original reports abstract

# Efficacy and Prognostic Factors of Sunitinib as First-Line Therapy for Patients With Metastatic Renal Cell Carcinoma in an Arab Population

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**PURPOSE** Antiangiogenic tyrosine kinase inhibitors have been the mainstay first-line therapy for metastatic renal cell carcinoma (mRCC). We reviewed the efficacy of first-line therapy with sunitinib in patients with mRCC in an Arab population.

**METHODS** Medical records of patients with mRCC treated at a tertiary care center in Saudi Arabia, during the period from 2007 to 2016, were reviewed. Demographic data, treatment received, response, and prognostic factors were analyzed.

**RESULTS** Fifty-five patients who received sunitinib were identified. The median age was 60 years (range, 18 to 78 years), and 42 of the 55 patients were men (76.3%). International Metastatic RCC Diagnostic Consortium prognostic scores for favorable/intermediate/poor were 14.5%/43.6%/38.2%, respectively. The median performance status was 1, and the median Charlson comorbidity index score was 9. Thirty-seven patients (67.2%) had cytoreductive nephrectomy. Thirty-seven patients (67.2%) had clear cell histology. Twenty-two patients (40%) underwent dose reduction. Twenty-seven patients (49%) received second-line therapy, and seven patients (12.7%) received third-line therapy. Response rates were complete response in one patient (1.8%), partial response in 17 (30.9%), stable disease in 10 (18.1), and disease progression in 20 (36.3%). Progression-free survival (PFS) and overall survival (OS) were 6.0 and 24.7 months, respectively. Univariate analysis showed statistically improved PFS for dose reduction ($P = .015$) and the development of hypothyroidism ($P = .03$). It also showed statistically improved OS for dose reduction ($P = .035$), hypothyroidism ($P = .0002$), and cytoreductive nephrectomy ($P = .0052$). Multivariate analysis showed statistically improved PFS for dose reduction ($P = .01$) and OS for development of hypothyroidism ($P = .007$).

**CONCLUSION** Our data for sunitinib in mRCC show significantly lower PFS than expected. The absence of prognostic value of the International Metastatic RCC Diagnostic Consortium scoring system and pathologic subtype warrant further investigation and possible inclusion of genetic scoring in this ethnic group of patients.

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## INTRODUCTION

Metastatic renal cell carcinoma (mRCC) carries a poor prognosis. With the exception of patients with solitary or localized few metastatic sites where metastasectomy may play a role in possible cure,[1-3] most patients die of advanced disease.[4-6] Over the past 13 years, antiangiogenic tyrosine kinase inhibitors (TKIs) have been the mainstay of therapy for mRCC.[7-11] Response to TKIs has been dependent on many factors including, but not limited to, time from diagnosis to treatment; performance status; and serum calcium, hemoglobin, and lactate dehydrogenase levels.[12,13] Although the Memorial Sloan Kettering Cancer Center risk score has shown prediction of survival in the TKI era,[14] the newer International Metastatic RCC Database Consortium (IMDC) risk stratification model has proven to be more relatively prognostic in patients with mRCC treated with TKIs.[15,16]

The efficacy of TKIs in mRCC has been established in publications from Western countries.[4,17,18] Data for their efficacy from this part of the world are lacking, and the validity of the Memorial Sloan Kettering Cancer Center and IMDC risk scoring systems has not been validated in patients from the Middle East.[19]

In this study, we evaluated the efficacy of sunitinib in the first-line setting in patients diagnosed with mRCC and studied the different risk factors, in particular the validation of IMDC risk stratification in patients from this part of the world.

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## CONTEXT

**Key Objective**

Determine the efficacy of sunitinib in metastatic renal cell carcinoma in Arab population. Validate the IMDC prognostic index in Arab patients with metastatic renal cell carcinoma treated with sunitinib. Determine the toxicity of sunitinib in Arab patients with metastatic renal cell carcinoma.

**Knowledge Generated**

Sunitinib results in lower progression-free survival in the studied group compared to published western data. The IMDC prognostic index could not be validated in the studied population.

**Relevance**

Data generated in one part of the world need to be confirmed and or validated in different parts of the world to ensure universal applicability.

## METHODS

This was a retrospective study. Medical records of patients 18 years of age or older with mRCC treated at our institution between February 2007 and December 2016 were reviewed. Patients were identified through the hospital tumor registry software CNExT (C/NET Solutions, Berkeley, CA). The following data were collected: age, sex, ethnicity, histology, Eastern Cooperative Oncology Group performance status, Charlson comorbidity index (CCI),[20] modified CCI (the index calculated excluding solid tumor score because all patients had mRCC), year of starting therapy, IMDC risk group, sites of metastasis, neutrophil/lymphocyte ratio, cytoreductive nephrectomy, starting dose, dose reduction (patients had dose reductions to 37.5, 25.0, and 12.5 mg), response to therapy, duration of response, progression, second- and third-line therapies, and survival. Patients were stratified into risk groups (favorable, intermediate, and poor) on the basis of the IMDC risk group. Toxicity data were also collected, including for hypertension, hypothyroidism, and hand and foot syndrome.

Radiology reports and films were reviewed for response assessment using Response Evaluation Criteria in Solid Tumors (RECIST v1.1).[21] Progression-free survival (PFS) was calculated from the date of initiation of first-line treatment until the date of progressive disease or death from any cause. Overall survival (OS) was calculated from the date of initiation of therapy until the date of death from any cause. Patients who were alive at the time of last follow-up were censored.

Descriptive statistics were used for patient characteristics, toxicity data, and best tumor response. PFS and OS were estimated using the Kaplan-Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazards model to assess the relationship between PFS/OS and baseline parameters, as well as for the relationship between PFS/OS and treatment-related toxicities. The log-rank test was used to assess statistical significance; $P < .05$ was considered significant. Tabulation and statistical data analysis were done using SAS statistical software application (version 9.4; SAS Institute, Cary, NC).

This research project was conducted in accordance with the ethical principles contained in the Declaration of

**TABLE 1.** Characteristics of Patients in Sunitinib Group (n = 55)

| Item | No. (%) |
|---|---|
| Median age, years (range) | 60 (18-78) |
| Sex | |
| Male | 42 (76.3) |
| Female | 13 (23.7) |
| Ethnicity | |
| Mid-Eastern Arab | 55 (100) |
| Pathologic subtype | |
| Clear cell | 37 (67.2) |
| Non–clear cell | 18 (32.8) |
| Liver metastasis | 18 (32.7) |
| Bone metastasis | 17 (31) |
| Cytoreductive nephrectomy | 37 (67.2) |
| IMDC risk group | |
| Favorable | 8 (14.5) |
| Intermediate | 24 (43.6) |
| Poor | 21 (38.2) |
| Unknown | 2 (3) |
| Year of diagnosis | |
| 2007-2010 | 34 (61.8) |
| 2011-2016 | 21 (38.2) |
| Charlson comorbidity index score, median (range) | |
| Total score | 9 (6-13) |
| Modified score | 3 (0-7) |
| Dose reduction | |
| Initial | 3 (5.5) |
| Subsequent | 22 (40) |
| Neutrophil/lymphocyte ratio, median (range)* | 2.1 (0.4-19.8) |

Abbreviation: IMDC, International Metastatic RCC Database Consortium.

*Fifty-three patients.

 

Helsinki (Edinburgh [2000] revision), Good Clinical Practice Guidelines, and the policies and guidelines of the institution in which it was performed. The study was approved by the institutional review board at our center.

The identities of patients who were studied remained anonymous because no identifying data or protected health information were recorded. All data were password secured to safeguard the confidentiality of collected patient data.

## RESULTS

### Patients and Disease Characteristics

Ninety-six patients with mRCC were identified. First-line therapy received was as follows: sunitinib (n = 55; 57.3%), pazopanib (n = 7; 7.3%), everolimus (n = 4; 4.2%), sorafenib (n = 2; 2.1%), temsirolimus (n = 1; 1.0%), bevacizumab/interferon (n = 1; 1.0%), paclitaxel/carboplatin (n = 1; 1.0%), and best supportive care (n = 24; 25%).

### Sunitinib Group: Patients and Disease Characteristics

Of 55 patients who received sunitinib, 42 (76.3%) were men, 13 (23.7%) were women, 37 (67.2%) had cytoreductive nephrectomy, 52 (94.5%) started with the full dose of 50 mg/day (4 weeks of treatment, 2 weeks off). Twenty-two patients (40%) had dose reductions: 16 to 37.5 mg, five to 25.0 mg, and one to 12.5 mg. Patient characteristics are listed in Table 1.

### Efficacy and Survival Analysis

The overall response rate was 32.7%, with one (1.8%) complete response and 17 (30.9%) partial responses. Ten patients (18.1%) achieved stable disease, and 20 (36.3%) had disease progression. The tumor control rate was 51%. Seven patients (12.7%) did not undergo evaluation. Nine patients (16.3%) were still on treatment at the time of study evaluation. Reasons for sunitinib discontinuation were disease progression in 40 patients and toxicity in six. Forty-six patients had disease progression; 27 of them received second-line therapy (n = 24, everolimus; n = 2, sorafenib; and n = 2, pazopanib), with a median PFS on second-line therapy of 4.2 months (95% CI, 2.23 to 14.5 months). The median duration of first-line therapy was 4.8 months (95% CI, 6.0 to 12.1 months), and the median time to best response was 3.0 months (95% CI, 3.0 to 4.8 months).

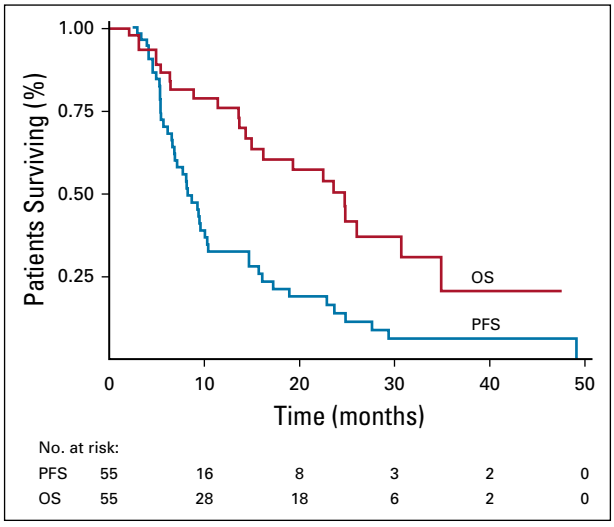


**FIG 1.** Kaplan-Meier plot of progression-free survival (PFS) and overall survival (OS) in 55 patients treated with sunitinib. PFS: median, 6.07 months; 95% CI, 4.0 to 7.6 months. OS: median, 24.7 months; 95% CI, 14.9 to 30.7 months.

**TABLE 2.** Incidence of Toxicity (all grades) Among 55 Patients Treated With Sunitinib

| Toxicity Item | No. (%) |
|---|---|
| Hypertension | 14 (25.5) |
| Hypothyroidism | 20 (36.4) |
| Fatigue | 5 (9.1) |
| Hand and foot syndrome | 17 (30.9) |
| Scrotal ulcers | 1 (1.8) |
| High transaminases | 1 (1.8) |
| Thrombocytopenia/neutropenia | 4 (7.3) |
| Electrolyte imbalance | 3 (5.4) |
| Stomatitis | 5 (9.1) |

With a median follow-up of 24.5 months, the PFS was 6.07 months (95% CI, 4.0 to 7.6 months; Fig 1), and OS was 24.7 months (95% CI, 14.9 to 30.7 months). PFS was 5.6 months for clear cell histology (95% CI, 3.5 to 11.9 months) and 6.6 months for non–clear cell (95% CI, 2.7 to 16.1 months), with $P = .719$. OS was 22.5 months (95% CI, 13.7 to 35.0 months) for clear cell histology and 26 months (95% CI, 5.4 to 30.7 months) for non–clear cell histology. Data on IMDC risk groups were available for 53 patients. The median duration of follow-up for IMDC risk groups favorable, intermediate, and poor was 24.5, 24.6, and 12.9 months, respectively. There was no significant difference in PFS and OS in patients with low-, intermediate-, or high-risk group according to IMDC risk groups.

Fourteen patients (25.5%) developed hypertension, 20 (36.4%) had hypothyroidism, and 17 (30.9%) had hand and foot syndrome. Other toxic events are listed in Table 2.

Univariate analysis of pretreatment prognostic factors and toxicity factors for PFS showed dose reduction ($P = .015$) and hypothyroidism ($P = .03$) as the only significant factors. For OS, cytoreductive nephrectomy ($P = .0052$), dose reduction ($P = .035$), and hypothyroidism ($P = .0002$) were of statistical significance (Table 3).

Multivariate analysis for the same risk and toxicity factors for PFS and OS showed the dose reduction to be of significance ($P = .01$) for PFS and the development of hypothyroidism as the only factor of statistical significance ($P = .007$) for OS (Table 4).

PFS and OS for patients who received second-line everolimus after sunitinib were 2.4 months (95% CI, 1.9 to 5.7 months) and 10.2 months (95% CI, 6.5 to 17.7 months), respectively.

**TABLE 3.** Univariate Analysis of Prognostic Factors for Patients Treated With Sunitinib

| | PFS | | OS | |
|---|---|---|---|---|
| **Item** | ***P*** | **Median (95% CI)** | ***P*** | **Median (95% CI)** |
| Age, years | | | | |
| ≤ 65 | .05 | 7.43 (4.0 to 13.3) | .57 | 22.5 (13.67 to 34.93) |
| > 65 | | 4.53 (2.8 to 6.0) | | 24.7 (4.93 to NR) |
| N/L ratio | | | | |
| > 2.1 | .71 | 5.47 (2.8 to 13.3) | .91 | 30.73 (13.6 to 34.93) |
| ≤ 2.1 | | 6.67 (4.0 to 11.97) | | 23.6 (14.33 to NR) |
| CRS | | | | |
| Yes | .09 | 6.87 (5.17 to 11.97 | .0052 | 26.0 (14.97 to NR) |
| No | | 4.0 (2.8 to 11.97) | | 14.33 (4.93 to 22.5) |
| Pathologic subtype | | | | |
| Clear cell | .72 | 5.67 (3.57 to 11.97) | .86 | 22.5 (13.67 to 34.93) |
| Non–clear cell | | 6.67 (2.73 to 16.1) | | 26.0 (5.4 to 30.73) |
| Year starting treatment | | | | |
| 2007-2010 | .77 | 6.77 (4.0 to 7.77) | .83 | 19.33 (13.67 to NR) |
| 2011-2016 | | 4.3 (2.77 to 11.97) | | 24.8 (11.43 to NR) |
| ECOG performance status | | | | |
| 0-1 | .67 | 6.67 (4.0 to 11.97) | .94 | 24.8 (13.67 to 34.93) |
| ≥ 2 | | 5.47 (2.8 to 7.67) | | 24.77 (4.93 to NR) |
| IMDC score | | | | |
| Favorable | .515 | 7.67 (4.0 to 20.0) | .85 | 26.0 (6.43 to NR) |
| Intermediate | | 6.0 (2.77 to 7.43) | | 24.77 (13.6 to NR) |
| Poor | | 5.47 (2.9 to 20.8) | | 30.7 (8.87 to NR) |
| CCI score | | | | |
| < Median | .487 | 7.43 (4.0 to 14.4) | .32 | 26.0 (13.67 to NR) |
| ≥ Median | | 5.47 (2.8 to 6.97) | | 23.6 (6.37 to 30.73) |
| Modified CCI score | | | | |
| < Median | .487 | 7.43 (4.0 to 14.47) | .32 | 26.0 (13.67 to NR) |
| ≥ Median | | 5.47 (2.8 to 6.97) | | 23.6 (6.37 to 30.73) |
| Dose reduction | | | | |
| Yes | .015 | 11.97 (5.47 to 20.0) | .035 | 30.73 (22.5 to NR) |
| No | | 3.57 (2.7 to 5.6) | | 14.97 (11.43 to 24.8) |
| Hypertension | | | | |
| Yes | .18 | 9.87 (4.3 to 14.47) | .06 | 34.93 (16.23 to 34.93) |
| No | | 5.17 (2.8 to 6.87) | | 14.97 (8.87 to 26.0) |
| Hypothyroidism | | | | |
| Yes | .03 | 7.27 (4.3 to 20.8) | .0002 | 34.93 (26.0 to NR) |
| No | | 4.53 (2.77 to 6.97) | | 14.97 (11.43 to 23.6) |
| HFS | | | | |
| Yes | .46 | 6.1 (2.9 to 14.4) | .212 | 26 (14.33 to NR) |
| No | | 5.67 (3.1 to 7.67) | | 22.5 (13.6 to 34.93) |

Abbreviations: CCI, Charlson comorbidity index; CRS, cytoreductive surgery; ECOG, Eastern Cooperative Oncology Group; HFS, hand and foot syndrome; IMDC, International Metastatic RCC Database Consortium risk score; N/L, neutrophil to lymphocyte ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

 

**TABLE 4.** Multivariate Analysis of Prognostic Factors for Patients Treated With Sunitinib

| | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| **Item** | ***P*** | **HR** | **95% CI** | ***P*** | **HR** | **95% CI** |
| Age | .35 | 1.02 | 0.98 to 1.06 | .58 | 0.99 | 0.94 to 1.04 |
| Pathologic subtype | .32 | 1.07 | 0.93 to 1.22 | .058 | 1.25 | 0.99 to 1.57 |
| IMDC risk score | .48 | 1.34 | 0.59 to 3.0 | .18 | 2.57 | 0.64 to 10.37 |
| CRS | .9 | 0.95 | 0.39 to 2.28 | .1 | 1.0 | 0.3 to 3.12 |
| Hypertension | .51 | 1.4 | 0.5 to 3.9 | .939 | 1.06 | 0.1 to 5.79 |
| Hypothyroidism | .25 | 1.92 | 0.62 to 5.91 | .007 | 23.36 | 2.36 to 230.5 |
| Dose reduction | .01 | 3.39 | 1.29 to 8.93 | .148 | 2.74 | 0.7 to 10.78 |

Abbreviations: CRS, cytoreductive surgery; HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; OS, overall survival; PFS, progression-free survival.

## DISCUSSION

This study represents the largest report on the efficacy of sunitinib in patients from the Arab world.[22] Of note, the predominance of male sex (76%), lower incidence of cytoreductive nephrectomy (67%), and higher incidence of non–clear cell histology could be reasons for the lower efficacy of sunitinib in our patient population compared with real-world data from other parts of the world.[18,23-27] More patients are also noted in the poor-risk group (accounting for 38% of the total population), which represents one of the highest reported figures for risk-group stratification.[15] Our response rate of 32.7% was similar to other studies, including the pivotal study of sunitinib and COMPARZ data.[28,29] However, our median PFS (6.07 months) was surprisingly low. This is supported by the low median duration of treatment (4.8 months). The low PFS in our region is further supported by a similar study reported in brief by Zekri et al.[30]

The median OS in our patient population was 24.7 months. This is equal to other reported real-world[5,18] data and poses the question of efficacy of second-line therapy compared with first-line sunitinib. However, the PFS of 4.2 months for patients who received second-line therapy does not support this hypothesis. Of interest, 49% of our patients who received sunitinib received second-line therapy while 12.6% received third-line therapy, which is comparable to most published data.[31-33] We have looked at other factors that may have affected the lower PFS in our patient population, including Eastern Cooperative Oncology Group performance status, CCI score, and year of starting therapy. Unfortunately, none of these factors could explain the lower PFS in our cohort. Our data have shown equal efficacy for sunitinib in patients with clear cell histology versus non–clear cell histology, a finding that needs to be further investigated. The high predominance of poor-risk group (38%) would have explained the low PFS in the whole group. However, PFS for the different risk groups, according to the IMDC risk stratification model, was 7.67, 6.0, and 5.5 months for favorable-, intermediate-, and poor-risk groups, respectively. Furthermore, OS in the IMDC poor-risk group was 30.7 months compared with 26.0 and 24.7 months for the favorable- and intermediate-risk groups, respectively. The discrepancy in OS in the poor-risk group could be explained by the shorter follow-up of this group of patients, but this does not explain the similar PFS in all three groups.

Forty percent of our patients had dose reductions while 5.5% started with doses lower than 50 mg daily. This compares favorably with other studies.[34,35] For example, in the COMPARZ study, dose reduction was done in 44% of the pazopanib group and 51% of the sunitinib group.[29] Thus, this would not explain the low PFS for sunitinib in our patient population. In fact, dose reduction may have contributed to a better PFS in other studies, possibly allowing more prolonged exposure to sunitinib because of lower toxicity.[36,37] This also seems to be the case in our study, with dose reduction being an independent prognostic factor for PFS.

The incidences of major toxic events in our study (hypertension, hand and foot syndrome, and hypothyroidism) matched other published reports.[38-42] Other adverse events had lower incidences, with neutropenia and thrombocytopenia occurring in 7.3% of patients and fatigue at a rate of 9.1%. This low figure was probably related to the retrospective nature of the study.

In our univariate analysis, the development of hypothyroidism was the only adverse event with significant prognostic value for better PFS and OS ($P$ = .03 and .0002, respectively). This prognostic value was lost for PFS ($P$ = .25) but maintained for OS ($P$ = .007) by multivariate analysis.

One factor that may account for lower efficacy in the treatment of mRCC was thought to be the absence of cytoreductive nephrectomy. In our patient cohort, 32.8% did not have cytoreductive nephrectomy, which represents a high figure compared with most reported prospective and retrospective studies.[29,43,44] Unfortunately, this hypothesis cannot fully explain our results because PFS for our patients who had cytoreductive nephrectomy was also 6.8 months. Moreover, recent data from the CARMINA trial did not show a significant advantage for patients who had nephrectomy over others.[45,46]

Besides the above, all other known prognostic factors of known significance in other studies (eg, neutrophil/lymphocyte ratio and pathologic subtype) did not show significant value in univariate and multivariate analyses.[47]

Recently, a 16-gene scoring system has been validated for patients with localized disease, predicting recurrence.[48] Whether a similar genetic signature would be a more valid system to risk stratify patients with metastatic disease and be more predictive than the IMDC model in different ethnic groups should be explored and is being investigated at our center.[49]

Limitations of our study include its retrospective nature, the small sample size, and it being from a single institution.

In conclusion, this retrospective study of sunitinib in patients with mRCC in the Arab world showed reduced efficacy compared with published studies in other populations of different ethnicity. The internationally used IMDC risk-stratification model did not yield significant prognostic value, along with other prognostic factors. Whether this is caused by other clinical factors or is solely related to ethnicity remains to be determined, preferably through prospective studies. A search for an alternative prognostic model, probably incorporating a genetic scoring system, may be warranted.


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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