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EFFECTIVENESS OF I AND II LINE CHEMO-TARGETED THERAPY ACCORDING TO THE SCHEME OXALIPLATIN + CAPECITABINE + BEVACIZUMAB (XELOX + BEV) IN PATIENTS WITH METASTATIC COLORECTAL CANCER (MCRC)

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The research involved 38 mCRC patients, aged 23-73 (medium age -55 years). Patients with mCRC were randomized into two groups. This mode of chemo-targeted therapy was conducted in the first group (20 patents) in a second line, since these patients previously were treated by the chemotherapy schemes FOLFIRI or FOLFOX. Patients were treated in the mode: Capecitabine in 2000mg/m2 2 times a day from the 1st to the 14th day, 2-hour infusion of capsular Oxaliplatin 130mg/m2, day 1, Bevacizumab 5mg/kg 1 time per 14 days.

The overall objective effect was obtained in 15 patients (39.5±7.9) %: in group 1 - in 7 patients (35.0 + 10.6%), in the 2group - 8 cases (44.4±11.7%), of which complete regression - in 1 (5%) and 2 (11.1%) cases, respectively. In 30% of cases the partial response and a greater number of stabilization (50% and 44.5% respectively) were reported. Progression of the process was observed at 15% in a group 1 and 11.1% of cases in group 2. Terms of remission were group 1 - 8.2 months, group 2 - 12.1 months.

Thus, XELOX + BEV shows the sufficient efficacy in patients with mCRC, both in I and II lines of chemotherapy, with an acceptable toxicity profile.

Keywords: Colorectal cancer, liver metastases, chemo-targeted treatment, vascular endothelial growth factor (VEGF).

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Relevance and purpose of research

Due to high frequency of propagation and low survival of patients, a colorectal cancer became a relevant issue in present oncology, 1 234 000 cases of colorectal cancers are registered per year in the world (GLOBOCAN 2008). In 2009 there were registered 1224 new cases of colon cancer and 1140 cases of rectum cancer in the Republic of Kazakhstan. If one will sum up these figures and combine two localizations under colorectal cancer, that disease will be in 4th place in the structure of oncologic morbidity (Arzykulov et al., 2010).

Chemotherapy of colon cancer was improved due to integration of the following medicines in the complex treatment: oxaliplatin, irinotecan, new peroral Capecitabine - xeloda, and target medicines - bevacizumab and cetuximab.

In metastatic colon cancer the most effective medicine of platinum based ones is oxaliplatin. Adding oxaliplatin to 5-fluorouracil with leucovorin let us increase the effectiveness of treatment by 28.4% and survival by 2.8 months in comparison with treatment in Mayo mode. In order to increase the effectiveness of a first-line treatment of colorectal cancer some research of the combined use of oxaliplatin and irinotecan + 5-fluorouracil / leucovorin was made. The overall response rate ranged from 42 to 78% according to various authors (Goldberg et al., 2004; Schalhorn et al., 2005). However, the addition of irinotecan to oxaliplatin in the 1st line treatment of colorectal cancer is not justified, because this combination significantly limits the ability of the 2nd line, not

increasing the effectiveness of treatment. Capecitabine (Xeloda), which has equal efficacy and less toxicity with 5-fluorouracil/leucovorin (Van Cutsem et al. 2001; Hoff et al., 2001), allows you to include the drug in the modern chemotherapy regimens for mCRC. Bevacizumab -the recombinant monoclonal antibodies which block the different isoforms of VEGF (Arzykulov et al., 2010; Goldberg et al., 2004; Schalhorn et al., 2005). Vascular endothelial growth factor (VEGF) is a powerful angiogenic factor. It serves as a factor in prolonging the life of endothelial cells through inhibition of apoptosis. Hyperexpression of VEGF is seen in 70-80% of patients. By 2009 it became known that addition of bevacizumab to multiple active drug therapy regimens increased the median of progression-free and overall survival of mCRC patients. The effectiveness of bevacizumab in combination with chemotherapy can be assessed in the following studies: Saltz et al., 2000, Kabbinavar et al., 2005, and Hurwitz et al., 2004, where the median of overall survival in the group of patients treated by bevacizumab ranges from 16.6 to 20.3 months (Saltz et al., 2000; Kabbinavar et al., 2005; Hurwitz et al., 2004). In combination with oxaliplatin-containing regimes bevacizumab is at the forefront in the treatment of mCRC, significantly improving the effectiveness of treatment and overall survival compared with the single chemotherapy. All of the above mentioned can be considered relevant for clinical studies aimed at optimizing the systemic therapies of mCRC.

The study discusses increasing efficiency in the treatment of patients with metastatic colorectal cancer.

Materials and methods

The study included 38 patients with mCRC, aged 23-73 (mean age -55 years): there were 16 men (42.1%) and 22 female (57.9%). General condition of patients on the Karnofsky scale - not less than 70%. Stages of the disease: T3N0-2M1-10 (26.3%), T4N1-2M1-8 (15.8%), T2-3N0-2M0-10(31.6%), T4N1-2M0-10 (26.3%).

Previously, the combined treatment of 20 patients was performed (surgery + chemotherapy). All of these patients came for treatment with disease progression after I-line chemotherapy under FOLFIRI or FOLFOX schemes (group 1). The remained 18 patients with mCRC entered the hospital for the first time (group 2). Lesion volume did not exceed 60% in case liver metastases (23-60.5%), while preserving its functionality. And 3 patients had the liver metastases combined with bone metastases of the skeleton, and 3 - with lung's metastases. In 2 cases there was a combined metastatic lesion of bone and lung. In one case the lung's metastases lesion was associated with ovarian cancer. As follow as from the above, the contingent of patients enrolled in the study had been very heavy. The diagnosis of all patients was verified histological.

Mandatory morphological verification of liver metastases was not assumed.

Patients were treated in the mode: Capecitabine in 2000mg/m2 2 times a day from the 1st to the 14th day, 2 - hour infusion of capsular oxaliplatin 130mg/m2, day 1, Bevacizumab 5mg/kg 1 time per 14 days. Antiemetics were ordered for cause. The use of colony-stimulating factors was not regulated.

The objective effect was evaluated after 3-4 courses of chemotherapy, according to Response Evaluation Criteria in Solid Tumors Group (RECIST). Assessment of the lesion was performed by ultrasound investigation (U.S.), X-ray computed (CT) or magnetic resonance imaging (MRI).

Results

The overall objective effect was obtained in 15 patients (39.5±7.9) %: in group 1 - 7 cases (35.0+10.6%), in 2 group - 8cases (44.4+11.7%), including a complete involution - in 1 (5%) and 2 (11.1%) cases, respectively. In 30% of cases the partial response and a greater number of stabilization were reported (50% and 44.5% respectively).

Progression of the process of 15% observed in group 1 and 11.1% of cases in group 2 (Table 1).

TABLE 1. THE EFFECTIVENESS OF TREATMENT

	Full effect	Partial effect	Stabilization	Progression
1group (n-20)	1 (5%)	6 (30%)	10 (50%)	3 (15%)
2 group (n-18)	2 (11,1%)	6 (33,3%)	8 (44,5%)	2 (11,1%)

Note: Period of remission: 1-st group - 8.2 month, 2-nd group - 12.1 month.

The satisfactory subjective tolerability of combination XELOX + bevacizumab should be noted. Nausea and vomiting were stopped easily. No cases of febrile neutropenia documented; however, 6 cycles of chemotherapy were delayed for a period of 1 to 2 weeks for normalization of peripheral blood. Diarrhea was usually of I and II levels, it was relieved by standard loperamide therapy. Neuropathy appeared in case of III and IV toxicity levels it affected the quality of patient's life. Prescribing of group B vitamins allowed reducing some symptoms of peripheral neuropathy. Hand-foot syndrome (HFS) developed mostly after the third course of chemotherapy, but the severity was not greater than II degree. Hypertension and epistaxis, typical side effects which occur when using bevacizumab, were of I and II toxicity levels. Hypertension was stopped through taking of the standard antihypertensive therapy; epistaxis required only topical treatment it was eliminated within 3 days on average.

Thus, XELOX + Bev demonstrate the sufficient efficacy in patients with metastatic colorectal cancer, both in I and II lines of chemotherapy, with an acceptable toxicity profile.

Bevacizumab in combination with oxaliplatin and capecitabine applied to the patients with metastatic colorectal cancer has been accompanied by low risk of complications, improves the treatment outcomes and increases a period preceding a progression, which gives a hope for improving of the long-term results of treatment of such patients.

In conclusion, XELOX + Bev show the sufficient efficacy in patients with mCRC, both in I and II lines of chemotherapy, with an acceptable toxicity profile.

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