ROLE OF LYMPHATIC POLYCHEMOTHERAPY AND EHF THERAPY IN TREATMENT OF COLORECTAL CANCER COMPLICATED BY CARCINOMATOSIS OF ABDOMINAL CAVITY

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ABSTRACT
Aim: to improve treatment results of colorectal cancer, complicated carcinomatosis of abdominal cavity, by associated using of endolymphatic chemotherapy (ELCT) and local extremely high frequency (EHF) therapy.

Materials and methods
I-group – 21 people (33.3%) performed colostomy, then neoadjuvant systemic chemotherapy by the scheme FOLFOX-4. It was held two cycles, after two cycles there were received cytoreductive surgery;
II group – 26 people (41.3%) received cytoreductive operations with early postoperative intra-abdominal chemotherapy by oxaliplatin (200 mg/m(2)) at day 1 and 5-FU 650 mg/m(2) from days 1 to 4.
III group – 16 people (25.4%) also performed colostomy, then used 2 courses of ELCT with local EHF therapy and all patients were received cytoreductive operations. ELCT was carried out injecting oxaliplatin-100 mg/m(2) a day during 12 hours and then 5 – FU in doze of 600 mg/m2 a day during 72 hours by the instrumentality of the dozer and LV-200 mg/m(2) (2-h intravenous infusion). During ELCT patients received local EHF therapy in abdominal cavity for an hour.

Results
After chemotherapy the partial regress of tumor observed in 1st group in 4.8 % and in 3rd –37.5 %, stabilization of process noted in 28.6 and 50% cases, progressing –66.7 and 12.5% cases correspondingly to groups. Histomorphologic study of malignant foci after ELCT+EHF therapy showed reduction of specific area of parenchyma cancer cell from 57 till 39% simultaneous growth of stroma from 40 till 58% and in necrosis area – from 1,8 till 2,5%. Mitotic activity of tumor cells in the 1st group decreased (average in 22 un.), but in 3rd group it decreased until 11 units.

Analysis of life span showed that in 1st group of patients 2-year survival rate was 66,7%. In 2nd group of patients 2-year survival rate was 42,3%.

Conclusion
ELCT+EHF-therapy has high clinic efficacy and promotes to decrease terms of progression of tumor process, increases life span from 0 till 24% and quality of life of the patients. ELCT+EHF-therapy brings to reduction of specific area of parenchyma in cancer cells from 57 till 39% with simultaneous growth of stroma area from 40 till 58% and necrosis area – from 1,8 till 2,5%. ELCT+EHF-therapy lowers mitotic activity of tumor cells, activates apoptosis, hemodynamic and metabolic rates.

INTRODUCTION
The problem of treatment of the rectal cancer became more important over the last years. Annually about one million of people were sick due to rectal cancer almost a half of them (440 thousand) dies. In Uzbekistan the rectal cancer is on the 4th place in the general structure of oncopathology. in 2008 there were registered 3,56 cases per 100 000 of population, 41,4% of them were revealed at stage III and 19,2% at stage IV. The 5 years survival due to colorectal cancer were 52,8%[1].

Progressing of carcinomatosis peritonem is a sign of severe form of cancer. Many factors influence on its frequency, including the presence of free cancer cells in the content of abdominal cavity. In disseminated colon cancer, there found free cancer cells in abdominal cavity in 54,7% cases 2,3. In these cases, the most important point belongs on cytoreductive operations.

According to the literature4-9 decreasing of tumor mass is able to increase the sensitivity of remained tumor tissues to medicamental and radiative therapy, specific weight of proliferous cells, and to improve cellular distribution of oxygen. Cytoreduction reduces the number of resistant clones, production of immunosuppressive peptides and relieves the immune system. Large mass of tumor tissues remain during cytoreductive operations; Therefore, the main treatment measure, directed to elimination of this malignant mass is intra-abdominal chemotherapy.

In the opinion of certain authors [7,10] unsatisfactory results of abdominal carcinomatosis treatment are resulted from bad permutation of antitumor preparations in abdominal cavity by systemic chemotherapy due to the presence of hemoperitoneal barrier. Regional chemotherapy is the most effective version in this condition as intra – abdominal hypothermic chemotherapy and endolymphatic chemotherapy (ELCT) using different radiomodifiers (chemical, physical) that provides selective rise of chemo sensitivity of tumor cells.

ELCT differs with low toxicity and therapeutic effectiveness[5,11,12]. During endolymphatic dosing of 5-fluorouracil into abdominal cavity reaches on average 24 hours and the time of maximal progress in abdominal cavity reaches to 6,7 hours when intravenous induction 3,8 hours. Using parameter of comparative bioavailability (B) (ratio of AUC in endolymphatic and intravenous induction) selectivity of endolymphatic induction in relation to abdominal cavity is been found out (B=2,5) wherewith highly perfusion organs (B=0,7)[6,13]. When used only surgical method of treatment three-year survival rate was 58, 4 %, but using preoperative ELCT it increased up to 78, 1%. ELCT with 5-Fluorouracil (5-Fu) and platydiam use with local perfusion organs relieves the immune system. Large mass of tumor tissues remain during cytoreductive operations; Therefore, the main treatment measure, directed to elimination of this malignant mass is intra-abdominal chemotherapy.
EHF-therapy, electron-seeking combinations (metronidazole and its derivatives, hyperglicemia, and a number of anticancer drugs[15-19] are often used as modifiers. In complex therapy of malignant neoplasms EHF therapy reduces postoperative complications, evidence of chemotherapy side effects, number of relapses and iniaditation, has hemoprotective and immunomodulatory effects.

The aim of our scientific research was to improve treatment results of colorectal cancer, complicated carcinomatosis of abdominal cavity, by associated using of lymphatic polychemotherapy and local EHF therapy.

MATERIALS AND METHODS

Our study included 63 patients that were treated in colorectal department of Republican Oncology Scientific Center of Uzbekistan from April 2005 till December 2009. Male were 66%, female - 34%. The patients aged from 18 to 62. At 38 patients were rectal cancer, 14 - sigmoid cancer, 6 - descending colon and 5 of them had transverse colon cancer. The study of histological structure showed that 17 patients had high differentiated, 24 - moderately differentiated, in 22 – low differentiated adenocarcinoma. In 89,5% patients observed locally advanced tumor process. The patients contingent studied was divided into three groups by the types of conducted treatment:

I group – 21 people (33.3%) performed colostomy, then neoadjuvant systemic chemotherapy by the scheme oxaliplatin-100 mg/m(2) and LV-100 mg/m(2) (2-h intravenous infusion) followed by 5-FU, 2,400 mg/m(2) (46-h continuous infusion) it was held two cycles, after two cycles they were received cytoreductive surgery;

II group – 26 people (41,3%) received cytoreductive operations with early postoperative intra-abdominal chemotherapy with early postoperative intra-abdominal chemotherapy by oxaliplatin (200 mg/m(2) from days 1 to 4. Patients allocation to groups depending on histological structure of timorous process presented in the Table 1. Patients carried out general clinic, biochemical examinations, hemodynamic and metabolic rates were studied in process of treatment.

RESULTS AND THEIR DISCUSSIONS

Postoperative complications were observed in 6 patients. In 1st group festering post-operative wounds were observed in 1 patient, in 2nd and 3rd groups - in 1 patient. From among surgical complications should be noted that wound abscess marked in 2nd group in 1 patient. Postoperative lethality made 3.2% (2 patients), out of them in 1st group died 1 patient (4.8%), in the 2nd group - 1 (3.8 %), in the 3rd group mortality was not observed. Lethality in all cases was connected with pathology of cardiovascular system revealed before operation. Thus, surgical complications after cytoreductive operations were observed generally in 1st and 2nd groups.

After chemotherapy the partial regress of tumor observed in 1st group only in 1 patient (4.8 %) and in 3 – 6 (37.5 %), stabilization of process noted in 6 and 8 (28,6 and 50%) patients, progressing - 14 and 2 (66,7 and 12,5%) patients correspondingly to groups. Histomorphologic study of malignant foci after ELCT+EHF therapy showed reduction of specific area of parenchyma cancer cell from 57 till 39% simultaneous growth of stroma from 40 till 58% and in necrosis area - from 1,8 till 2,5%.

Mitotic activity of tumor cells in the 1st group decreased (average in 22 un.), but using ELCT+EHF therapy it decreased until 11 units. The obtained data definitely testify biologic activity inhibition of tumor cells when used method ELCT+EHF.

Table 1. Patients allocation to groups depending on histological structure.

<table>
<thead>
<tr>
<th>Term (months)</th>
<th>1st group</th>
<th>2nd group</th>
<th>3rd group</th>
</tr>
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<tbody>
<tr>
<td>3</td>
<td>n=21</td>
<td>n=26</td>
<td>n=16</td>
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<td>6</td>
<td>7</td>
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<td>12</td>
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</tr>
<tr>
<td>24</td>
<td>19</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>72</td>
<td>51</td>
</tr>
</tbody>
</table>

Table 2. Distribution of patients by the period of progression process.

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In group, the patients received ELCT+EHF therapy during or directly after session, the following subjective treatment results were reached; pain began to decrease as by spread, so by intensity already after 10-15 minutes from the beginning of session; fully disappearance of painful syndrome came after 30-40 minutes. All patients experienced reduction of weakness and improvement of mood.

Further observation (12-13 days) showed that analgesic effect remained or increased, sleep improved, appetite normalized and weakness lessen. Number of lymphocytes and amount of hemoglobin gradually turned to initial amount, but mitotic index of lymphocyte increased in average from 2,1±0,24 till 10,5±0,67. Body weight enlarges up to 720±103 g. Analysis of long-term results of treatment showed that progression of disease during 2 years in all groups diagnosed in 96,8% patients (table.2). In 1st group progression of disease was not marked until 2 months; progression of disease developed in all patients at term from 2 to 22 months. In 2nd group disease progression is observed in all incidents within 4 to 24 months. In 3rd group disease progression began to observe after 6 months. In all they occurred in 13 patients (81,2%). In 3 patients tumor recurrent did not occurred during 2 years.

Analysis of life span showed that in 1st group of patients 2-year survival rate was 0%. In 2nd group of patients 2-year survival rate was 3,9%. Besides factual survival rate of patients we used the technique of estimation of actuarial survival rate. Calculation of actuarial survival rate made by Cutler and Edelen[17]. According to the data of actuarial survival rate was 3,9%. Besides factual survival rate of patients we used the technique of estimation of actuarial survival rate which passed 24% patients, which suffered progressing of tumor process, increases life span from 0 till 22 months. In 2nd group disease progression, is observed in all incidents within 4 to 24 months. In 3rd group disease progression began to observe after 6 months. In all they occurred in 13 patients (81,2%). In 3 patients tumor recurrent did not occurred during 2 years.

Pathogenetic effect of local hyperthermia bases on ability of thermal factor causes stable denaturation of protein structures in tumor cells, change rheological blood properties with disorder of blood flow microcirculation in the area of tumor and also increase permeability of cytoplasmic membrane at the expense of lipid peroxidation that results in penetration and depositing cellotoxic factor into cancer cell itself [13,18,20,21]. It is determined that synergistic effect combination of cisplatin+5-FU increases general cytoreductive surgery with using further ELCT+EHF-hyperthermia (3rd group) in 3,2 times exceed the rates of 1st group and in 10 times – of 2nd group. The use of ELCT+EHF-hyperthermia increases relapse-free period in average in 2 times.

Two-year survival rate passed 24% patients, which suffered from cytoreductive operations with following ELCT+EHF-hyperthermia. Comparative analysis of factual and actuarial survival showed that two-year survival rates in taking cytoreductive surgery with using further ELCT+EHF-hyperthermia (3rd group) in 3,2 times exceed the rates of 1st group and in 10 times – of 2nd group. The use of ELCT+EHF-hyperthermia increases relapse-free period in average in 2 times.

REFERENCES

2. Chissov VI, Starunskiy VV, Kovalev BN. Organizational context of early detection in malignant neoplasms. Russian oncological journal 2002; (2); p.43-45.
11. Nepomnyashiy YM, Moisnkeno TI. To morphologic explanation of neoadjvant chemotherapy of malignant tumor in habitat organism in various modification. Higher education establishments. Natural sciences 2004; (1); p.92-97.
18. Vashakmadze LA, Trahtenberg AX, Sidorov DV et al. Results of cytoreductive operations in metastatic colorectal cancer. IV congress of oncologists and radiologist of CIS. Baku. 2006; p.150