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- **МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ АНАЛИЗА ЭФФЕКТИВНОСТИ МЕДИЦИНСКИХ ТЕХНОЛОГИЙ ПРИ ПРОВЕДЕНИИ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ**

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A PHARMACOECONOMIC ANALYSIS OF IBRUTINIB IN THE TREATMENT OF MANTLE CELL LYMPHOMA

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Summary:
Mantle cell lymphoma (MCL) accounts for approximately 2% to 10% of the total number of lymphatic system tumours, the incidence rate in Western Europe and Scandinavia is approximately 0,5/100 000 people. Most MCL cases are aggressive lymphomas, and overall survival is in the range of 3 to 5 years, while the disease is characterized by a short time to progression. The objective of this study was to determine the better treatment option between temsirolimus and ibrutinib in the treatment of MCL, in terms of pharmacoeconomic analysis, by means of comparative cost-effectiveness assessment. The cost-effectiveness results obtained in this temsirolimus versus ibrutinib comparative study demonstrated that ibrutinib therapy was associated with lower cost per effectiveness unit when life years gained and quality-adjusted life years were utilized as effectiveness criteria. Obtained budget impact analysis results revealed that ibrutinib therapy resulted in budget saving.

Key words: *effectiveness analysis, utility analysis, cost analysis, cost-effectiveness analysis, cost-utility analysis, budget impact analysis, mantle cell lymphoma, health technology assessment, ibrutinib, temsirolimus, pharmacoeconomics, clinical economic analysis.*

Background

Mantle cell lymphoma (MCL) is a B-cell tumour characterized by excessive expression of the cell cycle regulating protein cyclin D1, which is a result of the t(11;14)(q13;q32) translocation or variant cytogenetic disturbances. In rare cases, a typical clinical picture and gene expression profile are associated with no translocation and cyclin D1 hyperexpression, while there is a cyclin D2 or D3 hyperexpression [17]. MCL accounts for approximately 2% to 10% of the total number of lymphatic system tumours, and the incidence rate in Western Europe and Scandinavia is approximately 0,5/100 000 population. Elderly men are mostly affected (occurrence median, 70 - 75 years; the men to women ratio is 2 – 4 : 1) [16, 20].

It should be mentioned at the same time that the occurrence rates of MCL vary by geographical region from 2,5% to 9,0% of the total number of lymphatic system tumours. The prevalence percentages of MCL (of overall lymphoma prevalence) are 2,5% to 4,0% in the USA, 7% to 9% in Europe, and 3% to 5% in Japan. This disease predominantly affects men (70% to 74%) aged 60 to 70 years. However, this condition may also occur at an earlier age: there is a description of an MCL clinical case in a 18-year-old female patient [1]. Based on the US Caucasian incidence statistics (0,7 per 100 000 people) [13], one can conclude that approximately 1 000 become afflicted in the Russian Federation every year.

The majority of MCL cases are aggressive lymphomas, and overall survival is in the range of 3 to 5 years, while the disease is characterized by a short time to progression (the first relapse is usually chemotherapy-resistant) [8, 9, 14, 15].

Ibrutinib is a targeted non-chemotherapeutic drug with a mechanism of action involving inhibition of one of the tyrosine kinases participating in the transmission of signals from the membrane to the nucleus in B-lymphocytes. Ibrutinib is used as monotherapy for MCL, and thus requires comparative pharmacoeconomic assessment versus a product that has an equivalent mechanism of action and is also given as monotherapy, temsirolimus. This medicinal product has been included in the European guidelines for the treatment of relapsed / refractory MCL and has a similar therapeutic target, being an inhibitor of another kinase of the B-cell signaling pathway, mTOR [22].

The objective of the study is to determine the better treatment option between temsirolimus and ibrutinib in the treatment of MCL, in terms of pharmacoeconomic analysis, by means of comparative cost-effectiveness, safety, and quality of life assessments.

The following tasks had to be achieved to reach the formulated objective:

1. Collection and analysis of clinical practice data obtained for ibrutinib and temsirolimus in patients treated for MCL.
2. Selection of effectiveness criteria for ibrutinib and temsirolimus in patients treated for MCL.
3. Cost analysis for the therapies being compared in patients treated for MCL.
4. The following types of analysis within the pharmacoeconomic study: budget impact analysis, cost-effectiveness analysis, and cost-utility analysis.

Effectiveness analysis

Effectiveness criteria analysis is a stage of the cost-effectiveness analysis undertaken within the framework of the reported study. Effectiveness analysis aims to find effectiveness criteria satisfying the study goals and, consequently, to obtain data characterizing the technologies being analyzed in terms of the effectiveness criterion selected [3, 5, 6]. An important stage of pharmacoeconomic research is the choice of special criteria (endpoints) that permit assessment of the effectiveness of the treatment regimens being compared, which allows a conclusion on the value they have for clinical practice. Pharmacoeconomics-related effectiveness criteria for treatment approaches being analyzed may include direct clinical effects, mediated clinical effects, changes in health indicators in the group of the medical intervention, and change in health-related quality of life.

The information search performed in the course of this study yielded outcomes of the ibrutinib and temsirolimus therapies in the treatment of MCL that employed two effectiveness criteria, LYG (life years gained) and QALY (quality adjusted life years). These results are described in the publications of Hess G. et al. (2009) and Wang M. et al. (2013), in which the study of ibrutinib and temsirolimus in the treatment of MCL corresponded to the goals of the described study. No other studies were identified that had used QALY assessment of ibrutinib therapy as a pharmacological treatment for relapsed / refractory MCL.

It should also be underlined that these effectiveness criteria (in the case of QALY, the term “utility” is more suitable) are characterized, with regard to

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pharmacoeconomic research, by the highest degree of importance compared with direct and mediated clinical effects, and consequently are of the greatest interest. The effectiveness and utility choice results and the values of these parameters obtained for the MCL treatment regimens being compared and expressed per year are presented in Table 1.

Table 1. . Results of the effectiveness and utility analysis for ibrutinib and temsirolimus in the treatment of MCL (for a period of one year) [10, 18]

Effectiveness (utility) criterion	Ibrutinib	Temsirolimus
Life years gained (LYG)	0,84	0,75
Quality-adjusted life years (QALY)	0,68	0,59

As the above table demonstrates, ibrutinib therapy produces better results in the treatment of MCL, as compared with temsirolimus. This conclusion can be made based on either life years gained analysis or quality-adjusted life years assessment [10, 18].

Cost analysis

Pharmacoeconomic studies involve comparison of obtained treatment outcomes and diagnosis with their cost in the respective health care system. Therefore, the degree of completeness and correctness of costs taken into account produce a direct effect on pharmacoeconomic investigation results, sometimes to complete reversion. This is why cost analysis is one of the key elements of any pharmacoeconomic study [4].

Direct medical, direct non-medical, and indirect costs were taken into consideration within the framework of the described study. The study had a time frame of one year.

The cost calculation per mg of drug produced 34 rubles and 1 835 rubles for ibrutinib and temsirolimus, respectively. The cost of one-month treatment for ibrutinib was found to be 573 680 rubles. The calculation made for temsirolimus demonstrated that the budget sum spent was 1 101 064 rubles for the first month of treatment and 550 532 rubles for the following months. Besides, administration of temsirolimus (by intravenous drip-feed) requires additional spending, including that of hospital stay. For the time frame specified, this cost was found to be 110 054 rubles. On the other hand, this cost analysis parameter is not applicable for ibrutinib, because it is supplied in the pharmaceutical form of capsules.

Another component of cost analysis is the cost of hospitalization for patients with MCL necessitated by complications developing during treatment of the underlying condition. It was assumed in this study that development of adverse effects, such as neutropenia, anaemia, and grade 3 – 4 thrombocytopenia, leads to hospitalization of the patient. At this stage, costs were calculated based on the health care standards adopted in the Russian Federation. The probabilities of these adverse effects, as well as the subsequent hospitalization costs and the final values obtained, are presented in Table 2.

Table 2.. Probabilities of adverse effects associated with the ibrutinib and temsirolimus therapies in the treatment of MCL [10, 17] and costs of their treatment (for a period of one year)

Parameter	Ibrutinib	Temsirolimus
Probability of hospitalization for neutropenia, %	16	15
Probability of hospitalization for thrombocytopenia, %	11	59
Probability of hospitalization for anaemia, %	10	20
Cost of neutropenia treatment, rubles	19 588	18 363
Cost of thrombocytopenia treatment, rubles	9 509	51 002
Cost of anaemia treatment, rubles	14 654	29 308
Total cost per year, rubles	**43 751**	**98 673**

Using the obtained results, we found out that ibrutinib used in the treatment of MCL was more likely to be associated with neutropenia (16%) compared with temsirolimus (15%). As a result, the cost of hospitalization for these patients was also higher in the ibrutinib group, by more than 1 000 rubles per MCL patient. On the other hand, patients treated with temsirolimus more frequently develop severe thrombocytopenia, as compared with ibrutinib-treated patients, 59% and 11%, respectively. This results in a greater sum of budget money spent in temsirolimus-treated patients, as compared with ibrutinib 51 002 rubles and 9 509 rubles, respectively. Similarly, the temsirolimus-based MCL treatment regimen is characterized by higher probabilities of grade 3 – 4 anaemia and, consequently, higher expenditure associated with the treatment of anaemia, as compared with ibrutinib therapy.

The final cost analysis carried out at this stage demonstrated that ibrutinib therapy is characterized by less spending on the treatment of adverse effects in hospitalized MCL patients, as compared with temsirolimus therapy: 43 751 rubles and 98 673 rubles. The most likely explanation for this result is the considerable difference in the cost of thrombocytopenia treatment between the compared groups.

Aspects taken into consideration for the indirect cost analysis included the mortality rates obtained for the treatment regimens being compared, as well as loss of work capacity resulting from hospitalization necessitated by the adverse effects described above and the administration of temsirolimus that had to be done in an in-patient setting. The number of days a patient has to spend in a hospital to have the drug administered is the same as the number of temsirolimus doses. The number of days a patient has to spend in a hospital because of developing adverse effects can be found in the active Russian health care standards that we used. The death probabilities in the ibrutinib and temsirolimus groups were 0,07 and 0,5, respectively. We found out that ibrutinib therapy in the treatment of MCL results in lower indirect costs, as compared with temsirolimus therapy, due to lower mortality and lower probabilities of adverse effects in the ibrutinib group, as well as due to the pharmaceutical form that does not require an in-patient setting: 34 972 rubles and 232 787 rubles, respectively.

The final cost analysis parameter (Table 3) included, apart from the aforementioned parameters, the cost of treatment of other adverse effects (anaemia, allergic reactions, nausea, vomiting, neurotoxicity), which accounted for an insignificant proportion of the overall value.

Table 3. Cost analysis results

Costs	Ibrutinib	Temsirolimus
Direct costs, rubles	6 928 513	7 366 808
Indirect costs, rubles	34 972	232 787
TOTAL, rubles:	**6 963 485**	**7 599 595**

On the basis of the obtained results, we established that ibrutinib therapy in the treatment of patients with MCL is associated with a lower cost as compared with temsirolimus, which was true for both direct and indirect costs.

Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is used to assess the cost of an effectiveness unit of the respective health care technologies being compared [11, 12]. Therefore, this type of pharmacoeconomic analysis permits comparison of health care technologies not only on the basis of obtained final cost analysis values, but also using cost-effectiveness ratio calculation. Cost-utility analysis may be viewed as an example of cost-effectiveness analysis that utilizes QALY values instead of the effectiveness parameters.

The cost-effectiveness ratio is determined by means of the following equation:

$$CER = \frac{Cost}{Ef}, \text{where}$$

CER is the cost-effectiveness ratio;
Cost is the cost of the technology being evaluated (rubles);
Ef is the effectiveness of the technology being evaluated.

This type of pharmacoeconomic analysis allows to determine the degree to which the cost of the technology being evaluated corresponds to its effectiveness, as well as to choose the best pharmacoeconomic alternative using obtained results.

As mentioned above, life years gained (LYG) and quality-adjusted life years (QALY) were selected as effectiveness criteria. The results of the reported cost-effectiveness analysis are presented in Table 4.

Table 4. Results of the cost-effectiveness analysis of the ibrutinib and temsirolimus therapies in the treatment of patients with MCL (effectiveness criterion: LYG)

Parameter	Ibrutinib	Temsirolimus
Costs, rubles	6 963 485	7 599 595
LYG, years	0,84	0,75
Cost-effectiveness ratio value	8 289 863	10 132 794

A graphic representation of the cost-effectiveness analysis results obtained for the ibrutinib and temsirolimus therapies in the treatment of patients with MCL, using LYG as the effectiveness criterion, is included in the Figure 1.

The obtained results allowed us to conclude that ibrutinib therapy used in the treatment of patients with MCL is characterized by lower cost per effectiveness unit per life year gained, as compared with temsirolimus therapy. The ibrutinib-based treatment regimen produces better effectiveness results in terms of LYG, which, combined with the previous conclusion, means that this therapy can be viewed as the dominant one from the standpoint of pharmacoeconomic analysis.

In the further course of this analysis, we performed a cost-effectiveness (cost-utility) analysis for the ibrutinib and temsirolimus therapies in the treatment of MCL using QALY values as the effectiveness (utility) criterion. The results of this analysis can be found in Table 5.

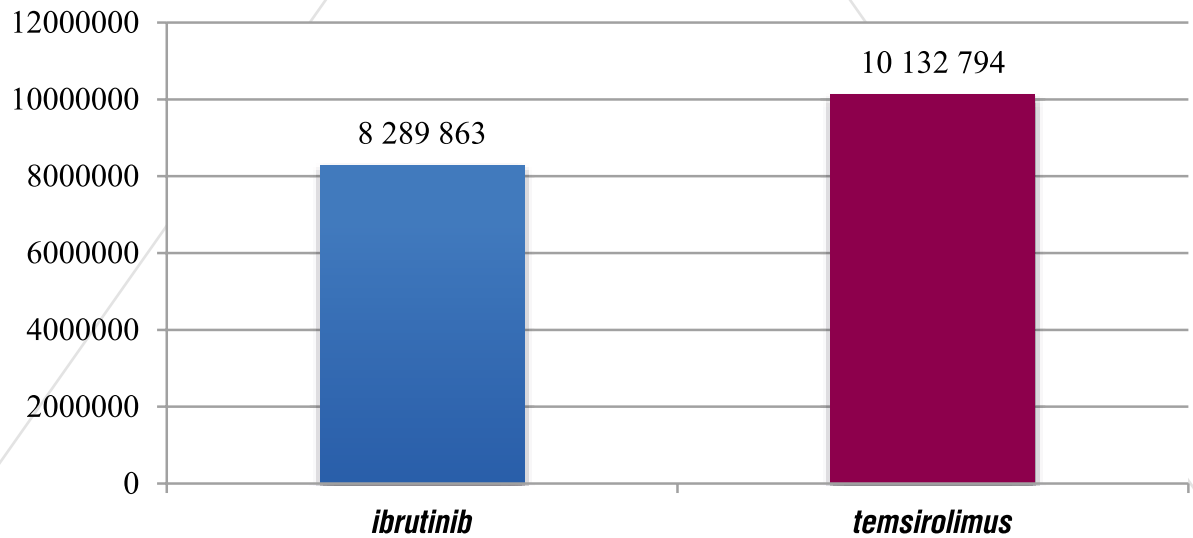
Table 5. Results of the cost-utility analysis of the ibrutinib and temsirolimus therapies in the treatment of patients with MCL (utility criterion: QALY)

Parameter	Ibrutinib	Temsirolimus
Costs, rubles	6 963 485	7 599 595
QALY	0,68	0,59
Cost-utility ratio	10 240 418	12 880 670

A graphic representation of the cost-utility analysis results obtained for the ibrutinib and temsirolimus therapies in the treatment of patients with MCL, using QALY as the utility criterion, is included in the Figure 2.

The obtained results allowed us to conclude that ibrutinib therapy used in the treatment of patients with MCL is characterized by lower cost per utility unit per QALY, as compared with temsirolimus therapy. The ibrutinib-based treatment regimen produces better utility results in terms of QALY, which, combined with the previous conclusion, means that this therapy can be viewed as the dominant one from the standpoint of pharmacoeconomic analysis.

Figure 1. The cost-effectiveness ratio values obtained with LYG as the effectiveness criterion



Budget impact analysis

Budget impact analysis involves assessment of all types of expenditure associated with the introduction of a new treatment regimen in relation to all types of expenditure associated with the already existing treatment option [2]. Costs are calculated according to the following equation:

$$BIA = Cost1 - Cost2$$, where

Cost1 is the total cost of the first treatment option (rubles);
Cost2 is the total cost of the second treatment option (rubles);
BIA (Budget Impact Analysis) is the result of the budget impact analysis (rubles).

As the presented results indicate, ibrutinib therapy is associated with budget saving, as compared with temsirolimus therapy, in the treatment of patients suffering from MCL. These results were obtained for one-year treatment of one patient. The sum of money saved was found to be 636 111 rubles.

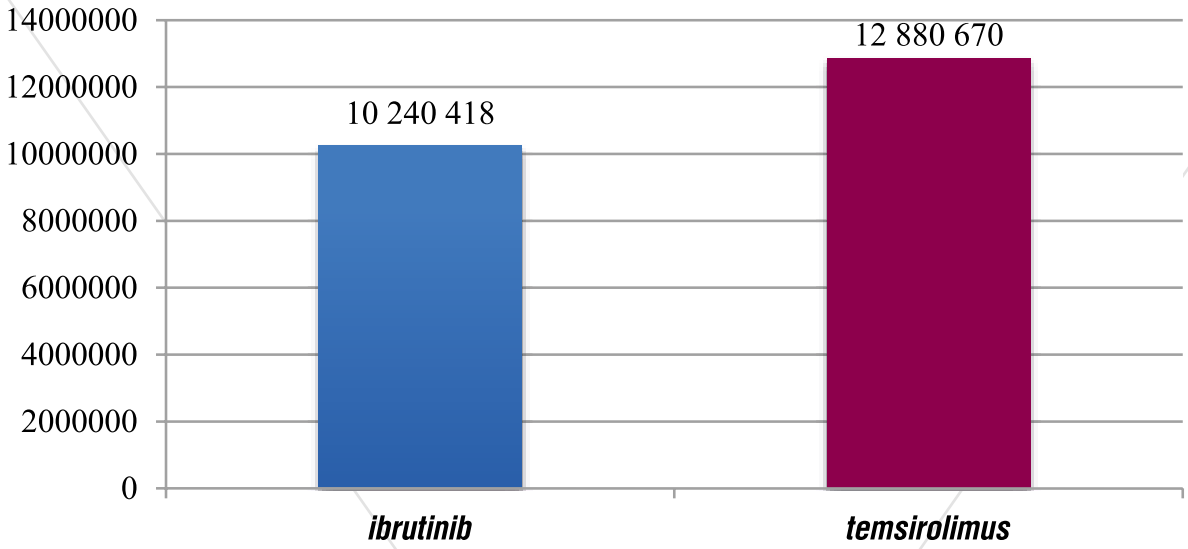
Results

1. The reported analysis yielded the following MCL treatment costs: the cost per year in the ibrutinib group was 6 963 485 rubles, whereas the cost per year in the temsirolimus group was 7 599 595 rubles.
2. The presented cost-effectiveness analysis in patients treated for MCL demonstrated that the cost-effectiveness ratio values for the therapies being compared were as follows when LYG were utilized as the effectiveness criterion: 8 289 863 in the ibrutinib therapy group and 10 132 794 in the temsirolimus therapy group.
3. The presented cost-utility analysis in patients treated for MCL demonstrated that the cost-utility ratio values for the therapies being compared were as follows when QALY were utilized as the utility criterion: 10 240 418 in the ibrutinib therapy group and 12 880 670 in the temsirolimus therapy group.
4. The presented budget impact analysis demonstrated that the budget saving in the ibrutinib therapy group was 636 111 rubles, as compared with temsirolimus therapy administered for one patient with MCL for a period of one year.

Conclusions

1. According to the cost-effectiveness analysis results obtained in this temsirolimus versus ibrutinib comparative study demonstrated that ibrutinib therapy was the dominant treatment option, being associated with lower cost per effectiveness unit when life years gained were utilized as the effectiveness criterion.
2. According to the cost-utility analysis results obtained in this temsirolimus versus ibrutinib comparative study demonstrated that ibrutinib therapy was the dominant treatment option, being associated with lower cost per utility unit when quality-adjusted life years were utilized as the utility criterion.
3. The budget impact analysis results obtained in this temsirolimus versus ibrutinib comparative study demonstrated that ibrutinib therapy resulted in budget saving.

Figure 2. The cost-utility ratio values obtained with QALY as the utility criterion



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