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Review

A Review of GERCOD Trials of Bimonthly Leucovorin Plus 5-Fluorouracil 48-h Continuous Infusion in Advanced Colorectal Cancer: Evolution of a Regimen

A. de Gramont,[1] C. Louvet,[1] T. André,[2] C. Tournigand[1] and M. Krulik[1] from the Groupe d'Etude et de Recherche sur les Cancers de l'Ovaire et Digestifs (GERCOD)

[1]Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, 75571 Paris Cedex 12; and [2]Hôpital Tenon (service du Pr Izrael), 4 rue de la Chine, 75020 Paris, France

The addition of leucovorin (LV) to 5-fluorouracil (5-FU) in advanced colorectal cancer has shown improved tumour response rates in many trials, but the optimal LV/5-FU regimen has yet to be determined. Seven studies carried out over the last 12 years to evaluate the safety and efficacy of various LV/5-FU regimens are reviewed. The initial bimonthly high-dose LV/5-FU regimen consisted of high-dose LV as a 2-h infusion followed by 5-FU as an intravenous (i.v.) bolus plus a 22-h continuous infusion (CI), repeated for two consecutive days every 2 weeks. A randomised comparison of this bimonthly high-dose LV/5-FU regimen and the NCCTG–Mayo Clinic regimen (LV [20 mg/m^2/day] followed by 5-FU bolus [425 mg/m^2/day] daily × 5, every 4 weeks) showed that the bimonthly high-dose LV/5-FU regimen was superior to the NCCTG–Mayo Clinic regimen in response rate and progression-free survival, but showed no difference in overall survival. In addition, toxicity was less with the bimonthly high-dose LV/5-FU regimen. These promising results led to a phase II trial of a simplified bimonthly high-dose LV/5-FU regimen consisting of LV (500 mg/m^2/day) and a 48-h CI of 5-FU (1.5–2 g/m^2/day) which has been administered alone or in combination. In summary, GERCOD-sponsored studies have further demonstrated that higher doses of both LV and 5-FU given as a CI can improve response rates still more with acceptable toxicity. Further studies are focused on the effectiveness of combination with oxaliplatin or CPT-11 in metastatic disease and the use of high-dose LV/5-FU regimens for colorectal cancer in the adjuvant setting. © **1997 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

THE ENHANCED efficacy of the combination of leucovorin (LV) and 5-fluorouracil (5-FU) over that of single-agent 5-FU in advanced colorectal carcinoma has been demonstrated in several randomised comparative clinical trials conducted over the last decade. A meta-analysis of nine such trials involving 1381 patients that compared 5-FU regimens with regimens containing 5-FU and LV found significantly improved tumour response rates when LV was added to the treatment regimen (23% versus 11%; response odds ratio 0.45; $P < 10^{-7}$) [1]. However, these improved tumour response rates with concomitant LV were not reflected in longer overall survival, which remained comparable for the two treatment arms (11.5 months for LV/5-FU; 11 months for 5-FU alone; $P = 0.57$) [1], and the optimal treatment regimen for advanced colorectal cancer is yet to be determined.

In an effort to improve treatment outcome, parameters of the LV/5-FU regimen have been varied in clinical trials, including dose, method of drug administration (bolus versus continuous infusion) and treatment schedule (weekly, bimonthly, monthly) [2–6]. No consistent relationship between the 5-FU and LV dose and/or schedule, and the ensuing response rate or survival has been observed. Even when a survival advantage is seen for the LV/5-FU regimen,

Correspondence to A. de Gramont.
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as in one study where both high- and low-dose LV/5-FU led to significantly longer survival than single-agent 5-FU (12.2, 12.0 and 7.7 months, respectively; $P = 0.037$ and 0.050, respectively), the longer survival is no greater than that found in other studies that failed to find a treatment effect [5, 7, 8].

In 1984, the Groupe d'Etude et de Recherche sur les Cancers de l'Ovaire et Digestifs (GERCOD) began a research programme aimed at improving response rates and outcome in advanced colorectal cancer, which has resulted in 16 phase I, II or III trials evaluating different treatment regimens for this disease. This report reviews results from seven of the most important trials and details the evolution of a bimonthly high-dose LV, high-dose 5-FU continuous infusion regimen that has been shown in several studies to produce improved response rates, even in patients previously treated with LV/5-FU regimens.

Background

Following encouraging results in phase I and II trials that indicated antitumour activity of the LV/5-FU combination, several randomised phase III trials were initiated to investigate further the magnitude of this activity [9]. Two major treatment strategies were initially developed: a weekly schedule, and a daily $\times 5$ schedule repeated every 4–5 weeks [3, 10]. One variant of the latter, the North Central Cancer Treatment Group (NCCTG)–Mayo Clinic regimen, was shown to increase patient survival and interval to progression, improve tumour response rates, and improve quality of life, over the use of 5-FU alone [5]. Significantly improved survival, interval to progression and response rates were seen with both the low- and high-dose LV regimens (20 mg/m^2 and 200 mg/m^2 with 5-FU at 425 mg/m^2 and 370 mg/m^2, respectively), but only the former regimen was associated with significant improvement in all quality-of-life variables. The authors note that the magnitude of the improvements seen with the LV/5-FU regimens are not great. A later comparative study confirmed the value of the low-dose LV/5-FU daily $\times 5$ regimen over 5-FU plus methotrexate in survival, tumour response and interval to progression [8]. Although the higher-dose regimen (LV at 200 mg/m^2/day) also led to significantly better tumour response and longer interval to progression in this study, a survival advantage over the low-dose regimen was not demonstrated when covariates were taken into account in the statistical analysis. No significant differences in efficacy were seen in comparisons of the low- and high-dose LV/5-FU regimens themselves. The authors concluded that neither regimen was superior to the other based on the outcome of this trial, but favoured the low-dose regimen because of cost issues. Thus, the question of the optimal LV and 5-FU dose levels remained unresolved.

In addition to dose magnitude and schedule, clinical trials have varied the method of administration of 5-FU (bolus or continuous infusion). Several arguments can be made in favour of continuous infusion (CI) over bolus dosing: given the short half-life of 5-FU (10–20 min) [11], it is important to maximise exposure to high levels of the cytotoxic agent when cells are in the S phase, the only time of vulnerability to 5-FU [11, 12]. In addition, a several-fold higher total tolerated dose of 5-FU can be delivered as a CI rather than via the bolus route [11, 13–16].

For example, in one clinical trial, 155 patients with measurable disease were randomised to receive either CI or bolus 5-FU [13]. Patients received either 5-FU CI at 750 mg/m^2/day for 7 days every 3 weeks, or bolus 5-FU at 500 mg/m^2/day over 30 min every 4 weeks. The median dose intensities were 1369 mg/m^2/week for CI and 558 mg/m^2/week for bolus infusion. After 2 months of treatment, the response rates for the CI and bolus groups were 19% and 8%, respectively, a significant difference ($P < 0.02$) [13].

Other clinical trials comparing single-agent 5-FU CI with bolus administration have found considerably higher response rates among patients in the CI arm [14–16]. Response rates in one randomised study involving 174 patients were 30% for those who received 5-FU (300 mg/m^2/day) as a prolonged CI versus 7% for patients who received bolus 5-FU (500 mg/m^2 daily $\times 5$, repeated every 5 weeks), a significant difference ($P < 0.001$) [14]. Survival, however, was similar for patients in the two arms (median survival 10 and 11 months, CI and bolus arms, respectively).

Survival (13 months versus 10.4 months) was also similar in two arms of a large randomised trial comparing protracted CI of 5-FU (300 mg/m^2/day) in 159 patients with bolus 5-FU (500 mg daily $\times 5$ and then 600 mg weekly $\times 6$) in 153 patients with advanced colorectal cancer [16]. The overall response rate was 28% versus 18% for single-agent 5-FU administered by CI versus bolus ($P = 0.045$).

LV can potentiate the effects of 5-FU administered as a CI, but does not appear to enhance the effects of 4-day or longer (28 days) 5-FU infusions [2, 15]. Toxicity patterns differ for the CI and bolus routes, with stomatitis and palmar–plantar erythrodysesthesia (hand–foot syndrome) more common after CI, and leucopenia more common after bolus administration. Toxicity is less with CI than bolus in most published reports [13–16].

THE GERCOD EXPERIENCE

Based on the preceding results showing advantages in both efficacy and safety for 5-FU regimens given as a CI, a series of studies was carried out under the sponsorship of GERCOD (Table 1) [17–23]. The initial goal was the evaluation of a high-dose LV/5-FU regimen given as a bolus followed by CI. *In vitro* synergism between 5-FU bolus and 5-FU infusion has been demonstrated [24]. To this end, a phase II study (study C85) was conducted in 37 chemotherapy-naive patients with advanced colorectal cancer who received the initial LV5FU2 regimen: first course, intravenous (i.v.) LV at 200 mg/m^2 in a 2-h infusion, followed by a 5-FU i.v. bolus at 300 mg/m^2, then 5-FU i.v. at 300 mg/m^2 in a 22-h CI (day 1) [17]. This procedure was repeated on day 2 (D2), and the whole cycle repeated beginning on day 14. The dose of 5-FU was increased in subsequent cycles if no toxicity was observed.

Results with this regimen of LV, 5-FU bolus and CI were one complete response (2.7%) and 19 partial responses (51.4%), with a median survival of 18 months [17]. Sixty-four per cent of the patients were alive at 1 year, and 21% were alive at 2 years. Median survival for responders was 21 months, for patients with stable or progressive disease, 12 months and 7 months, respectively. Covariates such as sex, age, performance status, tumour mass, site of metastasis, pretreatment alkaline phosphatase and 5-FU dose did not significantly affect survival. A decrease in carcinoembryonic antigen (CEA) was correlated with the response, with a decrease in CEA > 50% predictive of a response with 76.5% sensitivity [17].

Table 1. *Summary of the GERCOD studies reviewed*

Study regimen	C85 [17] Phase II LV5FU2	C91-1 [18] Phase III LV5FU2	C91-2 [19] Phase II LV5FU2H	C93-1 [20] Phase II FOLFUHD	C93-3 [21] Phase II FOLFIN	C91-2 [19] Phase II LV5FU2H	C93-2 [22] Phase II FOLFOX2	C94-1 [23] Phase II FOLFOX3
Population	Untreated	Untreated	Untreated	Untreated	Untreated	Pretreated	Pretreated	Pretreated†
Number	37	217/175*	31	101	50	37	46	30
Gender M/F	18/19	135/82	15/16	62/39	23/27	27/10	29/17	13/17
Median age	61.5	60.9	62.5	60.7	56	59.5	59.4	58.5
Liver metastases	68%	81%	74%	78%	86%	86%	85%	80%
Responses								
CR + PR	54%	32.6%*	37%	33.7%	44%	11%	45%	20%
Stable	21.6%	35.4%*	44%	44.6%	46%	43%	46%	50%
Progression	24.3%	32%*	19%	18.8%	10%	46%	7%	30%
Survival								
Median TTP	8.0 mo	6.4 mo	8.3 mo	8 mo	9 mo	6.5 mo	7 mo	6 mo
Median survival	18 mo	16.6 mo*	20 mo	18 mo	25 mo	12.3 mo	17 mo	10 mo
1 year	64%	62%*	63%	74%	82%	54%	72%	42%
2 year	21%	29%*	41%	37%	52%	20%	27%	NA
Grade 3–4 toxicity	5.4%	11.1%	12.9%	15.1%	42%	8.1%	46%	27%

*Measurable disease. †Refractory to LV/5-FU.
mo, months; CR, complete response; PR, partial response; TTP, time to progression; NA, not applicable.

Toxicity, moderate and controllable by dose reduction as specified in the protocol, included nausea after bolus 5-FU (in 11.5% of patients), manageable with metoclopramide, and diarrhoea not sufficiently severe to require i.v. hydration (17% of patients) [17]. The majority (73%) of the patients received the maximum 5-FU dose in the third treatment course, and there were no deaths related to drug toxicity.

This study confirmed that the LV5FU2 regimen, LV and 5-FU delivered via both bolus and CI routes, has antitumour activity in patients with metastatic colon cancer with manageable toxicity. Although toxicity usually limits the 5-FU dose that can be given via bolus to a range of 350–400 mg/m^2 over a period of 4–5 days, the CI schedule used in this initial phase II study allowed the monthly dose of 5-FU to reach 4 g/m^2 in 72% of the patients [17].

Perhaps most importantly, the median survival of 18 months was encouraging and appeared higher than reported with certain other LV/5-FU regimens [6, 8]. Even survival among patients with stable disease was relatively high (12 months), perhaps reflecting the effects of the treatment regimen [17]. To explore the value of the LV5FU2 regimen further, a randomised trial (study C91-1; Table 1) was initiated comparing a modified version of this regimen with the NCCTG–Mayo Clinic regimen [18].

Comparison of LV5FU2 and the NCCTG–Mayo Clinic regimen (study C91-1)

A randomised, phase III clinical trial involving 433 evaluable patients was conducted between February 1991 and April 1994 [18]. After stratification for performance status, presence of measurable disease and synchronous versus metachronous metastases, 216 patients were assigned to the NCCTG–Mayo Clinic regimen and 217 patients to the LV5FU2 regimen (Figure 1a). Patients in the NCCTG–Mayo Clinic arm received LV at 20 mg/m^2/day as an i.v. bolus followed immediately by 5-FU as an i.v. bolus at 425 mg/m^2/day daily $\times$ 5, with the cycle repeated every 4 weeks. The modified LV5FU2 regimen was LV at 200 mg/m^2/day as a 2-h i.v. infusion, followed by 5-FU as an i.v. bolus at 400 mg/m^2/day, then as a 22-h CI at 600 mg/m^2/day, repeated on two consecutive days. This cycle was repeated at 2-week intervals. Treatment continued until disease progression as long as the neutrophil count remained above 1500/mm^3, the platelet count above 100 000/mm^3 and toxicity was tolerable [18].

Results for the 348 patients with measurable lesions showed a response rate of 32.6% for LV5FU2 and 14.4% for the NCCTG–Mayo Clinic regimen ($P = 0.0004$) [18]. Median progression-free survival was 27.6 weeks for patients who received LV5FU2 and 22.0 weeks for patients who received the NCCTG–Mayo Clinic regimen ($P = 0.0012$), and median overall survival was 62.0 weeks and 56.8 weeks, respectively ($P = 0.067$) (Figure 2). A normalisation or decrease of > 50% in CEA levels occurred in 37.4% of patients receiving LV5FU2 versus 20.4% of patients receiving the NCCTG–Mayo Clinic regimen ($P = 0.002$) [18].

The proportion of patients with grade 3–4 toxicities was higher for the NCCTG–Mayo Clinic regimen than for LV5FU2 (23.9% versus 11.1%, $P = 0.0004$); the only treatment-related death in the study occurred in the group who received the NCCTG–Mayo Clinic regimen [18]. Additionally, more patients in this arm experienced grade 3–4 granulocytopenia (7.3% versus 1.9%), diarrhoea (7.3% versus 2.9%) and mucositis (12.7% versus 1.9%). There were no other clinically important differences between the two dosage groups [18].

These improved response rates and better safety profile were encouraging and supported the value of the LV/5-FU bolus/CI protocol. The LV5FU2 regimen allows a 2-fold increase in the dose of 5-FU compared to bolus administration [17]. Further modulation of the LV5FU2 regimen with hydroxyurea (study C91-2, Table 1) led to an overall response rate of 37% in previously untreated patients and to a rate of response plus stable disease of 54% in previously treated patients, suggesting that hydroxyurea can restore tumour cell sensitivity to 5-FU in some patients [19]. The survival curve for these previously untreated patients is shown in Figure 2. The potential value of higher doses of 5-FU is emphasised by recent work suggesting a relationship between the magnitude of the 5-FU dose and response rates in advanced colorectal cancer [25].

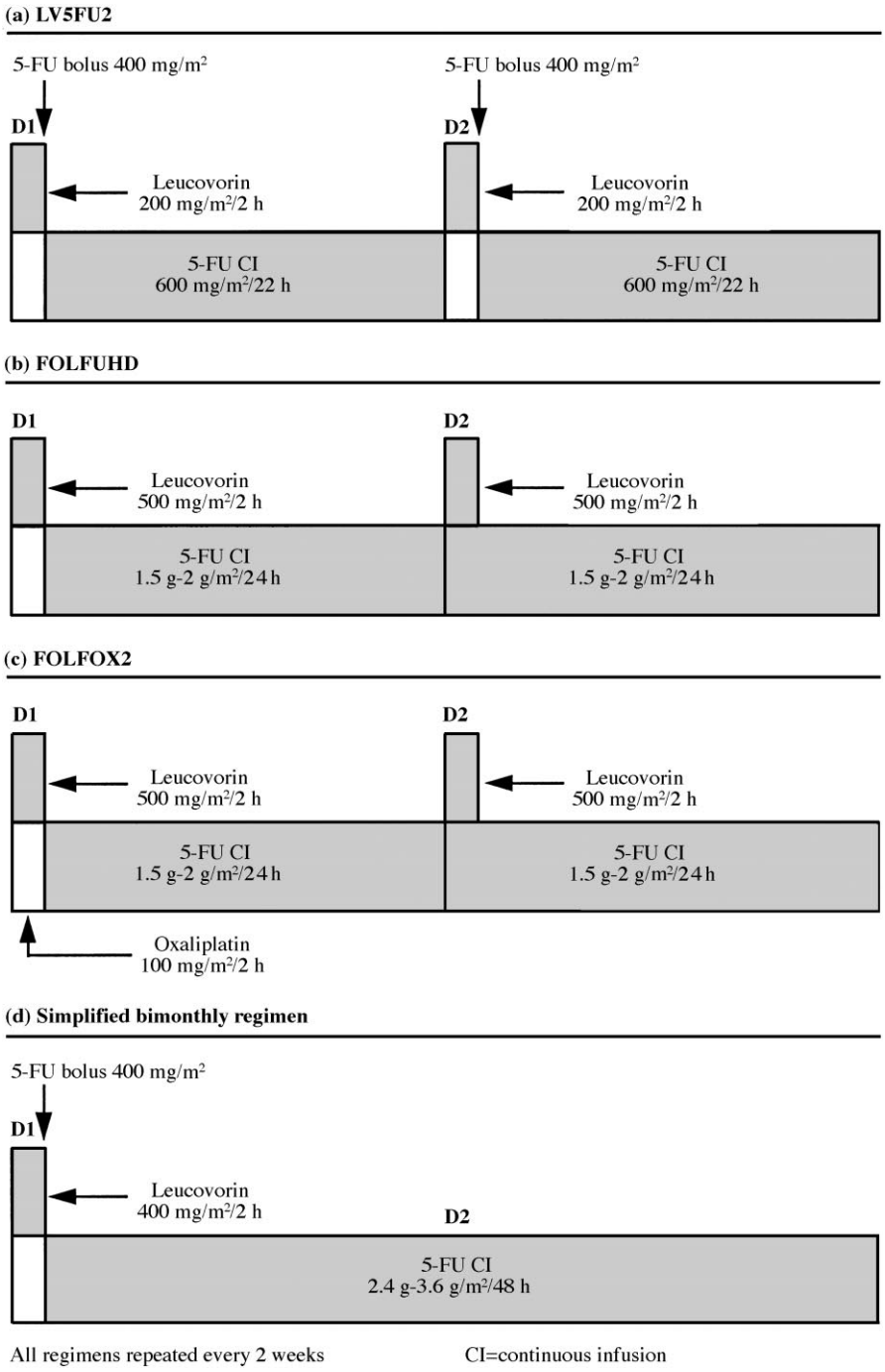

Figure 1. (a)–(d) show the four main regimens discussed in this review. High-dose LV is administered as a 2-h infusion, with higher doses than in LV5FU2 (a), in FOLFUHD, FOLFOX2, and the simplified bimonthly regimen (b)–(d). 5-FU is given as a bolus and as a continuous infusion (CI) in LV5FU2 (a), but as a CI only in all subsequent regimens (b)–(d).

In an earlier study involving 22 patients [26], 5-FU dose levels as high as 2600 mg/m^2/day were administered as a 24-h CI with high-dose LV (500 mg/m^2) and treatment was repeated weekly. Results showed overall response rates of 45%, with response rates of 30% in 10 patients previously treated with LV/5-FU regimens and 58% in 12 chemotherapy-naive patients. Toxicities included 11 episodes of grade 2 or 3 toxicity, most often diarrhoea. No myelosuppression was seen; 9 patients developed hand–foot syndrome. The above results supported further study of a high-dose CI regimen, and a phase II multicentre study (study C93-1, Table 1) was carried out using a regimen based on LV5FU2 [20].

High-dose LV, CI 5-FU (study C93-1)

A total of 101 patients with advanced colorectal cancer were enrolled in this trial and treated with the following bimonthly high-dose LV and high-dose 5-FU CI regimen (FOLFUHD; Figure 1(b): LV at 500 mg/m^2 as a 2-h i.v. infusion on day 1, followed immediately by a 48-h, 5-FU CI at 1.5–2 g/m^2/day [20]. A second 2-h infusion of LV at 500 mg/m^2 was started 24 h after the first LV infusion (D2). This regimen was repeated every 2 weeks. Patients received 5-FU at 1.5 g/m^2/day for the first two cycles, then 2 g/m^2/day in subsequent cycles if the neutrophil count was $>1500/mm^3$, the platelet count $>100\,000/mm^3$ and the

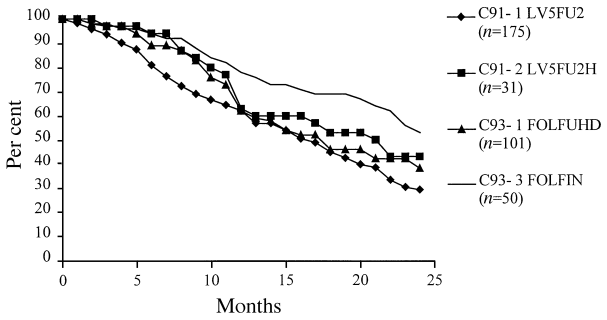

Figure 2. Survival curves of the studies in untreated patients with metastatic colorectal cancer.

maximal non-haematological toxicity $\leq$ WHO grade 2. If greater than grade 2 toxicity occurred, the dose of 5-FU was reduced from 2 to 1.5 g/m^2/day, and further reduced to 1.2 g/m^2/day if toxicity persisted [20].

The overall response rate in the 98 patients evaluated for efficacy was 33.7%, consisting of 5 complete responses (5%) and 29 partial responses (28.7%) [20]. Median progression-free survival was 8 months, and median overall survival was 18 months (Figure 2). Median time to progression in responders was 14 months. No significant differences in response rates were seen regardless of patients' prior histories of adjuvant chemotherapy. CEA normalised or decreased more than 50% from baseline in 46.8% of patients who had had increased CEA levels at baseline. 3 patients could not be evaluated because of early withdrawal, loss to follow-up and surgery, respectively [20].

Based upon data from 99 patients receiving 1449 chemotherapy cycles, the most common toxicity was nausea and vomiting, which occurred in 48% of the patients [20]. The next most common toxicities were mucositis (45%) and diarrhoea (42%). WHO toxicity grades 3–4 occurred in 15 patients (15%), including neutropenia in 4 patients (4%), 3 of whom had febrile neutropenia; grade 3 mucositis in 4 patients (4%); grade 3 nausea and vomiting in 2 patients (2%); grade 3 diarrhoea in 5 patients (5%); grade 3 hand–foot syndrome in 2 patients (2%), and alopecia in 4 patients (4%). 15 patients (15.2%) had no toxicity and 28 (28.3%) had a maximal toxicity of grade 1. A total of 73% of the patients were able to receive the full planned dose of 5-FU (2 g/m^2/day), while 22% received 5-FU at 1.5–2.0 g/m^2/day and 5% received 5-FU at 1.0–1.5 mg/m^2/day [20].

These results showed that the 5-FU bolus can be replaced by an increased dose of 5-FU when administered as a CI with no loss of efficacy (response rate of 33.7%) or increase in toxicity [20]. In spite of eliminating the bolus loading dose, the FOLFUHD regimen doubled the 5-FU dose delivered while resulting in less toxicity than the NCCTG–Mayo Clinic regimen. With FOLFUHD, 5-FU can be given every 2 weeks at a dosage of 1.8–2.1 g/m^2/24 h, or 7.2–8.4 g/m^2/month.

The same regimen entered another phase II study (Study C93-3, Table 1) in combination with low-dose alpha-interferon [21]. 50 patients were treated, yielding a response rate of 44%, a median progression-free survival of 9 months and a median survival of 25 months (Figure 2). This excellent survival was partially explained by surgery of metastases in 9 patients. However, toxicity was unacceptably high, with 42% of the patients experiencing grade 3–4 toxicity [21].

The effectiveness and low toxicity of the FOLFUHD regimen suggested that it could be combined with other antitumour drugs to enhance its effectiveness. To this end, a study (study C93-2) was initiated using the FOLFUHD regimen with the addition of oxaliplatin [22].

High-dose LV, CI 5-FU and oxaliplatin (study C93-2)

Oxaliplatin, *trans*-1-1,2-diaminocyclohexane oxalatoplatinum, is a new platinum compound with *in vitro* and *in vivo* antitumour activity demonstrated in preclinical studies involving colorectal carcinoma cell lines HT29 and colon 26 and 38 adenocarcinoma, as well as cell lines resistant to cisplatin [27–29]. An important clinical benefit is the lack of renal and haematological toxicity associated with oxaliplatin, whose dose-limiting toxicity is a cumulative sensory neuropathy. In two recent phase II trials, oxaliplatin as a single agent produced a 10% response rate with acceptable toxicity in patients with advanced colorectal cancer resistant to 5-FU [30, 31].

A phase II study was carried out involving 93 patients with metastatic colorectal cancer, half of whom had previously undergone chemotherapy, who received LV at 300 mg/m^2/day, 5-FU at 700 mg/m^2/day and oxaliplatin at 25 mg/m^2/day in a chronomodulated 5-day CI regimen repeated every 3 weeks [32]. A response rate of 58% was seen irrespective of treatment history, with a complete response rate of 19%. Median progression-free and overall survival were 10 and 15 months, respectively. Dose-limiting toxicities were diarrhoea (18% of courses) and vomiting (34% of courses), which were usually controlled with standard symptomatic therapy or dose reduction [32]. A subsequent randomised phase III trial in 186 previously untreated patients with metastatic colorectal carcinoma compared outcomes for a regimen given as a 5-day CI on a flat schedule or with chronomodulation (LV at 300 mg/m^2/day, 5-FU at 600 mg/m^2/day and oxaliplatin at 25 mg/m^2/day). Response rates were 49.5% for patients in the chronomodulation arm and 30% for patients in the flat arm. The major dose-limiting toxicities were stomatitis and peripheral sensory neuropathy [33].

Oxaliplatin shows considerable promise in treating patients with disease resistant to other commonly used agents for treating colorectal cancer. More recently, a report concerning two consecutive phase II trials in 106 patients with disease resistant to fluoropyrimidines described response rates of 11% and 10%, respectively, to oxaliplatin as a single agent, with peripheral sensory neuropathy being the dose-limiting effect [34]. The antitumour effect of oxaliplatin was considered modest but definite.

These preliminary studies provided evidence regarding the appropriate dose of LV, 5-FU and oxaliplatin for a phase II trial (study 93-2, Table 1) involving 46 previously treated patients with metastatic colorectal cancer, 24 of whom had progressed on other LV/5-FU regimens and 22 of whom had progressed on the same schedule of 48-h bimonthly high-dose LV and 5-FU, and were thus fully 'refractory' to the non-oxaliplatin portion of the regimen [22]. Patients received the FOLFOX2 regimen (Figure 1c), consisting of LV at 500 mg/m^2/day as a 2-h infusion, followed by a 24-h infusion of 5-FU at 1.5–2.0 g/m^2/day on day one (D1), with the cycle repeated on day two (D2). Oxaliplatin (100 mg/m^2) was administered on D1 as a 2-h infusion during the LV infusion without mixing. The dose of 5-FU was 1.5 g/m^2/day for the first two cycles and was increased in subsequent cycles to

2.0 g/m^2/day if maximal toxicity remained less than WHO grade 2. Cycles were repeated every 2 weeks. The dose reduction protocol called for the administration of oxaliplatin every second cycle only, in the event of WHO grade 1 peripheral neuropathy that persisted through six cycles. If persistent WHO neurological toxicity $\geq$ grade 2 with pain or functional impairment occurred, oxaliplatin was to be discontinued. The 5-FU dose was to be reduced from 2 to 1.5 g/m^2/day in case of other toxicity greater than grade 2, and reduced further to 1.2 g/m^2/day if such toxicity persisted [22].

Results with the FOLFOX2 regimen for the 45 assessable patients showed one complete response and 20 partial responses for an objective tumour response rate of 46%; the same proportion of patients (46%) had stable disease [22]. Of the fully refractory patients, 45.5% demonstrated a partial response, while another 45.5% demonstrated stable disease. Median progression-free survival for the entire group was 7 months, and median overall survival was 17 months. For the fully refractory patients, these values were 6 months and 16 months, respectively. CEA normalised in 3/38 (8%) of patients or decreased > 50% in 17/38 patients (45%) [22].

The dose-limiting toxicities with FOLFOX2 were neutropenia and peripheral neuropathy [22]. Overall, 9 patients (20%) had grade 4 toxicity; 12 (26%) had grade 3 toxicity; 17 (37%) had grade 2 toxicity; and 8 (17%) had grade 1 toxicity. Neutropenia grade 3–4 occurred in 18 patients (39%), with febrile neutropenia in 4 of these patients (9%). Although haematological toxicity necessitated treatment cessation in four cases, the remaining patients with grade 3–4 neutropenia did not experience a recurrence of this side-effect after dose modification. Haematological toxicity of grade 3–4 is a recognised side-effect of treatment with 5-FU and can usually be controlled with dose reduction. Hematopoietic growth factors were not needed in this study [22].

Grade 2–3 peripheral neuropathy occurred in 15 patients (33%), of whom 3 were able to resume oxaliplatin after dose modification [22]. This side-effect took two forms: a cold-induced acute dysesthesia that was always reversible and did not necessitate treatment discontinuation, and a peripheral sensory neuropathy characterised by paresthesias that at times compromised function and required treatment discontinuation. Although reversible, these paresthesias can last for months. Overall, one-third of the patients were able to receive the maximal 5-FU dose schedules (2 g/m^2/day), whereas 11 patients (24%) stopped treatment with oxaliplatin because of neurological toxicity before disease progression, and 6 patients (13%) stopped treatment for other toxicities [22].

The unusually high response rates with FOLFOX2 appear to represent an effective synergy between high-dose LV, high-dose 5-FU given as a 48-h CI and oxaliplatin. In particular, the high response rates for patients already refractory to the LV/5-FU regimen support such synergy. The median survival of 17 months was unusually high for patients with such advanced disease and was similar to survival seen in patients receiving LV and 5-FU as first-line therapy for metastatic disease. The positive outcome with FOLFOX2 prompted another phase II trial (study 94–1, Table 1) with modifications to decrease toxicity and evaluate the oxaliplatin dose intensity [23, 35].

30 patients who had progressed on the same bimonthly LV/5-FU regimen that was included in FOLFOX2 received the following: LV at 500 mg/m^2 as a 2-h infusion on D1 and D2; 5-FU 3 g/m^2 as a 48-h CI starting after LV D1; and oxaliplatin at 85 mg/m^2 (a lower dose than in FOLFOX2) as a 2-h infusion on D1 [23]. Cycles were repeated every 2 weeks until disease progression. A dose increase of 5-FU to 4 g/m^2 was performed if toxicity remained lower than WHO grade 2 after two cycles. Results showed partial responses in 6 patients (20%) and stable disease in 15 patients (50%), with a median progression-free survival of 6 months and median overall survival of 10 months. Toxicity $\geq$ WHO grade 3 included neutropenia in 7 patients (23%), thrombocytopenia in 5 patients (17%), anaemia in 1 patient (3%), allergy in 2 patients (7%) and alopecia in 4 patients (13%) [23].

These response rates were substantially lower than in the trial using the FOLFOX2 regimen, possibly as a result of the lower dose of oxaliplatin or patient selection factors [22]. A multicentre study is in progress using the lower-dose oxaliplatin regimen and if similar results are obtained, dose-intensity studies of oxaliplatin with LV and 5-FU will be needed [36].

Future studies of high-dose LV, CI 5-FU regimens

The high response rates using high-dose LV and CI 5-FU regimens have prompted several additional cooperative trials. A multicentre phase III trial is underway in Europe with 400 patients to compare outcomes with LV/5-FU alone and LV/5-FU plus oxaliplatin (study C95-1) [35]. In addition, a phase II trial is investigating the safety and efficacy of a simplified bimonthly high-dose regimen (study C96-2, Figure 1d). The regimen consists of a 2-h i.v. infusion of LV at 400 mg/m^2 on D1, followed immediately by a 5-FU bolus at 400 mg/m^2 and 5-FU at 2.4–3.6 g/m^2 as a CI for 48 h. This regimen, less expensive and more convenient to the patient, reflects a substantial attempt to decrease the cost of therapy. In France, two cycles (4 weeks) of the simplified regimen, including drugs, pumps and catheter maintenance, transportation, blood tests and medical fees, range between 4189 FF (approximately $70) and 6901 FF (approximately $1150), a 26 to 50% reduction compared to the LV5FU2 regimen. The estimated cost for one cycle of the NCCTG–Mayo Clinic regimen is between 3588 FF (approximately $600) and 16 380 FF (approximately $2700). The simplified regimen, the cornerstone of future combination studies, is now being studied in combination with oxaliplatin (FOLFOX6, study C97-1) or CPT11 (FOLFIRI, study C97-2).

Several clinical trials have recently evaluated the biomodulation of 5-FU by LV in the adjuvant setting [37–40]. An assumption underlying the use of adjuvant chemotherapy in colorectal cancer is that the cytotoxic agent may have increased efficacy after curative surgery has reduced the body's tumour burden. Although results from the majority of these studies are still incomplete, interim findings show that the use of adjuvant LV/5-FU may be associated with longer disease-free survival and 5-year survival than 5-FU/levamisole [38, 39]. A multicentre study is comparing LV5FU2 with a high-dose LV/5-FU daily $\times$ 5 regimen in the adjuvant setting (study C96-1).

CONCLUSION

It has been barely a decade since the publication of the first large study showing that LV enhances the effectiveness of 5-FU in advanced colorectal carcinoma [10]. Since then, considerable progress has been made in developing LV/5-FU

regimens that optimise response rates while maintaining manageable toxicity. A high-dose LV/high-dose 5-FU regimen has been shown to be more effective in terms of increased response rates and to result in less toxicity than single-agent 5-FU bolus regimens or low-dose LV/low-dose 5-FU regimens [5, 16]. GERCOD-sponsored studies have further demonstrated that higher doses of both LV and 5-FU given as a CI can improve response rates still more with acceptable toxicity. Finally, the increased effectiveness of an agent such as oxaliplatin in patients who have developed resistance to 5-FU regimens holds considerable promise for the future [18, 22].

Evidence increasingly shows that the high-dose LV/high-dose 5-FU CI regimen is associated with the greatest efficacy in terms of response rates and least toxicity of commonly used LV/5-FU combinations. The most significant challenge in the treatment of metastatic colorectal cancer is to translate higher response rates into longer survival, a goal of ongoing attempts to modify the dosage, timing and drug combinations of chemotherapy regimens. The addition of other agents such as oxaliplatin or CPT-11 to LV/5-FU regimens, and the use of combination chemotherapy in the adjuvant setting, ultimately may help reduce the death toll from colorectal cancer.

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