Cost-effectiveness Analysis of Sunitinib and Sorafenib Sequential Treatment of Metastatic Renal Cell Carcinoma

Toshihiro Shida^{1*}, Tomoyuki Kato², Norihiko Tsuchiya², Tadashi Shiraishi¹ and Tadao Inoue³

Division of Pharmacy, Yamagata University Hospital¹,

Department of Urology, Faculty of Medicine, Yamagata University²,

Department of Pharmacy, Ohu University³

Received June 28, 2017
Accepted September 4, 2017

Metastatic renal cell carcinoma (mRCC) often becomes resistant to drugs, and therefore requires sequential treatment with different types of chemotherapeutics. Two agents used for the sequential treatment of mRCC, sunitinib (Su) and sorafenib (So), have been reported to achieve similar clinical efficacy regardless of the sequence in which they are applied. There are differences, however, in the costs associated with regimens. The present study aimed to clarify the optimal administration sequence of Su and So in terms of economic impact from the perspective of public medical care. The health outcomes were analyzed according to overall survival and progression-free survival. The clinical data were drawn from the results of a previous meta-analysis. in 2017. Total costs of each regimen were calculated from direct costs, which were derived from hospital receipts and medical records of patients who were diagnosed with mRCC at Yamagata University Hospital. The cost-effectiveness was analyzed by a Markov chain Monte Carlo method. Long-term patient outcomes and costs were assessed for each treatment option according to the relative incremental cost-effectiveness ratio (ICER). We found that the total gain in life-expectancy and projected cost of each regimen were, respectively, 24.5 months and 22,123,106 yen for Su-So, and 30.0 months and 30,994,113 yen for So-Su. The ICER of So-Su versus that of Su-So was 1,612,910 yen / month, with an incremental effect of 5.5 months. Compared with Su-So, So-Su provided better health outcomes over time; however, the cost was also higher.

Key words — sunitinib, sorafenib, Markov model, cost-effectiveness, metastatic renal cancer

Introduction

Metastatic renal cell carcinoma (mRCC), the most common form of kidney cancer, was previously treated using cytokines such as interferon- α (IFN- α) and interleukin-2 in combination with traditional chemotherapeutic agents such as vinblastine.¹⁾ However, these therapeutic combinations had limited efficacy, and in 2006, an extensive review of phase III clinical trials determined that the median overall survival (OS) of patients receiving cytokine-based therapies for mRCC was less than 2 years.¹⁾ In 2008, the receptor tyrosine kinase inhibitors sunitinib and sorafenib

were approved for use in Japan, and were subsequently introduced as first-line therapies for mRCC. These drugs primarily inhibit angiogenesis by inactivating vascular endothelial growth factor pathways; and have improved prognostic outcomes and prolonged the median OS to approximately 3 years.^{2,3)}

Because of an increase in the average life-expectancy and a decrease in reproduction rates among Japanese citizens, the Japanese national medical expenditure has been growing in order to meet the demands of an aging population, reaching 40 trillion yen in 2013. Increasing medical expenses are therefore a serious economic con-

* 2-2-2, Iida-Nishi, Yamagata-shi, Yamagata 990-9585, Japan

cern in Japan, and efforts are subsequently being made to improve the efficiency of medical care and reduce costs. As new drugs are expensive, cost comparisons of novel chemotherapeutic agents are important determinants in clinical decision-making. Cost-effectiveness analyses, which take into account the clinical efficacy and supply costs of mRCC treatment options, have indicated that sunitinib and sorafenib are less cost-effective than IFN- α -based therapies.⁴⁾ Furthermore, molecular targeted drug therapy is rarely completed by only a single-agent treatment of primary treatment, and sequential therapy is performed, as also indicated in the clinical practice guidelines. Drug resistance may develop as cancer progresses, it is a common practice to use two or more different anti-cancer agents in succession. The SWITCH study,⁵⁾ an open-label randomized clinical phase III trial designed to evaluate sequential use of sorafenib followed by sunitinib (So-Su) versus use of sunitinib followed by

sorafenib (Su-So), found that both regimens were equally effective against mRCC. Several retrospective studies⁶⁻⁹⁾ have corroborated this result and established that the order of administration does not influence patient outcome. The purpose of the present study was to analyze the social and economic impact of So-Su versus that of Su-So treatment regimens in clinical practice, so as to guide cost-effective decision-making for first-line therapy of mRCC.

Methods

1. Analysis model

This was a retrospective observational study from the perspective of public medical care based on previously published data and medical records. A state transition model (Markov model¹⁰⁾) was developed to project long-term health outcomes and expenses of Su-So and So-Su regimens in the treatment of mRCC (**Fig 1**). The expected patient

Fig 1 Markov model of metastatic renal cell carcinoma

□ Decision Node; Regimen options, M: Markov Node; The Markov process in each regimen, ○ Chance Node; Probability branch point, ◁ Terminal Node; Terminal point.

outcomes and costs of both So-Su and Su-So were calculated. The transition model represents four health states: continue first-line, alive with progression of first-line, progression of second-line and death. In the two treatment regimens, each cycle was 42 days long. sorafenib was administered continuously for 42 days. sunitinib was orally administered for 28 days with a 14-day washout period. Modeling was performed using TreeAge 2016 software (TreeAge Inc). The expected health outcomes and costs until all patients dead were estimated by using the Markov model,¹⁰⁾ with 1 cycle being 1 month long.

2. Evaluation of health outcomes

Based on the results obtained from meta-analyses of Su-So and So-Su sequential therapy, reported by Wen *et al* in 2017,¹¹⁾ health outcomes (OS and progression-free survival [PFS]) were evaluated and the transition probabilities between the health states described in our Markov model were calculated.

3. Resource cost

We evaluated the treatment costs of patients who were diagnosed with advanced or recurrent renal cell cancer at Yamagata University Hospital between October, 2009 and December, 2016 and who followed a survey targeted regimen as the first line treatment.

Medical records and receipts were used to determine the consumption of drugs, tests and other medical supplies. Subsequently, cost calculations of the different treatment regimens were based on these direct clinical expenditures. Projected costs were estimated according to the standard dosage of each drug and prices listed in the Japanese Drug Price Standard 2014.

4. Evaluation of cost-effectiveness

The cost-effectiveness ratio (CER) was calculated according to the difference in costs between So-Su and Su-So intervention strategies. The incremental cost-effectiveness ratio (ICER) was then derived by factoring in life-expectancy (represented as the number of months gained by treatment), according to the following equation:

$$\text{ICER} = (\text{CER of So-Su} - \text{CER of Su-So}) / (\text{life-expectancy So-Su} - \text{life expectancy Su-So})$$

5. Sensitivity analysis

In order to assess the validity of our Markov model and uncertainty of clinical data and cost data, we performed a Monte Carlo simulation-based sensitivity analysis. In this simulation, the β distribution was set as the therapeutic effect, and the γ distribution was set as the cost.

6. Ethics approval and consent to participate

This research was approved by the Ethics Committees at Yamagata University Hospital (approval number: 38), and Ohu University (approval number: 184).

The present study was conducted in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects (February 28, 2017, partial revision) by the Ministry of Health, Labor and Welfare, Japan.

Results

1. Health outcomes

In **Table 1**, the transition probabilities between each health state are displayed, calculated based on the outcome of the meta-analysis performed by Wen *et al*.¹¹⁾ The transition probability from

progress-free to post-progress of first line was 0.0924 for So-Su, 0.0794 for Su-So, and that from post-progress of first-line to post-progress of second-line was 0.0872, 0.163, respectively.

2. Costs

The characteristics of patients are shown in **Table 2**. All the patients surveyed were male. There were no significant differences in other

Table 1 Transition probability

	First-line	Transition probability	Standard deviation
PFS(1)	Sorafenib	0.0924	0.0074
	Sunitinib	0.0794	0.0065
PFS(2)	Sorafenib	0.0872	0.0095
	Sunitinib	0.1613	0.0200
PPS	Sorafenib	0.0454	0.0013
	Sunitinib	0.0537	0.0040
Death	Sorafenib	0.0231	0.0007
	Sunitinib	0.0275	0.0023
All-PFS	Sorafenib	0.0384	0.0026
	Sunitinib	0.0480	0.0034

PFS: progression free survival, PPS: post-progression survival.

PFS(1): alive with progression of first-line, PFS(2): progression of second-line.

Transition probability were calculated by TreeAge2016 software (TreeAge Inc) based on the report of meta-analysis by Wen T *et al*⁽¹⁾.

Table 2 Patient background

	Sorafenib → Sunitinib	Sunitinib → Sorafenib	P
Number of patients	3	5	
Sex			
Male	3	5	—
Female	0	0	
Age (mean, range)	60.0	71.4	0.073
Body weight(mean, range)	57.7	62.2	0.281
ECOG performance status			
0	2	3	
1	1	2	
Histological type			
Clear cell	3	4	
Spindle cell	0	1	
Site of metastasis			
Lymph node	2	4	
Lung	2	5	
Liver	0	2	
adrenal gland	1	0	
Bone	3	0	
Anamnesis			
hypertension	1	4	
hyperlipidemia	1	2	
hyperglycemia	1	2	
Chronic renal failure	1	0	
Third-line treatment			
Axitinib	1	2	
Everolimus	2	1	
Sunitinib	0	2	

ECOG: Eastern Cooperative Oncology Group

parameters of So-Su and Su-So groups. The average cost of the So-Su treatment regimen was 973,363 yen per month for first-line treatment with sorafenib, and 970,417 yen per month for secondary treatment with sunitinib. In the Su-So group, the average cost was 1,017,592 yen per month for first-line treatment with sunitinib and 922,976 yen per month for second-line treatment with sorafenib (Table 3).

3. Cost-effectiveness

The cost-effectiveness analyses of each sequential treatment regimen were conducted using Markov predictive modeling. The cumulative projected

costs of Su-So and So-Su were 22,123,106 yen and 30,994,113 yen, respectively. The increase in life expectancy as a result of Su-So and So-Su treatment was estimated as 24.5 months and 30.0 months, respectively. The median ICER of So-Su to Su-So was 1,612,910 yen per month; the incremental effect on survival increased by 5.5 months (Table 4).

The probability distribution of ICER and projected life-expectancy of So-Su versus those of Su-So in a hypothetical cohort of 10,000 patients are shown in Fig 2A and Fig 2B, respectively. ICER was primarily distributed between 1,500,000 yen and 2,000,000 yen per month. The

Table 3 Cost data

	Sorafenib → Sunitinib			Sunitinib → Sorafenib		
	Mean (¥)	Confidence interval	SD	Mean (¥)	Confidence interval	SD
First-line	973,363	674,230~1,272,496	120,417	1,017,592	874,211~1,160,974	115,475
Second-line	970,417	771,730~1,169,103	79,982	922,976	735,674~1,110,279	150,848
Third-line	1,064,070	697,618~1,430,522	147,517	769,495	619,667~919,323	120,667

SD: standard deviation

Table 4 Cost-effectiveness analysis

Strategy	Cost (¥)	Incremental Cost (¥)	Effect (Month)	Incremental Effect (Month)	ICER (¥/Month)	CER (¥/Month)
Sunitinib → Sorafenib	22,123,106	—	24.5	—	—	902,984
Sorafenib → Sunitinib	30,994,113	8,871,007	30.0	5.5	1,612,910	1,033,137

CER: cost per effectiveness ratio, ICER: incremental cost-effectiveness ratio

Fig 2

Monte Carlo probability distribution incremental cost (A) and incremental effect (B) of Sorafenib followed by sunitinib against sunitinib followed by sorafenib

incremental effect was between 5.0 and 5.5 months. After accounting for additional variables using the Monte Carlo simulation, the cumulative projected cost of Su-So was 22,124,438 yen, with an increase in life-expectancy of 24.6 months. The projected cost of So-Su was 30,944,894 yen, with 30.1 months added to patients' life expectancy (Fig 3).

4. Sensitivity analysis

Result of 10,000 simulation, probabilistic sensitivity analysis, of incremental costs and incremental effects of So-Su against Su-So, it did not affect our result. In the cost-effectiveness acceptability curve, the probability that the ICER satisfied the allowable threshold was evaluated. The threshold allowed for ICER of So-Su was 1,600,000 yen / month (Fig 4).

Fig 3 Scatter plot of both regimens by Monte Carlo Simulation

● Sorafenib → Sunitinib, ▲ Sunitinib → Sorafenib

Fig 4 Cost-effectiveness acceptability curve by Monte Carlo simulation

The horizontal axis represents the limit value of the incremental cost-effectiveness ratio (ICER), and the vertical axis represents the probability of falling within the limit value of ICER. If willingness to pay of society exceeds 1,600,000 yen / month, it is judged that Sorafenib followed by sunitinib therapy is cost-effective. ■ Sorafenib → Sunitinib, ▲ Sunitinib → Sorafenib

Discussion

Malignant cancers are characterized by aberrant mutations that enhance their progression and resistance to chemotherapeutic agents. Treatment of mRCC usually requires the use of multiple drug agents, which may be applied in succession as the cancer progresses. Su-So and So-Su treatment regimens have both been used as sequential therapies for mRCC, with moderate success. Although patient outcomes have not differed according to the order in which they receive the agents, the optimal sequence for increasing cost-effectiveness of treatment is unknown. In this study, we conducted a Markov model-based predictive analysis of patient outcomes and costs associated with So-Su and Su-So treatment regimens, based on a combination of clinical evidence and records of treatment-related expenditures. We found that the So-Su regimen provided a better projected health outcome in comparison with that of Su-So; however, the cost was also higher.

Molecular targeted drug therapy for renal cell carcinoma is rarely completed by only a single-agent treatment of primary treatment. Although sequential therapy is performed in clinical practice, it is difficult to establish its effectiveness, and evidence is poor. Considering the third treatment, there are various sequences including re-challenge. Several alternative treatment regimens for mRCC exist, using different types of targeted chemotherapeutic agents. However, the criteria for assessing the effectiveness of individual treatment regimens differ; therefore, there is an absence of specific guidelines that recommend first-line treatment options. Large prospective clinical trials, such as the AXIS study,¹²⁾ RECORD-3 study¹³⁾ and INTORSECT study,¹⁴⁾ have been per-

formed to assess the success of sequential mRCC therapies. However, the optimal sequence of treatments remains a point of debate.

Various results have been reported for sequential therapy of sunitinib and sorafenib, but the optimal sequence is unknown.⁵⁻⁹⁾ We examined the effectiveness of sequential therapy of sunitinib and sorafenib by conducting a hypothetical cohort study based on the report of meta-analysis.¹¹⁾ As a result, So-Su was found to prolong survival by 5.5 months compared with Su-So, but that the cost was also higher. In meta-analysis, So-Su is significantly superior in PFS 2, and it seems that it contributes to the predicted value of our simulation. Based on probabilistic sensitivity analysis, it can be judged that So-Su is cost-effective if willingness to pay of society exceeds 1,600,000 yen / month.

In some countries, ICER standards have been established for allocating funds within the national healthcare insurance budget to new drugs. According to the National Institute for Clinical Excellence in the United Kingdom, the ICER for an individual therapeutic or novel technology should be within 20,000-30,000 pounds per quality-adjusted life year (QALY).¹⁵⁾ In the United States, the same metric is recommended to be within 50,000-100,000 dollars per QALY.¹⁶⁾ Although there are no clear standards defined in Japan, Shi-roiwa *et al* proposed that the ICER of a drug or health product should be lower than 5,000,000 yen per QALY.¹⁷⁾ This translates to 416,666 yen per month. According to our results, the ICER of So-Su to Su-So exceeds this limit, suggesting that the regimens are not sufficiently cost-effective. Our findings can be applied to a broad range of cases because the costs were estimated according to the standard dosage. From the economic standpoint, So-Su is less cost-effective compared with

Su-So. The NCCN Kidney Cancer Panel has listed sunitinib as a Category 1 option for first-line treatment of patients with relapsed or medically unresectable predominantly clearcell stage IV renal carcinoma (<https://www.tri-kobe.org/nccn/guideline/urological/english/kidney.pdf>, July 27, 2017). In clinical practice, sunitinib is often used as the first-line treatment, and it consistent with our findings in terms of cost-effectiveness. Given the increased number of cancer cases in Japan, use of expensive molecular targeted drugs may result in higher incremental cost, which will undeniably lead to posing a large financial burden on the country. Therefore, it is necessary to integrate economic evidence with clinical evidence in making therapeutic decisions on cancer treatment, especially for expensive molecular targeted drug therapies, so cost-effectiveness research is important.

The present study was designed to optimize mRCC treatment from social view-point. The Markov model is based on clinical effect, so it does not contain data on patients status and development of adverse effect. However, numerous analyses have been published that also incorporate an evaluation of QALY.¹⁸⁻²²⁾ The shift from cytokine-based therapies to other types of targeted agents has improved the prognostic outcomes such as PFS for mRCC patients. The benefit to society cannot only rest on monetary value, but the quality of life experienced. These clinical scenarios warrant further study by cost-utility analysis for government regulation of health spending.

Conflict of Interest

The authors have no conflict of interest to report.

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