

## Efficacy of Infusional Biomodulated 5-Fluorouracil in Metastatic Colorectal Cancer after Raltitrexed Failure

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**Abstract.** *Background: Treatment of metastatic colorectal cancer (CRC) with raltitrexed results in an objective response rate (OR) and overall survival (OS) comparable to bolus 5-fluorouracil (5-FU). A phase III trial found raltitrexed to be inferior to continuous infusion of 5-FU (ci5-FU). Patients and Methods: This phase II trial studied the activity and toxicity of methotrexate-modulated ci5-FU (ci5-FU/MTX) after failure of raltitrexed in patients with metastatic CRC. Results: Of 32 patients who received raltitrexed, 27 were evaluable for response. An OR was observed in 19%. Grade 3/4 toxicity occurred in 47% of patients. Eighteen patients received second-line ci5-FU/MTX. One complete response (CR) and five stable diseases (SD) were observed. CR and SD were observed in patients with raltitrexed-resistant disease. Toxicity to ci5-FU/MTX was mild and predictable, even in patients with severe toxicity under raltitrexed. Conclusion: ci5-FU/MTX is ineffective after failure of raltitrexed in patients with metastatic CRC. However, response to ci5-FU/MTX in patients with raltitrexed-resistant disease indicates incomplete cross-resistance.*

Raltitrexed (Tomudex<sup>®</sup>, AstraZeneca), a direct and specific inhibitor of thymidylate synthase, is licensed for the first-line treatment of advanced colorectal cancer (CRC). The recommended dose is 3mg/m<sup>2</sup>, administered as a 15-min intravenous infusion every 3 weeks (1). At this dose, a phase II clinical trial in advanced CRC reported an OR of 26% (2). Dose-limiting toxicities were myelosuppression, gastrointestinal symptoms, asthenia and asymptomatic elevation of liver transaminases. Three prospective randomized phase III clinical trials compared raltitrexed with bolus administration of 5-FU, modulated by leucovorin

(5-FU/LV)(3). There was no significant difference in OR in any of the comparative trials (14.3% to 19.3% in patients receiving raltitrexed and 15.2% to 18.1% in 5-FU/LV recipients). In two trials OS did not differ significantly, but one trial found a significantly longer survival in the 5-FU/LV group. The incidence of grade 3/4 mucositis and grade 3/4 leucopenia was lower in the raltitrexed group when compared to bolus 5-FU/LV, but anaemia occurred more frequently.

Only recently a comparison of raltitrexed to two regimens of ci5-FU (deGramont and Lokich regimens) was published (4). Raltitrexed was easier to administer, showed a similar OR and OS, but resulted in greater toxicity and inferior quality of life. Another study demonstrated that single agent ci5-FU was not effective as second-line therapy after raltitrexed in advanced CRC (5).

In the present prospective single institution phase II trial for patients with metastatic CRC, we investigated the anti-tumour activity and toxicity of first-line raltitrexed followed by second-line ci5-FU/MTX.

### Patients and Methods

**Patient selection.** A prospective single-centre phase II study was performed in patients with stage IV CRC who received raltitrexed as first-line and ci5-FU/MTX as second-line chemotherapy. All patients were treated in the Medical Oncology Department of the Oncologisch Centrum of the AZ-VUB, Brussels, Belgium.

Patients were eligible for this study if they met the following criteria: stage IV CRC; no previous chemotherapy for metastatic disease; at least 18 years old; at least one measurable lesion; a Karnofsky performance status >60%; no other malignancies or serious illnesses; no evidence of significant alteration of renal or hepatic organ function.

**Treatment.** Raltitrexed was administered at a dose of 3mg/m<sup>2</sup> as an intravenous infusion over 15 minutes, every 21 days. The dose was adjusted when a deterioration of the renal function was observed: patients with a clearance of 40-60ml/min received 75% of the normal dose.

ci5-FU/MTX (6) was administered as a 10-minute infusion of 40mg/m<sup>2</sup> MTX followed by 60mg/kg 5-FU over 48 hours, weekly for 4 weeks and every 2 weeks thereafter. 5-FU was infused by the

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use of a portable infusion pump (Deltec, Smiths Group). The use of oral leucovorin (8x25mg starting 24 hours post-MTX) for the prevention of MTX- associated mucositis was allowed.

Both treatments were continued until disease progression, unacceptable toxicity or patient refusal.

**Patient evaluation and follow-up.** Pre-treatment evaluation included a complete medical history and physical examination, a complete blood count, chemistry profile and carcinoembryonic antigen (CEA) measurement, a chest X-ray and a radiological tumour assessment by CT or MRI. A complete blood count was obtained before the start of each treatment cycle together with a serum chemistry profile, CEA measurement, physical examination and toxicity assessment. During study treatment patients had radiological tumour assessment every 12 weeks. Tumour response classification [complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD)] was derived from standard World Health Organization criteria (7). The time to progression (TTP) was defined as the interval between the initiation of treatment and the date when PD was first documented. Overall survival (OS) was defined as the time between the start of raltitrexed treatment and the date of death.

**Assessment of toxicity.** Toxicity was evaluated every week for the first six weeks for both raltitrexed and ci5-FU/MTX and every 3 and 2 weeks, for raltitrexed and ci5-FU/MTX, respectively, thereafter. Adverse events were graded according to the WHO criteria for the grading of toxicity (8).

## Results

**Patient characteristics (Table I).** Between October 1998 and July 2002, 32 patients with stage IV CRC received raltitrexed as first-line chemotherapy. After the occurrence of PD or unacceptable toxicity, 18 patients were given ci5-FU/MTX as second-line chemotherapy.

**Treatment.** During first-line therapy with raltitrexed, 32 patients received a total of 179 cycles. The mean number of cycles was 6 (range 2-19). During second-line treatment, 18 patients were given a total of 249 cycles ci5-FU/MTX, with a mean of 14 cycles (range 7-47).

**Tumour response (Table II).** Of the 32 patients who received first-line chemotherapy with raltitrexed, 27 (84%) were evaluable for tumour response. Five patients were not evaluable for response because no objective evaluation could be performed: in 3 patients raltitrexed was stopped prematurely due to unacceptable toxicity and 2 patients died before re-evaluation. The death of these 2 patients was considered not to be treatment- or disease-related. Sixteen out of 27 patients achieved a response, including 1 CR (4%), 4 PR (15%) and 11 SD (41%). The median TTP in responding patients was 6 months (range 4-12). The median TTP for the entire study population was 3 months (range 1-12). By the date of evaluation raltitrexed had been stopped in 20 patients because of PD and in 9 patients because of unacceptable toxicity.

Table I. Patient characteristics.

|                          | 1st line raltitrexed:<br>n=32 | 2nd line ci5-FU/MTX:<br>n=18 |
|--------------------------|-------------------------------|------------------------------|
| Sex:                     |                               |                              |
| Male                     | 19 (59%)                      | 9 (50%)                      |
| Female                   | 13 (41%)                      | 9 (50%)                      |
| Age at inclusion, years: |                               |                              |
| Median (range)           | 71.5 (43-80)                  | 72 (58-77)                   |
| Site of primary tumor:   |                               |                              |
| Colon                    | 20 (62.5%)                    | 11 (61%)                     |
| Rectum                   | 12 (37.5%)                    | 7 (39%)                      |
| Sites of metastasis:     |                               |                              |
| Liver                    | 24                            | 15                           |
| Liver only               | 14                            | 11                           |
| Liver and other sites    | 10                            | 4                            |
| Lung                     | 3                             | 1                            |
| Bone                     | 3                             | 2                            |
| Other                    | 12                            | 4                            |
| Local recurrence         | 5                             | 2                            |

Some patients had more than 1 extrahepatic localisation

Of the 18 patients who received second-line ci5-FU/MTX, first-line raltitrexed was stopped in 11 patients (61%) because of PD (two had PR as best response and three had SD) and in 7 patients (39%) because of unacceptable toxicity (one had PR, three had SD and three were not evaluable for response).

All 18 patients who received second-line ci5-FU/MTX were evaluable for response. One patient, who showed PD after 4 cycles of raltitrexed, achieved a CR (6%). Five patients (28%) showed SD: in 1 of these patients raltitrexed was stopped after 7 cycles because of PD; in the other 4 patients first-line chemotherapy was stopped because of unacceptable toxicity. Of the latter, three patients had not been evaluable for response and one achieved PR after 4 cycles but stopped treatment after 8 cycles because of raltitrexed-related interstitial pneumonitis. In this patient ci5-FU modulated by low dose LV was given instead of ci5-FU/MTX because of potential additional toxic effects of MTX to the lung parenchyma (9).

The median TTP in responding patients was 9 months (range: 4-24). The median overall TTP for second-line ci5-FU/MTX was 3 months (range: 1-24). Second-line chemotherapy was stopped in 17 patients because of PD and in one patient on request, after achieving PR.

**Overall survival.** By the date of analysis 21 patients (66%) had died. The median OS was 15 months (range: 2-40). Thirteen patients (72%) who received raltitrexed as first-line chemotherapy and ci5-FU/MTX as second-line chemotherapy had died by the date of analysis. The median OS in this group was 18.5 months (range: 6-40).

Table II. Tumor response to second-line ci5-FU/MTX according to the response to first-line raltitrexed.

| 1st line raltitrexed  |                                 | 2nd line ci5-FU/MTX  |                             |
|---|---------------------------------|--|-----------------------------|
| Evaluable number of patients/total number of treated patients:<br>27/32 |                                 | 18/18  |                             |
| Best response to raltitrexed  | Reason for stopping raltitrexed | Number of patients treated with sequential 2nd line ci5-FU/MTX according to the raltitrexed response | Best response to ci5-FU/MTX |
| CR: 1   | PD:1                            | 0  |                             |
| PR: 4   | PD:2                            | 2  | PD:2                        |
|   | Tox:2                           | 1  | SD:1                        |
| SD: 11  | PD:6                            | 3  | SD:1                        |
|   | Tox: 4                          | 3  | PD: 2                       |
|   | Death:1                         | 0  | PD: 3                       |
| PD: 11  | PD:11                           | 6  | CR:1                        |
|   |                                 |  | PD: 5                       |
| NE: 5   | Tox:3                           | 3  | SD:3                        |
|   | Death:2                         | 0  |                             |

**Toxicity.** First-line chemotherapy with raltitrexed was stopped in 9 patients (28%) because of unacceptable toxicity. The most common adverse events were gastrointestinal symptoms (nausea, vomiting, diarrhoea and anorexia), myelosuppression (anaemia, leukopenia and thrombocytopenia) and asthenia. An asymptomatic elevation of liver enzymes was observed in 21 patients (2 with grade 3). In 15 patients (47%) grade 3/4 toxicity was observed: grade 3/4 anorexia in 3 patients, grade 3/4 asthenia in 1 patient and grade 3/4 asymptomatic elevation of liver enzymes in 2 patients. Three patients developed grade 3 dermatitis of the pretibial region, completely reversible after withdrawal of raltitrexed. One patient developed grade 4 respiratory insufficiency due to interstitial lung disease, which was successfully treated with corticosteroids and withdrawal of the drug (9).

No patient stopped ci5-FU/MTX because of unacceptable toxicity. The most common adverse events were gastrointestinal symptoms and myelosuppression. In 1 patient grade 3/4 haematological toxicity was observed: anaemia and thrombocytopenia. Eight patients (44%) developed grade 1/2 stomatitis as compared to only 3 (9%) during first-line therapy.

## Discussion

Raltitrexed has demonstrated clinical activity in the treatment of metastatic CRC that is comparable to bolus 5-FU/LV regimens. Raltitrexed also has a comparable global toxicity profile and has a more convenient mode of administration (short *i.v.* infusion every 3 weeks) (2). However, when compared to infusional regimens of 5-FU, raltitrexed recently proved to be slightly inferior in terms of toxicity and quality of life (4, 10).

In the present study, the tumour response and toxicity to first-line raltitrexed followed by second-line ci5-FU/MTX in patients with metastatic CRC was investigated. The OR (CR and PR) on first-line chemotherapy with raltitrexed was 19%. This result is comparable to what had been observed in other phase II and III clinical trials with raltitrexed as first-line treatment for metastatic CRC (3, 4). In our study only 18 out of 32 patients who received first-line raltitrexed were treated with ci5-FU/MTX as second-line chemotherapy. The OR was 6%, suggesting that ci5-FU/MTX is not a very effective second-line treatment after failure of raltitrexed. A similar conclusion was drawn from a comparable trial using first-line raltitrexed followed by second-line single agent ci5-FU for advanced CRC (5, 10). Other chemotherapeutic agents such as oxaliplatin and irinotecan have been shown to be more active in second-line treatment of advanced CRC after 5-FU-based chemotherapy with tumour response rates of the order of 15-20% (11, 12).

However, the clinical benefit might be more significant as several patients with progressive disease under raltitrexed or unacceptable toxicity had disease stabilisation after being switched to ci5-FU/MTX. In particular, two patients who progressed under raltitrexed did show a response to second-line ci5-FU/MTX: one CR and one SD. We can thus conclude that resistance to raltitrexed does not necessarily imply resistance to ci5-FU/MTX. Infusional 5-FU could provide for more sustained inhibition of thymidylate synthase than raltitrexed and 5-FU has a broader mechanism of action. Both these elements could, at least in theory, account for superior antitumour activity.

The toxicity profile of raltitrexed in this study was comparable to the one observed in published trials with this agent. The most commonly encountered toxicities consisted of asthenia, asymptomatic elevation of liver transaminases, gastrointestinal and haematological toxicity. Two rare forms of grade 3/4 toxicities were documented. One consisted of dermatitis of the pretibial region and the other was a grade 4 interstitial pneumonitis, which was clearly drug-related.

The adverse events in second-line treatment with ci5-FU/MTX were generally mild and comparable with the known toxicity of ci5-FU (6). In addition, patients who stopped raltitrexed because of unacceptable toxicity and

continued with second-line ci5-FU/MTX tolerated this second-line chemotherapy very well. When compared to each other and taking into account the sequence of both treatments, raltitrexed can be considered a significantly more toxic treatment. This observation is in accordance with the findings of a recently published phase III study (4).

In conclusion, the present study demonstrated that ci5-FU/MTX, although it possesses an excellent tolerability profile and a better therapeutic ratio than raltitrexed, is probably not effective enough to be considered as a second-line treatment option for metastatic CRC patients after failure of raltitrexed. Raltitrexed is an active drug for the treatment of colorectal cancer. However, the relative significant toxicity profile of raltitrexed and the availability of novel, more active treatments and oral compounds such as capecitabine and UFT lead to the recommendation that this drug should be strictly limited to patients for whom the logistics or toxicities of the other available treatments are unacceptable and on condition of careful monitoring of the potential toxicities associated with this drug.

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