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Review

Efficacy, tolerability and management of raltitrexed (Tomudex™) monotherapy in patients with advanced colorectal cancer: a review of phase II/III trials

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Abstract

Raltitrexed (Tomudex™), a thymidylate synthase inhibitor, is an alternative to 5-fluorouracil (5-FU)/leucovorin (LV) for the first-line treatment of advanced colorectal cancer. Following the completion of four phase III studies with raltitrexed at the recommended dose of 3.0 mg/m^2, it is opportune to review the efficacy and tolerability data of raltitrexed and suggest guidelines for appropriate patient management. Data are analysed from four phase III and five phase II studies including over 1300 patients with advanced colorectal cancer, some of whom were elderly or received higher doses of raltitrexed. Median survival with raltitrexed was comparable to that of bolus or infusional 5-FU/LV in three of the four randomised studies and objective response rates in the four trials were similar for the two agents. Response rates were at least comparable in elderly patients in phase II studies. For the majority of patients, treatment with raltitrexed was well tolerated even at doses higher than that recommended or in the elderly. As with other cytotoxic agents, serious and potentially life-threatening side-effects can occur; nevertheless, adherence to simple patient guidelines should minimise the incidence of serious side-effects with raltitrexed; these include the assessment of renal function before each and every treatment, dosage adjustment in the presence of renal impairment and close monitoring with prompt treatment of toxicities, particularly diarrhoea and neutropenia.

Keywords: Raltitrexed; Tolerability; Creatinine clearance; Toxicity

1. Introduction

Raltitrexed (Tomudex™) is approved as monotherapy, at a dose of 3.0 mg/m^2 every 3 weeks, for the first-line treatment of advanced colorectal cancer (CRC) in over 40 countries worldwide. Like 5-fluorouracil (5-FU), raltitrexed is an inhibitor of thymidylate synthase (TS). However, 5-FU and raltitrexed inhibit TS via different mechanisms and with different specificities and binding sites on the enzyme. The different pharmacokinetic and pharmacodynamic properties of raltitrexed and 5-FU lead to distinct tolerability profiles.

Raltitrexed gives prolonged TS inhibition due to the rapid formation of polyglutamates and its subsequent retention within cells, enabling it to be administered in a convenient 3-week dosing schedule [1]. Accordingly, the mean terminal half-life of raltitrexed in patients with

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advanced solid tumours is 168 h (approximately 7 days) [2,3]. Raltitrexed is excreted essentially unchanged by the kidneys (40–50%) [3]; hence, its elimination has been investigated in patients with renal impairment. A study of 16 cancer patients showed that the terminal half-life of raltitrexed was statistically significantly longer in patients with mild-to-moderate renal impairment (0.42–1.08 ml/s) compared with those with normal renal function (>108 ml/s) (11.4 days versus 5.8 days, respectively, $P=0.03$) [2]. In comparison, 5-FU is rapidly eliminated, predominantly via catabolism in the liver [4]. During the first 24 h following intravenous (i.v.) administration, 90% of the 5-FU dose is excreted; it is, therefore, administered more regularly, generally on successive days or as a continuous infusion for maximum effect.

Raltitrexed has now been extensively evaluated in clinical trials involving patients with advanced CRC. The aim of this paper was to review the efficacy and tolerability data from nine phase II/III studies, involving over 1300 patients with advanced CRC who were treated with raltitrexed, and discuss implications for effective patient management.

2. Phase II/III trials of raltitrexed monotherapy in patients with advanced colorectal cancer

The recommended dose of raltitrexed (3.0 mg/m^2) was initially identified in a European phase I study [5]. Subsequently, a multinational phase II study (study 2) was conducted during 1992–1993 in patients with advanced CRC [6] (Table 1). Three randomised, open phase III studies, conducted between 1993 and 1996, compared raltitrexed (3.0 mg/m^2) with two regimens of bolus 5-FU plus leucovorin (LV): the Mayo regimen (5-FU 425 mg/m^2 i.v. bolus + LV 20 mg/m^2) in study 3 [7] and study 10 [8] and the Machover regimen (5-FU 400 mg/m^2 i.v. bolus + LV 200 mg/m^2) in study 12 [9]. As a phase I trial conducted in the USA had reported a maximum tolerated dose of 4.5 mg/m^2, suggesting a phase II dose of 4.0 mg/m^2 [10], study 10 also included a third arm, with raltitrexed at a dose of 4.0 mg/m^2. A further, recently completed phase III study (the Molecular Research Council (MRC) CR06 study), conducted in the United Kingdom, has compared raltitrexed (3.0 mg/m^2) with two infusional 5-FU regimens (de Gramont (5-FU 400 mg/m^2 iv bolus, 5-FU 600 mg/m^2 22-h infusion, LV 200 mg/m^2) and Lokich (5-FU 300 mg/m^2/day prolonged venous infusion (PVI)) in patients with advanced CRC [11]. The baseline characteristics of patients in the phase II and III studies were comparable with the exception of performance status; in studies 2, 3, 10 and 12 between 5 and 12% of patients had a performance status of 2 at entry compared with 22% in the MRC study.

Other clinical studies have investigated the use of raltitrexed at doses higher than the recommended dose of 3.0 mg/m^2. The 4.0 mg/m^2 arm of study 10 was closed early, because three treatment-related deaths were reported; however, two phase II studies have since been conducted in Canada and the USA with doses of raltitrexed >3.0 mg/m^2. The Canadian study used raltitrexed 3.5 mg/m^2 as first- or second-line therapy in patients who had not received prior treatment for metastatic disease [12] and the US study used raltitrexed 4.0 mg/m^2 as second- or third-line therapy for metastatic CRC [13]. Two further phase II studies, one in France [14] and one in Spain [15] have assessed the efficacy and tolerability of raltitrexed (3.0 mg/m^2) in elderly patients ($\geqslant$70 years).

3. Efficacy of raltitrexed monotherapy in patients with advanced colorectal cancer

In three of the four large, randomised phase III studies, median survival with raltitrexed (range 9.7–10.9 months), was comparable to that of the 5-FU/LV regimens (bolus or infusion) (Table 2). This range is also consistent with the values for median survival reported in the literature for standard 5-FU/LV regimens [16]. Median time to progression in studies 3, 10 and 12 ranged between 3.1 and 4.8 months for patients treated with raltitrexed and between 3.6 and 5.3 months for those treated with bolus 5-FU/LV; the difference between the treatment groups was not significant for study 3, but was significantly shorter for the raltitrexed-treated patients in studies 10 and 12. In the MRC CR06 study, progression-free survival (which includes patients who died without tumour progression) was reported rather than time to progression, although this was not a protocol-directed endpoint. Furthermore, the response rate was only a subsidiary endpoint of the MRC CR06 study and the measurement of responses did not use a standardised radiological technique or undergo external review. Nevertheless, there was no statistically significant difference between the median progression-free survival for the de Gramont and raltitrexed-treated patients (5.8 versus 4.8 months, $P=0.057$). Objective response rates with raltitrexed were similar to those of the 5-FU/LV regimens (bolus or infusion) in all four studies (Table 3).

Surprisingly, the response rate of 8% (95% Confidence Interval (CI): 0.9–15.1%) in the Canadian high-dose study (3.5 mg/m^2) was lower than response rates observed with standard raltitrexed treatment (3.0 mg/m^2) in the initial multinational phase II and subsequent phase III trials (14–19%). The efficacy results of the US high-dose study are under evaluation. Nevertheless, high response rates (complete or partial responses) were determined in elderly patients; 29% in the French study

Table 1
Methodology and patient characteristics

Study (Phase)	2 (II)	3 (III)	10 (III)	12 (III)	MRC CR06 (III)	High dose		Elderly	
						Canadian (II) (3.5 mg/m^2)	US (II) (4.0 mg/m^2)	French (II)	Spanish (II)
Total no. patients	177	439	378	452	905	56	60	51	98
No. patients given (randomised to) raltitrexed[a]	177	222 (223)	217 (217)	245 (247)	296 (301)	56	60	51	98
Comparator[b]	None	Mayo regimen	Mayo regimen	Machover regimen	de Gramont or Lokich regimen	None	None	None	None
Median age (range) (years)	61[c] (30–81)	61[c] (27–82)	61[c] (26–87)	60 (23–79)	63 (32–84)	64 (34–82)	68 (48–79)	75 (70–89)	75[c] (70–86)
Median no. raltitrexed cycles (range)	4 (1–18)	5 (1–25)	4 (1–21)	4 (1–19)	4 (1–18)	na	5 (1–10)	3 (1–20)	4 (1–13)
Median duration of therapy (range) (days)	na	106 (21–602)	85 (21–462)	89 (21–406)	84 (21–381)	na	89 (1–279)	na	na
No. participating countries	8	14	1	18	1	1	1	1	1
Prior chemotherapy for advanced disease	None[d]	None[d]	None[d]	None[d]	None[d]	None	Modulated 5-FU (30 patients) Failed 5-FU followed by irinotecan (30 patients)	None (Adjuvant chemotherapy (8 patients))	None

na, not available; MRC, Molecular Research Council.

[a] Raltitrexed administered as a 15-min infusion every 3 weeks.

[b] Mayo regimen: 5-FU 425 mg/m^2 intravenous (i.v.) bolus + leucovorin (LV) 20 mg/m^2; Machover regimen: 5-FU 400 mg/m^2 i.v. bolus + LV 200 mg/m^2; de Gramont regimen: 5-FU 400 mg/m^2 i.v. bolus, 5-FU 600 mg/m^2 22-h infusion, LV 200 mg/m^2; Lokich regimen: 5-FU 300 mg/m^2/day prolonged venous infusion (PVI).

[c] Mean age.

[d] Any adjuvant therapy stopped >6 months prior to study.

Table 2
Phase II/III studies—median survival

Study	Treatment (regimen)	Median survival (months)	Deaths during follow-up (%)	Hazard ratio (95% CI)	*P* value
2	Raltitrexed	11.2	47	–	–
3	Raltitrexed	10.1	89	1.09 (0.89–1.33)	0.42
	(Mayo)	10.2	85		
10	Raltitrexed	9.7	75	1.35 (1.07–1.71)	0.01
	(Mayo)	12.7	65		
12	Raltitrexed	10.9	75	1.15 (0.93–1.42)	0.20
	(Machover)	12.3	69		
CRO6[a]	Raltitrexed				
		8.7	50	0.99 (0.79–1.25)[a]	0.94[a]
	(de Gramont)	9.7	39		
	(Lokich)	9.9	32		
Canadian	Raltitrexed	na	na	–	–
US	Raltitrexed	na	na	–	–
French	Raltitrexed	na	na	–	–
Spanish	Raltitrexed	9.5	na	–	–

95% CI, 95% Confidence Interval; na, not available.
[a] Raltitrexed versus de Gramont.

and 24% in the Spanish study. The median overall survival in the Spanish study of elderly patients was 41 weeks (9.5 months).

4. Tolerability of raltitrexed monotherapy in patients with advanced colorectal cancer

4.1. Adverse events

The underlying features of raltitrexed toxicity are now well understood from these trials and the major dose-limiting toxicities are asthenia, gastrointestinal or haematological (myelosuppression) in nature [5–10,17].

4.2. Gastrointestinal toxicity

During phase II and phase III trials, using the recommended dose (3.0 mg/m^2), the incidence of grade 3/4 diarrhoea and grade 3/4 nausea/vomiting ranged from 10 to 14% and 9 to 13%, respectively (nausea and vomiting were reported separately in the MRC CR06 study) (Table 4). Similar incidences of grade 3/4 diarrhoea (13 to 19%) and grade 3/4 nausea/vomiting

Table 3
Phase II/III studies—objective responses[d]

Study	Treatment (regimen)	Minimum follow-up (months)	CR + PR (%)	Odds ratio (95% CI)	*P* value
2	Raltitrexed	11[a]	26	–	–
3	Raltitrexed	26	19	1.20 (0.73–1.97)	0.48
	(Mayo)		17		
10	Raltitrexed	12	14	0.86 (0.50–1.49)	0.60
	(Mayo)		15		
12	Raltitrexed	9	19	1.03 (0.65–1.63)	0.90
	(Machover)		18		
CRO6[b]	Raltitrexed	12 weeks	18	na	0.20[c]
	(de Gramont)		23		
	(Lokich)		25		
Canadian	Raltitrexed	na	8	–	–
US	Raltitrexed	na	na	–	–
French	Raltitrexed	na	29	–	–
Spanish	Raltitrexed	na	24	–	–

95% CI, 95% Confidence Interval; CR, Complete Response; PR, Partial Response; na, not available.
[a] Median.
[b] No external review.
[c] Raltitrexed versus de Gramont.
[d] Efficacy results under evaluation.

Table 4
Incidence of Grade 3/4 events that occurred in ⩾5% of patients treated with raltitrexed in large phase II/III trials

	Patients with adverse event (%)								
Study:	2	3	10	12	CR06[a]	High dose Canadian (3.5 mg/m^2)	US (4.0 mg/m^2)	Elderly French	Spanish
	($n=177$)	($n=222$)	($n=217$)	($n=245$)	($n=301$)[b]	($n=56$)	($n=54$)	($n=51$)	($n=90$)
Leucopenia	15	14	18	6	5	5	20	4	na
Neutropenia	na	na	na	na	8	13	67	2	2
Thrombocytopenia	1	4	5	3	3	na	6	2	na
Anaemia	2	9	9	5	3	na	11	12	2
Infection	0	5	6	4	na	na	7	10	na
Increase in transaminases	10	10	7	13	na	na	0	24	6
Nausea/vomiting	11	13	13	9	10 (nausea) 8 (vomiting)	9 (nausea) 5 (vomiting)	11	14	7
Severe asthenia/lethargy	12	6	18	5	19	13	2	20	1
Diarrhoea	10	14	10	10	12	na	6	10	3
Pain	0	5	14	5	na	na	11	na	na

na, not available.

[a] Anorexia was also reported by 11% of patients treated with raltitrexed in the Molecular Research Council (MRC) CR06 study, but was not reported in any of the other studies.

[b] Based on between 267 and 275 patients with data available, grade 3/4 toxicity at 6 or 12 weeks as reported by clinicians.

(8–9%) occurred in patients receiving bolus 5-FU/LV in studies 3, 10 and 12. The incidences of nausea and diarrhoea were statistically significantly higher following raltitrexed treatment compared with the de Gramont infusional 5-FU/LV regimen in the MRC CR06 study (10% versus 3% and 12% versus 3%, respectively, $P<0.01$ for both). Grade 3/4 mucositis was observed in ⩽3% of patients receiving raltitrexed in comparison with 10–22% of patients receiving bolus 5-FU regimens; this difference was statistically significant ($P<0.001$) in studies 3 and 12.

Neither raltitrexed doses of 3.5 or 4.0 mg/m^2 nor increased patient age appear to be associated with an elevated risk of grade 3/4 diarrhoea or nausea/vomiting in the phase II studies. Similarly, in study 3 there were no statistically significant differences in the incidence of grade 3/4 diarrhoea and nausea/vomiting between patients aged <60 years, 60–69 years or those ⩾70 years [18].

4.3. Haematological toxicity

Grade 3/4 leucopenia was reported by 14–18% of patients in studies 2, 3 and 10, although lower incidences were reported in the MRC CR06 and study 12 (5 and 6%, respectively). Similarly, varying incidences of leucopenia were reported in the studies using higher doses of raltitrexed, 5 and 20%, in the Canadian and US studies, respectively. The incidence of leucopenia was not reported for the Spanish study in elderly patients and did not appear to be affected by age in the French study, as it was only reported for 4% of the elderly patients in this trial. The incidence of severe leucopenia was lower with raltitrexed treatment than with bolus 5-FU/LV in studies 3, 10 and 12, with statistical significance in studies 3 and 10 ($P<0.001$). Although the incidence of severe neutropenia was statistically significantly lower following de Gramont infusional 5-FU/LV compared with raltitrexed in the MRC CR06 study (8% versus 3%, $P<0.01$), as expected for infusional 5-FU regimens.

Grade 3/4 thrombocytopenia and grade 3/4 anaemia were reported by 1–6% and 2–9% of patients, respectively, in the phase II/III studies, with no obvious differences for elderly patients or those receiving a higher dose of raltitrexed. Although the incidence of thrombocytopenia reported with raltitrexed treatment was only 3% in the MRC CR06 study, this was statistically significantly higher than with the de Gramont infusional 5-FU/LV regimen (0%, $P<0.01$). The incidence of severe anaemia was statistically significantly higher with raltitrexed treatment compared with bolus 5-FU/LV in study 3 only.

Although the incidence of infection did not appear to be affected by age or increasing dose in the phase II studies reported herein, there was a statistically significant difference ($P=0.0018$ on univariate analysis) in the incidence of infection between different age groups in study 3: the incidences of grade 3/4 infection were 0, 6 and 14% in patients aged <60 years, 60–69 years and ⩾70 years, respectively [18].

4.4. Other adverse events

The most frequently occurring adverse events, other than gastrointestinal or haematological toxicities, included asthenia and transient elevation in hepatic transaminases (typically peaking at the third cycle of

treatment and reversible on continuing treatment with raltitrexed). The reported incidence of severe asthenia/lethargy with raltitrexed was relatively low (5–6%) in studies 3 and 12 [6,9] but higher in studies 2 and 10, the Canadian high-dose study and the MRC CR06 study (12–19%). The higher incidence of lethargy with raltitrexed compared with 5-FU/LV treatment was statistically significant in the MRC CR06 study only (19% versus 8%, $P<0.01$).

Grade 3/4 transient elevation of hepatic transaminases were reported in 6–13% of patients receiving raltitrexed treatment in studies 2, 3, 10 and 12 and in the Spanish study in elderly patients. A higher incidence of 24% (12 patients) was found, however, in elderly patients in the French study. No cases of elevated transaminase levels were reported in the US high-dose study. The occurrence of elevated transaminase levels was not collected in the MRC CR06 study. The incidence of grade 3/4 increases in hepatic transaminases was statistically significantly higher with raltitrexed than with 5-FU/LV treatment in studies 3 and 12, but such changes were usually asymptomatic and self-limiting when not associated with disease progression.

4.5. Adverse events leading to death

Between 2.3 and 6.0% of patients in the large phase II/III studies had treatment-related deaths with raltitrexed (Table 5). Of the 26 treatment-related deaths in studies 3, 10 and 12, 17 occurred in patients who had calculated creatinine clearance values at some stage during their treatment that should have led to dose reductions, according to prescribing recommendations. Similarly, in the MRC CR06 study, 11 of the 18 treatment-related deaths occurred in patients who had a protocol violation (4 patients) or who had a predisposing factor indicating that caution was necessary (7 patients), such as prior pelvic radiotherapy, hydronephrosis or deteriorating performance status. Although the protocol for the MRC CR06 study specified the routine assessment of creatinine clearance prior to each administration of raltitrexed, creatinine levels were not documented routinely. One patient (2.0%) in the French study had a treatment-related death, the cause of which was unknown and three patients (3.1%) had treatment-related deaths in the Spanish study of elderly patients due to infection and/or gastrointestinal adverse events. Overall, the incidence of treatment-related deaths in the four phase III studies in patients who were treated with raltitrexed according to the protocol and who did not have predisposing factors to increased toxicity ranged between 0.6 and 2.0%.

The incidence of treatment-related deaths with raltitrexed is comparable with that following treatment with bolus 5-FU/LV: 6/212 patients (2.8%), 5/210 patients (2.4%) and 3/248 patients (1.2%) in studies 3, 10 and 12, respectively, had 5-FU-related deaths. When patients were excluded who did not have appropriate dose reductions or delays, or who were not treated according to the protocol, the overall raltitrexed-related death rate in studies 3, 10 and 12 were in line with those of bolus 5-FU/LV (1.3% versus 1.7%, respectively) [19]. There were three treatment-related deaths observed in the MRC CR06 study following administration of 5-FU/LV, one with the de Gramont regimen and two with the Lokich regimen.

No deaths have occurred in either of the phase II studies that used higher doses of raltitrexed. However, in the raltitrexed 4.0 mg/m^2 arm of study 10, three treatment-related deaths occurred after 31 patients had received this therapy: two were attributed to haematological adverse events and one to a combination of diarrhoea and thrombocytopenia. Consequently, the trial was temporarily closed, with permanent closure of the higher dose arm of the study, and further study entry and dose-reduction criteria were changed for patients with elevated creatinine concentrations. Patients with serum creatinine concentrations greater than the upper limit of normal were no longer considered eligible for the trial and all patients were required to have a normal creatinine concentration in order to receive a subsequent full dose of raltitrexed. For patients with abnormal serum creatinine concentrations, the creatinine clearance was calculated or performed and the subsequent dose of raltitrexed mod-

Table 5
Raltitrexed-related deaths in large phase II/III studies

Study:	2 ($n=177$)	3 ($n=222$)	10 ($n=217$)	12 ($n=245$)	CR06 ($n=301$)
All raltitrexed-related deaths (%)	4 (2.3)	9 (4.1)	9 (4.1)	8 (3.3)	18 (6.0)[a]
Deaths in patients with no appropriate dose reduction/protocol violations/caution was requested (%)	3 (1.7)	7 (3.2)	5 (2.3)	5 (2.0)	11 (3.7)
Deaths in patients who were treated according to the protocol and who did not have predisposing factors indicating that special caution was necessary (%)	1 (0.6)	2 (0.9)	4 (1.8)	3 (1.2)	7 (2.3)

[a] An additional patient died >30 days post-dosing.

Table 6
Dose modification based on creatinine clearance [20]

Creatinine clearance	Dose as % of 3.0 mg/m^2	Dosing interval
>1.08 ml/s	100	3-weekly
0.92–1.08 ml/s	75	4-weekly
0.42–0.90 ml/s	50	4-weekly
<0.42 ml/s	No treatment or stop treatment	

ified accordingly; these are now standard requirements for treatment with raltitrexed.

Across all the first three phase III studies, in both treatment groups, fatal adverse events that appeared to be causally related to study treatment were often due to a combination of diarrhoea complicated by neutropenia, as expected with cytotoxic agents of this class [19]. Similarly, 11 of the 18 patients with treatment-related deaths with raltitrexed in the MRC CR06 study presented with a combination of severe gastrointestinal and haematological toxicity.

5. Implications for patient management

Although raltitrexed provides a convenient first-line treatment option for patients with advanced colorectal cancer, patients and oncologists need to be aware of possible side-effects. As with all cytotoxics, careful patient management is necessary to prevent or reduce unacceptable toxicity. Although raltitrexed is administered as a convenient 3-weekly schedule, it is important for patients to be adequately monitored prior to and during treatment to ensure early detection and prompt management of toxicity. In addition, as approximately 50% of the dose of raltitrexed is excreted unchanged in the urine [2], it is essential that patients have evaluation of their renal function prior to and during their treatment with raltitrexed and that those with renal impairment have the dose of raltitrexed modified as shown in Table 6.

5.1. Recommendations for optimal patient management

The following recommendations, which are in line with treatment guidelines and raltitrexed prescribing information [20], should be followed:

1. Serum creatinine measurements should be performed prior to the initiation of treatment and before each subsequent treatment. For patients with abnormal serum creatinine before the first or any subsequent treatment, a creatinine clearance should be performed or calculated. Where serum creatinine may not correlate well with creatinine clearance due to factors such as age or weight loss, creatinine clearance should also be determined.

   The creatinine clearance may be calculated using the Cockcroft–Gault formula [21], which takes the gender, age and weight of the individual patient into consideration:

$$\text{Male patients: creatinine clearance} = \frac{88.4 \times (140 - \text{age}) \times \text{weight}}{72 \times \text{serum creatinine}}$$

$$\text{Female patients: creatinine clearance} = \frac{75.23 \times (140 - \text{age}) \times \text{weight}}{72 \times \text{serum creatinine}}$$

   where the units are: creatinine clearance, ml/min; age, years; weight (kg); serum creatinine, μmol/l.
2. In the presence of renal impairment, and particularly with creatinine clearances $\leqslant$1.08 ml/s, dose reductions and increases in the schedule from 3–4 weeks are necessary as shown in Table 6.
3. Full blood counts and liver function tests also need to be performed before each cycle of treatment. The use of raltitrexed in patients with pre-existing hepatic impairment is not recommended.
4. Based on the worst grade of gastrointestinal and/or haematological toxicity in the previous cycle, all subsequent doses of raltitrexed should be reduced in accordance with Table 7.

Table 7
Dose modification based on the worst grade of gastrointestinal and haematological toxicity in the previous cycle [20]

	Gastrointestinal toxicity[a]					
	WHO toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Haematological toxicity[b]	Grade 0	100	100	75	50	Stop treatment
	Grade 1	100	100	75	50	Stop treatment
	Grade 2	100	100	75	50	Stop treatment
	Grade 3	75	75	75	50	Stop treatment
	Grade 4	50	50	50	Stop treatment	Stop treatment

WHO, World Health Organization.
[a] Diarrhoea or mucositis.
[b] Leucopenia, neutropenia or thrombocytopenia.

5. Elderly patients should be monitored particularly closely for the development of gastrointestinal toxicity. Patients who develop signs of gastrointestinal toxicity should have their full blood counts monitored regularly for signs of haematological toxicity.
6. It has been suggested that LV could be used as a rescue agent for patients who present with severe antiproliferative toxicities following treatment with raltitrexed. *In vitro* and *in vivo* studies have indicated that LV would compete with raltitrexed for uptake into tissues and for polyglutamation, thus reducing its tissue concentration [22]. A similar dose has been recommended to that used for high-dose methotrexate (i.e. 25 mg/m^2 6-hourly, until symptoms resolve). Further use of raltitrexed in such patients is not recommended.

In addition, results reported at the American Society of Clinical Oncology (ASCO) meeting in 2000, suggest that the prophylactic use of the 5-HT$_3$ antagonist ondansetron reduces the severity of nausea and diarrhoea, preventing dehydration and use of the steroid dexamethasone reduces the incidence of fever and fatigue [23]. Prophylactic hydration may also be considered for patients who may be more susceptible to the cytotoxic effects of raltitrexed. Österlund and colleagues [24] also reported the use of metoclopramide or 5-HT$_3$ antagonists as antiemetics. Further anecdotal information indicates that some physicians use loperamide to manage diarrhoea.

6. Conclusions

Raltitrexed is an effective single agent for the first-line treatment of advanced CRC and may be used as an alternative to bolus or infusional 5-FU-based regimens. Data from phase III studies indicate that raltitrexed produces similar median survival times to that which can be achieved with standard 5-FU/LV regimens. In addition, its potential as combination therapy with a number of other agents is currently being evaluated. For the majority of patients, treatment with raltitrexed is manageable, but in a minority of cases it produces serious and potentially life-threatening side-effects, in particular diarrhoea and neutropenia. One of the most important indicators of this serious toxicity is renal function. For this reason, we recommend the routine measurement of serum creatinine levels prior to each and every study treatment and determination of creatinine clearance in any patient with an abnormal serum creatinine. Increasing experience with raltitrexed, further clinician and patient education, and the adoption of clear and straightforward patient guidelines for the use of raltitrexed, should minimise the incidence of serious side-effects.

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