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Randomised Trial Comparing Three Different Schedules of Infusional 5FU and Raltitrexed Alone as First-Line Therapy in Metastatic Colorectal Cancer

Final Results of the Fédération Francophone de Cancérologie Digestive (FFCD) 9601 Trial

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Key Words
Colorectal cancer · 5-Fluorouracil · Raltitrexed · Leucovorin · Continuous infusion

Abstract
LV5FU2 with high-dose leucovorin (LV), weekly infusional 5-fluorouracil (5FU) (AIO schedule) and raltitrexed have been demonstrated to be active agents in first-line treatment of colorectal cancer. We performed a 4-arm randomised trial to compare (1) a low-dose intravenous bolus of LV (20 mg/m^2), followed by an intravenous bolus of 5FU (400 mg/m^2), followed by a 22-hour continuous infusion of 5FU (600 mg/m^2) on day 1 and day 2/2 weeks (ldLV5FU2 arm), (2) a weekly continuous infusion of high-dose 5FU (2.6 g/m^2/week) for 6 weeks followed by a rest week (HD-FU arm) and (3) raltitrexed (Tomudex® arm; 3 mg/m^2/3 weeks) to standard LV5FU2. From 1997 to 2001, 294 patients were included. The 4 arms were well balanced for sex ratio, age, WHO performance status, the primary tumour site and prior adjuvant chemotherapy. Treatment was stopped due to low accrual. Two toxicity-related deaths were observed in the Tomudex

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arm. The treatments gave rise to different rates of grade 3–4 neutropenia (3, 4, 11 and 14% of the patients in the LV5FU2, ldLV5FU2, HD-FU and Tomudex arms, respectively, p = 0.028), leucopenia and vomiting. At least one episode of grade 3–4 toxicity was observed in 27, 25, 38 and 47% of the patients in the LV5FU2, ldLV5FU2, HD-FU and Tomudex arms, respectively (p = 0.016). An objective response was observed in 28, 21, 22 and 10% of the patients in the LV5FU2, ldLV5FU2, HD-FU and Tomudex arms, respectively (p = 0.04). Progression-free survival (PFS) of the patients in the Tomudex arm was statistically lower compared to that of patients treated with LV5FU2 or ldLV5FU2 (combined group; p = 0.013, log rank test). In conclusion, Tomudex is more toxic and yields shorter PFS than infusional 5FU. Despite the early closure of the study and the lack of power of the comparison, it seems that ldLV5FU2 could be considered as an active, easier and less expensive option for the treatment of metastatic colorectal cancer compared to classic LV5FU2 or weekly HD-FU.

Introduction

Colorectal cancer is the third most commonly diagnosed malignancy, accounting for 10–15% of newly diagnosed cancer cases in Europe. An estimated 783,000 new cases are diagnosed annually worldwide, and more than 38,000 in France [1–3]. Surgery is the only cure for limited-stage disease. Up to 30% of patients present with metastatic disease and approximately 50–60% ultimately develop metastatic disease [4].

The most widely used agent in the treatment of metastatic colorectal cancer is 5-fluorouracil (5FU), which was developed more than 40 years ago and is included in most palliative chemotherapy regimens for colorectal cancer. Numerous attempts have been made to improve the efficacy of 5FU through schedule modification and biomodulation. Lokich et al. [5, 6] clearly demonstrated the feasibility of continuous infusional 5FU as a treatment for colorectal cancer. Continuous infusional regimens are attractive due to the lack of significant haematological toxicity [5, 6]. A meta-analysis totalling 1,219 patients treated in six randomised trials confirmed the superiority of continuous infusional 5FU over bolus regimens in terms of response rates and toxicity. Even though overall survival was higher in the continuous infusion group, the medians were very similar [7]. The need for a central venous catheter with its inherent problems (e.g. infection, thrombi and slippage) and for a portable pump and the cost and inconvenience for the patients are the major problems associated with infusional regimens, especially when they are continuous. This is why shorter infusional schedules have been developed in Europe. In France, the so-called 'de Gramont' schedule combining bolus and 48-hour infusional 5FU has resulted in better response rates and progression-free survival (PFS) compared with bolus 5FU alone [8]. A large randomised EORTC (European Organisation of Research and Therapy against Cancer) trial recently showed that high-dose 5FU given as a weekly 24-hour infusion was better tolerated than bolus 5FU + leucovorin (LV) without any major advantage in terms of efficacy [9, 10]. This regimen has totally replaced bolus 5FU in routine practice in Germany.

In previous randomised trials that used 5-day 5FU schedules, the combination with low-dose LV yielded controversial response rates and similar survival rates compared with high-dose LV, with a lower toxicity profile [11–14]. The impact of the LV dose on toxicity and therapeutic effects in biweekly infusional schedules remained to be determined.

The clinical development of raltitrexed (Tomudex®, Astra-Zeneca Pharmaceuticals, Rueil Malmaison, France), a quinazoline analogue and the first of a new generation of direct and specific thymidylate synthase inhibitors, began in 1991. Three randomised trials [15] compared raltitrexed to bolus 5FU + LV. The first one showed no clear difference between this new agent and the reference arm. The following two studies showed a decrease in PFS with raltitrexed. Only one trial has compared raltitrexed to the more recent and more active LV5FU2 schedule [16, 17]. This trial incorporated a second randomisation with a comparison between discontinuation of chemotherapy after 3 months of treatment versus continuation which could have modified the results of the comparison of the two drugs.

The objectives of the present study were: (a) to evaluate the therapeutic effects and toxicity of high-dose LV versus low-dose LV combined with a biweekly schedule of 5FU, (b) to evaluate the weekly German schedule of 5FU alone and (c) to evaluate raltitrexed versus the so-called 'de Gramont' schedule.

Patients and Methods

Patient Selection

Patients were accrued to the study between March 1997 and March 2001. All patients had advanced recurrent metastatic adenocarcinoma of the colon or rectum and had not received prior systemic cytotoxic therapy for advanced disease. Patients could have received adjuvant cytotoxic chemotherapy provided it had ended more than 6 months before entry into the trial.

Eligible patients were aged at least 18 years, had at least one measurable lesion [defined according to World Health Organisation (WHO) [18] recommendations], an ECOG performance status ≤2 and no other malignancies (except for adequately treated carcinoma in situ of the cervix uteri or basal or squamous cell carcinoma of the skin); laboratory measurements had to be adequate (white blood cell count >4,000/mm^3, platelets >100,000/mm^3). Adequate renal function (creatinine level ≤2× normal value) and normal liver function tests (bilirubin level <1.5× normal value) were mandatory. Inadequately controlled cardiac ischaemia or insufficiency was an exclusion criterion.

All patients gave their written informed consent to participate in the study and in conformity with French law, approval was obtained from an appropriate Ethics Committee (Comité Consultatif de Protection des Personnes pour la Recherche Biomédicale of Bicêtre Hospital, Le Kremlin-Bicêtre, France). The study was performed in accordance with the Declaration of Helsinki (revised: Hong Kong, 1989) and good clinical practice guidelines.

Study Design and Treatment

This open-label, randomised, parallel-group, screening trial [19] was conducted with the participation of 39 centres of the French Federation of Digestive Oncology (FFCD 9601 trial) in France. After screening to establish eligibility, patients were randomly assigned by fax through a central randomisation system to receive treatment with 5FU + LV (the so-called 'de Gramont schedule': LV5FU2), the control arm, or the same schedule with lower doses of LV, or weekly infusional 5FU alone [the so-called Arbeitsgemeinschaft Internistische Onkologie of the German Cancer Society (AIO) schedule], or raltitrexed. Randomisation was stratified according to centre, previous adjuvant treatment (yes/no) and ECOG performance status (0 vs. 1 vs. 2) using a minimisation procedure.

There were 4 trial arms. In arm A, patients received standard LV5FU2, i.e. LV (200 mg/m^2), followed by a 10-min intravenous bolus of 5FU (400 mg/m^2), followed by a 22-hour intravenous continuous infusion of 5FU (600 mg/m^2) on day 1 and repeated on day 2. This treatment was repeated every 14 days. In arm B, patients received LV5FU2 with low-dose LV (ldLV5FU2), i.e. LV (20 mg/m^2), followed by a 10-min intravenous bolus of 5FU (400 mg/m^2), followed by a 22-hour intravenous continuous infusion of 5FU (600 mg/m^2) on day 1 and repeated on day 2. This treatment was repeated every 14 days. In arm C, they received the so-called AIO weekly schedule of 5FU, i.e. high-dose 5FU (2,600 mg/m^2) in a 24-hour intravenous continuous infusion on day 1, weekly for 6 weeks, followed by a 2-week rest every 7 weeks (HD-FU). Finally, patients in arm D received raltitrexed (Tomudex), i.e. 3 mg/m^2 as a short intravenous infusion every 3 weeks.

Dosing could be delayed for a maximum of 15 days until toxicity had resolved or was resolving. Diarrhoea and stomatitis had to resolve completely before treatment continuation.

Dose modifications were based on the worst grades of selected haematological (leucopenia, neutropenia, thrombocytopenia) and non-haematological (diarrhoea, stomatitis) toxicities observed in the previous cycle.

Patients in either treatment group continued therapy until disease progression or unacceptable toxicity occurred or until the investigator decided the patient was no longer benefiting from the treatment. After trial therapy, patients were treated at the investigators' discretion, although none of the patients who received 5FU were given raltitrexed.

Patient Assessment

Response, Time to Progression, Survival. Patients underwent pretreatment tumour assessment at baseline and were then evaluated for response every 8 weeks. At each time point, an overall tumour response was assigned based on the response of measurable lesions and on the evaluation of non-measurable but assessable lesions, provided by the investigators. Tumour dimensions were measured on computed tomography scans or magnetic resonance imaging. Tumour response was classified according to standard WHO criteria [18]. Complete responses were defined as the disappearance of all tumour masses. Partial responses were defined as more than a 50% reduction in the sum of the products of the two largest perpendicular dimensions of the target tumours, and no new lesions. Stabilisation was defined as a reduction of less than 50% in the size of the target tumours, and no new lesions. Tumour progression was defined as an increase of more than 25% in the target tumours, and/or a new tumour. Lesions were not considered measurable when they were inside the pelvis for rectal cancer. Regardless of whether trial therapy had stopped or not, response assessment continued until disease progression or death without evidence of progression. After progression, patients were monitored for survival and second- or third-line therapy at 12-week intervals.

Safety. Safety was evaluated at least monthly until 4 weeks after the end of therapy and included assessment of laboratory parameters and clinical adverse reactions. Clinical adverse events were described and graded according to criteria based on WHO recommendations for the grading of acute and subacute toxic effects [18].

Quality of Life. Patients were asked to complete the European Organisation of Research and Therapy against Cancer QLQ-C30 questionnaire [20] every 8 weeks until progression or the 24th week. It consisted of 30 items combined to yield 15 dimensions. Four dimensions were considered particularly relevant for the trial: global, pain, physical and emotional dimensions. A high score corresponded to better quality of life (QoL) for each scale with the exception of pain.

Statistical Considerations

The primary endpoint for this study was PFS defined as the interval between the date of randomisation and that of progression, or the date of death without progression (whatever the cause) or the date of the last follow-up for surviving patients without progression. The trial was planned according to the screening design proposed by Schaid et al. [19] with 1 control arm and 3 experimental arms. A maximum sample size of 720 patients with an interim analysis after the inclusion of 280 patients was planned (overall risk, $\alpha = 5\%$, $\beta = 20\%$). Due to low accrual and the arrival of new compounds, the interim analysis was cancelled and accrual was stopped. An independent data monitoring committee was in charge of reviewing toxicity data and efficacy results. Before performing any analyses, it was decided to first compare the LV5FU2 and ldLV5FU2 arms, and in the absence of a significant difference between these two arms, to pool them and to compare them to the two other experimental arms. Bonferroni's correction (0.05/3 = 0.0167) was used to take into account multiple comparisons when more than one comparison between arms was performed. The Kaplan-Meier method and the log rank test were used to estimate and

Table 1. Initial patient characteristics

		LV5FU2	ldLV5FU2	HD-5FU	Raltitrexed
Patients	Men	42	53	49	47
	Mean age ± SD, years	64 ± 8	64 ± 9	64 ± 8	63 ± 10
WHO performance status[1]	0	30	31	30	29
	1	31	29	30	30
	2	13	15	13	13
Tumour site	Right colon	16	18	18	12
	Transverse colon	2	4	7	3
	Left colon	6	10	6	7
	Sigmoid colon	32	27	28	29
	Rectum	18	16	13	21
	Missing data			1	
Differentiation	Well or moderately	63	67	64	64
	Poorly or undifferentiated	8	6	4	6
	Missing data	3	2	5	2
Stage (UICC)	I	0	6	0	1
	II	6	9	7	4
	III	7	11	5	10
	IV	59	45	54	55
	Missing data	2	4	7	2
Resection of primary	No	19	12	13	16
	Complete	50	59	54	53
	Incomplete	5	4	6	3
Prior resection of metastases	No	64	69	68	67
	Complete	5	3	4	4
	Incomplete	5	3	1	1
Adjuvant chemotherapy[1]	No	66	64	64	62
	Yes[2]	8	10	9	10
	Missing data		1		
Adjuvant radiotherapy	No	64	66	69	61
	Yes	9	9	4	11
	Missing data	1			

[1] Stratification factor.
[2] 5FU LV (folinic acid), Mayo Clinic regimen for 30/37 patients.

compare survival curves. The log rank test stratified or not on centres led to similar results, thus only tests adjusted to centres are presented. The cut-off date for analyses was September 30, 2001. They were performed according to the intent-to-treat principle. Repeated measurements of QoL were analysed with a generalised estimating equation model for multinomial data. In order to take into account the fact that QoL data were missing mainly because of disease progression, a dummy variable indicating at each measurement whether or not it was the last was included in the model [20]. The first 3 QoL questionnaires (weeks 8, 16 and 24) were studied and all models were adjusted to baseline. Furthermore, p values for heterogeneity between arms are provided. All reported p values are two-sided. Data were analysed using SAS statistical software (SAS Institute, Cary, N.C., USA).

Results

A total of 294 patients were randomised to treatment with LV5FU2 (74 patients), ldLV5FU2 (75 patients), HD-FU (73 patients) and raltitrexed (72 patients). Patients were enrolled from 39 centres during the 4-year period from March 1997 to March 2001. The median follow-up time was 34 months. The four treatment groups were comparable with respect to demographic and pretreatment characteristics (table 1). Most patients were more than 60 years old, and the colon was the most common primary tumour site. The liver, lymph nodes and lung were the most fre-

Table 2. Response rates

Response	LV5FU2 (n = 74)	ldLV5FU2 (n = 75)	HD-FU (n = 73)	Raltitrexed (n = 72)
Complete response	3 (4)	1 (1)	1 (1)	0 (0)
Partial response	18 (24)	15 (20)	15 (20)	7 (10)
Objective response*	28%	21%	22%	10%
Stable disease	26 (35)	40 (53)	37 (51)	38 (53)
Disease progression	19 (26)	17 (23)	18 (25)	18 (25)
Not assessable	8 (11)	2 (3)	2 (3)	9 (12)

* $p = 0.04$ (χ^2 test). Figures in parentheses indicate percentages.

quent sites of metastases. The number of metastatic sites was evenly distributed across the study groups.

Of the 294 patients enrolled, 293 (99%) received at least one cycle of the allocated chemotherapy and 96% completed 8 weeks of therapy. The most frequent reason for treatment discontinuation was progressive disease: 86, 83, 85 and 74% for the LV5FU2, ldLV5FU2, HD-FU and raltitrexed arms, respectively ($p = 0.004$).

All treatment groups adhered closely to the planned dosage regimens. For patients treated with 5FU, the mean daily dose was 94, 95 and 91% in the LV5FU2, ldLV5FU2 and HD-FU arms, respectively. For patients treated with raltitrexed, the mean daily dose was 98%. However, the median duration of treatment was significantly different between the treatment groups: LV5FU2: 140 days; ldLV5FU2: 139 days; HD-FU: 119 days; raltitrexed: 88 days ($p = 0.035$).

Objective Tumour Response

Twenty-one patients were not assessable for response because they died of early disease progression (14 patients), or of other causes (2 patients), were withdrawn from the study because of adverse events (4 patients), or were lost to follow-up evaluation (1 patient).

The objective response rate was different between the four treatment arms (table 2), with the lowest response rate in the raltitrexed arm. Nearly 25% of the patients in each arm had disease progression at the first evaluation (table 2).

The median duration of partial responses was: LV5FU2: 8.5 months (range 4.7–29.2); ldLV5FU2: 9.6 months (range 6.1–16.1); HD-FU: 7.1 months (range 4.5–34.2); raltitrexed: 7.0 months (range 4.2–26.5) (NS).

Survival

Progression-Free Survival. At the time of the cut-off date for the analysis (6-month minimum duration of follow-up), more than 95% of patients had disease progression or had died without documented progression. There was a difference between the arms in terms of PFS (fig. 1). The median was 5.3 and 5.4 months for the LV5FU2 and ldLV5FU2 arms, respectively ($p = 0.85$), and 4.8 months for the HD-FU arm, but the difference was not statistically significant ($p = 0.17$ compared with LV5FU2). However, PFS was lower in the raltitrexed arm: 4 months, with a significant difference when it was compared to PFS in the LV5FU2 arms (low- and high-dose LV analysed together; $p = 0.013$).

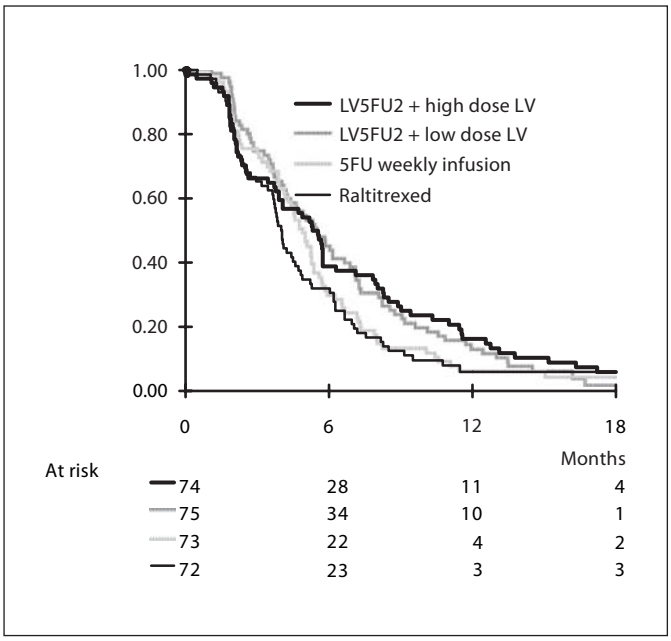

Fig. 1. PFS by treatment arms. Log rank tests stratified on centres: $p = 0.85$ between the two LV5FU2 arms, $p = 0.175$ between HD-FU and the two LV5FU2 arms, $p = 0.13$ between raltitrexed and the two LV5FU2 arms. LV = Leucovorin.

Table 3. Incidence (%) of WHO grade 3 and 4 adverse events

Type of toxicity	LV5FU2 (n = 74)	ldLV5FU2 (n = 75)	Weekly HD-5FU (n = 73)	Raltitrexed (n = 72)
Leucopenia (p = 0.0047)[1]	0	1	7	11
Neutropenia (p = 0.028)[1]	3	4	11	14
Thrombopenia	1	1	0	3
Fever	1	0	1	1
Infection	0	0	1	1
Vomiting (p = 0.005)[1]	5	3	8	18
Diarrhoea (p = 0.106)[1]	5	7	4	14
Mucositis (p = 0.131)[1]	3	1	5	0
Cutaneous (p = 0.490)[1]	5	3	1	1
Alopecia	0	1	3	0
Cardiac	0	0	1	0
Transaminases	1	1	1	6
Other (p = 0.216)[1]	4	11	14	13
At least one (p = 0.016)[1]	27	25	38	47

[1] Exact test.

Overall Survival. There was no significant difference (p = 0.37 between the two LV5FU2 arms, p = 0.25 between HD-FU vs. the two LV5FU2 arms) in median overall survival (fig. 2) for all randomised patients, with 13.1, 17.1, 14.6 and 12.2 months for the LV5FU2 (59 events), ldLV5FU2 (57 events), HD-FU (59 events) and raltitrexed (62 events) arms, respectively. However, when the survival of patients treated with raltitrexed was compared with that of patients in the two LV5FU2 arms, there was a trend in favour of these latter arms (p = 0.06).

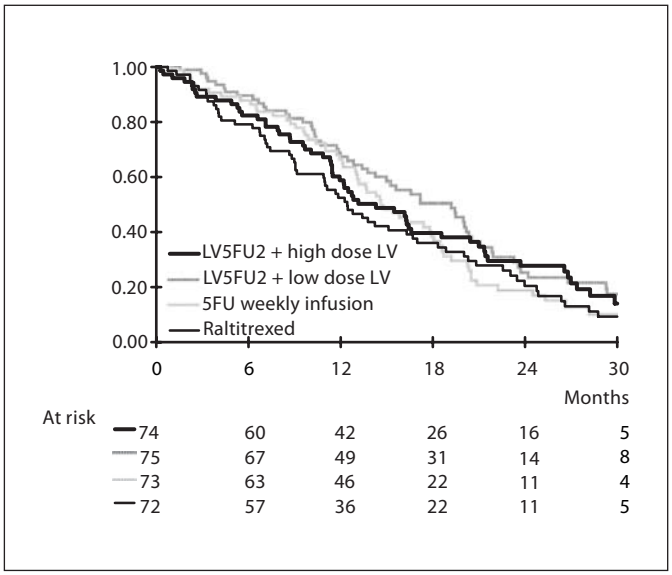

Fig. 2. Overall survival by treatment arm. Log rank tests adjusted to centres: p = 0.37 between the two LV5FU2 arms, p = 0.25 between HD-FU and the two LV5FU2 arms, p = 0.06 between raltitrexed and the two LV5FU2 arms. LV = Leucovorin.

Toxicity Profile

Compared with the raltitrexed group, patients in the LV5FU2 groups experienced a significantly lower incidence of grade 3–4 leucopenia, neutropenia and vomiting. Table 3 lists the number of patients with grade 3 and 4 adverse reactions. Overall, patients in the LV5FU2 arms were less likely (p = 0.016 for the comparison of the four groups by the exact test) to experience clinical grade 3–4 toxicity (27 and 25% for the standard LV5FU2 arm and ldLV5FU2 arm, respectively) than patients receiving weekly 5FU (38%) or raltitrexed (47%). The incidence of grade 3 or 4 toxicity was very similar in the two LV5FU2 arms. All types of grade 3–4 toxicity were less frequently observed with LV5FU2 than in the other two arms, except for skin toxicity (5 and 3 vs. 1% in both the HD-FU and raltitrexed arms).

Treatment interruption due to toxicity was observed in less than 5% of the patients in 5FU-containing regimens, but toxicity induced by raltitrexed led to a treatment interruption in 15% of the patients (p = 0.003, Fisher's exact test).

Treatment-related adverse reactions were fatal for 2 patients treated with raltitrexed (2 cases of neutropenia, diarrhoea, sepsis and death) and none in the other arms.

Table 4. Comparisons of QoL between arms for 4 domains of the EORTC QLQ-C30 questionnaire

Arms	Global OR	Pain OR	Physical OR	Emotional OR
LV5FU2	1	1	1	1
ldLV5FU2	1.37 (0.71–2.66)	0.89 (0.40–2.01)	0.97 (0.45–2.10)	0.63 (0.29–1.37)
HD-5FU	1.00 (0.50–1.99)	0.61 (0.26–1.41)	0.90 (0.43–1.89)	0.55 (0.25–1.23)
Raltitrexed	0.21 (0.11–0.42)	2.59 (1.14–5.88)	0.48 (0.23–0.99)	0.35 (0.15–0.78)
p	<0.0001	0.0009	0.10	0.02

Figures in parentheses indicate 95% CIs.

Quality of Life

Only 181 patients had a baseline questionnaire and at least one subsequently. Three hundred and thirty questionnaires were available out of 543 expected (61%). Two hundred and thirteen were missing because patients either had disease progression (23%), or stopped filling them out for other reasons (9%) or intermittently did not fill out some questionnaires (7%).

All QoL scales except physical functioning were significantly different between the 4 arms (global: $p < 0.0001$; pain: $p = 0.0009$; physical: $p = 0.10$; emotional: $p = 0.02$) with the raltitrexed arm always scoring worst (table 4). The odds ratios (95% confidence intervals) of raltitrexed compared to high-dose LV5FU2 were for the 4 scales respectively: 0.21 (0.11–0.42), 2.59 (1.14–5.88), 0.48 (0.23–0.99) and 0.35 (0.15–0.78). This means that patients receiving raltitrexed had worse global QoL, more pain, and experienced a more important physical and emotional impact of their cancer than patients receiving LV5FU2.

Discussion

This randomised phase III trial compared the efficacy and toxicity profiles of raltitrexed, HD-FU and ldLV5FU2 with those of standard LV5FU2 as first-line treatment for metastatic colorectal cancer. Even if raltitrexed was previously compared to LV5FU2 in a large phase III trial, confirmatory results are valuable. Furthermore, for the first time a weekly infusional schedule has been compared to a biweekly infusional regimen and also for the first time, low doses of LV have been tested in an infusional administration schedule.

Raltitrexed was proposed as a promising agent for first-line treatment of metastatic colorectal cancer. The simple administration schedule and a good toxicity profile were the main advantages of this new drug when it was compared to bolus 5FU and LV in the first randomised trial [21]. The efficacy results of the two other phase III studies came to slightly different conclusions [22, 23]. A similar response rate was demonstrated between the raltitrexed arm and the 5FU arm in all 3 published trials [21–23]. However, in 2 of them, PFS was statistically lower in patients who received raltitrexed. Although these PFS results did not influence overall survival in one study, in the other one overall survival was also lower in the raltitrexed arm versus the bolus 5FU and LV arm.

Our results in terms of PFS, the rate of objective responses and toxicity completely confirm those published by Maughan et al. [17]. These authors compared raltitrexed to LV5FU2 and prolonged continuous infusion of 5FU. Raltitrexed yielded similar response and overall survival rates to the LV5FU2 regimen and was easier to administer, but gave rise to greater toxicity and poorer QoL [17]. Even after the warning issued when the first raltitrexed-related toxic deaths were reported, which led to dose adaptations according to creatinine clearance, sudden severe toxicities leading to death are still possible, as in this trial. These 2 concordant studies have prompted us to state that raltitrexed should be restricted to patients in whom fluoropyrimidines are strongly contraindicated.

LV has been evaluated with different doses of 5FU and various modes of administration. LV was as effective at low doses (20 mg/m^2/day) as at 10-fold higher doses when combined with standard doses of 5FU over 5 days [13, 14]. These results allowed low doses of LV to be recommended in bolus administration schedules. Bolus 5FU over 5 days plus low doses of LV (the so-called 'Mayo Clinic' regimen) became a standard of care first-line therapy for metastatic colorectal cancer. Other trials addressing the same type of question achieved similar results whatever

the 5FU administration schedule [12, 24–26] and it has never been proven that the in vitro superiority of high doses of LV could be equated in clinical practice. However, this is the first time that low doses of LV are evaluated with infusional 5FU schedules. There was no significant difference between low and high doses of LV regarding efficacy or toxicity parameters. In particular, in terms of response, ldLV5FU2 yielded 21% of responses versus 28% with standard LV5FU2. With the drop in the price of LV during the past 10 years and the proven efficacy of low-dose LV, savings in product costs are clearly possible but also in terms of nursing time because low-dose LV is easier to administer (an intravenous push lasting a few minutes vs. a 2-hour infusion). However, this conclusion should be considered cautiously regarding the fact that the study closed prematurely and thus was underpowered.

Weekly 5FU is a frequently used regimen in Germany. A recently published study failed to demonstrate a difference in survival for weekly HD-FU compared with the Mayo Clinic regimen [9, 10]. Although the difference in PFS between the HD-FU and the LV5FU2 arms was not statistically significant at 4.9 and 5.4 months, respectively, these better results were obtained with less toxicity than in the HD-FU arm: grade 3–4 neutropenia was observed in 11% of the patients in the HD-FU arm versus 3 and 4% in the LV5FU2 and ldLV5FU2 arms, respectively. The rates of all other toxicities were lower in the two LV5FU2 arms than in the HD-FU arm, except for cutaneous toxicity.

Chemotherapy for metastatic colorectal cancer has changed during the past 10 years. The proven efficacy of combination chemotherapy regimens using irinotecan plus 5FU or oxaliplatin plus 5FU has led to more widespread use in European countries and in the USA [27–29]. However, it has yet to be clearly demonstrated that first-line single-agent therapy followed by a switch to a more aggressive schedule, in the event of progression, would be less efficient than first-line combination chemotherapy. Two large multicentric trials in Great Britain and France are addressing this question. The results of the first one have recently been presented; there was no difference in efficacy between the arms using sequential use of chemotherapy and the arms using combined chemotherapy in first line (5-arm trial) [30]. Furthermore, our study suggested the equivalence of low-dose LV versus higher doses. Thus, this option of low-dose LV could also be considered when combination chemotherapy involving irinotecan or oxaliplatin is given to patients.

It is difficult to analyse QoL during a chemotherapy trial, especially when there is a difference in the duration of the chemotherapy cycles. Missing data are a frequent additional problem. The comparison of QoL between the 4 chemotherapy arms, although limited in these respects, revealed similar results to the other endpoints. The poorest results were observed with raltitrexed.

In conclusion, raltitrexed is less active and more toxic than infusional 5FU and its use should be restricted to patients in whom fluoropyrimidines are strongly contraindicated. ldLV5FU2 seems to yield equivalent results to standard LV5FU2 and could be recommended as an option in first-line single-agent therapy for colorectal metastatic cancer. The infusional weekly 5FU schedule seems to be slightly more toxic than the biweekly schedule.

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