Overall Survival in Metastatic Renal Cancer in the Central Region of Morocco: A Real Life Experience Over One Decade

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Abstract

Background: Available treatments for metastatic RCC (mRCC) are usually non-curative. In the last decade, novel targeted therapies have significantly improved mRCC outcome. The objective in this study was to describe outcomes in patients with mRCC in Morocco.

Methods: 100 patients with mRCC were recruited between January 2008 and December 2018 in the Hassan II University Hospital of Fez. Data were retrospectively collected. Kaplan-Meier survival analysis was used to determine overall survival (OS) and progression free survival (PFS).

Results: Mean age of the patients was 58.6 years(±12). Sixty seven percent of patients were male. Clear cell carcinoma was the most common histological subtype (78%). According to the IMDC scoring, 72% of patients were in the intermediate and 18% in the poor risk groups. Seventy patients received targeted therapy. Overall response rate (according to RECIST criteria version 1.0) was 38.6%. The median PFS was 7.0 months (95% CI, 4.6 to 9.4). The median OS was 11.6 months (95% CI, 7.9 to 15.3). In the multivariate analysis, cancer specific mortality was impacted by treatment with VEGFR inhibitors (HR: 0.2; 95% CI, 0.1 to 0.4; p =0.001) and IMDC score (intermediate risk group HR: 3.5 (95% CI, 1.4 to 9.1; p =0.009); and poor risk group HR: 5.5 (95% CI, 1.9 to 16.1; p =0.002)).

Conclusion: This is the first report from clinical practice in an African country of OS data in mRCC. The study showed high mortality rates. However, outcomes of VEGFR inhibitors are consistent with studies investigating these treatments.

Background

Renal-cell carcinoma is the most common cancer of the kidney and accounts for 2.2% of all adult cancers worldwide [1]. In Morocco, basing on Grand Casablanca Cancer Registry, the incidence of kidney cancer from 2008 to 2012 was about 0.9%[2]. Clear cell is the most common subtype accounting for 70–85% of renal cell carcinoma [3]. In case of metastatic RCC (mRCC) the available treatments are usually non-curative. Over the last decade, targeted therapies including inhibitors of vascular endothelial growth factor receptors (VEGFR inhibitors), inhibitors of the mammalian Target of Rapamycin (mTOR inhibitors) and recently immune-check point inhibitors have significantly improved therapeutic results [4].However, few data about real life outcomes, beyond clinical trials, are available especially in developing countries. Our objective in this study was to describe patterns and therapeutic results including survival and adverse events in patients with mRCC in Morocco.

Methods

Patients:

100patients with mRCC were recruited between January 2008 and December 2018 in the Medical Oncology Department of Hassan II University Hospital of Fez, the main health structure that offers tertiary care in the Central Region of Morocco

Data collection including information on baseline patient, tumor characteristics, treatments, response and toxicity were retrospectively collected from the hospitals' electronic databases and from patients' medical records. This research was conducted in accordance with the institutional research ethics committee.

Staging, response and outcome evaluation:

Tumor stage at initial diagnosis was categorized according to the American Joint Committee on Cancer (AJCC) TNM classification of malignant tumors, 7th edition, 2009 [5].Patients received Sunitinib, Pazopanib, Sorafenib or were observed (untreated) according to availability of targeted therapies. Overall response rate (ORR) was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.0[6]. Progression-free survival (PFS) was defined as the time from start of therapy to disease progression or death, whichever occurred first. Overall survival (OS) was defined as time from diagnosis of metastatic disease to death by any cause. International Metastatic RCC Database Consortium (IMDC) score was used to determine the risk groups based on the presence of the following factors: karnofsky performance status (PS) less than 80%, haemoglobin inferior to the lower limit of normal, time from diagnosis to treatment less than 1 year, corrected calcium above the upper limit of normal, platelets greater than the upper limit of normal, neutrophils greater than the upper limit of normal. The patient was classified in the IMDC favorable risk group in case of absence of any prognostic factor, in the intermediate risk group in case of presence of 1 or 2 prognostic factors and in the poor risk group in case of 3 or more prognostic factors [7].

Statistical analysis

Descriptive statistics were used to describe baseline characteristics and treatment patterns using means and Standard deviations for continuous variables and frequencies for categorial variables. To determine risk factors affecting overall and progression free survivals, we used CHI-SQUARE test. Kaplan-Meier survival analysis was used to determine OS and PFS. Comparisons of outcome parameters were calculated using the Cox proportional hazard modeling analysis to estimate the hazard ratio (HR) of cancer specific mortality (CSM). We used a significance level of $p < 0.05$ for all tests. SPSS statistical software version 22 (IBM Corporation, New York, USA) was used for all analyses.

Results

Patients:

Mean age of the patients was 58.6 years (± 12). Sixty seven percentof patients were male. Seventy three percent of themhad ECOG (Eastern Cooperative Oncology Group) performance status of 0–1.The Majority (76%) had metastatic disease at presentation while 24% of the cases had localized disease at presentation and had undergone radical nephrectomy.

Clear cell carcinoma was the most common histological subtype (78%). At the time of diagnosis of metastatic RCC, lung was the most common site of metastases (58%), followed bone (35%) and liver (33%). According to the IMDC scoring, 10 % of patients were in the favorable risk group, 72%in the intermediate group, while18% were in the poor risk group. We summarized patient's baseline characteristics in table n°1.

Table 1
Base line patient's characteristics

Characteristics		N (%)
Sex	Male	67 (67)
	Female	33 (33)
Age (years old)	< 40	5 (5)
	40-60	50 (50)
	> 60	45 (45)
Pathological subtype (N=100)	Clear cell	78 (78)
	Papillary	8(8)
	Sarcomatoide	1(1)
	Chromophobe	4 (4)
	Others	9(9)
ECOG P.S	0-1	73(73)
	2	24 (24)
	> 2	3 (3)
Metastatic at presentation		76(76)
Metastatic recurrence after enlarged nephrectomy		24(24)
Cytoreductive nephrectomyin metastatic at presentation		24(24)
First line treatment (N=100)	Sunitinib	52 (52)
	Pazopanib	14 (14)
	Sorafenib	4 (4)
	Support care	30 (30)
Site of metastasis	Lung	58 (58)
	Liver	33 (33)
	Bone	35 (35)
	Lymph node	25 (25)
	Brain	2 (2)
IMDC scoring	Favorable	10 (10)
	Intermediate	72(72)
	Poor	18 (18)

Treatment:

First line treatment

70 patients received targeted therapy, 74.3% of them (N = 52) received Sunitinib, 20% (N = 14) Pazopanib and 5.7% (N = 4) Sorafenib. The overall objective response rate (ORR) was 38.6% and the clinical control rate was 75.7%. The median PFS was 7.0 months (95% CI, 4.6 to 9.4) (Fig. 1). 31.6% (24/76) of mRCC underwent cytoreductive surgery of the primary tumour.

Second line treatment

At the time of analysis 45.7% (N = 32) of patients were still in first line treatment. Among the patients who progressed (N = 38), 42.1% (N = 16) received second line treatment. The most commonly used therapies in the second line setting were Sorafenib(N = 5), Everolimus(N = 4), Pazopanib (N = 4) and Sunitinib(N = 3). The use of these drugs was based on their availability in the Hassan II University Hospital.

Tolerance:

The most commonly reported non-hematological grade 2 adverse events included fatigue (40.6%), mucositis (27.7%), hand-foot syndrome (22.8%) and diarrhea (20.8%). Hypertension was observed only in 10% of cases. The most hematological disturbances were anemia (39.6%), and leucopenia (13.9%). Hypothyroidismwas reported in 20% of cases. Grade 3–4 adverse events were reported in 5% of cases.

Survival and prognostic factors

After a median follow up of 12 months, the median OS was 11.6 months (95% CI, 7.9 to15.3) (Fig. 2). This survival varied from 4 months (95% CI, 2.6to 5.4) in the non treated group to 19 months (95% CI, 5.9 to 32.6) in the treated group.

In the multivariate analysis, cancer specific mortality was impacted by treatment with VEGFR inhibitors (HR: 0.2; 95% CI, 0.1 to 0.4; p = 0.001) and IMDC score (intermediate risk group HR: 3.5 (95% CI, 1.4 to 9.0; p = 0.009); and poor risk group HR: 5.5 (95% CI, 1.9 to 16.0; p = 0.002)).

Discussion

This retrospective study included patients with the diagnosis of mRCC treated at our department between 2008 and 2018. This analysis of “real world” offers information on treatment of patterns and outcomes of mRCC patients from the University Hospital of FEZ. In the present study, the median age and sex distribution were typical to kidney cancer [3].However, as this was a real-life study, we included patients with histology of non clear-cell mRCC (22%), ECOG performance status more than 1 (27%) and even untreated patients (30%), because of poor performance status or treatment unavailability, which was not the case in pivotal studies [8–15].

Some patterns of tumor aggressiveness were observed in our population comparatively to other real world studies [16–18] including the high rate of intermediate and poor risk groups (90%), of synchronous metastases (76%) andperformance status alteration (30%). The lattermay be explained by the delays between first symptoms and cancer diagnosis in our population [19]. All these reasons cited above explain the low overall survival in the population of the study (11.6 months, 95% CI, 7.9 to 15.3).Through univariate and multivariate analyses we could confirm the impact of VEGFR inhibitors on survival and prognostic value of IMDC score by showing significantly different survival rates.

Among the treated population, 74.3% of the cases received sunitinib as first line treatment reason for which we compared our therapeutic results with those of trials investigating (or comparing with) sunitinib (Table 2).

Table 2
Therapeuticoutcomes of sunitinib in phase III trials

Author	Motzer et al (8,9)	Motzer et al (10)	B. I. Rini et al (11)	B. I. Rini et al (12)	Motzer et al(13)	Motzeret al (14)	Choueiri et al (15)	Our study
Comparative trials	Sunitinib vs interferon	Pazopanib vs Sunitinib	Pembrolizumab –axitinib vs sunitinib	Atezolizumab – Bevacizumab vs sunitinib	Avelumab – axitinib vs sunitinib	Nivolumab-Ipilimumab vs sunitinib	Cabozantinib vs sunitinib	
N° of cases in Sunitinib group	375	548	429	461	444	546	78	
IMDC score	38	27	30.5	20	21.6	23	-	10
Favorable	56	59	57.3	68	62.2	61	81	72
Intermediate	6	9	12.1	12	16	16	19	18
Poor		5			0.2			
Not reported								
Objective response rate (%)	47	25	35.7	33	25.7	27	9	38.6
PFS m	11	9.5	11.1	8.4	8.4	8.4	5.3	7
OS m	26.4	29.3	not reached	34.9	-	26	21.2	19
Grade 3–4 AE (%)	-	74	70.6	54	71.5	63	65	5

In term of efficacy of the first line, our ORR (38.6%) was in the large range of response rates observed in thesunitinib phase III trials (varying from 47% in the pivotal study to 9% in the CABOSUN trial including exclusively intermediate and poor risk groups)[8–15].

The median PFS in the overall population was 7.0 months (95% CI, 4.6 to 9.4). This median was consistent with PFSmedians observed in sunitinib arms varying from 5.3 months in the CABOSUN trial to 11.1 months in the KEYNOTE-426 trial including more than 30% of favorable risk patients [8–15].

The incidence of grade 3 and 4 adverse events (AE) in our study was lower than the one in phase III trials, this may be due to underreporting in real life contrasting with rigorous collection of AE data in clinical trials [8–15].

Although 45% only could receive second line treatment, the median OS in population who received VEGFR inhibitors was similar to other real-life studies and even to sunitinib phase III trials [8–15].

Although our results are consistent with studies investigating these treatments, they should be interpreted with caution. Our limitations are that the data were obtained retrospectively from patients' records, the follow-up duration between patientswas variable and the sample size for each treatment agent was limited.

This is the first report, to our knowledge, of mRCC OS data from real-world clinical practice in an African country. Challenges consist on availability of targeted therapies in our populations and regionalization of cancer care to improve diagnostic delays and overall outcomes

Conclusion

This study showed a high mortality rates in our population; mostly because of late diagnosis at a stage of performance status deterioration leading to therapeutic abstention. We also confirmed, through this study, that VEGFR inhibitorsare effective and safe in our population.

Patient summary

In this report, we examined the results of survival in kidney cancer patients in the Moroccan population. We found high mortality rates due to late diagnosis and performance status deterioration and TKIs were well effective with acceptable tolerability.

Abbreviations

Adverse events (AE)

Cancer Specific Mortality (CSM)

ECOG (Eastern Cooperative Oncology Group)

Hazard ratio (HR)

International Metastatic RCC Database Consortium (IMDC)

Mammalian Target of Rapamycin (mTOR inhibitors)

Metastatic RCC (mRCC)

Overall Response Rate (ORR)

Overall Survival (OS)

Performance status (PS)

Progression Free Survival (PFS).

Response Evaluation Criteria in Solid Tumors (RECIST)

Vascular Endothelial Growth Factor Receptor (VEGFR)

Declarations

Consent for publication:

Not applicable.

Ethics approval and consent to participate:

The informed consent of the patient was not requested by the ethics committee as it is a retrospective study with the impossibility of obtaining the consent of all patients

Full name of the ethics committee: Fez University Hospital Ethics Committee.

Reference number: 10/19.

Committee reference:

the ethics committee follows a quality procedure for its operation, and is based for its deliberations on the declaration of Helsinki version 2008, the latest version of the ICH text concerning good clinical practices, the European directive (ref: 2001/20 / CE), the decision of the Ministry of Health N ° 02 / DRC / 00 of 03/12/2012, relating to biomedical research.

You will find below the opinion as well as the reference of the ethics committee.

Availability of data and materials:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

The authors received no specific funding for this study.

Author's contribution:

NM conceived the idea, ZB wrote the paper, KE, SE did statistics. LN, MB, KO, LA, SA, SM, FT, MF and HE contributed in collecting clinical data.

The work presented here was carried out in collaboration between all authors. All authors read and approved the final manuscript.

If our manuscript is accepted I will not be able to make any changes to the authors, or order of authors, of our manuscript once the editor has accepted our manuscript for publication.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. CA Cancer JC. 2018 Nov;68(6):394–424. doi: 10.3322/caac.21492. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.
2. Registre des Cancers de la Région du Grand. Casablanca 2008–2012.https://www.contrelecancer.ma/fr/documents/registre-des-cancers-de-la-region-du-grand-casab-3/.
3. Ljungberg B, Campbell SC, Choi HY, Cho HY, Jacqmin D, Lee JE, et al. The epidemiology of renal cell carcinoma. EurUrol. 2011 Oct;60:615–21.
4. Albiges L, Choueiri T, Escudier B, Galsky M, George D, Hofmann F, Lam T, Motzer R, Mulders P, Porta C, et al. A systematic review of sequencing combinations of systemic therapy in metastatic renal cancerEur Urol. 2015;67(1):100–10.

5. American Joint Committee on Cancer (AJCC).AJCC. Cancer Staging Manual. 8th edition. New York: Springer; 2017.
6. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000 Feb 2;92:205–16.
7. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carci- noma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin On- col. 2009;27:5794–9.
8. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM. Rixe O et al. Sunitinib versus interferon. alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007 Jan;11(2):115–24. 356(.
9. 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 ClinOncol. 2009;27:3584–90.
10. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013;369:722–31.
11. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019 Mar 21;380(12):1116–1127. doi: 10.1056/NEJMoa1816714. Epub 2019 Feb 16.
12. Motzer RJ, Powles T, Atkins MB, et al. IMmotion151: a randomized phase III study of atezolizumab plus bevacizumabvssunitinib in untreated metastatic renalcell carcinoma (mRCC).JClinOncol2018; 36:578 (http://ascopubs.org/doi/10.1200/JCO.2018.36.6_suppl.578).
13. Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.N Engl J Med. 2019 Mar 21;380(12):1103–1115. doi: 10.1056/NEJMoa1816047. Epub 2019 Feb 16.
14. Motzer RJ, Rini BI, McDermott DF, ArénFrontera O, Hammers HJ. Carducci MA et al. Nivolumab plus ipilimumab. versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019 Oct;20(10):1370–85. (19)30413-9. Epub 2019 Aug 16.. (:. doi: 10.1016/S1470-2045.
15. Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK, et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. J ClinOncol. 2017 Feb 20;35(6):591–597. doi: 10.1200/JCO.2016.70.7398. Epub 2016 Nov 14.
16. Schwab M, Hofmann R, Heers H, Hegele A. mRCC Outcome in the Treatment of Metastatic Renal Cell Carcinoma - A German Single-center Real-world Experience. In Vivo. 2018 Nov-Dec;32(6):1617–1622. doi: 10.21873/invivo.11422.
17. Poprach A, Fiala O, Chloupkova R, Melichar B, Lakomy R, Petrakova K, et al. Pazopanib for Metastatic Renal Cell Carcinoma: A Registry-based Analysis of 426 Patients. Anticancer Res. 2018 Jan;38(1):449–56.
18. Maroun R, Mitrofan L, Benjamin L, Nachbaur G, Maunoury F, Le Jeunne P, et al. Real life patterns of care and progression free survival in metastatic renal cell carcinoma patients: retrospective analysis of cross-sectional data. BMC Cancer. 2018 Feb 21;18(1):214. doi: 10.1186/s12885-018-4117-z.
19. Benbrahim Z, Zouiten O, Messoudi K, Atassi M, Amaadour L, Oualla K, et al. Wait times for diagnosis and treatment of lung cancer: Experience of the medical oncology department of Hassan II University Hospital of Fez. Glob J QualSafHealthc. 2019;2:65–9.

Figures

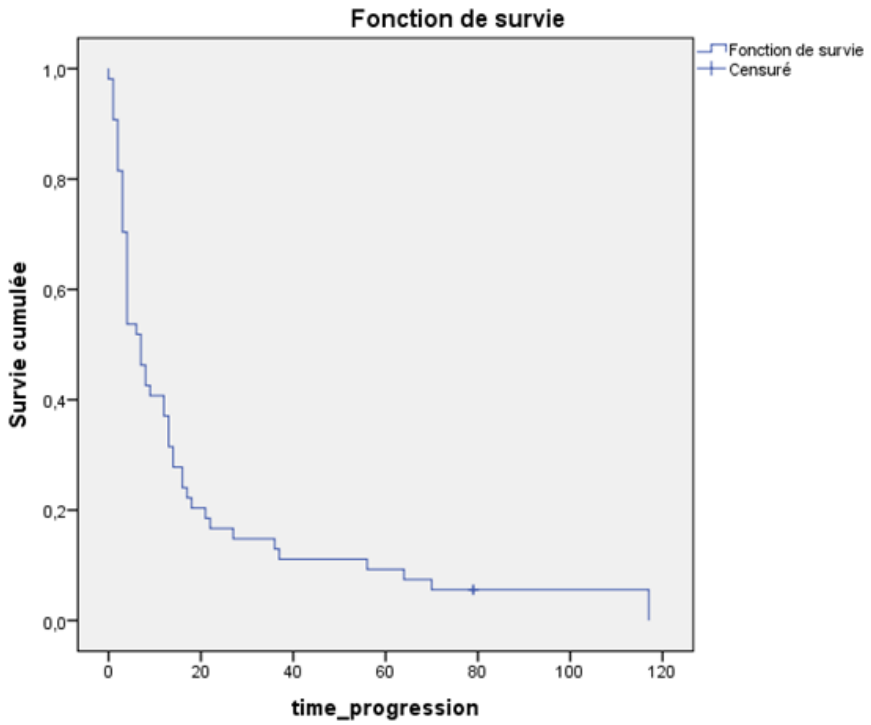

Figure 1

Progression free survivalcurve in treated patients with VEGFR inhibitors : mPFS : 7.0 months

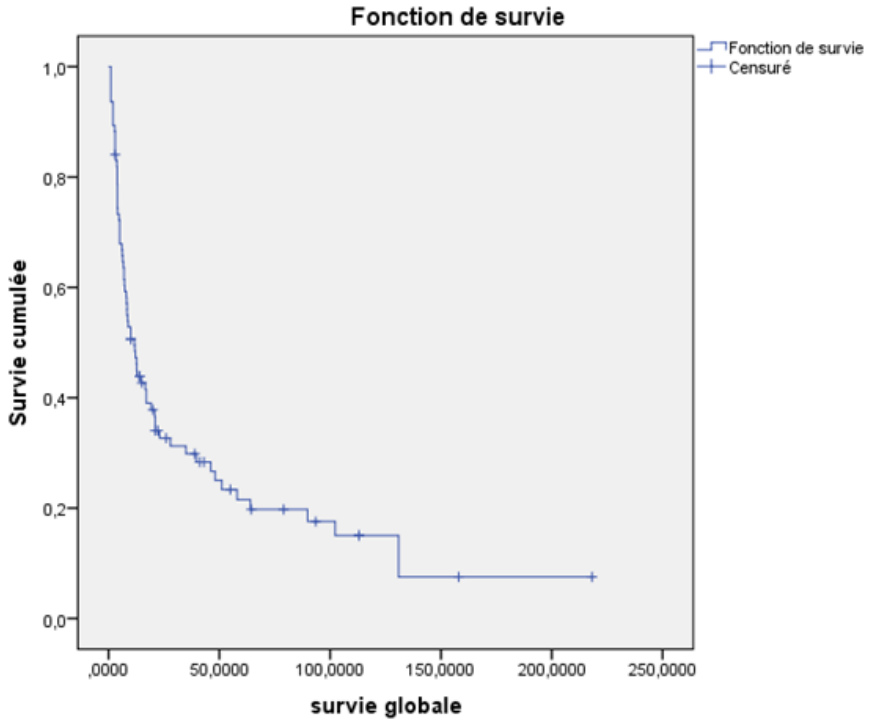

Figure 2

Overallsurvivalcurve of the overall population mOS : 11.6months