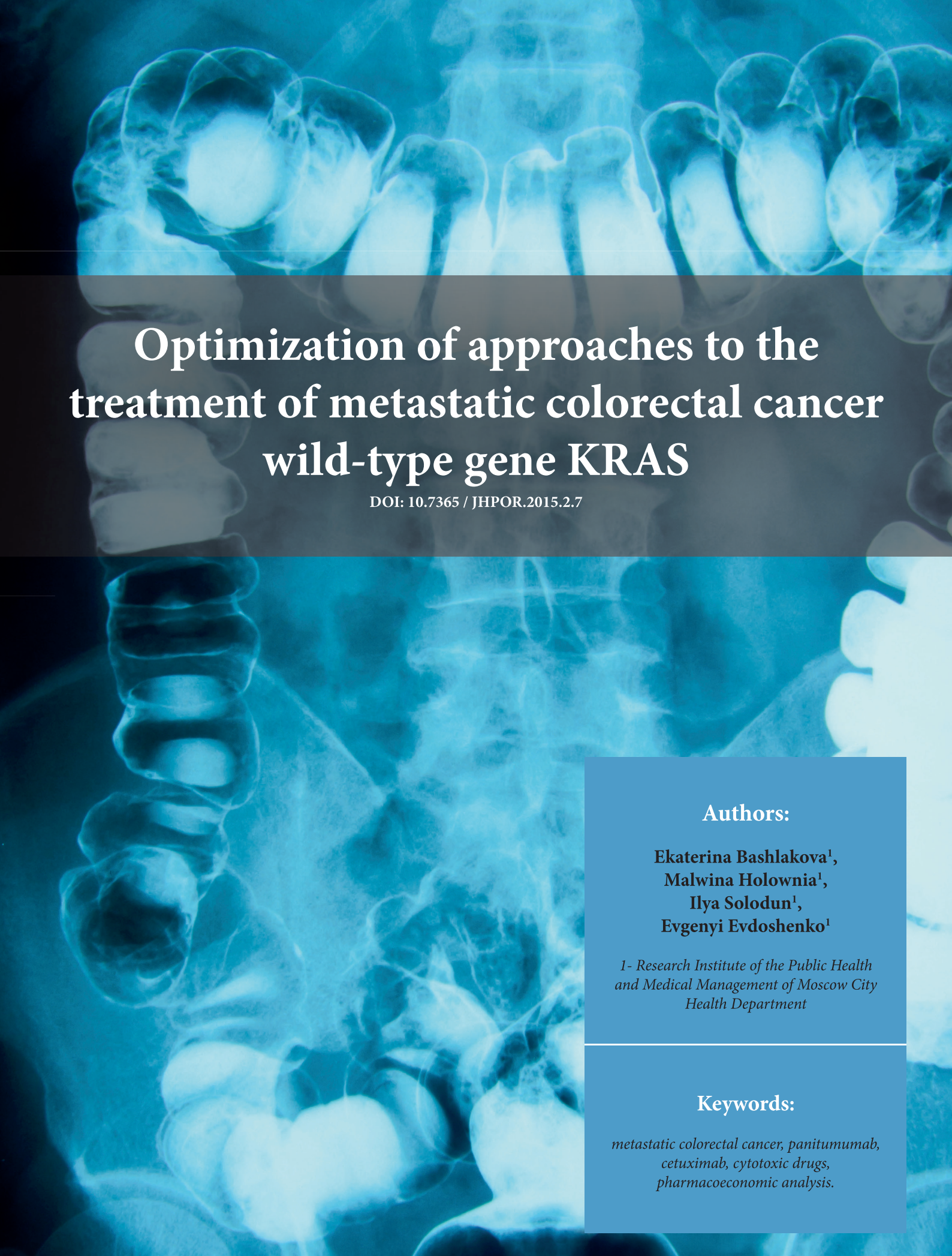

Optimization of approaches to the treatment of metastatic colorectal cancer wild-type gene KRAS

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Abstract

The results of the literature review of drug use for the treatment of metastatic colorectal cancer (mCRC) are presented. Analysis of the data showed that cetuximab (Erbitux) and panitumumab (Vectibix) are effective drugs for mCRC patients with KRAS wild-type in the first-line therapy, and the combination of standard chemotherapy regimen FOLFOX in combination with targeted therapy cetuximab (Erbitux) is the most optimal medical technology as compared with other combinations of chemotherapy and targeted drugs.

Background

Colorectal cancer (CRC) is the third cause of morbidity and mortality among malignant tumors[1]. At the time of diagnosis 35% of patients have stage III–IV disease and distant metastases, in 20–50% of patients with stages II–III metastases develop in one year. Mortality during the 1st year after diagnosis when there is no effective therapy is 70% in patients with colon cancer and 60% of patients with colorectal cancer[2]. The presence of the wild-type gene KRAS, reflecting in colon tumors in 60.8% of cases, determines the clinical course of cancer and the effectiveness of the therapy[3]. Surgery is the main method of treatment of colorectal cancer at an early stage (I-III stages). Basing on found data, 40% of initial patients undergo surgery[2]. Chemotherapy is used for metastatic colorectal cancer (mCRC) and inoperable tumors. For mCRC therapy cytotoxic drugs, including targeted drugs that increase the overall and progression-free survival, as well as achieve resectability of metastases in the liver and in patients with unresectable metastases – improve quality of life, are used[4].

An important element of health care at the present stage is a rational choice of medical technologies (including drugs), which is based on a comparative evaluation of alternatives taking into account efficacy, safety and feasibility of administration[5]. For this purpose, a comparative clinical and economic analysis for the medical technology of treatment of metastatic colorectal cancer with wild-type KRAS with the use of various drugs was conducted.

Methods

Search strategy: e-search of the information was performed in the database PubMed, Medline, Cochrane, ESMO) using the following keywords and word combinations in Russian and English languages: «cetuximab», «panitumumab», «bevacizumab» and «metastatic colorectal cancer» with limits «randomized clinical trials (RCT)», «review», «meta-analysis». Search period: November 2015. Search depth: fifteen full-scale years (2001-2015). Scope of search included results of the cost, economic, epidemiology and clinical studies. We found relevant publications with a high level of evidence for the efficacy and safety of chemotherapy drugs. All the obtained abstracts have been analyzed for the accuracy and the selected ones have been searched for the full publications. Recommendations from medicines agencies such as FDA, NICE, AOTM were used for analysis as well.

Results

Search showed that in the treatment of mCRC are used cytotoxic drugs among which are the most common – fluoropyrimidine, oxaliplatin and irinotecan. These drugs are used as monotherapy or in combination (FOLFOX 4, FOLFOX 6, FOLFIRI, XELOX and others)[6]. Main chemotherapeutic schemes for mCRC are presented in Table 1.

The main efficacy criteria for mCRC were overall survival, progression-free survival, the level (frequency) of clinical response, frequency of achievement of resectability of metastases in the liver; safety criterion – the toxicity profile (incidence of side effects I–IV degree).

Study S97-3 on comparative assessment of therapy schemes with oxaliplatin or irinotecan showed no significant differences between chemotherapeutic regimens FOLFIRI and FOLFOX6 in first line therapy in terms of the level of clinical response (54% and 56%) and progression-free survival (8.4 and 8.0 months)[7]. The second-line therapy FOLFOX has a statistically significant advantage as compared with FOLFIRI (clinical response – 15% and 4%, progression-free survival – 4.9 and 2.3 months, respectively) due to the greater number of patients that are able to receive the surgical removal treatment of metastases and minimal number of cycles of chemotherapy to achieve the same results. The main difference between the two combinations is the toxicity profile. Gastrointestinal disorders (nausea, vomiting, mucositis) and dermatological (alopecia) side effects III and IV degree of severity occur much more frequently in the FOLFIRI group, while neutropenia and neuropathy – in the group of FOLFOX[8].

To improve the effectiveness of treatment of mCRC in combination with chemotherapy regimens, the monoclonal antibody drugs – bevacizumab (Avastin), cetuximab (Erbitux), panitumumab (Vectibix) are used[4]. The results of evaluating the effectiveness of targeted therapies of mCRC in first-line therapy in patients with KRAS wild-type according to clinical studies presented in Table 2.

The addition of bevacizumab to oxaliplatin-based chemotherapy (Study N016966) or irinotecan (Study AVF2107g) improves survival as in the wild types and mutated KRAS

Chemotherapy scheme	Essential medicines that are included into regime
FOLFOX 4	oxaliplatin+5-fluorouracil+ folinic acid (leucovorin) for 4 months
FOLFOX 6	oxaliplatin+5-fluorouracil+ folinic acid (leucovorin) for 6 months
FOLFIRI	irinotecan+5-fluorouracil+ folinic acid (leucovorin)
XELOX	capecitabin+oxaliplatin

Table 1. Main chemotherapeutic schemes for mCRC

Study	PE	Regime	N	KRAS test (%)	LCR (%)	FS (months)	OS (months)
AVF2107g	OS	IFL ± Bev	67/85	28	37/60 (+23%)	7.4/13.5 (RR=0.44)	17.6/22.7 (RR=0.58)
PACCE	FS	Oks + Bev Irin	20358	82	56/48	12.5/13.5	19.8/27.7
CAIRO	FS	XELOX + Bev	156	71	50	10.6	22.4
CRYSTAL	FS	FOLFIRI ± CTX	350/316	89	40/57 (+17%)	8.4/9.9 (RR=0.70)	20.0/23.5 (RR=0.80)
OPUS	LCR	FOLFOX ± CTX	73/61	69	37/61 (+24%)	7.2/7.7 (RR=0.57)	18.5/22.8 (RR=0.85)
PRIME	FS	FOLFOX ± Pmab	331/325	93	48/55 (+7%)	8.0/9.6 (RR=0.80)	19.7/23.9 (RR=0.83)
COIN	OS	Oks ± CTX	367/362	81	57/64 (+7%)	8.6/8.6 (RR=0.96)	17.9/17.0 (RR=1.38)
NORDIC VII	FS	FOLFOX ± CTX	97/97	88	47/66 (-1%)	8.7/7.9 (RR=1.07)	22.0/20.1 (RR=1.14)

Table 2. Randomized clinical trials evaluating the efficacy of first-line therapy in patients with of mCRC in KRAS wild-type

Bev — bevacizumab; CTX — cetuximab; PE — primary endpoint; RR — relative risk; KRAS — proto-oncogene family of proteins RAS; N — number of patients; FS — free survival; OS — overall survival; Pmab — panitumumab; LCR — the level of clinical response.

of mCRC in[9,10]. Therefore, KRAS testing is not mandatory for the selection of mCRC patients to undergo therapy with bevacizumab. The highest efficiency is seen with irinotecan (OR = 0.54) compared with oxaliplatin (OR = 0.83), which is associated with a more pronounced synergistic effect of irinotecan and bevacizumab, as well as more prolonged administration of bevacizumab in the study of irinotecan (AFG2107g)[11]. In a clinical study of evaluating the efficacy of oxaliplatin compared with bevacizumab (N016966) therapy has been discontinued due to progression of the disease in 29% of patients in the bevacizumab group and 47% in the oxaliplatin group. Overall survival rate was 57% in the bevacizumab group versus 37% in the FOLFOX group. Median progression-free survival (PFS) increased from 5.5 to 9.2 months (RR = 0.50), median overall survival (OS) – from 12.9 to 16.6 months (RR = 0.79) in bevacizumab. The frequency of objective clinical response (OCR) was 55%, the incidence of metastases resectability achievement was 45%[11].

In the study MAX bevacizumab was used in combination with capecitabine. According to the results, the median PFS increased from 5.7 to 8.5 months (RR = 0.63), survival was similar in the treatment groups (RR = 0.87)[12].

In the analysis of clinical studies on the efficacy and safety of cetuximab showed that adding the drug to the scheme FOLFOX4 significantly improved the objective clinical response (OCR) (58% vs. 29%, relative risk (RR) = 3.33, 95% confidence interval (CI) 1.36–8.17; p = 0.0084) as first-line therapy in patients with wild-type KRAS metastatic colorectal cancer (mCRC) compared with FOLFOX4 without its addition. The median of overall survival (OS) and PFS was 30 and 12.3 months, when using Cetuximab + FOLFOX4 against 20.8 and 10.1 months when using only FOLFOX4, respectively[13]. Improving CR with the addition of cetuximab to FOLFOX4 also leads to an increase in frequency to achieve resectability of liver metastases in these patients (69.2% vs. 26.3%, respectively). Median PFS and OS in patients undergoing resection of metastases with the addition of cetuximab to FOLFOX4 – were 12.6 and 29.5 months, respectively[14].

By adding the drug cetuximab to FOLFIRI group in the first-line therapy of mCRC with wild-type KRAS was also

noted a significant improvement in objective clinical response (OCR) (57.3% vs. 39.7%, relative risk (RR) 2.069; 95% confidence interval (CI) 1.515–2.826; p≤0,001), PFS (9.9 vs. 8.4 months, RR = 0.696, 95% CI 0.558–0.867; p = 0.0012) and OS (28.3 vs. 19.6 months, RR = 0.643, 95% CI 0.480–0.862; p = 0.003) in patients with wild-type KRAS. In this group there was a significant increase in the frequency of achieving resection of liver metastases (5.1% vs. 2%, RR = 2.650, 95% CI 1.083-6.490; p = 0.0265)[15]. The incidence of adverse events with cetuximab was similar in both groups: sensory neuropathy (grade III–IV) was in group cetuximab + FOLFIRI group in 1% of patients, in the group of FOLFIRI – 2%, dermatological complications – 16% and 1%, nausea – 6% and 6%, infectious complications – 11% and 5%, neutropenia – 31% and 24%, diarrhea – 16% and 10%, respectively[16]. A comparative assessment of the effectiveness of using regimens cetuximab + FOLFOX6 and cetuximab + FOLFIRI in the first-line therapy of mCRC in patients with wild-type KRAS were noticed statistically significant differences in the groups have been identified: an objective clinical response (OCR) – 68% vs. 57% of patients (RR = 1.62, 95% CI 0.74–359; p = 0.23), the frequency of achieving resection of liver metastases – 38% vs. 30% of patients, PFS – 12.1 vs. 11.5 months (RR = 1.09, 95% CI 0.66–1.79; p = 0.01) and OS – 35.8 vs. 41.6 months (RR = 1.01, 95% CI 0.55–1.86; p = 0.01). The analysis, based on mutational status, showed that an objective clinical response (OCR) using both treatments in patients with EGFR and KRAS wild-type compared with patients who have a mutation in this gene, is statistically higher –70% vs. 41% of patients (RR = 3.42, 95% CI 1.35–8.66, p = 0.0080) with a frequency capabilities resection of 60% and 32% of patients, respectively (p≤0.0001)[4].

In assessing the effectiveness of using regimens and cetuximab + FOLFOX6 + XELOX cetuximab in first-line therapy of mCRC patients with KRAS wild-type showed a significant increase in OCR (64% vs. 57%, RR = 1.35, 95% CI 1.00–1.82; p = 0.049), but there were no statistically significant differences in the rate of resection of liver metastases (15% vs. 13%, p = 0.74), PFS (8.6 vs. 8.6 months, RR = 0.96, 95% CI 0.82–1.12; p = 0.60) and OS (17.9 vs. 17.0 months, RR = 1.04, 95% CI 0.87–1.23; p = 0, 67)[17].

Comparative analysis of the use of schemes FOLFOX6 + cetuximab and FOLFOX6 + bevacizumab as first-line systemic therapy for patients with EGFR with KRAS wild-type showed that the median time to progression was significantly higher with cetuximab + FOLFOX6 – 13.0 and 9.5 months, respectively (RR = 0.65; p = 0,029); the frequency of objective clinical response was similar when using both schemes – 58% in the cetuximab group and 53.5% - in the bevacizumab group; the median overall survival was 41.3 and 28.9 months, respectively (RR = 0.63; p = 0,058), the frequency of severe toxicity – in 91% and 83% of patients. The main reason for discontinuation of treatment was disease progression – in 24% of patients using cetuximab and in 27% - in the bevacizumab group (toxicity was the most common grade III–IV – neutropenia (32.3%), acne (15.2%) and diarrhea (11.1%)[17,18,19].

Thus, cetuximab (monoclonal antibody to the epidermal growth factor receptor (EGFR) in a combination with a scheme FOLFOX6 in first-line therapy of in patients with metastatic colorectal cancer and wild-type KRAS exceeds bevacizumab (monoclonal antibody to the vascular endothelial growth factor (VEGF) in overall survival and progression free survival.

The drug panitumumab in combination with FOLFOX4 regime improves the progression-free survival (PFS) of the disease when administered as first-line treatment of metastatic colorectal cancer in patients with KRAS wild gene as compared to the scheme without the inclusion (9.6 vs. 8.0 months, RR 0.80, 95% CI 0.66–0.97; p = 0,02), overall survival (23.9 vs. 19.7 months, RR 0.83, 95% CI 0.67–1.02), an objective clinical response rate (55% vs. 48%), as well as to achieve resectability rate of metastases (31% vs. 17%, RR 2.2, 95% CI 0.80–6.10)[16,20,21].

	Panitumumab (n=499)	Cetuximab (n=500)
Overall survival		
The frequency of overall survival (%)	383 (76.8%)	392 (78.4%)
Median survival (months) (95% CI)	10.4 (9.4–11.6)	10.0 (9.3–11.0)
Hazard ratio (95% CI)	0.97 (0.84–1.11)	
Progression-free survival		
Median of progression-free survival (months) (95% CI)	4.1 (3.2–4.8)	4.4 (3.2–4.8)
Hazard ratio (95% CI)	1.00 (0.88–1.14)	
Objective clinical response		
Frequency of objective clinical response (%) (95% CI)	22% (18–26%)	19% (16–23%)

Table 3. Indicators OB, PFS and CR in patients mCRC with KRAS wild-type with panitumumab (Vectibix) and cetuximab (Erbitux)

Clinical study	Adverse effects on the classification of NCI-CTC AEs	
	III degree (%)	IV degree (%)
OPUS		
CET+FOLFOX4 (n=38)	30/38 (79)	15/38 (39.5)
FOLFOX4 (n=49)	31/49 (63)	8/49 (16)
CRYSTAL		
CET+FOLFIRI (n=178)	144/178 (80.9)	69/178 (38.8)
FOLFIRI (n=189)	110/189 (58.2)	62/189 (32.8)
FIRE-3		
CET+FOLFIRI (n=171)	118/171 (69)	data not available
BEV+FOLFIRI (n=171)	115/171 (67.3)	data not available
PRIME		
PAN+FOLFOX4 (n=250)	142/250 (57)	70/250 (28)
FOLFOX4 (n=250)	125/249 (50)	50/249 (20)
PEAK		
PAN+FOLFOX6 (n=86)	60/86 (70)	17/86 (20)
BEV+FOLFOX6 (n=80)	43/80 (54)	15/80 (19)

Table 4. Randomized clinical studies on comparative assessment of the safety of medicines of mCRC first-line therapy in patients with KRAS wild-type

Indicators	Regime/drug				
	FOLFOX (oxaliplatin)	FOLFIRI (irinotecan)	Bevacyzumab (Avastin)	Cetuximab (Erbitux)	Panitumumab (Vextibix)
Mechanism of action	Inhibitor of DNA synthesis	Inhibitor of cellular enzyme topoisomerase I	Anti-angiogenic recombinant humanized monoclonal antibody	Monoclonal antibodies to the epidermal growth factor receptor (EGFR)	Monoclonal antibodies to the epidermal growth factor receptor (EGFR)
For the first time registered for mCRC (country, year)	2003, US	2003, US	2004, US	2004, US	2006, US
For the first time registered in Russia for treatment of mCRC (year)	2002	2006	2009	2015	2009
Effectiveness					
Overall survival					
Frequency of overall survival (%)	49.3	37.5	57	78.4	76.8
Median survival (months) (95% CI)	20.8	19.6	16.6	30	23.9
Progression-free survival					
Median of progression-free survival (months) (95% CI)	10.1	8.4	9.2	12.3	9.6
Objective clinical response					
Frequency of objective clinical response (%) (95% CI)	29	39.7	55	58	55
Achieving the resectability of liver metastases (%)	26.3	2	45	62.2	31
Safety					
Adverse events of III degree (%)	63	58.2	67.3	79	85
Adverse events of IV degree (%)	16	32.8	data not available	39.5	43

Table 5. A comparison of the main indicators of the effectiveness and safety of drugs for mCRC patients with KRAS wild-type

Adding panitumumab to the regime of FOLFIRI in second-line therapy of mCRC with wild type KRAS also leads to a significant increase in disease-free period as compared to using regime FOLFIRI without panitumumab (5.9 and 3.9 months, respectively, RR 0.73; p = 0.004), the frequency of OCR (35% vs. 10%) and OS (14.5 vs. 12.5 months, RR 0.85; p = 0.115)[4,22,23].

Comparative analysis of the efficacy of panitumumab (Vectibix) and cetuximab (Erbitux) showed no statistically significant differences in PFS and OS of compared drugs (Table 3)[2,24].

Along with high efficiency in the treatment of patients with wild-type KRAS colorectal cancer, two monoclonal antibodies (anti-EGFR MoAbs) have a high incidence of severe toxicity. Analysis of systematic reviews and meta-analysis (43 studies involving 29 793 patients) to evaluate the frequency and relative risk (RR) of severe and life-threatening adverse events in PubMed and Embase showed that the addition to the treatment of anti-EGFR MoAbs leads to an increased risk of diarrhea (23% vs. 12%) (OR = 1.66, 95% CI 1.52–1.80), dermatitis (26% vs. 1%) and mucositis (4% vs. 1%) (OR = 3.44, 95% CI 2.66–4.44)[17,18,25]. Comparative analysis of safety data treatment regimens is presented in Table 4.

Hypomagnesemia associated with the use of anti-EGFR MoAbs was observed in 34% of cases (95% CI 28.0–40.5), hypocalcemia and hypokalemia – 14.5% (95% CI 8.2–24.4) and 16.8% (95% CI 14.2–19.7), respectively. Thus, when evaluating treatments for metastatic colorectal cancer chemotherapy and chemotherapy with the addition of cetuximab there is an increased risk of hypomagnesemia and hypokalemia (severity degrees III-IV) in the group of chemotherapy and cetuximab in 7.14 – fold (95% CI 3.13–16.27; p <0.001) and 2.19 (95% CI 1.14–4.23; p = 0.019), respectively. The use of panitumumab in comparison with cetuximab is accompanied by the greater frequency of electrolyte abnormalities degrees III–IV – hypomagnesemia (RR = 18.29, 95% CI 7.29–48.41; p<0.001) and hypokalemia (RR = 3.3, 95% CI 1.32–8.25; p = 0.011)[26]. Thus, the main indicators of the effectiveness and safety of drugs for mCRC can be represented as in Table 5.

Analysis of the monthly cost of the treatment regimen of patients compared with the use of medicinal products prepared in pharmacoeconomic Markov model[2,24] is shown in Table 6.

Data from economic analysis of the scheme FOLFOX ± panitumumab (Vectibix) / cetuximab (Erbitux) in patients with metastatic colorectal cancer, with the expression of EGF receptors and non-mutated (wild)-type KRAS according to recommendations of the National Health and Care Exellence (NICE) 7/08/2015[2,24] are presented in Table 7 and 8.

When comparing the cost of managment of mCRC patients with wild-type KRAS, the monthly total costs of management of 1 patient with the drug cetuximab according to NICE (2015) amounted to £77 262, which is £2557 greater than for therapy with panitumumab – £74 705 and £38 437 using the standard regimen of FOLFOX. The cost of drug therapy for 1 patient during one treatment cycle was the lowest for the scheme FOLFOX – £2537 and the highest for therapy with cetuximab – £4895. Analysis of indicators of "cost-effectiveness" according to NICE showed that cetuximab in the treatment of metastatic colorectal cancer with KRAS wild-type is the least expensive medical technology (£109 820) in comparison with panitumumab (£239 007)[24] (Table 7).

According to Russian authors costs of 1 cycle of chemotherapy with FOLFOX scheme is £443 and for scheme FOLFIRI – £750[27]. Costs of 1 cycle of treatment with targeted drugs are presented in Table 9.

When comparing costs of drug therapy, the lowest cost is observed when using the scheme with FOLFOX – £443, the largest for panitumumab + FOLFOX – £2484 and panitumumab + FOLFIRI – £2178[27].

The inclusion of the drug in the list for reimbursement lead to increased sales of the drug on the market compared with other drugs, not included in the system of preferential support. The higher is the level of payments of the state and lower is the level of co-payment of patient, the greater availability of drugs is. In European countries there is no single approach to the inclusion of panitumumab and cetuximab into preferential lists. Panitumumab has been recommended for inclusion in the reimbursement list of Agency for Health Technology Assessment France Haute Aurorite de Sante (HAS), in 2012. Cetuximab was included in the system of preferential provision of Belgian Institut nationale d'assurance maladie-invalidité (INAMI) in 2009 and in the Czech Republic Státní ústav pro kontrolu léčiv (SUKL) in 2009[28,29].

Treatment scheme	Monthly costs (£)
cetuximab+FOLFOX4	5 083
FOLFOX4	1 546
FOLFOX6	1 616
XELOX	1 950
cetuximab+FOLFIRI	4 876
bevacezumab+FOLFIRI	3 345
FOLFIRI	1 339

Table 6. Comparative analysis of the monthly cost of the scheme mCRC patients with wild-type KRAS (Markov model), (National Health and Care Excellence (NICE)

				CET+FOLFOX versus		PAN+ FOLFOX versus
	CET+ FOLF-OX	PAN+ FOLFOX	FOLFOX	PAN+ FOLFOX	FOLFOX	FOLFOX
Life expectancy (years)	2.41	2.08	1.86		0.55	0.22
QALY	1.61	1.41	1.26		0.35	0.15
Cost of drug therapy of 1 patient (£)	4 895	2 995	2 537	1 900	2 358	458
Total cost of manage-ment of 1 patient (£)	77 262	74 705	38 825	2 557	38 437	35 880
ICER (cost/ QALY) vs. FOLFOX				12 792	109 820	239 007
ICER (cost/ QALY) on efficiency frontier	109 820	239 007	reference			

Table 7. Data from economic analysis of the scheme FOLFOX ± panitumumab (Vectibix) / cetuximab (Erbitux) in patients with EGFR (according to the recommendations of National Health and Care Excellence (NICE)

Note: CET – cetuximab, PAN – panitumumab, ICER – incremental cost-effectiveness ratio, QALY – quality adjusted life years

	CET+ FOLFIRI	FOLFIRI	CET+ FOLFIRI against FOLFIRI
Life expectancy (years)	2.21	1.75	0.46
QALY	1.53	1.23	0.30
Total costs (£)	85 197	40 027	45 170
ICER (cost/QALY)			149 091

Table 8. Data from economic analysis of the scheme FOLFOX ± panitumumab (Vectibix) / cetuximab (Erbitux) in patients with EGFR (according to the recommendations of National Health and Care Excellence (NICE)

Note: ЦЕТ – cetuximab, ICER – incremental cost-effectiveness ratio, QALY – quality adjusted life year

Chemotherapy scheme	Costs of 1 cycle of chemotherapy (£)
FOLFOX	443
FOLFIRI	750
Bevacyzumab+FOLFIRI	1252
Cetuximab+FOLFOX	1278
Cetuximab+FOLFIRI	1584
Panitumumab+FOLFIRI	2178
Panitumumab+ FOLFOX	2484

Table 9. Costs of cycle of chemotherapy with targeted therapies

Note: Prices of drugs are taken at the official site of the Russian procurement zakupki.gov.ru and converted into British pounds, according to the exchange rate of foreign currencies to Russian ruble of the Russian Central Bank, on 06.11.2015.

Discussion

Metastatic colorectal cancer is a common and serious problem worldwide. Treatment with properly selected drug (effective, safe and economically more favorable) can increase the life expectancy of patients, significantly improve their quality of life and reduce the costs from the state budget for the management of such patients. Analysis of the existing literature and data from clinical trials showed that currently in the treatment of inoperable metastatic colorectal cancer a large amount of drugs is used. Applied cytostatics and various chemotherapy regimens vary in their efficacy, safety and, what is also important, in economic-effectiveness. In recent years the pharmaceutical market, new targeted therapies for the treatment of metastatic colorectal cancer, among which the most interesting are cetuximab and panitumumab. In numerous randomized trials both drugs have demonstrated their high ability to significantly increase overall survival and progression-free survival and objective clinical response rate that allows to reach earlier resectability of metastases and reduce patient mortality. High efficacy is due to the high sensitivity of patients to treatment if they have a KRAS mutation, which is occurred with high frequency in patients with colorectal cancer. However, the drug cetuximab, according to numerous studies, and comparative analysis with other cytotoxic drugs is the best drug in the treatment of non-resectable metastatic colorectal cancer. In its application was observed the highest frequency of positive responses on all effectiveness indicators. The drug also showed a relatively good safety profile compared to other cytostatics. In pharmacoeconomic studies cetuximab also showed lower levels of the costs of patient management, drug therapy (despite the relatively high cost of the drug compared to the "old" regimen) due to both foreign and Russian data. The lowest "cost-effectiveness" ratio of cetuximab also confirmed that the use of this drug is the best medical technology in comparison to other cytostatic agents for the treatment of inoperable metastatic colorectal cancer.

Conclusion

Thus, during the comprehensive assessment (according to the literature review of foreign and Russian publications) efficiency, safety and cost-effectiveness of various schemes of chemotherapy, the use of the drug cetuximab as first-line therapy in patients with mCRC with the presence of wild-type KRAS is the most effective for the main clinical characteristics (overall survival, progression-free survival, objective clinical response, and the speed of resection of liver metastases) and most cost-effective (lowest "cost-effectiveness" ratio) technology, with similar to other targeted drugs safety profile. ■

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