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Original Paper

Raltitrexed (Tomudex™) Concomitant with Radiotherapy as Adjuvant Treatment for Patients with Rectal Cancer: Preliminary Results of Phase I Studies

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Radiotherapy, either alone or in combination with chemotherapy, may reduce local recurrence of rectal cancer following surgery and improve survival of patients with operable and advanced/recurrent/inoperable disease. Chemotherapy with 5-fluorouracil in combination with radiotherapy has been used both before and after surgery; however, the optimum schedule is unclear. In addition, alternative chemotherapy with raltitrexed (Tomudex™) may be more convenient and better tolerated. The preliminary results of three phase I dose-finding studies are described, combining escalating doses of raltitrexed with radiotherapy as pre- or postoperative treatment for operable rectal cancer or as treatment for advanced/inoperable/recurrent rectal cancer. The recommended dose of raltitrexed when combined with adjuvant radiotherapy is likely to be 2.6 mg/m^2 . This is a small dose reduction compared with the dose of raltitrexed for the treatment of advanced colorectal cancer (3.0 mg/m^2); however, toxicity appears to be lower using the pre-operative approach. Neo-adjuvant therapy with raltitrexed plus radiotherapy also demonstrated clinical activity in the pre-operative study, which showed that 22% of patients achieved a complete response and 56% a partial response. Once the recommended dose has been defined in each setting, large-scale studies will be undertaken as appropriate. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

RECTAL CANCER is one of the most prevalent cancers in the Western world, with an estimated 36 000 new cases per year in the U.S.A. alone [1]. Surgery remains the mainstay of treatment but local recurrence is common following surgery alone, with relapse rates of 25 and 50% in patients with Dukes' stage B and C disease, respectively [2]. Although adjuvant (or neo-adjuvant) radiotherapy, either alone or in combination with chemotherapy, can reduce local recurrence and possibly improve survival, the optimal timing of the radiotherapy (pre- or postoperative) and the optimal chemotherapy combination are not known. In the U.S.A., postoperative chemotherapy plus radiotherapy is the most widely used approach, whereas in Europe there has been a move towards pre-operative radiotherapy. The Swedish Rectal Cancer Trial has demonstrated improved survival in patients with resectable rectal cancer following five fractions of preoperative radiotherapy delivered within one week [3].

As drugs that are active in colon cancer are also active in metastatic rectal cancer, it is logical to combine these chemotherapy regimens with radiotherapy to treat rectal cancer. Chemotherapy with 5-fluorouracil (5-FU) in combination with radiotherapy has been used both before and after surgery. Pre-operative 5-FU and radiotherapy appeared to enhance tumour control and sphincter preservation compared with radiotherapy alone [4]. Similarly, postoperative administration of 5-FU and radiotherapy resulted in a lower incidence of metastases and of local recurrence than radiotherapy alone [2]. To date, there have been no large-scale

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randomised trials assessing the efficacy of postoperative adjuvant chemotherapy in patients with rectal cancer treated with pre-operative chemoradiation. An ongoing Italian multicentre randomised trial will further clarify the impact of adjuvant chemotherapy in these patients [5]. Radiotherapy, with or without chemotherapy, has also been shown to be an important palliative treatment for inoperable primary rectal cancer and pelvic recurrences [6].

Raltitrexed (Tomudex™) is an effective and convenient single agent currently used for the treatment of advanced colorectal cancer [7, 8]. It is as effective as 5-FU plus leucovorin and is associated with an acceptable toxicity profile [9]. Raltitrexed may, therefore, have potential clinical value as adjuvant therapy with radiotherapy.

Raltitrexed, like 5-FU, has been shown to be a radiation sensitiser both *in vitro* and *in vivo* [10]. *In vitro* raltitrexed has been shown to decrease the shoulder of radiation survival curves, and *in vivo* tumour growth delay was observed when raltitrexed was administered intermittently with fractionated radiation. Studies with raltitrexed *in vitro* support the idea that it acts as a radiation sensitiser by slowing or inhibiting the repair of DNA strand breaks. 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 which is the most sensitive phase of the cell cycle for radiation exposure. In the clinical setting, for a drug to be a radiation sensitiser it must be present 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 [11]. Infusional 5-FU does circumvent this problem to a certain degree. However, the long terminal elimination half-life of raltitrexed (approximately 1 week) negates the need for infusional administration.

This paper provides an overview of dose-finding studies of raltitrexed with radiotherapy as adjuvant treatment in operable rectal cancer, both pre- and post-surgery, and in patients with advanced/recurrent/inoperable rectal cancer.

PATIENTS AND METHODS

Preliminary results are reported on phase I trials based in the U.K. and Italy designed to determine the recommended dose of raltitrexed in combination with radiotherapy as postoperative [12] and pre-operative [13] treatment for rectal cancer, respectively. A third trial is investigating the combination of raltitrexed and radiotherapy in patients with inoperable/recurrent rectal cancer in the U.K. [14]. The participating centres for both U.K. trials are the Christie Hospital, Manchester and the Hammersmith Hospital, London. The Italian trial is conducted at a single study centre, Università Cattolica del Sacro Cuore, Rome.

Design

Three phase I studies of raltitrexed in combination with radiotherapy are underway. All three trials are open-label, non-comparative, dose-escalation studies of raltitrexed in patients with rectal cancer. The trials were conducted according to good clinical practice and approved by the ethics committees of the participating centres. Patients in study 1 were aged ≥ 18 years with Duke's Stage B or C adenocarcinoma of the rectum which had been excised completely, WHO performance status ≤ 2 and life expectancy of at least 12 weeks. In study 2, patients (aged 18–75 years) had clinical stage T3 (cT3) or node-positive biopsy-proven potentially resectable adenocarcinoma of the rectum with no distant metastases and performance status ≤ 2. Patients (aged ≥ 18 years) in study 3 had advanced, recurrent or inoperable rectal cancer, performance status ≤ 2 and a life expectancy of at least 12 weeks.

The treatment schedules for the studies are illustrated in Figure 1. In study 1, 50.4 Gy radiotherapy were delivered in 1.8 Gy daily fractions five times per week for 5–6 weeks. In study 2, 45 Gy (1.8 Gy daily fractions) were delivered to the posterior pelvis, five times per week for 5 weeks, and a 5.4 Gy boost was delivered using reduced radiation fields. After 6–8 weeks' rest, patients underwent surgery and intra-operative electron beam radiotherapy on the tumour bed (10 Gy). In study 3, 50 Gy (2.0 Gy daily fractions) were delivered to the posterior pelvis via 3 fields five times per week for 5 weeks. Single doses of raltitrexed were administered 1 h prior to radiotherapy on days 1 and 22 (studies 1 and 3) and on days 1, 19 and 38 (study 2). The planned dose levels of raltitrexed for studies 1 and 3 were 2.0, 2.6 and 3.0 mg/m^2 and for study 2 were 2.0, 2.5 and 3.0 mg/m^2.

Assessments

Toxicity was clinically assessed by haematology and biochemical tests and adverse events (including gastrointestinal and urinary toxicity). In studies 1 and 3 haematological assessment was performed prior to treatment and then weekly until 3 weeks after the last dose of raltitrexed. Biochemical assessments in these studies were carried out prior to treatment, within 7 days prior to the second dose of raltitrexed, and then 3 weeks after the second raltitrexed dose. In study 2, haematology and biochemistry assessments were analysed weekly during chemoradiation. All adverse events were

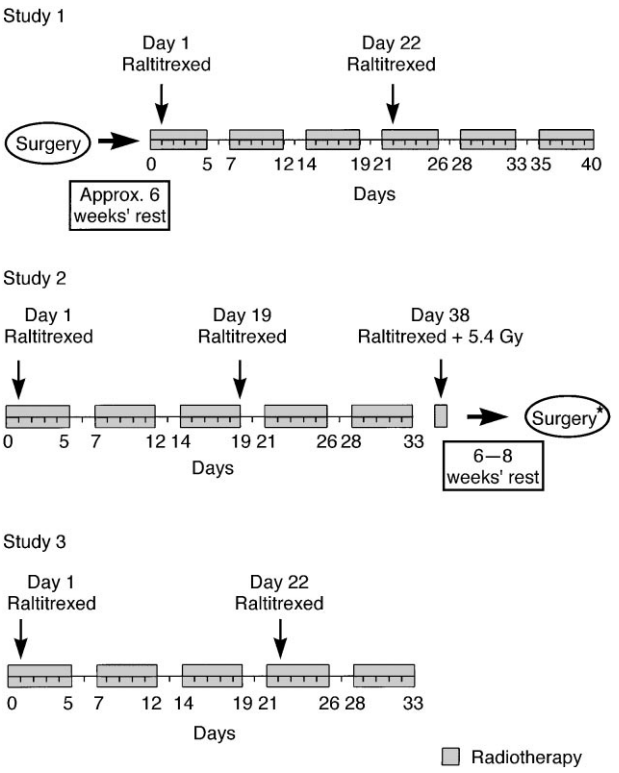

Figure 1. Treatment schedule for postoperative (study 1), pre-operative (study 2) and inoperable/recurrent (study 3) trials of raltitrexed plus radiotherapy. *Plus intra-operative radiotherapy 10 Gy.

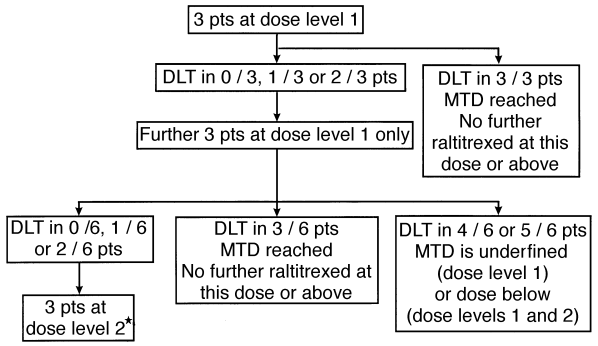

Figure 2. Planned dose-escalation schedule. *Repeat steps as for dose level 1. DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

recorded and assessed for their relationship to treatment by the investigator. Dose-limiting toxicity (DLT) in studies 1 and 3 was defined as any of the following: WHO grade 2 or above diarrhoea, considered subjectively to be unacceptable during radiotherapy; termination of radiotherapy; other unacceptable clinical side effects. In study 2, DLT was any Radiation Therapy Oncology Group (RTOG) grade 3 or 4 acute toxicity. The recommended dose was specified in all studies as one level below the maximum tolerated dose (as determined from the DLT). Patients were entered on each dose level in a similar manner in all three studies, as shown in Figure 2. In study 1, it was planned that once the maximum tolerated dose (MTD) had been reached, additional patients would be entered at the recommended dose.

The aim of all three studies was to determine the optimum dose of raltitrexed in combination with a fixed dose of radiotherapy, using conventional methodology for dose-escalation studies. The end-points of objective response, disease-free and overall survival were not primary objectives of these studies, and therefore were not measured uniformly. In study 2, tumour response was recorded as complete response, partial response or no change. The possibility of performing a sphincter-saving procedure was also assessed for low rectal tumours (< 50 mm from the anal-rectal ring).

RESULTS

Toxicity and dose assessment

DLTs for the studies are recorded in Table 1. In study 1, 14 patients (median age 62.5 years; 50% male) have been evaluated for toxicity; further patients have been recruited but evaluation of toxicity has not been completed. 2 out of 8 of these patients had DLT at dose level 1, none out of 3 patients had DLT at dose level 2 and all 3 patients entered had DLT at level 3. In study 2, 11 patients (median age 64.5 years; 45% male) have been recruited and evaluated for toxicity. No DLT was observed at dose level 1 or dose level 2. Of 2 patients entered at the third dose level, 1 patient has had DLT. In study 3, of the 15 patients recruited to date 2 patients had DLT at dose level 2 but neither of the 2 patients entered at dose level 3 have yet experienced DLT; 4 more patients will be recruited at this dose level before trial completion.

In study 1, DLTs of grade 3 elevation of transaminases (1 patient) and grade 4 diarrhoea (1 patient) were observed at dose level 1. 3 patients had leucopenia (two at grade 3 and one at grade 2) at dose level 3. One patient experienced DLT, grade 3 leucopenia, at dose level 3 of study 2. In study 3, 1 patient had grade 3 anaemia and grade 3 neutropenia, and 1 patient had grade 3 neutropenia, grade 4 leucopenia and grade 3 anaemia, both at dose level 2.

The recommended dose of raltitrexed when combined with adjuvant postoperative radiotherapy, as assessed in study 1, is likely to be 2.6 mg/m^2.

Tumour response

To date, 9 patients are evaluable for tumour response in study 2. 2 patients (22%) have achieved a complete response and 5 patients (56%) have achieved a partial response. Sphincter saving was obtained in 1 out of 4 patients (25%) with a low rectal tumour (< 50 mm from the anal-rectal ring).

Table 1. *Dose-limiting toxicities*

Raltitrexed dose (mg/m^2)	No. patients entered	No. patients with DLT	DLT
Study 1			
2.0	8*	2	Grade 3 increase in transaminases for > 14 days (1 pt); grade 4 diarrhoea for 10 days (from day 12 post 2nd cycle)
2.6	3	0	None
3.0	3	3	Grade 3 leucopenia (2 pts); grade 2 leucopenia and grade 3 diarrhoea (1 pt)
Study 2			
2.0	6	0	None
2.5	3	0	None
3.0	2	1	Grade 3 leucopenia
Study 3			
2.0	7†	0	None
2.6	6	2	Grade 3 anaemia and grade 3 neutropenia (1 pt); grade 3 neutropenia, grade 4 leucopenia and grade 3 anaemia (1 pt)
3.0	2	Too early†	Too early

*DLT was not observed in consecutive patients within the original cohort of 3 patients; therefore, extra patients were entered at this dose level.
†To date, none of these patients has experienced any dose-limiting toxicity (DLT). Pt, patient.

DISCUSSION

In the adjuvant postoperative radiotherapy study, DLT was observed in all 3 patients receiving raltitrexed at a dose of 3.0 mg/m^2. The recommended dose of raltitrexed when combined with adjuvant postoperative radiotherapy is, therefore, likely to be 2.6 mg/m^2. This dose reduction, compared with the dose of raltitrexed used for the treatment of advanced colorectal cancer (3.0 mg/m^2), is required in order to avoid pelvic toxicity and leucopenia when combined with radiotherapy. However, at the same dose level, toxicity appears to be lower using the pre-operative than the post-operative approach. Furthermore, the pre-operative approach allowed sphincter preservation in 1 of the 4 patients with a low-lying tumour. The apparent reduced toxicity observed with the pre-operative approach compared with the post-operative approach is in line with results observed with 5-FU; significantly fewer patients with resectable rectal cancer experienced grade 3/4 toxicity with pre-operative radiotherapy plus 5-FU and leucovorin compared with patients who received the same treatment postoperatively [15]. The maximum tolerated dose has not been reached in the pre-operative and advanced/recurrent/inoperable studies. As expected, preliminary data indicate that adjuvant therapy with raltitrexed plus radiotherapy may have clinical activity, with 78% of the evaluable patients in the pre-operative study responding to treatment.

CONCLUSIONS

The combination of raltitrexed and radiotherapy appears promising as adjuvant therapy for patients with operable rectal cancer. Once the recommended dose has been defined in each setting (pre- and postoperative), large-scale studies can be undertaken as appropriate. The combination also has potential for patients with inoperable rectal cancer and a dose-finding study is ongoing.

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