

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 their 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

ELCH+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. ELCH+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.

UDC Code & KEYWORDS

■ 616-006 ■ COLORECTAL CANCER ■ COMPLEX THERAPY ■ ENDOLYMPHATIC CHEMOTHERAPY ■ EXTREMELY HIGH FREQUENCY THERAPY ■

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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 peritoneum 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 permeation 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 tissue has 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 extremely high frequency (EHF) – therapy in combined treatment of local advanced cancer of low ampullary section of rectum allowed to increase five-year survival rate from 63 till 81% and decrease the rates of recurrent tumor in 20 till 10%[14].

EHF-therapy, electron-seeking combinations (metronidazole and its derivative), hyperglycemia, 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 innidiation, 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 poly-chemotherapy 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 their were received cytoreductive surgery;

II group - 26 people (41,3%) received cytoreductive operations with early postoperative intra-abdominal

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

Adenocarcinoma differentiation degree	1st group, n=21		2st group, n=26		3st group, n=16	
	N	%	n	%	N	%
High	6	28.6	7	26.9	4	25
Moderate	11	52.3	8	30.8	5	31.2
Low	4	19.1	11	42.3	7	43.8

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 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 EHF - therapy in abdominal cavity for an hour. EHF therapy was performed on the apparatus "Явь -1М" and was conducted from 1st till 5th day in ELCT by 5,6 mm wave length and frequency of 50 electromagnetic oscillations MHz within 60 minutes.

Patients' groups compared to tumor process spread. Character of cytoreductive operations is practically associated with all of them. Besides operative intervention in primary tumor in 96,8% of patient was performed belled lymph dissection, 50,8% - abdominoectomy, 19,1 % - exsection of urinary bladder or ureter, 15,9% - resection of small intestine, 9,5% - extirpation of hysterectomy with appendages.

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.

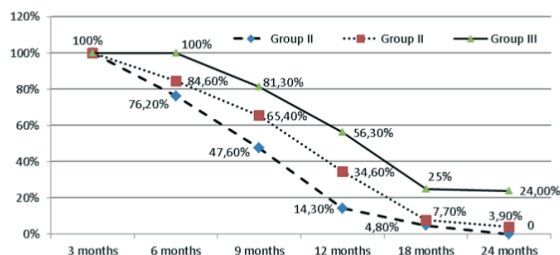
After chemotherapy the partial regress of tumor observed in 1st group only in 1 patient (4,8 %) and in 3 - 6 (37,5 %), stabilization of process noted in 6 and 8 (28,6 and 50%) patients, progressing - 14 and 2 (66,7 and 12,5%) patients correspondingly to groups. Histomorphologic study of malignant foci 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 2. Distribution of patients by the period of progression process

Term (months)	1-group n=21		2- group n=26		3- group n=16	
	n	%	n	%	n	%
3	7	33.3	5	19.2	0	0
6	8	38.1	6	23.1	2	12.5
9	5	23.8	11	42.3	6	37.5
12	1	4.8	3	11.5	2	12.5
18	0	0	1	3.8	2	12.5
24	0	0	0	0	1	6.3
Total	21	100	26	100	13	81.3

Picture 1. Actuarial survival. Comparative characteristic rates of 1-2 year patient survival of I, II, III groups.[17]



When studied hemodynamic and metabolic rates it was specified that almost in 90% of patients the condition of hemodynamics remained stable as before so after chemotherapy in all groups of patients. Just after session of the ELCT + EHF therapy happened the reliable growth of hemoglobin level, absolute number of erythrocyte and leucocytes, percentage of lymphocyte, decrease percentage of segmented neutrophil content.

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 $2,1 \pm 0,24$ till $10,5 \pm 0,67$. 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 Ederer[17]. According to the data of actuarial survival rate we obtained the following rates for research and control groups (picture 1).

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.

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 cellulotoxic factor into cancer cell itself [13,18,20,21]. It is determined that synergistic effect combination of cisplatin+5-FU increases general cytotoxicity in 10-15 times by combination with EHF therapy. In patients with initial reduced level of leucocyte peripheral blood, EHF therapy may increase it till the level that allows administrating course of chemotherapy[11,12,16,19,20,22,23]. Not depressing antitumor activity of chemicals (5-FU, cisplatin), EHF therapy considerably reduces evidence of their toxic effect (sickness, vomit, intestinal upset, body weight loss and etc.), that provides to carry out the treatment in corpore without changing terms and mode of chemotherapy[6,19,24-26].

CONCLUSIONS

1. Endolymphatic polychemotherapy and local 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.

2. The use of ELCH+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%.

3. Endolymphatic polychemotherapy and local EHF therapy lowers mitotic activity of tumor cells, activates apoptosis, hemodynamic and metabolic rates.

REFERENCES

1. Reports of ROSC, Ministry of Public Health of Republic Uzbekistan. Decease statistics and death rate from malignant neoplasms in 2008, Tashkent. Medicine 2009; p.52
2. Chissov VI, Starunskiy VV, Kovalev BN. Organizational context of early detection in malignant neoplasms. Russian oncological journal 2002; (2): p.43–45
3. Prorokov VV, Malihov AG, Knish VI. Modern principles of diagnostics and screening of rectal cancer. Practical oncology selected lectures S.Petersburg 2004; p.162–167
4. Crane CH, Skibber JM, Birnbaum EH. The addition of continuous infusion 5-FU to preoperative radiation therapy increases tumor response, leading to increased sphincter preservation in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2003; 57(1): p.84-89
5. Knish VI, Cherkes VL, Ananyev VS. Methods to improve the results of treatment of colorectal cancer. Russian Oncol Jour 2001; (5): p.25-27
6. Kurpeshev OK, Tsib AF, Mardinskiy YS. Development mechanisms and overcoming methods of tumor chemoresistance. Rus Onc J 2003, (2): p.50-53
7. Nevolskih AA. Influence of local hyperthermia on late result combination therapy locally advanced rectal cancer. Med Redio Scien Center of Rus AMS cand. Med. Scien, code of speciality 14.00.14 M 2001; p.19
8. Tsarkov PV, Vorobyov GI, Odaryuk TS. Place and role in balled aorta-iliac pelvic lymphadenectomy in treatment cancer of low ampullar section of rectum. Practical oncology: Selected lectures 2004; p.168–180
9. Zolotuhin SE, Dones VL, Melnik ND. Rectal cancer with generalization resulting process of palliative exsection. Thesis II congress of oncologists of CIS countries, Kiev. Oncology 2000; (22): p. 733.
10. Tamrazov RI. Preoperational thermoradiotherapy in combination therapy of patients with rectal cancer. Russian Oncol Scien Cen named after Blokhin NN, AMS cand. Med. Scien, code of speciality 14.00.14 author's abstract M. 2001; p. 25
11. Kayrak OS, Lisovskaya N, Kuzmenko Y. Modifier usage in conduction of endolymphatic therapy of patient malignant tumor. Thesis II congress of oncologists of CIS countries, Kiev. Oncology 2000; (22) p. 324
12. Kolesnik YA. Effect of endolymphatic polychemotherapy and local SHF-hyperthermia in multimodality therapy of rectal cancer. Clinical Surgery 1998; (8): p.32-33
13. Kunisaki C, Shimada H, Nomura M et al. Does continuous hyperthermic peritoneal perfusion have any prophylactic or therapeutic efficacy on peritoneal dissemination of gastric cancer? 4th International gastric cancer congress, NY, 2001; p.31
14. Nepomnyashiy YM, Moisenko TI. To morphologic explanation of neoadjuvant chemotherapy of malignant tumor in habitat organism in various modification. Higher education establishments. Natural sciences 2004; (1): p.92-97
15. Bedrosian I, Rodriguez-Bigas MA, Feig B. Predicting the node-negative mesorectum after preoperative chemoradiation for locally advanced rectal carcinoma. J Gastrointest Surg 2004; 8(1): p.56-63
16. Chushkin NA, Tupikina GN, Zaharov SN, Salo LY. The immediate result of thermoradiotherapy inoperable rectal cancer in patient aged and senility. Materials of Habrov Land Gerontol Confer Khabarovsk 2000; p.201-202

17. Cutler SJ, Ederer F. Maximum utilization of the table method in analyzing survival. *J Chron Dis* 1958; (8): p.699-712
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
19. Yonemura Y. A new treatment strategy for peritoneal dissemination peritonectomy intraoperative chemohyperthermia, and EPIC. 4th International gastric cancer congress. NY 2001; p.335
20. Katayama K, Kimura T, Iida A. et al.. Chemo hyperthermic peritoneal perfusion (CHPP) to treat peritoneal dissemination of gastric cancer 4th International gastric cancer congress. NY 2001; p.436
21. Nomura E, Niki M, Fujii K et al. Efficacy of intraperitoneal and intravenous chemotherapy and upper abdominal evisceration for advanced gastric cancer. 4th International gastric cancer congress. NY 2001; p.438
22. Akbarov ET. Results improving of cancer treatment of rectum by using long time endolymphatic and regional lymphatic polychemotherapy. In press. Tashkent 2005; p.24
23. Ruo L, Paty PB, Minsky BD. Results after rectal cancer resection with in-continuity partial vaginectomy and total mesorectal excision. *Ann Surg Oncol* 2003; 10(6): p.664-668
24. Abelivich AI, Ovchinnikov VA. New type of lymphodissection in rectal cancer with metastasis in groin glands. *Voprosi Oncologii* 2003; 49(6): p.766-768
25. Lehnert T, Golling M, Buchholz J. Locally recurrent rectal carcinoma. *Chirurg* 2004; 75(1): p.38-44
26. Levin YM. Endoecological medicine. *Medical bulletin* 2002; (5): p. 8