Cost-effectiveness analysis of treatment of patients with colorectal cancer with FOLFOX4 and XELOX regimens

Jakub Płaczek¹, Małgorzata Feldheim¹, Bogdan Żurawski², Jerzy Krysiński¹

Introduction. A comparison of the cost of an alternative treatment regimen is the basis of the rationalisation and cost effectiveness of cancer therapy. The aim of the study was to compare two alternative treatment regimens for colorectal cancer in the III and IV advancement stage (FOLFOX4 and XELOX).

Material and methods. A cost-effectiveness analysis was carried out on the basis of data collected retrospectively; considering 100 patients treated at the Oncology Centre in Bydgoszcz. A measure of the effectiveness of the therapy was the total survival time of patients. Data on the average survival time of patients has been obtained from clinical trials.

Results. The total cost of treatment per patient was 33 879.13 PLN in FOLFOX4. In XELOX the average cost per patient was 20 023.96 PLN. The endpoint, defined as the average survival time of patients treated with the FOLFOX4 scheme amounted to 27.25 months. In the case of the use of the XELOX regimen, the average survival time was 23.65 months. Incremental costs for additional units as a result of using the more expensive treatment regimen were estimated as 46 183.47 PLN.

Conclusions. The comparison of the two treatment regimens for colorectal cancer in stage III and IV, which were used in the Oncology Centre in Bydgoszcz, showed that the more expensive but more efficient treatment was FOLFOX4.

Key words: FOLFOX4, XELOX, cost-effectiveness analysis, colorectal cancer

Introduction

Colorectal cancer belongs to a group of cancers with increasing frequency of incidence in Poland and in other highly developed countries. Epidemiological data indicate an increasing incidence and mortality with age, both among men and women [1].

The basic method of treatment of colorectal cancer, especially in its early stages is surgical intervention. This concerns rectal cancer in particular, as the efficiency of other methods has not been proven [2]. The resection scope depends on the tumour location, vascularisation of the affected area and the advancement stage [3, 4].

In spite of the domination of surgery in the treatment of colorectal cancer, the application of adjuvant chemotherapy (regimens based on 5-fluorouracil, calcium folinate or disodium folinate, capecitabine and oxaliplatin) has a significant influence on increasing the 5-year survival period and future disease-free survival. Pharmacological treatment of the cancer may also be a neo-adjuvant (alone or in combination with radiotherapy) or palliative treatment. Drug regimens may also contain irinotecan, bevacizumab and cetuximab [1].

In recent years in foreign centres, some pharmacokinetic analyses have been performed comparing various drug regimens in the treatment of colorectal cancers [5–8]. The results of these analyses point to the fact that the most cost-effective regimen is XELOX. It must be stressed, however, that with regards to the varied financial situation of the health service and diversified drug prices, as well as differences in the approach of the public payer, it is difficult to compare the results of the pharmacokinetic studies performed abroad with the situation in Poland.

¹Faculty of Pharmacy, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland
²Prof. Franciszek Łukaszczyk Oncology Centre in Bydgoszcz, Poland
The objective of this paper is to perform a retrospective comparison of the costs and effects of chemotherapy based on the FOLFOX4 and XELOX regimens, applied in colorectal cancer patients with advancement stage III and IV at the F. Łukaszczyk Oncology Centre in Bydgoszcz.

The analysis allowed to determine how the cost was distributed in the applied treatment regimen and to show which regimen proposes a better method of treatment in the aspect of costs and benefits.

Materials and methods
The retrospective analysis comprised the documents of 100 patients treated in the outpatient clinic and hospital of the F. Łukaszczyk Oncology Centre in Bydgoszcz in 2008–2011. The inclusion criteria were: treatment at the Oncology Centre in Bydgoszcz, histopathologically confirmed diagnosis, advancement stage III and IV, performed surgery and the application of the first line of chemotherapy with the FOLFOX4 regimen (60 patients) or XELOX regimen (40 patients). The data characterising the patients are presented in Table I.

The study comprised the analysis of the cost efficiency carried out in accordance with the guidelines of the Good Pharmacoeconomic Practice. The criterion for the evaluation of the treatment efficiency was the average survival period. The study was performed from the perspective of a payer. The evaluation of the drug prices is based on the data from November 2014.

In both studied treatment regimens, the following types of treatment costs were taken into consideration: hospitalisation, outpatient treatment, diagnostic procedures, costs of cytostatic drugs and their preparation, the costs of other medication including the alleviation of adverse events and haematological complications, radiotherapy and consultation costs.

Results
Hospitalisation costs
The hotel costs, duration of hospital stays and the costs of one-day hospitalisation are displayed in Table II. This analysis takes into consideration the costs of the hospitalisation resulting from the treatment of the primary disease, diagnostic tests, adverse effects of the medication and the deterioration of the patients’ general condition. Treatment on the outpatient basis was carried out in the case of patients in good general condition with a good tolerance of chemotherapy or in the case of lack of vacancies in the hospital ward.

The total hospital stay in patients treated with the FOLFOX4 regimen was 2201 days, which gives an average amount of 36.7 days per patient with an average cost of 20 439 PLN. The aggregate duration of the hospital stay for those patients treated with the XELOX regimen was 443 days, which gives 11.08 days per patient on average with the mean cost of 6186.7 PLN.

The one-day hospitalisation period in the FOLFOX4 group was 71 days in total with the mean value per patient being 1.18 days and the average costs of 553.8 PLN; in the XELOX group — it was 265 and 6.63 days respectively with the average cost being 3219.7 PLN. The costs of outpatient hospitalisation were calculated according to the rate stipulated in the contracts with the National Health Fund, that is 468 PLN per patient. The cost difference in the case of one-day hospitalisation between the analysed treatment regimens is significant and amounts to 95 562 PLN in total and, calculated per patient, is 2665.95 PLN. The higher cost of one-day hospitalisation is generated by the XELOX regimen, which is the outcome of the outpatient character of this programme.

The costs of diagnostic tests
The costs of diagnostic tests were divided into two groups: laboratory tests and imaging tests (Tab. II). Out of the laboratory tests, the most frequent ones comprised the levels of the liver enzymes — creatinine and urea. Also CBC and CBC with differentials as well as the neutrophil absolute count were performed.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Duration of stay (days)</th>
<th>Cost (PLN)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (H)</td>
<td>Average (A)</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>2201</td>
<td>71</td>
</tr>
<tr>
<td>XELOX</td>
<td>443</td>
<td>265</td>
</tr>
</tbody>
</table>
The most frequent imaging tests in both groups of patients comprised: an abdominal ultrasound, P-A and lateral chest X-ray and histopathology.

Higher cost of diagnostic procedures is generated by the FOLFOX4 regimen. The difference between the analysed groups was 70,624.6 PLN, and, per one patient the difference amounted to 212 PLN. The higher cost of diagnostic procedures on the FOLFOX4 group was the result of the more frequent performance of tests such as CBC, CBC with differential, and costly examinations such as a colonoscopy or plain and contrast abdominal CT.

**Medication costs**

The constituents of the pharmacotherapy were the costs of the first line chemotherapy, the costs of consecutive lines of chemotherapy in the case of the failure of the first line, the costs of cytostatic drug preparation, the costs of gastroprotective medication (most frequently: ondansetron, metoclopramide and ornithine), infusion liquids, analgesic and psychotropic drugs as well as other medication.

Patients treated with the FOLFOX4 regimen, on the first day of therapy received oxaliplatin in a dose of 85 mg/m², calcium folinate in a dose of 200 mg/m² on the first and second day in 2-hour infusions and fluorouracil in a dose of 400 mg/m² in a bolus on day 1 and then 600 mg/m² in a 22-hour infusion on days 1 and 2. The treatment lasted 6 months in 12 cycles every 2 weeks.

In the XELOX group, capecitabine was administered in a dose of 1000 mg/m², twice per day for 14 days and oxaliplatin in a dose of 130 mg/m² i.v. on day 1. The cycles were repeated every 3 weeks. The treatment lasted 6 months.

The symptoms of significant drug toxicity, lack of response to cytostatic treatment as well as disease progression or relapse were quite frequently observed in these patients. In such cases, a second line of chemotherapy, and, in the case of the lack of improvement, some other cytostatic drugs were administered.

In both patient groups, the most frequently administered medication in consecutive lines of chemotherapy were the CLF1 regimen (irinotecan, fluorouracil and calcium folinate) and the LF4 regimen (fluorouracil i.v. infusion and fluorouracil i.v. bolus in combination with calcium folinate). Table III presents the costs of pharmacotherapy in the analysed groups.

**Cytostatic drugs have the largest share in total medications costs.**

**Costs of treatment for haematological complications**

One of the most frequent haematological complications in chemotherapy is neutropenia. Therefore, filgastrim was often applied in the FOLFOX4 group. In the XELOX group, incidences of severe anaemia were observed. Then the patients received transfusions of PRBC.

The total cost of treatment for haematological complications was calculated by means of summing up the cost of the medication used for the treatment of neutropenia and anaemia. This cost is almost twice as high as calculated per patient in the XELOX group. The difference results mostly from the application of PRBC.

**Radiotherapy costs**

In both patient groups, palliative and preoperative (as a constituent of radical treatment) radiotherapy was used. In FOLFOX4, radiotherapy was used in 13 patients, and in 6 cases it was preoperative radiotherapy whilst in 6 other patients — palliative. One patient received both types of irradiation.

Radiotherapy in the XELOX group was applied jointly in 3 cases, and in 2 patients it was a radical preoperative radiotherapy and in 1 case, radiotherapy had a palliative character.

The total cost of radiotherapy in the FOLFOX4 group amounted to 82,368 PLN, which makes 1372.8 PLN per

<table>
<thead>
<tr>
<th>Source of the cost</th>
<th>FOLFOX4</th>
<th>XELOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>448,201.5</td>
<td>256,401.3</td>
</tr>
<tr>
<td>Analgesic drugs</td>
<td>1419.87</td>
<td>29.01</td>
</tr>
<tr>
<td>Drugs affecting Gl tract</td>
<td>154.18</td>
<td>0.03</td>
</tr>
<tr>
<td>Drugs affecting circulatory</td>
<td>721.01</td>
<td>0.14</td>
</tr>
<tr>
<td>Psychotropic drugs</td>
<td>69.60</td>
<td>0.013</td>
</tr>
<tr>
<td>Other drugs</td>
<td>47.58</td>
<td>0.009</td>
</tr>
<tr>
<td>Infusion fluids</td>
<td>465.26</td>
<td>430.45</td>
</tr>
<tr>
<td>Total</td>
<td>451,079</td>
<td>258,575.5</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Source of the cost</th>
<th>Cost (PLN)</th>
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<tbody>
<tr>
<td>FOLFOX4</td>
<td>XELOX</td>
</tr>
<tr>
<td>Total cost</td>
<td>Average cost per 1 patient</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>448,201.5</td>
</tr>
<tr>
<td>Analgesic drugs</td>
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<tr>
<td>Total</td>
<td>451,079</td>
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</tbody>
</table>
patient. In the XELOX group, in turn, the average cost of irradiation per patient was 388.2 PLN.

The cost of medical consultations
The patients from the FOLFOX4 group had more frequent consultations: in their case, the total number of consultations is 680 and, calculated per one person: 11.33, whilst in the XELOX group, these figures are 386 and 9.65 respectively. In both groups, the oncological type of consultation was dominating.

The total cost of medical consultation in the FOLFOX4 group was 52 810.9 PLN and calculated as per patient amounted to 880.18 PLN. The cost of medical consultations in the XELOX group is lower, totalling 29 195.6 PLN, and, in calculation per patient is 729.89 PLN. The higher costs of medical consultations are the result of a higher frequency of visits to the oncology and chemotherapy clinics in connection with the administration of cytostatic drugs.

Total costs
Table IV presents the total treatment costs concerning the patients with colorectal cancer depending on the applied treatment protocol.

The total treatment costs of one patient treated with the FOLFOX4 protocol amounts to 33 879.13 PLN. In the case of the XELOX protocol, this cost is lower, totalling 20 023.96 PLN. In the FOLFOX4 group, the main share in the total cost belongs to hospitalisation costs (60.33%), followed by the cost of medication (22.19%) and diagnostic procedures (9.17%). In the XELOX group, the dominating cost group is made up of the costs of medication (32.3% of the total cost). A significant cost is generated by hospitalisation, outpatient treatment and diagnostic procedures (30.89%, 16.08% and 14.46% of the total costs respectively). Similarly to the FOLFOX4 protocol, the last share in the total costs is made up by the costs of the treatment of haematological complications.

Treatments costs and effectiveness
The criterion of the evaluation of the efficacy of the two alternative chemotherapy regimens (FOLFOX4, XELOX), was the average survival period of the patients. As the follow-up periods were relatively short, the information concerning the patients’ deaths could not be obtained. The evaluation of the therapeutic effects comprised the data from the published randomised clinical studies [5–10]. The results concerning the average survival period for patients with advancement stage III and IV colorectal cancer are collected in Table V.

A longer survival period was observed for patients treated according to the FOLFOX4 protocol (27.25 months). In the XELOX group, the median survival period was 23.65 months.

The published results of the clinical studies conclude that a more effective method of treatment of advancement stage III and IV colorectal cancer is chemotherapy with the FOLFOX4 regimen.

Incremental costs
In the analysis that was carried out, higher efficacy of the FOLFOX4 regimen in the treatment of advancement stage III and IV colorectal cancer was proven. The choice

Table IV. Total cost in the studied groups

<table>
<thead>
<tr>
<th>Source</th>
<th>FOLFOX4</th>
<th>XELOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost</td>
<td>2 032 748</td>
<td>800 958.3</td>
</tr>
<tr>
<td>Average cost per 1 patient</td>
<td>33 879.13</td>
<td>20 023.96</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Cost (PLN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation</td>
<td>1 226 368.00</td>
</tr>
<tr>
<td>Outpatient clinic</td>
<td>33 228.0</td>
</tr>
<tr>
<td>Diagnostic procedures</td>
<td>1 864 33.80</td>
</tr>
<tr>
<td>Drugs</td>
<td>451 079</td>
</tr>
<tr>
<td>Haematological complications</td>
<td>460.08</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>82 368</td>
</tr>
<tr>
<td>Medical consultations</td>
<td>52 810.9</td>
</tr>
</tbody>
</table>

Mean value

Table V. Average survival period for the patients with III and IV cancer advancement stage obtained from clinical studies

<table>
<thead>
<tr>
<th>Clinical study</th>
<th>Average survival period (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFOX4</td>
</tr>
<tr>
<td>[6]</td>
<td>40.2</td>
</tr>
<tr>
<td>[7]</td>
<td>17.7</td>
</tr>
<tr>
<td>[8]</td>
<td>19.7</td>
</tr>
<tr>
<td>[9]</td>
<td>31.5</td>
</tr>
<tr>
<td>[10]</td>
<td>–</td>
</tr>
<tr>
<td>Mean value</td>
<td>27.25</td>
</tr>
</tbody>
</table>
of the treatment protocol may, however, be decided only upon the performance of an incremental analysis. The objective of the incremental analysis is to determine the additional costs, connected with the introduction of the new programme and its comparison with the additional result obtained thanks to the execution of the new programme. The result of the analysis is presented in the form of an incremental cost-effectiveness ratio (ICER), defining the cost of obtaining any unit of result once the old programme is replaced by a new one or determining the savings from the deterioration of the result.

$$ICER = \frac{\text{the cost difference between the compared methods of treatment}}{\text{the results difference between the compared methods of treatment}}$$

In the analysed case, the ICER ratio amounts to the following:

$$IWEK = \frac{33 879.13 - 20 023.96 (PLN) / 2.27 - 1.97 (years)}{13 855.04 / 03 / 46 183.47 per year of life} = 13 855.04 / 03 = 46 183.47 PLN$$

An additional year of life in the case of patients with advancement stage III or IV colorectal cancer with the application of the longer and more efficient chemotherapy regimen "costs" the payer 46 183.47 PLN respectively.

**Sensitivity analysis**

In order to evaluate the influence of the change of the key parameters on the final outcome of the analysis, a one-way sensitivity analysis was performed. All the constituents of the direct medical costs were analysed in the scope ± 10% of the core value.

The influence of the change of the key parameters on the final result of the analysis depends on the share of the specific constituents of the cost in the mean cost per patient. Changes in the hospitalisation costs have the largest effect on the change of the incremental cost. The parameters whose change will significantly affect the total cost comprise also the costs of the outpatient visits and the costs of medication. The changes of the remaining costs do not have any significant effect on the final results of the analysis.

**Discussion**

As far as the frequency of incidence is concerned, colorectal cancer occupies a leading position in GI tract tumours. In recent years, some improvement of the efficiency of treatment of colorectal cancer has been observed in Poland (the rate of 5-year survival is 46% according to the EUROCare-4 study). However, in comparison with the countries of Western Europe and the United States of America (5-year survival rate — 56.2% and 65.5% respectively) these results are still unsatisfactory. The poor treatment results are affected by the late diagnosis of the cancer. In about 70% of patients, this cancer is diagnosed in the advanced stage, which has a bad prognosis (stage III — about 40%, stage IV — about 30%) [15].

The limited budget of the healthcare system brings about the necessity of choosing between treatment protocols with varied efficacy and costs. This choice is assisted by pharmacoeconomic analyses which determine the efficacy and cost-effectiveness of alternative treatment programmes, facilitating rational therapeutic decisions [16]. At the Oncology Centre in Bydgoszcz, one of the most frequently used treatment programmes has been the FOLFOX4 protocol. At the end of 2008, a new programme, XELOX, was introduced.

In the analysis which was carried out, it was shown that FOLFOX4 was the more effective and, at the same time, more expensive protocol of systemic treatment of colorectal cancer. The average cost of treatment of one patient at stage III or IV amounts to 33 879.13 PLN with an average survival rate of 2.27 years. In the case of the XELOX protocol, average treatment costs for one patient is 20 023.96 PLN with the mean survival period is 1.97 years. The efficacy of treatment was determined on the basis of the data from clinical studies.

In the XELOX group, the largest share in the total costs of the treatment of colorectal cancer in advancement stage III and IV at the Oncology Centre in Bydgoszcz was the cost of medication (32.3%). In the FOLFOX4 group, the costs of medication make up 22.19% of the total costs. In both analysed groups, the largest cost of pharmacotherapy is generated by the cytostatics drugs: in the XELOX group, they make up 99.16%, whilst in the FOLFOX4 group — it is 99.4% of the total cost of medication. The second largest constituent of the total costs in the XELOX group are the costs related to the hospitalisation of the patients (30.89%). In the FOLFOX4 protocol, hospitalisation is the dominating element in the costs (60.33%). The hospitalisation period of the patients in the studied groups differs significantly and is almost four times longer in the FOLFOX4 protocol. The administration of chemotherapy in the FOLFOX4 protocol has always been related to almost 3 days of hospital stay. In the XELOX protocol, the patients receive cytostatic drugs in a one-day hospitalisation. In an outpatient clinic, the patients are given oxaliplatin in the form of a 2-hour infusion and oral capecitabine. Hence the cost of the one-day hospitalisation in the XELOX group makes up 13.08% of the total costs and in the FOLFOX4 only 1.59% of the total cost of hospitalisation.

Diagnostic procedures have quite a large share in the total costs of the treatment costs (in XELOX — 14.46%, and in FOLFOX4 — 9.17%).

The bibliography presents a few pharmacoeconomic studies comparing FOLFOX4 and XELOX. In a Japanese study carried out by Shiroiwa et al. the costs and efficiency of the treatment of the first and second line of therapy of advanced colorectal cancer in FOLFOX4 and XELOX regimens were compared. The result of the therapy was defined as the
The objective of this work was to compare the costs of chemotherapy in FOLFOX4 and XELOX protocols applied in the Oncology Centre in Bydgoszcz. The analysis has shown that the treatment with the FOLFOX4 protocol is more expensive and more efficacious. It allows for the prolongation of the mean survival period in stage III and IV of colorectal cancer by 3.6 months. Incremental costs have been calculated in order to establish the cost of an additional year of life of a patient, with the application of the more expensive and more efficacious treatment protocol. This cost totalled 46 183.47 PLN for each year of life gained. From the point of view of the Agency for Health Technology Assessment and Tariff System (AOTMiT) the treatment is cost-effective because this amount fits between GDP indicators 1 and 3 per capita. A dominating constituent of the total cost in the XELOX group is the cost of medication. The FOLFOX4 protocol generates higher costs of hospitalisation and radiotherapy. The sensitivity analysis showed that the costs of hospitalisation, outpatient care and medication have the highest influence on the change of the final outcome.

It must be stressed that the application of chemotherapy based on oral capecitabine is undoubtedly related to increased comfort of treatment and a better quality of life. The therapy tolerance is good and the oral form of the drug is accepted by patients. The mental and physical comfort of the patients improves. They are able to lead a normal life. Sometimes it is also possible to continue one’s professional life. Treatment with the XELOX protocol allows for lowering the costs of hospitalisation mainly by means of shortening the period of hospital stay in comparison with the FOLFOX4 protocol. From the patient’s point of view, quality of life plays the most important role [17]. It must be pointed out that for capecitabine, the period of patent protection has expired and there are less expensive generic products on the Polish market. Thus, treatment with the XELOX protocol has become more cost effective from an economic point of view, depending on the patient’s condition and the advancement stage of the disease. The main factor which affects the choice of specific treatment strategy is its efficacy. The toxicity profile and the quality of life are of secondary importance. Therefore, the FOLFOX4 chemotherapy protocol remains the standard of first line treatment in colorectal cancer in advancement stage III and IV.

Conclusions

1. From the two treatment protocols of colorectal cancer in advancement stage III and IV, compared above and used in the Oncology Centre in Bydgoszcz, the FOLFOX4 regimen is both more expensive and more efficient.

2. The majority of the total costs of treatment is made up by the costs related to the hospitalisation of patients (the FOLFOX4 group) and the costs of medication (the XELOX group).
3. The incremental cost of gaining another year of life with the application of the FOLFOX4 protocol, as calculated per one patient is 46 183.47 PLN.

Conflict of interest: none declared

Jakub Płaczek, MSc
Faculty of Pharmacy of Medical College at the Nicolaus Copernicus University
Jurasza 2, 85–089 Bydgoszcz, Poland
e-mail: jakub.placzek@cm.umk.pl

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