Clinical Study of Combined Use of Tomudex (Raltitrexed) and Xeloda (Capecitabine) as First-Line Treatment for Patients with Metastasizing Colorectal Cancer

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We studied the efficiency of combined chemotherapy with tomudex and xeloda preparations in patients with metastasizing colorectal cancer. The treatment (240 courses) was effective in 75% patients. Time median before progression was 6.3 months, mean durations of partial remission and stabilization were 7.8 months, total survival 15.5 months, total survival after effective treatment was 18.2 months. The most prevalent manifestations of III-IV degree toxicity were neutropenia, diarrhea, and asthenia. Other symptoms of toxicity (increased transaminase level, bilirubin, nausea, vomiting) were observed in less than 3% courses. Thus, treatment with tomudex and xeloda are effective and safe for outpatient chemotherapy.

Key Words: *colorectal cancer; raltitrexed; capecitabin*

In comparative studies, tomudex and xeloda showed similar antitumor activity and lower toxicity compared to standard of 5-fluorouracil/leucovorin (5FU/LV) regimen [1]. According to results of three trials [2-4], the efficiency of tomudex was 15.2-18.1% *vs.* 14.3-19.4% provided by standard Mayo clinic regimen (5FU/LV) with similar time to disease progression. Xeloda was more effective than standard Mayo regimen (22.4 and 13.2%, respectively), the time to disease progression being similar [5].

Treatment efficiency of tomudex and long-term infusions of 5FU in first-line chemotherapy was 46% [6].

According to the results of pioneer studies, the combination of tomudex with peroral fluoropyrimidines (UFT and carmofur) can increase the efficiency of therapy of metastasizing colorectal cancer to 42-68% [7].

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The combination of raltitrexed with capecitabine in disseminated colorectal cancer was not evaluated.

We used the following chemotherapy regimen: tomudex in a dose of 2.6 mg/m^2 (drop intravenous infusions over 15 min only on day 1 of the cycle) and xeloda in a dose of 2000 mg/m^2/day (daily dose was divided into 2 parts) after meals on days 1-14 of the cycle. The treatment was repeated on day 22.

The aim of the study was to evaluate the efficiency and safety of this chemotherapy regimen.

MATERIALS AND METHODS

The study included 36 patients (16 men and 20 women; mean age 39-73 years) with metastases of colorectal cancer. All patients had histologically documented colon or rectal cancer and were not treated before for disseminated disease. Adjuvant 5-FU/LV chemotherapy was allowed in some cases, but it was discontinued at least 6 month before enrolling in the study.

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All patients had measurable manifestations of the disease, normal hematological indexes (leukocytes $\geq 4\times10^9$/liter, neutrophils $\geq 1.5\times10^9$/liter, platelets $\geq 100\times10^9$/liter, hemoglobin ≥8 g/dl) and normal biochemical parameters (bilirubin ≤2 normals, AST, ALT, alkaline phosphatase (AP) <3 normals in the absence of liver metastases or AST, ALT, and AP <5 normals in the presence of liver metastases) without renal dysfunction (creatinine clearance ≥60 ml/min).

Chemotherapy was discontinued, if progression of the disease or signs of drug toxicity were noted or if the patent refused the treatment. After completion of the course, the patients were followed up for at least 1 month for evaluation of delayed side effects. Toxicity of chemotherapy was evaluated by NCI-CTC criteria (National Cancer Institute Common Toxicity Criteria).

ECOG score (Eastern Cooperative Oncology Group) reflecting general state of the patients before the treatment was 0-1.

In all patients, the primary tumor was removed (rectal cancer in 10 patients and colon cancer in 26 patients).

Metastases were detected simultaneously with the primary tumor in 29 (80.6%) patients, within 3 years in 6 (16.7%), and later in 1 patient. The level of canceroembryonic antigen before treatment was normal in 3 (8.3%) patients, ≤50 mg/ml in 17 (47.2%) patients, and >50 ng/ml in 16 patients.

Liver metastases were detected in 35 patients (22 patients had only liver metastases and 13 patients had also metastases in other organs) and lung metastases were detected in 1 patient.

RESULTS

A total of 240 cycles of chemotherapy were performed. The number of cycles in patients varied from 2 to 20 (Table 1), the mean number of cycles per patient was 6.7±0.6.

TABLE 1. Distribution of the Number of Courses of Combined Chemotherapy with Tomudex and Xeloda in Colorectal Cancer

Number of treatment courses	Number of patients	%
2	2	5.5
3-4	7	19.5
5-6	11	30.6
7-8	10	27.8
9-10	3	8.3
>10	3	8.3

The total efficiency of treatment (complete or partial remission) was 36.1%, stabilization of the disease (6 months) was observed in 38.9% cases. Thus, the treatment was effective in 75% patients. The median time to disease progression was 6.3 month (5.7-6.9 months). The duration of the effect (partial remission and stabilization) was 7.8 months (4.7-10.9 months). The total survival was 15.5 months (13.1-17.9 months). The total survival in cases with effective treatment (partial remission and stabilization) was 18.2 months (13.9-22.5 months).

In cases with disease progression, second-line chemotherapy with irinotecan (19 patients) and oxaliplatin (3 patients) was performed.

In 3 cases, the treatment was discontinued because of toxicity.

Grade III-IV toxicity in most cases manifested in diarrhea (3.3%), neutropenia (1.7%), and asthenia (5%). Other symptoms of toxicity (increased transaminase level, bilirubin, nausea, and vomiting) were observed in less than 3% courses (Table 2).

Toxic effects determined changes in the chemotherapy regimen. The dose-limiting factors were gastrointestinal toxicity and hepatotoxicity (Table 3). In some cases, the dose of xeloda was reduced because of the development of the hand-foot syndrome.

TABLE 2. Side Effects of Combined Chemotherapy with Tomudex and Xeloda in Patients with Colorectal Cancer

Side effect	Grade III		Grade IV	
	abs.	%	abs.	%
Increased liver transaminases	6	2.5	—	—
Hyperbilirubinemia	1	0.4	—	—
Neurtopenia	3	1.3	1	0.4
Asthenia	11	4.6	1	0.4
Diarrhea	7	2.9	1	0.4
Vomiting	1	0.4		

TABLE 3. Changes in the Scheme of Combined Therapy with Tomudex and Xeloda after Development of Toxicity Symptoms in Patients with Colorectal Cancer

Correction	Cause	Number of patients
Reeduction of tomudex dose by 50%	Asthenia	1
	GIT+hematological toxicity	2
	Hepatotoxicity	5
	Hyperthermia	1
	Asthenia+GIT+hematological toxicity	1
	Hyperthermia, anorexia, asthenia	1
	GIT	2
	Hepatotoxicity, hematological toxicity	1
	GIT, hepatotoxicity	2
	Venous thromboses	1
	Stomatitis	1
Reduction of xeloda dose by 75%	GIT, hepatotoxicity	2
	Hepatotoxicity	3
	GIT	4
	Stomatitis, HFS	1
Reduction of xeloda dose by 50%	HFS	1
	GIT	2
	Polyneuropathy	1
	Hyperthermia	1
	Neutropenia, GIT	1
	GIT, asthenia	1
	Hepatotoxicity	1
	GIT, HFS	1
Delay of the cycle	Combined toxicity	25
Discontinuation of tomudex	Headache, edema	1

Note. GIT: gastrointestinal toxicity; HFS: hand-foot syndrome.

In 3 cases, the treatment was discontinued because of combination of toxicity symptoms: in 2 patients pronounced gastrointestinal symptom (grade III-IV diarrhea) was accompanied by hematological symptom (grade III-IV neutropenia) and in 1 patient pronounced edema was observed. No chemotherapy-related lethal outcomes were observed.

Thus, our findings suggest that combined treatment with tomudex and xeloda is an effective and safe outpatient chemotherapy regimen for patients with colorectal cancer.

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