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Original article

High- *versus* low-dose levo-leucovorin as a modulator of 5-fluorouracil in advanced colorectal cancer: A 'GISCAD' phase III study

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Summary

Background: Although leucovorin (LV) + 5-fluorouracil (5-FU) is considered the treatment of choice for advanced colorectal cancer in most countries, the optimal schedule of this combination has not yet been established. Low-dose LV appears to be as active as high-dose LV in the daily-times-five regimen, but no randomized study of the levorotatory stereoisomer (6S-LV) given at two different dose levels has been published.

Patients and methods: Between November 1991 and June 1994, 422 patients (all with measurable disease previously untreated with chemotherapy) were randomized to 6S-LV (100 mg/sqm/i.v.) + 5-FU (370 mg/sqm/15 min i.v. infusion), both administered for 5 days every 28 days (arm A), or to 6S-LV (10 mg/sqm/i.v.) + 5-FU (doses as above), also given for 5 days every 28 days (arm B). The primary endpoint of the study was the comparison of response rates (WHO criteria); the secondary endpoint was the assessment of survival and tolerability. No evaluation of the quality of life or the symptomatic effect of treatment was planned.

Results: The response rate was 9.3% in arm A (95% CI: 5.4–13.1), with 2 CR and 18 PR, and 10.7% in arm B (95% CI: 6.5–14.9), with 3 CR + 19 PR, without any significant difference ($P = 0.78$). The median time to progression was eight months in both groups and overall survival was 11 months, with no difference between treatments. Toxicity mainly consisted of gastrointestinal side effects (mucositis and diarrhoea), which were rarely severe (grade 3–4: 5%–10% of patients) and similar in the two groups.

Conclusions: In this large-scale multicentre trial, the low and high doses of 6S-LV appeared to be equivalent in terms of the biochemical modulation of 5-FU in advanced colorectal cancer although, for several reasons (including the timing and the strict criteria of response evaluation, the high number of patients with unfavourable prognostic factors, the multi-institutional nature of the study, the dose and modality of 5-FU administration), the response rate was lower than that reported in some of the other published studies. Given the considerable difference in economic cost between the two dosages, the use of high-dose 6S-LV in the daily-times-five regimen is not recommended in clinical practice.

Key words: biochemical modulation, colorectal cancer, 5-fluorouracil, high- *versus* low-dose, L-leucovorin

Introduction

The optimal treatment for advanced colorectal cancer has not yet been established: for more than 30 years, 5-fluorouracil (5-FU) has been the drug of choice but the response rate to bolus infusions is only 10% and median overall survival does not exceed one year [1]. Continuous efforts have been made to increase 5-FU activity by modifying the schedule of administration (short- or long-term continuous infusion, circadian rhythm modulated chemotherapy, etc.) and/or by adding biochemical modulators (leucovorin-LV, methotrexate, interferon-α, PALA, dipyridamole, hydroxyurea). Although the recent development of 5-FU analogues and innovative compounds has increased the therapeutic arsenal of medical oncologists, biochemical modulation is still of interest. LV has been shown to increase the activity of 5-FU in advanced disease [1] and to be of benefit in the adjuvant setting [2–5]. An important issue concerns the LV dose needed for optimal 5-FU modulation: the weekly schedule seems to require high doses whereas in the daily-times-five regimen low doses appear to be at least equally effective in terms of response rate, symptomatic relief and overall survival [6]. Moreover, since the publication of the results of a prominent trial [7] showing that the low-dose daily-times-five regimen has a better therapeutic index than the high-dose weekly schedule, the Mayo regimen has been considered the standard treatment for advanced colorectal cancer not only in North America, but also in much of Europe.

The levorotatory stereoisomer (6S) of LV represents the active form of the natural racemic compound, and its clinical activity was demonstrated in phase II studies [8, 9] in which the daily-times-five regimen was used at

high doses (50% of the racemic compound). Given that 6S-LV is commercially available in a number of European countries, comparative evaluation of the effect of two dose levels on the biochemical modulation of 5-FU appeared to be of interest and prompted our Group to initiate a phase III trial in advanced colorectal cancer in November 1991.

Patients and methods

Patient selection

Between November 1991 and June 1994, 422 patients were enrolled by 28 GISCAD-affiliated medical oncology centers (referral institutions and general hospitals). The patients were centrally randomized by the GISCAD Operational Office, and stratified by center in variously-sized blocks using an assignment ratio of 1 : 1.

The eligibility criteria included evidence of advanced colorectal cancer (with the exclusion of single or limited liver and lung metastases amenable to surgical resection); histological assessment of the primary tumour and, whenever possible, of the metastases; no previous chemotherapy for advanced disease (adjuvant treatment was permitted provided it had been completed at least one year before entry); at least one measurable lesion assessable by means of imaging techniques (X-rays, ultrasound, CT scan, NMR); aged 18–75 years; ECOG performance status of two or less; no other malignancies or serious illnesses; no significant hepatic, renal or cardiac failure, no brain metastases; and a life expectancy of three months or longer. All of the patients gave their informed consent in accordance with the policy of the respective institutions.

Treatment

6S-LV (Lederfolin, Cyanamid Lederle) was administered as a 100 (arm A) or 10 (arm B) mg/sqm i.v. bolus and immediately followed by 5-FU (Fluorouracile, Roche) 370 mg/sqm i.v. given as a 15-min infusion. Both drugs were administered for five consecutive days and recycled every four weeks.

Dose modifications were planned on the basis of haematological (leuco- and/or thrombocytopenia) and non-haematological (diarrhoea, mucositis) toxicity observed in the previous cycle and evaluated using WHO criteria [10]. In particular, in the instance of grade 1 myelosuppression (to be evaluated on day 1 of each cycle), therapy was interrupted until normalisation; in the instance of grade 2 myelosuppression, the treatment was discontinued until full recovery and then 75% of the 5-FU dose was administered; the dose was reduced by 50% in the instance of grade 3–4 leuco- and/or thrombocytopenia. If grades 2–4 mucositis or diarrhoea occurred, the treatment was interrupted until normalisation and then 50% of the 5-FU dose was administered; in the instance of good tolerance of this dose, the doses in every course in the subsequent cycles were increased by 100 mg/sqm/day until the initial dosage was restored. If tolerance was bad, the dose was reduced to 25% of its initial level. Upon the development of any other grade 3–4 toxicities (except alopecia), 50% of the 5-FU dose was administered. No reduction in the 6S-LV dose and no escalation of the 5-FU dose was planned.

Evaluation

After three courses of treatment, the patients were evaluated for objective tumour response: imaging by various techniques (CT scan and/or NMR and/or ultrasound for liver and abdominal metastases, chest X-ray with or without CT scan for lung lesions) was required in every case. The criteria were those recommended by the WHO [10]. Multiple reviewers at each institution, including one or two medical oncologists and a radiologist, were asked to confirm the magnitude of response; a central verification of the objective remission was not planned.

In the instance of complete response (CR), more courses were administered as consolidation and the patient was then strictly monitored, every partial response (PR) was treated until progression. When there was no change (NC), the patients received three further courses and, if they achieved a CR or PR, they were managed as above; in the case of NC or PD, they received the best supportive therapy only, as did those showing PD after the first three courses.

The median time to progression was calculated from the beginning of chemotherapy.

Survival was calculated from the start of chemotherapy using the Kaplan–Meier method [11], and the survival curves were compared using the log-rank test [12].

No formal assessment of quality of life and/or the palliative effects of treatment (symptomatic relief, pain reduction) was planned in this study.

Statistical considerations

With an expected response rate to the 'standard' treatment (high-dose 6S-LV) of 20%, the sample size was calculated in order to detect equivalence between the two regimens in terms of response rate, with an alpha error = 0.05 and a power (1-beta) = 0 80; 198 patients per arm were required with an accrual of three years. Objective responses were compared by means of Fisher's exact [13] and Pearson's chi-square tests [14]. Relative risk was calculated when appropriate, as well as its confidence interval. A multivariate analysis of survival was made using Cox's model [15], as was an analysis of the response rate

Results

During the 32 months of accrual, 216 patients were randomized to arm A (high dose 6S-LV), and 206 to arm B (low dose 6S-LV). Their characteristics are shown in Table 1: the two groups were well-matched in terms of their demographic data, performance status and sites of disease, and there was no evidence of any allocation bias. About 40% of the patients in each arm had multiple disease sites and nearly 50% were symptomatic, both of which are factors known to have a potentially negative impact on prognosis.

The median number of administered courses was five in both arms (range: 1 to 11), with an average delivered dose intensity that was 90% of that planned.

Efficacy

At the time of this report, the median follow-up is 22 months and most of the patients have died. The overall response rate is summarized in Table 2: no difference was observed between the two arms, in terms of the response rate (9.3% *versus* 10.7%, with 95% confidence intervals (CI) of 5.4–13.1 and 6.5–14.9, respectively) or the median time to progression (eight months in both groups). The five complete responses were obtained in four patients with liver and one with lung + liver metastases. Over 50% of the patients progressed during treatment; like these, the small number of patients (4% of the total) who did not receive adequate chemotherapy (refusal, loss to follow-up, or early death) were included in

the final analysis and considered as treatment failures, in accordance with the 'intent-to-treat' principle. At univariate and multivariate analysis, the comparative evaluation of objective responses in the two groups was not affected by any potential prognostic factor.

Survival

Figure 1 shows the Kaplan–Meier plot of the time to death: median survival was 11 months in the two groups, with no significant treatment-related difference.

Once again, multivariate analysis revealed no differences between the two arms.

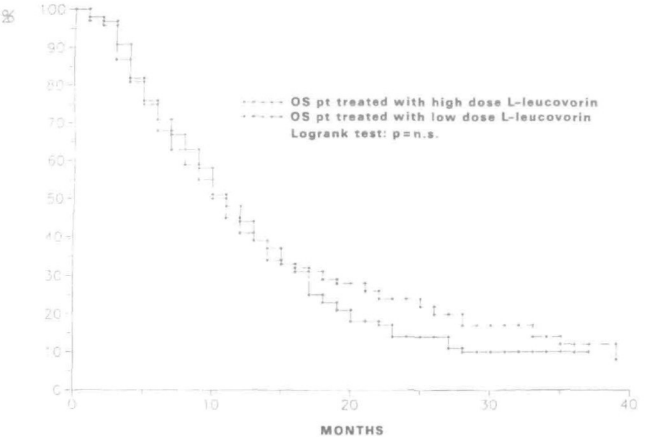

Figure 1. Overall survival.

Table 1 Patient characteristics.

	Arm A	Arm B
No. of patients	216	206
Mean age (range)	61 (31–75)	61 (32–74)
Gender		
Male	132	120
Female	84	86
Primary		
Colon	169	154
Rectum	44	49
NA	3	3
Site of metastases		
Liver	83	70
Lung	12	19
Local recurrence	9	8
Others	19	18
Multiple (with liver)	69	67
Multiple (without liver)	20	17
NA	4	7
Histological grading		
G1	16	32
G2	162	136
G3	28	31
NA	10	7
Performance status (ECOG)		
0	107	99
1	83	83
2	21	19
NA	5	5
Median number of courses (range)	5 (1–11)	5 (1–10)
Average delivered dose intensity (mg/sqm/week)	417	420

Abbreviation: NA – not assessed.

Table 2. Objective responses (WHO criteria).

	Arm A	Arm B	
CR	2	3	
PR	18	19	
NC	71	74	
PD	115	103	
Patients who did not receive adequate chemotherapy	10	7	
CR + PR	9.3%	10.7%	$P = 0.78$
(95% confidence intervals)	(5.4–13.1)	(6.5–14.9)	
Median time to progression	8 months	8 months	

Toxicity

The side effects observed are listed in Table 3: considering the worst level of toxicity occurring in each case, nearly half of the patients experienced diarrhoea and/or mucositis, but these were severe (grades 3 or 4) in only 5%–10% of cases, with two toxic deaths of uncontrollable diarrhoea (one in each arm). Although frequent, nausea and/or vomiting were rarely severe, and other side effects, such as myelosuppression, were very rare. There were no episodes of treatment-related cardiopathy and grades 3–4 alopecia affected fewer than 2% of the patients. Toxicity in the two arms was completely super-imposable.

Discussion

Although new analogues, such as uracil-tegafur [16] and doxifluridine [17], and innovative compounds such as raltitrexed [18], irinotecan [19] and oxaliplatin [20] are now available for the treatment of advanced colorectal cancer, 5-FU remains the reference drug in both clinical research and practice. Of the various attempts made over the last few years to increase drug activity by modifying the administration schedule, the most prom-

Table 3 Toxicity (WHO criteria).

	Grade 1	Grade 2	Grade 3	Grade 4
Arm A				
Nausea/vomiting	31%	14%	2%	1%
Diarrhea	27%	22%	7%	3%
Mucositis	21%	17%	5%	2%
Leucopenia	5%	4%	2%	1%
Thrombocytopenia	1%	1%	0%	0%
Arm B				
Nausea/vomiting	24%	10%	2%	0%
Diarrhea	20%	11%	3%	2%
Mucositis	19%	10%	4%	1%
Leucopenia	2%	5%	0%	1%
Thrombocytopenia	1%	0%	0%	1%

ising seems to be the use of continuous infusion, as has also been demonstrated by recent comparative studies [21]. Another approach has been that of biochemical modulation: i.e., the association of 5-FU with agents capable of increasing the activity and/or reducing the toxicity of the drug by means of interactions with its metabolic pathways. Of the various compounds evaluated in clinical trials, LV appears to be of particular interest: the response rate in phase III studies fluctuates from 15% to 48% and a meta-analysis [1] has established a cumulative value of 23%, which is significantly better than that of 5-FU alone, but there has been no increase in overall survival.

An important issue in the evaluation of LV + 5-FU is the definition of the best treatment schedule, particularly in relation to the dose of LV needed for optimal 5-FU modulation [22]: the weekly schedule seems to require high doses [23, 24], whereas in the daily-times-five regimen low doses appear to be at least equally effective in terms of response rate, symptomatic relief and overall survival [25, 26], and to allow for a considerable reduction in economic cost ($545 *versus* $4,110 for six months of treatment) [6]. From the experimental point of view, Cao and Rustum [27] recently developed a new study model and confirmed that the monthly regimen seems to be active also with low doses. On the other hand, Etienne and Milano [28] emphasized the importance of administering high doses of LV in order to achieve high plasmatic folate concentrations and to counteract the variability of the required concentrations.

A direct comparison of the two regimens most widely used in North America (weekly high-dose LV and daily-times-five low-dose LV developed at Roswell Park and Mayo Clinic, respectively) demonstrated the superior therapeutic index of the low-dose schedule, indicated by its similar activity but much lower financial cost and reduced need for hospitalization to manage treatment-related toxic effects [7]. Although the Mayo regimen (5-FU 425 mg/sqm plus LV 20 mg/sqm i.v. push daily for five days, with courses repeated at four- to five-week intervals) is considered the standard chemotherapy for advanced colorectal cancer in North America and is also widely used in Europe, the debate about the optimal LV dose is still open: some authors point to the different spectrums of toxicity of the two reference regimens and assert the freedom of choice of the individual clinician [29], whereas others claim that other methods of calculating economic costs lead to very similar profiles for the two regimens [30]. Moreover, a recent study demonstrated a lower response rate (17% *versus* 34%), when the Mayo regimen was compared to a bi-monthly combination of 5-FU bolus and continuous infusion with high-dose LV even though survival rates were similar [31].

The present study arose from the need to confirm the equivalence of activity of low- and high-dose LV (daily-times-five regimen) in the biochemical modulation of 5-FU in one European country. Our purpose was to evaluate the two regimens in a large number of patients with measurable disease followed in referral institutions and general hospitals in order to establish the reproducibility and feasibility of the treatment in clinical practice. As the health care system in our country is mainly based on public funding, the potential economic spin-off of a study comparing two regimens with such a great difference in drug costs prompted the Italian National Research Council to support the trial entirely.

An original and interesting aspect of our study concerns the use of 6S-LV: this is the active form of the natural racemic compound (in which 6S- and 6R- stereoisomers are equally represented) and was developed in its purified form in 1990. Phase II studies, carried out in North America and Europe [8, 9] evaluated 6S-LV in the high-dose daily-times-five regimen and demonstrated an activity that was comparable to that of the racemic compound; phase III trials directly comparing the two formulations of the drug were conducted both in the US (NCCTG) and Europe (Vienna). The first available results were reported in 1996: Goldberg [32], in a very large trial, observed no difference, in terms of response, survival and toxicity, among patients treated with high-dose 6 R,S- or 6S-LV, both given by i.v. route, or oral 6 R,S-LV in association with the same 5-FU dose as used in our study. Given that pure 6S-LV is the only formulation of the drug now available in various European countries (in Italy since May 1991), it seemed to be of interest to evaluate two dose levels of this compound in a large-scale pragmatic trial.

In analogy with the NCCTG trial [25], the low dose of LV used in our study was 10% of the high dose, and the reference schedule was the same as the one developed at Villejuif [33] in order to be able to make a comparison with the regimen considered 'standard' in Europe at the beginning of the nineties. Since the first endpoint of the study was to evaluate the response rate (on the basis of previous studies, it did not seem to be realistic to look for a difference in overall survival), only patients with measurable disease were included in the trial, and a large number of cases was required in order to demonstrate the equivalent activity of the two treatments. No formal evaluation of the quality of life and/or the symptomatic effects of treatment was made as the NCCTG data [25, 26] seemed to us exhaustive on these points. Accrual was very satisfactory, indicating a high level of interest in the trial, and allowing the study to be concluded four months before the planned date. The results clearly indicated that, also with the levorotatory stereoisomer, low LV doses are equivalent to high doses when attempting to biochemically modulate 5-FU in the context of a daily-times-five regimen in terms of response rate, survival and tolerability, suggesting that the lower dose should be favored for economic reasons in clinical practice and as the standard arm in future comparative studies.

Although the purpose of this trial was to compare the two different treatments without regard for their overall level of activity, the low response rate in both arms deserves some comment. The confidence limits corre-

spond to those reported in previous trials of 6S-LV, but clearly a response rate of no more than 10% is disappointingly lower than expected. We feel that the main reasons for this are the multi-institutional characteristics of the study itself (with the inclusion of a large number of patients, many of whom had potentially unfavourable prognostic factors, even though some important predictive elements like WBC count, LDH and CEA levels were not specifically studied), the strict evaluation of objective response (we required the use of imaging techniques in every case, which should be standard but are not always applied in every study) and the response evaluation after three courses of treatment (this probably misses some responses and can subject patients with progressive disease to unnecessarily prolonged treatment). Moreover, the 5-FU dose chosen in our trial was 13% lower than in the Mayo regimen and it is possible that the particular modality of the administration of 5-FU may also have played a role: the Nordic Group suggested that a 'short, not bolus' (10–15 min) infusion may be less active and toxic than a 'true' bolus (2–3 min) [34], and Wadler [35] has recently pointed out that biochemical modulation regimens are particularly sensitive to a number of variables, including the timing and duration of administration. Finally, it is noteworthy that recent large-scale comparative studies [18, 21, 31] in which the standard arm was represented by a low-dose LV daily-times-five regimen (usually the Mayo schedule) have reported much less activity for this combination in comparison with the first papers [25, 26], an observation which underlines the difficulty of making inter-trial comparisons and determining the true impact of a given therapy. Further evaluation of the factors which may influence assessment of activity in clinical trials and the usefulness of making a strict meta-analysis of all of the studies comparing low- and high-dose LV may be considered ancillary outcomes of this study and will be among our programs in the near future.

In conclusion, our data indicate that low and high doses of the levorotatory pure form of LV are equivalent when combined with 5-FU (in the context of the daily-times-five regimen) in advanced colorectal cancer: for financial reasons, the lower dosage should therefore be favored in clinical practice and as the reference treatment in future trials evaluating new drugs or combinations.

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