Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial

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Summary

Background This randomised trial compared three chemotherapy regimens in the first-line treatment of advanced colorectal cancer, in terms of their effect on overall and progression-free survival; other endpoints included toxicity, symptom palliation, and quality of life.

Methods 905 patients were randomly assigned the de Gramont regimen (n=303; folinic acid 200 mg/m², fluorouracil bolus 400 mg/m², and infusion 600 mg/m² on days 1 and 2, repeated every 14 days), the Lokich regimen (n=301; protracted venous infusion of fluorouracil 300 mg/m² daily), or raltitrexed (n=301; 3 mg/m² intravenously every 21 days). Analyses were by intention to treat.

Findings Median follow-up of survivors was 67 weeks. For the de Gramont, Lokich, and raltitrexed groups, respectively, median survival was 294, 302, and 266 days. The hazard ratios for overall survival were 0·88 (95% CI 0·70–1·12, p=0·17) for de Gramont versus Lokich, and 0·99 (0·79–1·25, p=0·94) for de Gramont versus raltitrexed. An increase in treatment-related deaths was seen on raltitrexed (de Gramont one, Lokich two, raltitrexed 18) due to combined gastrointestinal and haematological toxicity. Patients' assessment of quality of life showed that raltitrexed was inferior to the fluorouracil-based regimens, especially in terms of palliation and functioning.

Interpretation The deGramont and Lokich regimens were similar in terms of survival, quality of life, and response rates. The Lokich regimen was associated with more central line complications and hand-foot syndrome. Raltitrexed showed similar response rates and overall survival to the de Gramont regimen and was easier to administer, but resulted in greater toxicity and inferior quality of life.

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Introduction

Every year, 20 000 people in the UK[1] and 800 000 worldwide die from colorectal cancer.[2] Except in the rare situation of operable liver metastases, treatment for metastatic disease is not given with curative intent. The goals of medical intervention are therefore to improve the duration and quality of the patient's remaining life. In randomised trials of chemotherapy based on fluorouracil, the treatment extended survival by a median of 3·5 to 6 months over best supportive care.[3,4] In addition, despite treatment-related adverse effects, quality of life was maintained more effectively in patients given chemotherapy.[3] Therefore, efforts to minimise the burden of treatment while improving or maintaining efficacy are valuable.

Until recently, the mainstay of treatment has been fluorouracil. In the 40 years since the first description of this drug,[5] various treatment schedules have been developed. Compared with fluorouracil alone, biochemical modulation with folinic acid results in an improvement in response rates but no increase in survival.[6] The standard treatment in the USA is the North Central Cancer Treatment Group (NCCTG) regimen of fluorouracil plus folinic acid as an intravenous bolus on 5 consecutive days, repeated monthly.[7] However, this regimen has significant toxic effects, with 46% of patients in two randomised trials being unable to tolerate the full dose.[8] The de Gramont regimen of fluorouracil bolus and infusion with folinic acid, given over 2 consecutive days every 2 weeks,[9] has been compared with the NCCTG regimen. It produced similar survival (median 62·0 weeks *vs* 56·8 weeks with the NCCTG regimen, p=0·7) and had better response rates (32% *vs* 14%, p=0·0002) and progression-free survival (p=0·0065), and reduced toxic effects.[10] In Europe, therefore, fluorouracil infusions, despite their greater inconvenience and cost, have become standard practice because they combine good response rates with greater tolerability.

Another method of increasing the activity of fluorouracil without increased toxicity is protracted fluorouracil infusion, as originally described by Lokich and colleagues, which gives a response rate of around 30%.[11] This approach requires insertion of a central venous catheter and provision of a suitable pump, but thereafter it is a simple and low-cost method of treatment. A meta-analysis, comparing fluorouracil infusions with bolus administration, showed an improved response rate (22% *vs* 14%, p=0·0002) and a marginal improvement in survival (p=0·04) with infusions.[12] Haematological toxic effects were much less common, but hand-foot syndrome was more frequent with fluorouracil infusions.[13]

Raltitrexed is a quinazoline antifolate that specifically inhibits thymidylate synthase. It undergoes extensive intracellular polyglutamation by folyl polyglutamate synthase to metabolites that are up to 100 times more potent than the parent compound at inhibiting

thymidylate synthase.[14] In phase I studies, the dose-limiting toxic effects were fatigue, myelosuppression, and gastrointestinal symptoms. The drug is given as a 15 min infusion every 3 weeks.[15] It has been compared with regimens of bolus fluorouracil and folinic acid in three international phase III trials of 1340 patients in total.[16-18] All three trials showed similar response rates and overall survival for the two regimens, with a significantly lower rate of leucopenia and mucositis and a higher rate of self-limiting symptomless rises in aminotransferase activities in patients treated with raltitrexed. In two trials, progression-free survival was shorter in the raltitrexed than in the fluorouracil group.[17,18] Quality-of-life assessment in two of the trials[16,18] showed that raltitrexed was superior at 2 weeks but equivalent thereafter. Zalcberg[19] reviewed all three trials and reported a treatment-related death rate of 3·8%.

Our trial was designed to address the following question: in the palliative treatment of patients with advanced colorectal cancer, is a regimen of protracted fluorouracil infusions (Lokich) or raltitrexed similar in terms of overall survival to the de Gramont regimen and, if so, are there differences in the quality of life, pattern of toxic effects, and cost?

A second question, to be reported later, considered the duration of chemotherapy, by asking: in patients with stable or responding disease at 12 weeks, is there a survival benefit when chemotherapy is continued until progression, compared with a policy of stopping chemotherapy and rechallenging with the same regimen on progression?

Methods

Patients

Eligible patients had histologically confirmed adenocarcinoma of the colon or rectum, and locally advanced or metastatic disease at presentation. The protocol required that if systemic chemotherapy had been given previously, it must have been fluorouracil-based adjuvant therapy completed more than 6 months before trial entry. All patients had to have adequate bone-marrow and renal function (serum creatinine at or below 1·25 times the upper limit of normal and, if serum creatinine exceeded the upper limit of normal, creatinine clearance of more than 65 mL/min) and a WHO performance status of 0, 1, or 2.[20] Local ethics committees approved our protocol, and individual patients provided written informed consent.

Design and procedures

Patients were randomly assigned one of the study regimens by a telephone call to the Cancer Division of the MRC Clinical Trials Unit with a minimisation procedure, and stratification for clinician, status of disease, and WHO performance status. Patients assigned the de Gramont regimen were prescribed 2-weekly cycles of intravenous folinic acid 200 mg/m^2 (maximum 350 mg) given over 2 h, followed by fluorouracil as a 400 mg/m^2 bolus over 5 min, and a fluorouracil infusion of 600 mg/m^2 over 22 h, repeated on day 2, in most cases on an inpatient basis. Those assigned the Lokich regimen were prescribed continuous intravenous infusion of fluorouracil 300 mg/m^2 daily given via an ambulatory pump plus warfarin 1 mg/day by mouth. The dose of warfarin was reduced or stopped if the international normalised ratio rose above 2·0. Patients assigned raltitrexed were prescribed 3 mg/m^2 intravenously over 15 min every 3 weeks.

Dose reductions or delays were recommended for all three regimens for neutropenia, hand-foot syndrome, diarrhoea, and mucositis. In addition, for raltitrexed, dose reductions were recommended for impaired renal function, as shown by a decrease in glomerular filtration rate to less than 65 mL/min.

Pretreatment assessment included a full history and examination, full blood count, renal, liver, and bone profile, and determination of evaluable disease. Follow-up reports every 6 weeks included details of treatment, symptoms, response, and progression. After 12 weeks, disease burden was objectively reassessed, in most instances by computed tomography. Serious adverse events forms were completed and sent to the Clinical Trials Unit to cover the development of a new medical disorder or the deterioration of a pre-existing disorder (except for unequivocal progression of disease) during or after treatment.

Quality of life was assessed with the standard 30-item quality-of-life questionnaire (QLQ-C30[21]) of the European Organization for Research and Treatment of Cancer (EORTC), plus six pretested and similarly formatted trial-specific questions, and the 14-item hospital anxiety and depression scale.[22] All patients were asked to complete the forms before randomisation and then every 6 weeks in the clinic before their consultation.

Costs were assessed in a subset of 64 patients at five centres through the prospective collection by research nurses of resource-use data in relation to treatment, and by patients and carers of indirect use of health service resources in both secondary and primary care. The results of this economic evaluation will be reported elsewhere.

Statistical design and methods

The primary endpoint was overall survival. Secondary endpoints were quality of life, toxic effects, response rates, costs, and acceptability of treatment to patients.

All analyses were done by intention to treat. Comparisons were made between the control (de Gramont) and Lokich groups, and between the de Gramont and raltitrexed groups. Because patients could be rerandomised to "stop" or "continue" at 12 weeks, we made comparisons of response, toxic effects, and quality of life up to or at 12 weeks, or considered the change from baseline to 12 weeks. Survival was measured from the date of randomisation to the date of death, or the date of last contact for surviving patients. The Kaplan-Meier method was used to calculate the curves, and the Mantel-Cox version of the log-rank test to make treatment comparisons. Response, which was not externally reviewed, was assessed by clinicians at 12 weeks.

From the results of a previous trial,[23] the predicted survival at 18 months on the de Gramont regimen was about 10%. Survival on the Lokich and raltitrexed regimens was expected to be similar to that on the de Gramont regimen, and both regimens would be deemed to be clinically useful alternatives to the de Gramont regimen if they were shown not to be substantially worse. A reduction of 5–6% in survival was the maximum that was considered acceptable. To provide at least 90% power for detection of a 5% reduction in survival (eg, 10% with de Gramont and 5% with raltitrexed, corresponding to a hazard ratio of 1·3) at the 5% level (one-sided) required 500 events (about 560 patients) in each pairwise comparison. Thus, a minimum accrual of 840 patients (ie, three groups of 280) was planned.[24]

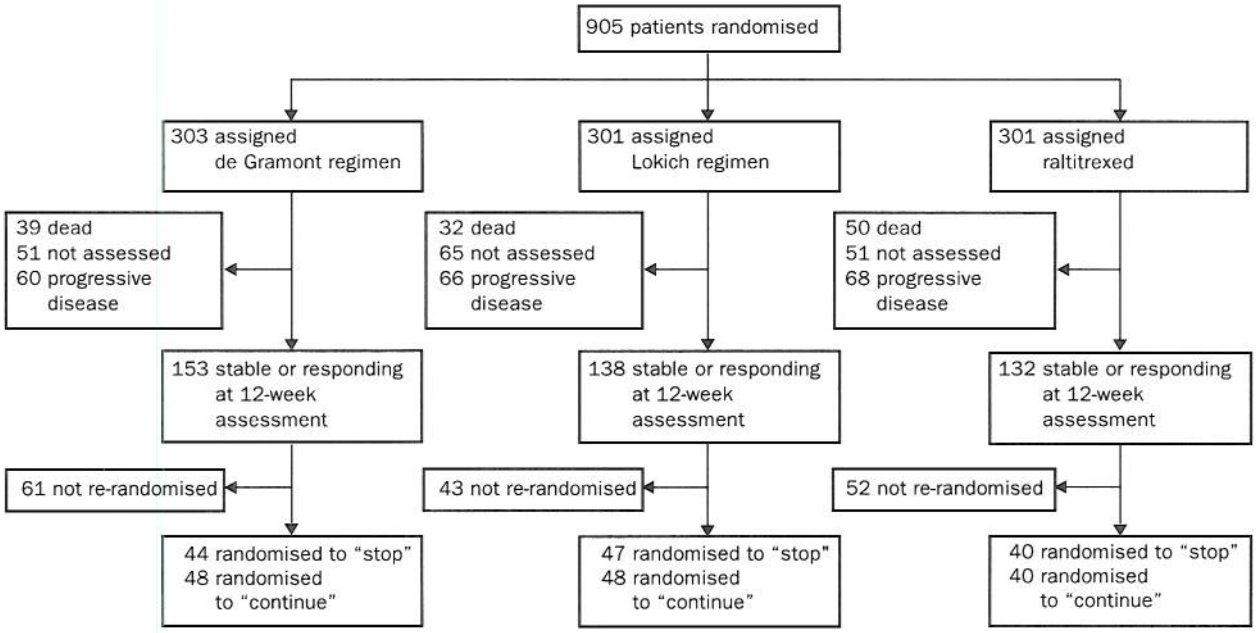

Figure 1: **Trial profile**

Compliance was defined as the number of completed quality-of-life questionnaires as a proportion of the patients who were alive at the specified timepoints.[25] Acceptable time windows were: for baseline, from 7 days before randomisation to after randomisation but before treatment; and for 6 weeks and 12 weeks, from 2 weeks before the time point to 3 weeks afterwards, the asymmetrical windows allowing for delays in chemotherapy. Several specific quality-of-life endpoints were predefined in the protocol: palliation of key symptoms, toxic effects, psychological effect, functional status, social functioning, and overall quality of life. The most important quality-of-life domain was deemed to be palliation, which can encompass improvement, control, and prevention of symptoms.[26] From a previous trial[23] the commonest symptoms at presentation (EORTC QLQ-C30 symptom scales for fatigue, pain, insomnia, and appetite loss) were combined into an overall symptom score. Palliation of individual symptoms was compared by calculation of the proportion of patients whose symptoms were prevented (nil at baseline, remained nil at 6 weeks and 12 weeks), controlled (mild at baseline, nil or mild at 6 weeks and 12 weeks), or improved (moderate or severe at baseline, nil or mild at 6 weeks and 12 weeks).[20] Function and overall quality of life were similarly compared by standardisation of the subscale score,[27] with scores of 0–24, 25–49, 50–74, and 75–100 taken to represent nil, mild, moderate, and severe. To assess toxicity, an overall score was created by combination of the EORTC QLQ-C30 symptom subscale scores for nausea and vomiting, dyspnoea, constipation, and diarrhoea, and the three trial-specific questions (dry or sore mouth, problems in eating or drinking, and discomfort with hands or feet). For each treatment, the proportion of patients who reported worsening of a symptom at 6 weeks or 12 weeks was calculated. Anxiety and depression scores were calculated from the hospital and anxiety depression scale[22] and treatments were compared by use of conventional cut-off scores (0–7 indicating normal, 8–10 borderline, and ≥11 probable clinical case) in terms of the proportion of patients with borderline or probable clinical case distress. Throughout the analysis of the quality-of-life data, because of multiple comparisons, a p value of 0·01 was judged significant.

An independent data-monitoring and ethics committee, consisting of two clinicians not entering patients in the trial and an independent statistician, was set up to meet about once a year to review the safety of the regimens, to recommend adjustments to the protocol, and to decide whether the trial should close or continue.

Results

Between May, 1996, and July, 1998, 905 patients from 45 UK centres were randomly assigned to the three groups (figure 1). Six patients (three de Gramont, one Lokich, two raltitrexed) were deemed ineligible. Baseline characteristics of the patients are provided in table 1.

584 (71%) patients received their prescribed 12-week course of treatment, although 162 (20%) had cycles delayed, doses modified, or both. Of the remainder, 208 (26%) had treatment stopped prematurely and 29 (4%) received no protocol treatment. The main reasons for delays and modifications were toxic effects and intravenous-line problems, and the reasons for stopping prematurely were toxic effects, death, and disease progression (table 2).

The overall time on protocol therapy was similar in the three treatment groups (de Gramont mean 101 days, median 90 days; Lokich 105 days, 85 days; raltitrexed 90 days, 84 days). However, a significantly smaller proportion of patients in the de Gramont group went on to receive second-line treatment (16% *vs* 29% for Lokich, p=0·0001; *vs* 25% for raltitrexed p=0·008).

267 patients (92 de Gramont, 95 Lokich, 80 raltitrexed) who were responding or had stable disease at the 12-week assessment were rerandomised to stop or continue on the same initial treatment regimen.

Clinicians reported on toxicity at each assessment; the numbers of patients in whom grade 3 or 4 toxic effects were reported at 6 weeks or 12 weeks are listed in

	de Gramont (n=303)	Lokich (n=301)	Raltitrexed (n=301)
Characteristic			
Age (years)			
Median	63	62	63
<45	7 (2%)	14 (5%)	14 (5%)
45–54	50 (17%)	66 (22%)	56 (19%)
55–64	114 (38%)	107 (36%)	99 (33%
65–74	103 (34%)	99 (33%)	115 (38%)
≥75	29 (10%)	15 (5%)	17 (6%)
Sex			
Male	210 (69%)	189 (63%)	200 (66%)
Female	93 (31%)	112 (37%)	101 (34%)
WHO performance status			
0	102 (34%)	98 (33%)	100 (33%)
1	133 (44%)	134 (45%)	135 (45%)
2	68 (22%)	69 (23%)	66 (22%)
Site*			
Colon	181 (63%)	197 (69%)	187 (65%)
Rectum	107 (37%)	88 (31%)	100 (35%)
Treatment of primary disease			
Primary resected*	227 (77%)	251 (87%)	233 (81%)
Previous radiotherapy*	48 (16%)	55 (19%)	58 (20%)
Previous adjuvant chemotherapy*	38 (13%)	42 (15%)	37 (13%)
Evaluability			
Objective measurable	245 (81%)	241 (80%)	240 (80%)
Objective unmeasurable	45 (15%)	45 (15%)	50 (17%)
Subjective	13 (4%)	15 (5%)	11 (4%)
Current disease status*			
Locally advanced	13 (4%)	13 (4%)	11 (4%)
Metastatic	134 (44%)	132 (44%)	132 (44%)
Locally advanced and metastatic	93 (31%)	91 (30%)	95 (32%)
Recurrent, no chemotherapy	35 (12%)	38 (13%)	35 (12%)
Recurrent, previous chemotherapy	27 (9%)	27 (9%)	28 (9%)
Colostomy			
Yes	93 (31%)	75 (25%)	74 (25%)
No	210 (69%)	226 (75%)	227 (75%)
Sites of metastases*			
Liver only	127 (44%)	118 (41%)	124 (43%)
Extrahepatic only	65 (22%)	58 (20%)	66 (23%)
Both hepatic and elsewhere	92 (32%)	104 (36%)	99 (34%)
No evidence of metastases	6 (2%)	7 (2%)	1 (0·3%)

Data are number of patients (%) unless otherwise stated. *Data missing for some patients: based on 860 for site, 872 for primary resection, 868 for previous radiotherapy, 864 for previous adjuvant chemotherapy, 904 for current disease status, and 867 for sites of metastases with data available.

Table 1: **Pretreatment characteristics of participants**

table 3. Compared with the de Gramont group, patients in the Lokich group had significantly more stomatitis, and patients in the raltitrexed group significantly more nausea, anorexia, diarrhoea, lethargy, thrombocytopenia, and neutropenia. Clinicians were not asked specifically about hand-foot syndrome, but reported it under "other symptoms" in 38 (13%) patients in the Lokich group.

21 treatment-related deaths were reported and, after central review, were confirmed as being caused by the protocol therapy (one de Gramont, two Lokich, 18 raltitrexed; de Gramont *vs* raltitrexed p=0·0002). Of the 18 deaths that were accepted as being directly related to raltitrexed toxicity, the presenting (overlapping in several cases) serious adverse events were diarrhoea (12), nausea and vomiting (ten), neutropenia (12), and thrombocytopenia (two). In almost every instance there was a combination of gastrointestinal and haematological toxic effects that led to death. The deaths were unrelated to pretreatment characteristics, cycle number, or institution. In four patients, protocol violations were identified. Three did not have protocol-directed dose adjustments, for unresolved grade 2 diarrhoea (two) and grade 4 thrombocytopenia (one), and the fourth patient was ineligible because fluorouracil had previously been given for metastatic disease. In seven of the remaining patients, the possible predisposing factors of previous pelvic radiotherapy (two), hydronephrosis with normal

	de Gramont	Lokich	Raltitrexed
Patients with full data	275	269	277
Received 12 weeks of protocol therapy			
Per protocol	154 (56%)	114 (42%)	154 (56%)
With delays	44 (16%)	24 (9%)	15 (5%)
With modifications	8 (3%)	24 (9%)	14 (5%)
With delays and modifications	7 (3%)	20 (7%)	6 (2%)
Did not complete 12 weeks of protocol therapy			
Stopped prematurely	50 (18%)	74 (28%)	84 (30%)
Did not start	12 (4%)	13 (5%)	4 (1%)
Reasons for delays or modifications*			
Toxic effects	18 (35%)	40 (62%)	29 (91%)
Line problems	7 (14%)	19 (30%)	0
Concomitant illness	10 (20%)	3 (5%)	2 (6%)
Administrative	12 (24%)	1 (2%)	0
Patient's choice	3 (6%)	1 (2%)	1 (3%)
Error	1 (2%)	0	0
Reasons for stopping prematurely†			
Toxic effects	9 (20%)	28 (39%)	32 (38%)
Death	13 (30%)	11 (15%)	28 (33%)
Deterioration/progression	12 (27%)	16 (22%)	17 (20%)
Patient's choice	7 (16%)	3 (4%)	5 (6%)
Line problems	0	12 (17%)	0
Concomitant illness	3 (7%)	2 (3%)	1 (1%)
Administrative	0	0	1 (1%)

*Based on 51 de Gramont, 64 Lokich,and 32 raltitrexed patients with delays and modifications and data available. †Based on 44 de Gramont, 72 Lokich, and 84 raltitrexed patients who stopped prematurely and with data available.

Table 2: **Initial 12 weeks of protocol treatment**

glomerular filtration rate (two), deteriorating performance status (two), or inadequate recovery after surgery (one) were observed. In the seven other patients, no predictive factor for toxic effects could be identified. One further patient died on day 68 after cycle 2 after a protracted period of intensive support that followed admission with severe treatment-related diarrhoea. This death therefore falls outside the usual criterion of toxic deaths within 30 days of treatment. However, the clinical picture was entirely consistent with the other reports.

Of the three treatment-related deaths in the non-raltitrexed groups, the patient in the de Gramont group developed septicaemia of sudden onset with diarrhoea and died on day 15. One of the patients in the Lokich group had severe mucositis 8 days after starting treatment and died 6 days later, and the other developed central-line-related septicaemia during an interval off therapy.

Central-line complications were documented in 42 patients in the Lokich group, thrombosis (15), infection (12), and technical problems (seven) being the predominant events. By comparison, only six such

	de Gramont*	Lokich*	Raltitrexed*
Toxic effect			
Nausea	8 (2·9%)	14 (5·1%)	26 (9·5%)†
Vomiting	9 (3·3%)	12 (4·4%)	21 (7·7%)
Anorexia	9 (3·3%)	17 (6·2%)	30 (11·0%)†
Alopecia	0	1 (0·4%)	0
Rash	4 (1·5%)	7 (2·6%)	7 (2·6%)
Stomatitis	1 (0·4%)	11 (4·1%)†	4 (1·5%)
Diarrhoea	9 (3·3%)	17 (6·3%)	34 (12·4%)†
Lethargy	21 (7·6%)	26 (9·5%)	53 (19·4%)†
Thrombocytopenia	0	0	9 (3·3%)†
Anaemia	4 (1·5%)	4 (1·5%)	8 (2·9%)
Leucopenia	5 (1·8%)	1 (0·4%)	14 (5·1%)
Neutropenia	7 (2·6%)	0	22 (8·0%)†

*Based on between 267 and 277 patients in the de Gramont group, 267 and 273 in the Lokich group, and 267 and 275 in the raltitrexed group with data available. †p<0·01 compared with the de Gramont group.

Table 3: **Grade 3 or 4 toxic effects reported by clinicians up to 12 weeks**

	de Gramont	Lokich	Raltitrexed
Evaluable patients	252	236	250
Complete response	4 (2%)	1 (0·4%)	3 (1%)
Partial response	55 (22%)	57 (24%)	43 (17%)
Stable disease	94 (37%)	80 (34%)	86 (34%)
Progressive disease	60 (24%)	66 (28%)	68 (27%)
Dead at 12 weeks	39 (15%)	32 (14%)	50 (20%)

Table 4: **Clinicians' assessment of response at 12 weeks**

complications were reported in the de Gramont group, although only about a third of centres were treating de Gramont patients as outpatients.

Since objective response was not the primary endpoint, radiological responses were not externally reviewed, and confirmatory scans were not mandatory. 738 (82%) patients were evaluable at 12 weeks (table 4). The rates of complete and partial responses were 23%, 25%, and 18% for the de Gramont, Lokich, and raltitrexed groups, respectively (de Gramont *vs* Lokich p=0·84, de Gramont *vs* raltitrexed p=0·20). Stable disease was documented in a further 34–37% in each group.

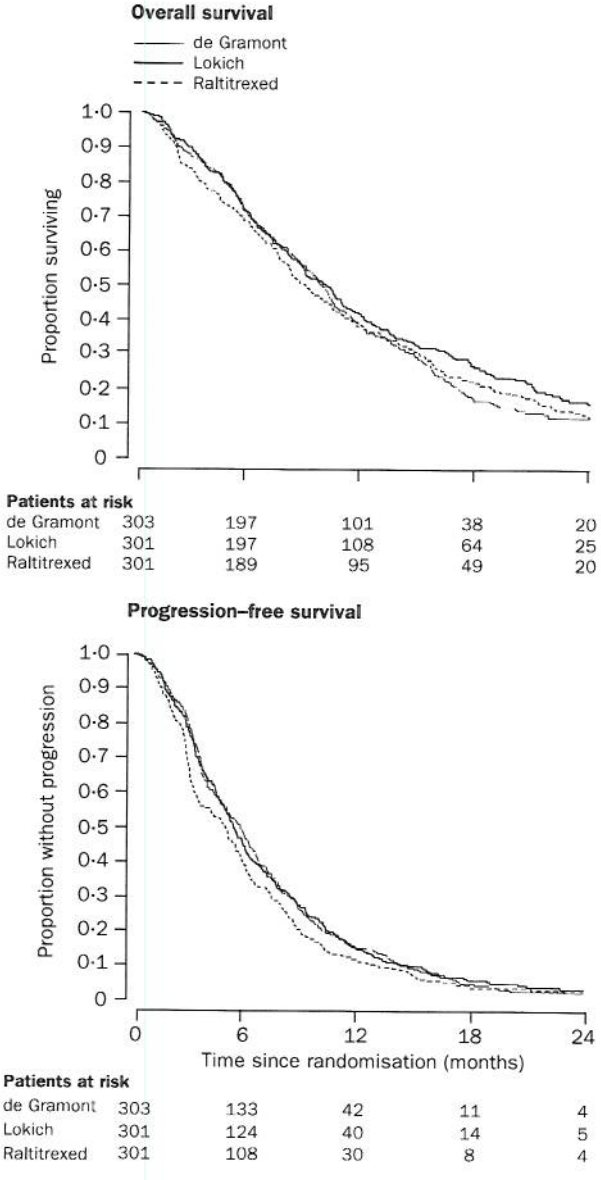

Figure 2: **Overall and progression-free survival**

Overall survival was the primary endpoint of the trial (figure 2). So far, 732 deaths have been reported (81% of patients) and the median follow-up of the 173 survivors is 67 weeks. For the de Gramont, Lokich, and raltitrexed groups, respectively, estimated median survival is 294 days (95% CI 262–314), 302 days (261–327), and 266 days (238–309), 1-year survival 37%, 40%, and 37%, and 2-year survival 12%, 16%, and 12%. By comparison with the de Gramont regimen, the hazard ratio for patients in the Lokich group was 0·88 (95% CI 0·70–1·12, p=0·17) and that for raltitrexed 0·99 (0·79–1·25, p=0·94).

Progression-free survival (figure 2) was not a protocol-directed endpoint. However, documentation of progressive disease based on clinical or radiological findings was required. Progression-free survival was worse in the raltitrexed group than in the de Gramont group (median 21 *vs* 25 weeks), although this difference was not significant (hazard ratio 1·18 [95% CI 0·94–1·46], p=0·057). There was no evidence of a difference between the Lokich and de Gramont groups (0·99 [0·80–1·23], p=0·92).

Of the 905 patients enrolled in the trial, 764 (84%) completed baseline questionnaires. The commonest symptoms reported as "quite a bit" or "very much" at presentation were need to rest (39%), tiredness (38%), weakness (32%), insomnia (32%), and pain (28%). 548 (64% of the 855 patients alive at 6 weeks) and 481 (62% of the 781 patients alive at 12 weeks) completed questionnaires at 6 weeks and 12 weeks. However, only 335 (43% of the patients alive at 12 weeks) completed questionnaires at all three assessment points. Although a significantly greater propotion of patients in the raltitrexed than Lokich group completed quality-of-life forms at 12 weeks (p=0·01), this difference was not reflected in the proportion of patients with baseline and one or two follow-up forms available.

Compared with these 335 patients, the 101 patients who completed baseline quality-of-life questionnaires but died before 12 weeks reported significantly worse baseline quality of life in virtually every characteristic, especially physical functioning, role functioning, overall quality of life, fatigue, appetite loss, dry or sore mouth, and dyspnoea (all p<0·0001). By contrast the only significant difference in baseline quality of life between the 335 with full data and the 328 patients who completed baseline quality-of-life questionnaires but missed either the 6-week or 12-week assessment, but survived beyond 12 weeks, was overall quality of life (p=0·01). There was no significant difference in the change of overall quality of life from baseline to 6 weeks in the patients who completed a 12-week form and those who did not.

Data from the 335 patients who completed baseline, 6-week, and 12-week quality-of-life assessments were used to assess the prespecified endpoints, and data from the groups who completed assessments at only baseline and 6 weeks, or baseline and 12 weeks, were used to confirm the findings.

There was no evidence of any substantial differences between the de Gramont and Lokich groups in terms of the proportion of the patients who reported palliation (either overall or individual items). However, patients in the raltitrexed group consistently reported worse palliation than those in the de Gramont group, especially for overall palliation (p=0·01) and for appetite loss (p=0·012; figure 3). Similarly, there were no differences between the de Gramont and Lokich groups in changes in any of the functioning scales, but raltitrexed was

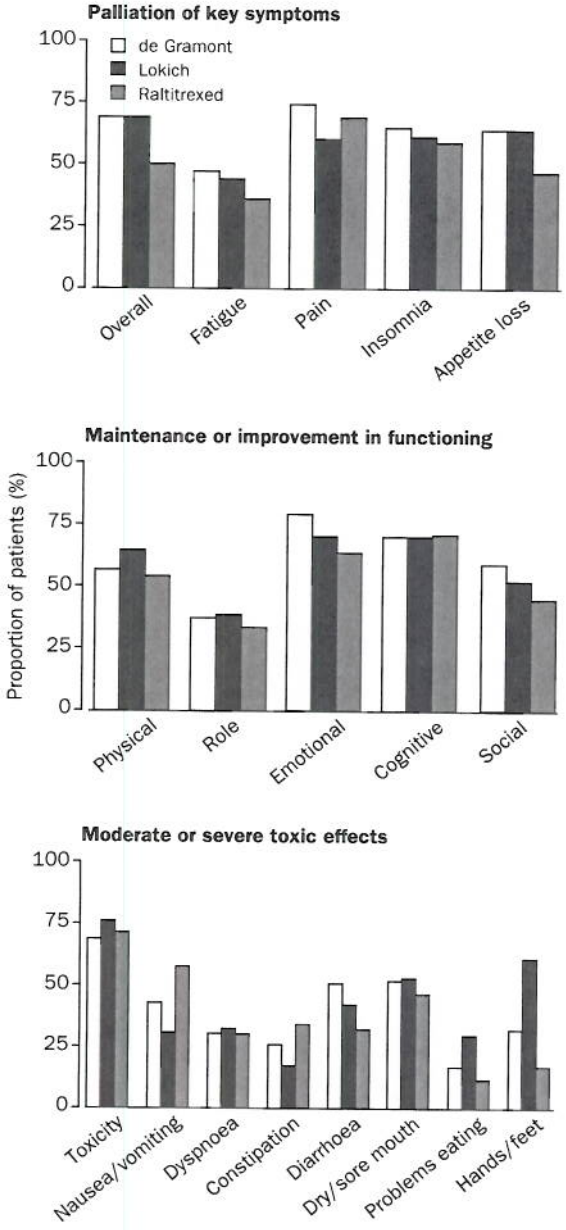

Figure 3: **Quality-of-life findings**

generally inferior to de Gramont particularly for emotional functioning (p=0·022; figure 3). Overall, similar proportions of patients reported moderate or severe toxic effects with the three regimens. Patients in the de Gramont group reported more diarrhoea (p=0·006 compared with raltitrexed), those in the Lokich group more problems with eating and drinking and hand-foot syndrome (p=0·0001 compared with de Gramont), and those in the raltitrexed group more nausea, vomiting, and constipation (figure 3).

The proportions of patients reporting borderline or probable clinical case anxiety and depression at baseline, 6 weeks, and 12 weeks are shown in figure 4. In terms of depression there were no significant differences over time or between treatments, but from baseline to 6 weeks there was a significant reduction of probable case anxiety in both the Lokich and raltitrexed groups (p=0·003 and <0·0001, respectively), and probable case and borderline anxiety in the Lokich group (p=0·005).

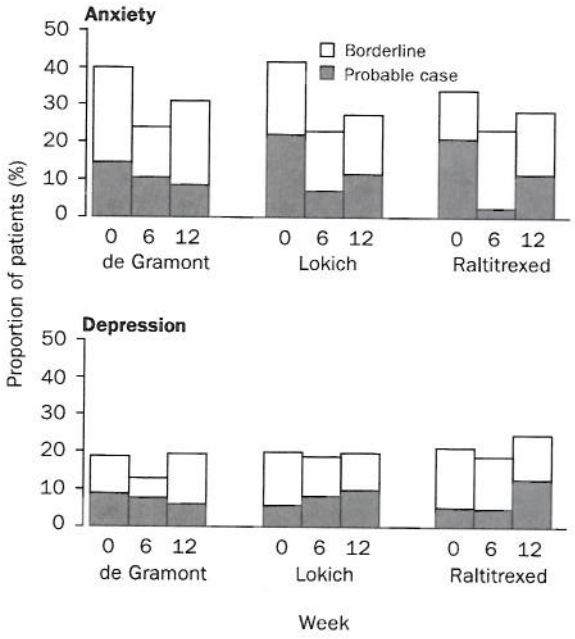

Figure 4: **Proportions of patients reporting borderline or probable clinical case distress from the HADS**

The 156 patients who had only baseline and 6-week quality-of-life data, and the 94 who had only baseline and 12-week data, showed very similar patterns of palliation, functioning, toxicity, and psychological distress to the subset with full data. For example, there were no major differences in terms of palliation between the de Gramont and Lokich groups, but patients in the raltitrexed group with only baseline and 6-week data reported worse overall palliation (p=0·026) and loss of appetite (p=0·0007) than those in the de Gramont group.

Two additional questions on the quality-of-life form asked patients about the acceptability of the treatment received. At 12 weeks, in response to "How much has your treatment interfered with your normal daily activities?", substantial proportions reported "not at all" or "a little". In addition, most patients in all three groups said that their treatment had been worthwhile (table 5). Despite the ease of administration of raltitrexed compared with the complexity of either admission for de Gramont or a central line for Lokich, patients in the raltitrexed group reported that they found the treatment less acceptable, and, compared with de Gramont, significantly less worthwhile (p=0·026). Further aspects of patients' health needs were assessed in a sub-study to be reported elsewhere.

	de Gramont	Lokich	Raltitrexed
Question			
How much has treatment interfered with your normal daily activities?			
Not at all	42 (26%)	41 (28%)	46 (28%)
A little	70 (43%)	61 (42%)	46 (28%)
Moderately	39 (24%)	32 (22%)	43 (26%)
Very much	11 (7%)	10 (7%)	28 (17%)
How worthwhile do you think your treatment has been?			
Not at all	4 (3%)	6 (5%)	4 (3%)
A little	9 (7%)	5 (4%)	14 (11%)
Moderately	35 (26%)	31 (25%)	46 (35%)
Very much	89 (65%)	80 (66%)	67 (51%)

Table 5: **Acceptability of treatment regimens to patients at 12 weeks**

Discussion

The entry requirements for this trial were intentionally broad to allow unrestricted accrual, thereby obtaining representative data. As a result, 22% of patients were of performance status 2; the median survival of such patients in previous trials was only 4 months.[28] Before the report of a survival advantage with second-line therapy,[29] treatment with irinotecan or oxaliplatin was unusual. (It occurred in only 6% of patients in our trial. Indeed, only 23% were given any second-line therapy compared with 57% in an Italian trial reported in 1999.[30])

The overall survival was similar for all three regimens, with median survival of about 10 months and 2-year survival of around 15%. These results accord with those of previous raltitrexed trials.[16–18]

Progression-free survival is being increasingly used as the primary endpoint in clinical trials in colorectal cancer because of the frequency of second-line therapy and its ability to affect overall survival. In this trial, although it was not a predefined endpoint, progression-free survival was poorer with raltitrexed than with the fluorouracil infusion regimens. A similar shortfall in progression-free survival has been seen in two of the three randomised trials comparing bolus fluorouracil with raltitrexed.

A major concern highlighted by our trial was the issue of treatment-related death. There were 18 treatment-related deaths (6·0%) with raltitrexed compared with one in the de Gramont group and two in the Lokich group. In an overview of the tolerability of raltitrexed in phase III trials in colorectal cancer, 35 (5·1%) of 684 patients experienced adverse events leading to death on raltitrexed compared with 29 (4·4%) of 656 on fluorouracil plus leucovorin regimens.[19] On further analysis, 26 of the 35 events seemed to be causally related to raltitrexed therapy, with a similar pattern of toxicity to those seen in our trial. Therefore the deaths in our trial are consistent with the previously recorded international experience. Three of the patients who died were prescribed raltitrexed on cycle 2 without appropriate (although modest) dose delay and reduction (for diarrhoea or thrombocytopenia). In the overview of tolerability of raltitrexed in previous trials, appropriate dose reductions were not made for 17 of the 26 patients who died.[19] Despite the apparent ease of administration of raltitrexed, very careful monitoring is clearly essential, with the closest attention to concomitant toxic effects and stringent application of dose reductions.

When the data monitoring and ethics committee reviewed the data, the members were aware of the increasing number of treatment-related deaths and also of the proportion of treatment-related deaths in the other phase III trials. However, despite circulation to all participating clinicians of a letter that emphasised the importance of extra care for patients in the raltitrexed group, in particular monitoring of renal function before every cycle,[31] seven of the 18 treatment-related deaths on raltitrexed occurred in the last 6 months of accrual and four were among the last 21 patients assigned raltitrexed. This finding was totally unexpected and the reasons for it unclear.

In some patients, long lasting intracellular retention of raltitrexed seems to lead to unacceptable and unpredictable toxicity. Some patients with low intracellular folate concentrations may both take up and retain raltitrexed more avidly. Low serum folate concentrations have recently been shown to correlate with increased toxicity with raltitrexed.[32] The policy of dietary folate supplementation in white bread in North America may have led to the higher tolerance of raltitrexed in the US phase 1 study (4 mg/m^2);[33] by contrast, the lower folate intake in the UK diet may predispose some patients to the greater toxicity seen in our trial. Management of raltitrexed toxic effects once established involves all the usual supportive measures. In addition, rescue with folinic acid (15 mg intravenously four times daily until full resolution) may be helpful to compete for folyl polyglutamate synthase when the raltitrexed-polyglutamate complex is cleaved, thereby increasing release of raltitrexed from the cell.[34]

Despite the large numbers of patients in this trial, deterioration and poor compliance meant that only 43% of those alive at 12 weeks completed quality-of-life questionnaires at baseline, 6 weeks, and 12 weeks. Such a reduction in numbers calls into question the generalisability of results, although there were only slight differences in baseline quality of life between the patients who completed all three assessments and those who (although alive) did not, and in the change in overall quality of life from baseline to 6 weeks in the patients who completed a 12-week form and those who did not. Thus, the main cause of non-compliance was probably poor organisation and other factors in some centres rather than a systematic bias in the types of patients. Although training days were provided, further effort is required in multicentre trials to educate and enthuse some centres about the importance of quality of life.

Since there was similar overall survival, quality of life became an important outcome measure. The de Gramont 2-day schedule and the Lokich continuous infusion regimen are cumbersome to deliver and potentially intrusive into patients' lives, and the complications related to central venous catheters are an additional burden. Therefore, raltitrexed with its 3-weekly schedule and short infusion time was expected to be associated with an improvement in patients' quality of life.

The finding that raltitrexed was inferior on nearly all quality-of-life domains and no less intrusive than either of the fluorouracil infusion regimens was unexpected, and added an extra dimension to the overall picture. Previous quality-of-life comparisons of raltitrexed and bolus fluorouracil and folinic acid showed raltitrexed to be superior at the 2-week time point after dosing, when mucositis was greatest,[18] and equivalent at other time points.[16,18] These contrasting findings underline the concern over the use of bolus fluorouracil and folinic acid regimens as the standard comparator for new agents with metastatic colorectal cancer, because they have high toxicity and are associated with worse quality of life than fluorouracil infusion regimens. Nevertheless, it is disappointing that palliation of fatigue was poor for all three treatments and overall less than two-thirds of patients benefited in terms of key symptoms.

The apparent inconsistencies between some of the results presented for the clinicians' and the patients' reporting of toxicity, especially diarrhoea, need some clarification. Compared with patients' self-reporting, clinicians are known to underestimate symptom severity;[35] but we should emphasise that clinicians were asked to report the worst severity of symptoms in the previous 6 weeks on a 5-point scale, and patients were asked to report the severity of symptom experienced over the previous week on a 4-point scale. Nevertheless, the size of the difference in the proportions reported is of concern.

This trial confirmed the benefits of the de Gramont regimen in the management of patients with metastatic colorectal carcinoma, with low toxicity albeit with high financial cost. Modifications of the regimen[36,37] will reduce these costs and make it simpler to deliver on an outpatient basis. This trial also established continuous fluorouracil

infusion as an excellent alternative regimen, equivalent to the de Gramont regimen on all major endpoints. Hand-foot syndrome is the commonest side-effect and does interfere with daily living, but patients seem to tolerate it with remarkable equanimity. The occurrence of central-line complications in 14% of patients supports the need for further data on prevention of thrombotic complications, and a large trial of this issue is underway in the UK.

Finally, although raltitrexed-related toxicity has been reported in all previous trials, this trial has highlighted the problem because of the low toxicity of the comparators. Raltitrexed is clearly an active drug that gives similar response rates and overall survival to the fluorouracil infusion regimens, but it has greater toxicity and results in inferior quality of life. It may be valuable in combination therapies and in patients for whom fluorouracil is contraindicated, but its future will depend on the ability to predict patients in whom toxic effects may occur (currently something we cannot do reliably), adoption of measures to prevent or reduce toxicity, and vigilance in its use.

British MRC Colorectal Cancer Working Party

The following clinicians entered patients: Addenbrooke's Hospital (P Corrie, C Wilson); Airedale General Hospital (S M Crawford); Birmingham Heartlands Hospital (I Geh, M J Leyland); Bishop Auckland General Hospital (S E Stock); Bradford Royal Infirmary (C Bradley); Bristol Oncology Centre (V L Barley, S Falk, J D Graham, E C Whipp); Castle Hill Hospital (J R T Monson); Charing Cross Hospital (M G Glaser, I W F Hanham, C Lowdell, R H Phillips); Cheltenham General Hospital (K Benstead, S Elyan, S Shepherd); Christie Hospital NHS Trust (H Anderson, R D James, E Levine); Churchill Hospital Oxford (A Jones, E M Sugden); City Hospital Birmingham (J Glaholm, D Peake, D Rea, D Spooner); Cookridge Hospital Leeds (C Coyle, D Sebag-Montefiore, M Seymour, M Snee); Essex County Hospital (S Tahir); Furness General Hospital (N J Sayer); Glasgow Royal Infirmary (M Soukop); Good Hope District Hospital Birmingham (J Glaholm); Hammersmith Hospital (C Vernon, H S Wasan); Hinchingbrooke Hospital (L T Tan); King's Mill Hospital Mansfield (E M Bessell); Maidstone Hospital (F McKinna, M O'Brien, D G L Pickering, G Sadler, J Summers); Manor Hospital Walsall (A D Chetiyawardana); Mount Vernon Hospital (R Glynne-Jones, P J Hoskin, E J Maher, A Makris); Newcastle General Hospital (J M Bozzino, A N Branson, U K Mallick, J T Roberts, W B Taylor); North Middlesex Hospital (S J Karp); North Staffordshire Royal Infirmary (F Adab); Northampton General Hospital (S Harris, D Levy, C Macmillan, J A Stewart); Peterborough District Hospital (K Eagle, C Wilson); Princess Margaret Hospital Swindon (D Cole); Queen Elizabeth Hospital Birmingham (J Glaholm, N James, D Kerr, D Rea, D Spooner); Queen Elizabeth Hospital Kings Lynn (M Daly); Raigmore Hospital Inverness (D Whillis); Royal Free and UCMS UCL (J Ledermann); Royal Preston Hospital (S Susnerwala); Royal South Hants Hospital (T J Iveson); Royal Surrey County Hospital (G Middleton, C Topham, S J Whitaker); Russells Hall Hospital Dudley (R Allerton, A Folkes); St James's University Hospital Leeds (T Perren, P J Selby); Salisbury District Hospital (T J Iveson); Scunthorpe General Hospital (T Screenivasan); Selly Oak Hospital Birmingham (D Kerr, D Spooner); Singleton Hospital Swansea (C Askill, T Joannides); South Cleveland Hospital (J Van der Voet); Southampton General Hospital (T J Iveson); Southend Hospital (A Lamont, J Prejbisz, A Robinson, C Trask); Taunton and Somerset Hospital (J D Graham); University College London Hospitals (J Ledermann); Velindre Hospital Cardiff (A Brewster, T Crosby, T Maughan, D Mort); Western Infirmary Glasgow (A Armour, P A Canney, D Dodds, T R J Evans, T Habeshaw, E Junor, N O'Rourke, K Palumbo, N S E Reed, D M Ritchie, A G Robertson C Twelves, P Vasey, H Yosef); Whittington Hospital (J Ledermann); Yeovil Hospital (S Falk); York District Hospital (D Bottomley).

The following local research nurses and data managers provided the trials office with the data: Addenbrooke's Hospital (S D'Ath); Airedale General Hospital (J Peace); Birmingham Heartlands Hospital (D Richardson); Bishop Auckland General Hospital (J Morgan); Bradford Royal Infirmary (A Barker); Bristol Oncology Centre (M Ball); Castle Hill Hospital (M D'Arcy, N Stocks); Charing Cross Hospital (M Gibson); Cheltenham General Hospital (S Anderson, A Ashton); Christie Hospital (A Burgess, H Ferns, C Wood); Churchill Hospital Oxford (S Palmer); Cookridge Hospital Leeds (H Cresswell, S Fallon); CRC Institute for Cancer Studies, Birmingham (J Barnwell, S Orme, F Sinclair, J Smith, M Whitlock); Furness General Hospital (H Martindale); Glasgow Royal Infirmary (S Stewart); Hammersmith Hospital (M Lynch); King's Mill Hospital, Mansfield (K Stainer); Maidstone Hospital (A Howard, C Ryan); Manor Hospital Walsall (N Robottom); Mount Vernon Hospital (A Bradshaw); Newcastle General Hospital (V Turnbull); North Middlesex Hospital (C Magyar); North Staffordshire Hospital Trust (M Evans); Northampton Centre for Oncology (N Perry); Nottingham City Hospital (C Gooch); Peterborough District Hospital (H Roe); Pinderfields General Hospital (D Barker, H Berry); Princess Margaret Hospital (L Peck); Queen Elizabeth Hospital King's Lynn (B Perryman); Raigmore Hospital Inverness (L Morrison); Royal Preston Hospital (J McCann); Royal South Hants Hospital (L Nokes, L Richardson); Royal Surrey County Hospital (S Brookes, J Moore); Russells Hall Hospital (R Bratt-Wyton); St James's University Hospital (S Hallam); Salisbury District Hospital (A Iveson); Singleton Hospital (J Ellis-Clarke); South Cleveland Hospital (R Donaghy); Southend General Hospital (M Phillips); Taunton and Somerset Hospital (J Briggs); University College London Hospitals (A Leary); Velindre Hospital (C John, R Houghton); Western Infirmary (A McInnes); Whittington Hospital (L Price); Yeovil Hospital (S Bulley); York District Hospital (A Camps). The CTU data managers were: Dionne Cain, Simon Clawson, and Barry Widmer. Janine Hale from University of Glamorgan Business School coordinated the Health Economic assessment.

Contributors

T S Maughan was the principal investigator and took the lead role in writing the paper. R J Stephens and C Johnston were responsible for data collection and analyses. All the named investigators contributed to the design of the trial and the writing of the paper.

Conflict of interest statement

R D James and P Hopwood have acted as consultants, and T S Maughan, R D James, J A Ledermann, M T Seymour, and P Hopwood have received honoraria and/or travel grants from AstraZeneca. D Kerr and M T Seymour were recipients of an MRC Strategic Link Project Grant which was jointly funded by the MRC and AstraZeneca.

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Clinical picture

Ischaemic ulcer from a chemical burn

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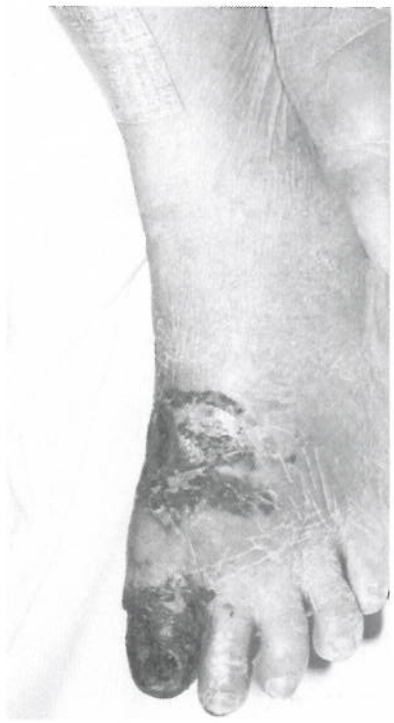

This 86-year-old diabetic Chinese woman with a painful ischaemic toe, used patches containing Chinese herbal medicine for pain relief. Note the similar angular delineation of the ulcer and the shape of the patch. The patches were used against medical advice. Diabetics are especially prone to chemical burns due to microvascular disease, neuropathy and impaired healing. Although we support the use of complementary medicines, we would not advocate the use of such patches on diabetic feet, as they may be caustic in nature.

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