Real-life management of metastatic renal cell carcinoma in the era of targeted therapies: Experience of a single center

Abir El-Ahmadie, MD; Fadi El Karak, MD; Colette Hanna, MD; Marwan Ghosn, MD

Hematology-Oncology Department, Faculty of Medicine, Saint Joseph University, Beirut, Lebanon

✉ *Corresponding Author: Pr. Marwan Ghosn*
Professor and Director of the Hematology & Oncology Department at Saint-Joseph University
Faculty of Medicine, Beirut – Lebanon.
Email: mghosn.hdf@usj.edu.lb

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Abstract

Aims: To obtain routine clinical practice data on the usage patterns and outcomes (safety and effectiveness) of targeted therapies in the management of mRCC in a single tertiary center in a developing country. **Methods:** A retrospective review of mRCC patients of any pathological subtype treated with targeted therapies between June 2006 and January 2013 was performed. Patients' characteristics, effectiveness and safety of treatment were reported. **Results:** 86 patients were screened of whom 70 were metastatic. Median age at diagnosis was 61.5 years, 79% of patients were men, 77.9 % underwent nephrectomy and 77% of the tumors were clear-cell carcinoma. Patients were diagnosed at a metastatic stage in 39.5% of the cases with more than one metastatic site (79 %). The majority of patients (73%) were of low and intermediate-risk category according to the MSKCC score. Forty nine patients received targeted therapy that consisted mainly of Sunitinib as first line (75.6%) and Everolimus as second line (52.6%). Median OS was 12 months (1-79) and PFS was 8 months (1-72). Side effects of more than grade 2 were noted in 84 % of treated patients. **Conclusion:** The study shows that the targeted therapies for mRCC offer significant benefit. It highlights the importance of developing better ways in evaluating patients and of making more efforts to get patients more closely followed. Finally, it shows the need to develop a prospective real-life studies to better understand the routine practice of the management of mRCC that goes beyond the simple application of guidelines.

Introduction

Renal cell carcinoma (RCC) accounts for 2%–3% of all adult malignancies, representing the seventh most common cancer in men and the ninth most common cancer in women [1]. The incidence of kidney cancer has been increasing worldwide, accounting for approximately 2% of all cancers [2].

In 2015, 325,433 new cases and 138,629 deaths are expected to occur [3]. Incidence and mortality rates were highest for men in more developed areas, where kidney cancer constituted 4% of all cancers [4]. In Lebanon, the last National Cancer Registry data published reported 147 new cases of Kidney cancer in 2008 which represents 1.5% of the total new cases [5]. The widespread use of abdominal imaging helped to significantly raise the proportion of small and incidental renal tumors and nowadays, more than 50% of RCCs are detected incidentally. However, a large number of patients with RCC still present with clinical symptoms.

Although the 5-year survival rates approximate 85% for patients with localized RCC, patients with advanced disease have a 5-year survival rate of only 10% [6]. Because there are no standard screening tests for RCC, up to one-third of patients have metastatic disease at diagnosis [7, 8]. In patients with distant metastases, the 5-year survival is 9.5% [9]. For early stage and localized RCC, surgery is the primary approach [10]. However, surgical resection of locally advanced disease is associated with a high recurrence [6] and no proven efficacy was demonstrated in the adjuvant setting [11-12]. Furthermore, in metastatic RCC (mRCC), surgery does not usually change disease progression [10, 13].

Kidney cancer subtypes include clear cell (85%) and the less common non-clear cell cancers, including papillary, collecting duct, and chromophobe RCC [14]. Approximately 80% of kidney tumors demonstrate clear-cell carcinoma histology [8, 15]

Immunotherapy with high-dose interleukin-2 or interferon-alpha is generally effective in some patients, particularly those with good performance status [14]. These agents are associated with low response rates (<15%) and significant toxicities, which often limit their use and affect patient quality of life [17].

MRCC is generally resistant to standard chemotherapy, radiotherapy and hormonal therapy. Objective response rates (ORR) of <10% have been reported with frequently used chemotherapeutic agents [18]. Cytokine therapy with interleukin-2 or interferon-alpha has until recently been considered the standard of care for the first-line treatment of mRCC. However, only 10%–20% of patients experience objective disease response [17–22] and both IL-2 and IFN-a are associated with significant toxicity in addition to the high risk of recurrence. Therefore, there was a high unmet medical need for the management of RCC

In view of these observations, there is a high unmet need for the management of mRCC.

Treatment of mRCC has undergone a major transformation over the past 5 years with the emergence of novel targeted therapies proven to provide benefit in mRCC. These include the multitargeted sunitinib [23], pazopanib [24], tyrosine kinase inhibitors (TKIs) sorafenib [26], axitinib [25], the humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab

[27], and the mammalian target of rapamycin (mTOR) kinase inhibitors temsirolimus [28] and everolimus [29].

However, our region has its own particularities in terms of drug availability and third parties reimbursement issues therefore not every recommendation is applicable and physicians find themselves trapped between gold standards and real life practice. Consequently, we conducted this study in order to present our experience in a single tertiary center in the management of newly diagnosed and/or progressive mRCC in order to obtain routine clinical practice data on the usage patterns and outcomes (safety and effectiveness) of targeted therapies in this setting.

Study Objectives

The **strategic objective** of this retrospective observational study is to obtain routine clinical practice data on the usage patterns and outcomes (safety and effectiveness) of targeted therapies in the management of mRCC.

The **primary objectives** were: to describe the epidemiological characteristics (age, tumor size, Fuhrman score, MSKCC score, histology…) of patients diagnosed with RCC in our institution; to describe physician-assessed effectiveness outcomes including response, progression free survival (PFS), and overall survival (OS)

The **secondary objective** was to describe safety of targeted therapies in routine clinical practice (based on adverse event reporting).

Study design and population

This study is a national single-center, observational (non-interventional on the therapeutic strategy) retrospective conducted on mRCC patients diagnosed or progressing between June 2006 and January 2013 in a single tertiary center (Hotel-Dieu de France University Hospital affiliated to the Faculty of Medicine at Saint-Joseph University, Beirut, Lebanon).

Eligibility criteria

MRCC of any pathological subtype treated with targeted therapies were eligible for the analysis. Patients who received prior immunotherapy as 1st line and targeted therapy as second-line treatment were also included. Measurable or evaluable disease was not required for inclusion in the analysis.

Study procedures and data collection

A systematic file review was conducted and data such as epidemiological characteristics, sequence of therapies received, tumor response, adverse events encountered, PFS and OS were reported.

Baseline demographic, clinical and laboratory data including those previously found to have prognostic value (performance status, time from diagnosis to treatment, blood calcium and lactate deshydrogenase values, hemoglobin…) [30-36] were collected retrospectively on all patients. January 2013 was chosen as the cut-off date of data collection.

Patients were classified according to the most widely used model for risk stratification: the Memorial Sloan Kettering Cancer Center model (MSKCC model) [31-32].

Tumor response was evaluated according to RECIST criteria.

Overall Survival (OS) was calculated from the time of initiation of targeted therapy to death as a result of any cause or was censored at the date of last follow-up. Progression Free Survival (PFS) was measured from the time of initiation of therapy to the date of drug discontinuation and/ or progression, objective tumor progression, or was censored at last available follow-up.

Side effects of grade 2 or more were measured using the WHO grading system. The toxicities of all treatments were reported together to highlight the most encountered adverse drug reactions that interfere in the patient's management.

Results

Patients' characteristics

From June 2006 to January 2013, 86 patients were screened for eligibility. A total of 70 patients had a metastatic disease of whom 12 had a rapid disease progression and didn't receive any treatment, 1 died and 8 were lost to follow-up, yielding a total of 49 patients who completed their treatment and were included in the analysis (figure 1).

Demographic and clinical characteristics of the study sample were presented in Table 1. The mean age of the patients was 61.5 years (31 – 81) where 68 (79%) were males. The baseline risk evaluation was low (22 patients), intermediate (28 patients) and high (5 patients). As for the staging at diagnosis, 18 patients (21%) were at stage 1, 13 patients (15.0%) at stage 2, 16 patients (18.6%) at stage 3, and 34 patients (39.5%) at stage 4.

The majority of patients received a nephrectomy (66.3%) and clear cell histology was diagnosed in 77% of the patients. Out of the 70 patients with metastatic disease, the number of metastatic sites were almsot equally divided between 1 site (17 patients, 20%), 2 sites (21 patients, 24.3%) and 3 or more sites in 25 patient (29%). The metastatic sites included mainly lung (33%), lymph nodes (18.5 %) and bone (18.5%). Finally, 66% of the patients developed metastatis less than 1 year from the date of diagnosis.

OS and PFS

Median OS was 12 months (1-79) and median PFS was 8 months (1-72) with a median duration of therapy of 10 months (1-79) (table 2). Stratifying the patients by risk score according to MSKCC criteria show that the patients with low risk had a better OS and PFS (12 mo, 8 mo) than the patients with high risk (7 mo, 4.5 mo) respectively (table 3).

Tumor response

There were 49 patients who received a first line treatment of whom 18 (36.7%) moved to second line therapy upon progression. The remaining 31 patients received first line therapy only, either because they progressed and were also unfit to pursue treatment because of their poor general condition (10 patients) or were lost to follow up (21 patients).

Therapy was effective in controlling the disease in 75.6% of the patients in the first line setting while it dropped to 33.5% in the 2nd line setting (table 4).

Side effects/ toxicities

Side effects and/or toxicities of grade 2 and more were reported in Table 6. A total of 134 events were presented by 41 patients out of the 49.

The most frequent adverse events were fatigue (26 events), cutaneous toxicities (24 events), hypertension (23 events) and gastrointestinal disturbances (21 events). As a consequence, dose reduction was necessary in almost 41% of the patients (20 out of 49) while therapy discontinuation or change was needed in

26.5% of the patients (13 out of 49). The remaining patients were monitored and treated symptomatically with no impact on treatment administration.
The majority of reported side effects were noticed in patients receiving Sunitinib (24 patients) followed by Everolimus.

Discussion

Characterized by a lack of early warning signs and diverse clinical manifestations, RCC has historically been a difficult malignancy to diagnose and treat. Because it remains clinically occult for most of its course, RCC is often diagnosed in advanced stages, usually by incidental radiologic study. In this cohort, 49% of the patients had metastatic disease at diagnosis which is comparable to the literature (25–30%). [4, 7, 35, 36, 37]. General population characteristics were similar to those of the literature [1].

Though ongoing studies are still evaluating the role of surgery as the first approach in the management of mRCC, the majority of our patients underwent nephrectomy (77.6 %) reflecting some delay in referring metastatic patients to oncologists and emphasizing the need of reinforcing the multidisciplinary management of RCC.

Sunitinib was the most used drug in the 1st line setting, in line with the guidelines. Five patients received Everolimus in the context of clinical trials and five patients received Interferon. It is noteworthy that the treatment selection was mainly guided by the availability, accessibility and reimbursement of targeted therapies in the market. Yet, the study shows that in our country, patients had timely access to the new treatments.

The study describes the real-life practice of managing RCC, including the non-clear cell category. This study has to be interpreted in light of its strengths and limitations. Being a retrospective study implies classical issues such as incompleteness of data collected and heterogeneity of patients' selection and management, which can be considered also as a strength in the context of real-life studies. To note that several attempts to address these concerns were made and included the use of consecutive patient sampling to reduce patient selection bias, the extra-efforts to gather as much data as possible. It is worth mentioning that "oral medication" represents a new challenge for both patients and oncologists. Patients may not present to the physician's clinic as frequently as required leading to missing data and loss of adequate follow-up. Nevertheless, we believe that such a bias has minimal effect on our results because of the study represents the clinical setting in real life.

Also, one of the limitations of this study was the use of the classical RECIST criteria to define disease progression which might not be nowadays the best modalities to assess effectiveness of targeted therapies [38]. Tumor's behavior under targeted therapy is different than classical chemotherapy. Physicians are often confronted to dissociated responses when the evaluation is conducted following the classical criteria. The span between the beginning of vascular alterations until the complete tumor necrosis might take longer time which explains the delayed or the paradoxal tumor size reduction. The delayed response represents a difficult situation to explain to the patients and even to the reimbursement bodies that request documentation of treatment efficacy for the continuation of treatment. Furthermore, relying only on PFS to assess treatment-outcome is not enough. Although, it has become a well-established endpoint for assessing the effectiveness of new therapeutic agents in the treatment of RCC, PFS relies more on the investigator's own discretion especially in retrospective observational study where no established assessment criteria was defined. Therefore, the OS remains an important outcome to be considered.
Moreover, in our study, the reporting of adverse events was not based on a standardized methodology which may result in over or under reporting depending on memory and interpretation of occurrences and clinical significance. Yet, the reported data represent the real-life evaluation of toxicities and their impact on treatment management.
The main strength of the study is the fact that, it is among few studies that describes the management of RCC in real-life in a single tertiary hospital in a developing country and to our knowledge the only one in Lebanon.

Conclusion

In conclusion, the study shows that the targeted therapies for advanced RCC offer significant benefit compared with prior approaches. It highlights the importance of developing better ways in evaluating patients and of making more efforts to get patients more closely followed. Finally, it shows the need to develop a prospective real-life studies to better understand the routine practice of the management of mRCC that goes beyond the simple application of guidelines.

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Tables

Table 1: Patients' characteristics

Criteria	TOTAL reviewed = 86
Median age at diagnosis	61.5 yrs (31-81)
Sex M F	 68 (79 %) 18 (18 %)
MSKCC score 0 1-2 More than 3 N/A	N=70 metastatic patients 22 (31.5 %) 28 (40 %) 5 (7 %) 15 (21.5 %)
No Surgery Partial nephrectomy Radical nephrectomy N/A	14 (16.3 %) 10 (11.6 %) 57 (66.3 %) 5 (5.8 %)
Tumor size (cm)	8,19
Staging at diagnosis 1 2 3 4 N/A	 18 (21%) 13 (15%) 16 (18.6%) 34 (39.5%) 5 (5.9%)
Histology Clear cell Papillary Bellini Chromophobe Other N/A	 66 (77%) 6 (7%) 2 (2%) 3 (3.5%) 1 (1.,1%) 8 (9.4%)

Localized	16 (19%)
Metastatic	
At diagnosis	36 (42%)
At progression	32 (37%)
N/A	2 (2 %)
Fuhrman	
1	3 (3.5%)
2	20 (23.5%)
3	26 (30%)
4	10 (11.6%)
N/A	27 (31.4%)
Number of metastatic sites	
None	16 (18.6%)
1	17 (19.8%)
2	21 (24.4%)
≥3	25 (29.06%)
N/A	7 (8.14%)
First metastatic site	
Lymph nodes	13 (18,5%)
Lung	23 (33%)
Liver	4 (6%)
Bone	13 (18,5%)
Local relapse	5 (7%)
Synchronous sites	12 (17%)
Interval from diagnosis to metastasis	
Less than 1 yr	
More than 1 yr	46 (66%)
N/A	22 (31%)
	2 (3%)

Table 2: Treatment type

	First line	2nd line	3rd line
Sunitinib	37 (75.6%)	4 (21%)	--
Everolimus	5 (10.2%)	10 (52.6%)	2 (50%)
Bevacizumab+IFN	1 (2%)	1 (5.3%)	1 (25%)
IFN	5 (10.,2%)	1 (5.3%)	--
Sorafenib	1 (2%)	1 (5.3%)	1(25%)
Temsirolimus	--	1 (5.,3%)	--
Total	49 (100%)	18	4

Table 3: Median OS and PFS according to MSKCC score

MSKCC score		PFS		OS	
All risk groups	N=49	8	(1-72)	12	(1-79)
Low risk (MSKCC score=0)	N_1=17	13	(1-54)	13	(1-79)
Intermediate risk (MSKCC score 1-2)	N_2=26	8.5	(1-72)	11.5	(1-75)
High risk (MSKCC score ≥3)	N_3=6	4.5	(1-6)	7	(1-18)

Table 4: Tumor response

	First line	2nd line	3rd line
Partial response	9 (18.4%)	1 (5.5%)	--
Stable disease	28 (57.2%)	5 (28%)	3 (75%)
Progression	10 (20.4%)	12(66.5%)	1 (25%)
--	2 (4%)	--	--
Total	49	18	4

Table 5: Summary of encountered side effects/ toxicities (grade ≥2)

Cutaneous (rash, hand-foot syndrome,…)	24
Fatigue	26
GI (mouth dryness, diarrhea, taste disturbances, GI upset,…)	21
Anemia	13
Myelosupression	16
Neurological side effects	2
Thyroid dysfunction	9
Total mentioned side effects/events	134

Figures

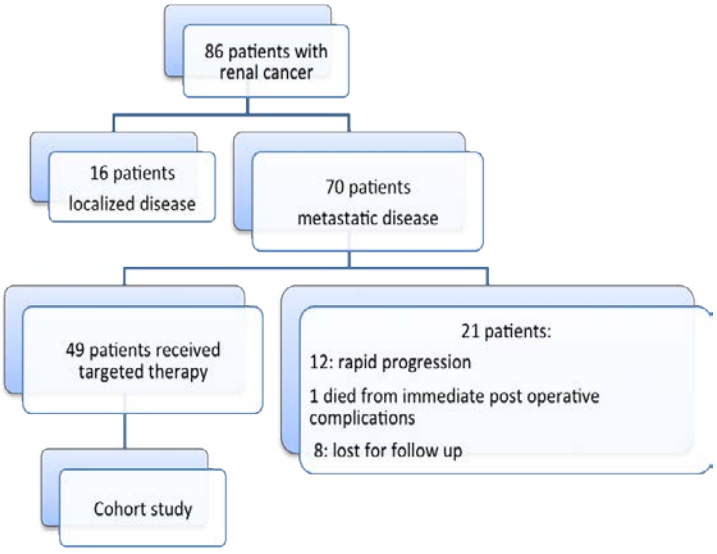

Figure 1: Patient's flow

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