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A Phase III Study of Recombinant Interleukin-2, 5-Fluorouracil and Leucovorin Versus 5-Fluorouracil and Leucovorin in Patients with Unresectable or Metastatic Colorectal Carcinoma

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135 patients with locally advanced or metastatic colorectal cancer were entered into a phase III trial evaluating the efficacy of chemoimmunotherapy [recombinant interleukin 2 (rIL2)/5-fluorouracil (5-FU) and leucovorin (LV)] versus chemotherapy alone (5-FU/LV). A cycle of chemoimmunotherapy comprised a constant intravenous infusion of rIL2 at a dose of 18 × 10^6 U/m²/24 h for 120 h, followed by three bolus injections of 5-FU (600 mg/m²) and LV (25 mg/m²) at weekly intervals. Patients receiving chemotherapy alone received 5-FU/LV at the same dose at weekly intervals for 6 weeks followed by a rest period of 2 weeks, constituting one cycle of therapy. A maximum of 6 months therapy was given in both arms of the study. The response rates (complete and partial responses) were 17% in patients receiving rIL2/5-FU/LV versus 16% in those in the 5-FU/LV arm of the study. Median survival and progression-free survival were comparable for the two groups of patients, although there was a trend for a prolongation of survival in patients receiving chemoimmunotherapy compared with chemotherapy alone, beyond 12 months. Retrospective subgroup analyses revealed a significantly increased survival in poor prognosis patients (ECOG 1) treated with rIL2/5-FU/LV when compared to those receiving chemotherapy alone. Therefore, further studies evaluating the dose and duration of chemoimmunotherapy in patients with metastatic colorectal cancer seem warranted.

Key words: recombinant interleukin-2, chemotherapy, advanced colorectal cancer, randomised trial
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INTRODUCTION

COLORECTAL CANCER continues to be a major cause of morbidity and mortality in Western societies. Surgical resection remains the mainstay of treatment, but approximately 40% of patients have lymph node metastases and one-fifth have distant metastases at the time of initial diagnosis [1]. Furthermore, the corrected 5-year survival rate is approximately 50% [2, 3] and, in specialised centres, has remained static over the last 50 years [4]. Although surgical resection of metastatic disease has been attempted, only a small number of patients with advanced

disease will benefit from this form of therapy [5]. Various chemotherapeutic agents and regimens have, therefore, been used to treat metastatic colorectal cancer [6]. The combination of 5-fluorouracil (5-FU) and leucovorin (LV) has been shown to be the most beneficial in terms of response rates and duration of effect [6]. The mechanism of action of this drug combination is unclear, but it is thought that LV promotes the binding of a 5-FU metabolite (fluorodeoxyuridylate) to the enzyme thymidylate synthetase, with resultant thymidine depletion and cell death [7]. However, the overall survival rates have been poor, with a 40% 1-year survival, and only 25% of patients being alive after 2 years [8].

An alternative approach to the treatment of metastatic colorectal cancer has been the use of cytokines. Interleukin 2 (IL2) is a 15 500 Da glycoprotein, secreted by T helper lymphocytes following activation by antigens or mitogens, and was originally described as a T-cell growth factor [9, 10]. IL2 has pleiotropic effects on the immune system. In particular, IL2 enhances natural cytotoxicity, mediated by natural killer (NK) and lymphokine-activated killer (LAK) cells [11, 12]. LAK cells, with their wide spectrum of anti-cancer cell cytotoxic effects, are believed to be important in the destruction of malignant cells, particularly with cytokine-induced immunotherapy [13]. IL2 also activates macrophages, enhancing their anti-tumour cytotoxicity. Through its effect on different lymphoreticular cells, it is a key regulator of the secretion of a wide range of lymphokines—interferon-γ (IFNγ), IL1, IL2, IL4, and tumour necrosis factors α and γ (TNFα,γ)—some of which are cytostatic and others cytotoxic [11, 14].

Initial studies showed that recombinant (r)IL2, either alone or in combination with LAK cells, could achieve response rates (partial and complete) in up to 17% of treated patients with metastatic colorectal cancer [13, 15]. However, experimental studies had shown that response rates of tumours to rIL2 therapy could be increased when used in conjunction with certain chemotherapeutic agents [16]. A recent review of rIL2 therapy in man, has also suggested that the best response rates are achieved when rIL2 is used in combination with chemotherapy [17]. Furthermore, a recent pilot study by Hamblin and associates [18] reported a response rate of 29% in patients with advanced colorectal cancer treated with rIL2 in combination with 5-FU. This latter response is better than the response rates documented for 5-FU alone (5–23%), although less than some of the response rates reported for combinations of 5-FU/LV (11–42%) [6].

A prospective, randomised multi-centre European study was, therefore, undertaken to evaluate the clinical efficacy (tumour response rate and patient survival) of rIL2 in combination with 5-FU/LV, compared with 5-FU/LV alone, in patients with metastatic and/or locally advanced (unresectable) colorectal cancer.

PATIENTS AND METHODS

Patients

A total of 135 patients with measurable metastatic or locally advanced colorectal carcinoma (Dukes C or D) were entered into the study; 133 patients were eligible for study. All patients had an ambulatory performance status (ECOG 0–1, Karnovsky ≥80%) with a life expectancy of greater than 3 months. Serum bilirubin and creatinine were within the normal range, unless elevated due to malignancy, and white blood cell (WBC) and platelet counts were greater than $>3 \times 10^9$/l and $>120 \times 10^9$/l, respectively. No patient had received systemic chemotherapy, radiotherapy or immunotherapy during the 4 weeks prior to entry into the trial. Patients were excluded if there was a significant history of cardiac disease, presence of substantial sepsis, a contra-indication to the use of pressor agents, the presence of organ allografts, evidence of CNS metastases or prior treatment with rIL2. Patients who were pregnant, lactating or were receiving corticosteroids were also excluded. After registration, all patients were stratified by centre (by telephone) and, using a random permuted blocks design, were allocated to one of the treatment arms. Ethical approval for the study to be undertaken had been given by the ethical committees of the participating institutions, and all patients gave signed, informed consent prior to participation in the study.

Treatment

rIL2/5-FU/LV. A constant intravenous infusion of rIL2 (Proleukin®, EuroCetus BV) was given on days 1–5 (18×10^6 U/m^2/24 h for a total of 120 h), followed 48 h later (day 7) by an intravenous bolus of 5-FU (600 mg/m^2) and LV (25 mg/m^2). The bolus of 5-FU and LV was then repeated on two further occasions at weekly intervals (days 14 and 21). This 4-week period of therapy constituted one cycle of treatment. Patients were then re-evaluated and re-staged after two cycles of therapy, and those with stable disease or those responding were treated with additional courses of therapy, up to a total of six cycles. If, however, they had progression of disease, therapy was stopped.

5-FU/LV. This was given as an intravenous bolus (5-FU 600 mg/m^2, LV 25 mg/m^2), at weekly intervals on six consecutive occasions followed by a 2-week rest period when no chemotherapy was given. This 8-week period constituted one cycle of treatment. Patients with stable disease or responding to therapy after the first cycle were given additional cycles up to a total of three. Therapy was stopped in patients with progression of disease.

Dose modification of rIL2. Treatment with rIL2 was temporarily discontinued if the following toxicities occurred: hypotension grade III or IV, significant cardiac arrhythmias, myocardial ischaemia, elevation of serum creatinine to 4.5 mg/100 ml, elevation of serum bilirubin to >5 mg/100 ml, bacterial sepsis, other serious side-effects or at the discretion of the investigator. Following episodes of hypotension (grade III or IV), elevation in serum creatinine to >6 mg/100 ml and/or elevation in serum bilirubin level to >5 mg/100 ml, or grade III neurotoxicity, the Proleukin® (rIL2) was subsequently administered at 50% of the original dose until it was clear that the toxicity was unlikely to recur.

Dose modification of 5-FU. 5-FU was delayed if the patient's WBC was less than 3×10^9/l and platelet count less than 100×10^9/l. If the WBC nadir was less than 2×10^9/l and/or platelet nadir less than 50×10^9/l, the dose of 5-FU was reduced by 50%. In addition, if there was diarrhoea or stomatitis the treatment was delayed until there was resolution of these side-effects.

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Evaluation of therapy

All patients had evaluable metastatic or locally advanced disease which could be measured either clinically or by using standard radiological imaging techniques—ultrasound, computerised tomography (CT) or magnetic resonance imaging (MRI). All patients were fully staged and evaluated prior to being entered into the study. All patients were restaged after 8 weeks of therapy (i.e. after two cycles of therapy in the rIL2/5FU/LV arm and after one cycle of therapy in the 5FU/LV arm) and assessment of disease response was according to WHO criteria [19]. Briefly, a complete response (CR) was defined as the disappearance of all known lesions, determined by two observations not less than 4 weeks apart. A partial response (PR) was defined as a greater than 50% reduction in tumour size (multiplication of the longest diameter by the longest perpendicular diameter); with multiple lesions, a PR was a greater than 50% decrease in the sum of the products of the perpendicular diameters of the multiple lesions, determined by two observations not less than 4 weeks apart. Stable disease (SD) was defined as less than a 50% decrease in total tumour size or less than a 25% increase in the size of the measurable lesions. Progressive disease (PD) was more than a 25% increase in the size of any measurable lesion or the appearance of new lesions. Overall survival, progression-free survival (PFS) and response duration were defined according to WHO criteria [19].

Statistical analyses

Objective response of the evaluable tumour was the primary endpoint of the study. Tumour response rates were compared between the two treatment groups using the χ^2 test. Overall survival was calculated from the date of randomisation until the last date that the patient was known to be alive. Overall the progression-free survival distributions were estimated by the Kaplan–Meier method, and comparisons between the two treatment groups were performed with the log rank statistic. The Cox proportional hazard model, using the stepwise procedure, was employed to assess the importance of potential prognostic factors on survival time, as well as to test the significance of treatment when adjusting for these factors.

The potential prognostic factors examined were age (≤60 years versus >60 years), performance status (ECOG 0 versus 1), sex (female versus male), time from diagnosis to start of treatment (≤24 months versus >24 months), prior surgery (yes versus no), prior radiotherapy (yes versus no), prior chemotherapy (yes versus no), lung metastases (yes versus no), liver metastases (yes versus no), metastases in the pelvis, urinary tract (yes versus no), lymph node metastases (yes versus no), other metastases (yes versus no) and the number of metastatic sites (1 versus 2 versus 3 or more). Differences at $P \leq 0.05$ were considered statistically significant. All statistical tests were two-tailed.

RESULTS

Patients

A total of 135 patients were randomised into the study, 66 to the rIL2/5-FU/LV group and 69 to receive 5-FU/LV, but only 129 started treatment and were fully available for assessment. 2 patients were ineligible at the start of the study, 1 having a second malignancy and the other cardiac disease, necessitating withdrawal from the study; 4 patients withdrew from the study prior to being treated. In 118 patients, the response of the metastatic tumour was evaluable, but in the other 11 patients the response to treatment was not evaluable. The details of the 133 eligible patients are shown in Table 1, with both treatment groups being comparable for age, sex, baseline performance status (ECOG 0 or 1), weight and body surface area. Analyses of the data were performed by intention to treat including all eligible patients. Data of the drop-out patients were included as far as data were available for these patients. Only the 2 ineligible patients were excluded from any of the analyses.

The patients in the rIL2/5-FU/LV arm had (i) a shorter time from initial diagnosis to appearance of metastatic disease, (ii) a shorter time from the appearance of the metastases to the commencement of therapy, and (iii) a shorter time from initial diagnosis to starting treatment ($P < 0.05$), and (iv) in the rIL2 group, 83% of the patients had only received surgery prior to treatment on this study, compared with 59% of patients in the control arm ($P < 0.05$).

Table 1. Patient characteristics of treatment groups

Characteristics	rIL2/5-FU/LV	5-FU/LV
Number of patients*	65	68
Withdrawals	1	3
Median age, years (range)	58.5 (32–75)	60 (22–78)
Sex		
Males	37 (57%)	37 (57%)
Females	28 (43%)	28 (43%)
Baseline performance		
ECOG 0	37 (57%)	42 (65%)
ECOG 1	28 (43%)	23 (35%)
Unknown		3
Weight, kg (range)		
Males	70.0 (49–93)	69.0 (51.8–100)
Females	60.7 (47–76)	59.0 (38.6–86.0)
Number of disease sites†		
One site	36 (56%)	47 (72%)
Two sites	20 (31%)	18 (28%)
Three or more sites	8 (13%)	
Diagnosis to treatment, months (median)	8.3	12.3
≤24 months	84%	75%
>24 months	16%	25%
Diagnosis to metastases, months (median)	0.1	6.1
≤24 months	91%	78%
>24 months	9%	22%
Metastases to treatment, months (median)	1.7	2.6
<2 months	61%	43%
2–3 months	13%	14%
>3 months	27%	43%
Prior therapy		
Surgery only	83%	59%
Chemotherapy	13%	19%
Radiotherapy	3%	20%
Site of disease		
Abdomen/peritoneum	9 (14%)	6 (9%)
Colon/rectum	6 (9%)	4 (6%)
Liver	54 (84%)	47 (72%)
Lung	13 (20%)	12 (18%)
Lymph nodes	11 (17%)	4 (6%)
Pelvis/urinary tract	5 (8%)	10 (15%)
Skin	1 (2%)	
Bone	1 (2%)	

* All patients excluding ineligible patients. † Disease sites of patients who withdrew were unknown.

Table 2. Total amount of recombinant interleukin-2 administered

% of planned dose	Number of treatment cycle					
	1	2	3	4	5	6
>80%	55 (86%)	35 (65%)	22 (65%)	15 (58%)	10 (63%)	5 (46%)
60–80%	6 (9%)	14 (26%)	7 (27%)	7 (21%)	4 (25%)	5 (46%)
<60%	3 (5%)	5 (9%)	5 (15%)	4 (15%)	2 (13%)	1 (9%)

Numbers shown are the numbers of patients and the % of the total number in each treatment cycle.

The percentage of patients with metastatic disease in only one site was less in the rIL2/5-FU/LV group, compared with the 5-FU/LV group (56 versus 71%). In the rIL2/5-FU/LV group, 13% of patients had three or more sites involved, compared with no patients in the 5-FU/LV group. The anatomical sites of disease are shown in Table 1, with liver being the most common site of metastatic disease, followed by lung and lymph nodes. More patients in the rIL2/5-FU/LV group had hepatic involvement, compared with the 5-FU/LV group—84% and 72%, respectively.

Therapeutic doses administered and numbers of patients in each cycle

rIL2. During the first cycle of therapy, 86% of patients received greater than 80% of the planned dose, but as the treatment progressed, fewer patients received the full dose of rIL2 in subsequent cycles. The number of patients treated in each cycle of therapy is shown in Table 2. The total number of treatment cycles administered in this treatment arm was 205.

5-FU/LV. The total dose of 5-FU/LV administered to patients in the two treatment arms was comparable, with 82–100% of patients receiving greater than 80% of the planned dose in all cycles (data not shown). The total number of treatment cycles administered in this arm of the study was 136.

Toxicity of therapy

The reasons for patients being removed from the study are shown in Table 3, and the treatment-related side-effects (grades III and IV) observed in the two treatment arms are detailed in Table 4. The number of patients experiencing grades III and IV side-effects (severe and most severe) was greater in the rIL2-treated group. There were two treatment-related deaths, both occurred in the 5-FU/LV group.

Table 3. Reasons for patients removed from treatment protocol

	rIL2/5-FU/LV	5-FU/LV
Study completed	9 (14%)	19 (29%)
Death		
Disease	2 (3%)	3 (5%)
Toxicity	0	2 (3%)
Disease progression	31 (48%)	35 (54%)
Patient request	8 (13%)	3 (5%)
Toxicity	7 (11%)	3 (5%)
Investigator decision	2 (3%)	0
Referred for surgery	2 (3%)	0
Other reasons	3 (5%)	0

Tumour responses

rIL2/5-FULV group (*Table* 5). 2 patients had a complete response and 8 had a partial response. The response rate was 17% (confidence interval (CI): 95% CI: 8–29%) of evaluable patients, and 15% (95% CI: 8–26%) of all patients. The duration of the response (median with range), was 8.2 (4.4–27.2+) months. A further 23 patients (38% of evaluable patients, 35% in total) had stasis of disease, the duration being 7.1 (1.8–20.0+) months (median and range). However, 27 patients (45% of those evaluable, 42% of all patients) had progression of disease.

5-FU/LV group (*Table* 6). 3 patients had a complete response and 6 had a partial response. The response rate was 16% (95% CI: 8–29%) of evaluable patients, and 13% (95% CI: 7–25%) of all patients. The duration of response (median with range) was 9.6 (3.6–12.4+) months. 27 patients (47% of those evaluable, 40% of all patients) had stasis of disease with a median duration of 7 months (range 2.4–30.1+ months). In addition, 22 patients (38% of those evaluable, 32% of all patients) had progression of disease.

There were no significant differences in the distribution of responses between the two treatment arms of the study.

Survival

The median survivals (ranges in parentheses) for the rIL2/5-FU/LV and the 5-FU/LV groups were 11.4 months (0.4–30.2+)

Table 4. Significant treatment-related toxicities

Toxicity	rIL2/5-FU/LV		5-FU/LV	
	Grade III No. (%)	Grade IV No. (%)	Grade III No. (%)	Grade IV No. (%)
Systemic symptoms: malaise, chills, myalgia, pain, fluid retention	6 (11%)	0	1 (2%)	1 (2%)
Pyrexia	12 (23%)	0	0	0
Cardiovascular: arrythmia, hypotension, infarction	7 (13%)	7 (13%)	0	0
Respiratory: dyspnoea, voice alteration	1 (2%)	2 (4%)	0	0
Renal: oliguria, renal failure	4 (8%)	2 (4%)	0	1 (2%)
Gastrointestinal: nausea, vomiting, anorexia, oral moniliasis	5 (9%)	0	2 (4%)	1 (2%)
Haematological: anaemia, leucopenia, thrombocytopenia, granulocytopenia	11 (21%)	0	5 (9%)	4 (8%)
Biochemical abnormalities: increases in serum bilirubin, SGOT, lactate dehydrogenase, alkaline phosphatase	18 (34%)	5 (9%)	9 (13%)	1 (2%)
Nervous system: confusion, syncope, peripheral neuropathy, somnolence	6 (11%)	1 (2%)	0	0
Skin: erythema, skin exfoliation	3 (6%)	1 (2%)	0	0

% of patients evaluable for toxicity in parentheses.

Table 5. Tumour responses to rIL2/5-FU/LV

Response	Number of patients	% of eligible patients	% of evaluable patients	Median overall survival months (range)	Progression-free survival months (range)	Response duration median (range)
Complete response (CR)	2	3%	3%	NR (8.1–28.1+)	7.7 (6.6–8.8)	5.1 (4.4–5.7)
Partial response (PR)	8	12%	13%	NR (6.0–30.2+)	9.8 (5.9–27.2+)	9.8 (5.9–27.2+)
CR + PR	10	15%	17%	NR (6.0–30.2+)	8.5 (5.9–27.2+)	8.2 (4.4–27.2+)
Stable disease	23	35%	38%	23.1 (1.8–29.3+)	7.1 (1.8–20.0+)	
Progression of disease	27	42%	45.0%	9.3 (1.4–24.4)		
Unable to determine	5	8%	—	11.2 (0.4–14.2)		
All patients	65			11.4 (0.4–30.2+)	7.8 (1.8–27.2+)	

NR, median not yet reached. + Censored data.

Table 6. Tumour responses to 5-FU/LV

Response	Number of patients	% of eligible patients	% of evaluable patients	Median overall survival months (range)	Progression-free survival months (range)	Response duration median (range)
Complete response (CR)	3	4%	5%	13.9 (12.1–13.9)	NR (7.3–12.3+)	NR (3.6–10.5)
Partial response (PR)	6	9%	10%	16.2 (6.5–19.6+)	7.1 (5.3–12.4+)	7.1 (5.3–12.4+)
CR + PR	9	13%	16%	15.3 (6.5–19.6+)	9.6 (5.3–12.4+)	9.6 (3.6–12.4+)
Stable disease	27	40%	47%	11.7 (3.1–30.1+)	7.0 (2.4–30.1+)	
Progression of disease	22	32%	38%	8.8 (1.0–15.9)		
Unevaluated	10	15%	—	1.1 (0.3–16.6)		
All patients	65			11.7 (0.3–30.1+)	7.3 (2.4–30.1+)	

NR, median not yet reached. – Censored data.

and 11.7 months (0.3–30.1+), respectively (log rank 2.51, $P = 0.113$, Figure 1). Progression-free survival was also similar between the two groups, being 7.8 months (1.8–27.2+) and 7.3 months (2.4–30.1+), respectively. Although there was a trend for prolongation of overall survival in patients treated with rIL2, with a divergence of survival after 12 months, this did not reach statistical significance.

The Cox regression model was employed to assess the effect of treatment on survival, whilst adjusting for the effect of potential prognostic variables. The analysis resulted in a significant treatment effect (χ^2 3.90, $P = 0.048$), with a risk ratio of 1.55 (95% CI: 1.00–2.38), indicating that the instantaneous death rate at each point in time for patients receiving 5FU/LV is 1.55 times the rate for patients receiving rIL2/5FU/LV. Of all

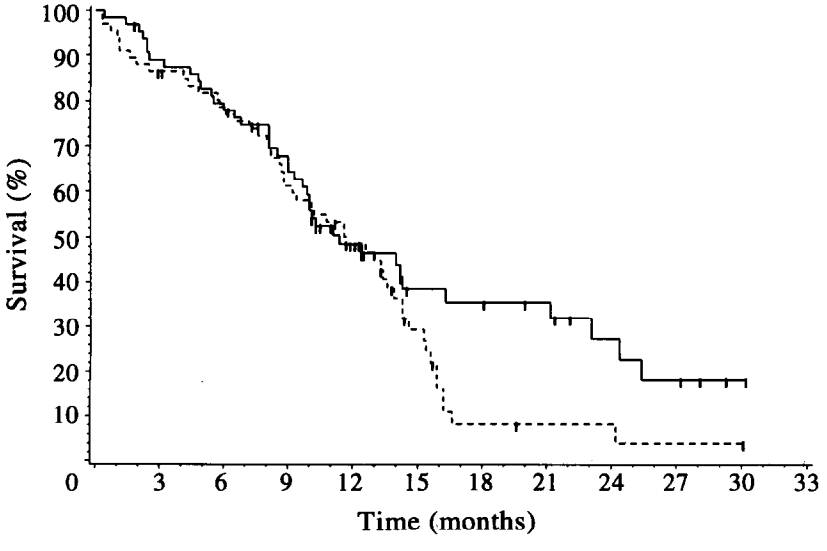

Figure 1. Kaplan–Meier survival curves for patients receiving either (i) rIL2/5-FU/LV (solid line) or (ii) 5-FU/LV (broken line) ($P = 0.113$).

the potential prognostic factors, performance status (ECOG 0 versus ECOG 1) had a significant effect on survival within the entire study population (χ^2 5.44, P = 0.02), with a risk ratio of 1.66 (95% CI: 1.08–2.54). An exploratory data analysis searching for a significant interactive relationship between treatment and performance status showed that, whilst patients with a good performance status survived equally well on either treatment, those with poor performance status (ECOG 1) seemed to survive longer receiving rIL2/5FU/LV (Figure 2). It is recognised that this association should be interpreted with caution due to retrospective subset analysis.

DISCUSSION

Clinical interest in the use of biological response modifiers (e.g. cytokines) in the treatment of malignant disease has focused on their interactions with other therapeutic agents. Cytokine-induced anti-tumour effects may result from stimulation of the host's anti-cancer immune defences and/or direct effects on the malignant cells themselves [20]. Similarly, chemotherapy has direct anti-tumour effects, in addition, to possible effects on the host's immune system—either inhibitory or stimulatory [21].

Our study has evaluated the role of rIL2, in combination with 5-FU/LV, in patients with metastatic or locally advanced colorectal cancer. The response rates, as assessed by reductions in tumour bulk, were comparable between the two groups (Tables 5 and 6). The rIL2/5-FU/LV group had an overall response rate of 15% of all patients (CR 3%; PR 12%) and in the 5-FU/LV group was 13% (CR 4%; PR 9%). These results were disappointing, when compared with results of previous studies, where patients with metastatic colorectal cancer were treated with rIL2, alone or in combination with 5-FU or with LAK cells [13, 15, 18, 22–25]. These were non-randomised, uncontrolled, phase I and phase II studies (with small numbers of patients, different doses and mode of administration of rIL2 and different treatment schedules); the response rates ranged from 0 to 33%. The duration of the response was not stated in these reported studies, except for one, where there was a median duration of response of 6 months, but survival data for these patients were not published. The combination of 5-FU/LV, given to patients with metastatic colorectal cancer, has achieved response rates of up to 42%, and survival rates at 12 and 24 months of approximately 40 and 20%, respectively [26, 27]. Recently, Yang and colleagues [28] reported the results of treating 25 patients with metastatic colorectal cancer with chemoimmunotherapy in a phase II study. The treatment regimen was different and more complicated than that of our study, used high doses of 5-FU and LV and high bolus doses of intravenous rIL2. They reported a 44% response rate (2 patients had complete responses and 9 had partial responses), but all these patients had demonstrated a major response to 5FU/LV before receiving rIL2 [28]. However, all responding patients relapsed, either during or after cessation of therapy, and 5 of 24 patients had died with a median follow-up of 17.5 months.

In our study, which is the first substantial, prospective, randomised investigation carried out to date, the survival rates were similar to some of the best reported for chemotherapy alone in colorectal cancer. The probability of survival was 50% at 12 months with either rIL2/5-FU/LV or 5-FU/LV. However, beyond 12 months and with prolonged follow-up, a trend became apparent for the rIL2/5-FU/LV group to have an improved survival compared with the patients receiving 5-FU/LV alone. This survival advantage did not reach statistical significance by univariate analysis (log rank test; P = 0.125), but using a multivariate analysis (SAS, PHREG procedure; P = 0.0018), it was found that the treatment varied with performance status. In other words, a retrospective subgroup analysis of the patients with a poorer performance status (ECOG 1) revealed that rIL2 treatment was associated with an improved survival when compared with patients receiving chemotherapy alone. However, since the subgroups were not previously defined, these results need to be interpreted with caution. The tumour doubling time for common tumours has been reported to vary from 70 to greater than 200 days [29, 30], and it is possible that rIL2, although not causing regression of the tumour, reduced the rate of tumour cell proliferation. There are data from tumour cell lines to show that cytokines can modulate tumour cell growth [20] or enhanced apoptosis in susceptible cells [31]. Such a possible mode of action may explain the prolongation of survival

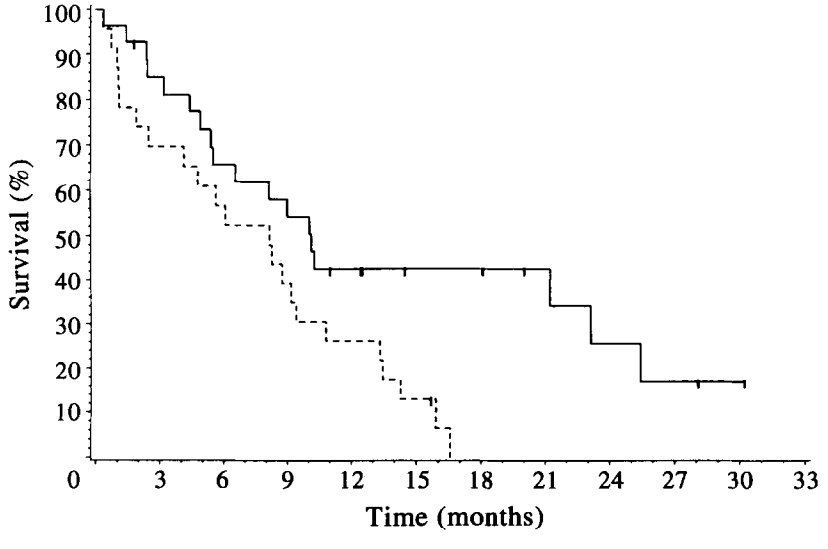

Figure 2. Kaplan–Meier survival curves for patients with performance status ECOG 1, receiving either (i) rIL2/5-FU/LV (solid line) or (ii) 5-FU/LV (broken line) (P = 0.015).

in a subgroup of rIL2/5-FU/LV-treated patients, apart from any beneficial effect of enhancement of anti-cancer host defences.

Side-effects in all major organ systems were observed following administration of rIL2, as shown in Table 4, but these were mainly grades 1 and 2 toxicities, with fewer patients experiencing severe or life-threatening side-effects (WHO classification). However, toxicity was the reason for stopping treatment in 11% of patients in the rIL2/5-FU/LV group. In contrast, in the 5-FU/LV group, 5% of patients had treatment stopped because of toxicity, but there were two deaths attributed to chemotherapy toxicity.

In summary, this randomised, controlled trial, comparing chemotherapy that included rIL2 with chemotherapy alone in patients with metastatic colorectal cancer has demonstrated that rIL2 does not increase clinically demonstrable tumour response rates. However, there appears to be a trend towards a prolongation of survival in the subgroup of patients with ECOG performance status of 1 who received rIL2 (although this could be a chance finding, since subgroup analyses were not predefined). Further confirmatory studies also evaluating the dose and duration of therapy with chemoimmunotherapy in patients with metastatic colorectal cancer seem warranted.

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