Raltitrexed plus radiotherapy for the treatment of unresectable/recurrent rectal cancer: a phase I study

R. D. James1*, N. Botwood2, C. C. Vernon2 & P. Price3

1The Kent Oncology Centre, Maidstone Hospital, Kent; 2Department of Clinical Oncology, Hammersmith Hospital, London; 3Department of Radiation Oncology, Christie Hospital, Manchester, UK

Received 26 March 2002; revised 13 November 2002; accepted 3 December 2002

Background: Current consensus is that a combination of radiotherapy and chemotherapy may provide the optimal treatment for patients with unresectable rectal cancer. Raltitrexed has proven efficacy in the treatment of advanced colorectal cancer and has an acceptable toxicity profile. The aim of this phase I study was to determine the recommended dose of raltitrexed in combination with radiotherapy in patients with unresectable/recurrent rectal cancer.

Patients and methods: Patients were treated with radiotherapy (25 fractions at 2.0 Gy per fraction) five times per week for 5 weeks. Raltitrexed was administered on days 1 and 22 at 2.0, 2.6 and 3.0 mg/m².

Results: A total of 20 patients were entered into the study. Dose-limiting toxicities were recorded in three of 20 patients following the first dose of raltitrexed; one patient at 2.6 mg/m² (grade 3 diarrhoea, grade 3 neutropenia and grade 2 pyrexia) and two patients at 3.0 mg/m² (one grade 3 neutropenia and one grade 4 diarrhoea). The most common non-haematological and haematological treatment-related adverse events were diarrhoea (11 of 20, two grade 3, one grade 4) and leukopenia (eight of 20, one grade 3, one grade 4), respectively.

Conclusions: The recommended dose of raltitrexed in combination with radiotherapy for future studies is 2.6 mg/m².

Key words: chemoradiotherapy, phase I, radiotherapy, raltitrexed, rectal cancer

Introduction

Surgery remains the treatment of choice for rectal cancer. However, many patients who present with apparently resectable tumours will ultimately have recurrence in the pelvis (local recurrence). Magnetic resonance imaging with a phased-array coil may help define resectable patients at high risk of local recurrence before surgery [1, 2]. A recently published randomised trial [the Dutch total mesorectal excision (TME) trial] showed that short-course pre-operative radiotherapy reduced the risk of local recurrence for patients with operable rectal cancer treated with TME [3]. Ongoing randomised studies in Europe are examining the value of pre- and post-operative radiotherapy in rectal cancer with or without concomitant chemotherapy for patients at high risk of local recurrence [4, 5].

Approximately 10% of patients are not amenable to resection at the time of presentation because of tumour fixity to surrounding pelvic organs. For such unresectable patients, pelvic radiation therapy provides palliation and local control, frequently with downstaging sufficient to allow resection [6]. Concomitant chemotherapy combined with radiotherapy may improve survival and reduce local recurrence by preventing and/or treating distant metastases as well as sensitising the effects of radiotherapy, but increases the risk of radiation-induced toxicity [7–9]. Optimal combinations of chemoradiotherapy have yet to be devised for both unresectable and resectable rectal cancers. The drug 5-fluorouracil (5-FU) has been the most common radiosensitiser for patients with rectal cancer, and a number of small phase I/II studies have recently revealed encouraging results using novel chemotherapy agents [10–17].

Raltitrexed is a specific thymidylate synthase (TS) inhibitor which provides an effective alternative to 5-FU-based therapy for patients with advanced colorectal cancer [18]. Unlike 5-FU, it inhibits TS by action at the folate site, enters cells via the reduced folate carrier and subsequently undergoes extensive polyglutamation within the cell to more potent forms. This prolongs its retention within the cell, enabling a convenient single-dose schedule once every 3 weeks. Furthermore, raltitrexed has manageable toxicity and, like 5-FU, has radio-sensitising properties [19], suggesting that it may be effective in combination with radiotherapy. A recent phase I, dose-escalation study of raltitrexed combined with post-operative pelvic radiotherapy in patients with rectal cancer has recently demonstrated a tolerable level of toxicity [20].

The aim of this phase I study was to determine the recommended dose (RD) of raltitrexed in combination with radiotherapy for patients with unresectable/recurrent rectal cancer.
Patients and methods

Study design
This was an open, non-comparative, dose-escalation study of raltitrexed in combination with a fixed dose of radiotherapy in patients with unresectable/recurrent rectal cancer. All patients gave written informed consent to participate in the trial and the study was conducted according to the principles of Good Clinical Practice and approved by the ethics committees of the participating centres. The study was conducted at two centres: the Christie Hospital NHS Trust in Manchester and the Hammersmith Hospital, Imperial College School of Medicine in London.

Patients
Eligibility criteria included: age ≥18 years; confirmed diagnosis of unresectable/recurrent rectal cancer; World Health Organization (WHO) performance status of two or less; life expectancy ≥12 weeks; no systemic chemotherapy within the past 12 months; no prior radiotherapy at the planned exposure area; non-pregnant; non-lactating. Patients were excluded if laboratory assessments within 14 days before the study treatment revealed the following abnormalities: a white blood cell count <4.0 × 10⁹/ml or a platelet count <100 × 10⁹/l; serum creatinine >upper limit of normal (ULN); serum bilirubin >1.25 × ULN or aspartate or alanine aminotransferase >2.5 × ULN.

Treatment
Patients were treated with radiotherapy (25 fractions at 2.0 Gy per fraction) by a planned volume to the pelvic area via three or four fields, five times per week for 5 weeks. Raltitrexed (Tomudex; AstraZeneca) was given at least 1 h after the radiotherapy on days 1 and 22, where day 1 was the first day of week for 5 weeks. Raltitrexed was administered at three dose levels, 2.0 mg/m² (dose level 1), 2.6 mg/m² (dose level 2) and 3.0 mg/m² (dose level 3) according to the dose escalation schedule detailed below. Data-sheet recommendations concerning dose reduction of raltitrexed as a function of serum creatinine and creatinine clearance were applied in this study [21]. If serum creatinine levels were abnormally high before dosing, the creatinine clearance was calculated. If the creatinine clearance was <25 ml/min, no further raltitrexed was administered. If the clearance was 25–65 ml/min, the dose of raltitrexed was reduced to 50%. The second dose of raltitrexed was reduced or omitted based on a combination of the highest WHO grade of leukopenia, neutropenia or thrombocytopenia and the highest WHO grade of diarrhoea observed after the first dose.

Dose-limiting toxicity (DLT) for raltitrexed was defined as: drug-related WHO grade 3 or 4 neutropenia or thrombocytopenia, or any drug-related WHO grade 2, 3 or 4 non-haematological toxicity. DLT for radiotherapy was defined as: significant and symptomatic moist skin desquamation at day 21; WHO grade 4 diarrhoea with abdominal pain; investigator concern at day 21 that general toxicity, if continued, would necessitate stopping radiotherapy treatment; other pelvic toxicities thought by the investigator to indicate unacceptable clinical side effects. Radiotherapy was stopped at the discretion of the radiotherapist.

At least three patients were treated at each dose level and there was no dose escalation within patients. If no DLT was observed in the first three patients, the next group of patients were enrolled at the next dose level. If no DLT was observed in the first three patients enrolled at the third dose level, a further three patients were enrolled at this dose level. If one of three or two of three patients had DLT, three further patients were enrolled at the same dose. If three of three patients had DLT, no more patients were given raltitrexed at that dose. Patients were not treated at the next dose level until all previous patients had completed their treatment. If one of six or two of six patients had DLT at the first or second dose level, more patients were enrolled at the next dose level. If none of six, one of six, or two of six patients had DLT at the third dose level, the maximum tolerated dose (MTD) would not have been reached; this dose would be considered the RD and no further patients would be treated. Otherwise, the RD was defined as the dose level of raltitrexed below the MTD. If at least three of six patients experienced DLT at any dose level, the MTD would have been reached and no further dose escalation would take place. If the MTD occurred at dose level 1, no RD would have been included.

The dose of raltitrexed was delayed or adjusted in the presence of toxicity or the development of renal impairment. The dose-reduction schedule is shown in Table 1. In the event of ongoing unacceptable or clinically relevant toxicity, dosing was delayed until all signs of toxicity were resolving or had resolved up to a maximum of 14 days. Diarrhoea and mucositis had to be resolved completely, whereas indicators of abnormal haematological and liver function should have returned to levels meeting the inclusion criteria. If after 14 days of delay these conditions were not met, no further treatment was given.

Tolerability assessments
Adverse events (AEs) were recorded and classified according to WHO grade and the investigators’ assessment of the relationship to study treatment. All AEs were followed to resolution and patients were followed for 28 days after the last treatment with raltitrexed or radiotherapy for any new AEs.

Biochemistry assessments were performed within 14 days before the first dose of raltitrexed, within 7 days before the second dose and 3 weeks after the second dose of raltitrexed. Haematology assessments were performed within 14 days before the first dose of raltitrexed and then weekly, including within 3 days before the second dose, until 3 weeks after the second dose. If a patient experienced diarrhoea grade ≥2, a blood count was performed immediately. All patients with grade 3 or 4 laboratory toxicities at the end of the treatment period were followed up until they had returned to grade 1 or 2, unless they were thought unlikely to improve due to the underlying disease.

Table 1. Raltitrexed dose reductions, expressed as a percentage of the first dose, based on the highest grade of toxicity

<table>
<thead>
<tr>
<th>Haematological toxicities*</th>
<th>Diarrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 0</td>
</tr>
<tr>
<td>Grade 0</td>
<td>100</td>
</tr>
<tr>
<td>Grade 1</td>
<td>100</td>
</tr>
<tr>
<td>Grade 2</td>
<td>100</td>
</tr>
<tr>
<td>Grade 3</td>
<td>75</td>
</tr>
<tr>
<td>Grade 4</td>
<td>50</td>
</tr>
</tbody>
</table>

*Leukopenia, neutropenia or thrombocytopenia.
A total of 20 patients with unresectable/recurrent rectal cancer were enrolled in the study [mean age 61.05 years (range 39–78); six females and 14 males]. Although it was intended that a maximum of six patients would be entered into the study at each dose level, in accordance with the study design, seven patients were recruited at dose levels 1 and 3. This was the result of an overlap in enrolment at the two different centres taking part in the trial, and the investigators felt it was ethically unsound to withdraw a patient once they had given their consent.

Non-haematological treatment-related adverse events

The most common treatment-related, non-haematological AE was diarrhoea, which was experienced by 11 of 20 patients. Two of these were grade 3 (one at dose level 1 and one at dose level 2) and one grade 4 at dose level 3. There were no other grade 3/4 non-haematological AEs. The next most commonly occurring non-haematological AEs were nausea and vomiting (five of 20 patients) and dehydration (three of 20 patients).

The most common haematological event experienced was leukopenia (eight patients). One case was grade 4 at dose level 2 and one grade 3 at dose level 3. There were no grade 3 or grade 4 haematological toxicities at dose level 1, four grade 3 (two anaemia and two neutropenia) and one grade 4 (leukopenia) at dose level 2, and four grade 3 (one anaemia, one leukopenia and two neutropenia) at dose level 3.

Of the 12 reported biochemical AEs only one was grade >2. Only two patients were involved and eight of 12 of the events occurred in one patient who died shortly after completing the first course of treatment.

Grade 3/4 non-haematological, haematological and biochemical treatment-related AEs are shown in Table 2.

Other non-specific AEs were not related to treatment with raltitrexed or radiotherapy, alone or in combination, and are therefore not discussed here.

**Dose-limiting toxicities**

DLTs were recorded in three of 20 patients following administration of the first dose of raltitrexed, one at dose level 2, and two at dose level 3 (Table 3). At dose level 2, one patient experienced grade 3 diarrhoea, grade 3 neutropenia and grade 2 pyrexia and subsequently died before administration of the second dose of raltitrexed. At dose level 3, one patient suffered grade 3 neutropenia and the second dose of raltitrexed was reduced to 75%. The other patient at dose level 3 was withdrawn from treatment altogether following the occurrence of grade 4 diarrhoea. One patient at dose level 3 refused blood tests and was not eligible for assessment.

**Discussion**

Of the 20 patients enrolled, three were recorded as experiencing DLT. Of these three patients, two received raltitrexed at a dose of 3.0 mg/m² and one at a dose of 2.6 mg/m². The latter patient died following the first course of treatment. Death was considered by the attending physician to be the result of progressive disease and not treatment-related. However, this was an entirely subjective assessment and it could be argued that any patient who experiences three DLTs, which were not resolved before death, should be considered as having a toxic death. In view of this, the investigators felt that the RD of raltitrexed when administered in combination with a ‘standard’ course of radiotherapy to patients with unresectable/recurrent rectal cancer should be 2.6 mg/m². This is the dose level below that which should have been recommended in accordance to the protocol definition of MTD and RD, and also lower than the data-sheet recommended monotherapy dose of 3.0 mg/m². The same dose reduction was also found to be necessary when raltitrexed and radiotherapy were combined as post-operative adjuvant treatment [20]. A dose reduction of 5-FU

---

**Table 2. Grade 3/4 treatment-related adverse events**

<table>
<thead>
<tr>
<th>Raltitrexed dose (mg/m²)</th>
<th>Adverse event</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>2.0 (seven patients)</td>
<td>Diarrhoea</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Elevated LDH</td>
<td>1</td>
</tr>
<tr>
<td>2.6 (six patients)</td>
<td>Diarrhoea</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Anaemia</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>2</td>
</tr>
<tr>
<td>3.0 (seven patients)</td>
<td>Diarrhoea</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Anaemia</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>2</td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase.

**Table 3. Dose-limiting toxicities (DLTs)**

<table>
<thead>
<tr>
<th>Raltitrexed dose level (mg/m²)</th>
<th>No. of patients</th>
<th>No. of patients with DLT</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>7</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>2.6</td>
<td>6</td>
<td>1</td>
<td>Grade 3 diarrhoea, grade 3 neutropenia, grade 2 pyrexia</td>
</tr>
<tr>
<td>3.0</td>
<td>7 a</td>
<td>2</td>
<td>Grade 3 neutropenia (1), grade 4 diarrhoea (1)</td>
</tr>
</tbody>
</table>

*aOne patient excluded due to protocol violation.*
was also required when it was used in combination with radiotherapy in patients with locally advanced rectal cancer [4]. However, a recent phase I/II study [22] reported acceptable toxicity levels in a much larger cohort of 67 chemonaive patients with T3–4 rectal carcinoma treated with pre-operative chemoradiation with raltitrexed at a dose of 3 mg/m². Only 9% of the patients (six of 67) experienced grade 3 toxicity and there were no grade 4 events.

The present study was not an investigation into resectability but a dose-escalation study to assess the feasibility of treatment before phase II. None of these patients received a surgical intervention, so no conclusions can be drawn on the safety or efficacy of the combination for patients who become operable. Efficacy results from phase I and phase II of an Italian study [22], however, demonstrated high rates of tumour response (40% and 66%, respectively) and sphincter-saving surgery (66% and 78%, respectively).

Two phase II studies of raltitrexed 2.6 mg/m² in combination with radiotherapy as first-line treatment for patients with unresectable/recurrent rectal cancer are ongoing and have recruited 290 and 36 patients.

Raltitrexed is an attractive alternative to continuous infusional 5-FU for combination with radiotherapy in advanced rectal cancer because of its more convenient administration. Toxicity is manageable provided data-sheet dose reductions are followed, as shown in this study.

Conclusion

The RD of raltitrexed in combination with radiotherapy in patients with unresectable/recurrent rectal cancer is 2.6 mg/m², which, in the majority of patients, demonstrated a manageable and more predictable toxicity profile.

References