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Cost-Effectiveness of Sorafenib for Metastatic Renal Cell Carcinoma: A Systematic Review

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ABSTRACT:

Introduction: Sorafenib is a multi-kinase inhibitor and decreases tumor cell proliferation. This study aimed to systematically review the existing evidence related to its cost-effectiveness.

Methods and Results: EMBASE, MEDLINE, PUBMED, Google Scholar, and the Scopus database were searched and articles were selected on the basis of their correlation with the economic evaluations of Sorafenib. The quality of the selected studies was assessed using the Quality of Health Economic Studies instrument. This review revealed costs per quality-adjusted life years in the range of US $89,160 to $118,825, depending on whether the setting was first-line or second-line and which comparator is utilized.
The results indicated that Sorafenib had not been considered as an appropriate treatment option for patients with metastasis Renal Cell Carcinoma (mRCC). Sorafenib was dominated (i.e. higher cost and lower efficacy) in comparison with Sunitinib in all cases. However, Sorafenib would be more cost-effective in comparison with bevacizumab plus interferon alfa in the treatment of mRCC.

Conclusion: Sorafenib was more effective with higher cost than Best Supportive Care but Sorafenib was not cost-effective in view of current willingness to pay threshold.

Keywords: renal cell carcinoma; pharmacoeconomic evaluation; Sorafenib, cost-effectiveness; systematic review

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1. Introduction

Renal cell carcinoma (RCC), which originates from or rooted within the renal cortex, constitutes 80 to 85 percent of primary renal neoplasms. Diagnosis median age is considered 65 years with a variable incidence over the world [1,2]; nearly 84000 cases of RCC and 35000 death cases resulting from kidney cancer were reported in the European Union in 2012 [3].
Nowadays, patients suffering from kidney cancer have better chances of 5-year survival compared to 50 years ago, increasing from 5-year survival rate of 34% in 1954 to 62% in 1996 and, then, to 73% from 2005 to 2011 [4,5]. However, fewer than 10% of patients with metastatic RCC (mRCC) had 5-year survival chances [6]. Unfortunately, RCC has a poor prognosis in a significant proportion of patients [7]. 25-30% of RCC patients have metastasis causing the majority of deaths related to RCC [8]. The evaluated economic burden of mRCC was about US $107-556 million in the US in 2006 [9].
Although, mRCC does not respond well to treatment, in terms of efficacy and safety, Sorafenib (SFN) fares better than other treatment strategies including surgery and systemic chemotherapy [9], in general. SFN is a multi-kinase inhibitor, which was approved for RCC in 2005 and decreases tumor cell proliferation. It is administrated 400mg orally twice a day. However, according to recent studies, dose-adjusted SFN regimen results in better efficacy-safety balance [10].
There are several approved treatments for RCC such as surgical interventions, Sunitinib (SUN), Everolimus, Axitinib, Bevacizumab (BVC), and Lenvatinib. In light of the ever-increasing costs of the healthcare system and a great expense of the newly introduced treatments, it has become more crucial than ever to choose more cost-effective treatments among different alternatives. Cost-effectiveness studies may provide healthcare decision-makers with the requisite insights to make informed choices.
Hence, this study was aimed to systematically review the economic evaluations of SFN in the treatment of RCC to

assist decision-makers to maintain costs and ensure access to effective treatments within limited healthcare budgets.

2. Methods

A systematic literature search in EMBASE, MEDLINE, PUBMED, Google Scholar, and the Scopus database was conducted between November 2004 and April 2018. The following key words were used in our search strategy: "Sorafenib", "renal", "kidney", "cancer", "carcinoma", "economic evaluation", "pharmacoeconomic evaluation", "cost-effectiveness", "cost-utility", "cost-benefit", and "cost-minimization". These keywords were limited to titles and abstracts.

2.1. Inclusion or exclusion criteria:

The search was limited to articles published in English. In addition, studies without a full text were left out. The studies included in our corpus also had to meet the following inclusion criteria:

- Dealing with adults suffering from metastatic or advanced renal cell carcinoma as patient population.
- Taking both cost and clinical consequences into account.
- Representing the SFN-containing therapy as one of the treatment arms.

The search strategy identified 254 articles and 5 studies' were selected based on their eligibility (Fig. 1).

2.2. Quality assessment

To evaluate the quality of the included studies, the Quality of Health Economic Studies (QHES) instrument, which is shown in table 1, was used. QHES score shows the quality of economic studies as follows: poor (QHES score<50), fair (QHES score ≥ 50 and <75), and good (QHES score≥75 and ≤100).

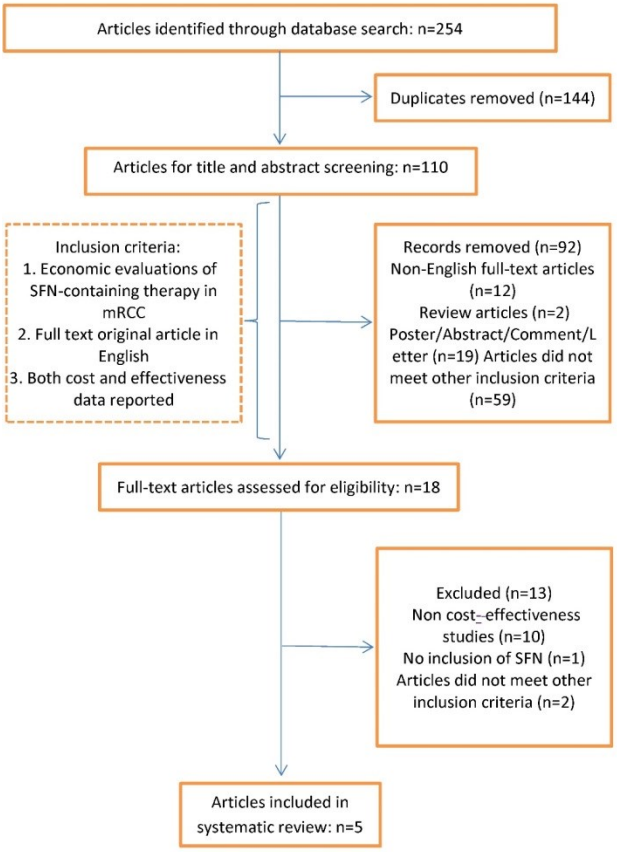

Figure 1. PRISMA diagram

Table 1. The Quality of Health Economics Studies (QHES) instrument

	Questions	Points
1	Was the study's objective presented in a clear, specific, and measurable manner?	7
2	Were the perspectives of the analysis (societal, third-party payer, etc.) and reasons for their selection stated?	4
3	Were variable estimates used in the analysis from the best available sources (i.e., randomized control trial - best, expert opinion - worst)?	8
4	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	1
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9
6	Was incremental analysis performed between alternatives for resources and costs?	6
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and negative outcomes?	6
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear and transparent manner?	8
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7
14	Did the author(s) explicitly discuss the direction and magnitude of potential biases?	6
15	Were the conclusions/recommendations of the study justified and based on the study results?	8
16	Was there a statement disclosing the source of funding for the study?	3
Total Points		100

3. Results

Overview

Five articles were identified in the PubMed database meeting the inclusion/exclusion criteria (Table 2). Two of them compared SUN with SFN and BVC plus interferon-α (BVC/IFN), one compared SFN versus Everolimus, and the other two compared SFN versus best supportive care (BSC). No more full-text study was detected in Google search engine. However, seven more abstracts were recorded. Although overall 12 studies dealt with some kind of cost analysis, only nine studies reported information on cost-effectiveness.

The Cost-effectiveness analyses of the SFN-containing therapy were conducted in four different countries including USA (n = 2), Spain (n = 1), Cyprus (n=1), and UK (n=1). Most of them were performed in a single country. Almost all studies adopted a healthcare system's or a payer's or third-party payer's perspective. Markov model was applied in all of the studies in a 6-year to life-time time horizon. A discount rate of 3% or 3.5% was used in the studies and all studies disclosed their source of funding.

All the included studies were published in medical journals implementing limited follow up time data in their models. Accordingly, all of them were considered medium level of evidences. The primary focus of the studies was comparing SFN, SUN, Everolimus, or BSC in the treatment of mRCC in terms of cost-effectiveness. Three studies had been sponsored by Pfizer, Bayer, and the UK National Health System. One study denied receiving any financial support (table 2). Cost-effectiveness results of SFN in metastatic renal cell carcinoma were shown on table 3.

Table 2. Characteristics of articles assessing cost-effectiveness of SFN in metastatic renal cell carcinoma

Study (year)	Country	Perspective	Currency/year	Economic model type	Time horizon	Discount rate	Funding source
Aller et al. (2011)	Spain	Third- party payer	Euro/2008	Markov	10 year	3%	Pfizer
Benedict et al. (2011)	USA/Sweden	Third- party payer	Dollars/2007	Markov	lifetime	3%	Pfizer
petrou et al. (2014)	Cyprus	Payer	Euro/2012	Markov	10 year	3.5%	No
Casciano et al. (2011)	USA	US payer	Dollar/2010	Markov	6 year	3%	Novartis
Hoyle et al. (2010)	UK	UK National Health Service	Pound/2008	Markov	10 year	3.5%	UK NHS Research

Table 3. Cost-effectiveness results of SFN in metastatic renal cell carcinoma

Study	Population	Comparator	Type of cost included	Cost	Effectiveness	ICER
Casciano et al.	mRCC	SFN VS Everolimus	post discontinuation treatments, drugs, nurse care, adverse event(AE), general practitioner visits, CT scans, and blood tests, surgical, radio therapeutics	$42,736 vs $124,379	LY: 0.533 vs 1.805 QALY: 0.382 vs 1.298	$89,160/QALY
Aller et al.	mRCC	SUN vs SFN and BVC/IFN	drug treatment costs; specialist visits; hospitalizations; general practitioner and nurse visits; laboratory testing of blood counts, metabolic panels and thyroid function; chest and/or pelvis CT scans; X-rays; MRI; AE	SFN: €119,541 SUN: €118,417 BVC/IFN: €141,634	LY:2.74 vs 2.90 vs 2.67 QALY: 1.70 vs 1.87 vs 1.71	SFN vs SUN: dominated SFN vs BVC/IFN: cost-effective*
Benedict et al.	mRCC	SUN vs SFN and BVC/IFN	drugs, specialist visits, hospitalizations, general practitioner and nurse visits; laboratory testing of blood counts, metabolic panels and thyroid function; chest/pelvis CT scans, X-rays and MRI,AEs	SFN: $382, 922 SUN:$369,346 BVC/IFN: $437,144	LY: 2.743 vs 2.900 vs 2.670 QALY: 1.706 vs 1.876 vs 1.714	SFN vs SUN: dominated SFN vs BVC/IFN: cost-effective*
Hoyle et al.	advanced RCC	SFN VS BSC	Drugs, medical management (computed tomography scans, monitoring, blood tests), AE, GP visit , nurse care	£23,860 vs £3,797	LY: 1.66 vs 1.30 QALY:1.18 vs 0.91	£75,398/QALY
Petrou et al.	advanced RCC	SFN VS BSC	Drugs, hospitalization, GP visit, nurse care, AE, Specialist, CT	€23780 vs €7330	QALY: 0.639 vs 0.478	€102,059/QALY

* less costly and less effective, but below the acceptable willingness to pay

3.1. Sorafenib versus best supportive care

Hoyle et al. [11] developed a Markov cohort model to evaluate the cost-effectiveness of SFN versus BSC as a second-line treatment employing data from a random clinical trial (RCT) by Escudier et al. [12]. Costs were calculated in pounds in 2008 with a 10-year time horizon and a 3.5% discount rate. The resources used on medical costs were based on national tariffs, experts' opinion, and published sources. The results illustrated that SFN was associated with the incremental effectiveness of 0.33 life years gained (LYG) and 0.27 quality-adjusted life years (QALYs). As a result, the incremental cost-effectiveness ratio (ICER) was estimated as £54,565 per LYG and £75,398 per QALY. Sensitivity analysis showed that the model was sensitive to effectiveness data for overall survival, health state utilities, and drug acquisition costs. Finally, the authors, who disclosed their employment in the UK NHS, concluded that although SFN was more effective than BSC, it was not cost-effective at the threshold of £30,000 [11].
In a different study, Petrou et al. [2] compared SFN as a second-line therapy to BSC employing a Markov model. The model was run in a 10-year time horizon from the payer perspective. Two single-arm trials were used to extract SFN efficacy data. The results indicated an incremental QALY of 0.161 (0.639 versus 0.478 QALY) together with an incremental cost of €16,450 (€23,780 versus €7,330) resulting in an ICER of €102059/QALY. In conclusion, the study mentioned the probability of SFN being cost-effective as 0% at the threshold of €60,000. The one-way sensitivity analysis illustrated that the result was sensitive to effectiveness (overall survival) and the price of products. As the authors noted, the most important limitation of their study was comparing SFN with BSC since some comparators such as Axitinib and Everolimus were available as second-line treatments. The study had not been sponsored [2].

3.2. Sorafenib versus Everolimus

Casciano et al. [13] compared the cost and effectiveness of SFN versus Everolimus in 2011 from a payer perspective in second-line setting after the failure of first-line SUN as well as in the second-line setting. A Markov cohort model was used with a discount rate of 3% and a 6-year time horizon. An incremental cost per QALY of $89,160 and $64,185/LYG were calculated for SFN in treatment of advanced RCC in comparison with Everolimus. The sensitivity analysis showed that the model was sensitive to treatment effectiveness variations (hazard ratio for overall survival), drug price, and health state utilities. Finally, this study, which had been funded by Novartis Pharmaceutical Corporation, concluded that SFN was not cost effective at the threshold of $50,000 [13].

3.3. Sorafenib versus Sunitinib

Benedict et al. [14] analyzed three new drugs as first-line treatments for mRCC including SUN, SFN, and BVC/IFN. A Markov model was utilized using a 3% discount rate from the third-party payer's perspective. All the costs were measured in US dollars in 2007. Given a lifetime horizon, the study demonstrated that SFN would result in lower QALYs gained and higher costs than SUN (1.706 versus 1.876 QALYs and $381,922 versus $369,346, respectively). As a result, SFN was found as a dominated strategy. The sensitivity analysis illustrated that the model was sensitive to hazard ratio for overall survival, costs of BSC, the price of drugs, and utilities associated with treatments [14].
Similarly, Aller et al. [7] adopted a Markov cohort model to estimate the comparative cost-effectiveness of SFN, SUN, and BVC/IFN from the third-party payer's perspective. The overall survival (OS) and progress free survival (PFS) of SFN was derived from two different trials in metastatic renal cell carcinoma [15,16]. Costs were reported in Euros in 2008 in a 10-year time horizon. LYs and QALYs were calculated as 2.74 and 1.7 for SFN and 2.9 and 1.87 for SUN, respectively. In addition, SFN was associated with an incremental cost of €1,124 compared to SUN (€119,541 versus €118,417). Finally, the results showed that SFN was the dominated alternative compared to SUN due to its higher cost and lower efficacy. The one-way sensitivity analysis showed that the result was sensitive to drug costs, utility values, and hazard ratio, for both OS and PFS[7].

3.4. Quality assessment (QHES)

The results of the quality assessment using the QHES instrument have been presented in Table 4.

Table 4. Quality assessment of studies using the QHES instrument

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Score
Aller et al.	√	√	x	√	√	√	√	√	√	√	√	√	√	√	√	√	92
Benedict et al.	√	±	√	√	√	√	√	√	√	√	√	√	√	√	√	√	98
Casciano et al.	√	±	√	√	√	√	√	±	√	√	√	√	√	√	√	√	94.5
Hoyle et al.	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	100
Petrou et al.	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	100
Statement frequency	5	5	4	5	5	5	5	5	5	5	5	5	5	5	5	5	---

It was found that the quality of the included studies was at a high level (Mean QHES Score: 96.9). The objectives of studies were clearly presented in all studies (Question 1). The perspective of the analysis had been stated in all studies. However, two studies have not stated any justification for the reasons of selection (Question 2). The best available source of data was utilized by all the studies except Aller et al. [7] using expert opinion (Question 3). When subgroup analyses were conducted, the groups were pre-specified (Question 4) and all the studies handled uncertainty by both one-way sensitivity analysis as well as probabilistic sensitivity analysis (Question 5). All studies performed incremental analysis among alternatives for effectiveness and costs (Question 6). In addition, all of the studies provided detailed information on the methods used to derive effectiveness (Question 7). Information on the discounting rate for costs or utilities had been stated in all of them. Regarding the time horizon, the study done by Casciano et al. [13] revealed that its shorter time horizon compared to other studies might not have covered for all relevant and important outcomes (Question 8). Moreover, all studies measured costs appropriately (Question 9).

The primary outcome measures had been clearly stated in all studies and other relevant outcomes were addressed (Question 10). In addition, the reliability and validation of health outcome measures had been tested before (Question 11). The model had been clearly explicated by the authors of all studies (Question 12). Then, the justification for the choice of the model and discussion on results, assumptions, and limitations had been given by all the studies (Question 13). The direction and magnitude of potential bias had also been discussed by the authors of all studies (Question 14) and the conclusions drawn by the authors of all studies were based on the study results and sounded reasonable (Question 15). Finally, all of them disclosed their source of funding for their studies (Question. 16).

4. Discussion and Conclusion

This is the first systematic review of the economic evaluation studies of SFN in RCC treatment. The cost-effectiveness of SFN has been evaluated in several distinct treatments? Therapy protocols (first- and second-line) against various treatment regimens. The findings in this study point to an incremental cost per QALY in the range of $89,160 to $118,825, depending on whether the setting is first-line or second-line and which comparator is utilized.

Overall, the results indicated that SFN had not been considered as a cost-effective treatment option for patients with mRCC. Briefly, SFN was dominated with a higher cost and lower efficacy than SUN in all cases [7,14]. However, compared to BVC/IFN, SFN was associated with lower cost as well as lower efficacy [14]. A closer look revealed that SFN would be more cost-effective than BVC/IFN in treating of mRCC.

Compared to BSC, SFN was costlier and more effective in all the studies. However, SFN was not considered as a cost-effective strategy due to its high calculated ICERs (£75,398 and €102,059), which was beyond an acceptable range [2,11].

All studies mentioned that the model was sensitive to clinical effectiveness (overall survival) and drug acquisition cost. In addition, some of them also showed sensitivity to health state utility [11,13]. Not only being sensitive to clinical effectiveness somewhat makes the result questionable, but also extrapolating clinical efficacy and treatment persistency from short-term RCTs to a long treatment period carries significant uncertainty and requires additional assumptions that are not well acknowledged in the literature.

For transferability of the results of these studies, in addition to noting different health care settings, different costs, different medical procedures, etc., willingness to pay should also be consider an important contributing factor. It should also be noted that willingness to pay threshold is not a rigid cut-off all over the world. For example, in the United States, a threshold of $50,000 per QALY is generally accepted to assess the cost-effectiveness of an intervention. Furthermore, health care authorities in Spain consider a treatment as a cost-effective strategy if it results in an ICER of ≤€50,000/QALY. In the UK, NICE advocated a cut-off at an ICER of £30,000 /QALY. So, the results should be interpreted with a view to or considering the specific willingness to pay threshold in different jurisdictions.

Generalizability of the trials to the wider patient population is another limitation in targeted studies. Most of the patients included in the clinical trials have had good performance and prognosis, clear cell mRCC, and undergone a prior nephrectomy. Accordingly, the generalizability of estimated overall survival to the wider patient population can prove a limiting factor. In addition, the generalizability of cost-effectiveness studies, which have been conducted in a specific country, to other health care settings may be limited due to the differences in costs between different countries such as developed and developing countries.

In sum, according to high quality published cost-effectiveness studies, SFN has not been considered as a cost-effective treatment option for patients with mRCC. To be more specific, three main conclusions were drawn from this systematic review: 1. SFN is dominated in comparison with SUN, 2. SFN is more effective and costly in comparison with BSC but not cost-effective at acceptable ICER thresholds, and 3) SFN is less effective and costly in comparison with BVC/IFN and could be considered cost-effective.

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