Anti-Cancer Drugs 1999, **10**, pp. 741–748

Clinical study

Phase II study of raltitrexed (Tomudex®) in chemotherapy-pretreated patients with advanced colorectal cancer

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Raltitrexed (Tomudex®), a novel folate-based inhibitor of thymidylate synthase, has demonstrated anti-tumour efficacy comparable with 5-fluorouracil and leucovorin in patients with advanced colorectal cancer (CRC). This phase II study was conducted to evaluate the anti-timor efficacy and tolerability of raltitrexed in patients with advanced CRC who had received one previous chemotherapy regimen. Raltitrexed was administered at a dose of 3.0 mg/m^2 i.v. over 15 min once every 3 weeks. Of 43 eligible patients, 53% had colon cancer and 47% rectal cancer. Objective responses were observed in 16% of patients [95% confidence interval (CI): 7–31%; seven partial responses). The median duration of response was 101 days (range: 45–239 days), the median overall duration of response was 145 days (range: 104–302 days) and the median survival was 11.6 months (95% CI: 9.4–14.7 months). Liver metastases showed a 17% (three of 18) response rate and lung metastases a 12% (three of 25) response rate. Adverse events of grade 3 or 4 reported for more than 5% of patients were neutropenia (23%), leukopenia (9%), reversible SGPT increase (7%) nausea/vomiting (19%), anorexia (14%), asthenia (9%) and hypotension (7%). Grade 3 or 4 diarrhea, stomatitis and alopecia were not observed. In summary, raltitrexed had an acceptable toxicity profile and promising anti-tumor activity against advanced CRC in patients who had received prior chemotherapy. Further clinical trials of combination chemotherapy using raltitrexed are warranted. [© 1999 Lippincott Williams & Wilkins.]

Supported by a research grant from Zeneca KK Pharmaceuticals, Japan.

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Key words: Chemotherapy, colorectal cancer, palliation, raltitrexed, thymidylate synthase inhibitor, Tomudex®, ZD1694.

Introduction

Colorectal cancer (CRC) is a common disease worldwide. In Japan, CRC is the third most common cause of death from cancer, after stomach and lung cancer.[1] The death rates for CRC in Japan are comparable with those of the US, at 16.1 and 9.8 deaths per 100 000 population for males and females, respectively.[1] Despite the continued search for improved treatments, the prognosis for patients with advanced CRC with current treatment options is poor.

5-Fluorouracil (5-FU) was introduced around 40 years ago, yet remains the mainstay of treatment for patients with advanced CRC. However, despite some advances, such as modulation with leucovorin (LV), only modest response rates and improvements in survival have been achieved with 5-FU regimens.[2] Such 5-FU regimens also involve relatively complex scheduling of drugs, requiring hospitalization or frequent clinic visits, and are associated with significant toxicity, predominantly diarrhea, stomatitis and myelosuppression. Therefore, the search continues for novel agents with improved efficacy, reduced toxicity and a more convenient administration schedule. One such novel agent, the topoisomerase I inhibitor irinotecan, has shown activity, especially as a second-line treatment for advanced CRC in a phase II study.[3] However, its association with leukopenia and gastro-

intestinal symptoms, especially diarrhea, has limited its use in Japan.

Raltitrexed (Tomudex®, ZD1694) is a quinazoline folate analog which, like 5-FU, acts by inhibiting thymidylate synthase (TS), a key enzyme in the *de novo* synthesis of thymidine triphosphate.[4] However, whereas 5-FU is non-specific and acts by competition of its metabolite with dUMP for the substrate-binding site of TS, raltitrexed inhibits TS specifically by competing with its tetrahydrofolate cofactor.[4,5] Raltitrexed gives more prolonged TS inhibition because, after rapid entry into the cell, it is extensively polyglutamated to forms that are more potent than the parent drug and are retained intracellularly.[6] Of note, raltitrexed and 5-FU are two pharmacologically distinct drugs that have an incompletely overlapping spectrum of anti-tumor activity in human tumor cell lines.[7,8]

The clinical development of raltitrexed began in 1991, and its efficacy and toxicity profiles have since been well defined in patients with advanced CRC. Indeed, a phase II study involving 177 patients confirmed promising efficacy with an objective response rate of 26%[9] and three large phase III comparative studies have demonstrated anti-tumor efficacy similar to 5-FU with LV (both Mayo and Machover regimens) in patients who had not received adjuvant chemotherapy within the previous year or prior systemic chemotherapy for advanced disease.[10-12] These results suggested that it would be worthwhile investigating the efficacy of raltitrexed in patients who had recently failed adjuvant chemotherapy or who had received prior chemotherapy for advanced disease. Phase I studies in Japan and Europe have reported anti-tumor activity and defined the recommended dose of raltitrexed as 3.0 mg/m^2 in patients with advanced CRC.[13,14] Therefore, in this phase II study we investigated the efficacy of raltitrexed 3.0 mg/m^2 administered once every 3 weeks to patients who had received one previous chemotherapy regimen.

Patients and methods

Patients

Patients with histologically confirmed advanced or metastatic CRC who had received only one previous chemotherapy regimen were eligible for inclusion in this study. This included patients whose disease had recurred within 6 months of completion of adjuvant chemotherapy or those who had received prior treatment for advanced disease. A washout period of at least 4 weeks was required between any previous chemotherapy and trial entry. Additional eligibility criteria included: age between 20 and 75 years; at least one measurable lesion; performance status $\leqslant 2$ on the scale of the Japan Society of Cancer Therapy (JSCT)[15]; life expectancy $\geqslant 3$ months; no prior treatment with LV or irradiation of the assessable lesion(s); no other malignancies or serious complications; adequate bone marrow reserve (white blood cells $4\text{-}12 \times 10^9$/l, platelets $\geqslant 100 \times 10^9$/l and hemoglobin $\geqslant 10$ g/dl); alkaline phosphatase, SGOT and SGPT levels less than 2 times the upper limit of normal (ULN) (if hepatic metastases had been documented, these parameters could be up to 5 times the ULN), serum bilirubin $\leqslant 1.5$ mg/dl, serum creatinine level $\leqslant$ ULN and blood urea nitrogen $\leqslant 25$ mg/dl.

All patients provided informed consent to participate in the study and approval was obtained from an institutional review board at each individual trial center. The study was performed in accordance with Good Clinical Practice.

Treatment

Raltitrexed was supplied by Zeneca KK Pharmaceuticals, Japan, as a lyophilized product. The reconstituted product was further diluted in saline or 5% glucose and administered as a short infusion over 15 min. Patients received raltitrexed at a single dose of 3.0 mg/m^2 once every 3 weeks for at least four cycles, unless disease progression or intolerable toxicity was observed.

Dose administration could be delayed for a maximum of 3 weeks until toxicity had resolved or recovered to the level specified by the inclusion criteria. Patients who did not meet these criteria after 3 weeks of delay were withdrawn from treatment. Dose modification was based on the worst grade of selected gastrointestinal (diarrhea, stomatitis) and hematological toxicities (neutropenia, thrombocytopenia) seen in the previous treatment cycle.

Efficacy and tolerability assessments

Objective tumor response was based on the change in size of measurable target lesions and the evaluation of all evaluable target lesions. Definitions of measurable and evaluable disease and response evaluation were based on the JSCT criteria.[15]

A complete response (CR) was attained if all lesions had completely resolved for at least 4 weeks and a partial response (PR) if there was a reduction

of 50% or more in the sum of the products of the perpendicular two largest diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions developing or the progression of any lesions. No change (NC) was defined as a reduction of less than 50% or an increase of less than 25% in the sum of the products of the perpendicular diameters of all lesions without any evidence of new lesions. Progressive disease (PD) was defined as an increase of greater than 25% from baseline or the appearance of new lesions. The duration of PR was defined as the interval from the onset of PR to progression. The overall duration of response was calculated from the first treatment to progression. Lesions were measured by computed tomography scan, magnetic resonance imaging or radiography every 3 weeks, where possible. An external panel of experts reviewed the findings of these investigations to assess any response to treatment. Another independent committee reviewed efficacy and safety results from an ethical point of view. Kaplan–Meier curves were plotted for survival.

Toxicities were graded according to JSCT criteria.[16] Evaluations included a full clinical examination, and hematology and biochemistry (including renal and liver function) tests at regular intervals. Plasma concentrations of raltitrexed were determined during the first cycle of treatment in selected patients to investigate the pharmacokinetics. The plasma concentration–time data were analyzed by non-linear regression with a three-compartment infusion model using MODFIT[17] to determine standard pharmacokinetic parameters. For one patient, the plasma concentration–time data were not well described by the fitted model and no pharmacokinetic parameters have been quoted.

The response rates of patients with advanced CRC who have received prior chemotherapy are low, even with drugs that have been approved for advanced disease; therefore, a response rate of 10–15% would be considered clinically useful. Assuming that the expected response rate was 15% and the threshold response rate was 5%, the number of patients required to reject the hypothesis [α=0.05 (one side) and β=0.2] was 43. Allowing for possible ineligible cases, the target number of patients was set at 45.

Results

A total of 45 patients with advanced CRC were recruited into the study between March 1996 and February 1998. The patients were followed until 30 September 1998, the data cut-off point for this analysis.

Two patients were regarded as ineligible: one patient had a marked decrease in platelet count, from 126×10^9/l at inclusion to 79×10^9/l just before the first administration of raltitrexed; another patient did not have a sufficient interval (only 25 days) between prior therapy (irinotecan) and study entry. These two patients were excluded from all analyses; the remaining 43 patients were assessable for response and toxicity.

The characteristics of the eligible patients are listed in Table 1. The median age of the patients was 59 (range: 39–73) years. Twenty-nine patients (67%) were male and the majority of patients (98%) had a performance status of 0 or 1. The major sites of metastases were lung (25 of 43; 58%) and liver (19 of 43; 44%). Prior chemotherapy included 5-FU (i.v. or oral), a combination of tegafur and uracil (UFT), or a combination of 5-FU and cisplatin, mitomycin or irinotecan.

A total of 212 cycles of raltitrexed was administered with a median of 4 cycles per patient (range: 1–14 cycles).

Table 1. Patient characteristics

Characteristic	No. of patients
Registered	45
Eligible	43
Median age (range), years	59 (39–73)
Male:female	29:14
Performance status	
0	35
1	7
2	1
Histologic differentiation	
well-differentiated	20
moderately differentiated adenocarcinoma	20
poorly differentiated adenocarcinoma	2
other	1
Metastatic site	
liver	19
lung	25
superficial lymph node	7
deep lymph node	9
other	11
Previous treatment	
surgery	43
adjuvant chemotherapy[a]	21
pretreatment for advanced disease[a]	24

[a]Two patients who had metastatic disease had a recurrence more than 6 months after completing their prior adjuvant chemotherapy and have therefore been included in both treatment groups.

Efficacy

All eligible patients with advanced CRC were evaluable for response (Table 2). Partial response was achieved in seven patients, giving an overall response rate of 16% [95% confidence interval (CI): 7–31%]. Of those patients who achieved a 50% or greater reduction in tumor size, the median time to achieve this reduction was 64 days (range: 19–97 days). Similarly, of those patients who responded to treatment, the median duration of PR was 101 days (range: 45–239 days) and the median overall duration of response was 145 days (range: 104–302 days). Twenty patients (47%) had NC and 15 patients (35%) had PD.

Of 40 patients who had received a 5-FU regimen previously, seven patients (18%) achieved PR. Organ-specific response rates for metastatic lesions were 17% (three of 18) for the liver, 12% (three of 25) for the lungs and 20% (one of five) for the superficial lymph nodes (Figure 1). No responses were noted for deep lymph nodes.

All deaths were included in the analysis for survival. At the data cut-off point, 24 patients (56%) had died. A Kaplan–Meier plot of survival is shown in Figure 2. The median survival duration of the entire cohort of patients was estimated to be 11.6 months (95% CI: 9.4–14.7 months).

Tolerability

Reported adverse events (AEs) are presented in Table 3. The major AEs were gastrointestinal and hematological toxicities. Most AEs were mild (grade 1 or 2), transient and/or easily manageable.

Asymptomatic and reversible elevations in serum transaminases (SGOT and SGPT) were common and usually returned to baseline. Grade 3 or 4 SGOT and SGPT increases were observed in 2.3 and 7.0% of patients, respectively. No patient was withdrawn from the trial due to increases in transaminase levels.

Other common AEs included anorexia (65%), asthenia (53%), nausea/vomiting (51%) and myelosuppression. Grade 3 or 4 adverse events occurring in at least 5% of patients were nausea/vomiting (19%), anorexia (14%), asthenia (9%), neutropenia (23%) and leukopenia (9%) (Figure 3). Severe diarrhea, stomatitis or alopecia were not observed.

Three patients died within 3 weeks of receiving the first cycle of raltitrexed and one patient died within 1 month of receiving the final cycle. The independent committee considered these deaths to be due to disease progression.

Pharmacokinetics

The mean (±SD) raltitrexed plasma concentration-time profile (Figure 4) shows a rapid initial decline

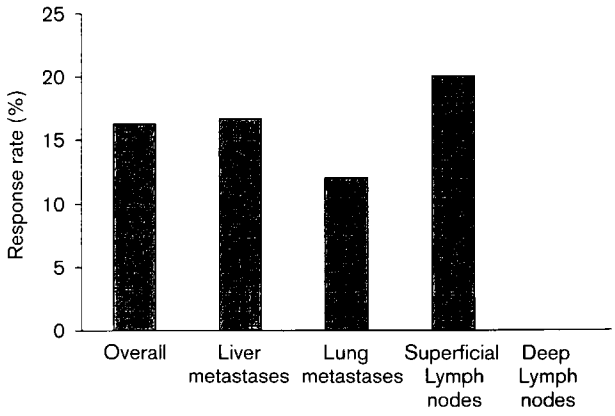

Figure 1. Response rate (%) according to the site of metastasis.

Table 2. Objective response[a]

	No. of patients	Response				
		PR	NC	PD	NE	Rate (%)
Overall	43	7	20	15	1	16.3
Metastatic site						
liver	18	3	5	10	0	16.7
lung	25	3	17	3	2	12.0
superficial lymph nodes	5	1	1	2	1	20.0
deep lymph nodes	8	0	5	2	1	0
Pretreatment						
5-FU regimen	40	7	18	14	1	17.5

PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable.
[a]Non-evaluable lesions excluded.

following the end of the infusion and two slower phases thereafter.

Pharmacokinetic parameters were obtained from 12 evaluable patients and the mean values (±SD) were: plasma clearance 42.1 (±11.1) ml/min, volume of distribution at steady state 585 (±187) l and terminal half-life 244 (±59.1) h. The mean values (±SD) for the maximum plasma concentration and the area under the plasma concentration time curve (AUC) were 749 (±241) ng/ml and 1949 (±371) ng.h/ml, respectively. Raltitrexed shows a long terminal half-life with 56–73% of the total AUC being under the terminal phase. Although the half-life is long with respect to the dosing interval of 3 weeks (504 h), the plasma concentrations before the second dose were close to the limit of detection of the assay (0.768 ng/ml).

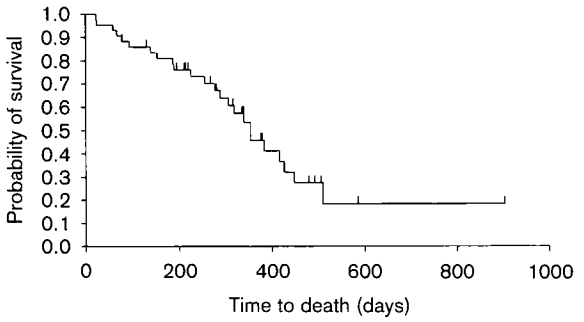

Figure 2. Kaplan–Meier survival curve.

Table 3. AEs

Adverse event	Grade (no. of patients)				Grade 3 or 4 (%)
	1	2	3	4	
Anorexia	14	8	6	0	14.0
Nausea and vomiting	10	4	8	0	18.6
Asthenia	13	6	1	3	9.3
Hypotension	2	1	3	0	7.0
Diarrhea	8	2	0	0	0
Stomatitis	6	3	0	0	0
Alopecia	0	1	0	0	0
Hemoglobin decrease	19	7	1	1	4.7
Neutropenia	5	5	8	2	23.3
Leukopenia	5	9	3	1	9.3
Thrombocytopenia	8	3	1	0	2.3
Alkaline phosphatase increase	13	8	1	0	2.3
SGOT increase	18	24	1	0	2.3
SGPT increase	12	27	3	0	7.0
Bilirubin increase	11	0	1	0	2.3
SCr increase	8	0	0	0	0
BUN increase	5	2	1	1	4.7

SCr, serum creatinine; BUN, blood urea nitrogen.

Discussion

This study confirms the effectiveness and tolerability of raltitrexed as a second-line treatment of advanced CRC. The characteristics of the patient population in this study were similar to those reported in other raltitrexed trials in this patient group.[10,12] However, the proportion of patients with liver metastases was lower than in the European studies as, in Japan, patients with liver metastases are frequently treated by hepatic arterial infusion.

The peak plasma raltitrexed concentration in this study is very similar to that reported after a 3.0 mg/m^2 dose in a phase I study of raltitrexed in Japanese patients, 716±270 ng/ml.[13] In the phase I study, sampling was restricted to 72 h and the terminal half-life and AUC values reported (97.4±37.2 h and 870±349 ng.h/ml, respectively) after a 3.0 mg/m^2 dose were therefore lower than those measured from sampling throughout the 21 day (504 h) dosing

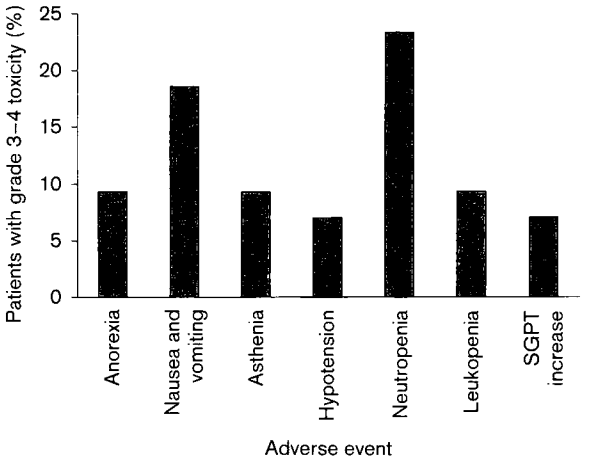

Figure 3. Grade 3–4 AEs reported by more than 5% of patients.

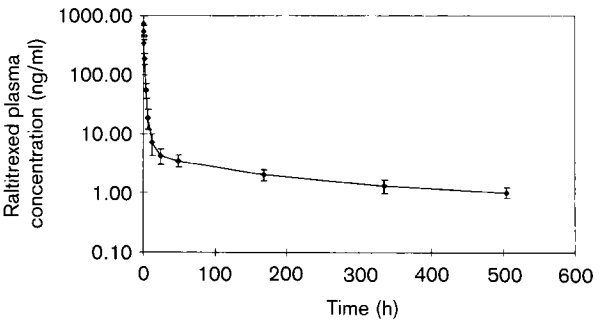

Figure 4. The mean (SD) raltitrexed plasma concentration–time profile (n=13).

interval on this study. The phase I study reported little accumulation when the plasma profiles for cycles 1 and 2 were compared, which is consistent with the low trough concentrations observed before redosing on this study (1.02 ± 0.21 ng/ml).

The plasma raltitrexed concentration-time profile and the derived pharmacokinetic parameters from Japanese cancer patients are comparable with the published information on Western cancer patients.[18,19] Raltitrexed shows a long terminal half-life (244 h) which represents approximately two-thirds of the total AUC. Pharmacokinetic modeling suggests that this long terminal phase is attributable to the slow release of drug from the third compartment which is consistent with the large observed volume of distribution (585 l).

In this study, second-line treatment with raltitrexed 3.0 mg/m^2 once every 3 weeks resulted in a response rate of 16%. This response is impressive considering that response rates of 19% were observed in the phase III multicentric randomized trials of patients with advanced cancer who had not received prior systemic chemotherapy for this indication.[10,12] This implies that, as most of the patients had received prior chemotherapy with 5-FU regimens, raltitrexed and 5-FU have an incompletely overlapping spectrum of antitumor activity against advanced CRC, such that resistance to 5-FU does not necessarily confer resistance to raltitrexed. Furthermore, Köhne *et al.* reported that raltitrexed could be safely given to patients who had experienced 5-FU toxicity.[20] These clinical observations suggested that raltitrexed might provide a therapeutic option in patients who had failed or were intolerant to 5-FU. This encouraged the initiation of a phase II pilot trial evaluating raltitrexed as second- and third-line therapy in patients with metastatic CRC.[21] Mature results from this study are awaited.

Preliminary results of a combination of 5-FU and raltitrexed have shown encouraging response rates in phase I studies.[22,23] Responses were also seen both in lung and liver metastases, which are common sites of metastasis in advanced CRC. In addition, another phase II study in Japan carried out in parallel showed a 24% (14 of 58) response rate for patients with previously untreated advanced CRC.[24]

The estimated median duration of survival in this study was 11.6 months; this compares favorably with reported median duration of survival in the three randomized phase III multicentric trials of 9.7, 10.3 and 10.9 months, respectively.[10–12]

The main reported toxicities were gastrointestinal and hematological in nature. However, most of these adverse events were mild and easily manageable, a finding which is consistent with the previous phase III trials of raltitrexed. Elevations in serum transaminase levels were generally asymptomatic and reversible, and did not lead to patient withdrawal. The observed incidences of nausea and vomiting (51%) and diarrhea (23%) were substantially lower than those observed in a Japanese phase II study of irinotecan, in which 73 and 63% of patients experienced these events, respectively.[3] Similarly, high incidences of nausea and vomiting (58%) and diarrhea (59%) have been recorded with 5-FU plus LV.[12] Notably, no patient had severe diarrhea in the present study. The observed incidence of severe leukopenia (9%) was also low compared with previous studies with 5-FU and LV,[10,12] and no patient experienced severe stomatitis or alopecia.

Against this background, raltitrexed has a simple and convenient dosing regimen comprising a 15 min infusion given once every 3 weeks. In the comparative phase III studies, patients receiving 5-FU+LV required hospitalization for five consecutive days per cycle. Taking into account the possible additional hospitalization before and after dosing, the total time of hospitalization could have a considerable impact on the quality of the patient's social life.[10–12] Furthermore, nausea and vomiting, diarrhea, stomatitis, and alopecia particularly affect the quality of life in patients, which is an important consideration in palliative care. As these toxicities occurred at a low incidence in this study, treatment with raltitrexed may also improve the quality of life of patients by avoiding these toxicities that occur more frequently with conventional treatment regimens. These considerations may also have a potential impact on the way that cancer patients are managed in Japan. Indeed, whereas patients were followed up at outpatient clinics in the above raltitrexed clinical trials, most patients received in-hospital care in the present study. Given that toxicities reported in this study were generally mild and manageable, and that the incidence of severe diarrhea was lower than that reported in phase III comparative studies,[10–12] it would appear that outpatient follow-up in Japan is also appropriate. This should provide patients with the opportunity to maintain a quality level of social functioning while receiving chemotherapy.

Conclusion

Raltitrexed provides effective palliative chemotherapy for patients with advanced CRC who have received prior chemotherapy, and it has the benefit of a favorable and manageable toxicity profile. Combined

with the convenient 3-weekly administration schedule these advantages render raltitrexed a promising option for the treatment of advanced CRC, irrespective of whether patients have previously received chemotherapy. The observed response rate in patients previously unresponsive to 5-FU implies that 5-FU and raltitrexed have an incompletely overlapping spectrum of antitumor activity against advanced CRC, such that resistance to 5-FU does not necessarily confer resistance to raltitrexed. Indeed, preliminary results of a combination of 5-FU and raltitrexed have shown encouraging response rates, suggesting that these agents act synergistically in patients with advanced CRC. Further clinical studies of combinations of raltitrexed with i.v. 5-FU or UFT are planned in Japan.

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(Received 10 April 1999; revised form accepted 10 June 1999)