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PHARMACOECONOMIC EVALUATION OF AXITINIB INTRODUCTION IN METASTATIC RENAL CELL CARCINOMA TREATMENT SCHEME

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Abstract: During the pharmacoeconomic analysis of axitinib use as a second-line therapy for mRCC, it was found that this target therapy regimen would significantly increase the time to progression, overall survival and annual survival rate. Despite the high cost of this treatment regimen at the horizon of ten year study, the treatment regimen including axitinib characterized by the lowest values of the cost-effectiveness ratio, reflecting the costs incurred by the health care system for patient's life saving, and incremental cost-effectiveness ratio, which was less than willingness to pay threshold.

Keywords: metastatic renal cell carcinoma, axitinib, pharmacoeconomic analysis.

Introduction

Kidney cancer - one of the most common cancer diseases with increasing number of incidence. The structure of solid cancers in the world of kidney cancer is a 2 - 3%, and an annual increase of 2%. In Russia in 2010 year of kidney tumors were initially diagnosed in 19,657 patients, and the increase in incidence from 2000 to 2010 years amounted to 31.44% of the annual growth rate of 2.77% [2]. Referring to epidemiological data, men suffer from this disorder is twice more often than women [1]. RCC is an aggressive malignancy with an unpredictable course. Up to 33 % of RCC cases are diagnosed at the advanced stage, and the remaining 67 % patients develop metastases within 5 years following radical surgery [3]. According to J. B. De Kernion, 50 % of all cases are or will later be metastatic [4]. According to Russian and international mRCC guidelines, the drug of choice as first-line targeted therapy in mRCC favorable and intermediate prognostic risk patients is tyrosine kinase inhibitor (TKI) sunitinib. This drug has demonstrated the highest level of evidence for its clinical effects on improving progression-free survival (PFS) and overall survival (OS) among the available therapeutic options. Additionally, the current guidelines recommend two alternative second-line treatments: mammalian target of rapamycin (mTOR) inhibitor everolimus or tyrosine kinase inhibitor (TKI) axitinib following first-line treatment failure. Those medications have also demonstrated high efficacy and safety in multiple randomized clinical trials [5-9]. Everolimus as targeted mRCC therapy was investigated in a Phase III placebo-controlled RCT with 416 subjects. This targeted treatment achieved median PFS of 4.9 months and median OS of 14.8 months with the objective response rate of 2 % [10]. Similarly, axitinib as second-line targeted treatment of kidney cancer was investigated in a comparative study with sorafenib. In this study, targeted axitinib therapy resulted in median PFS of 6.7 months, median OS of 20.1 months, with the objective response reported in 19 % of subjects [11-12].

Figure 1. Markov model for mRCC treatment

The most common Grade 3 or 4 adverse effects with everolimus were: anemia (5 %) and leukopenia (4 %); diarrhea (1 %) and nausea (1 %) have also been reported. Axitinib treatment was associated with diarrhea (11 %), nausea (2 %), headache (1 %) and hypertension (5 %). Targeted therapy discontinuation rate due to adverse effects was 10 % and 4 % with everolimus and axitinib, respectively [10-12]. The current healthcare system requires considering cost-effectiveness of therapeutic options besides their efficacy and safety when making decisions concerning utilization of any medication. Consequently, the objective of this study was a clinical & economic analysis of targeted mRCC treatment with axitinib and everolimus.

Materials and Methods

This pharmacoeconomic evaluation involved a comparison of four targeted mRCC treatments (Table 1) with the following medications:

- ✓ Sorafenib, the most frequently used TKI in the Russian healthcare settings.
- ✓ Sunitinib, TKI of choice as the first-line targeted treatment according to mRCC therapy guidelines.
- ✓ Everolimus, mTOR recommended as the second-line targeted mRCC treatment.
- ✓ Axitinib, TKI recommended also as the second-line targeted mRCC treatment.

Table 1. Targeted treatments compared

First line	Second line	Third line
Sorafenib	Everolimus	Palliative care
Sorafenib	Axitinib	Palliative care
Sunitinib	Everolimus	Palliative care
Sunitinib	Axitinib	Palliative care

Given that mRCC is a chronic condition, this study used a Markov model that allowed to evaluate subject distribution by treatment duration and targeted therapy used. The Markov model generated included 4 conditions with the Markov cycle duration of one month and the model horizon of 10 years (Figure 1):

The model presented was created in the manner that cost and efficacy per 100 subjects were analyzed for each therapeutic option. Based on the clinical efficacy data for the treatment options evaluated (Table 2), PFS models on first-line, second-line treatment and then on palliative care were created. The criterion for the initiation of the subsequent line was disease progression. Further, a total cost of mRCC therapy per patient was calculated for each targeted treatment option.

Table 2. Clinical trial results for targeted agents.

INN	Median PFS		Median OS		Objective response rate	
	1st line	2nd line	1st line	2nd line	1st line	2nd line
Axitinib [11-12]	-----	6.7 months	-----	20.1 months	-----	19 %
Everolimus [10]	-----	4.9 months	-----	14.8 months	-----	2 %
Sunitinib [13-14]	11.0 months	-----	26.4 months	-----	47 %	-----
Sorafenib [15]	5.7 months	-----	Not evaluated in RCTs	-----	5 %	-----

The structure of direct costs evaluated in this pharmacoeconomic analysis included: two lines of targeted treatment (Table 1); palliative care; management expenses for Grade 3 and 4 adverse effects (Table 4); diagnostic procedures.

The following sources for cost analysis data were used: standard of care for kidney cancer patients No. 774 dated November 20, 2006; European Society for Medical Oncology (ESMO) Clinical Practice Guidelines; Guidelines for palliative care in cancer patients; compulsory health insurance system rate agreements; State Register for Maximum Sale Prices; manufacturer's price list (for axitinib). Pharmacoeconomic results were expressed as cost-effectiveness parameters that reflect mean monthly treatment cost for mRCC patients, the cost of life years gained for the period of one to three years, and incremental cost-effectiveness ratio (ICER) that demonstrates the cost of additional life year.

It should be noted that this pharmacoeconomic evaluation used an annual 5 % discount rate for the cost calculation and treatment efficacy assessment.

Markov Model Results

The Markov model results showed that sunitinib and axitinib combination is associated with the maximum reduction of mortality, as well as with the greatest improvement of time to disease progression. Mean overall survival on sunitinib + axitinib therapy was 22.75 months or 1.90 years, whereas it was 1.59 / 1.67 / 1.81 life years with other targeted treatment options: sorafenib + everolimus; sorafenib + axitinib; sunitinib + everolimus, respectively. One-, two- and three-year survival with patients receiving sunitinib + axitinib is 68 %, 38 %, and 17 %, respectively. The corresponding values for patients receiving sorafenib and everolimus are 58 %, 25 % and 10 %, respectively; sorafenib + axitinib, 61 %, 29 % and 12 %, respectively; sunitinib + everolimus, 66 %, 34 % and 15 %, respectively. Markov model results for overall survival in years and mean life expectancy are graphically presented on Figure 2.

Figure 2. Survival and mean life expectancy in mRCC patients.

As can be seen from the data obtained, axitinib improved mean life expectancy and survival compared to everolimus, regardless of the first-line therapy.

Cost Analysis Results

The next analytical stage involved direct cost evaluation for mRCC treatment, with initial analysis of targeted therapy cost based on the following: Markov model results; drug dosing regimens stated in the prescribing information; drug cost according to the State Register for Maximum Sale Prices and the manufacturer's price list (for axitinib). The monthly targeted treatment cost calculated is presented in Table 3:

Table 3. Monthly cost of targeted mRCC treatments.

INN	Formulation	Price per package (excl. VAT)	Dosing regimen	Monthly treatment cost
Axitinib	1 mg tablets, 56 cc	30,475 rubles	10 mg daily	163 261 rubles
	5 mg tablets, 56 cc	152,377 rubles		
Everolimus	5 mg tablets, 30 cc	109,653 rubles	10 mg daily	181 918 rubles
	10 mg tablets, 30 cc	144,529 rubles		
Sunitinib	50 mg capsules, 28 cc	192,963 rubles	50 mg daily for 4 weeks, with a 2-week interruption between cycles	137 831 rubles
Sorafenib	200 mg tablets, 112 cc	122,079 rubles	800 mg daily	130 799 rubles

The next analytical stage involved cost evaluation for the management of Grade 3 and 4 treatment-emergent adverse effects. The list and frequency of adverse effects assessed, along with the mean treatment cost were determined based on clinical trial results and are provided in Table 4.

Table 4. Adverse effect frequency

Adverse effect	Sorafenib [15]	Sunitinib [13-14]	Everolimus [10]	Axitinib [11-12]
Diarrhea	14%	9%	1%	11%
Nausea / vomiting	2%	9%	1%	2%
Fluid retention / edema	1%	1%	0%	0%
Headache	15%	1%	0%	1%
Hypertension	2%	12%	0%	5%
Pruritus and rash	11%	1%	0%	0%
Anemia	0%	8%	5%	0%
Leukopenia	0%	8%	4%	0%
Mean treatment duration	6 months	11 months	4.7 months	7 months
Total cost	150 rubles per month	415 rubles per month	468 rubles per month	57 rubles per month

Total treatment costs for adverse effects were determined according to the standard of care in kidney cancer patients No. 774 dated November 20, 2006, as well as ESMO Clinical Practice Guidelines. It was assumed that Grade 3 and 4 adverse effects would necessitate a physician call and administration of appropriate treatment, and seven days of in-patient therapy in case of anemia and leukopenia.

The next stage of direct cost analysis for mRCC treatment was the cost evaluation for palliative care which included analgesics and Palliative care, as well as patient's stay at the hospital for up to 7 days. The total cost calculated was 2,916 rubles per palliative care patient-day.

The cost calculation for laboratory and imaging diagnostic procedures in mRCC patients was based on the procedure list and the frequency of their use according to the Standard of care for kidney cancer patients and the compulsory health insurance system rate agreement. The total cost for a set of diagnostic procedures was 7,825.00 rubles. [16]. Treatment efficacy assessment which involves performing these procedures is conducted every three months according to the RECIST criteria for tumor progression [17].

Finally, the total direct cost of mRCC treatment with a 10-year model horizon and a 5 % annual discount rate was calculated based on the data above. The mRCC therapy cost structure by treatment is graphically provided on Figure 3.

Figure 3. mRCC treatment cost structure.

As can be seen from the data presented, the less expensive mRCC treatment per patient with the cost of 1,805,179 rubles is the combination of sorafenib and everolimus; however, this saving was achieved due to the poorest overall survival. By contrast, the maximum total cost of 2,391,827 rubles was calculated for sunitinib + axitinib. It should be noted that the highest cost in this case is associated with the best overall survival which requires the longest use of healthcare recourses.

Axitinib as second-line targeted treatment was found to be associated not only with improved efficacy, but also with additional expenses of 140,148 rubles (7.6 %) in case of sorafenib as the first-line therapy and 122,347 rubles (5.1 %) in case of first-line treatment with sunitinib.

Figure 4. Mean monthly cost for treatment of a mRCC patient

The next stage of this pharmacoeconomic evaluation involved an incremental cost-effectiveness analysis that determined an additional life year cost for axitinib. The results obtained were assessed against the societal willingness-to-pay (WTP) threshold which was calculated as a three-fold gross domestic product value per person [18].

Figure 5. ICER values

An additional life year cost with sunitinib and axitinib was found to be less than WTP in the Russian Federation, i.e. extra expenses compared to everolimus-based treatments are economically viable. However, the cost for combination of axitinib and sorafenib was greater than the current WTP value, which means that this treatment scheme is less economically viable.

The final analytical stage evaluated the cost of one, two and three life years gained, calculated as the ratio of the total direct cost for the treatment duration to the survival in years. The analysis results are provided in Figure 6

The analysis of 1, 2 and 3 life year gain cost showed that axitinib, regardless of the model horizon and the first-line targeted agent, reduced healthcare expenses for life years gained in comparison to everolimus-based treatments. It should also be noted that treatment with sunitinib and axitinib was associated with minimum expenses for life years gained.

Therefore, given the lowest values for cost-effectiveness ratios, axitinib-based treatments were preferable as they require lower cost for life years gained and are the most advantageous therapeutic option evaluated when used with sunitinib.

Pharmacoeconomic Results

In order to determine the most cost-effective treatment strategy based on the information on the total direct cost for mRCC therapy and the Markov model results for mean overall survival and survival by years, a cost-effectiveness analysis was performed that allowed to evaluate the mean monthly treatment cost, the cost for an additional life year, as well as the cost for a life year gained for a period of one to three years.

As can be seen from the data provided in Figure 4, when sorafenib is used as the first-line treatment axitinib use is associated with additional expenses; however, those expenses were only 2,158 rubles (2.3 %) per month. By contrast, when sunitinib is used as the first-line treatment, axitinib use reduces expenses by 143 rubles (0.14 %) per month. Overall differences in the cost of targeted treatments compared were not significant.

Conclusion

Targeted agents with effects directed at specific molecules are now considered the most promising cancer treatments with improved efficacy. However, the high cost of these treatments somewhat hinders the active use of the most effective and safe therapies. Determining the therapeutic options with the best cost-effectiveness results in the Russian healthcare settings is at present of greatest relevance.

As can be seen from the results obtained, axitinib improved mean overall survival and life years gained regardless of the first-line treatment agent. At the same time, the best survival rates were associated with a longer use of healthcare resources and higher total direct cost; however, additional expenses did not exceed 5.1 to 7.6 % or not more than 2.3 % per monthly treatment cycle. Moreover, even though axitinib-based therapy required higher expenses, in the long run it reduced the cost of life years gained for the period of one to three years. Additionally, the best survival and most cost-effective treatment were observed with sunitinib and axitinib therapy. Therefore, based on the results obtained, introduction of axitinib as targeted second-line mRCC treatment is evidently the most advantageous option compared to everolimus, and the combination of axitinib and sunitinib is the most efficient of the therapeutic alternatives assessed in the Russian healthcare settings.

Figure 6. Life year gain cost

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