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Metabolism, excretion and pharmacokinetics of a single dose of [^{14}C]-raltitrexed in cancer patients

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Abstract Raltitrexed (Tomudex) is a specific inhibitor of thymidylate synthase and has recently been licensed in Europe for use in the treatment of advanced colorectal carcinoma. This study evaluated the metabolism, excretion and pharmacokinetics after a single dose of 3.0 mg/m^2 [^{14}C]-raltitrexed in patients with advanced solid malignancies not amenable to curative therapy. From April 1994 to July 1995, nine patients (six men and three women) were recruited into the study. Pharmacokinetics analysis was performed during the first cycle of treatment in all patients and, in two patients, limited sampling was done prior to and during the second cycle of treatment. The mean observed peak plasma concentration (C_{max}) was 700.6 ng/ml and the median time (t_{max}) to reach maximal raltitrexed concentrations was 15 min after the initiation of the infusion. After reaching C_{max} the drug declined in a triexponential manner with a terminal half-life of 257 h. The $AUC_{0-\infty}$ as predicted by the pharmacokinetic model was 2341.7 ng h ml^{-1}. Clearance was 41.3 ml/min, of which renal clearance accounted for 50–60%. Urinary collection for the measurement of radiolabeled drug revealed that renal excretion extrapolated to infinity accounted for 40% of the total radioactive dose. Faecal excretion accounted for only 3% of the dose when samples were collected to day 5 in the first six patients. Collection was extended to 10 days in the last three patients and faecal elimination accounted for 14% in these patients. Raltitrexed measurements prior to subsequent doses suggest that there was no accumulation of the drug with repeated administration. Low levels of radioactivity measured in the red cell pellets on days 15, 22 and 29 are likely to represent drug retained by newly forming red cells at the time of dosing. Examination of the urine revealed that the drug was excreted unchanged. The toxicities seen were in line with those encountered in previous studies. Grade 3 and 4 thrombocytopenia occurred in three patients and grade 3 neutropenia occurred in two patients.

Key words Pharmacokinetics · Thymidylate synthase inhibitors · Phase I trial · Raltitrexed

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Introduction

Raltitrexed (Tomudex, ZD1694; Zeneca Pharmaceuticals Limited) is a specific inhibitor of thymidylate synthase, the enzyme catalysing a critical step in de novo DNA synthesis, the production of thymidine monophosphate from deoxyuridine monophosphate.

Raltitrexed inhibits thymidylate synthase selectively in vitro [6]. Preclinical studies have shown that raltitrexed enters cells rapidly, predominantly via the reduced folate carrier (RFC). Once inside cells, it is converted efficiently by folylpolyglutamate synthetase to polyglutamated forms, which are markedly more potent inhibitors of thymidylate synthase than the parent compound. The polyglutamates are retained in cells and cause prolonged inhibition of thymidylate synthase, growth inhibition and cell death. In humans, plasma concentrations of raltitrexed have shown a triphasic decline after administration by a single 15-min intravenous infusion [2]. The apparent half-life of the terminal (gamma) phase ($t_{1/2\gamma}$) varied widely, ranging from 8.2 to 105 h. This prolonged $t_{1/2\gamma}$ may represent hydrolysis of the polyglutamated forms and slow release of raltitrexed from tissues into the circulation.

In a phase I trial a dose and schedule of 3.0 mg/m^2 every 3 weeks was identified as suitable for phase II investigation. Higher doses were associated with significant asthenia and antiproliferative toxicities, if they occurred, showed a tendency to be cumulative [2]. In

phase II trials, intravenous raltitrexed at a dose of 3.0 mg/m^2 given once every 3 weeks produced objective responses in several solid tumours, including colorectal [14], breast [12], ovarian [4], pancreatic [10] and non-small-cell lung cancer [5]. In these trials the safety profile of raltitrexed was consistent with that expected for an active cytotoxic agent of this class. As predicted, the most frequently observed toxicities were asthenia, diarrhoea, nausea and vomiting, leucopenia and reversible increases in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT). The most serious (life-threatening) toxicities were gastrointestinal toxicity and haematological suppression.

Recently, a phase III study has been completed in advanced colorectal carcinoma, comparing raltitrexed with 5-fluorouracil and low-dose leucovorin [3]. Although there was no difference in the response rates obtained for the two treatment arms, toxicity was lower in the raltitrexed-treated patients. Lower rates of grade 3 and 4 leucopenia and mucositis were seen and the patients spent less time in hospital.

A study recently completed has shown that the drug is predominantly renally excreted [9]. Patients with mild to moderate renal impairment experience more toxicity than those with normal renal function, and it is recommended that these patients should have a dose reduction of 50%. Patients with severe impairment should not receive raltitrexed.

Given the long terminal half-life of the drug, possibly due to extensive polyglutamation, other routes of excretion may be important in humans. Radiolabel studies in mice previously showed that at 24 h after the injection of radiolabeled raltitrexed the drug concentration in liver, kidney and gut epithelium was 50–100 times that in plasma [1, 7]. The majority of this drug (>80%) was polyglutamated. In rats and dogs the only compound detected in plasma is the unchanged drug. Elimination in the rat is predominantly faecal [8], but in the dog it is evenly balanced between the urine and faeces (data on Zeneca file).

This non-comparative trial was undertaken to determine the metabolism, excretion and pharmacokinetics of a single dose of [^{14}C]-raltitrexed in patients with advanced cancer.

Patients and methods

Patients

This study was performed between April 1994 and July 1995 at the Royal Marsden NHS Trust, London and Sutton, Surrey, United Kingdom. The study was approved by the Research Ethics Committee and was conducted in accordance with the principles of good clinical practice. All patients were required to give written consent. Nine adult patients with advanced cancer not amenable to curative therapy were recruited into the trial. Other entry criteria included an age of 18 years; normal bone marrow reserve; a serum creatinine level of <1.25 times the upper limit of normal; a serum bilirubin value of <1.25 times the upper limit of normal; ALT and AST levels of <2.5 times the upper limit of normal; a World Health Organisation (WHO) performance status of 0, 1 or 2; normal or compensated cardiac function; and a weight within 20% of the Metropolitan Life normal range for the patient's height and weight. Exclusion criteria included the presence of ascites or a pleural effusion, concomitant use of medication known to affect hepatic or renal function and cytotoxic therapy within 4 weeks of entry (6 weeks for nitrosoureas and mitomycin C). Patients were not entered into the study until all signs of toxicity from previous therapy had completely resolved.

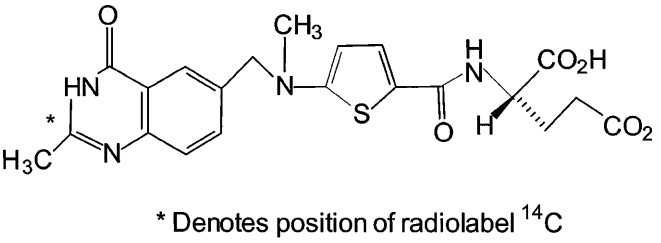

Fig. 1 Structure of [^{14}C]-raltitrexed

Trial treatment

Each patient received a single intravenous dose of 3.0 mg/m^2, 7.5 μCi/m^2 [^{14}C]-raltitrexed (Fig. 1) given as a 15-min infusion and was then monitored for 28 days. Patients showing clinical benefit after this first dose of raltitrexed could continue treatment with unlabeled drug at intervals of 3 weeks. In the event of toxicity, treatment could be delayed by up to 3 weeks or the dose of raltitrexed, reduced.

Assessments

The patients were admitted to hospital for the first course of therapy, and blood, urine and faecal samples were collected for 5 days from the first six patients and for 10 days from the last three patients. Patients were then reviewed at 1, 2, 3, and 4 weeks after dosing, and those who continued on treatment were then seen routinely at 3-weekly intervals for dosing and at 3 weeks after the last dose.

Prior to the first dose a physical examination was performed, vital signs were recorded, and an electrocardiogram, the tumour burden, the WHO performance status, haematology, electrolytes, renal function and hepatic function were assessed. These were repeated at each clinic visit prior to subsequent dosing. In addition, all adverse events were recorded and toxicities were graded according to WHO recommendations.

Pharmacokinetics

Raltitrexed pharmacokinetics were assessed after the first dose in all patients and, in two patients, limited sampling was performed after the second dose. The planned pharmacokinetic sampling schedule was pre-dose and 5, 10, 15, 20, 25, 30, 45, 60 and 90 min as well as 2, 3, 5, 8, 12, 24, 48, 72, 96, 144, 216, 336, 504 and 672 h after the start of the infusion. Whole blood, faecal homogenates and red-blood-cell pellets were oxidised prior to analysis. All samples of plasma, urine, faeces, whole blood and red-blood-cell pellets were assayed for radioactivity using a liquid scintillation counter. All plasma samples were assayed for raltitrexed using a radioimmunoassay (RIA) [2]. Selected urine samples were assayed by high-performance liquid chromatography (HPLC) to assess the metabolite patterns. These samples were concentrated by extraction from C_{18} bonded silica and evaporated to dryness under reduced pressure, and the residue was reconstituted in methanol. The extracts were then centrifuged at 1000 rpm for 5 min to remove

insoluble particles and the supernatants were then analysed. Chromatographic separation was achieved using an analytical Hichrom Hypersil ODS column and, after elution, detection was accomplished by UV absorbance at 225 nm together with radioactivity monitoring.

The peak plasma concentration (C_{max}) and the time to C_{max} (t_{max}) were calculated directly from raltitrexed concentration data. The area under the plasma concentration-time curve from the start of the infusion to the time of the last determined concentration (AUC_{0-tldc}) was calculated using the linear trapezoidal rule by the pharmacokinetic analysis programme PHASAR (version 1.2). A three-compartment intravenous infusion non-linear regression model with a weighting factor of 1/concentration was fitted to plasma concentration-time data using the TOPFIT analysis programme (version 5). The following secondary pharmacokinetic parameters were then calculated from the model: the AUC extrapolated to infinity ($AUC_{0-\infty}$); the volume of the central compartment (V) and volume at steady state (V_{ss}); the distribution phase half-life ($t_{1/2\beta}$ and the terminal phase half-life ($t_{1/2\gamma}$); and the clearance, which was calculated by division of the actual dose in milligrams by the $AUC_{0-\infty}$ value. A three-compartment pharmacokinetic model was chosen in preference to a two-compartment model on the basis of an improvement in the Akaike information. Urinary recovery of radioactivity was extrapolated using urinary recovery data from days 10, 14 and 29. The percentage of the dose excreted per hour was then plotted against the midpoint of each collection time and the $t_{1/2}$ was fitted by regression through the terminal time points. This half-life was used to extrapolate the urinary recovery to infinity. The calculations were performed using the pharmacokinetic data analysis programme PHASAR (version 1.2). Individual renal clearance was calculated by division of the 0 to 96-h radioactivity recovered in the urine by the trapezoidal AUC_{0-96} value.

Statistical methods

As prior data had not been collected after the administration of radiolabeled [^{14}C]-raltitrexed, six patients were initially to be included in the study. However, a further three patients were studied following the initial analysis, which indicated the need to extend the time of collection of urine and faeces to 10 days.

Results

The patients' characteristics are set out in Table 1.

Table 1 Patients' characteristics

	Patients (1)
Patients	9
M	6
F	3
Mean age (range)	54.8 (24–74) years
Performance status:	
0	5
1	3
2	1
Primary tumour:	
Adenocarcinoma of unknown origin	3
Non-small-cell lung cancer	2
Colorectal cancer	1
Breast cancer	1
Synovial sarcoma	1
Ovarian cancer	1

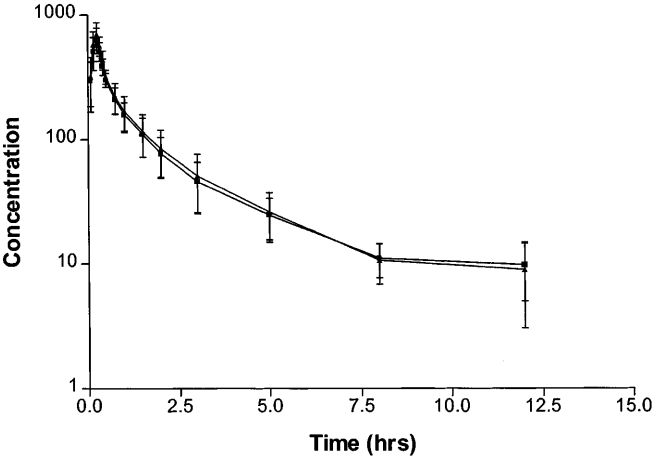

Fig. 2 Mean plasma raltitrexed and radioactivity concentrations measured for up to 12 h after dosing. –■– Plasma radioactivity ng · eq/ml; –▲– Plasma raltitrexed ng/ml

Pharmacokinetics

There was good correlation between total radioactivity, as measured in plasma over the first 24 h, with RIA measurements of raltitrexed (Fig. 2). The ratio of raltitrexed to total radioactivity in plasma was 1.09 and 1.04 at t_{max} and 5 h after dosing, respectively. For the first 5 h after dosing the concentration of radioactivity was higher in plasma than in whole blood – 1.46 times higher at t_{max} and 1.2 times higher at 5 h post-dosing (due to lower concentrations in the red cell fraction). The mean raltitrexed pharmacokinetic parameters obtained by the modeling techniques and the mean observed C_{max} and t_{max} and trapezoidal AUC values are summarised in Table 2. The C_{max} and t_{max} values predicted from the model are similar to the observed values (736.8 versus 700.64 ng/ml and 15.01 versus 15.0 min). After C_{max} was reached, raltitrexed concentrations declined in a triexponential manner, with the mean half-lives $t_{1/2\alpha}$, $t_{1/2\beta}$ and $t_{1/2\gamma}$, being 12 min, 103 min and 257 h, respectively.

Table 2 Plasma pharmacokinetic parameters

Parameter	Mean	SD	CV%
Model-derived:			
C_{max} (ng/ml)	736.8	164.9	22.4
$AUC_{0-\infty}$ (ng h ml^{-1})	2341.7	941.1	40.2
$t_{1/2\alpha}$ (min)	12	3.0	25.8
$t_{1/2\beta}$ (min)	103	16.2	15.6
$t_{1/2\gamma}$ (h)	257	62.9	24.5
CL (ml/min)	41.3	14.0	34.0
CL_{renal} (ml/min)	21.5	5.2	24.0
Compartment model-independent:			
Observed C_{max} (ng/ml)	700.6	165.3	23.6
Observed t_{max} (min)[a]	15.0	(median)	

[a] The value recorded for 5 patients was 15.0 min; 16, 16, 17 and 20 min were the data noted for the remainder. Some of the differences seen are due to the actual time samples were taken

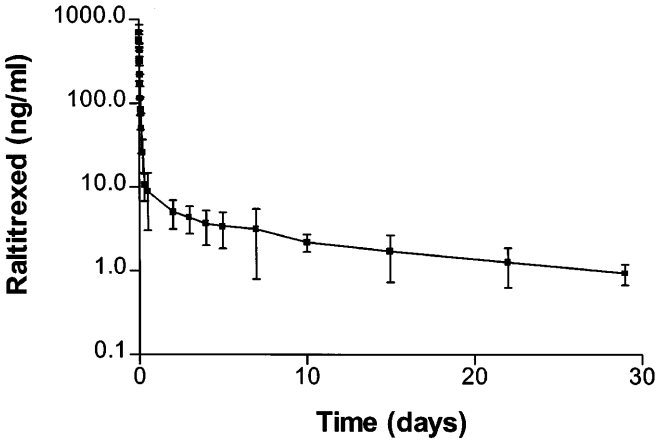

Fig. 3 Mean plasma raltitrexed concentration-time profile as determined over 30 days

There was a considerable range in the values recorded for the terminal half-life, 148–379 h.

However, the mean value was close to the elimination half-life estimated by the urinary data (261 h). The terminal phase, observed from 24 h onwards, accounted for approximately two-thirds of the total area under the raltitrexed concentration-time profile (Fig. 3). The contribution of the extrapolated area to the total area was approximately 20%, indicating that collection of samples for 29 days enabled adequate characterisation of the raltitrexed plasma concentration-time profiles in patients.

The plasma clearance was 41.3 ml/min, which is similar to the value reported in a previous study (66.7 ± 21.7 ml/min) [2]. The calculated renal clearance was 21.5 ml/min (range 11.2–28.3 ml/min) and this accounted for 50–60% of the total clearance in most patients, although in one patient it accounted for only 34%.

In two patients, limited sampling was done prior to and during the second course of raltitrexed. Raltitrexed plasma concentrations were low (0.84 ng/ml and below the limit of detection) prior to the second dose, and prior to the third dose in one patient the value was 1.58 ng/ml. Raltitrexed levels achieved during and after the infusion were similar to those achieved during the first course.

Urinary and faecal radioactivity

The recovery of radioactivity in urine and faeces, expressed as a percentage of the radioactive dose, is presented in Table 3. This shows that 21.7% of the radiolabeled dose was excreted in urine in the first 24 h; this increased to 28.8% at 10 days and, when extrapolated to infinity, reached 40.1%. Faecal recovery of radioactivity reached only 3% by day 5 in the first six patients but increased to 14% of the dose at day 10 for the last three patients, for whom collections were extended to this time point. This showed that faecal elimination is a significant route of excretion, and extending the collection period may have resulted in a further rise in this percentage. Samples of urine examined using HPLC showed a single peak that had a retention time similar to that of raltitrexed, suggesting that the drug was eliminated unchanged.

Red-blood-cell radioactivity

Raltitrexed levels fell to below detectable limits in both blood and red cell pellets at 24 h post-dosing. However, on days 15, 22 and 29, low levels of radioactivity were seen in red cell pellets. By day 29, red cell pellets' radioactivity ranged from 10.8 to 35.5 ng/mg (mean 20.7 ng/mg). The late appearance of radioactivity in red blood cells as compared with plasma is thought to represent polyglutamated metabolites of raltitrexed that have been formed in bone marrow cells at the time of dosing.

Table 3 Recovery of radioactivity in urine and faeces following administration of a single intravenous dose of [^{14}C]-raltitrexed [a](*NC* Not calculated)

Time after dose (h)	Recovery as a percentage of the delivered radiolabeled dose		Combined percentage
	Urine	Faeces	
0–24	21.70 ± 5.87	0.13 ± 0.20	21.83
24–48	1.56 ± 0.81	0.07 ± 0.08	1.63
48–72	1.55 ± 0.61	0.47 ± 0.58	2.02
72–96	1.42 ± 0.41	2.33 ± 2.65	3.75
96–120	1.56 ± 0.48	1.22 ± 1.60	2.78
120–144	1.00 ± 0.63	2.59 ± 1.86	3.59
144–168	1.02 ± 0.09	1.15 ± 1.99	2.17
168–192	1.11 ± 0.20	1.53 ± 0.60	2.64
192–216	0.92 ± 0.13	1.38 ± 1.24	2.30
216–240	0.80 ± 0.27	1.41 ± 1.25	2.21
Total 0–240	28.75 ± 7.53	14.40 ± 1.75	43.15
Total (extrapolated to infinity)	40.13 ± 13.80	NC	NC

[a] Each value shows the mean ± SD recorded for the nine patients for up to 120 h. Values noted from 120 to 240 h show the mean recorded for three patients

Table 4 Adverse events and laboratory abnormalities graded according to WHO recommendations

Effect	Number of patients (%)	
	Grade 3 or 4	All grades[a]
Laboratory values:		
Haemoglobin	0	7 (78)
Leucocytes	2 (22)	3 (33)
Platelets	3 (33)	3 (33)
Transaminases	0	3 (33)
Adverse events:		
Nausea/vomiting	1	9 (100)
Diarrhoea	1	4 (44)
Mucositis	2	3 (33)
Fever	0	4 (44)
Rash	0	1 (11)
Infection	0	6 (67)
Constipation	1	3 (33)
Pain	0	6 (67)
Aesthenia[b]	0	4 (44)

[a] Total number of drug-related WHO-graded events
[b] Graded as mild, moderate or severe; there was no case of severe aesthenia

Toxicity

A total of 24 (mean 2.8, range 1–5) cycles of treatment were delivered to 9 patients. The treatment was tolerated well by most patients. Toxicities are listed in Table 4. WHO grade 3 and 4 toxicities were/infrequently encountered; however, three patients did develop grade 3 and 4 thrombocytopenia and two developed grade 3 and 4 leucopenia.

Discussion

The decline of ZD1694 concentrations in plasma was triphasic with a long terminal half-life of 257 h, which is consistent with retention in tissues due to the extensive polyglutamation that occurs once the drug has entered cells. This value is greater than that reported in the first phase I trial (8.2–105 h), where sampling was done to day 4 only as compared with day 29 in the current study.

Analysis of the radioactivity in plasma, urine and faeces gave an accurate assessment of the fate of the initial dose of raltitrexed. Renal clearance accounted for 40% of the dose and faecal elimination, another 14% when sampling was carried out to day 10. In the first six patients, sampling was done only to day 5 and faecal elimination accounted for only 3% of the total dose. This was probably due to the sporadic nature of collection in this period as a reflection of the altered bowel function in these patients. Factors such as the extent of disease, the use of analgesics and hospitalisation could have contributed to this process. It is also likely that if the collection had continued for a longer time, the percentage of the radiolabeled dose collected in the faeces would have risen.

The compound(s) responsible for the radioactivity detected in the faeces was not determined. This may represent biliary excretion of raltitrexed either as intact or polyglutamated drug or as some other metabolite. Mucosal cells shed from the gastrointestinal tract that have taken up the drug may contribute to the faecal count. Preclinical data have shown that the gut mucosa in mice has a high concentration of raltitrexed after a single dose of the drug [7]. There appeared to be no metabolite in the plasma, and the drug was excreted unchanged into the urine as measured by radiochromatograms.

The pharmacokinetic model could predict the raltitrexed levels for three patients with differing terminal half-lives and clearance values. Assuming that treatment was given every 3 weeks at a dose of 3.0 mg/m^2, the patient with the shortest terminal half-life would be expected to have a plasma drug level prior to the sixth dose of 0.65 ng/ml, the patient with the longest terminal half-life would have a level of 3.17 ng/ml, and the patient with the slowest clearance would have a level of 2.21 ng/ml.

These data were supported by plasma levels of the drug determined prior to subsequent dosing in two patients that were low or undetectable. One patient had a level of 0.84 ng/ml and the other had a level below the study limit of quantification (<0.768 ng/ml). One patient who had measurements taken prior to his third dose showed a level of 1.58 ng/ml, suggesting that there is little, if any, accumulation of raltitrexed.

However, levels within tissues were not assessed during this study. Intracellular measurements of raltitrexed may provide data on the effect of the drug on normal tissue and, thus, provide an insight to toxicity associated with the drug. However, regular sampling of normal tissue is not feasible. Red blood cells may reflect uptake by dividing normal tissue cells and are easily accessible. Red cell pellets assayed for radioactivity had undetectable levels at 5 h after the dose. However, low levels were detected on days 15, 22 and 29, which probably reflects retention of drug by newly forming red cells in the bone marrow at the time of the infusion. It has been demonstrated that this phenomenon occurs after the administration of methotrexate [11] and lometrexol [13].

The drug was tolerated well with few serious adverse events, although there were three episodes of grade 3 and 4 thrombocytopenia. These episodes, however, were not associated with bleeding. Two patients had grade 3 and 4 leucopenia, but these events did not result in infections requiring hospitalisation. Other side effects were in keeping with those reported in other trials of raltitrexed.

This study confirms the long terminal half-life of raltitrexed and demonstrates that faecal excretion is a significant route of elimination in humans. Tissue retention due to extensive polyglutamation is likely to account for a significant proportion of a delivered dose, but there is no evidence that there is accumulation of the drug as measured by plasma levels determined prior to subsequent doses.

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