

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

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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.

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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.

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Table I. Patients' characteristics

Treatment protocol	FOLFOX4	XELOX
The number of patients in advancement stage III	33	23
The number of patients in advancement stage IV	27	17
Mean age of the patients	60.43	60.88
Men	30	24
Women	30	16

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 determinate 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 II. Hospitalisation (H) and outpatient (A) duration and costs

Protocol	Duration of stay (days)				Cost (PLN)			
	Total		Average		Total		Average	
	H	A	H	A	H	A	H	A
FOLFOX4	2201	71	36.68	1.18	1 226 368	33 228	20 439.47	553.8
XELOX	443	265	11.08	6.63	247 468	128 790	6186.7	3219.75

Table III. The cost of medication in the studied groups

Source of the cost	Cost (PLN)					
	FOLFOX4			XELOX		
	Total cost	Average cost per 1 patient	%	Total cost	Average cost per 1 patient	%
Chemotherapy	448 201.5	7470.05	99.4	256 401.3	6410.03	99.16
Analgesic drugs	1419.87	23.66	0.27	1160.45	29.01	0.45
Drugs affecting GI tract	154.18	2.57	0.03	28.77	0.72	0.006
Drugs affecting circulatory	721.01	12.02	0.14	468.59	11.71	0.11
Psychotropic drugs	69.60	1.16	0.013	35.09	0.88	0.008
Other drugs	47.58	0.79	0.009	50.86	1.27	0.011
Infusion fluids	465.26	7.75	0.09	430.45	10.76	0.1
Total	451 079	7517.98	100	258 575.5	6464.38	100

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 *p.o.* 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 in *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, filgrastim was often applied in the FOLFOX4 group. In the XELOX group, incidences of severe anaemia was 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 IV. Total cost in the studied groups

Source	Cost (PLN)					
	FOLFOX4			XELOX		
	Total cost	Average cost per 1 patient	%	Total cost	Average cost per 1 patient	%
Hospitalisation	1 226 368.00	20 439.47	60.33	2 474 68.00	6186.70	30.89
Outpatient clinic	33 228.0	553.8	1.64	128790	3219.75	16.08
Diagnostic procedures	1 864 33.80	3107.23	9.17	115 809.20	2895.23	14.46
Drugs	451 079	7517.98	22.19	258 575.5	6464.38	32.3
Haematological complications	460.08	7.67	0.02	528	13.22	0.06
Radiotherapy	82 368	1372.8	4.05	20 592	388.2	2.57
Medical consultations	52 810.9	880.18	2.6	29 195.6	729.89	3.6
Total	2 032 748	33 879.13	100	800 958.3	20 023.96	100

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

Clinical study	Average survival period (months)	
	FOLFOX4	XELOX
[6]	40.2	37.8
[7]	17.7	18.8
[8]	19.7	–
[9]	31.5	–
[10]	–	19.9
[11]	–	18.1
Mean value	27.25	23.65

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.

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

In the analysed case, the ICER ratio amounts to the following: $\text{IWEK} = 33\,879.13 - 20\,023.96 \text{ (PLN)} / 2.27 - 1.97 \text{ (years)} = 13\,855.04 / 03 = 46\,183.47$ per year of life

An additional year of life in the case of patients with advancement stage III and 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 $\pm 10\%$ 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 EURO-CARE-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 cytostatic 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 Shirowa 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

number of days without progression corrected with quality (QAPFSD). The study took into consideration only the direct medical costs. The analysis has shown that a dominating chemotherapy programme in the first and second line of treatment is XELOX. This protocol has turned out to be more efficient and cost-effective in comparison with FOLFOX4 [5].

A study comparing the costs of treatment of advanced colorectal cancer with the FOLFOX4 and XELOX protocol was carried out in China. The study was focused on the analysis of cost minimisation, with the assumption of comparable efficacy of both programmes. The study was carried out retrospectively on the basis of the medical history of the patients treated in two Hongkong hospitals. The direct medical and non-medical costs were considered. The analysis has shown that treatment with the XELOX protocol is more cost-effective [6].

The analysis of the cost minimisation in the treatment of patients in stage III of colorectal cancer was carried out in Italy (Aitini et al.). This was a retrospective study concerning patients in whom a radical procedure was performed and then adjuvant chemotherapy according to FOLFOX4 or XELOX protocols was implemented. The study has shown that the adjuvant treatment with the XELOX protocol allows for a decrease in the therapy cost by about 30% in comparison with the FOLFOX4 regimen. The largest share in the total treatment costs was made up by the costs related to the hospitalisation and implementation of the chemotherapy port (the FOLFOX4 group) or the medication costs (the XELOX group). It must be observed that the higher cost of chemotherapy based on the use of capecitabine is compensated by the savings resulting from the shorter hospitalisation period and the oral administration of the drug [7].

Some analogous results were obtained in the analysis of the cost minimisation carried out by Ruiz et al. They compared three treatment protocols used in patients with colorectal cancer, advancement stage III: FOLFOX4, XELOX and FLOX. The study has shown that the smallest cost of treatment was generated by the FLOX protocol, whilst the highest by FOLFOX4 [8].

The above studies have shown that XELOX is the least expensive alternative in the treatment of colorectal cancer in advancement stage III and IV. The authors also agree that the share of chemotherapy and hospitalisation in the total treatment cost is quite high. With regards to the high purchasing cost of capecitabine, XELOX is the more expensive chemotherapy protocol. This protocol, however, generates lower total costs of therapy in comparison with FOLFOX4, on account of the shorter hospitalisation period and the smaller use of hospital resources by the patients. An analogous cost distribution was obtained in this study.

It stems from the published data that the FOLFOX4 protocol is more effective than the XELOX protocol in the treatment of stage III and IV colorectal cancer.

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).

- 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

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References

- Krzakowski M, Herman K, Jassem J et al. *Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych*. Gdańsk: Via Medica, 2009.
- Jeziorski A, Towpik E, Szawłowski A et al. *Chirurgia onkologiczna*, tom IV. Warszawa: PZWL, 2009.
- Potemski P. Epidemiologia, badania przesiewowe i klasyfikacja zaawansowania klinicznego raka jelita grubego. *Onkol Prakt Klin* 2010; 6: 283–289.
- Olędzki J. Chirurgiczne leczenie nowotworów jelita grubego. *Współcz Onkol* 2006;10: 137–138.
- Diao C, Cheng RC, Zhang JM et al. Clinical observation of XELOX (Capecitabine puls Oxaliplatin): an adjuvant chemotherapy regimen used in stage III colorectal cancer. *Zhonghua Zhong Liu Za Zhi* 2008; 30: 147–150.
- Cassidy S, Clarke E, Diaz-Rubio E et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. *Br J Cancer* 2011; 105: 58–64.
- Douillard JY, Siena S, Cassidy J et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010; 28: 4697–4705.
- Baba H, Hayashi N, Emi Y et al. A multicenter phase II clinical study of oxaliplatin, folinic acid, and 5-fluorouracil combination chemotherapy as first-line treatment for advanced colorectal cancer: a Japanese experience. *Surg Today* 2011; 41: 1610–1616.
- Ducreux M, Bennouna J, Hebbar M et al. Efficacy and safety findings from a randomized phase III study of Capecitabine plus Oxaliplatin vs. infusional 5-FU/LV plus Oxaliplatin (FOLFOX6). *J Clin Oncol* 2007; 25: 4029 ASCO Annual Meeting Proceedings abstract.
- Diaz-Rubio E, Tabernero J, Gomez-Espna A et al. Phase III study of capecitabine plus oxaliplatin versus continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer. *J Clin Oncol* 2007; 25: 4224–4230.
- Krzemienicki K, Wysocki P, Protemski P. Skuteczna chemioterapia w warunkach domowych. Sesja satelitarna w ramach XIII Kongresu Naukowo-Edukacyjnego Polskiego Towarzystwa Onkologii Klinicznej 2010.
- Herman K, Sokołowski A, Kalita A, Ekonomiczne aspekty zwalczania raka. *Nowotwory J Oncol* 1997; 47: 785–796.
- Shiroiwa T, Fukusa T, Tsutani K. Cost-effectiveness analysis of XELOX for metastatic colorectal cancer based on the NO16966 and NO16967 trials. *Br J Cancer* 2009; 101: 12–18.
- Tse CV, Ng TW, Lee V et al. Cost-analysis of XELOX and FOLFOX4 for treatment of colorectal cancer to assist decision-making on reimbursement. *BMC Cancer* 2011; 11: 288–292.
- Aitini E, Rossi A, Morselli P et al. Economic comparison of capecitabine + oxaliplatin and 5-fluorouracil + oxaliplatin in the adjuvant treatment of colon cancer. *Cancer Manag Res* 2012; 4: 99–103.
- Ruiz C, Melchor J, Ruiz E et al. Costs of adjuvant chemotherapy with oxaliplatin in stage III colon cancer — comparing the three schemes standards: FOLFOX-4, FLOX and XELOX, INCAN, (http://www.ecco-org.eu/ecco_content/ECCO16_AbstractBook/index.html#/287/zoomed).
- Załuski J, Szoszkiewicz R. Xeloda w leczeniu rozlanego raka jelita grubego — doniesienie wstępne. *Współcz Onkol* 2003; 6: 428–433.