

Sorafenib for advanced renal cell carcinoma in real-life practice: a literature review*

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ABSTRACT

Sorafenib is a new treatment indicated for patients with advanced renal cell carcinoma who have failed prior cytokine-based therapy or are considered unsuitable for such therapy. Although treatment with sorafenib under 'ideal trial conditions' has been extensively studied, registration and reimbursement authorities are also interested in the behavior of sorafenib in real-life practice. This study aims to conduct a literature review of the dosage and treatment duration; safety, tolerability and effectiveness; costs and cost-effectiveness of sorafenib in routine clinical care. Studies were identified by searching PubMed, Embase, Centre for Reviews and Dissemination databases, Cochrane Database of Systematic Reviews, and EconLit up to November 2010. The literature search included articles published in peer-reviewed journals, congress abstracts, and internal studies of Bayer Schering Pharma. Eight studies were included. An open-label study observed stable disease for at least eight weeks in 80% of patients. The most common drug-related adverse events were hand-foot skin reaction, rash, hypertension, and fatigue. Although treatment with sorafenib led to fewer dose reductions, it was also associated with a shorter treatment duration, less time to progression and a shorter survival time as compared to sunitinib. Monthly health care costs were lower with sorafenib as compared to sunitinib. A post-marketing surveillance study showed that patients rated the tolerability and effectiveness of sorafenib as very good, good or sufficient. In conclusion, the current evidence is too limited to derive conclusions and existing studies suffer from methodological shortcomings.

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Keywords: Sorafenib; Advanced Renal Cell Carcinoma; Real-Life Practice; Literature Review

1. INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 2% of all cancer cases [1]. It is the most common form of kidney cancer and 25%–30% of patients present with advanced (metastatic) disease at time of diagnosis. An epidemiological literature review reported an annual incidence of advanced RCC in major European countries, the United States and Japan ranging from 1,500 to 8,600 cases [2]. The economic burden of advanced RCC has been estimated at \$107–\$556 million in the United States in 2006 [2].

Advanced RCC is a treatment-resistant malignancy: patients who present with advanced disease have a poor prognosis and median survival after diagnosis is less than one year. Few effective therapeutic options are available [3]. Surgery has limited or no effect. Cytokines, which have been the mainstay of therapy for RCC, are associated with significant toxicities. High dose interleukin-2 provides clinical benefit to a relatively small percentage of patients and has a significant toxicity profile. Interferon alpha is associated with a modest response rate and limited tolerability for many patients. For patients who fail cytokine therapy or for whom these therapies are not suitable, therapeutic options are limited. Therefore, the need for new and more effective therapies is high.

Treatment of advanced RCC may benefit from novel agents, such as molecularly targeted therapies. One such therapy, sorafenib (Nexavar®), is indicated for patients with advanced RCC who have failed prior cytokine-based therapy or are considered unsuitable for such therapy [4]. In preclinical models, sorafenib decreased angiogenesis through upstream inhibition of receptor tyrosine kinases Vascular Endothelial Growth Factor Receptor (VEGFR) and Platelet Derived Growth Factor Receptor (PDGFR) as well as serine/threonine kinases in

the RAF/MEK/Extracellular signal Regulated Kinase (RAF/MEK/ERK) pathway. Sorafenib also decreased tumor cell proliferation through upstream inhibition of receptor tyrosine kinases KIT and Fms like Tyrosine Kinase 3 (FLT-3) [5-7].

In a randomized discontinuation Phase II study, patients with metastatic malignancies, including RCC patients with stable disease on sorafenib therapy, were randomized to placebo or continued sorafenib therapy [8]. Progression-free survival in patients with RCC was significantly longer in the sorafenib group (163 days) than in the placebo group (41 days) ($p = 0.0001$, hazard ratio = 0.30).

In the largest, international, Phase III study in advanced RCC, the Treatment Approaches in Renal Cancer Global Evaluation Trial [TARGET] [9], sorafenib doubled median progression-free survival, 24 weeks versus 12 weeks, as compared with placebo ($p < 0.000001$; hazard ratio = 0.40; 95% confidence interval: 0.40-0.55). Age, Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic group, Eastern Cooperative Cancer Group Performance Status (ECOG PS) and prior therapy did not significantly affect the treatment effect size. In the second interim analysis for overall survival, the median survival was 19.3 months for patients randomized to sorafenib as compared to 15.9 months for placebo patients (hazard ratio = 0.77; 95% confidence interval: 0.63-0.95; $p = 0.015$). This second interim analysis was conducted following cross-over from placebo patients to active treatment at the recommendation of the data monitoring committee. The most common drug-related adverse events associated with sorafenib therapy are diarrhea, rash, alopecia and hand-foot skin reaction [4].

Treatment of advanced RCC with sorafenib under "ideal trial conditions" has been extensively studied. Literature studies have reviewed the pharmacodynamic and pharmacokinetic profile, therapeutic efficacy, tolerability, dosage and administration of sorafenib [10-12]. The cost-efficacy has been assessed in a number of economic evaluations [13]. In addition to such evidence, registration and reimbursement authorities are interested in the behavior of a drug in real-life practice, its effectiveness and cost-effectiveness. Such data provide evidence of the impact of a drug when for example patients do not fulfill the inclusion criteria for randomized controlled trials or do not fully comply with pharmacotherapy.

The aim of this study is to conduct a review of the international literature examining the treatment of advanced RCC with sorafenib in routine clinical care. The literature study focuses specifically on the dosage and treatment duration; safety, tolerability and effectiveness; costs and cost-effectiveness of sorafenib. The findings

may serve to aid local decision-makers in allocating scarce health care resources and to inform the prescribing behavior of physicians.

2. METHODS

2.1. Search Strategy

Studies were identified by searching PubMed, Embase, Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effects, National Health Service Economic Evaluation Database, and Health Technology Assessments Database), Cochrane Database of Systematic Reviews, and EconLit up to November 2010. Additionally, the bibliography of included studies was checked for other relevant studies. Search terms included 'renal cell carcinoma', 'kidney cancer', 'advanced', 'metastatic', 'nexavar', 'sorafenib', 'dosage', 'treatment duration', 'safety', 'tolerability', 'effectiveness', 'costs', 'cost-effectiveness', 'economic evaluation', 'real life', 'routine clinical care' alone and in combination with each other.

The literature search included articles published in peer-reviewed journals. Relevant congress abstracts were identified by searching the congress database of the American Society of Clinical Oncology and the Outcomes Research Digest, an electronic database of abstracts presented at conferences of the International Society of Pharmacoeconomics and Outcomes Research. Finally, Bayer Schering Pharma was contacted for any unpublished studies.

2.2. Inclusion and Exclusion Criteria

The review was limited to the use of sorafenib in advanced RCC. Other registered indications (i.e. hepatocellular carcinoma) fell outside the scope of this study.

The literature review included studies on the treatment of advanced RCC with sorafenib in real-life practice. Clinical studies exploring the safety, tolerability and efficacy of sorafenib under "ideal trial conditions" were excluded. Cost studies were included if they compared health care and/or other costs of sorafenib and an alternative treatment for advanced RCC. Evidence about cost-effectiveness was derived from economic evaluations. An economic evaluation was defined as a study comparing sorafenib with an alternative treatment in terms of both costs and consequences [14]. Economic evaluations were excluded if treatment of advanced RCC did not involve sorafenib or if studies analyzed a single intervention without a comparator.

The review was limited to studies published in English, French, Dutch, or German for practical reasons.

3. RESULTS

3.1. Search Results

Few studies have focused on the treatment of advanced RCC with sorafenib in real-life practice. The researcher identified 89 citations, but only eight studies were included in the review: two studies exploring dosage and treatment duration [15,16], two pre-marketing surveillance studies [17,18] and one post-marketing surveillance study [19], two analyses of a claims database [20,21], and one economic evaluation [22]. The characteristics of included studies are presented in **Table 1**.

3.2. Dosage and Treatment Duration

A retrospective analysis of a US claims database investigated dose-reduction patterns in patients with primary or advanced RCC treated with sorafenib or sunitinib [16]. The initial daily dosage was sorafenib 800 mg or sunitinib 50 mg. Demographic characteristics were similar between the two groups, except for a higher incidence of stroke (7.9% vs 3.6%, $p = 0.037$) and other cancer site (93.7% vs. 87.8%, $p = 0.036$) in the sorafenib group. Significantly more patients receiving sunitinib required dose reductions as compared with sorafenib (35.5% vs 16.9%; $p < 0.001$). Significantly more dose reductions occurred within the first three months with sunitinib than with sorafenib (65% vs. 25%, $p < 0.001$). The mean time to dose reduction was significantly longer for sorafenib than sunitinib (162 days vs 104 days, $p = 0.003$). These findings show that more dose reductions were required in patients who initially received sunitinib than in those who received sorafenib.

An Israeli study explored treatment duration and survival in patients with advanced RCC receiving first-line treatment with either sorafenib or sunitinib [15]. Demographic and claims data were extracted from a health services database. Treatment duration and patient survival were calculated and compared using a Kaplan-Meier analysis. The sample included 134 patients receiving sunitinib and 29 patients receiving sorafenib. There were no differences in demographic characteristics between patient groups. Mean treatment duration was 8.0 months (95% CI 6.8-9.0) and 5.7 months (95% CI 3.8-7.8) for sunitinib and sorafenib, respectively ($p = 0.071$). Mean survival time amounted to 11.3 months (95% CI 10.4-12.2) and 8.1 months (95% CI 6.1-10.1) for sunitinib and sorafenib, respectively ($p = 0.023$). It should be noted that this analysis enrolled a small number of patients receiving sorafenib. Also, future analyses must control for patient clinical characteristics, which may have been a major factor in treatment preferences, and might have influenced treatment duration and sur-

vival.

3.3. Safety, Tolerability and Effectiveness

A non-randomized, open-label expanded access programme included 2,504 patients from the United States and Canada who were treated with oral sorafenib 400 mg twice daily [18]. This programme provided access to sorafenib prior to regulatory approval and did not impose strict patient inclusion criteria. The most common drug-related adverse events were hand-foot skin reaction (18%), rash (14%), hypertension (12%), and fatigue (11%). Stable disease for at least eight weeks was observed in 80% of patients, partial response in 4% of patients, and complete response in one patient. Median progression-free survival amounted to 36 weeks (95% confidence interval: 33-45 weeks) and median overall survival was 50 weeks (95% confidence interval: 46-52 weeks). An additional analysis did not observe any substantial differences in safety and effectiveness of sorafenib between patients aged ≥ 70 and < 70 years [17].

A prospective, open-label, non-interventional, non-controlled, multicenter, observational Phase IV trial evaluated the effectiveness and safety of sorafenib treatment under daily-life conditions in Belgium [19]. A small sample of 41 patients was enrolled from 32 study centers. Twenty-four patients discontinued the study prematurely. The reason indicated most frequently was disease progression (11 patients). Only 34 and 15 patients could be evaluated after one and three months of observation, respectively. The effectiveness of sorafenib was judged sufficient, good or very good (as opposed to 'insufficient') for most patients after one month and after three months. The proportion of progression-free patients was 0.56 (95% confidence interval: 0.38-0.73) after one month and 0.73 (95% confidence interval: 0.45-0.92) after three months. The proportion tended to increase over time, though the fact that these proportions were calculated over the patients still observed (i.e. the "healthier" patients) could explain this trend. The tolerability was judged very good, good or sufficient for 71% of patients after one month and 67% of patients after three months. All patients experienced at least one adverse event, ten patients experienced at least one serious adverse event. Among the reported adverse events, there were eight patients with diarrhea, six patients with anorexia, five patients with hand foot skin reaction and five patients with rash. These adverse events are known side effects of sorafenib [4].

3.4. Costs

Based on an analysis of a US claims database, a retrospective study quantified the health care costs of patients

Table 1. Characteristics of studies included in literature review.

Country	Sample	Design	Interventions	Measures	Results	Conclusions
<i>Dosage and treatment duration</i>						
United States [16]	Patients with primary or advanced renal cell carcinoma	Retrospective study of claims database	Sorafenib 800 mg; sunitinib 50 mg	Number of dose reductions; time to dose reduction	Significantly more patients receiving sunitinib required dose reductions as compared with sorafenib (35.5% vs 16.9%; $p < 0.001$). Significantly more dose reductions occurred within the first three months with sunitinib than with sorafenib (65% vs. 25%, $p < 0.001$). The mean time to dose reduction was significantly longer for sorafenib than sunitinib (162 days vs 104 days, $p = 0.003$).	Significantly more dose reductions were required in patients who initially received sunitinib than in those who received sorafenib.
Israel [15]	163 patients with advanced renal cell carcinoma	Retrospective study of claims database	Sorafenib; sunitinib	Treatment duration; survival time	Mean treatment duration was 8.0 months (95% CI 6.8-9.0) and 5.7 months (95% CI 3.8-7.8) for sunitinib and sorafenib, respectively ($p = 0.071$). Mean survival time amounted to 11.3 months (95% CI 10.4-12.2) and 8.1 months (95% CI 6.1-10.1) for sunitinib and sorafenib, respectively ($p = 0.023$).	Treatment duration and survival time were longer for patients treated with sunitinib than for patients treated with sorafenib.
<i>Safety, tolerability and effectiveness</i>						
United States and Canada [17,18]	2,504 patients with renal cell carcinoma	A non-randomized, open-label study	Sorafenib 800 mg	Incidence of drug-related adverse events; treatment response; progression-free and overall survival.	Drug-related adverse events were hand-foot skin reaction (18%), rash (14%), hypertension (12%), fatigue (11%). Stable disease for at least eight weeks was seen in 80% of patients, partial response in 4% of patients, complete response in 1 patient. Median progression-free survival was 36 weeks (95% confidence interval: 33-45 weeks) and median overall survival was 50 weeks (46-52 weeks). There were no difference in safety and effectiveness between patients aged ≥ 70 and < 70 years.	The safety and effectiveness of sorafenib treatment was in line with data reported in the sorafenib drug information leaflet.
Belgium [19]	41 patients with advanced renal cell carcinoma	A prospective, open-label, non-interventional, non-controlled, multicenter, observational Phase IV trial	Sorafenib 800 mg	Number of progression-free patients; tolerability, number of patients experiencing adverse events	The proportion of progression-free patients was 0.56 (95% confidence interval: 0.38-0.73) after one month and 0.73 (95% confidence interval: 0.45-0.92) after three months. The tolerability was judged very good, good or sufficient for 71% of patients after one month and 67% of patients after three months. All patients experienced at least one adverse event, ten patients experienced at least one serious adverse event.	The effectiveness of sorafenib was judged to be sufficient or better by the majority of patients. The reported adverse events were known side effects of sorafenib.
<i>Costs</i>						
United States [21]	364 patients with primary or advanced renal cell carcinoma under 65 years of age	Retrospective study of claims database	Sorafenib; sunitinib	Health care costs (e.g. inpatient, outpatient, pharmacy costs)	Total monthly health care costs for the sunitinib group were significantly greater than for the sorafenib group (\$9,476 vs. \$7,426, $p < 0.01$), representing an annual extra cost of \$24,588 for sunitinib as compared with sorafenib. Incremental monthly inpatient, pharmacy and outpatient costs were \$861 ($p = 0.01$), \$889 ($p < 0.01$), and \$300 ($p = 0.14$) for sunitinib as compared with sorafenib.	Initial therapy with sunitinib was more expensive than sorafenib in patients with primary or advanced RCC under 65 years of age.

United States [20]	321 patients with advanced renal cell carcinoma	Retrospective study of claims database	Intravenous bevacizumab; sorafenib; sunitinib	Health care costs (e.g. inpatient, outpatient, pharmacy costs)	Total mean health care costs amounted to \$13,351, \$6,998, and \$8,213 per patient per month for bevacizumab, sorafenib and sunitinib, respectively ($p < 0.05$).	Health care costs of sorafenib treatment were lower than those of treatment with bevacizumab or sunitinib.
<i>Cost-effectiveness</i>						
Czech Republic [22]	31 patients with advanced renal cell carcinoma	Economic evaluation based on cohort study	Sorafenib; sunitinib	Adverse events; time to progression; costs to progression; mortality	The main adverse events were skin toxicity, oedema, arthralgia and other pain. The mean time to progression was 8.3 months with sorafenib and 10.4 months with sunitinib. The mean cost to progression was €1,069 with sorafenib and €1,566 with sunitinib. Nine patients died.	The analysis of direct medical costs in patients with advanced renal cell carcinoma proved high costs concerned with multikinase inhibitors' therapy.

with primary or advanced RCC who are privately insured and are aged under 65 years [21]. Health care costs included inpatient, outpatient and pharmacy costs. The sample consisted of 144 patients receiving sorafenib and 220 patients receiving sunitinib as initial therapy. At baseline, demographic characteristics between the two patient groups were similar. Total monthly health care costs for the sunitinib group were significantly greater than for the sorafenib group (\$9,476 vs. \$7,426, $p < 0.01$), representing an annual extra cost of \$24,588 for sunitinib as compared with sorafenib. Incremental monthly inpatient, pharmacy and outpatient costs were \$861 ($p = 0.01$), \$889 ($p < 0.01$), and \$300 ($p = 0.14$) for sunitinib as compared with sorafenib. This analysis showed that initial therapy with sunitinib was more expensive than sorafenib in patients with primary or advanced RCC aged under 65 years.

A US retrospective claims database analysis quantified the incremental costs associated with intravenous administration of bevacizumab as compared to sunitinib or sorafenib for the treatment of advanced RCC [20]. Patients receiving bevacizumab ($n = 109$) were matched 1:1 to patients receiving sorafenib or sunitinib. Drug, inpatient, outpatient and pharmacy costs were calculated per patient per month. Total mean health care costs amounted to \$13,351, \$6,998, and \$8,213 per patient per month for bevacizumab, sorafenib and sunitinib, respectively ($p < 0.05$). Assuming a median progression-free survival of 8.5 months as shown for bevacizumab, the incremental costs would be estimated at \$39,188-42,080 per patient as compared to those treated with sorafenib or sunitinib.

3.5. Cost-effectiveness

An economic evaluation assessed the cost-effectiveness of sorafenib and sunitinib in routine clinical care in the Czech Republic from a health care payer perspective [22]. Disease progression and costs (i.e. drugs, labora-

tory tests and hospitalization) were assessed every two months. Seventeen patients started therapy with sunitinib, eight of whom converted to sorafenib after progression. Three patients discontinued sunitinib therapy due to adverse events. Fourteen patients started sorafenib therapy, two of whom converted to sunitinib due to adverse events. Two other patients converted to sunitinib following progression. The main adverse events were skin toxicity, oedema, arthralgia and other pain. The mean time to progression was 8.3 months with sorafenib and 10.4 months with sunitinib. The mean cost to progression was €1,069 with sorafenib and €1,566 with sunitinib. Nine patients died. Cost and outcome measures were not combined into an incremental cost-effectiveness ratio.

4. DISCUSSION

This article has conducted a literature review of the treatment of advanced RCC with sorafenib in routine clinical care. The evidence is too limited to derive conclusions and studies suffer from methodological shortcomings. The current evidence base is restricted to a few studies presented at international conferences, one peer-reviewed article and one internal study of Bayer Schering Pharma. Furthermore, as advanced RCC is an orphan disease, the majority of studies suffered from small sample sizes.

Existing studies have primarily compared treatment with sorafenib or with sunitinib. Although treatment with sorafenib led to fewer dose reductions, it was also associated with a shorter treatment duration, less time to progression and a shorter survival time as compared to sunitinib. Monthly health care costs were lower with sorafenib as compared to sunitinib. A post-marketing surveillance study showed that patients rated the tolerability and effectiveness of sorafenib as very good, good or sufficient, although this study suffered from a small sample size and limited time horizon.

To date, little is known about the (cost-) effectiveness of sorafenib as compared with other approaches to treat advanced RCC in routine clinical care. Although analyses based on cohort studies, case-control studies, or before-and-after studies may suffer from a number of biases and do not always establish a causal relationship, such studies would provide information about the safety, tolerability, and effectiveness of sorafenib in real-life practice. Information derived from such studies could be integrated with cost information to conduct an economic evaluation of the cost-effectiveness of sorafenib as compared with other approaches to treat advanced RCC. It is important to examine the impact of a drug in real-life practice. Registration authorities wish to gain insight into the health gain of the drug in real-life patients, to identify rare adverse events, to explore the effectiveness in the long run, or to study the drug as a treatment for other diseases. Also, reimbursement authorities in some countries grant conditional reimbursement to a drug based on its cost-efficacy, while final reimbursement is granted based on its cost-effectiveness after the drug has been on the market for a number of years. For instance, on 1st April 2007, Belgian reimbursement authorities conditionally approved the reimbursement of sorafenib treatment for advanced RCC for a period of three years. The sponsor was obliged to submit complementary observational data including clinical and economic data within 1.5 to 3 years after conditional approval. Final reimbursement approval was granted in August 2010.

One instrument to sustain the ongoing evaluation of a drug may be the implementation of patient registries designed to collect the necessary data to follow up and evaluate uncertainties surrounding the longer-term effectiveness and cost-effectiveness of a drug [23]. The use of patient registries would support the decision-making process, inform clinical practice, and could provide information about long-term adverse events. However, patient registries have their limitations. A patient registry may be biased if the patient aetiology and disease severity change over time. Also, patient registries tend to collect data on a specific drug, but not on alternative treatments, thus providing partial information to calculate the cost-effectiveness of the drug relative to an alternative treatment. Furthermore, new treatment strategies may become available during the period covered by the registry. Therefore, patient registries need to be set up in a flexible way to collect sufficient data and to account for the evolution in patient population and treatment strategies over their lifetime.

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