Original Article

Cost Effectiveness of Regorafenib as Second-Line Therapy for Patients With Advanced Hepatocellular Carcinoma

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BACKGROUND: Regorafenib, a multikinase inhibitor, has demonstrated prolonged survival by 2.8 months as a second-line agent in patients with hepatocellular carcinoma (HCC) who progress on sorafenib therapy. The objective of the current study was to examine the cost effectiveness of regorafenib for the treatment of HCC. **METHODS:** The authors constructed a Markov simulation model of patients with unresectable HCC and Child-Pugh A cirrhosis who received treatment with regorafenib versus best supportive care. Model inputs for regorafenib effectiveness and rates of adverse events in patients with HCC were based on published clinical trial data and literature review. Quality-adjusted life years (QALYs) were calculated along with the incremental cost-effectiveness ratio (ICER) of regorafenib therapy. One-way sensitivity analyses also were conducted simultaneously on all model parameters and on various Monte-Carlo simulation parameters, and the regorafenib cost threshold at which cost effectiveness would be achieved was determined. **RESULTS:** Regorafenib provided an increase of 0.18 QALYs at a cost of $47,112. The ICER for regorafenib, compared with best supportive care, was $224,362. In 1-way sensitivity analyses, there were no scenarios in which regorafenib was cost effective. In cost threshold analysis, regorafenib would have to be priced at or below $67 per pill to be cost effective at an ICER of $100,000. **CONCLUSIONS:** Regorafenib is not cost effective as a second-line agent in the treatment of HCC, with a marginal increase in QALYs at a high cost. Lowering the cost of regorafenib or improving the selection of patients who can achieve maximal survival benefit would improve its value as a second-line treatment option for patients with HCC. *Cancer* 2017;123:3725-31. © *2017 American Cancer Society.*

KEYWORDS: hepatocellular carcinoma (HCC), incremental cost-effectiveness ratio (ICER), Markov, quality-adjusted life-year (QALY), RESORCE trial.

INTRODUCTION

Hepatocellular carcinoma (HCC) is an increasingly incident malignancy in the United States associated with significant morbidity and mortality.[1-3] Despite improvement over time, the majority of patients with HCC continue to present with advanced-state disease, for which curative treatment options are not possible and the prognosis is poor.[4,5] In the most recent 10-year period assessed by the National Cancer Institute's Surveillance, Epidemiology, and End Results program, primary liver cancer had the largest relative increase in mortality among all solid tumors.[6]

Systemic therapy is the primary treatment modality for patients with advanced HCC, including those with portal vein invasion or extrahepatic spread.[7] Similarly, there is increasing recognition of the role of systemic therapy for patients who progress after treatment with locoregional therapy, such as transarterial chemoembolization (TACE). Sorafenib, an oral multikinase inhibitor, is the only US Food and Drug Administration-approved first-line therapy for patients with advanced HCC.[8,9] Sorafenib was approved in patients with unresectable HCC based on results from the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, which demonstrated that patients who received sorafenib experienced a significantly prolonged time-to-radiologic progression (5.5 vs 2.8 months; $P < .001$) and improved overall survival (10.7 vs 7.9 months; $P < .001$).[10] On the basis of these data, sorafenib is the most commonly used systemic therapy in patients with advanced HCC, including expanded use in patients with Child-Pugh B and even some patients Child-Pugh C cirrhosis.[9] Cost-effectiveness analyses have demonstrated that sorafenib is cost effective in patients with Child-Pugh A cirrhosis, including in elderly patients, although it is no longer cost effective in patients with hepatic decompensation.[8]

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Until recently, there have not been any approved alternate therapies for patients who experience tumor progression or severe adverse events (AEs) while receiving sorafenib. Several therapies appeared to be promising in phase 2 studies but failed to improve survival when evaluated in larger phase 3 studies.[11-13]

Regorafenib is also a multikinase inhibitor that previously was approved for use in patients with metastatic colorectal cancer and advanced gastrointestinal stromal tumors.[14,15] The RESORCE trial, a double-blind, phase 3, randomized controlled trial, recently evaluated the efficacy of regorafenib compared with best supportive care in patients who experienced progression on sorafenib.[16] Patients who received regorafenib had a median survival of 10.6 months versus 7.8 months for the placebo group (*P* < .001).

An analysis of the cost effectiveness of regorafenib as a third-line agent in patients with metastatic colorectal cancer demonstrated that it was not cost effective compared with placebo, with an incremental cost-effectiveness ratio (ICER) of $900,000 per quality-adjusted life-year (QALY) gained in the base model, and the ICER did not reach $550,000 in any of the sensitivity analyses.[17] Those authors concluded that the cost effectiveness of regorafenib should be improved with the use of value-based pricing. With its new indication for HCC treatment, our objective was to examine the cost effectiveness of regorafenib as a second-line agent in the treatment of patients with advanced HCC.

MATERIALS AND METHODS

We constructed a Markov model of patients with advanced HCC in the setting of Child-Pugh A cirrhosis and an Eastern Cooperative Oncology Group performance status of 0 or 1. Rates of disease progression for patients who progressed on sorafenib were based on results from the RESORCE trial.[16] This model tracked health states of patients, as outlined in Figure 1. Patients who had received regorafenib continued on regorafenib until they experienced a grade 3 or 4 AE or radiographic HCC progression. Treated patients either moved in weekly cycles to best supportive care or died.

The model was constructed using Microsoft Excel and tracked costs, QALYs, and the ICER, comparing regorafenib versus best supportive care. Cost effectiveness was calculated from a health system perspective.

Model Inputs
Progression rates
HCC progression rates in the model were calculated to match the median overall survival, median progression-
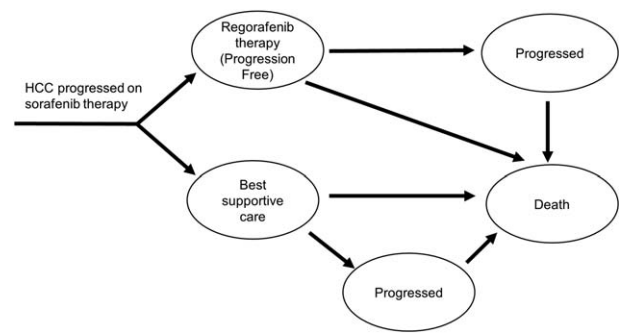

Figure 1. This is a Markov model structure for the current study with health states. HCC indicates hepatocellular carcinoma.

free survival, and median time-to-progression observed in the RESORCE trial.[16] We assumed constant HCC progression rates over time.

Adverse events
We included the impact of hypertension, hand-foot skin reaction, fatigue, and diarrhea, because these side effects were the most common clinically relevant grade 3 or 4 events in the trials of regorafenib for both HCC and colorectal cancers.[14,16] Rates of side effects were based on data from the RESORCE trial.[16] For the management of grade 1 and 2 AEs, we modeled the use of amlodipine 5 mg daily for hypertension, Eucerin cream for hand-foot skin reaction, and atropine/diphenoxylate and loperamide for diarrhea. Any occurrence of grade 3 and 4 AEs resulted in regorafenib discontinuation with resultant resolution of the AEs.

Health utilities
We calculated health utilities based on quality-of-life data (the EuroQol 5 dimensions questionnaire [EQ-5D] and the Functional Assessment of Cancer Therapy-Hepatobiliary Cancer) presented in the RESORCE trial.[16] Although that study reported a significant decrease in the quality of life of patients who received regorafenib, the quality-of-life decrement did not meet the threshold for a minimally important difference. The RESORCE trial did not compare the quality of life between patients and without tumor progression, so we assumed quality of life was not different between progressed and nonprogressed health states; however, health utilities in patients with and without HCC progression varied in sensitivity analyses. Health utilities were aggregated over weekly periods to calculate overall QALYs.

Costs
Both arms included the costs of side effects and best supportive care, including general liver disease management.

TABLE 1. Base-Case Model Parameters and 1-Way Sensitivity Analysis Ranges Derived From Prior Literature

Parameter	Value (Range)	Source
Outcome, mo		
Regorafenib		
Median overall survival	10.6 (9.1-12.1)	Bruix 2017[16]
Median progression-free survival	3.1 (2.4-3.8)	Bruix 2017[16]
Median time to progression	3.2 (2.6-3.9)	Bruix 2017[16]
Best supportive care		
Median overall survival	7.8 (6.6-9.1)	Bruix 2017[16]
Median progression-free survival	1.5 (1.4-1.6)	Bruix 2017[16]
Median time to progression	1.5 (1.4-1.6)	Bruix 2017[16]
Proportion of patients with adverse events		
Regorafenib		
Hypertension	0.152 (0.116-0.188)	Bruix 2017[16]
Hand-foot skin reaction	0.126 (0.092-0.16)	Bruix 2017[16]
Fatigue	0.091 (0.062-0.12)	Bruix 2017[16]
Diarrhea	0.032 (0.014-0.05)	Bruix 2017[16]
Best supportive care		
Hypertension	0.047 (0.017-0.077)	Bruix 2017[16]
Hand-foot skin reaction	0.005 (−0.005 to 0.015)	Bruix 2017[16]
Fatigue	0.047 (0.017-0.077)	Bruix 2017[16]
Diarrhea	0 (0-0)	Bruix 2017[16]
Weekly costs, US dollars		
Regorafenib per week on drug	4156 (3138-5174)	Red Book 2015[18]
Computed tomography imaging	234 (177-291)	Centers for Medicare and Medicaid Services, 2016[23]
Other care	174 (131-216)	Carr 2010[24]
Hypertension	8.70 (6.57-10.83)	Red Book 2015[18]
Hand-foot skin reaction	5 (3.78-6.23)	
Fatigue	0 (0-0)	
Diarrhea	14.84 (11.2-18.48)	Red Book 2015[18]
Utilities		
HCC progression free	0.76 (0.59 to 0.93)	Grothey 2013,[14] Bruix 2017,[16] Goldstein 2015[17]
HCC progressed	0.76 (0.59 to 0. 93)	Grothey 2013,[14] Bruix 2017,[16] Goldstein 2015[17]
Disutilities from adverse events		
Hypertension	−0.025 (−0.031 to −0.019)	Sullivan & Ghuschyan 2006[25]
Hand-foot skin reaction	−0.116 (−0.144 to −0.088)	Lloyd 2006[26]
Fatigue	−0.115 (−0.143 to 0.087)	Lloyd 2006[26]
Diarrhea	−0.103 (−0.128 to −0.078)	Lloyd 2006[26]
Duration of disutilities, d		
Hypertension	5 (3.8-6.2)	Goldstein 2015[17]
Hand-foot skin reaction	14 (10.6-17.4)	Goldstein 2015[17]
Fatigue	10 (7.6-12.5)	Goldstein 2015[17]
Diarrhea	5 (3.8-6.2)	Goldstein 2015[17]
Discount rate, %	3%	

Abbreviation: HCC, hepatocellular carcinoma.

Costs in the regorafenib arm included regorafenib medication costs as well as surveillance imaging associated with regorafenib monitoring. Regorafenib costs were based on weighted average costs from the Red Book ($165 per 40 mg)[18] and were adjusted based on the mean daily dose observed in the RESORCE trial (144 mg per day). Patients receiving regorafenib were modeled to receive 3 weeks on and 1 week off therapy, which is consistent with the treatment schedule detailed in the RESORCE trial. Discontinuation rates were modeled to match what was reported in the RESORCE trial. In addition to drug costs, patients receiving regorafenib were assumed to have contrast-enhanced abdominal computed tomography imaging at baseline and every 12 weeks until drug discontinuation or death. All costs were updated to 2016 dollars using a Gross Domestic Product deflator. The cost effectiveness of regorafenib was defined as an ICER (ie, the difference in cost of 2 possible treatments divided by the difference in effect) of $100,000 compared with best supportive care.[19-22]

Sensitivity Analysis

We derived parameter ranges from the literature and performed 1-way sensitivity analyses on all parameters as well as multiway sensitivity analyses on key parameters of interest. We also conducted a Monte-Carlo simulation of the model, simultaneously drawing all parameter values and their ranges to evaluate overall uncertainty in results. By using data from 10,000 iterations, we created cost-effectiveness acceptability curves, representing the

TABLE 2. Cost Effectiveness of Regorafenib in the Base-Case Scenario

Variable	Costs	QALYs	ICER
Best supportive care	$7408	0.63	
Regorafenib	$47,112	0.81	$224,362

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

likelihood that regorafenib would be considered cost effective at various willingness-to-pay levels for health gains (QALYs). We modeled the potential impact of HCC progression on health utilities, because HCC progression may negatively affect health-related quality of life. We also conducted a cost-threshold analysis to determine the pill cost at which regorafenib would become cost effective.

RESULTS

Base Case

The model inputs, including baseline values, the ranges included in sensitivity analyses, the costs and utilities, and their sources are listed in Table 1.[3,14,16-18,21,23-26] The progression-free and overall survival curves in our model for both the regorafenib and the placebo arms matched results from the RESORCE trial (Supporting Fig. 1a,b; see online supporting information). The overall results from the base case analysis are provided in Table 2. Regorafenib provided an additional 0.18 QALYs (65 quality-adjusted days) compared with best supportive care. The cost incurred with regorafenib treatment was $47,112 versus $7408 with best supportive care. Regorafenib was not cost effective, with an ICER of $224,362, compared with best supportive care in our base-case analysis.

Sensitivity Analysis

In 1-way sensitivity analyses, the parameters with the most influence on ICER were related to HCC progression, particularly overall survival, and the cost of regorafenib (Fig. 2). However, the ICER remained above $140,000 per QALY in each 1-way sensitivity analysis.

For the sensitivity analyses, in which we modeled decreases in health utility with HCC progression, the ICER rose to above $1,200,000 when the health utility associated with HCC progression was decreased to zero. If patients without HCC progression had improved health utility compared with the base case, then the ICER decreased but did not fall below $210,000 (Supporting Table 1; see online supporting information).

In 2-way sensitivity analyses, we varied the median overall survival with both regorafenib and best supportive care. By using the most optimistic survival for regorafenib (12 months) and the most pessimistic survival for best supportive care (6 months), the ICER became approximately $98,000 per QALY and thus was considered cost effective (Table 3). All shorter survival differences between the 2 arms would result in ICERs above the $100,000 threshold.

The Monte-Carlo simulation revealed that regorafenib therapy was unlikely to be cost effective, with an ICER exceeding $150,000, compared with best supportive care. The ICER was at least $100,000 per QALY in 99% of simulations and exceeded $200,000 per QALY in 61% of simulations (Fig. 3). If the willingness to pay for QALYs increases dramatically, then regorafenib becomes a more acceptable treatment strategy.

Cost-Threshold Analysis

Finally, we conducted a cost-threshold analysis to determine the pill cost of regorafenib at which it would become cost effective as a second-line therapy for HCC. Supporting Figure 2 illustrates the ICER versus the cost of regorafenib, which crosses $100,000 per QALY at a cost of $67 per pill.

DISCUSSION

Although regorafenib can provide an 2 additional quality-adjusted life months compared with best supportive care for advanced patients with HCC who progress on sorafenib, we did not identify it as a cost-effective therapy. Regorafenib consistently had ICERs >$100,000 per QALY in all 1-way sensitivity analyses and in every iteration of cost-effectiveness acceptability curves. In a cost-threshold analysis, the regorafenib pill cost would need to be reduced to $67 from its current price of $165 per pill to become cost effective.

Two-way sensitivity analyses indicated that regorafenib could be cost effective if the survival benefit over best supportive care was 6 months or greater. Although this exceeds the survival benefit observed in all-comer patients who progress on sorafenib, it may be possible to select a subgroup of patients in whom this survival benefit would be observed. It is increasingly clear that HCC is a heterogeneous tumor with differences in tumor biology and treatment responsiveness between patients. Similarly, the RESORCE trial focused on patients who progressed on sorafenib, selecting for patients who did not respond to multikinase inhibitor therapy, but it is possible that regorafenib may have a greater benefit for patients who are intolerant to sorafenib or for sorafenib-naive patients
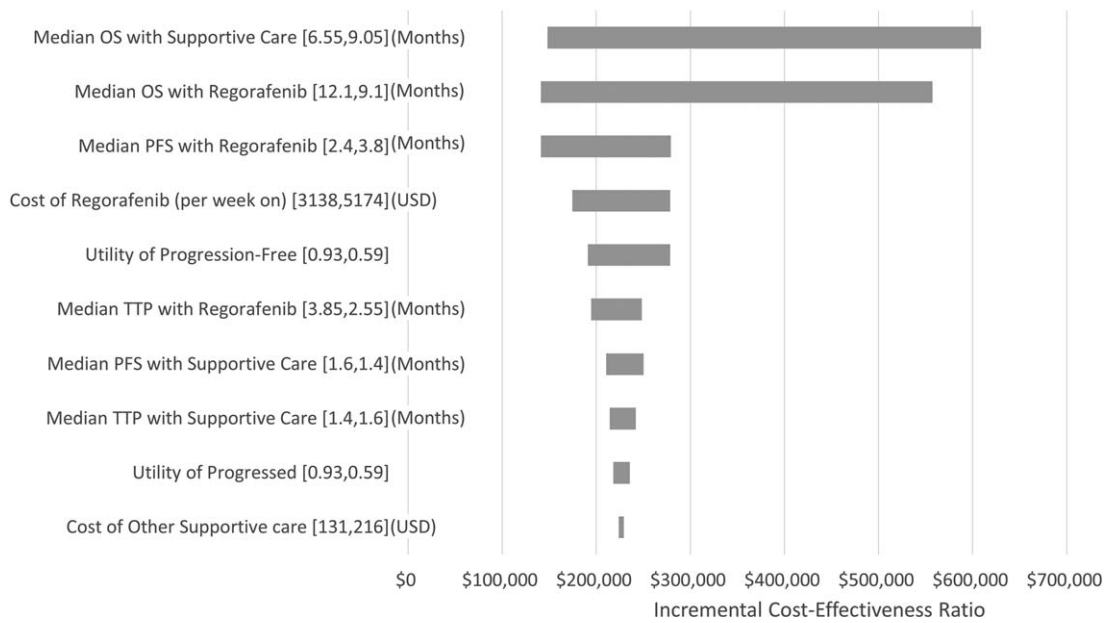
Figure 2. One-way sensitivity analyses illustrate changes in the incremental cost-effectiveness ratio as model parameters are varied over their ranges. OS indicates overall survival; PFS, progression-free survival; TTP, time to progression; USD, US dollars.

TABLE 3. Incremental Cost-Effectiveness Ratios per Quality Adjusted Life Year From Two-Way Sensitivity Analysis With Median Overall Survival Varied For Regorafenib and Best Supportive Care: Ratios in US Dollars per Quality-Adjusted Life-Years

Median overall survival	Best Supportive Care			
Regorafenib, mo	6 Months	7 Months	8 Months	9 Months
9	$191,041	$301,969	$753,008	—[a]
10	$145,736	$199,395	$321,341	$1,380,784
11	$118,888	$150,696	$208,009	$397,501
12	$98,386	$118,102	$148,779	$220,488

[a]Note that this category dominated, ie, it was more expensive and produced fewer quality-adjusted life-years.

Figure 3. Cost-effectiveness acceptability curves for regorafenib versus supportive care.

(ie, as first-line therapy). Unfortunately, we lack clinically useful biomarkers to predict response to systemic therapy in patients with HCC. In a secondary analysis of Sorafenib HCC Assessment Randomized Protocol (SHARP) data, high serum c-KIT levels and low hepatocyte growth factor concentrations at baseline trended toward predicting improved survival among sorafenib-treated patients[27]; however, to date, no prognostic biomarkers have been validated and/or adopted for routine clinical use.[28-31] Therefore, the discovery of clinically useful biomarkers that predict can response to regorafenib may improve its value as a second-line treatment for HCC.
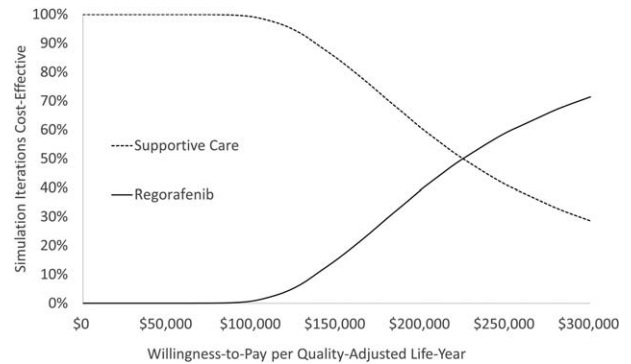
Cost effectiveness incorporates several important factors for deciding therapies, including cost, clinical effectiveness, and tolerability; however, it fails to consider patient preferences and the availability of other treatment regimens. The importance of pill cost and clinical effectiveness (survival benefit) on the cost effectiveness of regorafenib is discussed above. Although regorafenib can have a high rate of AEs, it appears to have minimal detrimental impact on health-related quality of life, because the regorafenib and placebo arms had no meaningful differences in quality-of-life scores.[16] These data were derived from efficacy trial-based data, so monitoring will be important to determine whether regorafenib is equally

well tolerated in postmarketing studies, as has been done for sorafenib in the Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib (GIDEON).[9] Like all discussions regarding cancer treatment, it will be important for providers to discuss and weigh potential pros and cons of regorafenib as second-line treatment. Decisions regarding the role of regorafenib must be determined considering each patient's preferences, goals of care, and quality of life. It is important to note that, currently, there are no effective alternative treatments for patients who progress on sorafenib, thus regorafenib is the only option for these patients and fills an important niche in HCC therapy. However, currently, several promising agents, including immunotherapy, are undergoing evaluation in phase 2 and 3 studies.[32] Given the rapidly changing landscape of HCC therapeutics, cost effectiveness will be increasingly important when considering potentially forthcoming second-line treatment options for patients with HCC.

Our study has notable strengths and weaknesses. We relied on modeling data from the RESORCE trial, which may not reflect real world practice. Patients in the RESORCE trial were highly selected and had excellent functional status and liver function. Real-world effectiveness is likely to be worse, as demonstrated with sorafenib therapy; therefore, this would make the ICERs for regorafenib even higher and would not change our overall study conclusions.[8] Patients in RESORCE also had a higher burden of extrahepatic versus intrahepatic disease, which reportedly has an impact on outcomes in HCC.[33] To address this limitation, we performed robust 1-way and 2-way sensitivity analyses, which indicated that regorafenib was not cost effective across a wide range of model inputs. This also was confirmed in our Monte-Carlo analysis and cost-effectiveness acceptability curves. Finally, we also evaluated regorafenib in all-comer patients who progressed on sorafenib. Although it was not cost effective when considered in a group, our analysis cannot account for potential individual differences in treatment responsiveness.

In summary, we have demonstrated that, although it is clinically effective, regorafenib may provide low value as second-line therapy for HCC. High costs, coupled with modest clinical effectiveness, are important considerations when selecting palliative second-line therapies for HCC. A significant reduction in the cost of regorafenib, to better reflect its overall clinical value, or better selection of patients in whom survival benefit can be maximized would greatly impact the cost effectiveness of regorafenib.

AUTHOR CONTRIBUTIONS

Neehar D. Parikh: Conceptualization, methodology, investigation data curation, writing–original draft, writing–review and editing, supervision, and project administration. **Amit G. Singal**: Conceptualization, methodology, data curation, writing–review and editing, and supervision. **David W. Hutton**: Conceptualization, methodology, formal analysis, investigation data curation, writing–original draft, writing–review and editing, supervision, and project administration.

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