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Overview of the tolerability of 'Tomudex' (raltitrexed): collective clinical experience in advanced colorectal cancer

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The tolerability of raltitrexed ('Tomudex', formerly ZD1694) was examined during phase I, II and III clinical studies involving around 1000 patients with advanced colorectal cancer. The dose-limiting toxicities in the phase I studies were gastrointestinal toxicity, haematological suppression and asthenia. Adverse events during phase II and III studies were consistent with those seen during phase I. In all comparative studies, mucositis and leucopenia were markedly less frequent and less severe in patients treated with raltitrexed than with 5-fluorouracil + leucovorin. Thrombocytopenia was more common with raltitrexed but was not associated with an increase in clinically significant haemorrhage. Elevated transaminases were frequently reported with raltitrexed but were usually reversible with continued dosing and were not associated with clinical sequelae. Patients treated with 5-fluorouracil + leucovorin experienced greater toxicity during early treatment cycles than those treated with raltitrexed. Fewer dosage reductions due to toxicity and greater quality-of-life benefits were observed in these early treatment cycles in patients treated with raltitrexed. Moreover, the incidence of fatal adverse events in patients given the recommended dose of raltitrexed was similar between groups. Raltitrexed thus provides some tolerability advantages compared with 5-fluorouracil + leucovorin, mainly with respect to leucopenia and mucositis, and less overall toxicity in early treatment cycles. The toxicity profile of raltitrexed is that expected of an antimetabolite.

Keywords: Advanced colorectal cancer, efficacy, 5-fluorouracil, raltitrexed, safety, tolerability, 'Tomudex'

Introduction

Colorectal cancer is a common disease and a major cause of cancer deaths [1,2]. Despite early diagnosis in some patients, the majority will develop advanced disease [3]. For those patients undergoing cytotoxic chemotherapy, 5-fluorouracil + leucovorin is the generally accepted standard therapy [4]. However, these regimens can cause considerable toxicity, in particular mucositis and leucopenia [5,6], necessitating dose reduction and/or delay in treatment, with resulting inconvenience to both patient and clinician [7].

Raltitrexed ('Tomudex', formerly ZD1694) is a specific inhibitor of thymidylate synthase, a critical enzyme in the *de novo* synthesis of DNA. Raltitrexed undergoes extensive polyglutamation within cancer cells, which prolongs intracellular retention times and increases affinity for thymidylate synthase, thus allowing a simple three-weekly dosing schedule [8,9]. Raltitrexed has been evaluated in an extensive clinical trial programme involving over 1000 patients with advanced colorectal cancer. This paper presents the safety, tolerability and, where assessed, quality-of-life results from the phase I, II and III studies. The efficacy results have been presented elsewhere [10–13], and are reviewed in this supplement [14].

Phase I, II and III studies

Phase I studies in Europe (61 patients, 16 with colorectal cancer) and in North America (50 patients, 38 with colorectal cancer) [10] indicated that the dose-limiting toxicities of raltitrexed were gastrointestinal, haematological (myelosuppression) and asthenia. These data are discussed in detail by Judson in this supplement [15].

The toxicity profile of raltitrexed was further characterized during a phase II study (study 2C) in patients with advanced colorectal cancer and was subsequently also compared with that of two different regimens of 5-fluorouracil + leucovorin (low-dose leucovorin, the Mayo regimen in studies 3 and 10, and high-dose leucovorin, the Machover regimen in study 12). Three randomized, open, parallel-group, phase III studies (Table 1) are discussed here. The patient population was similar in all four trials and typical of patients with advanced colorectal cancer.

An adverse event was defined as any detrimental change in the patient's condition, excluding progression of colorectal cancer, after the trial had started. During the trial, any such change was considered to be an adverse event in patients on active treatment irrespective of whether other factors may have contributed to the event, or whether or not the event was considered to be related to trial treatment. The end of the trial was set as 3 weeks following the last dose of raltitrexed and 4 weeks following the last dose of 5-fluorouracil + leucovorin. A serious

Table 1. Design of phase II and III studies

Study	2C	3		10		12	
Design	Phase II, open	Phase III, open		Phase III, open		Phase III, open	
Treatment	R	R	C	R	C	R	C
No. patients entered	177	223	216	217	210	247	248
No. patients treated	177	222	212	217	200	245	244
Median duration of treatment							
Cycles	4	5	3	4	4	4	4
Weeks	13	15.2	15.0	12.1	22.3	12.7	16.9
Minimum follow-up for safety (months)	18	15.5		12		9	
Comparator regimen	NA	5-FU + LV (L)		5-FU + LV (L)		5-FU + LV (H)	

R, raltitrexed; **C**, comparator drug; NA, not applicable. 5-FU + LV (L), 5-fluorouracil at 425 mg/m^2 per day + leucovorin at 20 mg/m^2 per day for 5 days every 4–5 weeks (Mayo regimen); 5-FU + LV (H), 5-fluorouracil at 400 mg/m^2 per day + leucovorin at 200 mg/m^2 per day for 5 days every 4 weeks (Machover regimen). For study 10, all analyses refer to the two-arm study of raltitrexed at 3 mg/m^2 versus low-dose 5-FU + LV.

Table 2. Grade 1–4 adverse events occurring in at least 2% of patients in phase III studies (irrespective of causality)

	Study 3		Study 10		Study 12	
	Raltitrexed (n=222) (%)	5-FU+LV (n=212) (%)	Raltitrexed (n=217) (%)	5-FU+LV (n=200) (%)	Raltitrexed (n=245) (%)	5-FU+LV (n=244) (%)
Leucopenia	23	36	25	50	14	23
Mucositis	24	62	26	72	17	66
Anaemia	18	11	19	11	15	7
Increased transaminases	22	5	17	3	24	2
Nausea/vomiting	61	54	78	70	58	57
Asthenia	40	26	74	67	40	31
Diarrhoea	36	56	43	65	40	59
Thrombocytopenia	5	2	6	4	6	2
Constipation	20	16	32	28	15	15
Infection	27	26	44	44	31	24
Fever	33	20	38	35	33	18
Pain	37	35	66	68	42	32
Haemorrhage	8	11	14	18	4	9
Peripheral oedema	14	4	24	18	10	3
Alopecia	5	15	6	27	7	17

5-FU + LV, 5-fluorouracil + leucovorin.

adverse event was defined as one that was fatal or life-threatening, caused or prolonged hospitalization, caused disability or incapacity, required medical intervention to prevent permanent damage, was a second primary cancer diagnosis, was a congenital abnormality, or resulted from an overdose.

The most frequent gastrointestinal events during the phase II study were nausea or vomiting (grade 3 or 4 in 11% of patients) and diarrhoea (grade 3 or 4 in 10%), and were usually grade 1 or 2 in severity [12,15]. Prophylactic anti-emetics were not required in this protocol. Grade 3 or 4 mucositis or mouth ulceration occurred in ≤2% of patients in this study. Leucopenia was common in the phase II study, the nadir generally occurring within 1 or 2 weeks of treatment, with recovery by the third week. Grade 3 or 4 leucopenia was less frequent (15%), but in a few patients was life-threatening or fatal, particularly in association with gastrointestinal toxicity. In two patients, grade 4 neutropenia was associated with fever or infection.

The most frequently occurring adverse events in the phase III studies in patients treated with raltitrexed or 5-fluorouracil + leucovorin (low or high dose) are shown in Table 2. The incidence of diarrhoea, leucopenia, mucositis, and alopecia was substantially higher in the 5-fluorouracil + leucovorin group than in the raltitrexed group in all three studies. Conversely, the incidence of increased transaminases, anaemia and peripheral oedema was substantially higher in the raltitrexed groups than in the comparator groups.

Gastrointestinal events

During the phase III studies there were no significant differences between the two treatment groups in the incidence of either grade 3 or 4 nausea or vomiting (9–13%

Table 3. Grade 3 or 4 adverse events occurring in at least 2% of patients in phase III studies (irrespective of causality)

	Study 3		Study 10		Study 12	
	Raltitrexed (n=222) (%)	5-FU + LV (n=212) (%)	Raltitrexed (n=217) (%)	5-FU + LV (n=200) (%)	Raltitrexed (n=245) (%)	5-FU + LV (n=244) (%)
Leucopenia	14*	30	18*	41	6	13
Mucositis	2*	22	3	10	2*	16
Anaemia	9	2*	9	4	5	2
Increased transaminases	10	0*	7	1	13	0*
Nausea/vomiting	13	9	13	8	9	9
Asthenia (severe)	6	2	18	10	5	2
Diarrhoea	14	14	10	13	10	19
Thrombocytopenia	4	1	5	3	3	0
Constipation	3	3	2	2	2	0
Infection	5	5	6	7	4	3
Fever	3	2	2	2	0	1
Pain	5	7	14	16	5	4
Haemorrhage	2	3	3	1	0	1

5-FU + LV, 5-fluorouracil + leucovorin. *Statistically significant using Holm's adjusted significance level.

raltitrexed, 8–9% 5-fluorouracil + leucovorin) or diarrhoea (10–14% raltitrexed, 13–19% 5-fluorouracil + leucovorin; Table 3). There were pronounced differences between the treatment groups, favouring raltitrexed, in the frequency of grade 3 or 4 mucositis (Table 3).

Haematological events

World Health Organization (WHO) grade 3 or 4 leucopenia was less common with raltitrexed than with 5-fluorouracil + leucovorin regimens (Table 3). In each phase III study the incidence of grade 3 or 4 leucopenia in the raltitrexed arm was at least 50% lower than in the comparator arm. This difference was statistically significant in studies 3 and 10. Grade 3 or 4 thrombocytopenia was more common with raltitrexed (3–5%) than 5-fluorouracil + leucovorin (0–3%) in all phase III studies. However, there was no difference in the incidence of severe haemorrhage between the treatments (raltitrexed 0–3%, 5-fluorouracil + leucovorin 1–3%).

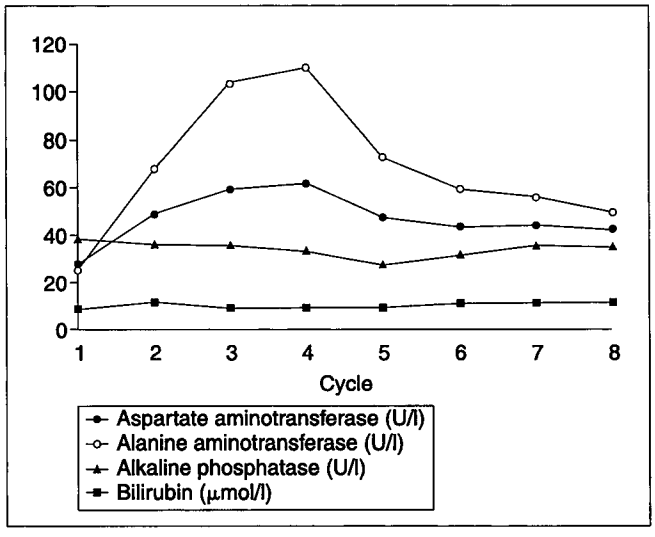

Fig. 1. Mean liver enzyme levels during raltitrexed by treatment cycle in study 3.

Liver transaminases

Transaminase elevations were common in patients receiving raltitrexed in all studies. Grade 3 or 4 transaminase elevations were infrequent in patients treated with 5-fluorouracil + leucovorin (0–1%) but were observed in 7–13% of patients randomized to raltitrexed. The difference between treatment groups was statistically significant in two of the three phase III studies (Table 3). Typically, in study 3, enzyme levels began to rise after the second course of raltitrexed, peaked in the third or fourth cycle and then declined with continued dosing (Fig. 1). However, patients remained asymptomatic, even during grade 3 or 4 events, and there was no association between these rises and the occurrence of asthenia or disease progression. Increases in alkaline phosphatase or bilirubin levels were rare and associated with disease progression. Similar transaminase rises were seen in rats dosed with raltitrexed during preclinical studies. Pathological examinations showed no evidence of liver abnormalities associated with elevated transaminases in rats. These rises were thought to be of no clinical significance.

Adverse events leading to death

The incidence of adverse events leading to death during treatment or follow-up in the phase III studies is presented in Table 4.

Table 4. Overview of adverse events leading to death in phase III studies

Adverse event leading to death	Phase III studies	
	Raltitrexed at 3 mg/m² (*n*=684)	5-FU + LV (LD + HD) (*n*=656)
During treatment	35 (5.1%)	29 (4.4%)
During follow-up	11 (1.6%)	4 (0.6%)
Causally related to treatment	26 (3.8%)	17 (2.6%)
No appropriate dose reduction	17 (2.5%)	6 (0.9%)
Treated to current recommendations	9 (1.3%)	11 (1.7%)

5-FU + LV (LD + HD), 5-fluorouracil + leucovorin (low dose and high dose combined). 'No appropriate dose reduction' refers to 13 patients whose doses were not modified following toxicity in a previous cycle, as specified in the protocol. A further four patients who had raised creatinine concentrations would also have received a reduced dose according to current recommendations.

Across all phase III studies, in both treatment groups, fatal adverse events that appeared to be causally related to trial therapy usually involved neutropenic sepsis and gastrointestinal toxicity, as expected with cytotoxic agents. Adverse event-related deaths occurred more often during the first treatment cycle with 5-fluorouracil + leucovorin than with raltitrexed, consistent with the relatively greater toxicity of 5-fluorouracil + leucovorin in early cycles. Forty-six of the patients given raltitrexed in the phase III studies suffered fatal adverse events (Table 4). Twenty-six of these deaths appeared to be associated with adverse events which were considered causally related to trial therapy, and 25 of these were combinations of haematological and gastrointestinal toxicities. Thirteen of these patients had not been given the modified doses recommended in the protocol, despite experiencing toxicity in the previous treatment cycle. Prompt management of diarrhoea and the resulting dehydration is essential. As experience with raltitrexed increases, the number of treatment-related deaths is expected to decrease. Raised creatinine levels were recorded for a further four patients who had not been given a reduced dosage according to current recommendations. Therefore, appropriate dosage modifications as currently recommended were not made in 17 of the 26 patients.

Of the 33 adverse event-related deaths among patients treated with 5-fluorouracil + leucovorin in the phase III studies, 17 patients suffered adverse events that were considered causally related to trial therapy. These patients had combinations of gastrointestinal toxicities (mucositis and/or diarrhoea), haematological suppression and infection or sepsis. Eleven of the 17 patients died during the first cycle of treatment and the remaining six died during cycles 2–4. Since most deaths occurred during the first cycle, they were not generally caused by lack of adherence to the protocol recommendations for dose modification following toxicity.

Dose modification

Overall, 30–38% of patients given raltitrexed and 47–69% of patients given 5-fluorouracil + leucovorin (low or high dose) required a dose modification because of toxicity (Table 5). Most dose modifications in the 5-fluorouracil + leucovorin group (31–48% of patients) were made following the first treatment cycle, in contrast to the raltitrexed group (5–7% of patients in the first cycle) in which modifications were made later (Table 5).

Dose modification was typically based on the worst WHO grade of selected haematological toxicity (leucopenia, neutropenia, thrombocytopenia) and non-haematological toxicity (mucositis, diarrhoea, rash) seen during the previous treatment cycle. The options available were to reduce the dose to 50% (raltitrexed) or 70% (5-fluorouracil + leucovorin), or to delay treatment for up to 21 days to allow resolution of toxicity, or to withdraw treatment permanently. Treatment was withheld in those patients who suffered WHO grade 3 or 4 mucositis, rash or diarrhoea at any time during the five days of administration of 5-fluorouracil + leucovorin. In addition, trial therapy was stopped for any patient who developed WHO grade 3 or 4 mucositis, rash or diarrhoea after receiving a reduced dose. In the absence of toxicity, or a previous dose reduction, the dose of 5-fluorouracil in a subsequent treatment course could be increased by 10%, on a

Table 5. Dose modification due to toxicity following the first treatment cycle and over the entire treatment course in all phase III studies

	Study 3		Study 10		Study 12	
	Raltitrexed	5-FU + LV	Raltitrexed	5-FU + LV	Raltitrexed	5-FU + LV
Dose reduction after first cycle (%)	5.3	32.6	7.0	48.0	5.3	31.3
No. patients in study after first cycle	209	175	202	181	228	217
Any dose modification/delay (%)	30.6	53.3	38.2	68.5	29.4	46.7

5-FU + LV, 5-fluorouracil + leucovorin.

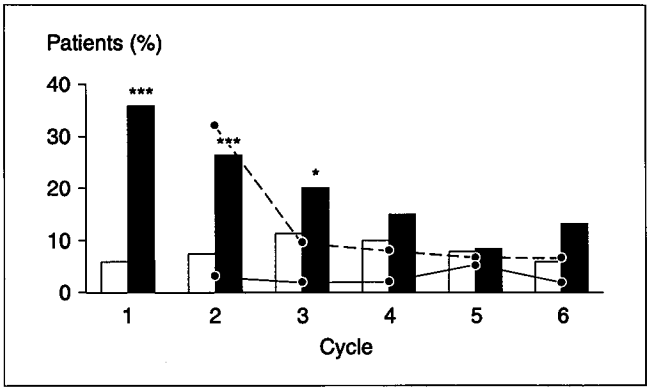

Fig. 2. Influence of treatment cycle on incidence of grade 3 or 4 haematological and non-haematological adverse events in study 3 (open bars, raltitrexed; closed bars, 5-fluorouracil + leucovorin) and corresponding dose modification (solid line, raltitrexed; broken line, 5-fluorouracil + leucovorin). $^{*}P = 0.036$, $^{***}P < 0.0001$.

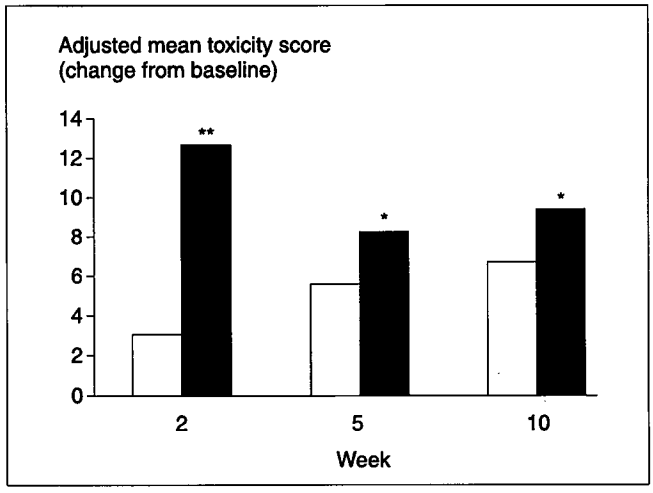

Fig. 3. Pre-defined toxicity-related symptoms in study 12. Bars represent changes from baseline in mean toxicity scores; open bars, raltitrexed; closed bars, 5-fluorouracil + leucovorin. $^{*}P < 0.05$, $^{**}P < 0.0001$.

maximum of two occasions. Escalation of the raltitrexed dose was not allowed.

In study 3, grade 3 or 4 haematological and non-haematological toxicity, and corresponding dose modifications, were assessed in each of the first six cycles of chemotherapy (Fig. 2). Haematological toxicity was based on haemoglobin, leucocytes, platelets and neutrophils, while non-haematological toxicity was based on WHO categories 'oral', 'diarrhoea' and 'cutaneous'. Toxicities were assigned to the current cycle of chemotherapy according to the date of onset of adverse events or date of laboratory samples, except that any toxicities occurring on the first day of a cycle were assigned to the previous cycle. Patients treated with 5-fluorouracil + leucovorin experienced greater toxicity during the first, second and third treatment cycles than those treated with raltitrexed.

Quality of life

Questionnaires from the European Organization for Research and Treatment of Cancer (EORTC) without the colorectal cancer add-on were used to assess quality of life in studies 3 and 10. Assessments were made after 0, 12 and 24 weeks in study 3, and after 0, 7 or 9, 12 and 24 weeks in study 10. Since no clear differences were seen between treatments, any potential effects of early toxicity on quality of life were not assessed in these studies.

In contrast, the two standard questionnaires used in study 12 showed highly significant benefits in quality of life across eight out of 12 dimensions in favour of raltitrexed during the first treatment cycle. Toxicity-related symptoms were significantly worse in patients treated with 5-fluorouracil + leucovorin than in those on raltitrexed after the first treatment cycle (week 2, Fig. 3; $P = 0.0001$) and over the treatment course (weeks 5 and 10; $P < 0.05$).

Discussion

These data show that the safety profile of raltitrexed is acceptable. As expected for a drug of this class, the major toxicities involved the haematological and gastrointestinal systems. However, these toxicities were usually mild-to-moderate and managed by conventional means. Raltitrexed showed advantages over 5-fluorouracil + leucovorin in both the incidence and severity of leucopenia and mucositis, and this was reflected in the greater proportion of patients continuing on the full dose of raltitrexed compared to the 5-fluorouracil + leucovorin group. Toxicity with 5-fluorouracil + leucovorin was seen particularly during early cycles in all studies; in study 12, where it was measured, this reflected significant quality-of-life benefits for raltitrexed during these early cycles.

Grade 3 or 4 transaminase increases were seen with raltitrexed, but were not associated with a clinically significant liver deterioration. As treatment was continued, the alanine aminotransferase in particular rose, but then fell to a normal level. In some cases this change in transaminases may have been mistaken for progression of the disease; only when the alkaline phosphatase rises as well should there be a high index of suspicion for disease progression. Otherwise these increases appeared to be of no clinical significance and resolved spontaneously with continued dosing.

The incidence of deaths related to adverse events in both treatment groups was similar throughout the phase III studies and was also comparable to the range reported for 5-fluorouracil + leucovorin in the literature [16]. In

patients suffering severe and life-threatening toxicity and/or a reduced creatinine clearance, it is important to adhere to guidelines for dosage reductions and delays in subsequent cycles. Prompt management of diarrhoea and the resulting dehydration is essential. Patients with a creatinine clearance of 25–65 ml/min should be given 50% of the recommended dose, once every 4 weeks, and those with a creatinine clearance of less than 25 ml/min should not be treated with raltitrexed.

The tolerability of raltitrexed compared with 5-fluorouracil + leucovorin in terms of mucositis and leucopenia has important implications for the management of patients with advanced colorectal cancer. A subgroup analysis of United Kingdom patients in study 3 showed that drug costs for managing side effects were halved in the raltitrexed group [17]. The convenient raltitrexed dosing schedule (a single 15-min infusion, once every 3 weeks), which minimizes the time spent in hospital for therapy, may confer further benefits in the use of health care resources.

Conclusions

As for any cytotoxic agent, management of side effects is a key issue, as the appropriate duration of antimetabolite therapy is vital to a successful outcome.

Raltitrexed provides some tolerability advantages, mainly with respect to a reduction in leucopenia and mucositis. Elevations in transaminases were reversible and self-limiting, and of no clinical significance. The toxicity profile of raltitrexed is that expected of an antimetabolite and will be further improved by strict adherence to dose reductions. Therefore, raltitrexed provides a convenient alternative to current 5-fluorouracil + leucovorin regimens, and, in addition, may offer a better quality of life early in treatment.

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