МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ АНАЛИЗА "ВЛИЯНИЯ НА БЮДЖЕТ"

РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ
PHARMACOECONOMIC ANALYSIS OF VEMURAFENIB IN TREATMENT OF INOPERABLE OR METASTATIC MELANOMA IN PATIENTS WITH BRAF V600 MUTATION

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Summary: Objective of this study was to determine cost-effectiveness of vemurafenib in treatment of inoperable or metastatic melanoma in patients with BRAF V600 mutation from Russian healthcare system perspective and a long-term use. Cost-effectiveness analysis (CEA) has been used and cost-effectiveness ratio (CER) has been calculated. Incremental analysis has been conducted with calculation of incremental cost-effectiveness ratio (ICER) when exceeding the costs and effectiveness of one of the studied regimens as compared to the other one. Cost analysis included calculation of the following direct costs (DC): the cost of the main disease treatment (cutaneous melanoma, CM) – costs of the drug; the cost of laboratory and instrumental methods of investigation as well as hospitalizations and outpatient treatment; the cost required to determine exon 15 BRAF mutation in melanoma; the cost of the drug therapy aimed at management of adverse events (AEs) caused by the drug when treating the main disease. Two medical technologies have been assessed (anti-tumor regimens depending on the chosen method): vemurafenib at a dose of 960 mg twice a day; dacarbazine at a dose of 1000 mg/m2 i/v every 3 weeks. Mathematical modelling underlies this study. As a result it has been demonstrated that the use of vemurafenib strategy in treatment of metastatic melanoma in patients with BRAF V600 mutation had better progression-free survival (PFS) rate throughout the entire modelling horizon. The use of vemurafenib in treatment of metastatic and inoperable melanoma in patients with BRAF V600 mutation is economically advisable taking into account the data on effectiveness (PFS). The use of vemurafenib in patients with BRAF V600 mutation is an absolutely innovative medical technology which currently does not have any alternative. Vemurafenib may be indicated for inclusion in reimbursement lists for treatment of patients with this mutation.

Keywords: pharmacoconomics, vemurafenib, melanoma, target therapy, BRAF V600 mutation

Background
Cutaneous melanoma (CM) is a malignant tumor of neuroectodermal origin which develops from transformed melanocytes predominantly located in the skin (in 90%) [1]. Data from the modern epidemiology studies demonstrate the rapid increase of CM incidence in different countries including the Russian Federation (RF) which allows us to consider this fact as a global trend. It should be also noted that despite the fact that CM constitutes only about 4% of all skin cancer cases worldwide, it causes up to 80% of death outcomes [2-4]. Thus, CM incidence in the RF is 6.09 per 100,000 population, and mortality is 1.5 per 100,000 population. Increase in mortality rate was 14.7% throughout 2002-2012 [1; 5]. Effectiveness of routine chemotherapy remained extremely low for over 30 years due to a lack of specificity in mechanism of action. According to the results of one of the meta-analyses, median overall survival (OS) was 6.2 months, and median progression-free survival (PFS) was only 1.7 month [6].

As a result it has been demonstrated that the use of vemurafenib strategy in treatment of metastatic melanoma in patients with BRAF V600 mutation had better progression-free survival (PFS) rate throughout the entire modelling horizon. The use of vemurafenib in treatment of metastatic and inoperable melanoma in patients with BRAF V600 mutation is economically advisable taking into account the data on effectiveness (PFS). The use of vemurafenib in patients with BRAF V600 mutation is an absolutely innovative medical technology which currently does not have any alternative. Vemurafenib may be indicated for inclusion in reimbursement lists for treatment of patients with this mutation.
Methods

Industry standards of the “Clinical Economic Study” applied in the RF have been used during conduction of the clinical economic analysis [21-25]. Cost-effectiveness analysis (CEA) has been used and cost-effectiveness ratio (CER) has been calculated. Incremental analysis has been conducted with calculation of incremental cost-effectiveness ratio (ICER) when exceeding the costs and efficiency of one of the studied regimes as compared to the other one. This analysis is conducted to determine additional expenses (costs) in order to prevent 1 case of death and/or to save the life for 1 year (or other parameters).

Costs. Cost analysis included calculation of the following direct costs (DC): the cost of the main disease treatment (cutaneous melanoma, CM) – costs of the drug; the cost of laboratory and instrumental methods of investigation as well as hospitalizations and out-patient treatment; the cost required to determine exon 15 BRAF mutation in melanoma; the cost of the drug therapy aimed at management of adverse events (AEs) caused by the drug when treating the main disease. Treatment costs were assessed based on www.imshealth.com web-portal data [26], State Register of Marginal Selling Prices [27], based on the RF Government Decree dated November 28, 2014 “On the Programme of State Guarantees for Free of Charge Medical Care for Citizens for 2015 and for Planned Period of 2016 and 2017” [28], Master Rate Agreement for 2015 (MRA) [29].

Treatment effectiveness. In order to determine effectiveness criteria, systematic analysis of literature data on the use of chemotherapeutic drugs in treatment of metastatic and inoperable CM has been conducted. Efficacy assessed according to the results of randomized clinical studies (RCS) and meta-analyses was used as an effectiveness criterion. Based on the data from clinical studies on the use of specified medical technologies, progression-free survival (PFS, months) was chosen as the main effectiveness criterion of the therapy.

Structure of the models. “Decision tree model” was used for clinical economic assessment of the drug in treatment of metastatic and inoperable CM [30]. The model of care provided to a patient with metastatic or inoperable melanoma was constructed during the first stage of pharmacoeconomic analysis. Large RCT BRIM-3 [17] served as the basis for the model; during this study demographic parameters of the assessed patient cohort and the relation between the medical care strategies have been determined. "Decision tree model" was created in such a way that costs and effectiveness were analyzed in each branch of the model for a group consisting of 100 patients. Then the treatment cost was calculated for one patient from each group (Figure 1). The model construction was started from the choice of the drug for treatment of metastatic or inoperable CM: vemurafenib at a dose of 960 mg twice a day; dacarbazine at a dose of 1000 mg/m2 i/v every 3 weeks. Then the patients entered the Markov cycle. Moreover, it was allowed for the patients from dacarbazine group to receive medical care in accordance with the Order of the Ministry of Healthcare of Russia dated November 7, 2012 No. 604n “On Approval of a Standard of Specialized Medical Care in Cutaneous Melanoma, Generalization and Relapse (Chemotherapeutic Treatment)”. This standard requires the average treatment course of 10 days. Thus, the patients were hospitalized every 3 weeks for 10 days in order to receive the chemotherapy course in the settings of a specialized oncology in-patient department. As opposed to dacarbazine group, the patients from vemurafenib group received medical care in the out-patient settings. Moreover, they underwent diagnostic procedures every 8 weeks in accordance with the RECIST criteria for assessment of the neoplastic process progression. The first-line therapy was discontinued in case of disease progression. Disease progression was considered as a final stage of the Markov cycle. The cycle duration was 1 month, maximal modelling horizon was 12 months. Probabilities of developing specific AEs during the assessed therapy strategies were additionally evaluated taking into account the costs of the medical care for their management. “Decision tree model” diagram and the Markov cycle for the model of patients with CM are presented in Figures 1 and 2.

Sources of data for mathematical modelling. The disease cost, probability of development of certain events when using different therapy strategies in patients with metastatic and inoperable CM such as effective treatment rate and complication rate were determined via evaluation model. Table 1 summarizes effectiveness parameters of the first-line therapy of CM in patients with BRAF V600 mutation.

![Figure 1](image1.png)

**Figure 1.** «Decision tree model» to assess pharmacoeconomic effectiveness of the first-line therapy of metastatic or inoperable CM

![Figure 2](image2.png)

**Figure 2.** Diagram representation of transition sequences in the Markov cycle when using different strategies of the first-line chemotherapy in patients with metastatic or inoperable CM and BRAF V600 mutation.
Vemurafenib: 960 mg twice a day; Dacarbazine: 1000 mg/m² i/v every 3 weeks; CI – confidence interval.

During the process of OS and PFS modelling, the tables of model state in the Markov cycle depending on time were compiled based on the Kaplan-Meier survival curves for each chemotherapy cycle presented in RCS [17; 31].

Treatment cost of the main disease (CM). Treatment cost of the main disease (inoperable and metastatic CM) was calculated including the cost of the first-line therapy with chemotherapeutic drugs from the assessed strategies (Table 2).

The cost of laboratory and instrumental methods of investigation, supportive therapy and diagnostic drugs [32]. Procedures included in the list of consultative and diagnostic medical care were as follows: medical services for disease diagnostics (examination, consults, laboratory and instrumental methods of investigation); medical services for treatment of the disease, condition and for treatment monitoring (examination, consults, laboratory methods); the list of drugs for medical use registered at the territory of the Russian Federation specifying average daily and course doses; the types of nutritional care including specialized dietary therapy products. The cost of medical care according to the specified standard [32] was drawn up based on the MRA for “Malignant Neoplasms of Connective and Other Soft Tissues. Melanoma” and constituted 33,740.80 rubles.

The cost of medical care was compiled based on the list of services for diagnostics of response to therapy from the Standard of Specialized Medical Care in Cutaneous Melanoma, Generalization and Relapse (Chemotherapeutic Treatment), the Order of the Ministry of Healthcare of the Russian Federation dated November 7, 2012 No. 604n. To assess the cost of services, the rates for medical services from the Master Rate Agreement, Saint Petersburg, were used (Appendices 12, 13) [29]. Total cost of services was 872.26 rubles. Diagnostic examinations for assessment of therapy response were conducted every 8 weeks according to RECIST recommendations. Therefore, the patients will be examined 3 times during the progression-free period in vemurafenib strategy, and the total cost of the medical care will be 2,616.78 rubles or 436.13 rubles/month.

The cost of BRAF exon 15 mutation detection in melanoma. The cost of BRAF exon 15 mutation detection in melanoma is 2200 rubles. Considering the overall population of patients with inoperable or metastatic melanoma in case of diagnostics, the cost of the test per one patient with detected BRAF mutation is 3,666.67 rubles. Proportion of patients with BRAF V600 mutation is 60%.

The cost of medical care in case of AE. The cost of therapy aimed at management of AEs occurring while using the first-line therapy drug for inoperable and metastatic CM consisted of the cost of drugs, out-patient visits and hospitalization due to AE development. Data provided for vemurafenib are taken from the global study on safety of vemurafenib [33]; data provided for dacarbazine on the incidence of anemia, neutropenia, thrombocytopenia are taken from the Phase III study comparing Dacarbazine and Dacarbazine regimens in the therapy of metastatic melanoma. Data on the remaining AEs are taken from BRIM-3 study. When calculating the cost for AE management in comparison groups, it was assumed that in case of a mild or moderate reaction (Grade 1-2) the out-patient treatment is required (foreseen in the MRA [29] for the proper nosology or clinical condition). Severe AEs (Grade 3 or 4) were associated with patient’s hospitalization. If there were no reliable data on the procedure of providing medical care and duration of hospitalization in chemotherapeutic treatment complications, average duration of hospitalization was reported in similar clinical statistical groups (C56s) [29].

Total costs of the assessed strategies of the first-line therapy in inoperable and metastatic CM. Total costs of using the assessed strategies are provided in Table 3 for the calculation period of 1 month.

<table>
<thead>
<tr>
<th>The list of costs</th>
<th>Vemurafenib</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs for BRAF mutation diagnoses</td>
<td>531.40</td>
<td>0</td>
</tr>
<tr>
<td>Costs for the drug therapy</td>
<td>375,701.53</td>
<td>3,115.93</td>
</tr>
<tr>
<td>Costs for consultative diagnostic care, additional drugs</td>
<td>436.13</td>
<td>33,740.80</td>
</tr>
<tr>
<td>Total</td>
<td>379,804.33</td>
<td>36,856.73</td>
</tr>
</tbody>
</table>

Vemurafenib: 960 mg twice a day; Dacarbazine: 1000 mg/m² every 3 weeks.

Results

Cost-effectiveness analysis. The cost of each treatment strategy per patient from a target group was assessed in the main scenario. Total DCs were calculated using the compared strategies. Modelling time horizon was 12 months for all comparison strategies. As a result, the greatest DCs were observed for vemurafenib strategy (3,135,337 rubles), modelling horizon was 1 year. Total costs for dacarbazine were 12.1 times lower (258,621 rubles per one patient). Moreover, the greatest difference was observed due to the different cost of the drug course. The costs for the first-line therapy drug in vemurafenib treatment group constituted 3,039,425 rubles per one patient; meanwhile, the corresponding sum in dacarbazine group was 13,635 rubles. It should be noted that the costs of chemotherapy course when using vemurafenib strategy were 7,827 rubles which is 18.8 times less than corresponding costs of dacarbazine strategy (147,650 rubles). Distribution of therapy costs demonstrated that percentage ratios of DCs for the therapy components in the groups of the drugs under consideration (vemurafenib and dacarbazine) significantly differed when reviewing the strategies overall.

Table 1. Effectiveness parameters of compared strategies [17].

<table>
<thead>
<tr>
<th>Effectiveness parameters</th>
<th>Vemurafenib, n = 337</th>
<th>Dacarbazine, n = 338</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival, months</td>
<td>13.6 [95% CI 12.0–15.2]</td>
<td>9.7 [95% CI 7.9–12.8]</td>
</tr>
<tr>
<td>Median progression-free survival, months</td>
<td>6.9 [95% CI 6.1–7.0]</td>
<td>1.6 [95% CI 1.6–2.1]</td>
</tr>
</tbody>
</table>

Table 2. The costs of drugs for chemotherapy.

<table>
<thead>
<tr>
<th>Drug (INN)</th>
<th>Trade name</th>
<th>Pharmaceutical form</th>
<th>Price (rubles)</th>
<th>Dose for 1 month of therapy, mg*</th>
<th>Cost of 1 month of therapy, rubles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td>Zelboraf</td>
<td>tablets 240 mg N56</td>
<td>87663.69</td>
<td>57 600</td>
<td>375701.53</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Dacarbazine-LANS</td>
<td>Lyophilize for preparation of solution for i/v administration 200 mg N1</td>
<td>242.35 [27]**</td>
<td>2572</td>
<td>3115.93</td>
</tr>
</tbody>
</table>

* - average human body surface area – 1.73 m²; average human body weight – 75 kg.

** - including 10% value added tax (VAT); INN – international non-proprietary name; Vemurafenib: vemurafenib at a dose of 960 mg twice a day; Dacarbazine: dacarbazine at a dose of 1000 mg/m² every 3 weeks.
While proportion of the drug costs in case of vemurafenib strategy was 97%, the similar proportion of costs in case of dacarbazine use was 5%. Moreover, 57% of costs in dacarbazine group were spent on the in-patient treatment (as opposed to 0.25% in vemurafenib strategy). It should also be noted that in case of dacarbazine use 38% of the therapy costs were caused by AE management, while the corresponding parameter in vemurafenib group was 3%.

The incidence of different AEs was assessed in comparison groups throughout the follow-up period. Such complications as impaired hepatic function and arthralgia of all grades were more often observed in vemurafenib group. When reviewing Grade 1-2 complications, such complications as vomiting, nausea, fatigue and asthenia were more often observed in dacarbazine group. When comparing ≥ Grade 3 complications it should also be noted that such complications as rash (5%), photosensibility (2%) and squamous cell carcinoma (12%) were observed only in vemurafenib group. At the same time thrombocytopenia and neutropenia were registered only when using dacarbazine (10% and 4%, respectively).

Progression-free survival (months) was considered as effectiveness criterion. As data presented in Table 1 show, the strategy of vemurafenib use was more effective as compared to dacarbazine strategy. Effectiveness parameter “Median PFS” in this strategy was 6.9 months. Similar parameter for dacarbazine strategy was more than 4 times lower (only 1.6 months). Changes in conditions over time throughout one year were also reviewed. Corresponding results are provided in Figure 3.

As data presented on Figure 3 indicate, greater probability to maintain progression-free state was observed throughout the entire modelling horizon when using vemurafenib strategy as compared to dacarbazine.

Regarding the cost-effectiveness ratio, vemurafenib strategy was more effective as compared to dacarbazine (according to median PFS parameter), however, it was also more expensive alternative. CER coefficients characterizing effectiveness of total overall costs for treatment of one patient regarding the effectiveness parameter “Median PFS” constituted 161,638 and 454,397 rubles for dacarbazine and vemurafenib strategies, respectively.

ICER was calculated considering the fact that vemurafenib strategy was more effective but also more expensive (Table 4).

As data presented in Table 4 show, the strategy of using vemurafenib for treatment of inoperable or metastatic melanoma in patients with BRAF V600 mutation was more expensive, however more effective as compared to dacarbazine strategy. Cost increase constituted 2,876,816 rubles; effectiveness increase was 5.3 for “PFS, months” parameter. Corresponding ICER for vemurafenib strategy was 542,777 rubles/month.

Sensitivity analysis. In order to verify the results of analysis when the entry parameters changed, sensitivity analysis was performed. This analysis was conducted via multiple simultaneous measurements of such parameters as effectiveness and the drug cost. As a result, during simultaneous multiple measurements of the above-mentioned parameters vemurafenib strategy remained both more effective and the most expensive. Sensitivity analysis confirmed the results obtained in the main scenario.

**Discussion**

Comparative pharmaco-economic analysis of vemurafenib (Zelboraf®) in treatment of inoperable or metastatic melanoma in patients with BRAF V600 mutation was for the first time conducted in the Russian settings. Two medical technologies were assessed (anti-tumor regimens of CM therapy depending on the chosen method): vemurafenib at a dose of 960 mg twice a day; dacarbazine at a dose of 1000 mg/m² i/v every 3 weeks. As a result it has been demonstrated that the greatest DCs were observed for vemurafenib strategy (3,135,337 rubles), modelling horizon was 1 year. Total costs for dacarbazine regimen were 12.1 times lower and constituted 258,621 rubles per one patient. Moreover, the greatest difference was due to different cost of the drug course: 3,039,425 rubles for vemurafenib and 13,635 rubles for dacarbazine.

Attention is drawn to different distribution of DC constituents for each treatment strategy. In particular, 57% of costs in dacarbazine group were spent on the chemotherapy course (as opposed to 0.25% for vemurafenib strategy). The costs of in-patient treatment when using vemurafenib strategy were 7,827 rubles which is 18 times lower than corresponding costs of dacarbazine strategy (147,650 rubles). Additionally, it should be noted that in case of dacarbazine use, 38% of the therapy costs were caused by AE management, while the corresponding parameter in vemurafenib group was 3%. Therefore, additional resources are required from the healthcare system for chemotherapy (CT) and AE management when using dacarbazine strategy. During comparative assessment of effectiveness, the vemurafenib regimen strategy proved to be more effective; corresponding PFS parameter for this strategy was 6.9 months; it was more than 4 times lower for dacarbazine strategy (1.6 month). After additional consideration of changes in conditions throughout the modelling period it was determined that throughout the entire modelling horizon there were more chances to remain in the progression-free state when using vemurafenib strategy as opposed to comparison strategy (dacarbazine).

**Table 4. ICER calculation for compared strategies (PFS parameter).**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>DC, rubles</th>
<th>Cost increase, rubles</th>
<th>Effectiveness (PFS, months)</th>
<th>Effectiveness increase</th>
<th>ICER (PFS, months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td>3,135,337</td>
<td>2,876,716</td>
<td>6.9</td>
<td>5.3</td>
<td>542,777</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>258,621</td>
<td></td>
<td>1.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.** Changes in condition “First-Line Therapy” throughout one year in comparison groups.
zine strategy regarding the cost-effectiveness ratio; however, it is also a more expensive alternative. Cost increase constituted 2,876,816 rubles; effective-ness increase was 5.3 for “PFS, months” parameter.

Despite the fact that up to date the incremental cost-effectiveness ratio has been usually compared to the society’s willingness-to-pay threshold when determining economic advisability of healthcare technology, such compari-
son is not always possible. One of the first works dedicated to this problem includes analysis conducted by Marseille E. et al in 2015 [34] where it has been convincingly demonstrated that uniform methods to calculate the so-
ciety’s willingness-to-pay threshold cannot be used in countries with more than 100-fold difference in GDP per capita. The authors also point out that any new technology exceeds the society’s willingness-to-pay threshold when analyzing innovative drugs in such areas of medicine where the last century technologies are still used. It is the most pronounced when assessing the drug for treatment of metastatic tumors where cytotoxic chemotherapeutic drugs designed over 20 years ago had been used up to recently. Thus, nowadays in modern oncologic drug therapy innovative drugs are actually compared to placebo that costs extremely little.

Our analysis has demonstrated that, besides economic parameters, individuals making decisions must consider peculiarities of melanoma’s in-
cidence and malignancy as well as the absence of alternative innovative drugs for its treatment in the RF nowadays, and given the high vemurafenib effectiveness (in terms of both PFS and OS) they should make decisions on reimbursing the cost of vemurafenib from the budget of public health service taking into account the complex of factors.

Conclusions

1. The use of vemurafenib strategy for CM therapy in patients with BRAF V600 mutation demonstrated the best PFS parameter throughout the entire modelling horizon.
2. The use of vemurafenib in treatment of metastatic and inoperable CM in patients with BRAF V600 mutation is economically advisable taking into account the data on effectiveness (PFS).
3. The use of vemurafenib for treatment of disseminated CM in patients with BRAF V600 mutation is an absolutely innovative medical technology and currently does not have any alternative. BRAF diagnostics makes it possible to select therapy with maximally proved effectiveness for each patient. Therefore, vemurafenib may be included for inclusion in the reimbursement lists for treatment of disseminated melanoma patients with this mutation.

Study limitations

Conducted pharmacoeconomic analysis has the following peculiarities referring to the study limitation parameters. Foremost, data on effectiveness obtained in the settings of RCS differ from the settings of real practice and modeled conditions. Secondly, direct costs for care related to a certain nosology were calculated considering the standards of therapy registered in the RF, while description of patient population and effectiveness parameters were taken from the foreign studies.

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