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# ANALYSIS OF RESEARCH ON THE BENEFITS OF CLINICAL AND ECONOMIC EFFECTIVENESS, SAFETY OF INNOVATIVE DRUG CETUXIMAB IN THE TREATMENT OF COLORECTAL CANCER

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***Метою роботи*** *є аналіз та систематизація даних літератури щодо переваг клінічної та економічної ефективності, безпеки цетуксимабу в лікуванні колоректального раку.*
***Матеріали та методи.*** *Дослідження проводилися з використанням баз даних в мережі Інтернет: PubMed; Адміністрації з контролю за ліками та харчовими продуктами (Food and Drug Administration), Європейського агентства лікарських засобів (European Medicines Agency). Використано ретроспективний, логічний, статистичний та системно-аналітичний методи дослідження.*
***Результати.*** *Проведений аналіз клінічних даних свідчить про додаткову корисність, високу ефективність цетуксимабу при лікуванні пацієнтів з метастатичним КРР RAS дикого типу та експресією рецепторів епідермального фактора росту EGFR в порівнянні з іншими препаратами. Цетуксимаб виявляє синергічну дію з рядом цитостатичних лікарських засобів (ЛЗ), а також підвищує ефект променевої терапії, при цьому посилення токсичних реакцій при спільному застосуванні не спостерігається. Включення цетуксимабу в схему лікування збільшує резектабельність первинно нерезектабельних метастазів в печінку, а також виживання без прогресування як у оперованих пацієнтів, так і в неоперабельних випадках. Препарат визнаний відносно безпечним. Шкірні висипи, викликані цетуксимабом, пов'язані зі значним поліпшенням показників загального виживання, виживання без прогресування і загальної частотою відповіді. Застосування цетуксимабу у пацієнтів КРР супроводжується меншим економічним навантаженням на бюджет лікарського забезпечення онкологічних хворих, ніж бевацизумаб. Слід зазначити, що створення біосимілярів цетуксимабу дозволить зменшити вартість лікування та підвищити доступ до терапії КРР.*
***Висновки.*** *Таким чином, доведено, що цетуксимаб є не тільки клінічно ефективним та відносно безпечним ЛЗ для лікування КРР, але також показана його економічна ефективність та додаткові переваги в порівнянні з іншими препаратами, зокрема бевацизумабом*
***Ключові слова:*** *цетуксимаб, колоректальний рак, клінічна та економічна ефективність, безпека, рецептор епідермального фактора росту*

## 1. Introduction

Statistics show that over the past 100 years, the oncopathology has moved from the tenth place to the second by the level of morbidity and mortality in the world, second only to diseases of the cardiovascular system. According to the WHO, every year 10 million people are ill again. According to WHO, cancer deaths by 2030 will increase by 45 % compared to that in 2007 [1].

## 2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

Oncopathology remains one of the most urgent and expensive non-communicable diseases that the health system faces. Celis et al. argue that the combination of innovative prevention and treatment strategies in the modern European cancer center will enable long-term survival of 3 out of 4 cancer patients by 2030 in countries with well-developed health systems [2].

## 3. Analysis of recent studies and publications in which a solution of the problem are described and to which the author refers

During the last decade, targeting therapy has dominated the oncology. Thus, in clinical practice, the treatment of solid and hematological malignant tumors is increasingly used anti-tumor monoclonal antibodies targeting specific antigens on the surface of cancer cells. The main advantages of such antibodies are a long half-life, low toxicity and high specificity [3].

Colorectal cancer (CRC) is one of the most common malignant neoplasms. Every year in the world more than 800 thousand new cases of CRC are registered, and the number of deaths exceeds half of new patients. Cetuximab is one of the antitumor monoclonal drugs for the treatment of CRC.

Along with the successes in healthcare, it should be noted that the cost of treatment for cancer has increased significantly in recent years and is projected to increase. The mentioned threatens the possibility of long-term access of patients to cancer care. In some cases, it has noted the minor advantages of new anticancer drugs, so an increase in life expectancy was 1.2–2.7 months [4].

Ferguson et al. note that there is no need to pay a premium for innovative medicines if they do not increase life expectancy for at least three months compared with existing standards [5]. Experts from the UK report similar timeframes (in terms of increasing survival) in assessing the significance of new drugs in the terminal stage of cancer [6]. The Cancer Research Committee of the American Cancer Society has identified an increase in the median of absolute survival in the range of 2.5–6 months for a number of tumors as a minimum indicator of additional benefit. It determines clinically meaningful results for a new cancer drug (depending on the type of tumor) [7]. In Germany, the (Institute

for Quality and Efficiency in Health Care-Home, IQWIG, an independent organization that assesses the quality and effectiveness of medical technologies and products) allocates 6 grades of availability/absence of additional therapeutic benefits: significant; moderate; minimal; additional clinical benefit is not subject to registration; lack of proven added efficiency; the benefit is less than that of the comparator [8].

**4. The field of research considering the general problem, which is described in the article**

In the literature it has discusses the high cost of new innovative drugs that exhibit similar efficacy in comparison with pharmaceuticals already available in the pharmaceutical market. In recent years, attention to this problem has increased significantly. The specified causes the necessity of further researches concerning an estimation of additional clinical usefulness of innovative drugs in comparison with existing preparations for treatment of oncological diseases.

**5. Formulation of goals (tasks) of article**

The aim of the work is to analyze and systematize literature data on the benefits of clinical and economic efficiency, safety of cetuximab in the treatment of colorectal cancer.

**6. Presentation of the main research material (methods and objects) with the justification of the results**

Studies were conducted using databases on the Internet: PubMed; Food and Drug Administration, European Medicines Agency. It has used retrospective, logical, statistical and system-analytical research methods.

In order to reduce the unpredictable increase in the cost of innovative drugs for the treatment of cancer, widespread use of comparative clinical efficacy studies is needed when discussing new therapies and identifying explicit benefits to drugs that are already being used in clinical practice. The systematic data on the significant clinical benefits of cetuximab, which have been studied in randomized trials, are given in Table 1.

The reported data indicate that cetuximab is an effective drug for the treatment of patients with metastatic CRC with wild-type RAS and expression of epidermal growth factor receptors EGFR: in combination with irinotecan-based chemo-therapy or prolonged infusion of 5-fluorouracil / folinic acid and oxaliplatin as first line of therapy; as monotherapy in the case of ineffectiveness of previous chemotherapy based on oxaliplatin or irinotecan, as well as intolerance to irinotecan. The inclusion of cetuximab in the treatment regimen increases the resectability of primary nonresectable metastases in the liver, as well as survival without progression in both operated patients and in inoperable cases. Patients with a common disease, metastases that can not become operable, need to prolong their life as much as possible, maintaining its acceptable quality, preventing or reducing the manifestation associated with the tumor of the symptoms. Cetuximab in combination with FOLFOx and FOLFIRI regimens increases the response to treatment, progression-free survival. The use of cetuximab in the second and third line of therapy increases the objective effect and overall survival.

The major side effects of cetuximab are skin reactions. Their presence, according to most studies, is a factor that correlates with the effectiveness of treatment with the inclusion of cetuximab. Thus, a meta-analysis of 13 clinical trials has shown that skin rashes caused by cetuximab are associated with a significant improvement in overall survival, progression-free survival and overall response rates [31].

Data from another meta-analysis, which included 38 studies, indicate that cetuximab and panitumumab chemotherapy has different toxicity profiles in terms of the frequency of severe side effects. Cetuximab was associated with lower skin toxicity, acne and paronychia were more commonly observed, but fewer cases of skin cracks and itching than when using panitumumab [32].

Although numerous placebo-controlled studies of cetuximab are an important indication of its efficacy, there is a higher degree of evidence of its clinical benefits. A recognized standard of evidence-based medicine is a meta-analysis of the results of numerous studies.

A meta-analysis of 5 comparative studies of the efficacy of the VEGF inhibitor (bevacizumab) with EGFR inhibitors (cetuximab or panitumumab) has been conducted with metastatic CRC wild-type RAS. The advantage of EGFR-inhibitor therapy compared with VEGF inhibitors relative to overall survival was found [33].

Meta-analysis of 10 studies was of interest that evaluates the prognostic role of primary tumor localization in metastatic CRC in patients receiving cetuximab. The authors conclude that in patients with left-sided CRC the prognosis is better than in patients with right-sided illnesses when treating cetuximab [34].

An updated systematic meta-analysis of 5 studies (1,464 patients) was performed to determine the efficacy of cetuximab plus FOLFIRI or FOLFOX as the first line of treatment for metastatic CRC in wild type KRAS patients. It has been found that the use of cetuximab is a potentially effective approach to improving the results. However, it has reported 3rd and 4th grade adverse events in the group of wild-type RAS patients, namely neutropenia and diarrhea. There was a higher incidence of diarrhea of 3 or 4 degrees for cetuximab plus Folfiri, no significant difference with respect to neutropenia was detected. The drug is considered relatively safe [35].

The data of the research carried out by other authors confirmed not only the efficacy, but also the relative safety of cetuximab in different subgroups and populations of patients and led to the approval of its use in the treatment of metastatic CRC.

Table 1

Systematized data on the effect of cetuximab on increasing the life expectancy of cancer patients

| Study | Effect of cetuximab on survival rates |
|---|---|
| 1 | 2 |
| Randomized study EPIC (1 298 patients) | The combination of cetuximab + irinotecan significantly increased survival to progression (4.0 months versus 2.6 months (only with irinotecan application), respectively) [9]. |
| Randomized study CRYSTAL (1217 patients) | The combination of cetuximab with FOLFIRI (irinotecan, 5-fluorouracil/folinic acid) significantly increased the efficacy of treatment from 38.7 to 46.9 % and median survival without progression from 8.0 to 8.9 months, reducing the risk of progression of the tumor process to 15 %. The tolerability of the combination of FOLFIRI + cetuximab was satisfactory [10]. |
| Randomized study (1198 patients) | Cetuximab has shown efficacy in combination with FOLFIRI in tumors with the wild KRAS gene. Indicators of survival without progression (median 9ю9 months versus 8ю4 months, respectively) and overall survival (median 23ю5 months versus 20ю0 months) were significantly higher in the cetuximab group [11]. |
| Multicenter study BOND (329 patients) | Median survival without progression and overall survival was for the group cetuximab + irinotecan 4.1 and 8.6 months for the group cetuximab in mono-regime – 1.5 and 6.9 months [12]. |
| Randomized study AIO CRC-_group (177 patients) | The efficacy and safety of XELOX regimens (capecitabine and oxaliplatin) and XELIRI (capecitabine and irinotecan) in combination with cetuximab in the I line of treatment in patients with metastatic CRC have been identified [13]. |
| Randomized study COIN-B (169 patients) | It has compared to 2 regimens for cetuximab and chemotherapy: after 12 weeks of treatment with "FOLFOx (oxalipatin, 5-fluorouracil, folic acid) + cetuximab weekly", treatment interrupted or preserved cetuximab, then "FOLFOx + cetuximab" was repeated with similar follow-up treatment. Progression-free mediums were 12.0 and 13.7 months for the discontinuation and continued therapy with cetuximab, respectively. In the ongoing cetuximab group, the survival rate exceeded that in the intermittent treatment group (18.4 versus 20.1 months, respectively) [14]. |
| Randomized controlled study (138 patients) | In a study on the use of cetuximab in combination with chemotherapy compared with chemotherapy in patients with unresectable metastases in the liver, patients with cetuximab exhibited higher three-year survival (41 % vs. 18 %) and median overall survival (30.9 versus 21.0 months ) [15]. |
| Randomized study (40 patients) | It has evaluated the efficacy of a two-week treatment with cetuximab and irinotecan as the third line for CRC patients. Median survival without progression, overall survival were 5.7 and 15.1 months [16]. |
| Randomized study (289 patients) | With the use of cetuximab as the first line of therapy in patients with CRC wild type KRAS, survival without progression and overall survival were 11.1 and 26.8 months [17]. |
| Randomized study (40 patients) | Combination therapy: cetuximab, irinotecan, oxaliplatin, capecitabine, of wild-type CRC patients are associated with a high level of response: mean survival without overall progression and overall survival were 17.8 and 62.5 months respectively [18]. |
| Randomized study (188 patients) | In patients with RAS and BRAF mutant tumors, the overall response rate was higher in the cetuximab group compared to bevacizumab (52 % vs. 40 %), but comparative results were obtained for progression-free survival [19]. |
| Randomized study (52 patients) | The polymorphisms of VKORC1, NAT2, ABCB1 genes are related to the efficacy of irinotecan, oxaliplatin, 5-fluorouracil and cetuximab in patients with CRC, with the highest survival rate of 4 years [20]. |
| Randomized study (54 patients) | In patients with refractory metastatic BRAF mutant CRC, the combination of cetuximab and enocarpenib has showed promising clinical activity and tolerability. Median survival without progression weres 3.7 and 4.2 months for dual and triple therapy groups [21]. |
| Randomized study (110 patients) | The use of cetuximab as the first line of therapy in combination with oxaliplatin in patients with left-sided wild-type CRC is largely due to longer overall survival (36.2 versus 12.6 months) and survival without progression (11.1 versus 5.6 months) than the right- sided wild-type CRC [22]. |
| Randomized study (153 patients) | It has estimated the efficacy of cetuximab plus Folfox as the second-line therapy of CRC wild type KRAS. Survival without progression was in the Folfox group plus cetuximab 6.9 months against 5.3 months in the Folfox group. The median of overall survival: 23.7 versus 19.8 months, respectively [23]. |
| Randomized study (29 patients) | It has shown the effectiveness of cetuximab in patients with CRC with chemorefractory codon KRAS G13D. The median overall survival was 8.0 months in the cetuximab group and 7.6 months in the group - cetuximab plus irinotecan [24]. |

Continuation of the Table

| 1 | 2 |
|---|---|
| Randomized study (400 patients) | In patients with CRC wild type RAS, the average overall survival rate was higher in the Folfiri plus cetuximab group than in the Folfiri plus bevacizumab group (33.1 months versus 25.0 months), progression-free survival was comparable between groups [25]. |
| Randomized study (293 patients) | It has demonstrated the high efficacy of cetuximab in patients with CRC wild-type KRAS with FCGR2A H/H genotypes: the benefits of overall survival were 5.5 months [26]. |
| Randomized study (40 patients) | When using cetuximab in combination with XELOX in wild-type CRC patient's survival without progression and overall survival were 6.5 and 24.3 months [27]. |
| Non-randomized study (37 patients) | When using cetuximab in combination therapy of the third line in wild-type CRC patient's survival without progression and overall survival were 5.5 and 13.5 months [28]. |
| Randomized study (34 patients) | The efficacy and good tolerability of cetuximab in combination with irinotecan in Japanese patients with CRC wild-type KRAS have been shown. Survival without progression was 6 months; overall survival was 12.9 months [29]. |
| Randomized study (56 patients) | Median survival without progression in patients with unresectable metastases in the liver on treatment of Folfox and cetuximab was 10.8 months, Folfiri and cetuximab – 10.5 months [30]. |

There is an analysis of economic efficiency using FIRE-3 clinical data to predict survival and life expectancy of FOLFIRI plus cetuximab or bevacizumab regimens as the first line of the metastatic CRC wild-type RAS treatment. Compared with bevacizumab, KRAS wild type patients receiving first-line cetuximab gained 5.7 months of life at a cost of $46266, for an incremental cost-effectiveness ratios of $97223/ per life year ($122610/ quality-adjusted life year). For extended RAS wild type patients, the incremental cost-effectiveness ratios was $77339/ per life year ($99584/ quality-adjusted life year). Treatment with cetuximab was cost-effective in 80.3 % of cases, given the willingness to pay $ 150000 per year. The analysis shows that treatment with cetuximab and FOLFIRI in patients with metastatic CRC wild type RAS improves clinical outcomes and uses financial resources more effectively than bevacizumab and FOLFIRI [36].

The large evidence base obtained in the course of numerical clinical studies suggests additional benefits, high efficacy, acceptable cetuximab safety and lower cost of treatment compared to other drugs. It should be noted that the production of cetuximab biosimilars will reduce the cost of treatment and improve access to CRC therapy.

**7. Conclusions from the conducted research and prospects for further development of this field**

1. Conducted analysis of clinical data suggests additional utility, high efficacy of cetuximab in the treatment of patients with metastatic CRC RAS wild type compared to other drugs. Cetuximab exhibits a synergistic effect with a number of cytostatic drugs, and also increases the effect of radiotherapy, with no increased toxic reactions when co-administered. The drug is considered relatively safe.

2. The use of cetuximab in patients with CRC is accompanied by a lower economic burden on the budget of drug provision for cancer patients than bevacizumab.

3. It has been shown that cetuximab is not only a clinically effective and relatively safe drug for the treatment of CRF, but also demonstrates its cost-effectiveness and additional benefits compared to other drugs, including bevacizumab.

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