COST-EFFECTIVENESS OF TREATMENT IN RENAL CELL CARCINOMA ADJUSTED TO THE CLASSIFICATION MODELS

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ABSTRACT

***Introduction**: The emergence of new drugs, their combinations and different treatment schemes, make determining the effectiveness of current treatments in clinical practice necessary and highlights the need for an evaluation of its economic impact on the health system. A retrospective study was conducted to evaluate the cost-effectiveness of first line treatment adjusted to the main classification models.*

***Materials and methods**: The primary end points were: median overall survival (mOS) and median progression-free survival (mPFS) times. The evaluation of cost-effectiveness throughout treatment was assessed by calculating the incremental cost-effectiveness ratio (ICER) based on the cost per year of life gained (YLG).*

***Results**: The study included 88 patients, grouped according to the drug used for first-line treatment. An increase of 4.9 (p = 0.000) in mPFS and 12.6 months (p = 0.000) for mOS was found among patients treated with sunitinib compared with those treated with temsirolimus. By adjusting the mPFS treatments according to the main classification models, we observe that a statistically significant difference remains between the treatments in both the Memorial Sloan-Kettering Cancer Center (MSKCC) and Hudes model. This was not found in the Heng model, in which there is a slight statistically insignificant difference in favor of temsirolimus. No differences were found in the mOS in any case. In the poor prognosis group, which is the prognostic criteria required for the use of temsirolimus, the incremental cost of sunitinib per month free of progression would be of 3,098.2€.*

***Conclusions**: Based on these results it appears that the use of temsirolimus as the most effective option for patients with a poor prognosis, as defined by the criteria in the pivotal trial of temsirolimus or the MSKCC model, may be questionable. However, a larger population would be needed in both groups to determine the relevance of these results.*

***Keywords**: sunitinib, temsirolimus, poor prognosis, Heng, Hudes, MSKCC.*

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Introduction

Renal cell carcinoma (RCC) represents 2-3% of all cancers. Its incidence is higher in men than in women; for 60-70 year olds the male to female ratio is 2:1[1]. In 2008, the incidence of this cancer was 3.2% in Europe and 2.6% in the United States with a mortality of 2.6% and 2.9%, respectively.

The present study was conducted at the Central University Hospital of Asturias (HUCA), the referral hospital for the treatment of RCC in the Principality of Asturias, Spain, whose total population was 1,085,289 in 2009 and where kidney cancer had a incidence of 2.4% and accounted for 2.5% of all cancer deaths that year[2,3].

The RCC has a wide variety of prognostic factors. These can be classified into anatomical, histological, molecular and clinical[1]. Currently, clinical prognostic factors are used for the classification of patients with advanced RCC (aRCC)[4,5].

The classification model published by Motzer et al. at the Memorial Sloan-Kettering Cancer Center (MSKCC) is used in most clinical trials[6]. Since the publication of this classification, new prognostic factors related to patient survival have appeared, as have new ways of classifying patients according to them. Thus in 2005, Mekhail et al. at the Cleveland Clinic Foundation (CCF)[7] conducted a study that provided validation for the factors in the MSKCC and added two more classification factors: previous administration of radiotherapy, and the presence of individual metastases. They found further that the latter factor could be replaced by the number of metastatic sites. In the pivotal trial of temsirolimus, Hudes et al.[8] established a classification of "poor prognosis", which would indicate temsirolimus, from the factors of the MSKCC model along with the presence of ≥2 sites of metastases[7].

Systemic treatment for aRCC has also evolved since the eruption of cytokines into clinical practice, the incorporation of tyrosine kinase inhibitors, anti-VEGF and, more recently, mTOR-inhibitors. Currently, the possibility of using them in combination is being studied, as well as with new drugs such as axitinib and tivozanib[9-13].

In the HUCA protocol, which is based on the MSKCC model[6] and is consistent with the ESMO and NCNN[4,5] guidelines, the use of bevacizumab with alpha-interferon or sunitinib in patients of good-intermediate prognosis has been established as the first-line aRCC treatment, and the use of temsirolimus is the first-line treatment for patients classified as having a poor prognosis.

The emergence of new drugs, their combinations and different treatment schemes, make determining the effectiveness of current treatments in clinical practice necessary and highlights the need for an evaluation of the economic impact of these treatments on the health system. This kind of assessment not only contributes to establishing the place of existing treatments in therapy, but also would facilitate subsequent comparative analysis of existing treatments with future innovations, as they begin to enter treatment protocols.

In a previous study, published in Molecular and Clinical Oncology in November 2014, effectiveness of first-line treatment in aRCC classified by the poor-prognostic factors established by MSKCC plus one validated by Mekhail et al. was reported. The present study focuses on the cost-effectiveness evaluation of treatments used for aRCC in the HUCA according the main prognostic classification models (MSKCC, Heng) and to the Hudes' model created from the pivotal trial of temsirolimus[8].

Materials and methods

An observational retrospective study was conducted in patients initiating first-line systemic treatment for aRCC in the HUCA. In order to be included in the study, patients must have been over the age of 18, diagnosed with CCR, and must have initiated first-line treatment between 2008 and 2011 with targeted therapy.

Patients were monitored until July 2013. Patients who developed other advanced malignancies that required chemotherapy and those who showed a predominant sarcoma component in their histology for which non-targeted therapies were used were excluded from the study.

The variables used to assess the effectiveness of the treatments were median overall survival (mOS) and median progression-free survival (mPFS). The OS was calculated from the treatment start date until the date of death from any cause, or failing that, until the date of starting palliative treatment. The PFS was calculated as the time from the treatment start date to the first documentation of objective disease progression, as defined by the oncologist, or to death from any cause, whichever occurred first. Both were determined by the Kaplan-Meier method and the potential differences in first-line treatment and the different prognosis groups were determined by the Log Rank test. These differences were considered statistically significant if they were associated with a value of $p < 0.05$.

The evaluation of cost-effectiveness throughout treatment was assessed by calculating the incremental cost-effectiveness ratio (ICER)[14] based on the cost per year of life gained (YLG). The calculation of the cost of the treatment included the cost of the treatment, the cost of administration, if necessary, and the cost of dispensing the treatment. The cost of the treatment was calculated as the average of the cost treatment until progression, and in this way, not only was the cost of the standard treatment

scheme (sunitinib: 6-week cycle, 50 mg orally once daily for 4 weeks, followed by 2 weeks without treatment; temsirolimus: 25 mg weekly administered by intravenous infusion) considered, but also the cost of the dose reductions and the treatment adherence. The drug cost was based on the 2012 wholesale acquisition cost based on the Spanish national database (Temsirolimus 25-mg vial: 910€/vial, Sunitinib 50-mg tablets: 5.254,4€, Sunitinib 25-mg tablets: 2.642,0€, Sunitinib 12.5-mg tablets: 1,323.9€)[15].

The calculation of the cost of administration and/or dispensing was calculated based on the use of relative value units (RVU)[16, 17] to evaluate the quantity of resource utilisation along with the cost per unit of the resource based on the HUCA salary scales[18]. This clinical management tool (RVU) has been used in several hospitals and departments within the Spanish Health System to evaluate departmental services[17]. The costs for successive lines of treatment were not taken into account, nor were other indirect costs (adverse event-related costs, routine follow-up, etc.)[16, 17, 18].

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

Results

During the inclusion period, 94 patients initiated first-line treatment for aRCC in the HUCA. Of these, five were excluded following the criteria described in the methods section. Of the 88 patients included in the study, 71 were treated with sunitinib as the first-line treatment (standard treatment scheme: six week cycle, 50 mg orally once daily for four weeks, followed by two weeks without treatment) and 17 were treated with temsirolimus (standard treatment scheme: 25 mg weekly administered by intravenous infusion).

The average dose intensities in the group of patients treated with sunitinib and temsirolimus was 87.3% and 93.5%, respectively.

A total of 78 patients (88.7%) were treated according to the hospital protocol in which patients with a good to intermediate prognosis are treated with sunitinib, and patients with a poor prognosis are treated with temsirolimus (MSKCC criteria). In successive lines, axitinib, bevacizumab, everolimus, dovitinib, sorafenib and pazopanib were used for treatment, besides those previously mentioned.

The median age was 66 years (range: 45–86 years); 67 patients (76.1%) were male. Median Karnofsky index (IK) at baseline was 77.8%. Of all patients, 74 (84.1%) had distant metastases at the time of diagnosis, and 69 (78.4%) had undergone a nephrectomy. From the histological perspective, 61 patients (69.3%) had clear-cell histology (ccRCC), 8 papillary, 9 mixed, and 1 chromophobe; histological findings were unavailable for the remainder of the patients.

At the end of the follow-up period, 68 patients (77.3%) had died, 4 were receiving palliative care, 12 continued treatment and 4 remained under surveillance.

The mPFS and mOS in the group of patients treated with sunitinib was 8.4 months (95% CI: 5.9-11.0 months) and 19.6 months (95% CI: 8.2-31.0 months), respectively. In the case of temsirolimus, the mPFS and mOS were 3.5 months (95% CI: 1.6-5.4 months) and 7.0 months (95% CI: 2.4-11.6 months), respectively.

Depending on the first-line drug used, differences of 4.9 ($p = 0.000$) and 12.6 months ($p = 0.000$) in the mPFS and the mOS, respectively, were found among patients treated with sunitinib compared with those treated with temsirolimus.

The average cost of treatment for patients who completed treatment, based on the total number of doses received through the end of follow-up was 6,469.4€ in the case of temsirolimus (including 214.1€ for administration/dispensing). In the case of sunitinib, the cost was 18,236.3€ (including 16.5€ for administration/dispensing). The incremental cost-effectiveness of first-line sunitinib compared with temsirolimus, unadjusted for quality of life, was calculated as 11,206.6€ per YLG.

Based on the fact that temsirolimus is indicated for patients with a poor prognosis, for a more accurate assessment of cost-effectiveness, the effectiveness should be adjusted according to the risk group. Considering that, the average cost of treatment for poor-prognosis patients, according to the criteria of the pivotal trial of temsirolimus, was 6,175.9€ (including 204.7 € for administration/dispensing) in the case of temsirolimus and 14,541.2 € (including 14.9 € for administration/dispensing) in the case of sunitinib. In terms of effectiveness, we observed no differences in OS in any model for the first-line therapy, which is why we could not assess the incremental cost-effectiveness of sunitinib compared to temsirolimus based on incremental cost per year of life gained.

However, based on PFS, with an increase of 2.7 months in PFS among patients treated with sunitinib compared with those treated with temsirolimus, the incremental cost of sunitinib per progression free month would be 3,098.2€

Patients treated with sunitinib were mainly classified as good-intermediate prognosis patients according to the main classification models while almost all patients treated with temsirolimus were classified as poor-prognosis patients (Table 1).

		GP N (%)	IP N (%)	PP N (%)
MSKCC (6)	Sunit	18 (33.3%)	27 (50%)	9 (16.7%)
	Tem	0 (0%)	1 (7.1%)	13 (92.9%)
	Total	18 (26.5%)	28 (41.2%)	22 (32.4%)
Hudes (8)	Sunit	25 (44.6%)	12 (21.4%)	19 (33.9%)
	Tem	0 (0%)	0 (0%)	16 (100%)
	Total	25 (34.7%)	12(16.7%)	35 (48.6%)
Heng (9)	Sunit	18 (34.6%)	22 (42.3%)	12 (23.1%)
	Tem	0 (0%)	1 (7.1%)	13 (92.9%)
	Total	18 (27.3%)	23 (34.8%)	25 (37.9%)

GP: good prognosis group IP: intermediate prognosis group N: number of patients PG: prognostic group PP: poor prognostic group Sunit: sunitinib Tem: temsirolimus.

Table 1: Distribution of patients according to the classification models.

In Table 2, the effectiveness of first-line treatment (in terms of PFS and mOS) can be seen depending on the different prognosis groups and classification models in our study.

As shown in Table 3, adjusted by first-line treatment, it appears that no model presents a statistically significant difference in PFS among the different prognosis groups. Only in the Heng model was it observed that while there is no difference in the overall model itself, there are significant differences between the poor and good prognosis groups. Regarding the effect of first-line treatment on PFS, for both the MSKCC model and Hudes' model, a statistically significant difference between first-line treatments was maintained in favor of sunitinib.

However, in the Heng model, there was a slight statistically insignificant difference in favor of temsirolimus. Regarding the OS adjusted for first-line treatment, we note that there are statistically significant differences between prognostic groups and no significant differences between first-line treatments in any model.

			GP (95% CI)	IP (95% CI)	PP (95% CI)
MSKCC (6)	mPFS	Sunit	10.4	6	3.4
			(8.1- 12.8)	(4.9-7.2)	(0.0-7.8)
		Tem	-	2.4	3.1
				(NA)	(0.4 -5.8)
	mOS	Sunit	34.4	13.2	11.1
			(22.7 - 46.1)	(10.1 - 15.6)	(0.0-30.9)
		Tem	-	12	6.3
				(NA)	(0.1 - 12.6)
Hudes (8)	mPFS	Sunit	10.4	5.9	5.8
			(6.8 - 14.1)	(5.6 - 6.3)	(2.7 - 8.9)
		Tem	-	-	3.1
					(0.9 - 5.2)
	mOS	Sunit	34.4	13	11.2
			(29.7 - 39.0)	(9.9 - 16.1)	(4.3 -18.0)
		Tem	-	-	8
					(3.4 - 12.7)
Heng (9)	mPFS	Sunit	10.4	6.5	2.7
			(8.1- 12.8)	(3.4 - 9.6)	(1.1 - 4.2)
		Tem	-	2.4	3.1
				(NA)	(0.4 - 5.8)
	mOS	Sunit	34.4	14.8	6.3
			(22.7 - 46.1)	(0.0 - 34.1)	(0.0 - 15.2)
		Tem	-	12	6.3
				(NA)	(1.8 - 10.8)

CI: confidence interval GP: good prognostic group IP: intermediate prognostic group mOS: median Overall Survival mPFS: median Progression-free survival MSKCC: Memorial Sloan-Kettering Cancer Center NA: not available PP: poor prognostic group Sunit: sunitinib Tem: temsirolimus.

Table 2: mPFS and mOS of first-line treatment, separated according to prognostic classification group.

Discussion

Comparing the characteristics of patients included in our study with those observed in the literature[1] it is noted that the average age is similar, as is the predominance of males. The ratio of the different types of histology are lower than that in the literature[1,5,19-21] especially in the case of chromophobe histology. This is perhaps caused by the large proportion of mixed histology without a predominant histology or by the proportion of patients who could not provide data from pathologic anatomy.

In addition to the general limitations of observational studies, the main weakness of this study is the small number of deaths included. This may be due in part to insufficient follow-up of patients over time, but also may be due to the transfer of some

patients to palliative care, meaning a loss of monitoring in some cases, which could have decreased the value of the mOS.

			p	Exp(B) (95% CI)
MSKCC (6)	mPFS	MSKCC	0.22	
		GP-IP	0.213	1.523 (0.785 - 2.953)
		GP-PP	0.095	2.118 (0.878-5.109)
		1st Line	0.039	2.610 (1.048-6.503)
	OS	MSKCC	0.004	
		GP-IP	0.025	2.487 (1.122-5.515)
		GP-PP	0.001	5.347 (1.988-14.382)
		1st Line	0.628	1.233 (0.528-2.880)
Hudes (8)	PFS	Hudes	0.144	
		GP-IP	0.715	1.165 (0.514-2.641)
		GP-PP	0.053	1.872 (0.992-3.533)
		1st Line	0.014	2.498 (1.206-5.173)
	OS	Hudes	0	
		GP-IP	0.073	2.095 (0.934-4.698)
		GP-PP	0	4.293 (2.058-8.732)
		1st Line	0.432	1.326 (0.656-2.681)
Heng (9)	PFS	Heng	0.059	
		GP-IP	0.231	1.524 (0.765-3.306)
		GP-PP	0.017	2.680 (1.191-6.031)
		1st Line	0.062	2.224 (0.960-5.155)
	OS	Heng	0	
		GP-IP	0.05	2.268 (1.001-5.138)
		GP-PP	0	6.416 (2.504-16.441)
		1st Line	0.854	1.077 (0.488-2.377)

CI: confidence interval exp(B): exponentiation of the B coefficient (odds ratio) GP: good prognostic group IP: intermediate prognostic group OS: median Overall Survival PFS: median Progression-free survival PP: poor prognostic group.

Table 3: Differences in PFS and OS between prognosis groups adjusted by first-line treatment.

In our study, 71 patients were treated with sunitinib as the first-line therapy. Of these, 9 patients (12.7%) abandoned treatment due to adverse effects, which is a smaller proportion than observed in the pivotal trial of Motzer[10], but was higher than in Gore's trial[11] for the same main reasons (diarrhoea, mucositis and asthenia). Regarding treatment effectiveness, our study presents a median PFS somewhat lower than in the other published studies by Motzer[10,22] (11 months) and Gore[11] (10.9 months).

We observed shorter mOS compared with the pivotal trial published by Motzer[10, 22] (26.4 months) although it was higher than observed in the trial by Gore[11] (18.4 months).

In spite of this, neither of these differences in mOS or mPFS appears to be significant compared with published studies. The perceived differences between our work and the pivotal trial can be explained mainly by three reasons. Firstly, 12.7% of our patient population had non-ccRCC histology, which is associated with a worse prognosis[23], whereas in the pivotal study only patients with ccRCC histology were selected. Secondly, 98% of patients in the pivotal trial were classified as having a good to intermediate prognosis according to MSKCC criteria versus 83.3% in our study. And finally, the pivotal trial established a minimum IK of 70% (with 38% of patients with IK 70-80%) for inclusion, whereas in our study the minimum IK was 50% (54.9% with IK 70-80% and 5.6% with IK < 70%). Another factor that may have influenced the results was the higher median age in our study (65 vs. 62 years).

Considering the characteristics of the studied population, we found more similarities with the study presented by Gore[11]. This, like our work, has patients with IK <70% (43% with 70–80% and 15% with IK < 70%) and a similar percentage of patients with non-ccRCC histology (11%). However, there are differences in other aspects that may have influenced the results, for example, a larger proportion of patients were classified as having a good to intermediate-prognosis according to MSKCC criteria, (64.8% vs. 82.4%) and there was a higher median age in our study (66 vs. 62 years). The proportion of patients with a prior nephrectomy was similar between the present study and the comparative studies.

Regarding patients who were treated with temsirolimus as a first-line treatment (17 patients, 19.3% of the total), 11.8%[2] did not progress. In our study there were 3 patients who discontinued treatment (10%), slightly above the Hudes pivotal trial[8]. All patients classified as having a poor prognosis, according to the criteria established in the pivotal trial, and in our study, showed an inferior mPFS (5.5 months) and an inferior mOS (10.9 months) than the pivotal trial.

In this case the differences can also be explained by several reasons. In our study, 52.9% of the patients had a prior nephrectomy vs. 66% of patients in the pivotal trial; 76.5% had clear cell

histology compared with 80% of patients in the pivotal trial; and finally, the average age in our study was 65.9 years while in the pivotal trial it was 58 years. However, due to the small number of patients treated with temsirolimus in our study, these results must be considered with particular caution.

In our study, we observed significant differences between sunitinib and temsirolimus for both mPFS (4.9 months; $p < 0.001$) and mOS (12.6 months; $p < 0.001$). However, adjusting for the effect of treatment on OS by the main classification models (MSKCC, Heng) and by the model derived from the Hudes pivotal trial of temsirolimus, we observed no differences according to the first-line treatment used, probably due to successive lines of treatment, and other differences between different risk groups were maintained. In the case of PFS, adjusting for treatment according to the different classification models, it was observed that significant differences remain between first-line drugs in the MSKCC and Hudes classification models in favor of sunitinib, but not in the Heng model.

It is noteworthy that despite the low number of patients, there are statistically significant differences in favor of sunitinib in mPFS in the poor prognosis patient group, contrary to what might be expected[5] by classifying patients according to the Hudes' classification model used in the pivotal trial of temsirolimus. The differences in mPFS found by classifying patients according to the MSKCC and Heng models were less relevant. The last one was found not statistically significant.

Based on the fact that temsirolimus is indicated for patients with a poor prognosis, we have adjusted the effectiveness according to the risk group. As there is no difference in terms of OS, we have assessed the ICER of sunitinib in terms of PFS with an ICER of 3,098.2€ per progressions free month compared with temsirolimus in poor-prognosis patients. Despite this, it should be assessed the influence of quality of life and the successive lines of treatment to evaluate the most cost-effective option because from a cost-minimization analysis perspective, temsirolimus could be the least costly treatment for poor-prognosis patients as there is no differences in years of life gained.

Our results demonstrated somewhat lower mPFS and mOS in patients treated with sunitinib and temsirolimus than has been reported in the literature. This may be due to the difference in key variables between patient populations (such as age, IK, histology) that influence mPFS and mOS, among other reasons. While there were no statistically significant differences in OS when adjusting the treatment effect by the prognostic classification models, probably due to successive lines of treatment, differences in PFS are maintained in the models of MSKCC and Hudes. Based on these results it appears that sunitinib could be the most effective option for poor-prognosis patients according to the criteria of the pivotal trial of temsirolimus or the MSKCC model but as there is no difference in terms of years of life gained, only in progression free survival time, it could be debatable if it is the most cost-effective option. However, a larger population would be needed to determine the relevance of these results, and especially to assess the best option depending on the Heng model, which collates the ESMO[4] guidelines for validating and updating the Motzer model in MSKCC.

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