Original Study

Using Interferon Alfa Before Tyrosine Kinase Inhibitors May Increase Survival in Patients With Metastatic Renal Cell Carcinoma: A Turkish Oncology Group (TOG) Study

Mehmet Artaç,[1] Hasan Şenol Çoşkun,[2] Levent Korkmaz,[1] Murat Koçer,[3] Nazım Serdar Turhal,[4] Hüseyin Engin,[5] İsa Dede,[6] Semra Paydaş,[7] Berna Öksüzoğlu,[8] Hakan Bozcuk,[9] Ahmet Demirkazık[6]

Abstract

Survival outcomes of interferon-alfa and tyrosine kinase inhibitors for 104 cases of metastatic renal cell carcinoma were included in this study. First-line interferon-alfa treatment before tyrosine kinase inhibitors had an additive survival affect.

Background: We aimed to investigate the outcomes of interferon alfa and sequencing tyrosine kinase inhibitors (TKIs) in patients with metastatic renal cell carcinoma. **Patients and Methods:** This multicenter study assessing the efficacy of TKIs after interferon alfa therapy in the first-line setting in patients with metastatic renal cell carcinoma. Patients (n = 104) from 8 centers in Turkey, who had been treated with interferon alfa in the first-line setting, were included in the study. Prognostic factors were evaluated for progression-free survival (PFS). **Results:** The median age of the patients was 57 years. The median PFS of the patients treated with interferon alfa in the first-line was 3.6 months. A total of 61 patients received TKIs (sunitinib, n = 58; sorafenib, n = 3) after progression while on interferon alfa. The median PFS among the TKI-treated patients was 13.2 months. In the univariate analysis for interferon alfa treatment, neutrophil and hemoglobin level, platelet count, and Karnofsky performance status were the significant factors associated with PFS. In the univariate analysis for TKI treatment, neutrophil and hemoglobin levels were the significant factors for PFS. The median total PFS of the patients who had been treated with first-line interferon alfa and second-line TKIs was 24.9 months. **Conclusion:** This study showed that first-line interferon alfa treatment before TKIs may improve the total PFS in patients with metastatic renal cell carcinoma.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■
Keywords: Cytokine therapy, VEGF inhibitors, Progression free survival, Sorafenib, Sunitinib

Introduction

Renal cell carcinoma (RCC) accounts for approximately 2% of all cancers.[1] On admission, one-third of patients with RCC are at the metastatic stage.[2] Chemotherapy resistance is very high in patients with RCC.[3] Only a limited subset of patients (≤ 20%) benefit from cytokine therapy.[4-7] It has been shown that the median progression-free survival (PFS) was 4.7 months for patients with metastatic RCC who received interferon alfa as a first-line treatment.[8]

[1]Department of Medical Oncology, Necmettin Erbakan University Meram Medical Faculty, Konya, Turkey
[2]Department of Medical Oncology, Akdeniz University Medical Faculty, Antalya, Turkey
[3]Department of Medical Oncology, Süleyman Demirel University Medical Faculty, Isparta, Turkey
[4]Department of Medical Oncology, Marmara University Medical Faculty, Istanbul, Turkey
[5]Department of Medical Oncology, Bülent Ecevit University Medical Faculty, Zonguldak, Turkey
[6]Department of Medical Oncology, Ankara University Medical Faculty, Ankara, Turkey
[7]Department of Medical Oncology, Cukurova University Medical Faculty, Adana, Turkey
[8]Department of Medical Oncology, Ankara Oncology Training and Research Hospital, Ankara, Turkey
[9]Department of Medical Oncology, Akdeniz University Faculty of Medicine, Antalya, Turkey

Submitted: Oct 14, 2015; Revised: Apr 20, 2016; Accepted: Apr 25, 2016

Address for correspondence: Mehmet Artaç, MD, Professor, Necmettin Erbakan University, Meram Medical Faculty, Department of Medical Oncology, 42080 Konya, Turkey
E-mail contact: mehmetartac@yahoo.com

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2016.04.021

The activation of the vascular endothelial growth factor (VEGF) pathway was produced by hypoxia-induced transcription factors in RCC.[9] Hence, VEGF tyrosine kinase inhibitors (TKIs) are the most appropriate treatment strategy for patients with metastatic RCC. Sunitinib is a TKI that targets VEGF receptors 1, 2, and 3, as well as for FLT-3, KIT, and platelet-derived growth factor receptor beta.[10] Sorafenib is another oral multikinase inhibitor that inhibits the RAF/MEK/ERK signaling pathways.[11]

In a phase II trial of sunitinib following cytokine treatment, the median PFS was 8.7 months.[12] Subsequently, in a phase III randomized trial conducted in patients with metastatic RCC comparing first-line sunitinib versus Interferon alfa, the median PFS was 11 months versus 5 months, respectively.[13] The final survival analyses and updated results were reported in 2009.[14] The median overall survival (OS) time was greater in the sunitinib group than in the interferon alfa group (26.4 months vs. 21.8 months, respectively). In the interferon alfa arm, two-thirds of patients received sunitinib (33%) or another VEGF inhibitor. Patients were grouped on the basis of baseline clinical features using the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria (favorable, intermediate, and poor). Interestingly, the median OS times had not been reached with either treatment in the favorable-risk group. At 2 years, 72% of those in the sunitinib group versus 76% of those in the interferon alfa group were alive in the favorable-risk group. Moreover, the only statistically significant difference for median OS noted between treatment groups was with respect to post-study sunitinib use ($P < .001$).

After phase III randomized studies comparing TKIs and interferon alfa in the first-line setting, TKIs were approved as a first-line treatment for metastatic RCC in most developed countries. However, in some developing countries like Turkey, TKIs are still used after cytokine treatment failure. The present study investigated the survival outcomes in Turkish patients who had been treated with interferon alfa in the first-line setting, and who were sequentially treated with TKI therapy as a second-line systemic therapy.

Patients and Methods

Patients

A total of 104 Turkish patients with metastatic RCC were enrolled in this study. The MSKCC criteria were used to define the risk category. High-risk criteria include Karnofsky performance status < 80%, elevated lactate dehydrogenase levels, low hemoglobin levels, elevated serum corrected calcium levels, and time from diagnosis to the start of systemic therapy < 1 year.[8] The patients who received interferon alfa as a first-line treatment and if eligible, those who received TKI as a second-line treatment after progression with interferon alfa were included in this study.

Study Design

This is a national, multicenter, retrospective trial that assessed interferon alfa and TKI treatments in patients with metastatic RCC. The study was approved by the ethics committee at Necmettin Erbakan University, Meram Faculty of Medicine. The study was carried out in accordance with the Declaration of Helsinki and all applicable regulations.

Interferon alfa was administered via subcutaneous injection 3 times weekly using 3, 5, or 10 million units (mu) according to patient tolerance and clinician preference. Sunitinib was administered orally at a dose of 50 mg once daily for a 4-week-on, 2-week-off dosing schedule. Sorafenib was administered orally at 400 mg twice daily. Intrapatient dose reduction or interruption of either drug was performed to manage adverse events. Treatment was continued until disease progression or until unacceptable toxicities developed.

Efficacy

PFS and OS were evaluated for both interferon alfa and TKI-treated patients; PFS and OS were also assessed for patients whose disease progressed with interferon alfa and who subsequently received TKIs. Laboratory results (hematologic analysis and serum chemistry) were evaluated.

Statistical Analysis

Time-to-event analyses were performed using the Kaplan-Meier method and the Cox proportional hazards model with 2-sided 95% confidence intervals (CIs) for the medians and hazard ratios (HRs) of the survival data. A Cox proportional hazards model was established to detect potential influences of baseline characteristics including age, gender, and other known risk factors on PFS.[8] Each prognostic factor was preliminarily evaluated by univariate analysis. Significant factors that had a P value < .05 also were evaluated via multivariate analysis. Statistical differences between PFS were determined with the log-rank test. All accumulated data from participants were analyzed via SPSS 20.0 software package.

Results

Between 1998 and 2012, the data of 104 patients with metastatic RCC from 8 national centers were collected. The patients' median age was 57 years (range, 29-88 years). Twenty-six percent (n = 27) of the patients were female, and 74% (n = 77) were male. Sixty-five patients (62.5%) had clear cell histology, and 15 patients had non-clear cell histology. We were not able to obtain the histopathology results for 24 patients. Nephrectomy was performed for 75 patients, and another 11 patients had metastatic disease at the time of diagnosis. The surgical status of 18 patients was not known. In addition, 5.7% (n = 6), 26.9% (n = 28), and 25.9% (n = 27) of patients received 3, 5, and 10 mu of interferon alfa, respectively. We could not find the data for 43 patients (41.5%) with respect to the interferon alfa dosage that they received. The Fuhrman grade status was 1, 2, 3, and 4 for 2 (1.9%), 20 (19.2%), 21 (20.2%), and 14 (13.5%) patients, respectively. The Fuhrman grade for 47 patients (45.2%) was not known. Metastatic sites were bone, lung, liver, lymph nodes, brain, soft tissue, ovarian, and cardiac in 6 (5.7%), 26 (24.5%), 7 (6.6), 4 (3.8%), 1 (0.9%), 1 (0.9%), 1 (0.9%), and 1 (0.9%) patients, respectively.

A total of 24 (23.1%) of the 104 patients included in this study had died, and the status of 1 patient was not known. As such, we could not calculate the median OS of all patients. Four (3.8%) patients died during interferon alfa treatment. Seventeen (16.3%) patients were still receiving interferon alfa therapy. Three (2.9%) patients stopped receiving interferon alfa because of stable disease, and 2 (1.9%) patients with stable disease rejected receipt of interferon alfa treatment. These 5 patients had stable disease and did not receive TKI. Seventy-eight (75%) patients stopped interferon

Table 1 Patient Demographics and Characteristics With PFSs

	Interferon Alfa		TKI		Interferon Alfa + TKI[b]	
	No. (%)	mPFS (mos)	No. (%)	mPFS (mos)	No. (%)	mPFS (mos)
Treatment						
Interferon alfa	104 (100)	**3.6 (CI, 2.7-4.5)**				
TKI (sunitinib or sorafenib)			63 (100)	**13.2 (CI, 1-27)**		
Sum of interferon alfa + TKI					61 (100)	**24.9 (CI, 8.7-41.3)**
Risk score (MSKCC)[a]						
Favorable (0)	14 (14.2)	2.9	11 (18)	–[c]	10 (16.4)	–[d]
Intermediate (1 or 2)	47 (44.3)	3	29 (47.5)	**13.2**	29 (47.5)	**14.7**
Poor (≥3)	8 (7.5)	2.9	6 (9.8)	**7.8**	6 (9.8)	**9.7**
Not known	35 (34)	*P* = .155	17 (27.8)	***P* = .002**	16 (26.3)	***P* = .001**
Karnofsky performance status						
Greater than 80	54 (51.9)	**3.6**	37 (59.4)	**22**	36 (59)	**25.6**
Lesser than 80	15 (14.4)	**2.2**	9 (14.1)	**7.8**	9 (14.7)	**10.7**
Not-known	35 (33.7)	***P* = .005**	17 (26.6)	***P* = .010**	16 (26.3)	***P* = .018**
Interferon dosage						
3 mu 3 times in 1 wk	6 (5.7)	**3**	4 (6.4)	3.8	4 (6.5)	7.2
5 mu 3 times in 1 wk	28 (26.9)	2.8	18 (28.6)	13.2	18 (29.5)	30.6
10 mu 3 times in 1 wk	27 (25.9)	**5.1**	17 (26.9)	7	16 (26.3)	37.7
Not known	43 (41.5)	***P* = .09**	24 (38.1)	*P* = .262	23 (37.7)	*P* = .481
Time from diagnosis to starting systemic therapy		4.1		13.2		14.7
<1 year	77 (74)	2.7	44 (69.8)	15.9	43 (68.2)	24.9
>1 year	27 (26)	*P* = .389	19 (30.2)	*P* = .222	18 (31.8)	*P* = .199
Age (y), median, 57 (range, 29-88 years)		4.4		22		28.9
<57 years	49 (47.1)	3.5	25 (40.6)	9.8	24 (39.3)	12.9
>57 years	55 (52.9)	*P* = .455	38 (59.4)	*P* = .232	37 (60.7)	*P* = .193
Gender		3		22		14.7
Male	77 (74.1)	4.1	48 (76.6)	12.9	46 (75.5)	27
Female	27 (25.9)	*P* = .515	15 (23.4)	*P* = .573	15 (24.5)	*P* = .282
Surgery (nephrectomy)						
Performed	75 (72.1)	3.5	48 (76.1)	12.9	46 (75.4)	15.8
Not performed	11 (10.5)	2.5	7 (11.1)	21.9	7 (11.4)	25.5
Not known	16 (17.4)	*P* = .127	8 (12.8)	*P* = .177	8 (13.1)	*P* = .501
Localization						
Right	40 (38.4)	3.9	25 (39.6)	13.2	23 (37.7)	12.9
Left	45 (43.3)	3	29 (46)	12.9	29 (47.5)	24.9
Not known	19 (18.3)	*P* = .980	9 (14.2)	*P* = .863	9 (14.7)	*P* = .497
Histopathology						
Clear cell	65 (62.5)	3.5	43 (68.2)	13.2	42 (68.8)	24.9
Not clear cell	15 (14.4)	6.7	8 (12.7)	10.5	7 (11.4)	12.2
Not known	24 (23.1)	*P* = .181	12 (19.1)	*P* = .305	12 (19.6)	*P* = .114
Fuhrman grade						
1	2 (1.9)	–	1 (1.5)	–	1 (1.6)	–
2	20 (19.2)	3	16 (25.4)	22.7	15 (24.5)	30.7

Table 1 Continued

	Interferon Alfa		TKI		Interferon Alfa + TKI[b]	
	No. (%)	mPFS (mos)	No. (%)	mPFS (mos)	No. (%)	mPFS (mos)
3	21 (20.1)	3.7	13 (20.6)	10.5	12 (19.6)	12.2
4	14 (13.5)	5.5	7 (11.2)	6.7	7 (11.4)	10.6
Not known	47 (45.3)	$P = .995$	26 (41.3)	$P = .256$	26 (42.6)	$P = .123$

The significant values are indicated in bold ($P < .05$).
Abbreviations: CI = Confidence interval defined as 95%; mPFS = median progression free survival; MSKCC = Memorial Sloan Kettering Cancer Center; No = number of patients; TKI = tyrosine kinase inhibitor.
[a]Risk factors include; Karnofsky performance scale < 80, serum lactate dehydrogenase level > 1.5 × the upper limit of normal, serum hemoglobin level < the lower limit of normal, corrected serum calcium level > 10 mg/dl, time since first diagnosis < 1 year.
[b]The sum of median PFSs of the patients who received interferon alfa and TKI treatment sequentially was also calculated to evaluate the additive effect of interferon alfa to TKI therapy.
[c]In this favorable risk group of patients, the median duration of follow-up was 20.8 months (range, 1.8-55.5 months), and the patients have not still reached their median PFS.
[d]In this favorable risk group of patients, the median duration of follow-up was 24.9 months (range, 3.8-58.1 months), and the patients have not still reached their median PFS.

alfa due to disease progression, and 17 of them were out of our follow-up. Moreover, 28 (45.9%) TKI-treated patients progressed during therapy, while 23 (37.7%) patients are still continuing TKI therapy with stable disease. Finally, 1 (1.6%) patient stopped TKI because of toxicity. The status of TKI usage was not known for 3 (4.9%) of the patients, and 6 (9.8%) patients died while on TKI treatment.

The median PFS of the interferon alfa therapy group was 3.6 months (95% CI, 2.7-4.5 months) among the 104 metastatic RCC patients. The median PFS for the TKI therapy groups (sunitinib, n = 58; sorafenib, n = 3) was 13.2 months (95% CI, 5.6-20.8 months). To illustrate the additive effect of interferon alfa, the sum of the PFS times of interferon alfa and TKI therapies was also calculated; the overall PFS was 24.9 months (95% CI, 8.7-41.3 months) in those patients who received interferon alfa as a first-line therapy and received a TKI as a second-line therapy following disease progression (n = 61).

No significant differences were found for age, gender, surgery, histopathology, localization, and Fuhrman grade status for either PFS of interferon alfa or TKI therapy groups. The PFS of the patients who received a dosage of interferon alfa of 10 mu (5.1 months) was greater than that of those who received a dosage of 3 mu (3 months) ($P = .09$). The PFSs of interferon alfa, TKI, and the sum of interferon alfa + TKI therapies were significantly higher in the patients whose Karnofsky performance scores were > 80 than those who had a score < 80 ($P = .005$, $P = .028$, and $P = .018$, respectively) (Table 1).

MSKCC scoring did not show any effect on interferon alfa PFS. However, there was a significant effect on PFS of TKI treatment and total PFS (sum of the PFS times of TKI and interferon alfa therapies) ($P = .003$ and $P = .001$, respectively). The favorable-risk group of patients did not reach the median PFS.

Only hemoglobin level and Karnofsky performance score significantly influenced the PFS of TKI treatment. The PFS of TKI treatment was 2.5 times greater in patients with a Karnofsky performance score > 80 and it was 0.34 times less in patients who had lower than normal hemoglobin levels. In the univariate analysis, the PFS of interferon alfa was 2.36 times greater in those patients with a Karnofsky performance score > 80, and it was 0.40 times less in patients with lower than normal hemoglobin levels. The PFS of interferon alfa was also 0.26 and 0.36 times lower in those patients whose neutrophil levels and platelet levels were higher than normal, respectively. Significant parameters noted in the univariate analysis (neutrophil level, hemoglobin level, platelet count, and Karnofsky performance status) were also analyzed using multivariate Cox regression analysis. There was no significance in multivariate analysis (Table 2); however, only neutrophil level approached significance ($P = .06$). The predictors were also evaluated to determine whether there was any correlation between any of these factors. Hemoglobin, platelet, and neutrophil levels were all significantly correlated with each other across all comparisons. Only hemoglobin level was significantly correlated with Karnofsky performance score. All effecting factors affecting OS were analyzed using the Kaplan-Meier method (Figure 1).

Discussion

This retrospective study showed that the median PFS of the patients who received interferon alfa as first-line therapy and TKI as second-line therapy was 24.9 months. While the median PFS of interferon alfa treatment was 3.6 months, it was longer for the TKI treatment (13.2 months). The PFS of the patients who received a dosage of 10 mu of interferon alfa was greater than those patients who received 3 mu. Neutrophil level, hemoglobin level, platelet count, and Karnofsky performance status influenced the PFS of interferon alfa significantly. As such, we concluded that a risk assessment of Turkish patients with RCC might be best performed with these parameters. According to our study, high neutrophil levels, low hemoglobin levels, high platelet counts, and low Karnofsky performance status were bad prognostic factors. A correlation analysis of these predictors was also performed. It can be said that complete blood count may be useful for the evaluation of patients with metastatic RCC when estimating survival outcomes. The median OS could not be calculated because most of the patients with metastatic RCC were still alive.

Interferon alfa and TKI treatments were compared in a Japanese study including 48 patients.[15] This study showed that interferon alfa was not inferior to TKI therapy in metastatic RCC. The median PFS in the interferon alfa group (20 months) was not significantly different from that in the TKI group (16 months). The median PFS of interferon alfa was shorter in our study (3.7 months); however, the median PFS of TKI treatment was longer than expected in the TKI group treated following interferon alfa treatment (13.2 months). Only patients with a favorable MSKCC score had been enrolled in the Japanese study. We did not stratify any of the

Table 2 Univariate and Multivariate Cox Regression Analysis for Interferon Alfa PFS, TKI PFS, and (Interferon Alfa + TKI) PFS

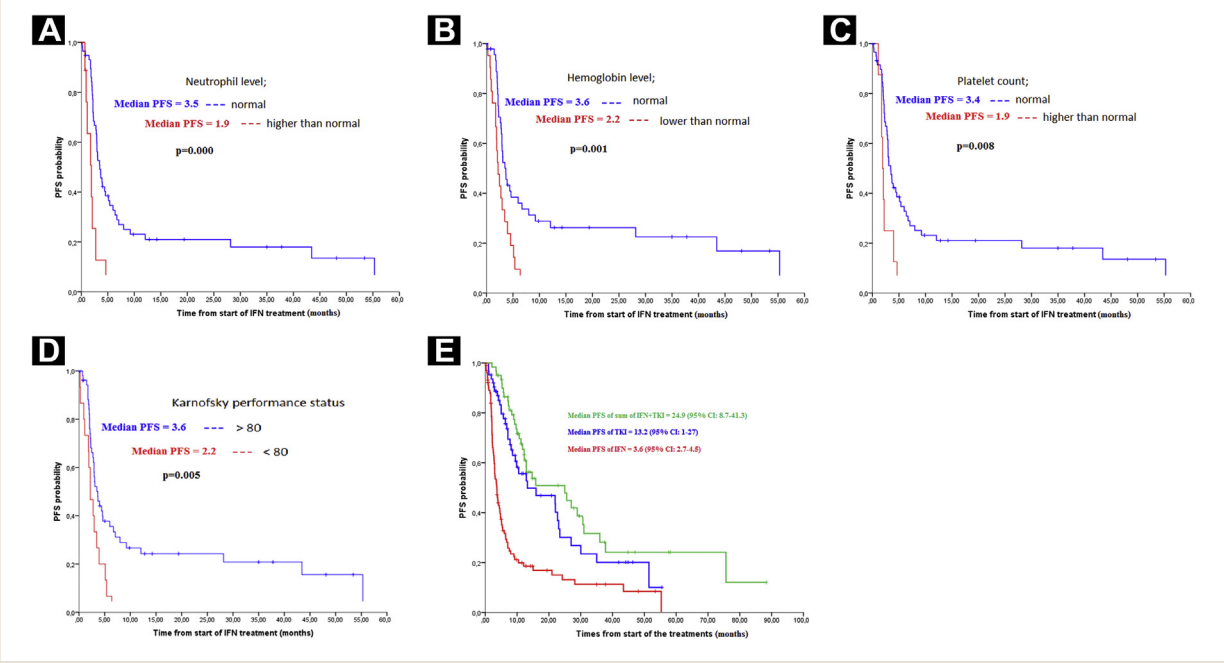
	Interferon Alfa PFS						TKI PFS						(Interferon Alfa + TKI) PFS					
	Univariate			Multivariate			Univariate			Multivariate			Univariate			Multivariate		
Parameters	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95%CI**	***P***	**HR**	**95% CI**	***P***
Hemoglobin level, lower or normal	**0.405**	**0.229-0.716**	**.002**	0.593	0.288-1.24	.157	**0.343**	**0.136-0.864**	**.023**	0.406	0.143-1.152	.09	**0.304**	**0.121-0.767**	**.012**	0.534	0.149-1.909	.334
Karnofsky performance score	**2.36**	**1.272-4.379**	**.006**	1.756	0.818-3.767	.148	**2.506**	**1.074-5.851**	**.034**	1.802	0.700-4.640	.222	**2.713**	**1.151-6.392**	**.022**	2.118	0.757-5.930	.153
Neutrophil level, higher or normal	**0.265**	**0.121-0.582**	**.001**	**0.295**	**0.127-0.685**	**.005**	0.404	0.131-1.244	.114	—	—	—	**0.314**	**0.098-1.006**	**.051**	0.46	0.113-1.877	.279
Platelet count, greater or normal	0.367	0.169-0.797	.11	—	—	—	0.602	0.172-2.107	.427	—	—	—	0.48	0.133-1.728	.261	—	—	—
Nephrectomy	1.719	0.847-3.487	.133	—	—	—	1.571	0.536-4.605	.41	—	—	—	1.442	0.494-4.211	.503	—	—	—
Interferon alfa dosage	1.981	0.792-4.704	.148	—	—	—	0.641	0.185-2.221	.483	—	—	—	1.001	0.484-2.073	.997	—	—	—
Age	1.105	0.992-1038	.198	—	—	—	0.995	0.963-1.028	.749	—	—	—	1.001	0.970-1.033	.949	—	—	—
Time from diagnosis to starting systemic therapy <1 year or not	0.808	0.496-1.316	.391	—	—	—	1.559	0.747-3.421	.227	—	—	—	1.683	0.754-3.757	.204	—	—	—
Neutrophil to lymphocyte ratio	1.031	0.961-1.106	.394	—	—	—	1.024	0.933-1.125	.618	—	—	—	1.014	0.920-1.118	.778	—	—	—
Gender	0.848	0.515-1.396	.516	—	—	—	0.697	0.302-1.609	.398	—	—	—	0.634	0.274-1.465	.286	—	—	—
Calcium level, higher or normal	0.766	0.300-1.957	.578	—	—	—	0.448	0.129-1.551	.205	—	—	—	0.467	0.135-1.609	.228	—	—	—
LDH >1.5 × ULN or normal	0.874	0.372-2.052	.757	—	—	—	0.643	0.211-1.959	.437	—	—	—	0.604	0.199-1.833	.373	—	—	—
Creatinine level, higher or normal	1.023	0.583-1.796	.936	—	—	—	0.799	0.334-1.911	.614	—	—	—	0.957	0.436-2.101	.914	—	—	—
Risk score between intermediate and poor[a]	0.666	0.305-1.452	.306	—	—	—	0.389	0.143-1.056	.064	—	—	—	0.409	0.153-1.096	.076	—	—	—
Risk score between favorable and poor[a]	0.453	0.169-1.217	.116	—	—	—	**0.058**	**0.007-0.494**	**.009**	—	—	—	**0.05**	**0.006-0.429**	**.006**	—	—	—
Risk score between favorable and intermediate[a]	0.577	0.277-1.204	.143	—	—	—	**0.258**	**0.074-0.901**	**.034**	—	—	—	**0.164**	**0.037-0.729**	**.018**	—	—	—

The significant values are indicated in bold ($P < .05$).

Abbreviations: CI = Confidence interval; HR = hazard ratio; Interferon alfa + TKI PFS = the sum of median PFSs of the patients who received interferon alfa and TKI treatment sequentially was also calculated to evaluate additive effect of interferon alfa to TKI therapy; LDH = lactate dehydrogenase; PFS = progression-free survival; TKI = tyrosine kinase inhibitor; ULN = upper limit of normal.

[a]The MSKCC risk score was also analyzed in Table 1 with the Kaplan-Meier method, but the risk score was not entered into the multivariate analysis in the Cox regression hazard model because there were linear dependencies between the other univariately effective factors.

Figure 1 A. Kaplan-Meier Curves of the First-Line Progression-Free Survival (PFS) according to Interferon Alfa Therapy in Association With Neutrophil Count. B. Kaplan-Meier Curves of the First-Line PFS according to Interferon Alfa Therapy in Association With Hemoglobin Level. C. Kaplan-Meier Curves of the First-Line PFS According to Interferon Alfa Therapy in Association With Platelet Count. D. Kaplan-Meier Curves of the First-Line PFS According to Interferon Alfa Therapy in Association With Performance Score. E. Kaplan-Meier Curves of the Progression-Free Survival According to First-Line (Interferon Alfa), Second-Line (tyrosine Kinase Inhibitors; TKIs), and Together (Interferon Alfa Sequencing With TKIs)



patients based on a given risk group in our study. The median PFS of the interferon alfa treatment in the literature is 4.7 months as well. It can be argued that investigating certain risk factors may constitute a very important choice in the assessment of survival in metastatic RCC. Per our results, the MSKCC scoring system did not show any differences in the PFS of interferon alfa; however, the PFS of TKI was significantly different between intermediate- and poor-risk groups. Conversely, in the favorable-risk group of our patients, at the time of this writing, the patients have not yet reached the median PFS.

Motzer et al investigated the survival outcomes of interferon alfa and prognostic criteria for patients with metastatic RCC.[8] The median OS and time-to-progression were 13 months versus 4.7 months, respectively. As such, the time-to-progression of this study was longer than the PFS in our study. The OS decreased gradually among the poor-risk patients as a function of the 3 risk groups (favorable, intermediate, and poor; 30 months, 14 months, and 5 months, respectively). However, in our study, we did not find a relationship between these risk factors and the MSKCC scoring system. Risk factors may change among different populations and treatment types (eg, interferon alfa vs. TKI).

Esbah et al designed a Turkish study to evaluate the outcomes of sequential therapy (interferon alfa, TKIs, mammalian target of rapamycin) and prognostic factors in patients with metastatic RCC.[16] The median OS was 23 months among all patients with metastatic RCC and 20 months in patients treated with TKIs. The median PFS was 11 months for TKI-treated patients, which is similar to the findings of Motzer et al.[17] However, the median PFS was 19 months in the low-risk group. According to the MSKCC and Heng[18] risk classifications, the median OS time differed between groups. The median OS improved with an increasing number of sequential therapies. We showed that the sum of PFS times of interferon alfa and TKI therapies was 24.9 months. In Esbah et al's study, the median PFS of interferon alfa treatment was 2 months, which is lower than both that from the literature and in our study. The investigators concluded that the reason for this might be that, in these patients, the physician requested that the patients switch to TKI therapy.

Motzer et al randomized patients with untreated metastatic RCC to either the sunitinib or interferon alfa treatment group. This phase III trial showed that treatment with sunitinib extended the PFS time when compared with interferon alfa treatment. The median PFS in the sunitinib group (11 months) was 6 months longer than that in the interferon alfa group (5 months).[13] The median PFS of TKI treatment in our study (13.2 months) was similar to that of Motzer et al's study; however, treatment with interferon alfa therapy before TKI therapy extended the duration of PFS (24.9 months). As such, we assumed that, although TKIs are chosen globally as the first-line treatment for metastatic RCC, interferon alfa therapy might be better as the first-line treatment, especially in those patients within a favorable prognostic group.

There are several limitations in our study. First, the OS and PFS times of all patients who received either TKI or interferon alfa did

not reach their respective endpoints. Second, we could not obtain some patient parameters. We did not have the data of interferon alfa dosages in all patients. We do not have the data about dose modifications and interruptions of TKI treatments. Finally, we were also unable to calculate the median OS in our study. As such, the MSKCC risk scoring method and its relationship to OS could not be evaluated.

Prospectively designed studies should be performed to investigate risk parameters in patients with metastatic RCC. TKI therapies are preferred as the first-line treatment for metastatic RCC; however, the additive effect of interferon alfa should be kept in mind when treating the favorable and intermediate prognostic group of patients. This study demonstrated that increasing the number of therapeutic lines in sequential therapy prolonged the PFS of patients with metastatic RCC.

Clinical Practice Points

- Nowadays, VEGF tyrosine kinase inhibitors (TKIs) are the most appropriate firstline treatment strategy for metastatic RCC patients. However, we investigated the effect of interferon-alpha treatment in the firstline setting of metastatic RCC. Using IFN-alpha before TKI treatment may improve the total PFS in mRCC patients. The effect of IFN-alpha should be kept in mind in mRCC.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Motzer RJ. New perspectives on the treatment of metastatic renal cell carcinoma: an introduction and historical overview. *Oncologist* 2011; 16(Suppl 2):1-3.
2. Molina AM, Motzer RJ. Clinical practice guidelines for the treatment of metastatic renal cell carcinoma: today and tomorrow. *Oncologist* 2011; 16(Suppl 2): 45-50.
3. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *N Engl J Med* 1996; 335:865-75.
4. Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. *J Urol* 2000; 163: 408-17.
5. Wirth MP. Immunotherapy for metastatic renal cell carcinoma. *Urol Clin North Am* 1993; 20:283-95.
6. Law TM, Motzer RJ, Mazumdar M, et al. Phase III randomized trial of interleukin-2 with or without lymphokine-activated killer cells in the treatment of patients with advanced renal cell carcinoma. *Cancer* 1995; 76:824-32.
7. Vogelzang NJ, Lipton A, Figlin RA. Subcutaneous interleukin-2 plus interferon alfa-2a in metastatic renal cancer: an outpatient multicenter trial. *J Clin Oncol* 1993; 11:1809-16.
8. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002; 20:289-96.
9. Shweiki D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature* 1992; 359:843-5.
10. Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 2003; 9:327-37.
11. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; 356:125-34.
12. Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; 24:16-24.
13. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; 356:115-24.
14. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009; 27:3584-90.
15. Sazuka T, Nihei N, Nakamura K, et al. Interferon treatment for Japanese patients with favorable-risk metastatic renal cell carcinoma in the era of targeted therapy. *Korean J Urol* 2015; 56:205-11.
16. Esbah O, Demirci U, Helvaci K, et al. Sequential therapy and prognostic factors in metastatic renal cell carcinoma: single centre experience. *J BUON* 2014; 19:1062-9.
17. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006; 295:2516-24.
18. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009; 27:5794-9.