RESEARCH ARTICLE

Efficacy and Safety of Raltitrexed Combinations with Uracil-Tegafur or Mitomycin C as Salvage Treatment in Advanced Colorectal Cancer Patients: A Multicenter Study of Anatolian Society of Medical Oncology (ASMO)

Oktay Bozkurt[1]*, Halit Karaca[1], Aydin Ciltas[2], M Ali Kaplan*3*, Mustafa Benekli[2], Alper Sevinc[4], Umut Demirci[5], Tulay Eren[6], Hilmi Kodaz[7], Abdurrahman Isikdogan[3], Metin Ozkan[1], Suleyman Buyukberber[2]

Abstract

Background: There is no standard treatment for patients with colorectal cancer (CRC) progressing after irinotecan and oxaliplatin treatment. Here we aimed to retrospectively evaluate the efficacy and tolerability of raltitrexed in combination with oral 5-fluoropyrimidine (uracil tegafur-UFT) or mitomycin C as salvage therapy in mCRC patients. Materials and Methods: A total of 62 patients who had received raltitrexed combined with UFT or mitomycin C were identified between December 2008 and June 2013. They were given raltitrexed 2.6 mg/m² (max 5 mg) i.v. on day 1 in combination with either oral UFT 500 mg/day on days 1-14 every 3 weeks (group A) or mitomycin C 6 mg/m² i.v. on day every 3 weeks (group B). Results: Forty-two patients (67.7%) were in group A and 20 (32.2%) in group B. In 15 patients (24%) grade 3/4 toxicity was observed, resulting in dose reduction, and in 13 patients (20.9%) dose delay was necessary. The median progression free survival (PFS) was 3 months (95%CI 2.65-3.34) and median overall survival (OS) was 6 months (95%CI 2.09-9.90) in the whole group. Median PFS was 3 months (95%CI 2.60-3.39) in group A *vs* 3 months (95%CI 1.64-4.35) in group B (p=0.90). Median OS was 6 months (95%CI 2.47-9.53) in group A *vs* 12 months (95%CI 2.83-21.1) in group B (p=0.46). Conclusions: The combination of raltitrexed with UFT or mitomycin C seem to be a salvage therapy option due to safety profile and moderate clinical activity in heavily-pretreated mCRC patients.

Keywords: Raltitrexed - uracil-tegafur - mitomycin C - salvage treatment - colorectal cancer

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Introduction

Colorectal cancer (CRC) is the third most common neoplasm in Turkey and in the world and their incidence has increased in recent years (Jemal et al., 2010; Karaca et al., 2011). At diagnosis, 30-40 per cent of colorectal cancer patients have metastatic disease. For patients with advanced colorectal cancer treatment is usually palliative and mainly consists of systemic chemotherapy (Scheithauer et al., 1993). Despite palliative chemotherapy can relieve symptoms and prolong survival, the prognosis remains poor (Poon et al., 1989; Scheithauer et al., 1993). Since the introduction of drugs like oxaliplatin and irinotecan, the combination of these drugs with 5-FU and LV is considered standard chemotherapy for advanced colorectal cancers (Rougier et al., 1998; Tournigand et al., 2004; Fuchs et al., 2007).

The combination of chemotherapy with targeted biological agents such as antiepidermal growth factor receptor (anti-EGFR) and antivascular endothelial growth factor (anti-VEGF) monoclonal antibodies has increased the median OS, but advanced disease remains mostly incurable (Hurwitz et al., 2004; Van Cutsem et al., 2009; Peeters et al., 2010). Third and further line therapy options are limited for patients whose disease has progressed after they have received target therapies with the most active chemotherapy. Regorafenib can be considered a therapy option in patients with chemotherapy- resistance disease, however should only be discussed in patients in good condition, after information about the potential benefits and adverse effects of the treatment (Foubert et al., 2013).

Mitomycin C (MMC) is a natural alkylating agent

*[1]Department of Medical Oncology, Faculty of Medicine, Erciyes University, Kayseri, [2]Department of Medical Oncology, Faculty of Medicine, Gazi University, Ankara, [3]Department of Medical Oncology, Faculty of Medicine, Dicle University, Diyarbakir, [4]Department of Medical Oncology, Gaziantep University, Faculty of Medicine, Gaziantep, [5]Ankara Atatürk Research and Teaching Hospital, [6]Ankara Numune Research and Teaching Hospital, Ankara, [7]Department of Medical Oncology, Faculty of Medicine, Trakya University, Trakya, Turkey *For correspondence: bozkurt.oktay8@gmail.com*

which is isolated from Streptomyces caespitous. It has been shown that it is effective in the treatment of stomach, pancreas, colon and breast carcinoma (Sartorelli, 1986). Mitomycin C studies have shown that the most significant efficacy is achieved in advanced stage colorectal cancer patients and the response rates are between 10-15% (Seitz et al., 1998; Chester et al., 2000). Oral 5-fluoropyrimidine (Uracil Tegafur-UFT) is a compound of tegafur and uracil in a 1:4 molar rate and is an oral anticancer chemotherapeutic agent that can be absorbed in the small intestine. Uracil increases the tegafur's antitumoural activity by inhibiting 5-FU catabolism through hepatic dihydropyrimidine dehydrogenase (Cho et al., 2003). Oral UFT manufactures a higher 5-FU plasma level than tegafur that can be reached by an IV 5-FU injection of the with same dosage (Takiuchi et al., 1998). UFT has similar antitumor efficacy with less toxicity compared to i.v. 5-FU in chemotherapy-naive in metastatic colorectal cancer patients (Carmichael et al., 2002; Douillard et al., 2002). Raltitrexed is a quinazoline folate-based specific thymidylate synthase inhibitor that potently and specifically inhibits thymidylate synthase. Raltitrexed has been shown to be active as single agents in the treatment of advanced colorectal cancer (Kemeny et al., 1993; Moertel, 1994; Zalcberg et al., 1996; Cunningham, 1998). In one phase III study in advanced stage colorectal cancer patients, raltitrexed had the same efficacy as fluorouracil/ leucovorin and a lower toxicity profile (Cunningham et al., 1995).

In this study, the objective was to evaluate the efficacy and tolerability of raltitrexed in combination with oral UFT or MMC as salvage therapy in metastatic CRC patients who have failed the standard oxaliplatin-based or irinotecan-based chemotherapy.

Materials and Methods

Data were obtained from chart reviews of mCRC patients in seven oncology departments in Turkey. A total of 62 patients who had received raltitrexed combined with oral UFT or mitomycin C were identified between December 2008 and June 2013. All patients had previously failed irinotecan and oxaliplatin-based regimens in combination with fluoropyrimidines. The patients had received raltitrexed 2.6 mg/m^2 (max 5mg) i.v. on day 1 in combination with either oral UFT 500 mg/day on days 1-14 every 3 weeks (group A) or mitomycin C 6mg/m^2 i.v. on day every 3 weeks (group B). Treatment was continued until progressive disease (PD) or significant toxicity was observed. Response evaluation was based on RECIST criteria every 2-3 cycles chemotherapy. To monitor disease progression, tumour markers, imaging methods and clinical evaluations were used. Toxicity was evaluated according to the National Cancer Institute (NCI) common toxicity criteria, and dose reductions or dose delaying were made according to side-effects. In case of grade 3/4 severe adverse event, a 25% dose reduction of all cytotoxic agents was done. For statistical analyses of the study data SPSS 18.0 software was used. Unmeasured data were calculated as %. Survival analysis was performed using the Kaplan-Meier method. For significance of area under the curves the log-rank test was used. To determine relationship the between variables the Pearson correlation coefficients were calculated. Statistically significant differences were defined as comparisons resulting in $p<0.05$.

Results

The patients' median age was 51 years old (range 18-76); 35 patients were (56.4%) male and 27 patients were (43.6%) female. The site of the primary tumor was rectum in 20 patients (32.2%) and colon in 42 (67.8%). Sixteen patients had ECOG performance status (PS) 2, all the others had PS 0 or 1. Thirty five patients (56.4%) were diagnosed with metastatic disease. Palliative or curative surgical procedures were applied to 56 of the patients (90.3%) and twenty seven patients (43.5%) was received adjuvant chemotherapy. The most common site of metastasis was the liver (66.1%) in 41 patients, followed by the lungs (27.4%) in 17 patients, peritoneum (13%) in 8 patients, and lymph nodes (6%) in 4 patients. In 94% of patients a biological agent was used for therapy. KRAS status was available for all patients, 31 were wild type (50%) and 31 were mutated (50%). Cetuximab was used combined with chemotherapy in 45% of patients. Forty-two patients (67.7%) were in group A and 20 (32.2%) in group B. Patients received group A combinations in the third, fourth and fifth lines of chemotherapy while group B protocol was applied in the second and third lines (Table 1). While most patients (90%) received raltitrexed in the third and subsequent lines, in 6 patients (10%) it

Table 1. Chemotherapy Regimens and Treatment Lines

Treatment regimen	Adjuvant	First line	Second line	Third line	Fourth line	Fifth line
UFT/ Raltitrexed	-	-	4	9	20	9
Raltitrexed/MMC	-	-	2	18	-	-
Oxaliplatin-based	17	17	25	9	11	-
Irinotecan-based	-	43	17	4	6	-
MMC/UFT	-	-	-	1	-	-
Irinotecan/cetuximab	-	-	7	9	2	-
Capecitabine	-	2	2	3	-	-
5-FU/LV	10	-	-	2	-	-
UFT	-	-	2	1	4	-
Irox	-	-	-	1	-	-

*Irinotecan-based: capecitabine+irinotecan, irinotecan+bevacizumab, 5-FU/ leucovorin+irinotecan, 5-FU/leucovorin+irinotecan+bevacizumab, 5-FU/leucovorin+irinotecan+cetuximab; Oxaliplatin-based: capecitabine+oxaliplatin, 5-FU/ leucovorin+oxaliplatin, 5-FU/leucovorin+oxaliplatin+bevacizumab, 5-FU/leucovorin+oxaliplatin+cetuximab; Irox: irinotecan+oxaliplatin; LV, leucovorin; MMC, mitomycin C, UFT, Uracil Tegafur

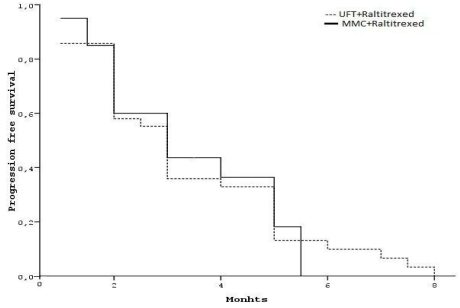

Figure 1. Progression Free Survival (PFS) in Group A (Raltitrexed +UFT) *vs* in Group B (Raltitrexed +MMC)

was used in the second line. In four of the six patients who received raltitrexed in the second line, oxaliplatin resistance occurred and two of them had oxaliplatin allergies. Group A combination median cycle number was 3 (min-max:1-12). One patient (2.4%) received one cycle, 12 patients (28.6%) received two cycles, 12 patients (28.6%) three cycles and 17 patients (40.4%) four and more cycles. Group B combination median cycle number was 3 (min-max:1-8). Eighteen of the patients (90%) received 3 or more cycles of chemoterapy. Overall, 28 patients (67%) experienced some toxicity in group A and 10 patients (50%) in group B, usually grade 1-2. The main toxicities were gastrointestinal and haematologic The most common severe grade 3/4 toxicities were increased liver transaminases in six patients, diarrhoea in three patients, nausea-vomiting in three patients, fatigue in three patients, neutropenia in three patients, thrombocytopenia in one patients and anemia in one patients. No toxic death was observed. Treatment-related side effects are shown in (Table 2). In general, both regimens were well tolerated. Dose adjustment was required 13 (31%) patients in group A, 2 (10%) patients in group B. In eight patients (13%) from group A and five (8%) from group B a delay occurred in administration of the treatment. Median PFS was 3 months (95%CI 2.65-3.34) and median OS was 6 months (95%CI 2.09-9.90) in the whole group. Median PFS was 3 months (95%CI 2.60-3.39) in group A *vs* 3 months (95%CI 1.64-4.35) in group B (p=0.90) (Figure 1). Median OS was 6 months (95%CI 2.47-9.53) in group A *vs* 12 months (95%CI 2.83-21.1) in group B (p=0.46) (Figure 2). Partial response in six patients (11%), stabile disease in 10 patients and progressive disease in 46 patients were observed (Table 2).

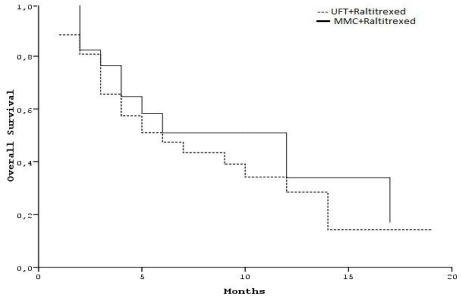

Figure 2. Overall Survival (OS) in Group A (Raltitrexed +UFT) *vs* in Group B (Raltitrexed +MMC)

Table 2. Treatment-Associated Toxicities and Response to Chemotherapy

Toxicity		National cancer institute common toxicity criteria			
		I	II	III	IV
Anemia	Raltitrexed/MMC	1			
	UFT/ Raltitrexed	3	1	1	
Thrombocytopenia	Raltitrexed/MMC	2			
	UFT/ Raltitrexed	2	1	1	
Neutropenia	Raltitrexed/MMC				
	UFT/ Raltitrexed	1	1	3	
Fatigue	Raltitrexed/MMC	1	3	1	
	UFT/ Raltitrexed	1	3	2	
Diarrhoea	Raltitrexed/MMC	2			
	UFT/ Raltitrexed	2		2	1
Nausea	Raltitrexed/MMC	1			
	UFT/ Raltitrexed	1	2	2	
Emesis	Raltitrexed/MMC				
	UFT/ Raltitrexed	2	1	1	
Astenia	Raltitrexed/MMC		2		
	UFT/ Raltitrexed	1	2		
Increased transaminases					
	Raltitrexed/MMC	4	3	2	
	UFT/ Raltitrexed	6	3	2	2
Response to chemotherapy (n(%)		CR	PR	SD	PD
Raltitrexed/MMC		0 (0)	2 (10)	3 (15)	15 (75)
UFT/ Raltitrexed		0 (0)	4 (10)	7 (16)	31 (74)

*CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

Discussion

It has been proved that chemotherapy and biological therapy combinations are effective in colorectal cancer as a first and second line therapy. Second line therapy is given to more than 60% of patients who have disease progression in first line therapy (Grothey et al., 2004; Tournigand et al., 2004). Despite the continuation of good performance status in some patients, in the following stages drugs which can be used as an alternative are limited and there are only a few studies that show salvage therapies' efficacy (Rosati et al., 2003; Lim et al., 2005; Jonker et al., 2007; Bitossi et al., 2008; Michalaki et al., 2010; Alkis et al., 2011; Francois et al., 2012; Ferrarotto et al., 2012).

Raltitrexed has been shown to be active as single agents in the treatment of advanced colorectal cancer (Kemeny et al., 1993; Moertel, 1994; Zalcberg et al., 1996; Cunningham, 1998). Randomised trials comparing raltitrexed with FU-based chemotherapy in advanced CRC have showed similar efficacy in both treatment arms and a reasonable toxicity profile. Raltitrexed is associated with a lower incidence of severe leucopenia and mucositis than 5-FU but a higher incidence of anaemia and elevation of transaminases (Cunningham et al., 1995; Cocconi et al., 1998).

Table 3. Salvage Therapies Studies in Metastatic CRC

Author	Type	N	Drug(s) combined	RR	Survival (months)
Rosati et al. (2003)[25]	Phase II	21	MMC/Raltitrexed	0%	PFS; 2,3/OS; 5
Francois et al. (2003)[26]	Phase II	21	MMC/UFT	NA	OS ;6
Michalaki et al. (2010)[27]	Retrospective analysis	44	MMC/UFT	9.30%	PFS; 5/OS; 7,5
Alkış et al. (2011)[28]	Retrospective analysis	22	MMC C/UFT/lokoverin	NA	PFS; 3(A)/OS; 7 (A)
		17	MMC/infüzyonel (5-FU)/ LV	NA	PFS; 7(B)a/OS; 12 (B)
Laurenz et al. (2007)[36]	Retrospective analysis	41	MMC/UFT/LV	7.30%	PFS; 2,5/OS; 6
Lim et al. (2005)[30]	Phase II	21	MMC/kapesitabin	4.80%	PFS; 2,6/OS; 6,8
Ferrarotto et al. (2012)[29]	Retrospective analysis	109	Single use mitomisin C and multiple agents	NA	PFS; 1,7/OS; 4,5

*MMC, mitomycin C; RR, response rate; 5FU, 5-fluorouracil; PFS: Progression failure free survival; LV, leucovorin; OS, overall survival; NA: not available a Statically significant difference between control arm

Raltitrexed and 5-fluorouracil inhibit thymidylate synthase (TS), an essential enzyme in the de novo synthesis of DNA, but through different mechanisms and with different binding sites. This status suggests that raltitrexed and UFT combinations can have a synergistic effect. Raltitrexed is an option in patients who have severe toxic reactions due to deficiency of dihydropyrimidine dehydrogenase (DPD) enzyme activity which is important for 5-FU refractory or 5-FU metabolism and deactivation, or in patients with heart diseases in whom fluorouracil is contraindicated, or in patients who do not want a central catheter. In this study, the objective was to evaluate the efficacy and tolerability of raltitrexed in combination with UFT or mitomycin C as salvage therapy in metastatic CRC patients.

In our study, in salvage therapy for all patients, median PFS was 3 months (95%CI 2.65-3.34) and median OS was 6 months (95%CI 2.09-9.90) in the whole group. Median PFS was 3 months (95%CI 2.60-3.39) in group A *vs* 3 months (95%CI 1.64-4.35) in group B (p=0.90). Median OS was 6 months (95%CI 2.47-9.53) in group A *vs* 12 months (95%CI 2.83-21.1) in group B (p=0.46).

Despite overall survival being different between the two groups, the difference was not significant statistically. This status can be explained by the fact that group A combinations were received in a further line, the number of patients was different in the two groups and group B patients received dose dense therapy. Studies that have evaluated chemotherapeutic agents such as raltitrexed, mitomycin C, UFT, and capecitabine in salvage therapies are summarised in (Table 3). Four of the studies used retrospective analysis and three of the studies were phase 2. Except studies for one of these studies, our results were the same. The studies with the same results as ours had a limited number of patients. Ferrarotto et al. study's had more patients. The median time to treatment failure (TTF) was 1.7 months and median OS was 4.5 months in 109 refractory metastatic colorectal cancer patients who received mitomycin C alone or mostly combined with capecitabine (Ferrarotto et al., 2012). In that study the main reason for the lower survival data compared to our study and other studies, is that some of the patients (47%) had received single MMC therapy and in further lines.

In our study group grade 3/4 toxicity was seen in 15 patients (20.9%). Myelotoxicity was seen more in the UFT+ raltitrexed group. Due to toxicity in 15 patients (24%) dose reduction was initiated and dose delay was necessary in 13 patients (21%), but no toxic death was observed. In general, it was tolerated well in both protocols. Grade 3/4 toxicity rates were similar as our study in salvage therapy studies. There are studies on target therapy agents in metastatic colorectal cancer used as salvage therapy (Jonker et al., 2007; Grothey et al., 2013). Jonker et al. reported a PFS of 1.8 months and OS of 4.6 months in 572 patients with colorectal cancer refractory to irinotecan, oxaliplatin and fluoropyrimidine, who received single agent cetuximab or best supportive treatment (Jonker et al., 2007). In one phase III trial randomized 760 patients to receive regorafenib or placebo plus best supportive care, with an improved overall survival as a primary endpoint. Patients had previously failed all standard therapies, including 5FU, oxaliplatin, irinotecan, bevacizumab, and anti-EGFR drug in mCRC patients with KRAS wild-type cancers. The median OS was 6.4 months for regorafenib and 5.0 months for placebo. Hazard ratio for progression-free survival was 0.49 (95%CI 0.42-0.58; p<0.0001), median PFS was 1.9 months for regorafenib and 1.7 months for placebo. The most recently reported grade 3 adverse effects were hand-foot syndrome (16%), fatigue (9%), hypertension (7.2%), diarrhoea (7%) and skin rash (5.8%) (Grothey et al., 2013). When target drugs are used as a single agent is limited efficacy, usage of them is limited due to high cost and access difficulties to drugs.

No activity difference was reported between the regimens administered as salvage therapy in mCRC patients who were refractory to oxaliplatin and irinotecan, therefore it is more rational to use more tolerable drugs. The mitomycin C+ raltitrexed combination was used as an alternative in patients who did not want central catheters, in patients with toxic reactions due to lack of dihydropyrimidine dehydrogenase (DPD) enzyme activity and in patients with cardiac disease in whom fluorouracil is contraindicated.

As a result, raltitrexed in combination with UFT and mitomycin C may be an alternative therapy with acceptable toxicity profile in advanced stage mCRC patients who have received previous chemotherapy.

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