Study of the effectiveness of first-line treatment in renal cell carcinoma

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Abstract. The emergence of novel drugs corresponds with the determination of the effectiveness of the current treatments used in clinical practice. A retrospective observational study was conducted to evaluate the effectiveness of first-line treatments and to test the influence of the prognostic factors established using the Memorial Sloan-Kettering Cancer Center (MSKCC) and the analysis of Mekhail's study for two or more metastatic sites. The primary endpoints were median progression-free survival (mPFS) and median overall survival (mOS) times. A total of 65 patients were enrolled and the mPFS and mOS of the patients treated with sunitinib (n=51) were 9.0 and 20.1 months, respectively, and for the patients treated with temsirolimus (n=14) these were 3.0 and 6.2 months, respectively. In the poor-prognosis (PP) group, a difference of 1.2 months (P=0.049) was found in mPFS depending on the first-line treatment. A difference of 4.1 months (P=0.023) was also found in mPFS when classified by histology (clear verses non-clear cell) in the sunitinib-treatment group. When stratified by the prognostic group, differences of >7 months (P<0.001) were found between the groups. Therefore, it was concluded that the effectiveness of the treatments was reduced compared to previous studies and differences were found in the PP group when classified by first-line drug and histology. Additionally, the influence of prognostic factors on OS and the value of stratifying patients using these factors have been confirmed.

Introduction

Renal cell carcinoma (RCC) accounts for 2-3% of all tumours, with a higher incidence in 60-70 year-old males compared to females, at a ratio of 2:1 (1). In 2008, the incidence of this type of cancer was 3.2% in Europe and 2.6% in the USA, with a mortality rate of 2.6 and 2.9%, respectively. In the same year, the RCC incidence in Spain was 2.3% and it accounted for 1.8% of all the cancer mortalities (2). The study was conducted at the Central University Hospital of Asturias [Hospital Universitario Central De Asturias (HUCA); Oviedo, Asturias, Spain], which is the referral hospital for advanced renal cell carcinoma (aRCC) treatment in the Asturias, which had a population of 1,085,289 inhabitants in 2009. The incidence of renal cancer in this region was 2.4% and it accounted for 2.5% of all the cancer mortalities that year (3,4).

Histologically, RCC is classified into several types: Clear cell (ccRCC; accounting for 80-90% of RCC), papillary type I and II (10-15%), chromophobe (4-5%) and collecting duct of Bellini (<1%) (5-7).

Several risk factors have been identified in association with RCC and the most significant factors are smoking, obesity and hypertension (5-7).

RCC also has a broad variety of prognostic factors, which can be classified into anatomical, histological, clinical and molecular factors (1). Clinical prognostic factors are currently used to classify patients with aRCC. The tiered-grading model published at the Memorial Sloan-Kettering Cancer Center (MSKCC) by Motzer *et al* (8) in 2002 is used in clinical trials and by the European Society for Medical Oncology (ESMO) (9). The model defines the following poor-prognostic factors: Low Karnofsky performance status (KPS<80%); lactate dehydrogenase levels, >1.5 times the upper limit of normal; haemoglobin levels below the limit of normal; corrected calcium levels, >10 mg/dl; and time from diagnosis to start of systemic therapy, <1 year. In this model, patients are divided into three risk or prognosis groups depending on how many factors are found.

Since this classification was published, novel prognostic factors associated with patient survival have been identified. Thus, in 2005, a study by Mekhail *et al* (10) was conducted that validated the factors established in the MSKCC. The study also performed prior administration of radiotherapy and individual metastatic sites in the retroperitoneal lymph nodes, lung and liver. The study found that the factors regarding the individual metastases site could be replaced by the number

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of metastatic sites, whereby the presence of two or more metastatic sites was a poor-prognostic factor.

Based on these two models, in the pivotal study of temsirolimus (11) the MSKCC-prognostic factors and the presence of two or more metastatic sites from the Mekhail *et al* (10) trial were established as poor-prognostic factors. As opposed to the Mekhail *et al* trial, in the pivotal study all the metastatic sites were considered, as opposed to only the retroperitoneal lymph nodes, lung and liver.

Subsequent studies (12,13) have assessed the influence of other poor-prognostic factors, including platelet and neutrophil levels above the upper limit of normal and the presence of bone metastases among others.

Systemic treatment of aRCC has also progressed from the emergence of cytokine use in clinical practice, to the addition of tyrosine kinase inhibitors, anti-vascular endothelial growth factor and, more recently, mammalian target of rapamycin pathway inhibitors (9-11,14-18). Currently, the combined use of these drugs is being studied, as well as newly developed agents (axitinib and tivozanib) (11,14-18).

The aRCC treatment protocol utilised at HUCA, following the ESMO and the National Comprehensive Cancer Network guidelines (9,19), states that the first-line therapy of choice for aRCC is bevacizumab (combined with interferon-α) or sunitinib in patients with a good or intermediate prognosis and temsirolimus in patients with a poor prognosis.

The emergence of novel drugs, their combinations and different regimens, means that the effectiveness of current treatments used in clinical practice should be determined. This may not only help to establish their place in existing treatment possibilities, but is likely to also aid subsequent comparative analyses with future innovations, as they are added to treatment protocols. A retrospective observational study was conducted to assess the effectiveness of first-line treatments and the influence of the prognostic factors established by MSKCC and the method validated by Mekhail *et al* (10) (two or more metastatic sites).

Materials and methods

Patients. A retrospective observational study of patients who commenced first-line systemic therapy for aRCC at HUCA was conducted between January 2008 and November 2010. The patients were followed up until April 2012. The patients who developed other advanced cancers requiring chemotherapy were excluded from the study.

Endpoints assessed. The primary endpoints used to assess the effectiveness of systemic therapy were median progression-free survival (mPFS) and median overall survival (mOS). PFS was calculated from the start date of the treatment to the date of progression or fatality. OS was calculated from the start date of the treatment to the date of fatality from any cause, or in its absence, to the date of the start of the palliative treatment. The mPFS and mOS were determined by the Kaplan-Meier method and the potential differences, according to first-line treatment and different prognosis groups, using the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference.

Establishing prognostic factors. Poor-prognostic factors established by MSKCC (8), plus one validated by the Mekhail *et al* (10) study (two or more metastatic sites), were used only when considering pulmonary, retroperitoneal lymph node and hepatic metastatic sites. The patients were stratified into different prognostic groups according to the number of poor-prognostic factors, as established by Mekhail *et al* (10). The patients in the good-prognosis (GP) group had one or no factor, the intermediate-prognosis (IP) group had two factors and those in the poor-prognosis (PP) group had more than two factors.

Consent. The Ethics Committee of Central University Hospital of Asturias (Spain) approved the study. Consent was obtained for use of patient data.

Results

Patient characteristics. During the inclusion period, 71 patients started first-line systemic treatment for metastatic renal cell cancer at HUCA. According to the aforementioned exclusion criteria, six patients were excluded. Of the 65 patients included in this study, 51 were treated with first-line sunitinib repeated at 6-week cycles at a dose of 50 mg administered once daily for 4 weeks, followed by 2 weeks without treatment; the remaining 14 patients were treated with temsirolimus at a weekly dose of 25 mg.

The median age was 65 years (range, 45-82 years) and 51 patients (78.5%) were male. The median KPS at the start of treatment was 80% (range, 50-100%). Of all the patients, 51 (78.5%) had distant metastases at the time of diagnosis and the same number of patients had undergone nephrectomy. With regards to the histological characteristics, 43 patients (66.2%) had clear cell histology (ccRCC), six (9.2%) had papillary, six (9.2%) exhibited mixed histology and one (1.5%) had chromophobe features. Histology could not be obtained in the remaining patients (13.8%).

By the end of the follow-up, 34 patients (52.3%) had succumbed, 13 (20.0%) were receiving palliative treatment, 14 (21.5%) continued with cancer therapy, two (3.1%) remained in surveillance and two (3.1%) were lost during the follow-up.

Classification of patients. According to the stratification criteria, 27 patients (41.5%) were classified in the GP group, 16 (24.6%) in the IP group and 22 (33.8%) in the PP group. The mOS values were 33.9 [95% confidence interval (CI), 20.6-47.1], 13.0 (95% CI, 2.0-24.1) and 5.7 months (95% CI, 2.7-8.6), respectively. There were statistically significant differences in mOS between the different prognostic groups ($P<0.001$) (Fig. 1).

All the patients in the GP and IP groups were treated with first-line sunitinib, except for one patient who received temsirolimus. In the PP group, 13 patients (59.1%) were treated with temsirolimus and nine (40.9%) with sunitinib.

Of the patients treated with first-line sunitinib, 27 (52.9%) were classified in the GP group, 15 (29.4%) in the IP group and nine (17.6%) in the PP group. Taken together, the mPFS and mOS of these patients were 9.0 (95% CI, 5.6-12.5) and 20.1 months (95% CI, 6.4-33.8), respectively. When assessing the patients treated with sunitinib by prognostic group, it was found that the mPFS for the GP, IP and PP groups were 12.4 (95% CI, 8.2-16.6), 6.8 (95% CI, 2.4-11.3) and 4.2 months

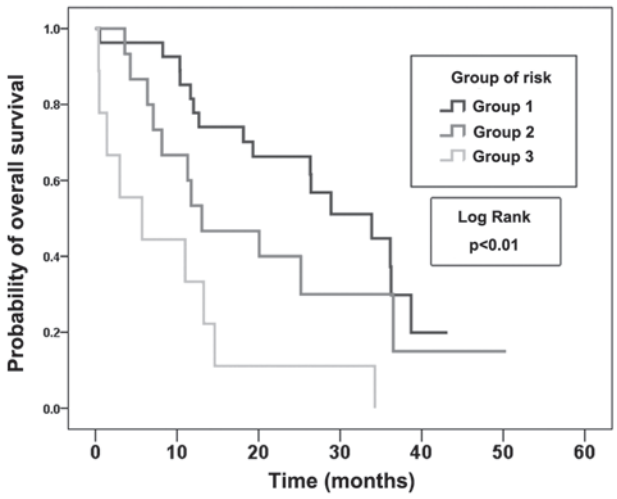

Figure 1. Kaplan-Meier estimates of the overall survival time by group of risk. Group 1, good-prognosis group; Group 2, intermediate-prognosis group; Group 3, poor-prognosis group.

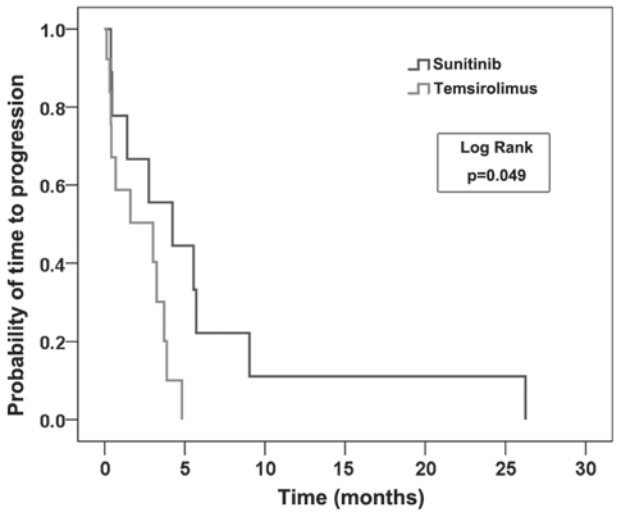

Figure 2. Kaplan-Meier estimates of the progression-free survival time by first-line treatment in the patients with a poor prognosis.

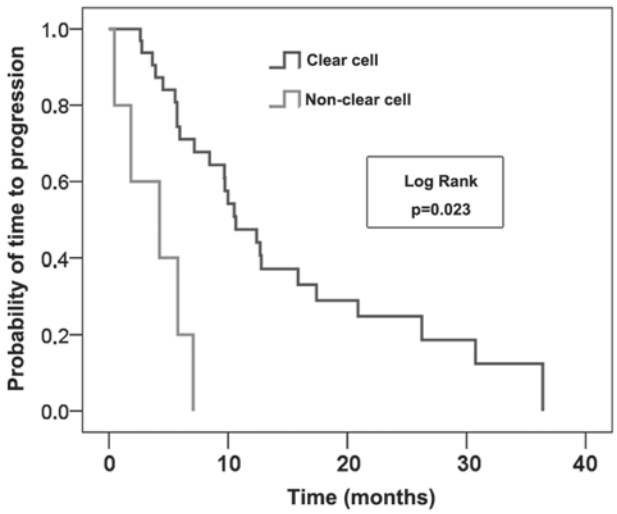

Figure 3. Kaplan-Meier estimates of the progression-free survival time by histology in the patients treated with sunitinib.

(95% CI, 0.0-8.6), respectively, and these differences were statistically significant (P=0.014). The mOS of the same groups were 33.9 (95% CI, 20.6-47.1), 13.0 (95% CI, 2.0-24.1) and 5.7 months (95% CI, 0.0-6.4), respectively, and these differences were also found to be statistically significant (P=0.01).

In the case of the patients treated with first-line temsirolimus (n=14), all except one were classified in the PP group. The mPFS and mOS of these patients were 3.0 (95% CI, 0.3-5.8) and 6.2 months (95% CI, 2.8-9.6), respectively.

Comparing the results of mPFS in the PP group according to the first-line drug used, there was a difference of 1.2 months (P=0.049) in mPFS between the patients treated with sunitinib [nine patients; 4.2 (95% CI: 0.0-8.6 months)] verses those treated with temsirolimus [13 patients; 3.0 (95% CI: 0.0-6.7 months)] (Fig. 2).

With regards to the histological type, the patients treated with sunitinib were found to have a difference in mPFS of 4.1 months (P=0.023) among the patients with ccRCC [43 patients; 9.7 (95% CI: 5.0-14.4 months)] verses patients with non-ccRCC [7 patients; 5.6 (95% CI: 1.5-9.7 months)] (Fig. 3). No statistically significant differences were observed in the mOS of these two cases.

Discussion

The characteristics of the patients included in the present study are consistent with those observed in a previous study (1), with regards to age and male predominance. The most common histology was clear cell, followed by papillary and chromophobe. The observed proportions of clear cell and chromophobe histology were lower compared to other studies (1,5), possibly due to the high proportion of patients without predominant histology and missing histology data.

In the present study, only metastases associated with a poor prognosis (lung, liver and retroperitoneal lymph nodes) were quantified. The proportion of lung metastases was similar to that expressed in previous studies, but lower in the case of liver metastases (6,7,19).

In addition to the limitations inherent in the observational studies, the main weakness of the present study is the low number of fatalities that were registered. This is partly due to patients being transferred to palliative care, which meant a loss of follow-up in certain cases. This may have resulted in an underestimation of the mOS value.

Table I summarizes the clinical and demographic characteristics of the patients, as well as the results of the study in association with the first-line treatment administered and the different studies published. The patients receiving first-line treatment with sunitinib in the study were observed to have a slightly lower mPFS than the figure published in the pivotal study (9.0 vs. 11 months) (14) and in the treatment-naive patient subgroup in the study by Gore *et al* (15) (9.0 vs. 11.1 months). In addition, the mOS for these patients was lower compared to the pivotal study (20.1 vs. 26.4 months), although it was higher compared to the study by Gore *et al* (15) (20.1 vs. 18.1 months) (14). When the mPFS value by prognostic group was analysed, in comparison to the Gore *et al* (15) data, it was found that the GP in the present study had a slightly lower mPFS (12.4 vs. 14.6 months), but a higher mOS (33.9 vs. 24.7 months). However, the IP had a lower mPFS

Table I. Results of the previous studies.

Study	Treatment	n	Efficacy, months (95% CI)	PG[a]	mA	KPS	cc-H	CNS	Nephr	(Refs.)
Present	S	51	mPFS: 9.0 (5.6-12.5) mOS: 20.1 (6.4-33.8) mPFS-GP: 12.4 (8.2-16.6) mPFS-IP: 6.8 (2.4-11.3) mPFS-PP: 4.2 (0.0-8.6) mOS-GP: 33.9 (20.6-47.1) mOS-IP: 13.0 (2.0-24.1) mOS-PP: 5.7 (0.0-6.4) mPFS-cc: 9.7 (5.0-14.4) mPFS-non-cc: 5.6 (1.5-9.7)	GP-52.9 IP-29.4 PP-17.6	65	No	64.7	Yes	88	
	T	14	mPFS: 3.0 (0.3-5.8) mOS: 6.2 (2.8-9.6)	IP-7.1 PP-92.9	64	No	71.4	Yes	43	
Motzer *et al*	S vs. INF	750	mPFS: 11.0 (10.0-12.0) vs. 5 (4.0-6.0) mOS: 26.4(23.0-32.9) vs. 21.8(17.9-26.9)	GP-38 IP-56 PP-6	62	70	100	No	91	(14)
Gore *et al*[b]	S	1370	mPFS: 11.1 (9.9-12.4) mOS: 18.1 (17.1-19.7) mPFS-GP: 14.6 mPFS-IP: 8.5 mPFS-PP: 4.1 mOS-GP: 24.7 mOS-IP: 14.4 mOS-PP: 5.3	GP-36.3 IP-44.2 PP-8.6 MD:10.8	59	No	86	Yes	89	(15)
Hudes *et al*	T vs. INF	209	mPFS: 5.5 (3.9-7.0) vs. 3.1 (2.2-3.8) mOS: 10.9 (8.6-12.7) vs. 7.3 (6.1-8.8)	PP-100	58	Yes	81	Yes	66	(11)

[a]Except for the present study, all the other studies followed the MSKCC criteria; [b]only treatment-naive patients. n., number of patients; CI, confidence interval; PG, % in each prognostic group; mA, median age; KPS, minimum Karnofsky performance status; cc-H, % patients with clear cell histology; CNS, metastases in the central nervous system; Nephr, % prior nephrectomy; S, sunitinib; mPFS, median time to progression-free survival; GP, good-prognosis group; mOS, median overall survival time; IP, intermediate-prognosis group; PP, poor-prognosis group; T, temsirolimus; INF, interferon-α; MD, missing data.

(6.8 vs. 8.5 months) and mOS (13.0 vs. 14.4 months). Regarding the PP, the results were similar for mPFS (4.2 vs. 4.1 months) and mOS (5.7 vs. 5.3 months).

There are three possible key reasons for the differences found between the present study and the pivotal study. Firstly, 11.8% of the population in the present study had non-ccRCC histology, which is associated with a worse prognosis (20), whereas the pivotal study only selected patients with ccRCC histology. Secondly, 98% of patients in the pivotal study were classified as GP or IP according to the MSKCC criteria vs. 82.4% in the present study, according to the criteria previously described. Finally, the pivotal study defined a minimum value of 70% for KPS as an inclusion criterion (38% of patients had a KPS score of 70-80%), whereas the minimum KPS value in the present study was 50% (65%, KPS 70-80%; and 4%, KPS <70%). Another potentially influential factor was the higher median age in the present study (65 vs. 62 years).

With regards to the characteristics of the study population, more similarities with the study by Gore *et al* (15) were found. The latter study, as in the present study, included patients with a KPS <70% (43%, KPS 70-80%; and 15%, KPS <70%) and a similar percentage of patients with non-ccRCC (11%). However, differences in other aspects could have influenced the results, including the higher proportion of patients in the GP or IP groups using the MSKCC criteria (66.1 vs. 82.4%) and a higher median age in the present study (65 vs. 62 years). The proportion of patients with nephrectomy was similar in the present study to the other studies analysed.

Comparing the results of temsirolimus in the present study with the pivotal study (12), a lower mPFS and mOS was found in patients in the present study (3.0 and 6.2 vs. 5.5 and 10.9 months, respectively). In the present study there may also be several different explanations for the differences: The lower proportion of patients with KPS >70% (7.1 vs. 20%), the lower

proportion of patients with clear cell histology (66.6 vs. 80%) and a higher median age (63.5 vs. 58 years). However, since only a few patients were treated with temsirolimus in the present study, these results should be considered with particular caution.

Notably, despite the small number of patients, statistically significant differences were found in mPFS in the PP-group patients when classified by the first-line drug used, in favour of sunitinib. This also applied to patients treated with sunitinib when classified by tumour histology, in favour of clear cell histology, with results similar to those reported in a previous study (21). The fact that differences were not found in mOS in either of these two cases may be due to the small number of patients and the subsequent therapies that were administered.

Of the 65 patients included in the study, the differences in mOS of 20.9 months between the GP and IP groups, and 7.3 months between the IP and PP groups were statistically significant (P<0.001). Although the study design did not allow comparative conclusions to be drawn, this minimal difference of 7.3 months was slightly higher than the difference found in the first study by Motzer *et al* (22) (6.4 months), but was lower compared to the MSKCC study (8.9 months) (8) and the study by Mekhail *et al* (10.1 months) (10). A comparison could not be made with the model proposed by Heng *et al* (12), as the latter did not provide mOS data in the GP group. Notably, there is a tendency towards a more homogeneous distribution of patients in the different prognostic groups, in the present study and in the Mekhail *et al* (10) study.

With regards to the limitations of the study based on the results obtained and despite the fact that a comparative design was not intended, the results conclude that mPFS and mOS of the patients receiving first-line therapy with sunitinib and temsirolimus were lower compared to previous studies. These differences are attributable to several factors, as aforementioned, but do not appear to be relevant in principle. Of note are the statistically significant differences found, despite the small number of patients, in mPFS classified by the first-line drug used in patients in the PP group in favour of sunitinib and the mPFS differences in the group of patients treated with sunitinib classified by tumour histology (clear verses non-clear cell). Although a study with a larger size is required to confirm these differences, re-evaluation of the most suitable option for patients with poor prognosis is necessary. Additionally, these result show patients can be stratified by these factors, with differences of more than seven months between the different prognostic groups. This result may be useful in refining the risk score models in future stratifications. However, a study with a larger sample size is required to confirm these differences. Therefore, these results show the influence of the prognostic factors on OS and how patients can be stratified by these factors, with differences of more than seven months between the different prognostic groups.

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