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Original Paper

Raltitrexed (Tomudex™) in Combination with Platinum-based Agents and/or Anthracyclines: Preliminary Results of Phase I Clinical Trials

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Three ongoing, dose-escalation, phase I studies are evaluating the combination of raltitrexed with oxaliplatin or anthracyclines (with and without cisplatin). In study 1, patients with advanced solid tumours received 2.0–3.75 mg/m^2 raltitrexed, followed 45 min later by 85–130 mg/m^2 oxaliplatin (2-h infusion) every 3 weeks. In study 2, patients with advanced oesophageal or gastric adenocarcinoma received 2.0–3.0 mg/m^2 raltitrexed with 50 mg/m^2 intravenous (i.v.) epirubicin and 60 mg/m^2 i.v. cisplatin every 3 weeks. In study 3, patients with advanced or metastatic gastric cancer received 2.5–3.5 mg/m^2 raltitrexed followed by 30–60 mg/m^2 i.v. doxorubicin every 3 weeks. In all studies, raltitrexed was given as a 15-min infusion. All the combinations evaluated were administered in convenient 3-weekly schedules and were generally well tolerated. Recommended doses for raltitrexed and oxaliplatin are the same in combination as for single-agent use, i.e. 3.0 mg/m^2 raltitrexed and 130 mg/m^2 oxaliplatin. The recommended dose of raltitrexed in combination with cisplatin and epirubicin is 2.5 mg/m^2. No dose-limiting toxicities were observed during co-administration of the full single-agent doses of raltitrexed and doxorubicin (3.0 mg/m^2 and 60 mg/m^2, respectively); dose escalation is continuing. Preliminary efficacy results were encouraging, particularly for the combination of raltitrexed and oxaliplatin in patients with mesothelioma and advanced colorectal cancer. Preliminary data from these phase I studies suggest that the combination of raltitrexed with platinum-based agents and/or anthracyclines may represent useful regimens for the treatment of patients with advanced cancer. Further studies are required to identify the most effective combinations of raltitrexed with both established and new anticancer agents.

Key words: raltitrexed, anthracyclines, oxaliplatin, doxorubicin, colorectal cancer, mesothelioma
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INTRODUCTION

THYMIDYLATE SYNTHASE (TS) catalyses the reductive methylation of deoxyuridylate to thymidylate, the rate-limiting step in the *de novo* synthesis of deoxythymidine triphosphate (TTP). Since TTP is the only nucleotide specifically required for DNA synthesis, TS has been postulated to be an ideal target for anticancer drugs.

Raltitrexed (Tomudex™) is a quinazoline-based water-soluble antifolate, which is extensively and efficiently polyglutamated. These polyglutamated forms are more than 100 times more potent inhibitors of TS than the parent drug and are retained intracellularly allowing a convenient 3-weekly administration schedule. Raltitrexed has been shown to be beneficial in the treatment of advanced solid tumours, such as colorectal cancer [1, 2].

Oxaliplatin is a new platinum derivative that acts similarly to cisplatin by producing DNA adducts which block both replication and transcription [3–6]. Dose-limiting toxicity (DLT) consists of reversible peripheral neuropathy, while haematologic and renal toxicity are minimal [7]. Oxaliplatin administered as a single agent has shown potent activity in

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advanced colorectal cancer [7, 8]. Moreover, the addition of oxaliplatin to the traditional 5-fluorouracil (5-FU)/leucovorin (LV) regimen has significantly improved response rates, even in patients with 5-FU/LV-refractory metastatic colorectal cancer [9–11], although a survival benefit has not been demonstrated. Since raltitrexed and oxaliplatin are both known to be active agents in metastatic cancer, it was logical to investigate the combination of these two compounds. The rationale for combining thymidylate synthase inhibitors such as raltitrexed with oxaliplatin is based on their different modes of action, the convenience of the dosing regimens and their non-overlapping principal toxicities.

Patients with advanced oesophageal or gastric adenocarcinoma have a poor prognosis and the goal of treatment is usually palliation [12, 13]. Although clinical trials have identified compounds with some activity in gastric cancer, no single-agent treatment can currently be recommended [13]. However, combination chemotherapy has demonstrated modest survival benefits compared with best supportive care alone [14–16].

Many of the active regimens used in advanced gastric cancer include 5-FU in combination with an anthracycline, such as doxorubicin or epirubicin, and frequently a third agent, such as cisplatin. Standard treatment in the U.K. remains the ECF regimen, which combines epirubicin, cisplatin and continuous infusion of 5-FU every 3 weeks. Following encouraging results in a number of early studies [17, 18], a large randomised trial recently reported that ECF results in survival and response advantages, tolerable toxicity and better quality of life compared with the FAMTX regimen (5-FU, doxorubicin and methotrexate) in patients with advanced oesophagogastric cancer [19]. Despite the advantages of the ECF regimen, a significant drawback is the requirement for continuous infusion of 5-FU via a Hickman line with complications requiring removal of the central venous line occurring in up to 15% of patients [19].

Continuous infusional 5-FU exerts at least part of its antitumour activity through inhibition of TS. Unlike 5-FU, the TS inhibitor raltitrexed is administered as a single 15-min infusion once every 3 weeks. The use of raltitrexed in place of 5-FU in the above combination regimens would, therefore, provide a more acceptable dosing schedule. Furthermore, the toxicity profiles of raltitrexed and anthracyclines do not completely overlap, although both can cause myelosuppression, mucositis and diarrhoea.

This paper will provide an overview of three ongoing phase I studies in which raltitrexed is being used in combination with oxaliplatin or anthracyclines (with and without cisplatin).

PATIENTS AND METHODS

Preliminary results are reported from an ongoing phase I trial based in France which is evaluating the combination of raltitrexed and oxaliplatin [20]. Two other phase I trials are studying the combination of raltitrexed with anthracyclines at oncology centres in the U.K. and North America. The U.K. trial is investigating raltitrexed in combination with epirubicin and cisplatin (ECT regimen) [21], whereas in the North American trial raltitrexed is administered concomitantly with doxorubicin [22].

Study 1: raltitrexed/oxaliplatin

The aim of this trial was to determine the maximum tolerated doses (MTDs) of concomitant raltitrexed and oxaliplatin in patients with advanced solid tumours. Raltitrexed was administered as a 15-min infusion followed 45 min later by a 2-h infusion of oxaliplatin every 3 weeks. This administration sequence was based on preclinical studies with 5-FU and cisplatin, which have similar modes of action to raltitrexed and oxaliplatin, respectively [23]. Raltitrexed was escalated from 2.0 mg/m^2 to 3.75 mg/m^2, and oxaliplatin was escalated from 85 mg/m^2 to 130 mg/m^2 (Table 1). Anti-emetic drugs were systemically given and included ondansetron or granisetron and steroids.

The trial was designed to include 3 to 6 patients at each dose level until the MTD was reached. If no DLT was observed after 2 cycles of treatment in the initial 3 patients at any dose level, escalation to the next dose occurred. If 1/3 or 2/3 patients experienced DLT, an additional 3 patients were enrolled at the same dose level. The MTD was defined as the dose where 3/6 patients experienced DLT or one dose below the toxic dose, which was indicated by DLT in 3/3 or $\geq$ 4/6 patients. The recommended dose was defined as one dose level below the MTD. Patients continued on treatment for as long as a clinical benefit was observed. After each cycle, treatment was delayed and/or the doses of both drugs were reduced according to the toxicities experienced by the patient.

Toxicity was graded according to the National Cancer Institute (NCI) common toxicity criteria. DLT was defined as $\geq$ grade 3 diarrhoea, mucositis or thrombocytopenia; grade 4 leucopenia or neutropenia; or any other toxicity $\geq$ grade 2 (except alopecia and increases in transaminases). The clinician assessed the disease of the patient at entry to the study and after at least 2 cycles of treatment and recorded his overall objective response of the patient's disease under the categories complete response, partial response, no change or progression.

Study 2: raltitrexed/epirubicin/cisplatin (ECT)

This study enrolled patients with metastatic or locally advanced, inoperable, oesophageal or gastric adenocarcinoma. The ECT regimen comprised a 15-min infusion of raltitrexed with intravenous (i.v.) administration of 50 mg/m^2 epirubicin and 60 mg/m^2 cisplatin on a 3-weekly cycle up to a maximum of six cycles. Standard hydration and anti-emetic protocols were followed.

6 patients were entered at each of three raltitrexed dose levels (2.0, 2.5, 3.0 mg/m^2). Dose escalation occurred after each of the 6 patients had completed at least one cycle of chemotherapy, with no intrapatient dose escalation. The MTD was defined as the dose level where 2/6 patients experienced DLT. Dose modifications were based on

Table 1. *Dose escalation of raltitrexed in combination with oxaliplatin: study* 1

Dose level	Raltitrexed (mg/m^2)	Oxaliplatin (mg/m^2)	No. patients entered
1	2.0	85	3
2	2.5	85	3
3	2.5	110	3
4	3.0	110	3
5	3.0	130	16
6	3.5	130	14
7	3.75	130	6

A protocol amendment was submitted to allow dose escalation to continue to dose level 7. Further patients were recruited at dose levels 5 and 6 since the maximum tolerated dose had not yet been reached.

Table 2. Dose escalation of raltitrexed in combination with doxorubicin: study 3

Dose level	Raltitrexed (mg/m^2)	Doxorubicin (mg/m^2)	No. patients entered
1	2.5	30	3
2	2.5	40	3
3	2.5	50	3
4	2.5	60	3
5	3.0	60	4*
6	3.5	60	0
7	3.5	70	0

*An additional patient was entered at dose level 5 to replace a patient who was unevaluable for haematological toxicity after failure to report for weekly blood tests.

toxicity. In addition, dose modifications of raltitrexed and cisplatin were based on the glomerular filtration rate.

Toxicity was graded according to the NCI common toxicity criteria. DLT was defined as any grade 4 myelosuppression, $\geq$ grade 3 complicated myelosuppression, $\geq$ grade 2 stomatitis or any non-haematological toxicity (excluding emesis and alopecia) of $\geq$ grade 3 and was based on the toxicity of the first cycle only.

Study 3: raltitrexed/doxorubicin

Patients recruited to this study had advanced or metastatic gastric cancer. Raltitrexed was administered as a 15-min infusion followed by an i.v. bolus of doxorubicin every 3 weeks. The dose of raltitrexed was initially fixed at 2.5 mg/m^2 and doxorubicin was escalated from 30 to 60 mg/m^2 (Table 2). If no DLT was observed at this dose level, the doxorubicin dose was fixed at 60 mg/m^2 and raltitrexed was escalated to 3.5 mg/m^2. If DLT had still not been observed, the dose of doxorubicin was increased to 70 mg/m^2.

Initially 3 patients were enrolled at each dose level. If none of these patients experienced DLT, escalation to the next dose could proceed. If 1 patient experienced DLT, 3 additional patients were recruited at the same dose level. If no further DLT was observed, dose escalation could proceed but, if more than 1 patient experienced DLT, the MTD was declared. The recommended dose was defined as one dose level below the MTD. Modification of doses, which allowed both agents to be adjusted, was based upon combinations of grade 3 or 4 haematological and non-haematological toxicity in the previous cycle. Patients continued on treatment until there was objective disease progression, unacceptable toxicity, a maximum of 450 mg/m^2 doxorubicin, or a decision by patient or investigator to discontinue treatment.

Toxicity was graded according to the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) expanded common toxicity criteria. DLT was based upon toxicity in the first cycle, and was defined as grade 4 neutropenia for at least 7 days or febrile neutropenia; grade 3 thrombocytopenia or bleeding; any grade 3 or 4 non-haematological toxicity (excluding nausea, vomiting, alopecia or grade 3 increase in transaminases); renal insufficiency (CrCl < 65 ml/min); or cardiac insufficiency (chronic heart failure, left ventricular ejection fraction < 40% or > 20% decrease). Efficacy was assessed using standard NCIC CTG objective response criteria (based upon WHO criteria).

RESULTS

Study 1: raltitrexed/oxaliplatin

To date, 48 patients have been enrolled, including 17 with mesothelioma and 11 with colorectal cancer (Table 3). Most patients (85%) had undergone previous treatment.

No DLT was observed at the first four dose levels; DLT at dose levels 5 and 6 included severe asthenia and gastrointestinal tract toxicity. In addition, two cases of amaurosis

Table 3. Patient characteristics: studies 1, 2 and 3

Treatment	Patients *n*	Male patients %	Median age years (range)	Tumour site	*n**	PS 0-1 at study entry %	Prior treatment %
Study 1							
Raltitrexed 2.0–3.75 mg/m^2	48	65	57 (42–65)	Mesothelium	17	48	85
15-min infusion + oxaliplatin				Colon and/or rectum	11		
85–130 mg/m^2 2-h infusion				Kidney	6		
3-weekly				Lung	4		
				Adrenal	4		
				Ovary	2		
				Pancreas	1		
				Other	3		
Study 2							
Raltitrexed 2.0–3.0 mg/m^2	18	89	58 (21–75)	Stomach	11	89	0
15-min infusion + epirubicin				Gastro-oesophageal junction	6		
50 mg/m^2 i.v. bolus + cisplatin							
60 mg/m^2 i.v. infusion 3-weekly				Oesophagus	1		
Study 3							
Raltitrexed 2.5–3.5 mg/m^2	16	56	59 (37–76)	Liver	7	63	6†
15-min infusion + doxorubicin				Stomach	6		
30–70 mg/m^2 i.v. bolus				Abdomen	5		
3-weekly				Ascites	5		
				Nodes	5		
				Other	8		

*In study 3, eight patients had 1 or 2 tumour sites and eight patients had 3 or more sites. †One patient had prior radiotherapy. PS, ECOG performance status; NA, not available; i.v., intravenous.

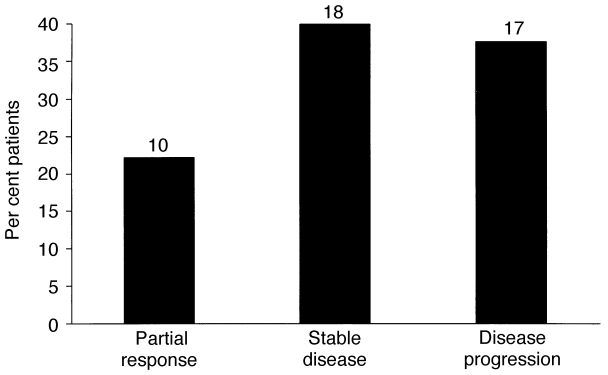

Figure 1. Tumour response in all evaluable patients treated with raltitrexed in combination with oxaliplatin: study 1.

fugax were observed at dose level 6 which precluded any further increase in oxaliplatin dose. The toxic dose was considered to be dose level 7 (3.75 mg/m^2 raltitrexed, 130 mg/m^2 oxaliplatin) since 4/6 patients required a dose reduction due to diarrhoea and/or vomiting (2 patients) or peripheral neurotoxicity (2 patients). The MTD was thus taken to be dose level 6 (3.5 mg/m^2 raltitrexed and 130 mg/m^2 oxaliplatin). The recommended dose is likely to be a combination of 3.0 mg/m^2 raltitrexed and 130 mg/m^2 oxaliplatin. At this dose, haematological toxicity was mild and there were no cases of alopecia.

Of the 45 patients evaluable for efficacy, 10 (22%) showed a partial response and 18 (40%) had stable disease (SD) (Figure 1). Interestingly, 8 of the 17 patients with mesothelioma (47%) achieved a partial response, including 2 patients with cisplatin-resistant tumours who improved dramatically, and 7 had SD. Furthermore, 6 of the 10 evaluable patients with heavily pretreated colorectal cancer had stable disease which was associated with an improvement in disease-related symptoms in some cases.

Study 2: raltitrexed/epirubicin/cisplatin (ECT)

18 patients have been entered, the majority of whom were male (89%) (Table 3). 10 patients had metastatic and 8 had locally advanced cancer. None of the patients had received any previous chemotherapy for advanced disease.

DLT was observed in 1 patient at a raltitrexed dose of 2.0 mg/m^2 (grade 3 neutropenia plus grade 4 thrombocytopenia, sepsis and stomatitis) and 1 patient at 2.5 mg/m^2 (grade 4 uncomplicated neutropenia). The MTD of raltitrexed was 3.0 mg/m^2 as two patients experienced DLT at this dose (grade 4 neutropenia; grade 4 diarrhoea plus grade 3 neutropenia). The recommended dose of raltitrexed in combination with epirubicin and cisplatin is likely to be 2.5 mg/m^2. At this dose level there was no severe non-haematological toxicity.

Study 3: raltitrexed/doxorubicin

To date, 16 patients with advanced or metastatic gastric cancer have been enrolled and treated at the first five dose levels. Most patients had multiple disease sites, including the liver, stomach, abdomen, ascites and nodes (Table 3). None of the patients had previously been treated with chemotherapy and only 1 patient had received radiotherapy.

No DLT was observed at the first five dose levels. Grade 3 or 4 toxicity seen with raltitrexed (2.5 or 3.0 mg/m^2) plus doxorubicin (60 mg/m^2) was comparable with that observed in a previous NCIC CTG study of doxorubicin alone in patients with breast carcinoma (Table 4) [24]. Since the MTD has not been reached, patients are currently being recruited to dose level 6 (3.5 mg/m^2 raltitrexed and 60 mg/m^2 doxorubicin).

Table 4. Comparative grade 3 or 4 toxicity of doxorubicin alone and in combination with raltitrexed: study 3

Toxicity	Patients with grade 3 or 4 toxicity	
	Raltitrexed 2.5 or 3.0 mg/m^2 plus doxorubicin 60 mg/m^2	Doxorubicin 60 mg/m^2 alone*
Granulocytopenia	67%	87%
Thrombocytopenia	14%	3%
Stomatitis	14%	7%
Nausea	14%	17%
Vomiting	0%	13%
Febrile neutropenia	14%	10%

*Data for doxorubicin alone are from a previous National Cancer Institute of Canada Clinical Trials Group Study [24].

9 patients were evaluable for efficacy. One patient with locally advanced disease achieved a complete response lasting for more than 48 weeks. A further 2 patients with metastatic disease showed partial responses of 36 and 56 weeks' duration, respectively. Thus, 3 patients achieved a durable objective response. The remaining 6 patients had a best response of SD, although 4 progressed between 9 and 12 weeks.

CONCLUSIONS

In these studies, raltitrexed was combined with oxaliplatin in patients with advanced solid tumours, and with anthracyclines, either in the presence or absence of cisplatin, for the treatment of advanced gastric cancer. Preliminary results from these three phase I studies are encouraging.

The recommended doses for raltitrexed and oxaliplatin are the same in combination as for single-agent use, i.e. 3.0 mg/m^2 raltitrexed and 130 mg/m^2 oxaliplatin. This combination was well tolerated, with mild haematological toxicity and no alopecia. The principal toxicities observed were asthenia and gastrointestinal effects.

Mesothelioma presents a particular challenge to the oncologist since there is currently no standard treatment for this condition, and the activity of raltitrexed or oxaliplatin monotherapy is unknown [25, 26]. In this context, the results seen with the combination of raltitrexed and oxaliplatin are promising. Almost half of the patients with mesothelioma had a partial response to treatment, including 2 patients with cisplatin-resistant disease. In addition, more than half of the patients with advanced colorectal cancer experienced disease stabilisation and, in some cases, this was associated with an improvement in disease-related symptoms. This observation is also encouraging as this group of patients had previously failed to respond to a range of other chemotherapy regimens. Phase II studies are underway to investigate the efficacy of the raltitrexed and oxaliplatin combination in malignant mesothelioma and untreated advanced colorectal cancer, and the results are awaited with much interest.

The MTD of raltitrexed in combination with cisplatin (60 mg/m^2) and epirubicin (50 mg/m^2) was 3.0 mg/m^2. The recommended dose of raltitrexed in this regimen is, therefore, likely to be 2.5 mg/m^2. Treatment at this dose level was well tolerated, with only mild non-haematological toxicity.

Further studies are required to define the activity of the ECT regimen in the treatment of lower oesophageal and gastric adenocarcinomas. Early results from two other studies have confirmed that the toxicities of raltitrexed and cisplatin do not overlap [27, 28]. No DLTs were observed in patients with metastatic non-small cell lung cancer at doses up to 3.0 mg/m^2 raltitrexed and 80 mg/m^2 cisplatin [27]. In patients with locally advanced or metastatic head and neck cancer who received 2.0 or 2.5 mg/m^2 raltitrexed and 100 mg/m^2 cisplatin, the only serious toxicity was cisplatin-induced renal failure [28].

Raltitrexed was well tolerated in combination with doxorubicin. No unexpected or dose-limiting toxicities were observed during co-administration of the full single-agent doses of raltitrexed and doxorubicin (3.0 mg/m^2 and 60 mg/m^2, respectively). Dose escalation of both agents is continuing. In the future, it may be possible to further enhance the cytotoxicity of this regimen by the addition of a platinum-based agent.

In conclusion, preliminary data from these phase I studies suggest that the combination of raltitrexed with platinum-based agents and/or anthracyclines may represent useful regimens for the treatment of patients with advanced cancer. All the combinations evaluated were administered in convenient 3-weekly schedules and were generally well tolerated. Further studies are required to identify the most effective combinations of raltitrexed with both established and new anticancer agents.

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