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Raltitrexed

A Review of its Pharmacological Properties and Clinical Efficacy in the Management of Advanced Colorectal Cancer

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Synopsis

Raltitrexed (ZD-1694) is a quinazoline-based folate analogue that exerts its cytotoxic activity by the specific inhibition of thymidylate synthase. In vitro studies show that raltitrexed is actively transported into cells and is then rapidly and extensively metabolised to a series of polyglutamates. These metabolites are significantly more potent inhibitors of thymidylate synthase than the parent drug and are retained intracellularly, producing prolonged cytotoxic effects without the need for continuous drug exposure.

Phase III clinical trials in patients with advanced colorectal cancer evaluated

raltitrexed 3 mg/m^2 administered as a 15-minute intravenous infusion once every 3 weeks. This schedule produced objective response rates of 14.3 to 19.3%, which were similar to those in patients treated with fluorouracil plus leucovorin (15.2 to 18.1%). Median survival durations ranged from 9.7 to 10.9 months with raltitrexed treatment and from 10.2 to 12.7 months with fluorouracil plus leucovorin.

The major toxicities associated with raltitrexed involve the haematological and gastrointestinal systems, although severe asthenia also occurred in 6 to 18% of patients receiving the drug. Grade 3 or 4 nausea or vomiting occurred in up to 13% of raltitrexed recipients and grade 3 or 4 diarrhoea in up to 14%. Similar incidences of grade 3 or 4 nausea or vomiting and diarrhoea were seen with fluorouracil plus leucovorin treatment. Raltitrexed generally showed significant advantages over fluorouracil plus leucovorin with respect to the incidence of leucopenia and mucositis. A greater proportion of raltitrexed than fluorouracil plus leucovorin recipients were able to receive the scheduled dosage.

Thus, with its similar efficacy to fluorouracil-based regimens, convenient administration schedule and favourable tolerability profile, raltitrexed provides clinicians with a worthwhile alternative to fluorouracil-based treatment for patients with advanced colorectal cancer.

Antitumour Activity

The antitumour agent raltitrexed (ZD-1694) is a quinazoline-based folate analogue that produces cytotoxic effects by the specific inhibition of thymidylate synthase. Raltitrexed is actively taken up into cells by the reduced folate-methotrexate cell membrane carrier and then undergoes rapid, extensive metabolism by folylpolyglutamate synthetase to a series of polyglutamates. Polyglutamated forms of raltitrexed are significantly more potent inhibitors of thymidylate synthase than the parent drug, and their intracellular retention leads to prolonged inhibitory effects. Raltitrexed is a considerably more potent inhibitor of human colon tumour cell lines than fluorouracil. Raltitrexed given once daily for 15 days produced a growth delay of 15 days in 10 of 10 human tumour xenografts at doses lower than its maximum tolerated dose. In contrast, with a similar administration schedule, fluorouracil and methotrexate achieved this effect at their maximum tolerated doses in 4 and 2 xenografts, respectively.

Synergistic effects on antitumour efficacy *in vitro* were observed with certain combinations of raltitrexed and fluorouracil. The extent of the interaction depended on the administration schedule and dosage of the 2 drugs, although no consistent pattern that produced maximum synergism has emerged. Synergistic cytotoxic interactions have also been found between raltitrexed and the active metabolite of irinotecan.

Pharmacokinetic Properties

Maximum plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) for raltitrexed vary approximately linearly with dose, although there is considerable interpatient variation. C_{max} is reached during or shortly after intravenous infusion, with a mean of 833 μg/L in patients with a variety of solid tumours receiving raltitrexed 3.0 mg/m^2.

Plasma concentrations of raltitrexed declined in a triphasic manner. The distribution half-life (0.8 to 3 hours) and the terminal elimination half-life ($t_{½\gamma}$; 8.2 to 105 hours) were independent of dose.

The major route of raltitrexed elimination is urinary excretion of the parent drug. Patients with mild to moderate renal impairment had a significantly prolonged $t_{½\gamma}$ and a 2-fold greater AUC than patients with normal renal function.

Clinical Efficacy

In a phase II clinical trial in 176 patients with advanced colorectal cancer, raltitrexed 3 mg/m^2 once every 3 weeks demonstrated an overall response rate of 25.6%. The median time to disease progression was 4.2 months and the median survival duration was 11.2 months.

In 3 phase III clinical trials involving a total of more than 1300 patients with advanced colorectal cancer, raltitrexed (3 mg/m^2 once every 3 weeks) and fluorouracil plus leucovorin regimens (fluorouracil 425 mg/m^2 plus leucovorin 20 mg/m^2 or fluorouracil 400 mg/m^2 plus leucovorin 200 mg/m^2, once daily for 5 days every 4 or 5 weeks) produced similar objective response rates of 14.3 to 19.3% and 15.2 to 18.1%, respectively. Median survival duration in patients treated with raltitrexed was similar to that in fluorouracil plus leucovorin recipients in 2 phase III studies (10.9 *vs* 12.3 months and 10.1 *vs* 10.2 months). In a third study median survival duration was 12.7 months for patients treated with fluorouracil plus leucovorin versus 9.7 months in recipients of raltitrexed, a significant difference. However, the duration of treatment with fluorouracil plus leucovorin was almost twice that of raltitrexed in this trial. Median time to disease progression ranged from 3.1 to 4.8 months with raltitrexed treatment and 3.6 to 5.3 months with fluorouracil plus leucovorin treatment.

Raltitrexed also provides similar palliative benefits to fluorouracil plus leucovorin in patients with advanced colorectal cancer. Gains in bodyweight of ≥5% were observed in 13 to 21.1% of raltitrexed recipients compared with 15.7 to 27.4% of those receiving fluorouracil plus leucovorin. Improvements in WHO performance status scores were seen in 36.4 to 39.1% of raltitrexed recipients and in 29.7 to 40.8% of patients receiving fluorouracil plus leucovorin.

Pharmacoeconomic Considerations

The mean direct monthly costs of raltitrexed treatment (£1117.85, 1994/1995 pounds sterling) were similar to or less than those of various fluorouracil regimens (£954.03 to 2028.52) in a retrospective audit of patient notes in a large English hospital. The greater acquisition costs of raltitrexed compared with fluorouracil plus leucovorin were at least partially offset by lower outpatient costs. The combined in- and outpatient costs of raltitrexed treatment were lower than those of any of the other regimens.

Raltitrexed was quicker and less costly to prepare than fluorouracil-based regimens and consequently was associated with significantly lower pharmacy charges.

Drug costs for management of raltitrexed-related toxicity were approximately half those for toxicity associated with an intermittent fluorouracil-based administration regimen.

Tolerability

The most common adverse events associated with raltitrexed (3 mg/m^2 once every 3 weeks) in phase III trials were gastrointestinal and haematological in nature. Grade 3 or 4 diarrhoea occurred in 10 to 14% of patients and grade 3 or 4 nausea or vomiting in 9 to 13% of raltitrexed recipients. These events were seen in a similar proportion of patients receiving fluorouracil 425 mg/m^2 plus leucovorin 20 mg/m^2 or fluorouracil 400 mg/m^2 plus leucovorin 200 mg/m^2 once daily for 5 days every 4 or 5 weeks.

Markedly fewer raltitrexed recipients experienced grade 3 or 4 mucositis (2 to 3%) than patients treated with fluorouracil plus leucovorin (10 to 22%), although the incidence of severe asthenia was higher in those receiving raltitrexed (6 to 18%) than in those treated with fluorouracil plus leucovorin (2 to 10%).

The incidence of grade 3 or 4 leucopenia associated with raltitrexed treatment

(6 to 18%) was approximately half that with fluorouracil plus leucovorin (13 to 41%).

Treatment-related deaths occurred in similar proportions of patients treated with either raltitrexed (3.8%) or fluorouracil plus leucovorin (2.6%).

In phase III trials, 62 to 71% of raltitrexed recipients were able to receive the planned dosage without the need for dosage modification or delay because of toxicity, in contrast to 32 to 53% of fluorouracil plus leucovorin recipients.

One phase III trial found significant benefits in favour of raltitrexed over fluorouracil plus leucovorin for a range of quality-of-life parameters including physical symptoms, psychological condition, general activity and mobility during the first treatment cycle. However, no clear differences between treatments in terms of quality of life were noted in the other 2 trials.

Dosage and Administration

In phase II and III clinical trials, patients with advanced colorectal cancer received raltitrexed 3 mg/m^2 as a 15-minute intravenous infusion once every 3 weeks. Dosage was reduced in patients who developed severe haematological or gastrointestinal toxicity and was delayed for up to 21 days to allow resolution of toxicity.

Patients with mild to moderate renal impairment should have the dose of raltitrexed reduced by 50% and the frequency of administration reduced to every 4 weeks.

Raltitrexed (ZD-1694) is a quinazoline-based folate analogue (fig. 1) that exerts its antitumour activity by the specific inhibition of thymidylate synthase. This enzyme catalyses the reductive methylation of deoxyuridylate to thymidylate which, after metabolism to thymidine triphosphate, is exclusively incorporated into DNA (fig. 2). Inhibition of thymidylate synthase leads to breakages in single- and double-stranded DNA and ultimately produces the cytotoxicity observed with raltitrexed.

1. Antitumour Activity

In vitro studies have demonstrated that raltitrexed undergoes active cellular uptake via the reduced folate-methotrexate cell membrane carrier and is then rapidly metabolised by folylpolyglutamate synthetase to polyglutamates (fig. 2).[1-3] Intracellular polyglutamates are detected within a few minutes of *in vitro* exposure to raltitrexed. After 4 hours, parent drug represented less than 5% of the total drug pool in human W1L2 cells.[1,3]

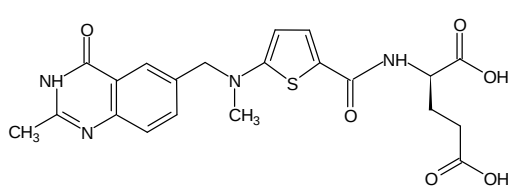

Fig. 1. Chemical structure of raltitrexed (ZD-1694).

Polyglutamation increases the potency of raltitrexed through the accumulation of species which are significantly more active as thymidylate synthase inhibitors than the parent compound [inhibition constant (K_i) of tetraglutamate for mouse and human thymidylate synthase = 1 to 2 nmol/L compared with ≈60 to 90 nmol/L for the parent drug].[1,4,5] In addition, polyglutamate derivatives have a ≈100-fold greater specificity for thymidylate synthase over dihydrofolate reductase.[1]

Concentrations of raltitrexed required to produce 50% growth inhibition (IC_{50}) in both mouse and human tumour cell lines were generally between 1 and 10 nmol/L.[1,2,5-7]

Intracellular retention of polyglutamates leads to prolonged inhibition of thymidylate synthase without the necessity for continuous drug exposure.[8]

Five of 6 human colon tumour cell lines were highly sensitive to raltitrexed, under either continuous exposure (IC_{50} 1.3 to 3.9 nmol/L) or short

exposure (IC_{50} ≈80 nmol/L) conditions. In contrast, fluorouracil, even in combination with leucovorin, was considerably less potent against these cell lines, with IC_{50} values between 330 and 5800 nmol/L under continuous exposure conditions, and ≈150 000 nmol/L under short exposure conditions. A sixth cell line, however, was more resistant to raltitrexed than fluorouracil plus leucovorin.[7,9]

Synergism was demonstrated in HCT-8 colon cancer cells when raltitrexed was administered for 4 or 24 hours, followed by fluorouracil for 7 days. No synergism was found when both drugs were administered concurrently or when fluorouracil preceded raltitrexed.[10] However, another study, in HCT-8 and HT-29 colon cancer cells, found that simultaneous administration of both drugs for 24 hours produced significant synergistic cytotoxicity.[11] The same investigation showed that raltitrexed administered for 24 hours followed by 1 hour of fluorouracil also resulted in synergistic interaction for all drug ratios. Reversing the schedule (fluorouracil for 1 hour before a 24-hour incubation with raltitrexed) produced strong antagonism with high doses of fluorouracil and low doses of raltitrexed and synergism with low doses of fluorouracil and high doses of raltitrexed.

Synergistic *in vitro* cytotoxic effects between raltitrexed and SN 38, the active metabolite of the topoisomerase I inhibitor irinotecan, have also been noted; these appear to be highly dose, time and sequence specific. Sequential rather than simultaneous administration of raltitrexed and SN 38 resulted in synergistic activity in human colon cancer cells, and the magnitude of this effect was greatest when SN 38 was given first and higher relative doses of raltitrexed (10 : 1 ratio) were used.[12] Synergistic effects were also demonstrated in another study in human colon carcinoma cell lines exposed to SN 38 for 4 hours followed by raltitrexed for 4 hours, although the reverse sequence produced additive or antagonistic effects.[13] Simultaneous administration of raltitrexed and SN 38 for 24 hours produced a synergistic cytotoxic interaction in 1 study.[14]

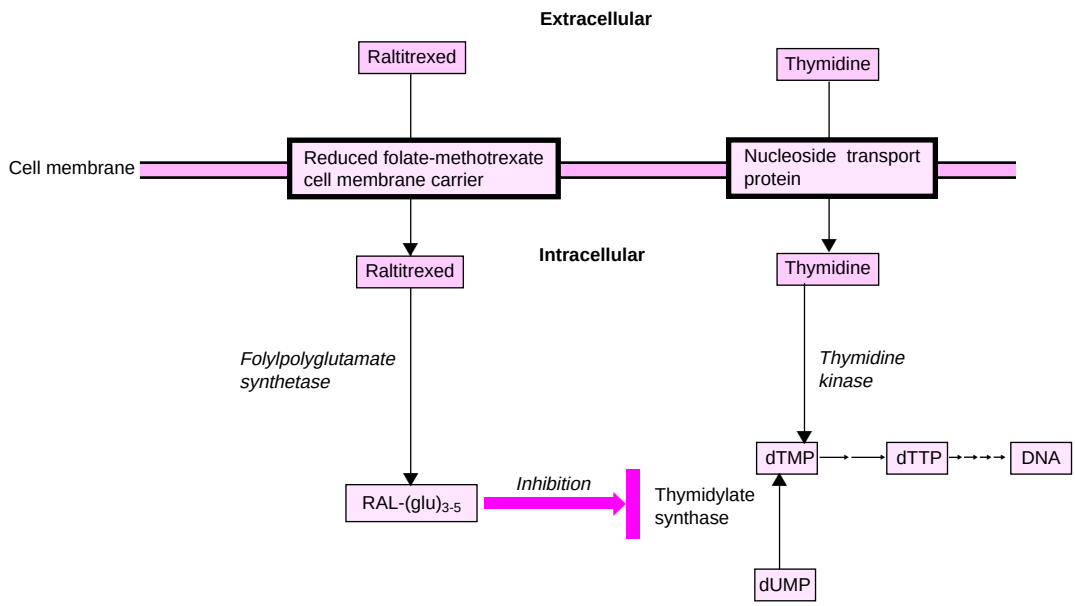

Fig. 2. Schematic representation of the mode of action of raltitrexed, and the role of thymidylate synthase in the synthesis of DNA. *Abbreviations:* dTMP = thymidylate; dTTP = thymidine triphosphate; dUMP = deoxyuridylate; RAL-$(glu)_{3-5}$ = polyglutamated raltitrexed species.

Raltitrexed has also shown cytotoxic activity in murine tumour models.[7,15-17]

Raltitrexed administered once daily for 15 days, at doses below its maximum tolerated dose (doses ranged from 1 to 100 mg/kg/day) produced a growth delay of 15 days in 10 human tumour xenografts (3 lung, 2 ovarian, 4 colon, 1 gastric). In contrast, maximum tolerated doses of methotrexate or fluorouracil, given once daily for 15 days, produced this effect in 2 (small cell lung, ovarian) and 4 (small cell lung, ovarian, colon, gastric) of 10 xenografts, respectively.[18]

2. Pharmacokinetic Properties

The pharmacokinetic profile of raltitrexed was investigated in 61 patients with a variety of solid tumours.[19] The drug was administered intravenously over 15 minutes at a constant infusion rate. Although considerable interpatient variability was found, maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) varied approximately linearly with raltitrexed dose. At 3.0 mg/m^2 (n = 13), mean C_{max} was 833 μg/L and mean AUC extrapolated to infinity was 1090 μg/L · h. Plasma concentrations of raltitrexed peaked during or shortly after the infusion and then declined in a triphasic manner. The distribution half-life ranged from 0.8 to 3 hours and the terminal elimination half-life ($t_{½\gamma}$) from 8.2 to 105 hours; both variables were independent of dose.

Radiolabelling studies found no evidence of metabolic degradation in humans and showed that the major route of raltitrexed elimination is urinary excretion of the parent drug.[20] Patients with mild to moderate renal impairment [creatinine clearance 1.5 to 3.9 L/h (25 to 65 ml/min)] had a significantly prolonged raltitrexed $t_{½\gamma}$ and a 2-fold greater AUC than patients with normal renal function.[20] Accordingly, dose and treatment frequency reduction is recommended for patients with mild to moderate renal impairment (section 6). Patients with creatinine clearance less than 1.5 L/h should not be treated with raltitrexed.

There were no clinically relevant differences in the pharmacokinetic profile of raltitrexed between patients with mild to moderate hepatic impairment (total bilirubin 1.25 to 3 times the upper limit of normal, with AST or ALT 3 to 10 times the upper limit of normal) and those with normal hepatic function.[21]

3. Clinical Efficacy

The clinical efficacy of raltitrexed in patients with advanced colorectal cancer has been investigated in a noncomparative phase II trial[22] and in 3 phase III comparisons with fluorouracil plus leucovorin.[23-25] Patients recruited into these studies had not received prior chemotherapy for advanced disease, although they may have received adjuvant cytotoxic chemotherapy which had been completed at least 1 year before entry. To be eligible for inclusion patients were also generally required to have the following: ≥1 measurable lesion; WHO performance status ≤2; absence of other malignancies or serious illnesses; adequate hepatic and renal function as determined by laboratory analysis.

Tumour responses were evaluated on the basis of WHO recommendations and modified International Union Against Cancer criteria.[26,27] These included the following: complete response (disappearance of all known disease determined by 2 observations not less than 4 weeks apart); partial response (decrease of ≥50% in the sum of the products of the 2 largest perpendicular diameters of measurable lesions); stable disease (≤25% increase in indicator lesions with no new lesions appearing); progressive disease (≥25% increase in size of 1 or more lesions or the appearance of new lesions). End-points of efficacy in all clinical trials included the time to disease progression, median survival duration and the objective (complete plus partial) response rate. In addition, palliative benefits of treatment were assessed in some trials.

A European phase II trial in 176 patients with advanced colorectal cancer treated with raltitrexed 3 mg/m^2 found an objective response rate of 25.6%, a median survival duration of 11.2 months

Table I. Efficacy of raltitrexed (RAL) in patients with advanced colorectal cancer: summary of phase II and phase III clinical trials

Reference	Treatment regimen[a] (mg/m^2)	No. of evaluable pts	Median duration of treatment		Response rate (% of pts)			Median time to disease progression[e] (mo)	Median survival duration (mo)
			cycles	wk	PR[b]	CR[c]	SD[d]		
Phase II (noncomparative) trial									
Zalcberg et al.[22,28,29]	RAL 3	176	4	13	23.3	2.3	49	4.2	11.2
Phase III (randomised, comparative) trials									
Cocconi[24,28-30]	RAL 3	245	4	12.7	15.4	3.2	51.4	3.9[f]	10.9
	FU 400 + LV 200	244	4	16.9	14.5	3.6	52.4	5.1[f]*	12.3
Cunningham et al.[23,28,29]	RAL 3	222	5	15.2	15.7	3.6	35.0	4.8	10.1
	FU 425 + LV 20	212	3	15.0	13.0	3.7	32.4	3.6	10.2
Pazdur & Vincent[25,28,29]	RAL 3	217	4	12.1	11.5	2.8	33.2	3.1	9.7
	FU 425 + LV 20	200	4	22.3	13.8	1.4	40.0	5.3*	12.7†

a RAL was administered as a 15-min intravenous infusion once every 3wk while FU plus LV was given as rapid intravenous injections once daily for 5 days, every 4 or 5wk.

b Decrease of ≥50% in the sum of the products of the 2 largest diameters of measurable lesions.

c Disappearance of all measurable and assessable lesions documented at 2 observations 4wk apart.

d ≤25% increase in indicator lesions with no new lesions appearing.

e ≥25% increase in size of 1 or more lesions or the appearance of new lesions.

f Pts receiving RAL were assessed significantly earlier for progression than those receiving FU plus LV.

Abbreviations and symbols: CR = complete response; FU = fluorouracil; LV = leucovorin; PR = partial response; pts = patients; SD = stable disease; * $p \leq 0.005$, † $p = 0.01$ *vs* RAL.

and a median time to disease progression of 4.2 months (table I).[22,28]

On the basis of these results, 2 large, randomised international phase III trials comparing raltitrexed with fluorouracil plus leucovorin were conducted. Cunningham and colleagues[23] compared raltitrexed 3 mg/m^2 with fluorouracil 425 mg/m^2 plus leucovorin 20 mg/m^2 (Mayo regimen) in 434 patients, while Cocconi[24] compared the same dosage of raltitrexed with fluorouracil 400 mg/m^2 plus leucovorin 200 mg/m^2 (Machover regimen) in 489 patients. In both studies, raltitrexed was administered as a 15-minute intravenous infusion once every 3 weeks while fluorouracil and leucovorin were given as rapid intravenous injections once daily for 5 days, every 4 or 5 weeks.

A third North American phase III study differed from the other trials by comparing raltitrexed 3 mg/m^2 (n = 217) or 4 mg/m^2 (n = 32) with fluorouracil 425 mg/m^2 plus leucovorin 20 mg/m^2 (Mayo regimen) [n = 200]. The 4 mg/m^2 raltitrexed treatment arm was included on the basis of a North American phase I study, which suggested that the maximum tolerated dose of raltitrexed was 4.5 mg/m^2.[31] However, as a result of unacceptable toxicity (including 3 therapy-related deaths) in this treatment arm, the trial was stopped and restarted as a 2-arm study.[25] Patients receiving raltitrexed 3 mg/m^2 continued treatment and were included in subsequent analyses.

Table I summarises efficacy data from all 3 comparative trials.

3.1 Tumour Response

There was no significant difference in objective response rates between treatment groups in any of the 3 comparative trials (fig. 3). These ranged from 14.3 to 19.3% in patients receiving raltitrexed and from 15.2 to 18.1% in fluorouracil plus leucovorin recipients.[23-25,28] The proportion of patients achieving a complete response ranged from 2.8 to 3.6% with raltitrexed and from 1.4 to 3.7% with fluorouracil plus leucovorin; corresponding values for patients achieving a partial response were 11.5 to 15.7% and 13 to 14.5%.

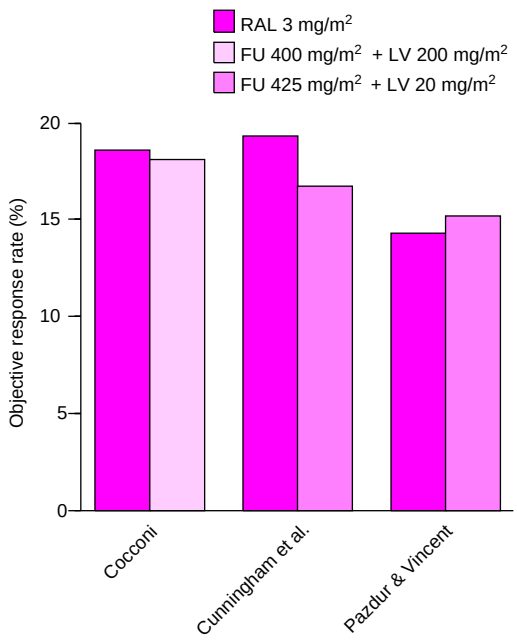

Fig. 3. Objective response rates in patients with advanced colorectal cancer. Comparison of raltitrexed (RAL) with fluorouracil (FU) plus leucovorin (LV) regimens in phase III clinical trials by Cocconi (n = 489),[24] Cunningham et al. (n = 434),[23] and Pazdur and Vincent (n = 417).[25] RAL was administered as a 15-minute intravenous infusion once every 3 weeks; FU plus LV were given as rapid intravenous injections once daily for 5 days, every 4 or 5 weeks.

The proportion of patients with stable disease was similar between treatment groups in all studies and ranged from 33.2 to 51.4% in raltitrexed recipients compared with 32.4 to 52.4% in those receiving fluorouracil plus leucovorin.[28]

The median time to disease progression was 3.1 to 4.8 months in raltitrexed recipients and 3.6 to 5.3 months in patients receiving fluorouracil plus leucovorin.[23-25,28] Patients who died without documented disease progression were classified as having progressive disease. Two studies reported that the time to disease progression was greater in fluorouracil plus leucovorin than in raltitrexed recipients;[24,25,28] however, these results may have been influenced by study design. In 1 trial, patients receiving raltitrexed were assessed significantly earlier than those receiving fluorouracil plus leucovorin.[24,28] In the other,[25,28] the duration of treatment with fluorouracil plus leucovorin was almost twice that of raltitrexed; problems with toxicity in the raltitrexed 4 mg/m^2 treatment arm (subsequently closed) may have led investigators to adopt a lower relative threshold for discontinuation of raltitrexed therapy in the lower dose arm.[28]

3.2 Survival

Median survival duration in phase III studies was 9.7 to 10.9 months for patients treated with raltitrexed and 10.2 to 12.7 months for those given fluorouracil plus leucovorin (table I).[23-25,30] In 2 studies, survival duration did not differ significantly between treatments.[23,24] However, 1 trial found that survival in recipients of fluorouracil plus leucovorin was significantly longer (12.7 months) than in recipients of raltitrexed (9.7 months).[25] The problems in study design that are discussed in section 3.1 may have also influenced this result.[28]

3.3 Palliation of Symptoms

In general, the palliative benefits of treatment with raltitrexed were similar to those with fluorouracil plus leucovorin in the 3 phase III studies.[28] Gains in bodyweight of ≥5% were observed in 13 to 21.1% of raltitrexed recipients compared with 15.7 to 27.4% of patients receiving fluorouracil plus leucovorin. Improvement in WHO performance status scores was seen in 36.4 to 39.1% of raltitrexed-treated patients and in 29.7 to 40.8% of patients receiving fluorouracil plus leucovorin. In addition, in one study,[24] more than 80% of patients with disease-related symptoms at the time of study entry reported improvement in symptoms after treatment with either raltitrexed or fluorouracil plus leucovorin.[28]

4. Pharmacoeconomic Considerations

Cost-minimisation analyses of raltitrexed therapy indicate that the increased acquisition cost of the drug compared with fluorouracil plus leucovo-

rin is at least partially offset by treatment-linked savings.

In a retrospective audit of patient notes at the Royal Marsden Hospital, England, the mean monthly costs (which included chemotherapy, concomitant medication, intravenous fluids, laboratory tests, consumables, inpatient and outpatient stays, operations and a telephone helpline for patients with infusion pumps) of treating advanced colorectal cancer patients with raltitrexed were similar to or less than those of various fluorouracil-based regimens.[32] Costs for each regimen (1994/1995 pounds sterling) were as follows:

- raltitrexed 3 mg/m^2, 15-minute intravenous infusion every 3 weeks = £1117.85;
- fluorouracil 425 mg/m^2 plus leucovorin 20 mg/m^2, rapid intravenous injections once daily for 5 days every 28 days = £954.03;
- fluorouracil 300 mg/m^2 per day, continuously via an ambulatory pump = £1207.61;
- fluorouracil 400 mg/m^2 bolus injection plus leucovorin 200 mg/m^2 2-hour infusion, followed by 22-hour infusion of fluorouracil 400 mg/m^2, for 2 days at 14-day intervals = £2028.52.

It should be noted, however, that some major cost drivers, which would increase costs associated with intermittent fluorouracil administration (nursing time to set up infusions and pharmacy charges), were not considered in the analysis because of the absence of data. When costs were divided into their different components, although monthly drug aquisition costs were higher for the raltitrexed 3 mg/m^2 regimen (£456.52) than the intermittent fluorouracil 425 mg/m^2 plus leucovorin 20 mg/m^2 regimen (£74.16), this was partially offset by lower outpatient costs (£137.51 compared with £329.96). The combined in- and outpatient costs of raltitrexed were lower than those for any of the other regimens.

A separate study found significantly lower pharmacy charges for raltitrexed (£12.50, 1996 pounds sterling) than for several fluorouracil-based regimens (intermittent regimens £75.00, continuous infusion £94.00).[33,34] Raltitrexed was significantly quicker and less costly to prepare than the other regimens. Disposable cost was £0.62 for raltitrexed and £4.58 to £30.46 with the other regimens. Time cost was £2.87 for raltitrexed and £5.24 to £13.16 with the other regimens.

A further study assessed the drug costs associated with management of chemotherapy-related toxicity.[35] Data for this analysis were derived from 62 patients who were recruited into the phase III trial by Cunningham et al.[36] The mean total drug cost for toxicity management was approximately 50% lower with raltitrexed (£64, 1995/1996 pounds sterling) than with the fluorouracil regimen (£139), with the costs of managing infection, nausea and vomiting, pain, abdominal pain and mucositis all being lower in the raltitrexed group.

5. Tolerability

Tolerability data are available from more than 800 patients with advanced colorectal cancer who received raltitrexed and more than 650 patients who received fluorouracil plus leucovorin in phase II and phase III clinical trials (fig. 4).[23,29] In general, these data are consistent with findings in phase I studies which indicated that the dose-limiting toxicities of raltitrexed were gastrointestinal, haematological (myelosuppression) and asthenia.[19]

Overall, the incidence of WHO grade 3 or 4 diarrhoea in raltitrexed recipients (10 to 14%) in clinical trials was similar to that in patients receiving fluorouracil plus leucovorin (13 to 19%).[29] Grade 3 or 4 nausea or vomiting occurred in 9 to 13% of raltitrexed recipients and in 8 to 9% of fluorouracil plus leucovorin recipients.[29] However, the incidence of grade 3 or 4 mucositis was much lower with raltitrexed (2 to 3%) than with fluorouracil plus leucovorin (10 to 22%).[29] The incidence of severe asthenia ranged from 6 to 18% with raltitrexed treatment and 2 to 10% with fluorouracil plus leucovorin.[29]

The incidence of grade 3 or 4 leucopenia seen with raltitrexed (6 to 18%) was less than half that with fluorouracil plus leucovorin (13 to 41%) in

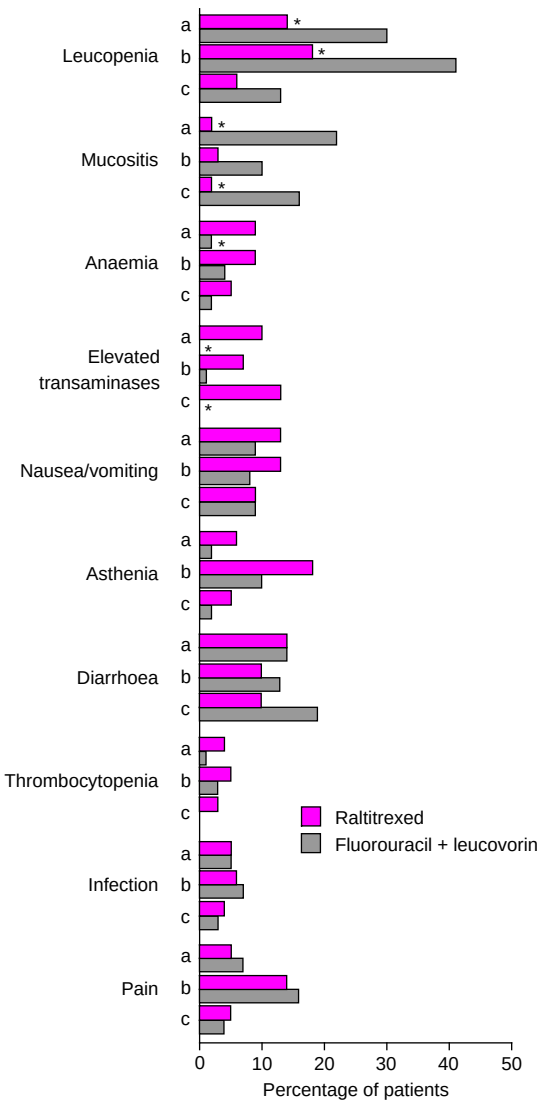

Fig. 4. Tolerability of raltitrexed 3 mg/m^2 in patients with advanced colorectal cancer. Adverse events of WHO grade 3 or 4 severity (except asthenia, which was severe but not WHO graded) occurring irrespective of causality in ≥5% of patients in phase III clinical trials by Cunningham et al. (a) [n = 434],[23] Pazdur & Vincent (b) [n = 417][25,29] and Cocconi (c) [n = 489].[24,29] Raltitrexed was given as a 15-minute intravenous infusion once every 3 weeks and fluorouracil 425 mg/m^2 plus leucovorin 20 mg/m^2[23,25]or fluorouracil 400 mg/m^2 plus leucovorin 200 mg/m^2[24]were given as rapid intravenous injections once daily for 5 days, every 4 or 5 weeks. * Statistically significant *vs* comparator using Holm's adjusted significance level.

comparative trials, although the incidence of infection did not differ between treatments.[29] While there was a slightly greater incidence of thrombocytopenia in patients receiving raltitrexed (3 to 5%) than in those receiving fluorouracil plus leucovorin (0 to 3%), the incidence of severe haemorrhage was similar in each treatment group.[29] Anaemia occurred in more raltitrexed (5 to 9%) than fluorouracil plus leucovorin recipients (2 to 4%).[29]

Elevation of liver transaminases was more common with raltitrexed treatment than with fluorouracil plus leucovorin in comparative trials. Grade 3 or 4 transaminase elevations were observed in 7 to 13% of patients receiving raltitrexed compared with 0 to 1% of those receiving fluorouracil plus leucovorin.[29] However, these elevations tended to resolve with continued treatment, patients remained asymptomatic, and there was no association with asthenia or disease progression. Consequently, they are unlikely to be clinically significant.

A similar incidence of death related to adverse events was found with raltitrexed and fluorouracil plus leucovorin regimens in phase III trials. There were 26 deaths in 684 recipients of raltitrexed during phase III studies that were considered related to treatment (3.8%). However, 17 of these deaths were in patients who did not receive appropriate dosage modifications following toxicity/impaired renal function during a previous cycle of raltitrexed.[29] 17 deaths occurred in 656 patients who received fluorouracil plus leucovorin in phase III trials that were considered related to treatment (2.6%).[29] Six of these deaths were in patients who did not receive appropriate dosage modifications. The majority of deaths in both treatment groups involved neutropenic sepsis and gastrointestinal toxicity.

More raltitrexed than fluorouracil plus leucovorin recipients were able to receive the planned dosage without the need for dose modification or delay because of toxicity (62 to 71% *vs* 32 to 53%).[29] The difference in the requirement for dose reduction between treatment groups was larger than the difference in inappropriate lack of

dose reductions between the 2 groups. Interestingly, most of the dosage modifications in the fluorouracil plus leucovorin group were made after the first treatment cycle (29 to 49% of patients). In contrast, only 5 to 7% of raltitrexed recipients required dosage modification after the first treatment cycle.

Quality-of-life assessments were conducted in all phase III trials. One study[24] found significant benefits in favour of raltitrexed in terms of physical symptoms, psychological condition, general activity, mobility and general quality of life during the first treatment cycle.[29] Of special note was the finding that toxicity-related symptoms were significantly worse in fluorouracil plus leucovorin recipients than in those receiving raltitrexed after the first treatment cycle (week 2; $p = 0.0001$) and over the treatment course (weeks 5 and 10; $p < 0.05$).[29] In the 2 other trials, little or no difference in quality of life was evident between treatment groups.[25,29,36] However, neither study involved assessments during the first few weeks of treatment and so any potential effects of early toxicity on quality of life could not be evaluated.[29]

6. Dosage and Administration

Patients with advanced colorectal cancer in phase II and III clinical trials received raltitrexed 3.0 mg/m^2, administered as a 15-minute intravenous infusion once every 3 weeks. This was established as the optimum dosage regimen in an earlier phase I study.[19]

Dosage reductions of 50% were made if grade 3 or 4 toxicity (especially combinations of myelosuppression and diarrhoea) occurred. If grade 3 or 4 toxicity occurred after a reduced dose, patients were withdrawn from therapy. Administration of raltitrexed could be delayed for up to 21 days until all toxicity had resolved.

It is recommended that the dose of raltitrexed be reduced by 50% and frequency of administration reduced to every 4 weeks in patients with mild to moderate renal impairment [creatinine clearance 1.5 to 3.9 L/h (25 to 65 ml/min)].[20] Raltitrexed should not be given to patients with creatinine clearance <1.5 L/h (25 ml/min).

7. Place of Raltitrexed in the Management of Advanced Colorectal Cancer

Colorectal cancer is one of the most common cancers in the Western world, and mortality from this disease ranks third only behind lung and breast cancer in women, and lung and prostate cancer in men.[37] Each year in the US and Europe, more than 300 000 new cases are diagnosed and over 150 000 patients die of the disease.[38,39] Accordingly, the impact of this disease on the health system and on society in general is substantial.

Radical surgery of the primary tumour remains the only potential cure for colorectal cancer, with success depending largely on the tumour stage. For stage I disease (Duke's stages A and B-1; invasion to the muscularis propria without nodal involvement) there is ≈90% probability of a cure. This is reduced to about 70% for stage II disease (Duke's stage B-2; invasion into or through the serosa or non-peritonealised pericolic tissue without nodal involvement) and about 35% for stage III disease (Duke's stage C; metastases to regional lymph nodes).[40] It is generally accepted that patients with Duke's stage C colon cancer benefit from adjuvant fluorouracil-based chemotherapy,[41] and this is now considered standard practice in many countries. In addition, adjuvant radiotherapy has a role in the treatment of rectal cancer,[41] although this has yet to be clearly defined.

Overall, approximately 50% of all patients with colorectal cancer eventually develop advanced disease, and chemotherapy and supportive care are the mainstay of treatment for this group.

Over the past 35 years, fluorouracil has been the most consistently used chemotherapeutic agent for the treatment of advanced colorectal cancer. However, response rates with bolus fluorouracil monotherapy are typically in the order of 10 to 15%[42] and survival duration is about 10 months.[43] Efforts have been made to improve the efficacy of fluorouracil by modifying the administration

schedule and by combining the drug with other antineoplastic or biochemical modulating agents. Some of these measures have led to improved overall tumour response but further gains in survival have been modest. In addition, fluorouracil treatment is associated with a moderately high incidence of leucopenia and mucositis, and most fluorouracil-based administration schedules are complex, requiring prolonged or frequent hospital visits. Fluorouracil has a complex mechanism of action, with both thymidylate synthase inhibition and RNA-directed effects contributing to antitumour activity and toxicity.[8]

It is against this background that raltitrexed, a cytotoxic agent with a greater specificity for the inhibition of thymidylate synthase than fluorouracil, was developed. Phase II and III clinical trials of this drug in patients with advanced colorectal cancer reported objective response rates ranging between 14 and 26% with a median survival duration of 9.7 to 11.2 months. These values show that the antitumour efficacy of raltitrexed is similar to that of fluorouracil plus leucovorin.

However, additional factors to be considered when evaluating a new chemotherapeutic agent that is essentially palliative are its tolerability profile and ease of administration, as both contribute directly to patient quality of life. In these respects, raltitrexed represents an advance over fluorouracil-based regimens. Raltitrexed is associated with a markedly lower incidence of mucositis and leucopenia than fluorouracil plus leucovorin although some less common adverse events (e.g. asthenia, anaemia) were seen in a greater number of raltitrexed than fluorouracil plus leucovorin recipients. Importantly, raltitrexed has a simple administration schedule comprising a single short infusion once every 3 weeks. This should provide greater patient convenience than fluorouracil-based regimens which commonly involve treatment administration on 5 consecutive days every 4 weeks. The simple raltitrexed administration schedule should also produce savings in nursing, pharmacy and medical time, which will at least partially offset the increased acquisition cost compared with fluorouracil-based regimens.

Although raltitrexed is currently approved only for use as a single agent in advanced colorectal cancer, clinical trials investigating its use in combination with fluorouracil, irinotecan or oxaliplatin are under way.[44] In addition, its potential role as an adjuvant treatment in colon cancer, and as a component of combined adjuvant chemo- and radiotherapy in rectal cancer, is being evaluated.[44]

In conclusion, raltitrexed offers similar efficacy to fluorouracil-based regimens in the palliation of advanced colorectal cancer with a favourable tolerability profile and simple administration schedule. It therefore represents a worthwhile advance in the management of this disease and provides oncologists with a convenient alternative to fluorouracil-based regimens.

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