Clinical Decision Analysis of First-line Regimens for Advanced Recurrent Renal Cell Carcinoma

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Sunitinib and sorafenib as well as interferon- α (IFN- α) are first-line therapies for advanced or recurrent renal cell carcinoma. Although the efficacy of molecular targeted drugs appears indisputable, some research suggests that they are not significantly effective compared to cytokine therapies in terms of progression-free survival. The therapeutic effects of new drugs depend on the decision of doctors and hospitals, which is partially based on the evaluation of cost-effectiveness of these therapies. The purpose of this study was to analyze the clinical decisions involved in selecting IFN- α , sunitinib, and sorafenib regimens and to identify the best regimen for the first-line treatment of advanced or recurrent renal cell carcinoma based on clinical and economic evidence.

The health outcomes of the therapies considered in this study were analyzed based on the literature on randomized controlled clinical trials of the drugs. The total costs of the regimens were calculated on the basis of direct costs obtained from medical records of patients diagnosed with advanced or recurrent renal cell carcinoma at Yamagata University Hospital. Cost-effectiveness was analyzed by the Markov chain Monte Carlo (MCMC) method. The study was designed from a social viewpoint.

The MCMC analysis revealed that the incremental cost per effectiveness ratios of sunitinib and sorafenib to IFN- α were 746,919 yen and 421,930 yen per life month, respectively. Molecular targeted drugs are superior to IFN- α in terms of health outcomes but are less cost-effective.

Key words — sunitinib, sorafenib, Markov chain Monte Carlo method, incremental cost per effectiveness ratios (ICER), quality-adjusted life year (QALY)

Introduction

Renal cell carcinoma patients are estimated to account for 1–2% of all adult carcinoma patients and 20–30% of them have metastases at diagnosis.¹⁾ Cytokines such as interferon- α (IFN- α) or interleukin-2 were the primary treatment options for metastatic renal cell carcinoma. However, they had limited efficacy and the median overall survival (OS) after metastasis diagnosis was approximately 1 year.²⁾ In 2008, sunitinib and sorafenib were approved in Japan and since then, molecular targeted drugs have been used in stan-

dard regimens for metastatic renal cell carcinoma. These drugs have improved prognostic outcomes and prolonged the median OS to approximately 3 years.^{3, 4)} Sunitinib and sorafenib are receptor tyrosine kinase inhibitors and affect vascular endothelial growth factor receptors. Both are approved in Japan as first-line treatment drugs for advanced or recurrent renal cell carcinoma. However, some research suggests that there is no significant difference in the progression-free survival (PFS) between cytokine therapies and molecular targeted therapies.⁵⁾ The therapeutic effects of new drugs depend on the decision of doctors and hospitals,

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which is partly based on the evaluation of cost-effectiveness of these therapies.

As the population ages and fewer babies are born, Japanese national medical expenditure has been growing year by year and it has reached 40 trillion yen in 2013. Increasing medical expenditure is one of the most serious concerns in the country. Reducing medical costs, particularly the supply costs, is important. Although few reports have been published on the cost-effectiveness of chemotherapy drugs used in Japan, pharmacoeconomic analysis of these drugs is necessary to evaluate the therapeutic benefits of molecular targeted drugs. Considering that these new drugs are expensive, the supply cost is one of the major factors to be considered while comparing the efficacy of chemotherapies.

The present study was performed to analyze the

clinical decisions involved in selecting IFN- α , sunitinib, and sorafenib therapies and to identify the best regimen for the first-line treatment of advanced or recurrent renal cell carcinoma based on clinical and economic evidence.

Methods

1. Analysis model

This is a retrospective observational study from a social viewpoint. A state transition model (a Markov model) was developed to describe the clinical courses in the treatment of advanced or recurrent renal cell carcinoma (**Fig 1**). The transition model represents three health states: alive without progression (progress-free), alive with progression or relapse (post-progress), and dead (death). We simulated the expected costs resulting

Fig 1 State transition model (a Markov model) of clinical courses in treatment of advanced or recurrent renal cell carcinoma
 □: Decision Node; Regimen options, M: Markov Node; Markov process in each regimen, ○: Chance Node; Probability branch point, △: Terminal Node; Terminal point

from the treatment of non-resectable advanced renal cancer over a period of 100 months using a hypothetical Markov model.

2. Target patients

We evaluated the clinical decisions taken for patients newly diagnosed with advanced or recurrent renal cell carcinoma at the Department of Urology, Yamagata University Hospital between January 1, 2013 and December 31, 2015 and who followed a regimen involving IFN- α , sunitinib, or sorafenib as the primary treatment. IFN- α was injected subcutaneously every other day, thrice a week. The dose was 300 IU on week 1, 600 IU on week 2, and 900 IU on week 3–6. 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.

3. Evaluation of health outcomes

Based on the results of randomized controlled clinical trials of IFN- α , sunitinib, and sorafenib treatments for advanced or recurrent renal cell carcinoma, health outcomes (OS and PFS) were evaluated^{6–11)} and the transition probabilities between the three health states in Markov model were calculated.

4. Resource use and costs

Medical records and receipts were used to examine the usage of drugs (including drugs used for adverse effects prevention), tests, and medical supplies. The costs of the regimens were calculated on the basis of direct costs, which included drug acquisition, test, medical supply, and personnel costs. The costs were estimated according to the standard dosage of the drugs and the drug acquisition costs were based on the Japanese drug price standard 2014. The costs of tests were computed

based on the medical remuneration points revised in 2014.

5. Evaluation of cost-effectiveness

We used the life months gained as health outcome and calculated cost per effectiveness ratios (CER) and incremental cost per effectiveness ratios (ICER):

ICER=

$$\frac{\text{CER of a molecular targeted drug} - \text{CER of IFN-}\alpha}{\text{Expected life time of a molecular targeted drug} - \text{expected life time of IFN-}\alpha}$$

6. Ethical consideration

The protocol of this study was reviewed and approved by Yamagata University Hospital Ethics Committee before the study was begun (No 196). The present study was conducted in compliance with “Ethical Guidelines for Medical and Health Research Involving Human Subjects (enacted on December 22, 2008)” by the Ministry of Health, Labour and Welfare, Japan.

Results

1. Health outcomes

Table 1 shows the reported PFS and OS of the three regimens and **Table 2** shows the transition probabilities between health states. Median PFS of IFN- α , sunitinib, and sorafenib was 5.3 months (3.9–6.7), 11.6 months (9.4–30.9), and 7.1 months (5.7–8.4) respectively, while median OS was 21.8 months (17.9–26.9), 29.8 months (18.9–32.9), and 23.1 months (19.9–23.2), respectively. The transition probability from progress-free to post-progress was 12.26% for IFN- α , 5.80% for sunitinib, and 9.30% for sorafenib and that from post-progress to death was 3.13%, 2.30%, and 2.96%, respectively.

Table 1 Health outcomes of sunitinib, sorafenib and IFN- α regimens

Reference No	PFS Median (month)	95% CI		OS Median (month)	95% CI	
		Min	Max		Min	Max
Sunitinib						
6)	11.0	11.0	13.0	26.4	23.0	32.9
7)	12.2	7.8	48.8	33.1	14.8	not reached
Sorafenib						
8)	—	—	—	16.9	10.5	23.2
9)	5.7	5.0	7.4	—	—	—
10)	9.1	7.3	9.5	29.3	29.3	not reached
11)	6.5	4.7	8.3	—	—	—
IFN- α						
6)	5.0	4.0	6.0	21.8	17.9	26.9
9)	5.6	3.7	7.4	—	—	—

IFN: interferon, PFS: progression-free survival, OS: overall survival, 95%CI: 95% confidence interval.

Table 2 Transition probabilities between health states

	Probability	Median (month)	95% CI		Monthly probability
			Low	Up	
PFS					
IFN- α	50%	5.3	3.9	6.7	0.123
Sunitinib	50%	11.6	9.4	30.9	0.058
Sorafenib	50%	7.1	5.7	8.4	0.093
OS					
IFN- α	50%	16.5	14.0	20.2	0.041
Sunitinib	50%	18.2	9.5	2.0	0.038
Sorafenib	50%	22.2	14.2	14.8	0.031
PPS					
IFN- α	50%	21.8	17.9	26.9	0.031
Sunitinib	50%	29.8	18.9	32.9	0.023
Sorafenib	50%	23.1	19.9	23.2	0.030

IFN: interferon, PFS: progression-free survival, OS: overall survival, PPS: post progression survival, 95%CI: 95% confidence interval.

2. Costs

Tables 3 and 4 show backgrounds of target patients and the drug acquisition and test costs, respectively. Most of the target patients were clear cell cancer. The proportion of acquisition costs of molecular targeted drugs was larger than that of IFN- α ; the test and medical supply costs were also higher for the molecular targeted drug regimens. There was negligible difference in costs between sunitinib and sorafenib.

probable health states of the target patients. According to the base case analysis, the acquisition costs of IFN- α , sunitinib, and sorafenib were 1,426,770 yen, 6,655,200 yen, and 4,380,278 yen per month, respectively. The life months gained were 22 months, 29 months, and 29 months, respectively. Markov chain Monte Carlo analysis revealed that ICER of sunitinib and sorafenib to IFN- α were 746,919 yen and 421,930 yen per life month, respectively (**Table 5**).

3. Cost-effectiveness

Figure 2 illustrates the simulated curves for

Discussion

Since the approval of sunitinib and sorafenib in

Table 3 Characteristics and clinical parameter of patients

	IFN- α	Sunitinib	Sorafenib	<i>P</i>
Number of patients	4	10	4	
Sex				
Male	2	8	3	0.26 ^{a)}
Female	2	2	1	
Age (median, range)	78.5 (62-85)	62 (38-69)	61 (48-77)	0.06 ^{b)}
Body weight	69.6 (39.6-72.0)	60.8 (38.0-76.5)	56.1 (44.6-74.9)	0.99 ^{b)}
Histological type				
clear cell	4	8	3	
papillary	0	2	0	
spindle cell	0	0	1	
ECOG performance status				
0	2	8	2	
1	0	2	2	
2	2	0	0	
Site of metastasis				
lung	4	4	3	
lymph node	1	5	2	
liver	0	2	1	
peritoneum	1	0	0	
bone	0	4	1	
adrenal gland	0	1	1	
Anamnesis				
hypertension	3	7	1	
hyperlipidemia	0	3	0	
hyperglycemia	1	1	0	
hyperuricemia	0	2	1	
cerebrovascular diseases	2	0	1	
asthma	0	1	0	
chronic gastritis	0	1	0	

a) χ^2 -test, b) one-way ANOVA. IFN: interferon, ECOG: Eastern Cooperative Oncology Group.

Table 4 Drug acquisition and test costs

	Drug Cost (%)	Other Drugs	Examination Cost	Total Cost
IFN- α	284,550 (86.71)	463	43,150	328,163
Sunitinib	838,040 (90.99)	3,162	79,867	921,069
Sorafenib	785,820 (90.34)	3,110	80,925	869,855

IFN: interferon, Other Drugs: drugs used for adverse effects prevention.

(¥)

Fig 2 Simulated curves for probable health states

The simulated curves represent three health states: alive without progression (progress-free), alive with progression or relapse (post-progress), and dead (death). — IFN- α , - - - sunitinib, ... sorafenib.

Table 5 Cost-effectiveness of sunitinib, sorafenib and IFN- α regimens

Regimen	Effectiveness (month)	Drug acquisition cost (¥)	CER	ICER
IFN- α	22	1,426,770	64,853	–
Sunitinib	29	6,655,200	229,490	746,919
Sorafenib	29	4,380,278	151,044	421,930

IFN: interferon, CER: cost per effectiveness ratio, ICER: incremental cost per effectiveness ratio.

2008, molecular targeted drugs have been standard chemotherapy regimens for metastatic renal cell carcinoma. However, as they are more expensive than the older drugs such as IFN- α , their cost-effectiveness and health outcomes should be considered while comparing the efficacy of regimens. In this study, we developed a state transition model (a Markov model) to describe the clinical courses for patients with advanced or recurrent renal cell carcinoma and analyzed the health outcomes and cost-effectiveness of the new and old therapies.

ICER of sunitinib and sorafenib to IFN- α were 746,919 yen and 421,930 yen per life month, respectively. It is stated that the ICER should be within 20,000–30,000 pounds per quality-adjusted life year (QALY)¹²⁾ in the United Kingdom, and it should be within 50,000–100,000 dollars per QALY in the United States.¹³⁾ Although there are no clear standards defined in Japan, Shiroiwa *et al*¹⁴⁾ reports that it is 5 million yen per qualitative adjustment year. It means 416,666 yen per month, and the ICER of the molecular targeted drug therapies considered in this study exceed this criterion. Sunitinib and sorafenib regimens have better health outcomes than the IFN- α regimen do, however, they are less cost-effective. These results can be applied to a broad range of cases as the costs were estimated according to the standard dosage. Other drug expenses and test costs of the molecular targeted drug regimens were also higher than those for the IFN- α regimen were, and the countermeasures against ad-

verse effects involved several expenses. Our results indicate that molecular targeted drugs are less cost-effective compared to IFN- α and not suitable as first-line treatment.

Sorafenib and sunitinib had similar expected life times, but ICER of the former was 324,989 yen lower than that of the latter. Although sorafenib is only recommended as the second-line therapy after failure of cytokine therapy¹⁵⁾ and is selected in a clinical setting when it is inevitable to use molecular targeted drugs, sorafenib is more cost-effective than sunitinib is. The US National Comprehensive Cancer Network Guidelines recommend that, for clear cell renal carcinoma, sorafenib should be used for carefully selected patients (<https://www.tri-kobe.org/nccn/guideline/urological/english/kidney.pdf>, March 7, 2017), but some reports suggest that it is effective for papillary renal cell carcinoma.^{16, 17)} Therefore, histological types should be taken into account in evaluating cost-effectiveness.

The present study was designed from a social viewpoint. Molecular targeted drugs have contributed to the remarkable improvement in the prognostic outcomes of renal cell carcinoma treatments. This implies a higher PFS and, thus, the notion of ICER has become more important because considering the patients' quality of life is essential in the evaluation of regimens.

Conflict of Interest

We have no financial relationships to disclose.

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