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D.A. PULATOV[1], J.M. IBRAGIMOV[1], S.V. KAMISHOV[1]

[1]Republican Cancer Research Center of the Ministry of Health of Uzbekistan, Tashkent, the Republic of Uzbekistan

Comparative assessment of chemoresistant colorectal cancer treatment toxicity

The article provides comparative data on polychemotherapy (PCT) toxicity in patients with colorectal cancer (CRC) resistant to fluoropyrimidine-containing regimens. Two PCT regimens, FOLFOX4 and CAPOX, were compared in their clinical effect and toxicity. The clinical effect toxicity was assessed by the relevant approved international scales NCI-CTC (2010) and REGIST (2009), respectively. The obtained results showed higher chemotherapy toxicity in PCT-resistant patients vs. the patients with positive clinical outcome. Former studies [1, 2] have shown that the toxicity (namely, nephro- and hepatotoxicity) increases with sensitivity to PCT due to tumour lysis syndrome.

Preliminary definition of signs of resistance will allow predicting both the efficiency and the toxicity of PCT. The provided data on the efficiency and the toxicity of various CT regimens for different groups of patients with disseminated forms of CRC is the basis for determination of clinical prerequisites for the occurrence of tumour resistivity or sensitivity to fluoropyrimidines (5-fluorouracil). In the future, in case of expressed toxicity, these studies will be the starting point for developing the most effective methods of accompanying therapy.

Keywords: *colorectal cancer, chemoresistant, toxicity of polychemotherapy.*

Introduction. Up to 95% of individual differences in the efficacy and toxicity of cytostatic were found to be genetically determined [3, 4]. The pharmacogenetic features of 5-fluorouracil and its derivatives have not been studied enough. This is due to the complexity of metabolism and the mechanism of action of 5-fluorouracil and its analogues which requires a simultaneous study of numerous genes. However, along with high activity, these drugs are characterized by significant toxicity that limits the possibilities of chemotherapy, leading to a reduction in the dose, and often the withdrawal of the drug. Clinical experience shows that some patients tolerate well the standard doses of 5-fluorouracil quite while for others they are too toxic [2, 5]. Therefore, it is necessary to search for genetic markers that allow predicting the efficacy and toxicity of 5-fluorouracil and its derivatives in order to optimize the treatment outcome by prescribing the individual chemotherapy regimen based on genetic test results. Currently, our center is conducting genetic and biochemical studies to study the presence of predictors of resistance and sensitivity of tumors to a particular chemotherapy drug or a combination thereof.

Purpose of the study was a comparative assessment of the severity of toxic manifestations in patients with colorectal cancer (CRC) resistant to polychemotherapy (PCT) fluoropyrimidine-containing regimens.

Material and methods. The clinical effect and toxicity of FOLFOX4 regimens (Oxaliplatin 85 mg / m^2 on Day 1, 5-Fluorouracil 1000 mg / m^2 on Days 1-2, Leucovorin 200 mg / m^2 on Days 1-2 biweekly) and CAPOX (Capecitabine 1000 mg / m^2 BID for 14 days, Oxaliplatin 130 mg / m^2 1 day triweekly) were studied in 84 patients with metastatic CRC (mCRC), of them, 54% men, and 46% women. The average age of men was 57.2 ± 0.2 years, of women – 65.4 ± 0.4 years. Patients underwent 2-4 courses of treatment then the effect of PCT was evaluated on the RECIST scale (2009). In the case of full response (disappearance of all lesions for at least 4 weeks) or partial response (reduction of measurable lesions by 30% or more), the patients were referred to the group of patients with sensitive tumours. With the progression of the process (increase of lesions by 20%, or appearance of new lesions) or signs of stabilization (no reduction sufficient for evaluation as a partial effect, or an increase that can be estimated as progression), the tumour was considered as insensitive to treatment.

Group 1 of "treatment-sensitive" patients included 48 (57.1%) patients with complete (29%) and partial (71%) regression. Group 2 of the patient "resistant to CT" included 36 (42.9%) patients, of them, half – with the disease progression, and half – with stabilization of disease.

The degree of toxicity and its manifestations were evaluated according to the NCI-CTC toxicity scale (2010) which presumes five levels of side-effect intensity: 0 – no changes; level I – minimal changes that did not affect the overall activity of the patient, with a slight change in lab indicators that did not require correction; level II – the changes that disrupted normal activity and laboratory data that required correction; level III – the disorders that required active symptomatic treatment and caused a delay or discontinuation of chemotherapy; level IV - life-threatening consequences that required immediate discontinuation of chemotherapy [1].

The overall status of patients in the treatment process was assessed by WHO scoring scale (ECOG-WHO). The active or close to normal physical condition was assessed at 0-1 points. If the patient could spend more than 50% of the daytime out of bed – 2 points, if the patient had to spend more than 50% of the daytime in bed – 3 points. The general condition of the patient, unable to service himself, was assessed at 4 points.

Results. Out of the 84 patients with mCRC who received 2-4 courses of palliative PCT according to the FOLFOX and CAPOX regimen, 14 (16.7%) patients had the total regression of the process, 34 (40.5%) – partial regression, 19 (22.6%) – stabilization of the process, and 17 (20.2%) showed progression of the disease (Table 1).

Table 1 – Comparison of the localization of primary lesion in patients with mCRC (n = 84) and sensitivity to fluorine pyrimidine-containing regimens of PCT (FOLFOX, CAPOX)

Parameter	Sensitivity to treatment, n=48 (57,1%)				Resistance to treatment, n=36 (42,9%)			
	Total response		Partial response		Total response		Partial response	
	Abs	%	Abs	%	Abs	%	Abs	%
Ascending colon	5	35,7	9	26,5	6	31,6	3	17,6
Transverse colon	3	21,4	12	35,3	3	15,8	2	11,8
Descending colon	3	21,4	7	20,6	2	10,5	3	17,6
Sigmoid colon	2	14,3	3	8,8	3	15,8	4	23,5
Rectum	1	7,1	3	8,8	5	26,3	5	29,4
Total	14	16,7	34	40,5	19	22,6	17	20,2

Tumours sensitive to CT in most cases had their primary nidus in the ascending colon (62.2%) and transverse colon (56.7%). At that, the complete regression was more often observed in patients with damage in the ascending colon (35.7%), and partial – with damage in the transverse colon (35.3%). Patients with resistant tumours in most cases had the tumour primary nidus in the rectum (55.7%). Stabilization was more often observed in patients with damage in the ascending colon (31.6%), and progression – with the primary nidus in the rectum (29.4%).

Patients with mCRC most often had the secondary nidus in the liver (25%) and lungs (22.6%), less often – in the brain (3.6%). Combined lesion of two organs was observed in 19 (22.6%) patients; of them, in 11 (13.1%) cases it was lungs and liver, and in 8 (9.5%) – lungs and bones (Table 2). The highest frequency of objective response (PR + CR) was observed with metastases in the liver – 16 (76.1%) cases and lungs – 12 (63.1%) cases. Out of the 3 patients with metastases in the brain, 2 had stabilization, and 1 case – the progression of the process. Among the patients with combined distant metastases (lungs + liver, or lungs + bones), no response to treatment was 2-3 times more likely than the sensitivity to treatment. Relatively better results in liver, lung and spleen lesions were obviously associated with more developed blood supply to those organs and a better response to chemotherapy and other treatment.

Out of 84 patients with CRC and distant metastases, 67 (79.8%) has experienced the CT toxicity, and 17 (20.2%) had no toxicity signs (Table 3). The comparison of those indicators depending on the sensitivity to treatment has shown a higher CT toxicity among drug-resistant patients (83.4% vs. 77.1%). A higher toxicity in resistant patients could be due to incomplete splitting of drugs into nontoxic metabolites due to disorders in the enzyme systems involved in the elimination of CT agents.

The most common types of toxicity in patients receiving fluoropyrimidine-containing regimens were gastrointestinal (n=21, 25%) and haematological (n=20, 23.8%) disorders. Gastrointestinal toxicity was more frequent in patients sensitive to treatment (n=24, 29.2%), while hepatic toxicity was more frequent in patients resistant to treatment (n=9, 25%). That might be due to a stronger damaging effect of CT agents and / or to the insufficiency of gene dependent enzyme system, intermediate toxic products of decomposition into hepatocytes. Though cardiotoxicity was rare in both groups, it was twice higher in in resistant patients (16.6% vs. 8.3% in sensitive patients).

The toxicity level analysis (Table 4) has shown that the patients who received fluoropyrimidine-containing regimens had no situations that required immediate discontinuation of PCT (level IV). However, nearly a quarter of the patients required an advanced accompanying therapy (level III). Most of the patients (76%) did not require or required minor corrections against toxicity manifestations (levels I and II). Resistant patients had level III toxicity1.5 times more often, and it required correction of accompanying therapy. Level II toxicity was 1.8 times more often among resistant patient vs. those who responded to treatment. Level I toxicity manifested by minor symptoms not requiring correction of accompanying therapy was twice more often among resistant patients.

Table 2 - Comparison the localization of distant metastases in mCRC patients (n = 84) and the sensitivity to fluoropyrimidine-containing regimens of PCT (FOLFOX, CAPOX)

Parameter	Sensitive to treatment, n=48 (57,1%)				Resistant to treatment, n=36 (42,9%)				Total	
	Full regression		Partial regression		Full regression		Partial regression			
	Abs	%	Abs	%	Abs	%	Abs	%	Abs	%
Liver	4	19	12	57,1	3	14,3	2	9,5	21	25
Lung	2	10,5	10	52,6	4	21	3	15,8	19	22,6
Spleen	3	25	5	41,7	3	25	1	8,3	12	14,3
Lungs + liver	2	18,2	2	18,2	3	27,3	4	36,4	11	13,1
Bones	2	20	4	40	2	20	2	20	10	11,9
Bone	1	12,5	1	12,5	3	37,5	3	37,5	8	9,5
+Lung	-	-	-	-	1	33	2	66	3	3,6
Brain	14	16,7	34	40,5	19	22,6	17	20,2	84	100
Total										

Table 3 - Types of toxicity response to treatment in mCRC patients depending on the sensitivity to CT

Toxicity	Sensitive to treatment (n=48)		Resistant to treatment (n=36)		Total (n=84)	
	Abs.	%	Abs.	%	Abs.	%
Gastrointestinal	14	29,2	7	19,4	21	25
Hematologic	12	25	8	22,2	20	23,8
Hepatotoxicity	7	14,6	9	25	16	19
Cardiovascular	4	8,3	6	16,6	10	11,9
No signs of toxicity	11	22,9	6	16,6	17	20,2

Table 4 - Gastrointestinal toxicity in patients with mCRC depending on the sensitivity to PCT

Patient groups	Toxicity level			Total
	I	II	III	
Sensitive patients	28 (58,3%)	11 (23%)	9 (18,75%)	48 (57,1%)
Resistant patients	10 (27,8%)	15 (41,7%)	11 (30,56%)	36 (42,9%)
Total	38 (45,2%)	26 (30,95%)	20 (23,85%)	84

The general condition of patients to CT suffered less than among non-sensitive patients (Table 5). Patients in Group 1 had active condition or close to normal condition 1.7 times more often than in Group 2. Half of the patients from both groups had their general condition at the level of 2 points. The condition at the level of 3 points (more than 50% of the daytime spent in bed) was 2.7 times more common among resistant patients. The general condition of 1 female patient with partial regression of the process was assessed at 4 points as she was unable of self-service due to concomitant arthrosis of knee joints and finger joints, however, it did not affect the toxicity of treatment.

Table 5 - Gastrointestinal toxicity in patients with CMCR depending on sensitivity to PCT

No. of points	Resistant patients, (n=36)		Sensitive patients, (n=48)	
	Abs.	%	Abs.	%
0-1	8	22,2	18	37,5
2	18	50	24	50
3	10	27,8	5	10,4
4	-		1	2,1

Conclusions. Patients sensitive to FOLFOX and CAPOX regimens had 71% cases of partial and 29% cases of complete regression. The group resistant to treatment had 20% cases of progression and 20% cases of stabilization of the disease. 62.2% of patients sensitive to CT and 35.7% of cases of complete regressions had a primary lesion in the ascending colon. Progression was more often (29.4%) observed in case of localization in the rectum.

Objective response was most frequent in the case of metastases in liver (n=16, 76.1%) and lungs (n=12, 63.1%), and least frequent – in the case of combined distant metastases (lung + liver, or lungs + bones) and metastases in the brain.

The CT toxicity was more often among the resistant patients (83.4% vs. 77.1%); and in 25% of cases it was hepatic toxicity. Level II-III toxicity that required adjustment of treatment was 1.5-2 times more often in PCT-resistant patients. Patients whose overall condition was assessed at 3 points (more than 50% of the daytime spent in bed) were 2.7 times less in the group of well-responding mCRC patients.

The study has shown a bit higher toxicity in case of resistant forms of mCRC which required a bigger amount of accompanying therapy. The preliminary determination of the molecular-genetic signs of resistance will allow predicting both the efficiency and toxicity of PCT. Planning of accompanying therapy will allow avoiding or reducing the unwanted complications of PCT.

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