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PRELIMINARY STUDY RESULTS OF MULTIPLE DRUG RESISTANCE IN PATIENTS WITH ADVANCED TYPES OF COLORECTAL CANCER

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ABSTRACT

In the department of coloproctology of NORC MH RUz 17 patients with disseminated forms of colorectal cancer was made the study of oncogenes and complex treatment by 2 protocols using FOLFOX-4 regime and FOLFIRI regime. In second protocol there used 2 sessions of endolymphatical polychemotherapy FOLFOX-4 regime against EHF-hyperthermia. All patients were performed additional investigations directed to study the presence of multiple drug resistance in them where definition of p53, bcl-2 oncogene expression. In our observations we followed resistance to FOLFOX-4 scheme in 4 patients, and to FOLFIRI scheme in 2 cases. In our studies hyperexpression of oncoproteine p53 was correlated with the effect of conducted therapy whereas hyperexpression of oncoproteine bcl-2 showed therapy resistance.

UDC Code & KEYWORDS

■ 616-006 ■ COLORECTAL CANCER ■ MULTIPLE DRUG RESISTANCE ■ (MDR) ONCOGENES P53 ■ BCL-2■

INTRODUCTION

Chemotherapy is one of the components of combined and complex treatment of colon malignancies. Despite the absolute advantages of modern anticancer chemotherapy the problem of enhancement of treatment efficiency of oncological patients remains urgent as usual [3,5]. Besides high toxicity of cytostatic agents that restricts the performance of adequate chemotherapy, tumor resistance is an important impediment to realize desirable effect of therapy. One of the most spread types of resistance is a so-called multiple drug resistance (MDR) when the onset of resistance to one of the cytostatic agents is accompanied with resistance to other drugs which differ from structure and pharmacodynamics [6,7].

Multiple drug resistance is induced (acquired) in most of tumors, i.e. expression of ABC-transporters and loss of sensitivity to chemotherapy is being developed under drug affection that initially kill tumor cells effectively. According to data of American anticancer society [7] in 50% of oncological patients is registered initial resistance to anticancer preparations and in 49 % of cases resistance to them are manifested under treatment.

Many scientists think [1,2,3] that the rise of membrane glycoprotein, functioning of glutathione system, change of genes and proteins that are responsible for apoptosis, as well as necrotic factor and vascular endothelial factor of cell growth is significant in the development of mechanism of tumor resistance to conducted chemotherapy.

One of the considerable mechanisms of chemoresistance of tumor cell is impossibility to induce its apoptosis. This can be related both with gene hyperexpression responsible for excretion of cytostatic agents from cell (transport genes of MDR family: multidrug resistance gene-1 - MDR-1, breast cancer resistance protein-BCRP, lung resistance-related protein-lrp, multidrug resistance-associated protein-MRP),and with gene mutations responsible for apoptosis. (p53, BCL-2, Rb etc.) [4,6].

MATERIAL AND METHODS

17 patients with advanced types of colorectal cancer received complex treatment in the department of coloproctology of NCC of MH RUz. Observation period for patients was from 3 months to 1 year. After symptomatic operation (colostoma application) palliative chemotherapy by 2 protocols was made:

Protocol- I (13 patients) regime FOLFOX-4 (2 sessions): Oxaliplatin 100 mg/m2 - 1 day; 5-FU 3,0 gr– 46 hour infusion; leukovorin 200 mg/m2 i/v – 1day; at tumor sensitivity to chemotherapy continue chemotherapy session till 6 cycles. In 4 patients developed tumor chemo-resistance and further patients were received FOLFIRI regime by: Irinotekan 180 мg/м2 - 1day; 5-FU 3,0 gr – 46 hour infusion;.

Protocol- II (4 patients). 2 sessions of endolymphatical polychemotherapy by FOLFOX-4 scheme against extremely high frequency (EHF) -hyperthermia. At tumor sensitivity to chemotherapy the treatment was conducted up to 6 cycles. 2 chemoresistant patients continued to receive FOLFIRI by scheme.

Patients were divided as follows: 10 women and 7 men aged between 24 to 71 years. By stages: T4N2M0-13, T4N2M1- 4. Morphologically, adenocarcinoma of various stages of differentiation was observed in most of cases and mucinous carcinoma - in 3 patients. All 4 patients received EHF-therapy of abdominal cavity with source direction to primary tumor during endolymphatical polychemotherapy.

All patients were made additionally investigations directed to study the presence of multiple drug resistance in them via definition of oncogene expression p53, bcl-2. Clinical effect of therapy was assessed by the following indices: toxicity of chemotherapy; objective condition of patients by WHO ECOG scale.

RESULTS AND THEIR DISCUSSION

No complications were after symptomatic operations. In 14 days after symptomatic operations patients started receiving sessions by 2 protocols. After 2 sessions of polychemotherapy there studied its effect by above stated criteria.

Study of side effects of conducted therapy made by FOLFOX-4 scheme showed the following results: hematological toxicity of I degree was revealed in 3 patients, of II degree in 1 patients; neurotoxicity of II degree was detected in 3 patients. To diagnose the toxicity of II degree reduction of the dose of chemicals was carried out. No signs of endotoxemia followed in the use of FOLFIRI regime. Objective patients state was assessed in 2 balls in 11patients , in 3 balls -6 patients by WHO ECOG scale. In

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morphological investigation of biopsy material there found medical pathomorphosis of I degree in 5, II degree in 4 patients. To identify p53 hyperexpression (+++) was detected in 9 patients and showed high rates of apoptosis in tumor tissues. To identify bcl-2 hyperexpression of the protein was revealed in 5 patients. Dynamic control for tumor condition using USD and CT showed the following data: tumor regress on 50% was noted in 4; on 25% in 2 patients. Stabilization of process was noted in 5 patients. Tumor progressing was observed in 6 patients. 4 patients died against the background of tumor progressing. Along with antitumor effect of chemotherapy it is necessary to note the complications associated with the performance of these procedures. (rapture of the lymphatic vessel and extravasation of chemical preparation in soft tissues). Locally this complication demonstrated as lymphangoit-in one patients.

CONCLUSION

Result obtained presented that multiple drug resistance is able to develop after performance of various forms and methods of polychemotherapy. In our observations we followed resistance to FOLFOX-4 scheme in 4 patients, and to FOLFIRI scheme in 2 cases. Thus, resistance is developed after endolymphatical introduction of chemical in 2 cases. Study of oncomarkers and detection of the role in the effect of conducted drug therapy in patients with advanced types of colorectal cancer can allow further prognoses the currency of this process and assess the effect of conducted therapy. Hyperexpression of oncoproteine p53 correlated the effect of conducted therapy whereas hyper expression of oncoproteine bcl-2 demonstrated therapy resistance.

In particular:

1. It is necessary to carry out the study of oncomarkers p53, bcl-2v to prognose the effect of therapy in patients with advanced forms of colorectal cancer.

2. It should be carry out the regime of FOLFOX-4 in 1 line of polychemotherapy and as second FOLFIRI regime.

3. The use of endolymphatical chemotherapy with EHF-therapy results in valuable regression of tumor in patients with hyperexpression p53 gene that promotes improvement of remote therapy outcomes for patients with advanced stage of rectal cancer.

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