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Xeloda as first-line therapy of metastatic colorectal cancer - our experience

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BACKGROUND: *Results of phase III clinical studies comparing efficacy of Xeloda vs. standard 5-FU/FA protocols as first line therapy of metastatic colorectal carcinoma (MCRC), have shown better efficacy of Xeloda, with less toxic adverse effects, apart from hand-foot syndrome.*

METHODS: *From January 2000 to May 2001 the study enrolled 54 patients with MCRC, 38 males and 16 females, aged 30-78 years. All patients had metastatic diseases. In 33 the primary tumor was in colon, in 21 in rectum. All patients received Xeloda 2500 mg/m^2/day in two daily doses, during 14 days followed by 7 days of pause. Dose intensity was 88,79% +/- 9,2. For efficacy evaluation the WHO criteria and tumor markers CEA and CA 19-9 were used.*

RESULTS: *Overall response rate was 47%, with 13% complete responses, 34% partial responses, 38% stable disease and 15% disease progression. No significant difference was found between patients with regard to localization of primary tumor (colon or rectum). There was no significant difference in response rate when compared 27 patients with adverse events of capecitabine ('hand and foot' syndrome and diarrhea) and those without them. Response rate in a subgroup of 21 evaluable (out of 29) patients with initial signs of liver dysfunction was worse ($p<0.005$) in comparison with patients with normal liver function. Most frequent adverse events were 'hand and foot' syndrome (52%) and diarrhea (24%), or both (14%). Other adverse events, up to grade 2 toxicity, were sporadically reported; however, hematological toxicity was significantly more common in a subgroup of patients with compromised liver function ($p<0.007$).*

CONCLUSION: *This study has shown that Xeloda is a good monotherapy choice, with high response rate as first line therapy of metastatic CRC. Adverse events do not influence response. Liver dysfunction is a poor prognostic parameter. Therapy with Xeloda is convenient and relatively safe in patients with liver dysfunction, where administration of other cytotoxic agents is not possible.*

KEY WORDS: *Colorectal Neoplasms; Antimetabolites; Antineoplastic; Combined Chemotherapy Protocols; Neoplasm Metastasis; Treatment Outcome*

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INTRODUCTION

Since 1957, when fluoropyrimidine derivative 5-Fluorouracil (5-FU) was synthesized, up to nowadays, this chemotherapeutic agent has been widely used for treatment of patients with colorectal cancer. During last 45 years majority of investigational efforts has been directed towards increase of 5-FU efficacy. During 1960 and 1970, 5-FU was used mostly as monotherapy with response rate 8% to 85%, as reported in literature. Other drugs, like nitrosourea derivatives and mitomycin C did not manage to increase efficacy when used in combination with 5-FU (MOF, BOF etc.) (1). In 1980, certain progress was achieved thanks to 5-FU biomodulation and 5-FU based therapeutic regimens. Continuous infusion enabled significant increase of response rate and modest improvement in overall survival (2). Numerous substances were used as 5-FU biomodulators with dif-

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ferent success. Most of them were withdrawn as ineffective (3). Only biomodulation with leucovorin proved to be effective as shown by increased response rate, but without significant influence on overall survival (4), and, as such, it was introduced in most of the standard therapeutic regimens. That is how well known and commonly used therapeutic schemes, Mayo Clinic, de Gramon, Roswell Park, AIO Geman, Ardalan, have became standard protocols. During 1990 there were several new agents with mechanism of action different from thymidylate synthetase inhibition, with irinotecan and oxaliplatina among them. These drugs have brought important improvement in patients' survival, when used as first line therapy in combination with 5-FU or as monotherapy in second-line treatment of metastatic disease. Combination with oxaliplatin enabled tumor resectability in 50% of patients with primary unresectable liver metastases (5). Further progress in therapy of CRC was made by development of new oral fluoropyrimidines, synthesized with aim to overcome complications related to continuous infusion, central venous catheters, and large variations in 5-FU bioavailability that made it inappropriate for oral administration. In that sense, two strategies were developed. The first one was combining oral fluoropyrimidine (tegafur) with dihydropyrimidine dehydrogenase inhibitor (eniluracil) (UFT). Another one was synthesis of the molecule, which can be activated on its way to the malignant cell, which was actually achieved with capecitabine (Xeloda). After gastrointestinal absorption capecitabine is hydrolyzed in the liver by carboxylesterase to produce 5'-Deoxy-5-Fluorocytidine, and this molecule is then deaminated by cytidine deaminase, an enzyme located primarily in hepatic and neoplastic tissue, to produce 5'-Deoxy-5-Fluorouridine. The last enzymatic step, selective tumor activation of 5'-Deoxy-5-Fluorouridine to 5-FU is catalyzed by thymidine phosphorilase, thus minimizing systemic exposure to 5-FU (6). Level of thymidine phosphorilase is higher in most solid tumors than in the corresponding normal tissues. Capecitabine has demonstrated a high activity in preclinical xenograft models of colorectal, breast, gastric and cervical cancer (7,8). During last several years capecitabine has been investigated in numerous phase III clinical trials and compared with standard 5-FU based protocols. Results of these studies (9,10), which compared efficacy of capecitabine and standard protocols with 5-FU/FA in first-line therapy of MCRC, show that capecitabine is more effective than Mayo Clinic protocol and equally effective as de Gramon and German AIO infusion schemes. It also has significantly less toxic adverse events, apart from "hand and foot" syndrome. These results were the basis for initiation of study in three Yugoslav centers, aimed to investigate efficacy and tolerability of Xeloda monotherapy as first-line therapy of MCRC (11,12).

PATIENTS/MATERIALS AND METHODS

Between January 2000 and May 2001, three centers in Serbia included 54 patients with MCRC; 38 males and 16 females, aged 30-78 years (Table 1); In 33 patients (61%) primary tumor was located in colon, whilst in 21 (39%) it was located in rectum. All patients had metastatic CRC, and in 28 (54%) of them this was the initial episode of metastatic disease (Table 2).

Table 1. Demographic data

No. of patients		N=54
Age (years)	X± SD	57.5 ± 12.0
	median (rang)	58.0 (30 - 78)
Gender		
Males	n (%)	38 (70.4%)
Females	n (%)	16 (29.6%)
Karnofsky performance	X± SD	90.9 ± 9.4
Status (%)	median (rang)	90 (70 - 100)

Table 2. MCRC baseline status

	n (%)
Disease evaluation	
Measurable	30 (55.6%)
Unmeasurable	24 (44.4%)
Localization	
Colon/rectum	7 (13.0%)
Liver	50 (92.6%)
Lung	11 (20.4%)
Lymph nodes	1 (1.9%)
Bone	2 (3.7%)
Other	4 (7.4%)
Adrenal glands	1
Peritoneum	2
No. of meta-localizations	
1	37 (68.5%)
2	15 (27.8%)
3	1 (1.9%)
4	1 (1.9%)

All patients received Xeloda in dose of 2500 mg/m^2/day divided in two daily doses, during 14 days, followed by 7 days of pause, when the cycle was repeated at the same dosage. For disease evaluation the WHO criteria and tumor markers CEA and CA 19-9 were used. Tumor markers were elevated in u 50 (98%) patients. A subgroup of 29 patients had liver dysfunction before trial start - defined as abnormal liver function tests (elevated bilirubin, transaminase, gama-GT and/or alkaline phosphatase); five patients had elevated total bilirubin > 5xUNL (upper normal limit). Study procedures were performed in accordance with the ethical standards of the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association.

RESULTS

Out of 54 enrolled patients, 47 were evaluable for efficacy. There were total of 304 capecitabine cycles conducted with median of 6 cycles (range 1-9) per patient. Dose intensity for the whole group was 88.79% +/- 9.27 (63.73 - 102.96). Overall response rate (ORR) was 47%, with 13 % (6/47) of complete responses

(CR), 34% (16/47) of partial responses, 38% (18/47) of stable disease (SD) and 15% (7/47) of diseased progression (PD) (Figure 1).

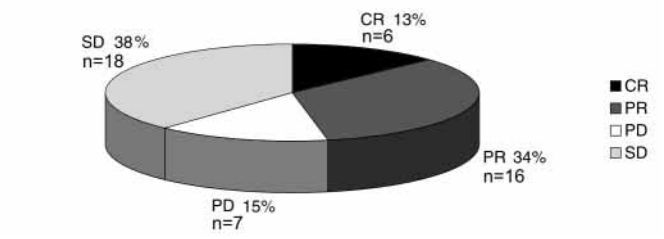

Figure 1. Response rate

There was no statistically significant difference in therapeutic response between patients' localization of primary tumor in colon and those with tumor localized in rectum, nor with regard to the free interval from operation to appearance of metastases. There was no significant difference in therapeutic response in a subgroup of 27 patients with recorded adverse effects of capecitabine ('hand and foot' syndrome and diarrhea) (Figure 2).

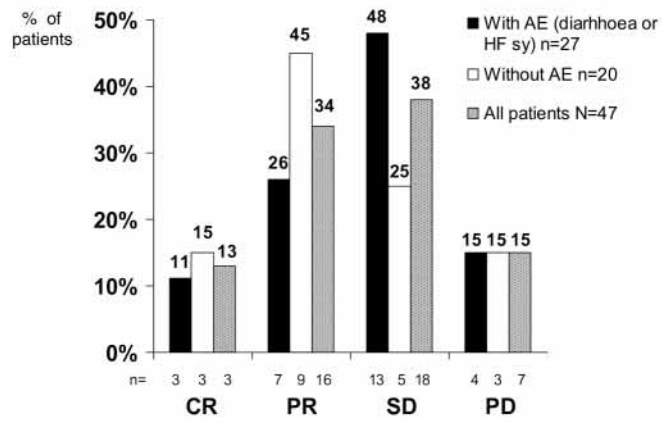

Figure 2. Response rate in patinets with adverse events

There was statistically significant difference ($\chi^2=8.06$; $p<0.005$) in response rate comparing 26 evaluable patients with initial signs of liver dysfunction, i.e. those with elevated bilirubin or transaminases, gama-GT and/or alkaline phosphatase at the beginning of treatment, and those without liver dysfunction (Figure 3). The most common adverse events were 'hand and foot' syndrome (in 52% patients, 26/47) and diarrhea (in 24% patients, 12/47), or both (in 14% patients, 7/47). Other grade 2 toxicities were reported sporadically, with hematological toxicity being more pronounced in a subgroup of patients with liver dysfunction ($Z=-2.72$; $p<0.007$). Global assessment of safety done by investigators showed capecitabine tolerability profile was evaluated as 'excellent' or 'very good' in 70% of patients.

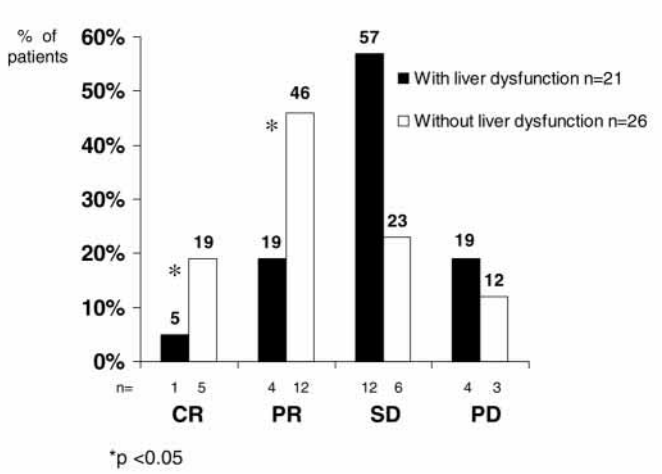

Figure 3. Response rate in patinets with liver dysfunction

DISCUSSION

Oral use of capecitabine, with equal efficacy as 5-Fluorouracil and leucovorin infusion regimens, is more convenient from patients' point of view, primarily due to better comfort, lack of central venous catheter placement and numerous possible complications related to this procedure. Besides, during treatment a patient can continue with daily activities. Overall response rate in this study was surprisingly high. It should be noted that dose intensity was almost ideal, but also the fact that response evaluation was performed according to the WHO criteria in each center without evaluation of an independent committee (13). In addition, for efficacy evaluation the level of tumor markers as additional criteria was incorporated, so that a CR could not be assigned without normalization of tumor markers, which were elevated in 98% of patients before treatment start. Similarly, a partial response (PR) with increased tumor markers was considered a SD, while SD with increased tumor markers of over 50% was regarded a PD. On the other hand, a SD with decreased tumor markers by over 50% was regarded as PR. By additional analysis of response rate without evaluation of tumor markers, no significant difference in response rate was found.

It was surprising that no statistical significance in response rate was found between patients with primary tumor at different locations, colon and rectum, considering evident difference in biological characteristics of these tumors (14).

In some patients with CR, grade III adverse effects (hand and foot syndrome) were reported. This has brought us to thinking that perhaps patients with pronounced adverse effects have better therapeutic response due to longer drug clearance, which provides longer drug exposure of tumor tissue (15). On the other hand it is possible that therapeutic response in these patients can be worse because adverse effects can lead to dose modification or increased dose interval between cycles, which can further lead

to lower dose intensity. However, in our patients adverse events did not have any adverse influence on therapeutic response (Figure 2).

Response analysis in a subgroup of patients with liver dysfunction showed statistically significantly lower overall response in these patients (Figure 3) as compared to the remaining patients with normal liver function. Earlier evaluation of the effect of treatment in patients with hyperbilirubinemia induced by liver metastases indicated relative safety of capecitabine administration in these patients and possibility of its use in this patient group (11). Capecitabine monotherapy has been proved as safe without significant adverse events. The expected capecitabine adverse events included diarrhea or 'hand and foot' syndrome or both adverse events in majority of our patients. However, these adverse events were reversible, easily managed with symptomatic treatment and did not require therapy withdrawal, except in one patient with total colectomy and huge small bowel resection with consequent malabsorption and uncontrolled diarrheas. Hematological toxicity was most prominent in 5 patients with initial hyperbilirubinemia. These results have proved once again that liver metastases and liver dysfunction represent poor prognostic signs in treatment of these patients.

Thanks to its pharmacokinetic and pharmacodynamic properties by which it imitates continuous 5-FU infusion with significantly less adverse events and at least equal efficacy, capecitabine is a medicine that probably could replace 5-FU in standard MCRC treatment protocols. On the other side we should wait for results of numerous clinical trials with combination of capecitabine and other agents in order to define its precise place in treatment of MCRC. Anyway, according to the results of this study capecitabine is a good monotherapy option as first line therapy of MCRC.

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