Raltitrexed plus oxaliplatin in the second-line treatment of metastatic colorectal cancer

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The primary endpoint of this study was to evaluate the efficacy (objective response rate; ORR) of combined chemotherapy with raltitrexed plus oxaliplatin as second-line treatment in patients with metastatic colorectal cancer (CRC). Secondary endpoints were overall survival (OS), time to progression (TTP) and toxicity (NCI-CTC criteria).

The target population were patients with metastatic colorectal adenocarcinoma who progressed after first-line chemotherapy. Treatment consisted of raltitrexed 3 mg/m^2 as a 15-minute intravenous (IV) infusion followed 45 minutes later by oxaliplatin 130 mg/m^2 IV as a 2-h infusion on Day 1, repeated every 3 weeks until further disease progression (PD), unacceptable toxicity or the decision of the patient.

A total of 51 patients, all with WHO performance status 0–2 received a median of 6 treatment cycles (range 1–11). After 3 cycles, 8 of the 47 evaluable patients (17%) had experienced an ORR, 28 patients (59.6%) had experienced stable disease (SD) and 11 patients (23.4%) had PD. After 6 cycles, 1 of the 29 evaluable patients (3.5%) had an ORR, 13 patients (44.8%) had SD and 15 patients (51.7%) had PD. After a median follow-up of 48.9 weeks, median TTP was 18 weeks and median overall survival was 54.4 weeks. Treatment was well tolerated; grade 3 toxicities occurred in only 5/51 patients (9.8%). The most common toxicities were paraesthesia (62.7%), diarrhoea (23.5%), nausea (41.2%), vomiting (33.3%), hepatotoxicity (25.5%), and hematological toxicity (41.2%).

In conclusion**,** the combination of oxaliplatin plus raltitrexed appears to be effective and well tolerated as second-line therapy in patients with disseminated CRC.

Key words: colorectal cancer, palliative chemotherapy, raltitrexed, oxaliplatin

Colorectal cancer (CRC) is one of the most common causes of cancer mortality in the world. Despite a wide spectrum of preventive programmes, the incidence of this malignancy is rising in the Czech Republic and there are approximately 7400 new cases and 4300 deaths (mostly as a result of liver metastases) in this country each year. Radical resection in patients with solitary metastases or local relapse may prolong survival; however, in more than 80% of patients the disease is inoperable (clinical stage IV) at the time of diagnosis. Palliative chemotherapy may be administered to patients with disseminated disease with the aim of retarding tumor growth. Several randomized clinical studies have shown that compared with best supportive care (BSC) alone, palliative chemotherapy can improve median overall survival (OS) in patients with locally advanced or metastatic disease. Median OS in patients receiving chemotherapy is approximately 11 months compared with approximately 5 months in those receiving BSC alone. Despite the associated adverse event (AE) burden, it also improves patients' quality of life (increases time without symptoms, slows down weight loss, reduces pain).

5-Fluorouracil (5-FU) has been used in the treatment of CRC for almost 50 years. Objective response rates (ORRs) for 5-FU monotherapy range between 7–18%. A meta-analysis of nine randomized clinical studies has shown that the efficacy of 5-FU can be almost doubled by the addition of leucovorin (FA)[1–5]. The most common chemotherapy regimens used in the first-line treatment of CRC are bolus regimens of 5-FU/FA, such as: 5-FU/FA Mayo, 5-FU/FA Machover, or 5-FU/FA Roswell Park, which are associated with ORRs ranging between 20–30%. Continuous infusion of 5-FU (as in the AIO high-dose 5-FU plus calcium folinate]

and De Gramont regimens) is associated with significantly higher ORRs [6, 7].

New cytostatics such as raltitrexed, a specific inhibitor of thymidylate synthetase, and capecitabine, have different mechanisms of action so are associated with different tolerability profiles. Such new cytostatics are used in the treatment of metastatic CRC in the outpatient setting. They have comparable efficacy in terms of time to progression (TTP) and median OS in the first-line setting as standard therapy with 5-FU/FA regimens [8–12].

Oxaliplatin is another cytostatic agent with a similar, but not completely identical mechanism of action to cisplatin, which has previously been shown to be effective in the treatment of metastatic CRC. ORRs of up to 18% have been observed with oxaliplatin in previously untreated patients, whereas ORRs of approximately 10% have been reported in the second-line setting [13–15]. Oxaliplatin is commonly used in combination with continuous infusion of 5-FU/FA in the FOLFOX regimen, based on its synergism with 5-FU. As a first-line therapy, ORRs with the FOLFOX regimen exceed 50%, and this combination is associated with significantly increased TTP compared with 5-FU/FA alone (TTP 8.7 months versus 6.1 months, $p<0.001$). Median OS was similar for the two regimens: 19.9 months and 19.4 months, respectively [16–20]. The FOLFOX regimen is also effective in the neoadjuvant setting in patients with non-resectable liver metastases. In a study including 151 patients with metastatic liver disease, GIACCHETTI et al reported that neoadjuvant treatment with the FOLFOX resulted in resectable disease in 77 (51.0%) patients. Fifty-eight (38.4%) patients were able to have macroscopically complete resections, and half were still alive at a median follow up of 7 years [21, 22].

Irinotecan, an inhibitor of topoisomerase I, was introduced into clinical practice for the treatment of advanced, 5-FU-refractory CRC, and has demonstrated efficacy as both a first- and a second-line treatment. In the second-line setting in patients with 5-FU-refractory CRC, irinotecan (125 mg/m^2/week) was associated with an ORR of 14.1% and a median OS of 9.9 months [23]. CUNNINGHAM et al compared the efficacy of BSC plus irinotecan (300–350 mg/m^2, repeated every 3 weeks) with BSC alone in patients with 5-FU-refractory CRC. In this study, patients receiving irinotecan had significantly improved 1-year survival (36.2% versus 13.8%), improved quality of life and better control of disease-related symptoms compared with those receiving BSC alone [24]. Two multicentre Phase II trials have compared the efficacy of irinotecan (300–350 mg/m^2) with continuous 5-FU as second-line chemotherapy treatments [25, 26]. Patients treated with irinotecan had significantly improved median OS (10.8 months versus 8.5 months, respectively) and TTP (4.2 months versus 2.9 months, respectively) compared with those receiving continuous 5-FU. Several other studies have also demonstrated the benefits of irinotecan in the treatment of metastatic CRC [27–29]. Two randomized Phase III trials comparing 5-FU/FA with 5-FU/FA/irinotecan (FOLFIRI) as first-line treatments for advanced CRC showed higher ORRs, improved symptom control, and better TTP and OS for the irinotecan combination [30–32]. As a result, this combination regimen was recommended as the standard first-line chemotherapy for patients with metastatic CRC.

In the last decade there has been significant progress in the treatment of CRC with the use of new antiproliferative agents and combination regimens. An important question remains; which patients are indicated for monotherapy and which are indicated for combination treatment? This has been investigated in a retrospective analyses of data from several Phase III first-line CRC trials. This analysis suggested that combination treatment may be of benefit in patients with any of the following characteristics: age <65 years, performance status 0, physiological lactate dehydrogenase [LDH], bilirubin, leucocytes count, haemoglobin ≥11 g/dl, previously untreated disease, or having only one site metastases. It was suggested that all other patients should receive sequential monotherapy, as it is associated with a more favorable tolerability profile compared with combination regimens.

Here, we report the results of a study evaluating the efficacy of combined chemotherapy with raltitrexed plus oxaliplatin (TOMOX) as second-line treatment in patients with metastatic CRC.

Patients and methods

Patients were treated at the Masaryk Memorial Cancer Institute, and University Hospital, Brno, Czech Republic. The primary end point of the study was to determine the efficacy in terms of ORR of a TOMOX regimen in patients with metastatic CRC progressing after first-line chemotherapy. Secondary end points were OS, TTP, and toxicity.

Inclusion criteria. The study included patients aged between 18 and 70 years with histologically confirmed metastatic, non-resectable colorectal adenocarcinoma, progressing after first-line palliative chemotherapy (last chemotherapy treatment ≥4 weeks before study entry). Several first-line chemotherapy regimens were administered to the patients included in this study. In patients with a good performance status (PS) and no contraindication to irinotecan, either the FOLFIRI regimen or the weekly modifications of the FOLFIRI (Saltz's) regimen were used. In patients whose PS deteriorated following surgery, and/or those at risk of obstructive ileus, 5-FU/FA Mayo or de Gramont regimens were administered. Monotherapy with irinotecan was given in patients with disseminated disease and to those with possible resistance to 5-FU (relapsed within 6 months of adjuvant chemotherapy). Irinotecan monotherapy was also given to patients who had experienced 5-FU intolerance in the adjuvant setting (eg those with dihydropyrimidine dehydrogenase deficiency, toxicoallergic exanthema, or cardiotoxicity), and to those with severe cardiac deficiency, arrhythmia or unstable angina pectoris. An overview of the

first-line regimens received by the patients included in this study is presented in Table 1.

Other inclusion criteria were: PS 0-2, a life expectancy ≥3 months, at least one measurable metastatic lesion by computed tomography (CT), adequate haematological parameters (absolute neutrophil count $\geq 2x10^9$/l, platelet count $\geq 100x10^9$/l, haemoglobin ≥90 g/l), adequate liver function (bilirubin ≤2x upper normal limit [ULN], serum transaminases ≤2.5x ULN), and adequate renal function (serum creatinine ≤1.25x ULN, or creatinine clearance ≥65 ml/min). Written informed consent was obtained from all patients.

Exclusion criteria. Patients who had received >1 line of chemotherapy, those with symptomatic central nervous system metastases, bone metastases alone, carcinomatous leptomeningitis, infection, or previous cancer history (except for resolved cervical carcinoma or basal cutaneous carcinoma) were excluded from this study. Pregnant or lactating women, those with paraesthesia greater than National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade 1, and those in which raltitrexed or oxaliplatin were contraindicated were also excluded.

Treatment. TOMOX treatment consisted of raltitrexed 3 mg/m^2, given as a 15-minute intravenous (IV) infusion, followed 45 minutes later by oxaliplatin 130 mg/m^2 IV as 2-h infusion on Day 1, repeated every 3 weeks until disease progression (PD), response assessed as stable disease (SD) on two consecutive occasions, unacceptable toxicity or decision of the patient. Patients received premedication with serotonergic 5-HT3 receptor antagonists (setrons) to prevent nausea and also received an IV infusion of 10% calcium chlor-

Table 1. An overview of the types of first-line cytostatic regimens administered to the patients included in this study prior to TOMOX therapy

Regimen	Drug dose (mg/m^2)	Route of application	Days of application	Interval
5-FU/FA (Mayo) 5-Fluorouracil, leucovorin	425 20	IV bolus IV bolus	Days 1–5 Days 1–5	Every 4 weeks
5-FU/FA (de Gramont) 5-Fluorouracil, leucovorin	Leucovorin 200 mg/m^2 2-h IV infusion, 5-FU IV bolus 400 mg/m^2, 22-h continuous IV infusion of 5-FU 600 mg/m^2 (Days 1 and 2)			Every 2 weeks
5-FU/FA/IRI-Saltz 5-Fluorouracil, leucovorin, irinotecan	Irinotecan 125 mg/m^2 IV 1-h IV infusion followed by leucovorin 20 mg/m^2 IV bolus and 5-FU 500 mg/m^2 IV (Days 1, 8, 15, and 22)			Every 6 weeks
FOLFIRI 5-Fluorouracil, leucovorin, irinotecan	Irinotecan 180 mg/m^2 1.5-h IV infusion (Day 1). Leucovorin 200 mg/m^2 2-h IV infusion, followed by 5-FU 400 mg/m^2 IV bolus, and 22-h continuous IV infusion of 5-FU 600 mg/m^2 (Days 1 and 2)			Every 2 weeks
Irinotecan	Irinotecan 350 mg/m^2 1.5-h IV infusion (Day 1)			Every 3 weeks
Irinotecan weekly	Irinotecan 125 mg/m^2 1-h IV infusion (Days 1, 8, 15 and 22)			Every 6 weeks
Capecitabine	Capecitabine 1250 mg/m^2 PO twice daily (Days 1–14)			Every 3 weeks

Table 2. Schedule of study assessments

Day	D1	D7	D14	D 21/1	D7	D14	D 21/1	D7	D14	D21
Physical examination (including blood pressure, pulse, temperature)	×			×			×			×
Karnofsky status, weight	×			×			×			×
Neurological assessment	×									×
Haematology (incl. complete blood count with diff.)	×	×	×	×	×	×	×	×	×	×
Coagulation (INR)	×									×
Biochemistry*	×									×
Liver tests†				×			×			
CEA	×									×
Lung X-ray	×‡									×
CT (including abdomen, pelvis)	×‡									×
ECG	×				If clinically indicated					
Adverse events				×			×			×
Chemotherapy administration	×			×			×			×
Concomitant medication	×			×			×			×

D – Day; *Biochemistry: urea, creatinine, sodium, potassium, chloride, glucose, transaminases (SGOT, SGPT, GGMT), bilirubin, lactate dehydrogenase, alkaline phosphatase; † Liver tests: transaminases (SGOT, SGPT, GGMT), bilirubin, lactate dehydrogenase, alkaline phosphatase; ‡ Performed ≤4 weeks before chemotherapy.

Table 3. Toxicities resulting in oxaliplatin and/or raltitrexed dose modification (oxaliplatin 100% = 130 mg/m^2; raltitrexed 100% = 3 mg/m^2)

	NCI grade			
	1	2	3	4
Haematological toxicities				
Anaemia (Hb)	100%	100%	100%*	100%*
Neutropenia (ANC)	100%	100%	75%	75%
Thrombocytopenia (PLT)	100%	100%	75%	75%
Gastrointestinal toxicities				
Vomiting†	100%	100%	Oxaliplatin 75%	Oxaliplatin 50%
Diarrhoea‡	100%	Raltitrexed 75% Oxaliplatin 100%	Raltitrexed 50% Oxaliplatin 75%	Discontinuation
Mucositis‡	100%	100%	Raltitrexed 75%	Raltitrexed 50%

Oxaliplatin dose modification for neurological toxicities

	Duration of toxicities		
	1–7 days	>7 days	Persistent between cycles
Paraesthesias/dysaesthesias of short duration that resolve and do not interfere with function (grade 1)	100%	100%	100%
Paraesthesias/dysaesthesias interfering with function, but not activities of daily living (grade 2)	100%	100%	100 mg/m^2
Paraesthesias/dysaesthesias with pain or with functional impairment that also interfere with activities of daily living (grade 3)	100%	100 mg/m^2	Treatment discontinuation

Raltitrexed dose modification for renal toxicities

Creatinine clearance	Dose modification	Interval between cycles
>65 mL/min	100%	3 weeks
55–65 mL/min	75%	4 weeks
25–54 mL/min	25%	4 weeks
<25 mL/min	Treatment discontinuation	

*After red blood cell transfusion; † If not controlled by maximal anti-emetic prophylaxis; ‡ If the patient experienced diarrhoea or mucositis ≥ grade 3 in the courses following dose reduction they were withdrawn from the study.

atum in 100 ml of saline, and an IV infusion of 10% magnesium sulphuricum in 100 ml of 5% glucose before oxaliplatin administration to prevent neurotoxicity [33]. Hematological and biochemical parameters were assessed before enrolment and were also monitored during the study (Tab. 2).

Efficacy assessments. Response Evaluation Criteria in Solid Tumors (RECIST) were used to evaluate tumor response after 3 and 6 cycles of chemotherapy, via CT scan, X-ray and tumor markers measurements (Tab. 2). OS was also assessed.

Toxicity assessments. Toxicity was evaluated according to NCI-CTC criteria. Before each course of chemotherapy, creatinine clearance was measured in patients with abnormal serum creatinine levels and the dose of raltitrexed adjusted accordingly (Tab. 3). Chemotherapy was postponed/reduced in cases of haematological, gastrointestinal, renal or other toxicity, as shown in Table 3. Once the dose was reduced it was never increased in subsequent cycles. The next course of chemotherapy could be delayed for a maximum of 15 days.

Statistical analyses. Data for this study were summarized using standard statistical measures. For continuous variables such as age, duration of chemotherapy treatment etc, data were described in non-parametric robust terminology (e.g. as median, minimum and maximum values). For nominal parameters such as response to treatment, adverse events etc, data were presented as. absolute numbers along with percentage values.

Standard KAPLAN-MEIER analysis was applied in the evaluation of overall survival including estimation of median value [34]. These analyses were performed using Statistica for Windows – version 6 [35].

Results

Patient and disease characteristics. Between October 2001 and July 2004, a total of 51 patients were treated. Patient characteristics are shown in Table 4. The patient's group comprised 29 men and 22 women, with a median age 56 years, and metastatic CRC (colon: 49.0%, rectum: 37.3%, rectosigmoid: 13.7%). Seventeen patients (33.3%) had received prior adjuvant chemotherapy and most (40 patients [78.3%]) had received irinotecan as first-line treatment either as monotherapy or in combination with an IV bolus or continuous 5-FU/FA regimen. The liver was the most common site of metastases with this type of metastases present in 39 patients (76.5%). More than one site of metastatic disease was present in 24 patients (47.1%).

Treatment. Patients received a median of 6 cycles of TOMOX (range 1–11 cycles) and a total of 260 cycles were administered. Median duration of TOMOX treatment was 18 weeks (range 3.3–35 weeks). The reason for discontinuing treatment was PD in 35 patients (68.6%), toxicity in 8 patients (15.7%) and a combination of PD and toxicity in 1 patient (2%).

Efficacy. Four patients have not reached 3 cycles of chemotherapy and so are not yet evaluable for response. Eight of the 47 evaluable patients (17.0%) experienced a partial response (PR), 28 patients (59.6%) experienced SD, and 11 patients

Table 4. Patient characteristics (n=51)

Median age, years (range)	56 (38–79)
Proportion male:female	29:22
Performance status ECOG, n (%)	
PS 0	34 (66.7)
PS 1	17 (33.3)
Tumor localisation, n (%)	
Colon	25 (49.0)
Rectum	19 (37.3)
Rectosigmoid	7 (13.7)
Adjuvant chemotherapy, n (%)	17 (33.3)
First-line chemotherapy, n (%)	
5-FU/FA (Mayo, de Gramont)	10 (19.6)
5-FU/FA/irinotecan (Saltz)	17 (33.3)
FOLFIRI	8 (15.7)
Irinotecan (weekly, q 3 weeks)	15 (29.4)
Capecitabine	1 (2.0)
Number of metastatic sites, n (%)	
Median, range	2 (1–3)
1 metastatic site	27 (52.9)
>1 metastatic site	24 (47.1)
Sites of metastatic disease, n (%)	
Liver	39 (76.5)
Abdominopelvic involvement	25 (49.0)
Pulmonary	11 (21.7)
Soft tissue	2 (3.9)
Skeletal	2 (3.9)
Median number of TOMOX cycles (range)	6 (1–11)
Median time on TOMOX, weeks (range)	18 (3.3–35)

Table 5. Best overall response to TOMOX treatment (n=51)

	No. patients after 3 cycles	Percentage of the 47 evaluable patients after 3 cycles	No. patients after 6 cycles	Percentage of the 29 evaluable patients after 6 cycles
PR	8	17.0	1	3.5
SD	28	59.6	13	44.8
PD	11	23.4	15	51.7
NE	4	–	18	–

NE – non-evaluable, PD – disease progression, PR – partial response, SD – stable disease

(23.4%) had PD after 3 cycles of chemotherapy. No complete responses were observed. Eighteen patients have not yet received 6 cycles of chemotherapy. One of the 29 evaluable patients (3.5%) experienced a PR, 13 patients (44.8%) experienced SD, and 15 patients (51.7%) had PD after 6 cycles of chemotherapy (Tab. 5, Fig. 1). In patients with PD, the median TTP was 18 weeks (range 4–37 weeks) and the median follow up was 48.9 weeks (range 16.7–128 weeks). Median OS was 54.4 weeks, with 25 percentage OS 90.5 weeks and 75 percentage OS 34.2 (Fig. 2).

Toxicity. No grade 4 toxicity was observed and the only grade 3 toxicities were leukopenia (3 patients [5.9%]), vomiting (1 patient [1.9%]) and diarrhea (1 patient [1.9%]). All the AEs that were observed during the course of this study are shown in Table 6.

Discussion

CRC is the most common cancer of the digestive system, and is a very serious health problem in the Czech Republic. Randomized clinical trials have demonstrated the benefits of adjuvant treatment after curative resection of stage III CRC. The standard adjuvant treatment is 6 cycles of 5-FU/FA (Mayo regimen). In the palliative treatment of disseminated disease, the type of chemotherapy used depends on several different parameters. These include the patient's PS, age, comorbidities, hepatic and renal function, haematological and biochemical parameters, number, size and localisation of metastatic lesions, previous chemotherapy (and response to it), tolerance to chemotherapy, the degree of histological differentiation, proliferative activity, angiogenesis, and ploidity of the tumor, and several other new predictive parameters.

A meta-analysis of the clinical trials of palliative chemotherapy in patients with metastatic CRC has demonstrated benefits in terms of OS and quality of life versus BSC alone. The addition of irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) to 5-FU/FA regimens increase the ORR and OS and may enable a second liver resection to take place in those with liver metastases. Randomized Phase III clinical trials have demonstrated the benefits of combination chemotherapy over monotherapy as first-line therapy for metastatic CRC. Recent efforts have focused on optimising treatment options for patients experiencing progression following first-line therapy. The treatment administered depends on

Table 6. Adverse events occurring during TOMOX treatment (n=51)

	No. patients (%)								
	Paraesthesia	Mouth ulcers	Constipation	Diarrhoea	Vomiting	Nausea	Hepatotoxicity	Thrombocytopenia	Leucopenia
G1	27 (52.9)	1 (1.9)	3 (5.9)	8 (15.7)	13 (25.5)	19 (37.3)	10 (19.6)	4 (7.8)	6 (11.8)
G2	5 (9.8)	–	–	3 (5.9)	3 (5.9)	2 (3.9)	3 (5.9)	4 (7.8)	4 (7.8)
G3	–	–	–	1 (1.9)	1 (1.9)	–	–	–	3 (5.9)
Total	32 (62.7)	1 (1.9)	3 (5.9)	12 (23.5)	17 (33.3)	21 (41.2)	13 (25.5)	8 (15.7)	13 (25.5)

G – National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade

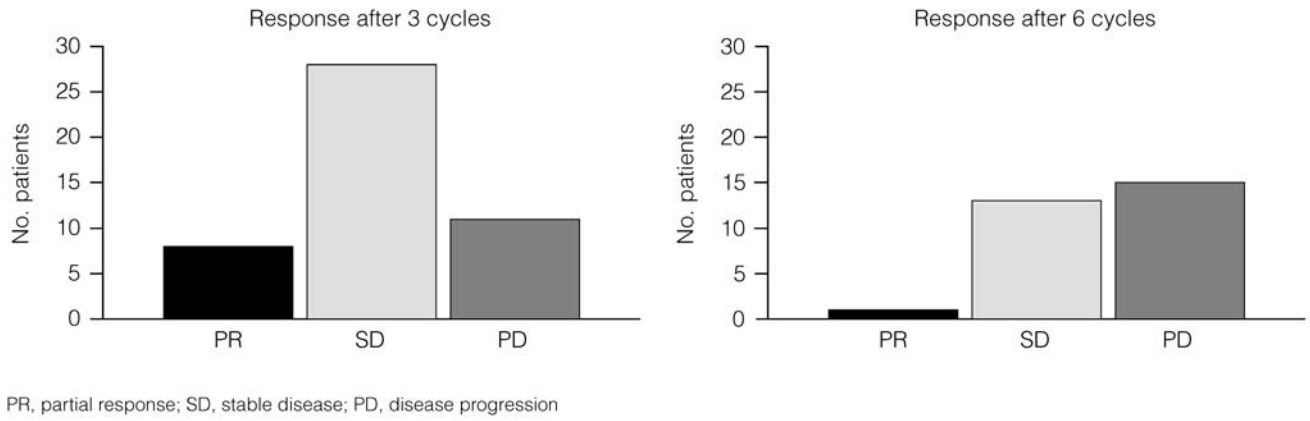

Figure 1. Best overall response to TOMOX treatment after 3 and 6 cycles of treatment.

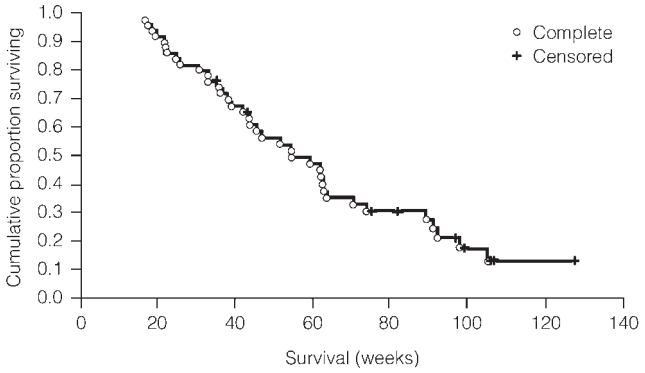

Figure 2. Kaplan-Meier analysis of overall survival in patients receiving TOMOX treatment.

many factors such as the patient's PS, any toxicity with previous chemotherapy, and TTP on previous treatments. In the Phase III GERCOR trial, TOURNIGAND et al compared the efficacy (TTP and OS) and tolerability of first-line FOLFIRI treatment followed by second-line FOLFOX6 treatment (arm A) with sequential FOLFOX and FOLFIRI as second-line therapy (arm B) in metastatic CRC. In addition to the primary objectives, this trial also aimed to identify the optimum therapeutic sequence. After first-line therapy, the ORR was 56% and TTP was 8.5 months with the FOLFIRI regimen compared with a 54% ORR and a TTP of 8 months with the FOLFOX regimen. In arm A second-line therapy with FOLFOX resulted in a ORR of 15% compared with 4% in arm B (FOLFIRI) [36]. Based on these data FOLFIRI was recommended as first-line therapy in metastatic CRC.

Raltitrexed and oxaliplatin are effective cytostatic agents in metastatic CRC. They have different mechanisms of action, favorable toxicity profiles, and are not cross-resistant with each other. Furthermore, both agents are suitable for use in the outpatient setting. Based on these facts, and preclinical studies that showed an additive effect for these drugs in combination, we conducted a clinical study of TOMOX as second-line therapy in patients with metastatic CRC. The current published data from clinical trials using raltitrexed and oxaliplatin in combination are summarized in Table 7. This combination has proved to be effective as a first-line treatment, being associated with ORRs ranging from 43% to 62% [37–40]. Data from four Phase II clinical studies using TOMOX as a second-line therapy in CRC have now been published. VAN CUTSEM et al reported an ORR of 16% in 50 patients receiving TOMOX, [43] whereas SCHEITHAUER et al reported an ORR of 33% in 36 patients, with 47% of patients experiencing SD [46]. This discrepancy in results may be due to differences in the previous first-line therapy received by the patients in the two studies. In VAN CUTSEM's study, 17 patients had previously received a first-line bolus 5-FU/FA regimen, 6 patients had received a continuous infusion 5-FU/FA regimen, and 2 patients had received locoregional chemotherapy with 5-FU. Only 11 patients (30%) in this study had received 5-FU/FA/irinotecan as their first-line therapy. In the present study, 40 patients (78%) had 5-FU/FA plus irinotecan or irinotecan alone as first-line therapy, and 24 patients (47%) had multiple sites of metastases. In this context, the results reported here for second-line TOMOX treatment appear to be quite encouraging.

In conclusion, the ORR after 3 and 6 cycles of TOMOX treatment was 17.0% and 3.5%, respectively, with 59.6% and 44.8% of patients experiencing SD and 23.4% and 51.7% having PD at these time points. The median TTP was 4.5 months, after a median follow-up of 12.2 months and median OS was 13.6 months. Treatment was well tolerated with the most common AEs being hematological toxicities, diarrhea and vomiting.

The combination of oxaliplatin plus raltitrexed appears to be an effective and well-tolerated second-line therapy for patients with disseminated CRC and has the advantage that it can be administered in the outpatient setting.

Table 7. Review of the data from Phase II clinical studies including TOMOX as first- or second-line treatment for metastatic colorectal cancer

Clinical study	No. patients	Regimen	ORR, %	TTP, months	MOS, months	G3/4 neutropenia, %	G3/4 non-haematological toxicities
1st-line Cascinu[37]	58	Raltitrexed (3 mg/m^2 Day 1) oxaliplatin (100 mg/m^2 Day 1) q 3 weeks	50	6.5	>9	17.0	Diarrhoea 7% Neurotoxicity 10% ↑ transaminases 17%
1st-line Neri[38]	37	Raltitrexed (3 mg/m^2 Day 1) oxaliplatin (130 mg/m^2 Day 1) q 3 weeks	43	10.3	NA	NA	Diarrhoea NA Neurotoxicity NA ↑ transaminases NA
1st-line Seitz[39]	66	Raltitrexed (3 mg/m^2 Day 1) oxaliplatin (130 mg/m^2 Day 1) q.3 weeks	54	6.2	14.6	30.0	Diarrhoea 17% Neurotoxicity NA ↑ transaminases 34%
1st-line Douillard[40]	63	Raltitrexed (3 mg/m^2 Day 1) oxaliplatin (130 mg/m^2 Day 1) q 3 weeks	62	6.3	NA	16.5	Diarrhoea 9% Neurotoxicity 0% ↑ transaminases NA
1st- and 2nd-line Martoni[41]	46	Raltitrexed (3 mg/m^2 Day 1) oxaliplatin (130 mg/m^2 Day 1) q 3 weeks	16	5	NA	NA	Diarrhoea NA Neurotoxicity 16% ↑ transaminases 24%
1st- and 2nd-line Laudani[42]	45	Raltitrexed (3 mg/m^2 Day 1) oxaliplatin (130 mg/m^2 Day 1) q 3 weeks	29	4	9	0	Nausea/vomiting 8% Diarrhoea 8% Neurotoxicity 13%
2nd-line Van Cutsem[43]	50	Raltitrexed (3 mg/m^2 Day 1) oxaliplatin (130 mg/m^2 Day 1) q 3 weeks	16	4.6	7.1	7.4	Diarrhoea 12% Neurotoxicity 6% ↑ transaminases NA
2nd-line Murad[44]	12	Raltitrexed (3 mg/m^2 Day 1) oxaliplatin (120 mg/m^2 Day 1) q 3 weeks	33.4	6.5	7.0	20.0	Diarrhoea 10% Vomiting 6%
2nd-line Alonso[45]	45	Raltitrexed (2 mg/m^2 Day 1) oxaliplatin (85 mg/m^2 Day 1) q 2 weeks	33	NA	15.9	0	Asthenia 14% Nausea/vomiting 3% Diarrhoea 3% Constipation 3% ↑ transaminases 3%
2nd-line Scheithauer[46]	36	Raltitrexed (3 mg/m^2 Day 1) oxaliplatin (130 mg/m^2 Day 1) q 3 weeks	33	6.5	NA	22.0	Diarrhoea 5% Neurotoxicity 10% ↑ transaminases 5%

MOS – median overall survival, NA – not available, ORR – objective response rate, TTP – time to progression, ↑ – elevation.

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