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PROSPECTS FOR USE OF TARGET DRUGS IN NEOADJUVANT CHEMOTHERAPY OF COLORECTAL CANCER METASTASIS IN THE LIVER (REVIEW)

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SUMMARY

To increase the effectiveness of chemotherapy (CT) of metastases of colorectal cancer (CRC) in the liver therapy, targeted drugs are used, usually in combination with standard CT. However, at present, there is not enough clinical research data confirming the effectiveness of a combination of various chemotherapy regimens with drugs-inhibitors of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) in conditions of neoadjuvant chemotherapy in this category of patients, which indicates the need for similar studies.

Key words: colorectal cancer, liver metastases, preoperative chemotherapy, targeted drugs.

Colon cancer is one of the most common malignant tumors, annually in the world from 800 thousand to 1.2 million patients with colorectal cancer and about 600 thousand deaths from these diseases are registered (approximately 56% of all cases). In 20% of patients with colorectal cancer (CRC) at the time of diagnosis, distant metastases are detected, primarily in the liver, and in 50% of patients metastases develop during the course of the disease, which becomes the cause of their death [1,3,11-15].

To date, surgery has been the only treatment to achieve long-term survival in patients with liver metastases of CRC. However, only a small group of patients (15-20%) can count on a potentially radical treatment, including removal of the primary tumor of the colon and liver resection. At the same time, traditional liver resection in operable patients allows achieving a 5-year survival rate of 21-37%. Recent advances in chemotherapy (CT) for metastatic colorectal cancer have significantly expanded the indications for treatment of patients at all stages of the

disease, while the prevalence of the disease determines the difference in treatment tactics. Modern combined regimens of systemic chemotherapy have achieved 60% of the local tumor response and up to 20% of initially inoperable patients can be transferred to the surgical group after neoadjuvant treatment [2,4,6, 17].

Neoadjuvant chemotherapy can affect detectable and latent metastases, reducing the volume of the tumor mass, reducing the risk of dissemination during surgery and making possible surgery more radical. In addition, preoperative chemotherapy determines the sensitivity of the tumor to specific drugs, which is taken into account in the appointment of adjuvant treatment. Based on current evidence, the guidelines of the European Society for Medical Oncology (ESMO) suggest that the need for perioperative systemic therapy is determined by "technical criteria for resection and prognostic considerations." Preoperative surgery is warranted in patients with clearly resectable disease and a favorable prognosis; while perioperative FOLFOX or XELOX should be considered when resectability or prognostic criteria are unclear or “not excellent” [4,11,16,18,20].

Despite the fact that the use of cytotoxic drugs significantly improved the relapse-free survival rate of patients with metastatic colorectal cancer, targeted drugs are currently used to increase the effectiveness of therapy, usually in combination with standard chemotherapy. Their action is aimed at inhibiting the cell cycle and DNA repair pathways, induction of apoptosis of tumor cells. Thus, the targeted anti-VEGF drug bevacizumab, which is a monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and inhibits its activity, inhibits angiogenesis and thus tumor growth and metastatic progression, is currently used to treat metastatic colorectal cancer. In addition, recent studies indicate its pro-apoptotic activity, also based on blocking VEGF, which inhibits intracellular signaling pathways that trigger apoptosis. There are also high hopes for blockers of epidermal growth factor receptors (EGFR). When using monoclonal antibodies against epidermal growth factor receptors C225 (cetuximab) in combination with irinotecan after progression with 5-fluorouracil and then irinotecan, in patients with high EGFR levels, the overall effect was 22.5%. Similar studies are carried out in combination with oxaliplatin [7,8,10,12, 15,19].

Current guidelines suggest oxaliplatin-based doublet chemotherapy (FOLFOX / XELOX) as a neoadjuvant therapy for the selection of resectable CRLM, while FOLFIRI or FOLFOXIRI are alternatives. A meta-analysis showed that the addition of molecular targeted therapy had a higher overall response than CT (68% versus 43%), but did not improve survival. Similar results were also observed in the new EPOC study, which examined the effect of combining cetuximab with perioperative systemic chemotherapy: patients who received cetuximab actually had worse disease-free survival (14.1 versus 20.5 months in controls). Given these results, the authors do not recommend adding cetuximab to standard perioperative chemotherapy regimens. Bevacizumab, as well as FOLFIRI in neoadjuvant mode, show a response of 66.7% for resectable liver metastases in patients with CRC, however, whether this leads to an increase in disease-free survival remains to be determined [5,10, 7, 21].

The optimal chemotherapy regimen for transferring patients with metastatic colorectal cancer to an operable state is still unclear. The standard doublet scheme of XT FOLFOX or FOLFIRI had a degree of such transition from 9% to 33%. Compared with FOLFIRI, FOLFOXIRI boosted triplet CT improves the rate of secondary R0 resection from 12% to 36% and median progression-free survival from 6.9 to 9.8 months. and average overall survival from 16.7 to 22.6 months, although due to greater, but manageable toxicity, for example, peripheral neuropathy and neutropenia. The addition of targeted drugs is recommended in current guidelines, however, there is no specific supporting evidence. In another study, taking bevacizumab with XELOX / FOLFOX only moderately improved resectability (from 6.1% to 8.4%) and relapse-free survival (from 8 to 9.4 months), but did not prolong overall survival [6,7].

According to a recent meta-analysis, the combination of bevacizumab and FOLFOXIRI gives more promising results - the rate of transfer of patients to an operable R0 form was 28.1%, and the median overall and disease-free survival was 30.2 and 12.4 months. respectively. Numerous randomized studies have shown that the addition of cetuximab to chemotherapy for inoperable colorectal cancer with the wild-type (WT) proto-oncogene KRAS improved the R0 resection rate by 2–3 times. However, an increase in total resection from 11% to 18% did not lead to an increase in survival in the meta-analysis. Panitumumab, another anti-EGFR agent, also increased the rate of therapeutic resections when added to FOLFOX (29% versus 17%) for inoperable CRC with KRAS-WT [9,12,19, 22, 23].

Thus, at present, there are no reliable data confirming the effectiveness of a combination of various chemotherapy regimens with drugs that inhibit vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) in conditions of neoadjuvant chemotherapy in patients with CRC with liver metastases. Therefore, new studies are needed regarding the use of targeted drugs to improve the immediate and long-term results of treatment in this category, as well as the advantages of their use in preoperative chemotherapy.

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