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COMPARATIVE EVALUATION OF THE COMPLEX TREATMENT OF RECTAL CANCER PATIENTS (CHEMOTHERAPY AND X-RAY THERAPY, UKRAIN MONOTHERAPY)

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Summary: *A total of 48 patients suffering from rectum cancer were included in this randomized study conducted at the Proctology Department of the Donetsk Regional Anti-Cancer Center. Patients in group I (24 patients) received an intensive course of high fractional X-ray therapy (cumulative dose up to 25 Gy) with direct protracted endolymphatic chemotherapy with 5-fluorouracil (5-FU) instilled in 600 mg/m^2 each day before operation, up to a cumulative dose of 5 g. The 24 patients in group II were treated with Ukrain as monotherapy, 10 mg each second day before operation (up to a cumulative dose of 60 mg) and a total of 40 mg after surgical intervention. Repeated Ukrain courses (100 mg/per course) were also given 6 months after surgical operation. In each ease preoperative treatment was followed by routine surgical operation. Prolongation morbi were found to have developed 14 months later in six patients in group I (25.0%), whereas in group II they were found only in two cases (8.3%). Comparative investigation of objective and subjective signs, analysis of results of instrument and X-ray data, as well as dynamic study of the histological structure of rectal tumors, indicate that Ukrain exerts a more potent malignotoxic and immunomodulating action than other types of anticancer treatment.*

Introduction

The unsatisfactory results of 5-fluorouracil (5-FU) application for the treatment of colorectal cancer patients as well as its high toxicity drives the search for new, more effective remedies (1, 2). The chelidonin thiophosphoric acid derivative Ukrain (USA patent No. 4.970.212, 1990) seems to be a promising agent for the treatment of colorectal cancer. The special immunological activities of Ukrain (NSC-631570) have been demonstrated not only *in vitro* (3-8), but also *in vivo* and in clinical studies (9-13). The malignotoxic properties of Ukrain have been tested on different cancer cell culture lines, *i.e.*, EORTC, the Netherlands: E90/029, W122, UKRS-22; NSC-62388657 National Cancer Institute, USA NSC: 63 1570-W/1 (14, 15). In addition, Nowicky *et al.* have reported increased tumoricidal action of Ukrain on murine adenocarcinomas (11).

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Comparative assessment carried out at the National Cancer Institute (Bethesda, Maryland, USA) revealed that the cytotoxic effect exerted by Ukrain upon human colon carcinoma cell culture lines (Cola 205, DLD-1, HCC-2998, HTC-116, HT29, KM12, KM20L2, SW620) was 100-fold higher than the cytotoxic effect of routinely used 5-FU (13). As was pointed out in the EORTC study, the colorectal cell line CXF displays high sensitivity to toxic Ukrain action. The malignotoxic properties of Ukrain *in vitro* are now undoubted, but special study of the correlation between the effects of Ukrain *in vitro* and clinical experience needs to be carried out. The purpose of this study was to investigate the above-mentioned problem and to evaluate the efficacy of Ukrain as a new potent drug in the treatment of colorectal cancer.

It is quite understandable that any cytostatic drug exerting malignotoxic action inevitably leads to general toxic action and immune system suppression in colorectal cancer patients. Oncological therapy would ideally require maximum toxicity against tumor cells and minimal toxicity to the organism. Special attention has been drawn to the stimulation of the immune system. Ukrain seems to be a good combination of the above-mentioned properties (12). In this study, based on clinical observation, we tried to estimate the therapeutic possibilities of Ukrain in the treatment of a severe disease like colorectal cancer, in comparison with traditionally used radiation therapy and endolymphatic chemotherapy with 5-FU.

Patients and methods

A total of 48 patients (30 men and 18 women) suffering from rectal cancer or who had been treated at the Proctology Department of the Donetsk Regional Anticancer Center were enlisted in a randomized study which was approved by the Ethics Commission of the Center. The patients' ages ranged from 36-66 years, the mean value was 56.3 years. The experimental groups were made up of patients with rectal tumors corresponding to T3-4N0M0 and T3-4N1-3M0 stages of TNM classification without severe accompanying disease or complications of the basic process. Histological verification of tumors carried out in each case before starting the special treatment revealed adenocarcinomas at different degrees of differentiation in 89.7% of cases.

All patients were subdivided into two randomized groups. Patients in group I (n=24) received a preoperative intensive course of high-fractional X-ray therapy (6 Gy daily, up to 25 Gy) with direct endolymphatic chemotherapy with 5-FU (600 mg/m^2 daily), up to a cumulative dose of 5 g. After preoperative treatment all patients underwent a surgical operation. Group II comprised 24 patients who received monotherapy with Ukrain (Nowicky Pharma, Vienna, Austria): i.v. injections of 10 mg each second day before surgical operation (up to 60 mg cumulative dose) and a total of 40 mg during the postoperative period. Additional repeated courses (100 mg Ukrain per course) were performed 6 months after surgical intervention.

Only patients without verified distant metastases were included in the randomized study. Metastatic invasion into regional lymphatic glands was found in 56.3% of cases (Table I). Where necessary, patients received corrective infusion, cardiotropic and general reinforcement therapy.

The complex preoperative study involved the determination of tumor dimensions and mobility, general and biochemical analysis of the blood and urine, assessment of immune status (T- and B-lymphocytes count, concentrations of immunoglobulins A, M, G; plasma content of the circulating immune complexes (CIC) and phagocytic activity of neutrophils). In addition, the immune-enzymatic method was used to determine the blood content of

Table I *Distribution of colorectal cancer patients according to TNM-classification*

TNM staging	Patient groups	
	5-FU + X-ray therapy	Ukrain therapy
T3N0M0	2	1
T3N1M0	2	2
T3N2M0	1	1
T3N3M0	3	1
T4N0M0	8	10
T4N1M0	1	2
T4N2M0	3	2
T4N3M0	4	5
Total	24	24

5-FU = 5-flurouracil

α-fetal protein (AFP) and carcino-embryonal antigen (CEA). Additional topographical data were obtained by means of abdominal sonography and computerized tomography. X-ray studies of the lungs and other examinations were also performed. Tumor dimensions, as measured by rectoscopy, fibroscopy and irrigoscopy, varied from 2.8±3.4 cm to 8.6±9.8 cm.

Results

After finishing the specific preoperative treatment for each group, repeated dynamic followup examinations were performed. These included assessment of patients' general condition, expression of pain syndrome, and measurement of tumor dimensions. The toxicity of chemotherapy with reference o its influence on hemopoiesis was also determined for all groups of patients. The most expressed signs of the toxic action of chemotherapy were found in patients in group I who received combined endolymphatic chemotherapy and radiation therapy. The mean value of the Karnofsky index decreased from 71.3 to 66.4. In contrast, practically no toxic effects were found in patients in roup II, treated with Ukrain. Moreover, in these atients an improvement in the general condition nd appetite was observed, as well as the disappearance of partial intestine impassability. Group II patients displayed a certain improvement in hemopoiesis with a statistically significant rise in erythrocyte and lymphocyte counts, while patients treated with combined endolymphatic chemotherapy and radiation therapy showed a tendency to develop anemia and lymphopenia. The Karnofsky Index increased to 78.3% from 70.8%. The most pronounced changes in immune status were also observed in group II patients who received Ukrain monotherapy (Table II). In this group a substantial rise in the T- and B-lymphocyte counts, increased phagocytic activity of neutrophils, and an increased content of immunoglobulins A, M, and G were observed. Reduced plasma concentration of AFP, CIC and CEA was characteristic for group II patients. No marked changes in immune status were detected in group I patients.

Reduced tumor dimensions were found in both groups of patients after preoperative therapy. Preoperative X-ray therapy in combination with endolymphatic 5-FU led to resorption of tumors in up to 18% of cases, while the mean value of tumor resorption with Ukrain monotherapy was 22%. Various kinds of rectal resection were performed following preoperative therapy. The majority of the surgical interventions (95.2%) were sphincter-saving in character and involved various kinds of abdominal-anal resections of the rectum. Two

Table II *Some parameters characterizing the immune status and hemopoiesis of patients*

Parameters	5-FU + X-ray therapy		Ukrain therapy	
	before	after	before	after
Erythrocytes	3.9 ± 0.35	3.4 ± 0.21	3.9 ± 0.36	4.11 ± 0.24
Leukocytes	9.2 ± 0.96	7.4 ± 0.88	9.3 ± 1.21	9.1 ± 1.51
Lymphocytes	23.8 ±3.17	17.6 ± 2.17	23.9 ± 4.01	28.6 ± 4.12
Rod-shaped	11.8 ± 2.57	13.8 ± 3.21	12.1 ± 2.56	9.4 ± 8.87
Segmented	55.8 ± 3.7	57.6 ± 2.96	55.3 ± 3.61	53.4 ± 3.58
Eosinophils	3.5 ± 1.11	2.8 ± 0.93	3.2 ± 0.84	4.3 ± 1.24
Monocytes	5.6 ± 1.09	5.9 ± 1.13	6.1 ± 1.13	5.8 ± 1.08
Proteins	71.02 ± 2.18	67.4 ± 1.31	69.2 ± 2.03	76.1 ± 2.67
Bilirubin	18.1 ± 3.12	21.6 ± 3.18	18.6 ± 2.64	16.9 ± 2.21
T-lymphocytes	38.8 ± 2.86	34.1 ± 2.79	39.3 ± 3.26	46.2 ± 3.48
B-lymphocytes	9.12 + 1.37	8.4 ± 1.89	9.14 ± 1.36	11.2 ± 2.71
Neutr. phag. activ.	80.2 ± 1.91	85.4 ± 1.51	86.4 ± 2.02	98.1 ± 2.1
CIC	279.2 ± 17.6	296.1 ± 19.31	273.1 ± 18.1	211.6 ± 15.31
AFP	28.7 ± 2.81	30.1 ± 3.03	26.2 ± 2.01	5.1 ± 0.84
CEA	4.8 ± 1.02	4.5 ± 0.87	4.8 ± 0.91	1.2 ± 0.18
MCA	16.2 ± 1.83	18.4 ± 2.12	17.8 ± 1.93	4.1 ± 0.76
IgA	2.93 ± 0.86	3.14 ± 0.56	2.87 ± 1.17	4.12 ± 1.63
IgM	0.76 ± 0.11	0.86 ± 0.18	0.72 ± 0.12	0.96 ± 0.21
IgG	12.6 ± 1.85	14.2 ± 1.47	12.8 ± 1.42	19.1 ± 2.34

5-FU = 5-flurouracil; CIC = circulating immune complexes; AFP = α-fetal protein; CEA = carcio-embryonal antigen; MCA = mucin-cancer antigen.

patients with tumors of the anal canal underwent resection according to Keny-Mylse. In total, postoperative complications developed in nine (18.8%) cases. Postoperative complications were found to develop mainly in patients from group 1 – 7 cases (29.1%). In contrast, no postoperative purulent inflammatory complications were revealed in group II patients. Atony of the urinary bladder developed in two (8.3%) patients treated with Ukrain monotherapy.

Clinical observation of all patient groups was conducted for a period of 14 months. Six months after the first course of Ukrain monotherapy, all patients in group II were subjected to repeated Ukrain treatment with 10 mg i.v. every other day, up to a cumulative dose of 100 mg. In the course of observation of group I patients who received complex chemotherapy and X-ray therapy, the continuation of tumor development was observed in eight cases (33.3%). Relapses of the colorectal tumor into the small pelvis parenchyma were registered in five cases (20.8%) and metastases to the liver in three cases (12.4%). These problematic patients were subjected to a repeated course of the complex chemotherapy and X-ray therapy. One patient (4.1%) with metastatic liver injury died 11 months following surgical intervention.

In contrast, prolongation morbi were detected in only four patients (16.6%) in group II who received Ukrain monotherapy during pre- and postoperative periods. Of these, one man had a tumor relapse in the pararectal parenchyma, and one woman had multiple metastases to the liver. The man was subjected to an additional two courses of therapy with Ukrain (100 mg per course) in combination with X-ray treatment aimed at the site of the relapse. This succeeded in stabilizing the situation. The woman received symptomatic hepatotropic therapy. In all

cases prolongation morbi were revealed in patients who had metastasis in regional lymphatic nodes.

Discussion

Ukrain monotherapy considerably improved the state of oncological patients before surgical intervention, while radiation and chemotherapy caused immune system suppression and impairment of some metabolic and homeostatic mechanisms. These led to a worse prognosis for further treatment. It must be mentioned that pronounced sclerosis and heavy bleeding of the minor pelvic tissues during surgical intervention, which normally occurs after chemo- and radiation therapy, proved to be practically absent after Ukrain pretreatment. The latter proved to facilitate considerably surgical interventions and to bring about fewer intra- and postoperative complications. Over 2 years observation, eight group I patients (33.3%) had rectal cancer relapses and four group II patients (16.6%) expreienced rectal cancer relapses. This is certainly indicative of the greater efficiency of the complex therapy based on Ukrain administration in colorectal cancer patients.

Conclusion

The data obtained in the course of this randomized investigation of patients suffering form tumors located in the ampullar part of the rectum points to the conclusion that Ukrain monotherapy exerts a more powerful anticancer and immune system stimulating effect in comparison with traditional, broadly-used 5-FU chemotherapy in combination with X-ray treatment. Therefore, we can recommend Ukrain as the most effective preparation for adjuvant therapy of colorectal cancer.

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