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Preoperative chemoradiation with raltitrexed ('Tomudex') for T2/N+ and T3/N+ rectal cancers: a phase I study☆

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Abstract

The use of raltitrexed ('Tomudex') as concomitant chemotherapy during preoperative radiotherapy in chemonaïve patients with stage II/III rectal cancer has been examined in this study and its recommended dose in conjunction with radiotherapy investigated. Forty-five Gray (Gy) of radiotherapy (1.8 Gy daily, 5 days per week) was delivered to the posterior pelvis, followed by a 5.4 Gy boost. Single doses of raltitrexed (2.0, 2.5 and 3.0 mg/m^2) were administered on days 1, 19 and 38. Only 1 of the 15 patients entered experienced a dose limiting toxicity (DLT) (grade 3 leucopenia) at the 3.0 mg/m^2 dose level. The overall response rate was 80% (five complete responses, seven partial responses). These preliminary data suggest that raltitrexed is a well tolerated and effective treatment when combined with preoperative radiotherapy in patients with stage II/III rectal cancer. The recommended dose of raltitrexed for future phase II studies will be 3.0 mg/m^2.

Keywords: Raltitrexed; Rectal cancer; Preoperative radiotherapy; Toxicity; Recommended dose

1. Introduction

Postoperative chemotherapy combined with radiotherapy has been shown to reduce local recurrence and improve survival in patients with rectal cancer compared with surgery alone [1] and postoperative radiation alone [2]. Furthermore, postoperative chemoradiation prolonged the disease-free interval in patients with rectal carcinoma following surgery, compared with surgery alone, although no significant difference was observed in overall survival [3]. Concomitant chemoradiation for rectal cancer is generally based on 5-fluorouracil (5-FU) either given alone or modulated with a second agent. The administration of 5-FU (500 mg/m^2) for 3 days concomitant with radiotherapy has been used for 30 years [4], and is the schedule used in the majority of randomised trials of chemoradiation [2–7]. Toxicity varies according to the method of 5-FU delivery: bolus 5-FU tends to cause diarrhoea, leucopenia and mucositis, whereas infusional 5-FU is associated with mucositis and dermatitis [8].

In the last few years, encouraging results have been reported for preoperative chemoradiation in resectable rectal cancer. In several Phase II trials [9–14], preoperative chemoradiation has achieved high rates of tumour downstaging with increased feasibility of surgical sphincter preservation and with a promising rate of pathological complete response (9–29%). Preoperative acute toxicity was generally low in these studies, but the optimal combination between drugs and radiotherapy has yet to be defined.

Raltitrexed ('Tomudex'), a quinazoline folate analogue which acts as a specific thymidylate synthase (TS) inhibitor [15], is currently indicated for the treatment of advanced colorectal cancer [16,17]. Raltitrexed is polyglutamated on entering cells, resulting in markedly enhanced potency and duration of TS inhibition and permitting a 3-weekly schedule of administration [18]. In patients with advanced colorectal cancer, raltitrexed has been shown to produce similar response rates to 5-FU plus leucovorin and have a predictable and man-

☆ 'Tomudex' is a trademark of the AstraZeneca group of companies.

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ageable toxicity profile [19]. Interestingly, raltitrexed, like 5-FU, has been shown to be a radiation sensitiser both *in vitro* and *in vivo* [20]. The use of raltitrexed as concomitant chemotherapy during radiotherapy for rectal cancer may, therefore, be expected to lead to enhanced efficacy compared with radiotherapy alone.

The principal aim of this study was to determine the recommended dose of raltitrexed when delivered concurrently with preoperative radiotherapy, in patients with potentially resectable clinical stage II/III rectal cancer.

2. Patients and methods

2.1. Patient selection

Eligibility criteria included: histologically confirmed primary adenocarcinoma of the middle and low rectum; clinical stage [21] T3N0-2M0 or T2N1-2M0; age >18 years; Karnofsky performance status >60; non-pregnant, non-lactating; no prior chemotherapy, immunotherapy or radiotherapy to the pelvis. The following laboratory entry criteria were required: leucocyte count $\geqslant 4000\times10^6$ cells/l granulocyte count $\geqslant 1500\times10^6$ cells/l; haemoglobin level $\geqslant 100$ g/l; platelet count $\geqslant 100\times10^9$ cells/l; serum creatinine $\leqslant 132.6$ μmol/l; bilirubin level $\leqslant 25.65$ μmol/l. All patients were required to provide signed, informed consent prior to study entry. This study was performed after approval by the local Ethics Committee.

2.2. Treatment

Raltitrexed was administered as a short intravenous (i.v.) infusion over approximately 15 min once every 19 days. Using this slightly reduced interval between the raltitrexed administrations (raltitrexed is usually administered every 21 days), it was possible to deliver three doses of the drug during a standard radiotherapy treatment (Fig. 1). Prophylactic antiemetic therapy was administered only on the day of drug delivery.

Radiation therapy was delivered to the whole pelvis to a dose of 45 Gy (clinical target volume (CTV) 2) and a boost to the tumour mass of 5.4 Gy was added to reach the total tumour dose of 50.4 Gy (CTV 1). CTV 2 included the tumour, the mesorectum and the internal iliac nodes. The box or three-field technique was used: the lateral border of anteroposterior–posteroanterior radiation fields was 1.5–2 cm outside the true bony pelvis; the inferior border was 1 cm above the anal verge in tumours of the middle rectum and just below the anal verge in tumours of the lower rectum; the superior border was at least 2 cm above the tumour and not inferior to the sacral promontory; corner blocks were used to exclude extra pelvic normal tissues. The posterior border of the lateral fields was a minimum of 1.5 cm behind the anterior bony sacral margin and the anterior border at the most posterior aspect of the symphysis pubis. The CTV 1 included the primary tumour mass with 2 cm radial margins.

The prescribed dose was 45 Gy to the pelvis (planned target volume (PTV) 2) plus a boost dose of 5.4 Gy to the primary tumour mass (PTV 1), in order to achieve the total dose of 50.4 Gy to the tumour [22]. Fractionation was conventional: 1.8 Gy/day, five sessions a week. Radiotherapy started on Monday for all patients, and radiation was delivered with a linear accelerator (LINAC). All the patients were treated in the prone position on a modified table-top device to displace the small bowel from the fields (Up–Down Table) [23].

Surgery was performed 6–8 weeks after the completion of chemoradiation. The choice of the surgical procedure (abdominoperineal resection (APR), low anterior resection (LAR), or coloanal anastomosis resection (CAR)) and performance of a temporary colostomy were at the surgeon's discretion. Removal of the entire mesorectum and a distal rectal margin of at least 2 cm (for sphincter preservation) were strongly recommended. Specimens were inked for radial margin determination. Biopsies were performed in any gross residual area where there was suspicion of residual tumour or in any tumour bed considered to be at risk.

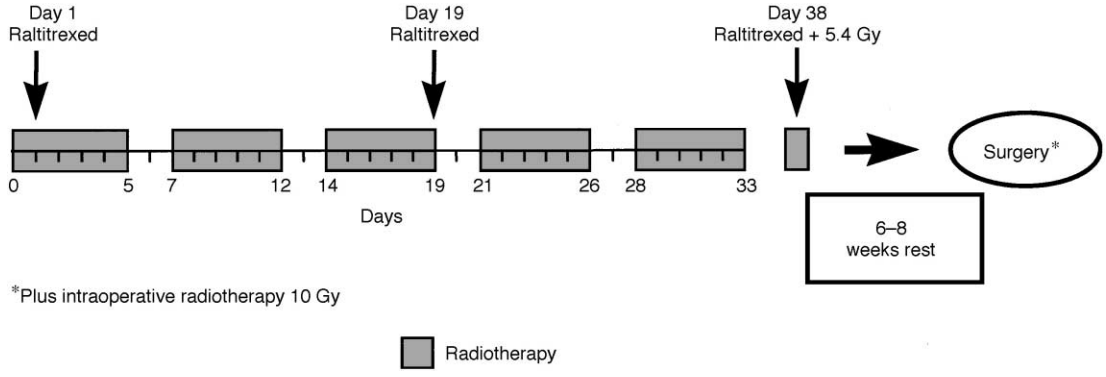

Fig. 1. Treatment plan.

The tumour bed also received an intra-operative radiotherapy boost (10 Gy) by electron beam (6 meV). The target of the boost was chosen according to the size of the resected tumour and the area of pelvic wall thought to be more at risk of residuals. The intra-operative radiotherapy was delivered under anaesthesia; vital parameters were monitored during this process.

2.3. Toxicity

Haematological and liver toxicity were graded based on the World Health Organization (WHO) criteria [24]. Dose-limiting toxicity (DLT) was defined as grade 3 or 4 Radiation Therapy Oncology Group scale acute toxicity [25].

2.4. Dose-escalation schedule

Patients were entered to one of three dose levels; raltitrexed 2.0, 2.5 and 3.0 mg/m^2. The maximum tolerated dose (MTD) was defined as the dose of raltitrexed that caused limiting toxicity in $\geqslant 50\%$ of the patients treated (i.e. at least 3 of a 6-patient cohort). The maximum dose to be tested was 3.0 mg/m^2, as this is the recommended dose of raltitrexed as a single modality therapy. In the absence of DLTs, only 3 patients were to be treated at the first two dose levels. At the third dose level, it was planned to treat at least 6 patients because it was anticipated that this dose level would be associated with toxicity.

2.5. Patient evaluation

Patients were assessed at baseline by digital examination, pelvic computed tomography (CT) scan, transrectal ultrasound, liver ultrasonography, chest X-ray, barium enema and proctoscopy with biopsy. Restaging was performed 5–6 weeks after preoperative treatment. In a weekly meeting of all specialists involved in the diagnostic investigation, data from single examinations were compared and the definitive combined staging and tumour response recorded [26].

2.6. Response criteria

Tumour response was assessed according to WHO criteria [24]. Clinical response was evaluated with respect to a reference index (percentage of circumference involved multiplied by cranio-caudal length of tumour) [12].

3. Results

3.1. Patient characteristics

In total, 15 patients were entered into the study at the dose levels shown in Table 1. The majority of patients had TNM stage T3N1 tumours (10 patients); 4 patients had stage T3N2 and 1 had T2N1 tumours (Table 2). The mean volume of irradiated small bowel, defined as the volume of small bowel receiving a dose $>50\%$ of the prescribed dose, was 15 cm^3 (range: 0–70 cm^3).

3.2. Toxicity

All patients completed the planned course of chemoradiation without interruptions. No patient required hospitalisation due to toxic reactions and there were no treatment-related deaths. Haematological and non-haematological toxicities are listed in Tables 3 and 4, respectively. No DLT occurred at the first two dose levels. Six patients were treated at the first dose level because the third accrued patient was mismanaged receiving growth factor for a grade 2 haematological toxicity; no other patients received growth factor. At the third dose level, 1 patient experienced a DLT of uncomplicated grade 3 leucopenia, recovered in 3 days without discontinuing radiotherapy. The most frequent toxicities were acute proctitis and cystitis, requiring medication in 5 and 3 patients, respectively. 8 patients developed changes in their liver biochemistry tests, but these were generally temporary and reversible. One

Table 1
Dose levels

Dose level	Raltitrexed (mg/m^2)	Radiotherapy (Gy)	No. patients entered	No. patients with DLT
1	2.0	50.4	6	0
2	2.5	50.4	3	0
3	3.0	50.4	6	1

Gy, Gray; DLT, dose limiting toxicity.

Table 2
Patient characteristics

Total no. patients	15
Sex	
Female	8
Male	7
Median age, years (range)	66 (37–73)
Performance status (ECOG score)	
0	3
1	11
2	1
Tumour stage	
T2N1	1
T3N1	10
T3N2	4
Distance between the lower pole of tumour and anal-rectal ring	
Average (mm) (range)	60 (0–90)
No. >50 mm	9
No. <50 mm	6
Average length of tumour (mm) (range)	42.5 (30–75)

ECOG, Eastern Co-operative Oncology Group.

patient had dehiscence of the anastomotic suture during the postoperative period.

3.3. Response evaluation

All patients underwent surgery (anterior resection, 10 patients; abdominoperineal resection, 5 patients). In addition, all 15 patients were evaluated for response, of whom 5 patients had a complete response and 7 had a partial response; overall response rate, 80%. Furthermore, 3 patients had minor responses which were classified as stable disease. Of the 5 patients who had a complete response, 2 patients had complete microscopic disappearance of tumour cells and 3 only had microscopical tumour foci at pathological examination. In 1 of 6 patients for whom the distance of the tumour from the anal margin was <50 mm, a sphincter-saving procedure was performed. At pathological examination, the following stages were observed: pT3N1M0, 3 patients; pT3N0M0, 4 patients; pT2N0M0, 2 patients; pTmicN1M0, 1 patient; pTmicN0M0; 3 patients; pT0N0M0, 2 patients (Table 5).

Table 3
Haematological toxicity

Toxicity	Grade (RTOG)	Raltitrexed dose (mg/m^2)		
		2.0 ($n=6$)	2.5 ($n=3$)	3.0 ($n=6$)
Anaemia	1	1	–	–
	2	1	–	–
Leucopenia	1	1	–	2
	2	3	2	–
	3	–	–	1
Neutropenia	1	2	1	2
	2	1	1	1

RTOG, Radiation Therapy Oncology Group.

Table 4
Non-haematological toxicity

Toxicity	Grade (RTOG)	Raltitrexed dose (mg/m^2)		
		2.0 ($n=6$)	2.5 ($n=3$)	3.0 ($n=6$)
Cystitis	1	2	1	3
	2	1	1	1
Diarrhoea	1	1	–	–
Nausea/vomiting	2	–	–	1
Proctitis	1	2	–	3
	2	1	2	2
Serum alanine transaminase	1	1	2	1
	2	2	–	2
Serum aspartate transaminase	1	3	1	1
	2	–	–	1
Skin	1	–	2	1
	2	1	–	–

RTOG, Radiation Therapy Oncology Group.

4. Discussion

This phase I study reports the first clinical experience with concomitant raltitrexed during preoperative radiotherapy for potentially resectable rectal cancer. Only 1 patient experienced a DLT of myelosuppression (grade 3 leucopenia) at a raltitrexed dose of 3.0 mg/m^2. 3.0 mg/m^2 of raltitrexed, which is the dose recommended for single agent use in advanced colorectal cancer was, therefore, defined as the recommended dose for phase II studies. This is higher than the dose of 2.6 mg/m^2 recommended for use in combination with postoperative radiotherapy [27]. This apparent reduced incidence of toxicity with preoperative raltitrexed compared with the postoperative approach is in line with results observed with 5-FU [28].

Toxicities observed at the recommended dose of raltitrexed 3.0 mg/m^2, and lower dose levels, combined with preoperative radiotherapy were generally mild or moderate; no patient experienced any grade 3/4 non-haematological toxicity and only 1 patient had a haematological toxicity of grade 3 leucopenia. There were no cases where treatment was discontinued because of adverse events at any dose level, and treatment was completed by all patients without interruptions. A safety review of grade III/IV toxicities from the three phase III studies of raltitrexed ($n=861$ patients) showed that compared with 5-FU-based regimens, raltitrexed is associated with a significantly lower incidence of mucositis and leucopenia, similar incidences of diarrhoea and thrombocytopenia, and a significantly higher incidence of increased transaminases in two of the three studies. Such changes were usually self-limiting and asymptomatic. The overall incidence of grade III and IV haematological and non-haematological toxicities from the three phase III studies was 10% with raltitrexed [29]. At

Table 5
Tumour downstaging

Clinical stage at baseline	Stage at pathological examination
T2N1M0 (1 patient)	T2N0M0 (1 patient)
T3N1M0 (10 patients)	T0N0M0 (2 patients)
	T_{mic}N0M0 (3 patients)
	T2N0M0 (1 patient)
	T3N0M0 (3 patients)
	T3N1M0 (1 patient)
T3N2M0 (4 patients)	T_{mic}N1M0 (1 patient)
	T3N0M0 (1 patient)
	T3N1M0 (2 patients)

the recommended dose of 3 mg/m^2, the incidence of leucopenia was 1.8 and 2.0% for the first and second cycles of raltitrexed alone, respectively. The results of this study confirm the findings of the above review. Interestingly, patients treated in this study showed a very low incidence of diarrhoea (1/15, grade 1), which compares with an incidence of grade 3/4 diarrhoea of 8–19% in some studies of concomitant preoperative 5-FU-based chemoradiation [9,10,30]. Based on from previous studies, the expected incidences of diarrhoea of grades III and IV following the first and second cycles of raltitrexed are 2.6 and 2.4%, respectively [29]. There were minor changes in serum transaminase levels, but these were reversible and not clinically significant. The low levels of toxicity observed in this study are probably due to the low amount of the small bowel irradiated.

The rationale for combining cytotoxic agents, such as 5-FU, and radiotherapy is based on their ability to act as radiosensitising agents, although a spatial co-operation resulting in better local control afforded by the radiotherapy and the control of micrometastases by chemotherapy is claimed by some authors [31–33]. The potential of 5-FU to enhance the tumoricidal action of radiotherapy was demonstrated in several laboratory studies [34–37]. These studies showed that cell-kill enhancement develops gradually during 24 h or more of continuous exposure to 5-FU after each irradiation, and the higher the dose of 5-FU the stronger the enhancement. The tumour response to 5-FU depends on whether the drug is administered by bolus injection or continuous infusion [37].

Studies with raltitrexed *in vitro* and *in vivo* support the idea that it also acts as a radiation sensitiser and that it does so by slowing or inhibiting the repair of DNA strand breaks [20]. This mechanism of action has also been proposed for 5-FU, although it has also been suggested that 5-FU blocks cells in S-phase, the most sensitive phase of the cell cycle for radiation exposure. Radiosensitisation, however, requires the presence of the drug when the repair of the radiation damage is taking place. This limits the use of bolus 5-FU which has a serum half-life of less than 20 min [38]. Infusional 5-FU does circumvent this problem to a certain degree, however, it causes complications associated with the use of central infusion catheters [39]. Recently, Martenson and co-workers [40] reported the results of a phase I study of 5-FU, administered by protracted venous infusion, in combination with oral leucovorin and pelvic radiation therapy. 5 of the 40 entered patients had venous thrombosis; 4/5 thromboses occurred at the site of the central catheter used for protracted i.v. infusion. As a result, 2 patients received less than half of their protocol-specified therapy [40]. In addition, the high cost of administration of a continuous infusion limits the use of this regimen [39].

Studies on the radiosensitising properties show that *in vitro* raltitrexed decreased the shoulder of radiation survival curves, and *in vivo* tumour growth delay was observed when raltitrexed was administered intermittently with fractionated radiation [20]. Based on these radiosensitising properties and the long terminal elimination half-life of raltitrexed, ranging from 101 to 279 h [41,42], raltitrexed-based concurrent chemotherapy is an interesting alternative to infusional 5-FU and may result in enhanced efficacy.

In this study, 12 responses were observed amongst the 15 patients treated with concomitant raltitrexed and preoperative radiotherapy. The responders included 2 (13%) patients with complete pathological responses and 3 (20%) patients with microscopic tumour foci only at pathological examination. In addition, 7 patients showed partial responses and three minor responses, classified as stable disease, were observed. Of the 6 patients for whom the distance of the tumour from the anal margin was <50 mm, 1 had a sphincter-saving procedure. Compared with clinical stage at baseline, tumour downstaging was observed in 7 (47%) patients and nodal downstaging in 14 (93%) patients. No evidence of nodal involvement was observed in 11 (73%) patients. This result is comparable to that observed with concomitant infusional 5-FU and mitomycin C, and radiotherapy, in which tumour and nodal downstaging were observed in 57 and 73% of the patients, respectively [12].

In conclusion, raltitrexed concomitant with pelvic radiotherapy has allowed the outpatient administration of the regimen with manageable toxicity. The main drug-related toxicities were leucopenia and increased level of serum transaminases, all of which were reversible and manageable. Based on this study, raltitrexed plus radiotherapy shows preliminary evidence of high antitumour activity in rectal cancer. The recommended dose of raltitrexed combined with preoperative radiotherapy, for future phase II studies, is 3.0 mg/m^2 administered every 19 days.

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