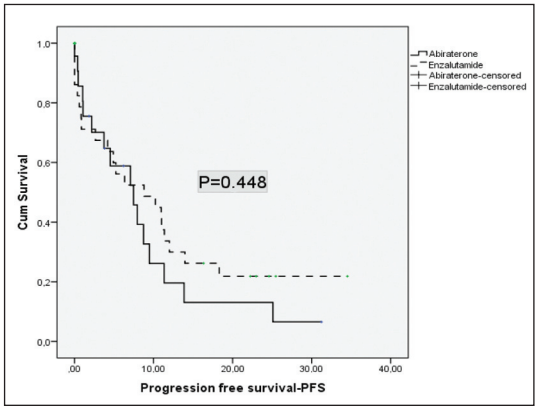

FIGURE 3: Progression-free survival.

13.60±8.70 months. In the AFFIRM study investigating the effectiveness of enzalutamide use in the postdocetaxel setting, PFS was 8.3 months and OS was 18.4 months, whereas the response rate was 54%.[6] In this study, PFS was 10.23±3.35 months and OS-2 was 23.46±4.01 months.

TABLE 3: Univariate Cox proportional hazard regression analysis for prediction of OS-2.

	HR (95% CI)	p value
Age (years)	1.278	0.483
ECOG PS	1.486	0.327
Gleason score	1.019	0.958
Metastasis site	0.968	0.914
Metastatic foci number	0.593	0.395
Treatment (ABI or ENZA)	0.829	0.571
PSA response	1.678	**0.023**

HR: Hazard ratio; CI: Confidence interval; PSA response: more than 50% reduction in PSA value at the 3rd month; ECOG PS: European Cooperative Oncology Group performance score; ABI: Abiraterone; ENZA: Enzalutamide.

In the COU-AA-302 study investigating the effectiveness of abiraterone use in the predocetaxel setting, PFS was 16.5 months and OS was 34.7 months.[7] In this study, PFS was 1.06±0.02 months and OS-2 was 12.03±3.64 months. In the PREVAIL study investigating the effectiveness of enzalutamide use in the predocetaxel setting, PFS was 20 months and OS was 35.3 months.[8] In this study, PFS was 11.36±4.81 months and OS-2 was 17.33±8.98 months.

Compared with the literature, both PFS and OS in the predocetaxel setting were significantly shorter in our study, particularly in patients in the ABI group. This may be because of the low number of patients and the fact that these drugs can be administered after docetaxel in our country as previously stated; however, it can be used with off-label approval when the patient cannot take docetaxel because of accompanying co-morbidities. As a result, this patient group also constitutes a more fragile group.

In our study, the OS of patients with PSA response in both ABI and ENZA groups was better than those without PSA response. Armstrong et al. reported that the decrease in PSA value in the third month in patients receiving enzalutamide was associated with an improvement in PSA progression free survival (PSA-PFS: defined as time to first PSA failure), radiological PFS, and OS.[9] Miller et al. reported that the use of abiraterone in patients with low baseline PSA levels was associated with better OS.[10] In our study, the OS of patients having a decrease in PSA of more than 50% at the 3rd month control was found to be better. However, in

TABLE 4: OS-2 according to PSA response.

	All	ABI group	ENZA group	p value
PSA responsive				
Patients (n)	33	14	19	
OS-2	25.80±3.25	23.33±1.61	28.43±3.27	0.649
PSA nonresponsive				
Patients (n)	22	9	13	
OS-2	11.73±2.58	12.03±0.44	9.63±3.47	0.900

PSA responsiveness was defined as patients with a PSA reduction of more than 50% at three months after initiation of treatment; OS: Overall survival; PSA: Prostate-specific antigen; ABI: Abiraterone; ENZA: Enzalutamide.

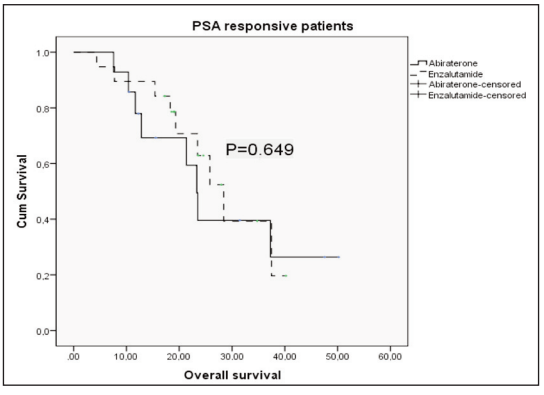

FIGURE 4: Overall survival-2 in PSA responsive patients. **PSA:** Prostate-specific antigen.

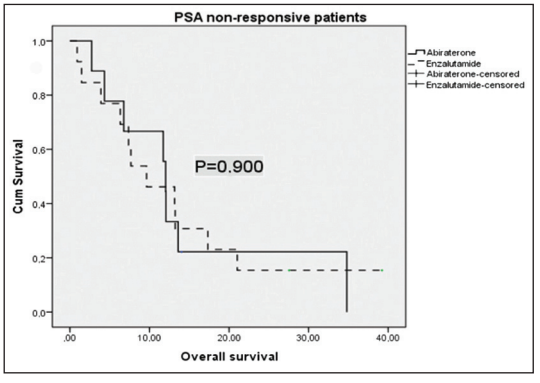

FIGURE 5: Overall survival-2 in PSA nonresponsive patients. **PSA:** Prostate-specific antigen.

TABLE 5: PFS and OS-2 according to lines of abiraterone/enzalutamide therapy.

	ABI group	ENZA group	p value
First line (n)	3	5	
PFS (months)	1.06±0.02	11.36±4.81	<0.0001
OS-2 (months)	12.03±3.64	17.33±8.98	0.544
Second line (n)	19	28	
PFS (months)	7.93±0.96	10.23±3.35	0.702
OS-2 (months)	13.60±8.70	23.46±4.01	0.433

n: Number of patients; PFS: Progression-free survival; OS-2: Overall survival-2; the time from the initiation of abiraterone/enzalutamide to death from any cause; ABI: Abiraterone; ENZA: Enzalutamide.

Cox regression analysis, no association was found between baseline PSA value and survival times.

The survival time of the patient group with liver metastasis is shorter than other patients as reported in the literature.[11] In our study, no significant difference was observed between the patient group with visceral metastasis and the other groups. This may be because of a smaller number of patients with isolated visceral metastases in both ABI and ENZA groups.

In our study, 1 (4.3%) of 23 patients in the ABI group had Grade 2 fatigue and 1 (4.3%) had Grade 2 hypertension, whereas Grade 3 and 4 side effects were not observed. In the final analysis of the COU-AA-301 study, side effects of all grades associated with abiraterone use were evaluated, and fatigue (47%), back pain (33%), nausea (33%), fluid retention (33%), arthralgia (30%), and constipation (28%) were determined. The investigators reported, in order of frequency, that adverse events requiring special attention were fluid retention and edema (33%), hypokalemia (18%), cardiac disorders (16%), abnormal liver function tests (11%), and hypertension (11%).[5]

In our study, 2 (5.5%) of the 36 patients in the ENZA group had Grade 2 nausea and 4 (11.1%) had Grade 2 fatigue, whereas Grade 3 and 4 side effects were not observed. In the PREVAIL study, the most common side effects of all grades associated with the use of enzalutamide were fatigue (36%), back pain (27%), constipation (22%), arthralgia (20%), decreased appetite (18%), and hot flush (18%). The investigators reported side effects that require special attention such as cardiac adverse event (10%), acute renal failure (4%), ischemic or hemorrhagic cerebrovascular event (1%), alanine transaminase elevation (1%), and seizure (1%).[8]

Although both drugs have similar mechanisms of action, their side effect profiles are different. In our study, because of the small number of patients and the retrospective design, possible deficiencies in data entries may have caused less incidence of side effects to be reported compared with the literature data.

This is a retrospective study which is the most crucial limitation. Therefore, patient groups are heterogeneous. A small number of patients is another crucial limitation. However, we believe that the evaluation of real-life data is also very valuable.

CONCLUSION

In conclusion, both abiraterone and enzalutamide are effective treatment agents in mCRPC treatment. Both agents have manageable side effects. The decrease in the PSA value is a crucial predictive marker in the evaluation of treatment efficiency.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Özlem Nuray Sever;* ***Design:*** *Aykut Bahçeci;* ***Control/Supervision:*** *Özlem Nuray Sever, Aykut Bahçeci, Havva Yeşil Çınkır, Mustafa Yıldırım;* ***Data Collection and/or Processing:*** *Özlem Nuray Sever, Aykut Bahçeci, Havva Yeşil Çınkır, Mustafa Yıldırım;* ***Analysis and/or Interpretation:*** *Özlem Nuray Sever, Aykut Bahçeci;* ***Literature Review:*** *Özlem Nuray Sever, Aykut Bahçeci;* ***Writing the Article:*** *Özlem Nuray Sever;* ***Critical Review:*** *Özlem Nuray Sever, Aykut Bahçeci, Havva Yeşil Çınkır, Mustafa Yıldırım;* ***References and Fundings:*** *Özlem Nuray Sever, Aykut Bahçeci, Havva Yeşil Çınkır, Mustafa Yıldırım;* ***Materials:*** *Özlem Nuray Sever, Aykut Bahçeci, Havva Yeşil Çınkır, Mustafa Yıldırım.*

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