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A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802)

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Background: This multicenter adjuvant phase III trial evaluated the addition of irinotecan to LV5FU2 in colon cancer patients at high risk of relapse.

Patients and methods: A total of 400 patients with histologically proven primary colon cancer with postoperative N1 detected by occlusion/perforation or N2 were randomised to: A—LV5FU2 [leucovorin 200 mg/m^2, 2-h infusion, 5-fluorouracil (5-FU) 400 mg/m^2 bolus, 600 mg/m^2 22-h continuous infusion, days 1 and 2] or B—LV5FU2 + IRI (irinotecan 180 mg/m^2 90-min infusion day 1 + LV5FU2) fortnightly for 12 cycles. Primary end point was disease-free survival (DFS).

Results: Median follow-up was 63 months. Significantly more T4 tumours and 15 or more positive lymph nodes were observed in arm B. 5-FU relative dose intensity (RDI) was >0.80 for 94% and 77% in arms A and B, respectively ($P < 0.001$). Irinotecan RDI was >0.80 for 70% patients. There were more grades 3 and 4 neutropenia in arm B (4% versus 28%, $P < 0.001$). The 3-year DFS was 60% [95% confidence interval (CI) 53% to 66%] and 51% (95% CI 44% to 58) in arms A and B, respectively. No difference was observed [hazard ratio (HR) = 1.12, 95% CI 0.85–1.47, $P = 0.42$] even when adjusted for prognostic factors (adjusted HR = 0.98, 95% CI 0.74–1.31, $P = 0.92$). The 5-year overall survival (OS) was 67% (95% CI 59% to 73%) and 61% (95% CI 53% to 67%) in arms A and B, respectively.

Conclusion: Adjuvant LV5FU2 + IRI compared with LV5FU2 alone in patients at high risk of relapse showed no improvement in DFS and OS.

Key words: adjuvant chemotherapy, colon cancer, irinotecan

introduction

Colorectal cancer (CRC) is the second cause of cancer death with an estimated 254 000 deaths from CRC worldwide in 2000 [1]. In France the overall incidence of CRC is 36 500 new cases per year of which 70% are colon cancer [2].

Since 1996 the standard chemotherapy for patients with stage III colon cancer is monthly 5-fluorouracil (5-FU) combined with leucovorin (LV) for 6 months (Mayo regimen) [3, 4].

Previously developed in metastatic colorectal cancer (MCRC), the semimonthly LV5FU2 regimen has been compared with the monthly 5FULV in the adjuvant setting and showed no statistically significant difference in overall survival (OS) but showed a better safety profile [5]. The combination of irinotecan (IRI) with 5-FU in MCRC has been shown to improve the tumour response rate, progression-free survival and OS when compared with 5-FU alone [6, 7].

In France, at the time we initiated the trial, the regimen combining LV5FU2 and IRI (180 mg/m^2) every 2 weeks had just become standard treatment in first-line MCRC. These data provided a background to compare this new combination to the LV5FU2 regimen alone in the adjuvant setting.

Considering the higher risk of toxicity, especially diarrhoea, of LV5FU + IRI given after primary tumour surgery, we chose to evaluate this regimen in a stage III population at a particularly high risk of recurrence defined by patients with more than three involved lymph nodes (N2) or N1 detected by perforation or occlusion [3, 8].

The FNCLCC/FFCD intergroup decided to conduct this adjuvant trial to evaluate the addition of irinotecan to LV5FU2 in terms of disease-free survival (DFS), OS and safety in stage III CRC patients at a high risk of relapse.

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The first results on 3-year DFS were presented at the American Society of Clinical Oncology (ASCO) meeting in 2005 [9]. In this paper, we report the final analysis of the trial in terms of 5-year OS.

patients and methods

patient eligibility

The eligibility criteria were the following: histologically proven colon cancer with complete resection of primary tumour (R0), nonmetastatic, with high-risk stage III i.e. N2 (more than three positive lymph nodes) or N1 detected by occlusion or perforation. Patients were aged between 18 and 75 years, without another concomitant or previous cancer (except curatively resected skin cancer or *in situ* cervical carcinoma), with a neutrophil count >2000/μl; platelets >100 000/μl; serum bilirubin <1.25 × upper normal limit (UNL); aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase <3 × UNL. Noneligibility criteria were histology other than adenocarcinoma, rectal cancer <10 cm from the anal margin or with preoperative radiotherapy, incomplete resection, myocardial infarction within the six last months or uncontrolled coronary insufficiency, inflammatory intestinal disease, pregnant or nursing women. Written informed consent was required for all patients before inclusion in the trial. The study was carried out in accordance with the principles of the Declaration of Helsinki and Good Practice Guidelines. The protocol was reviewed and approved by the Ethics Review Committee of St Eloi, Montpellier, France.

study treatments

Patients were randomised to either arm A (LV5FU2 alone) which consisted of leucovorin 200 mg/m^2/day as a 2-h infusion followed by bolus 5-FU 400 mg/m^2/day and a 22-h continuous infusion of 600 mg/m^2/day, repeated for two consecutive days every 2 weeks for 12 cycles or arm B (LV5FU2 + IRI) which consisted in the same LV5FU2 semimonthly regimen, with the addition of irinotecan 180 mg/m^2 during 90-min infusion on day 1 for 12 cycles. Dose adjustments were defined according to the most important toxicity grade. In the case of hand–foot syndrome, only the dose of infusional 5-FU was to be reduced by 20%. In case of haematological nonrecovery (neutrophils <1500/μl or platelets <100 000/μl) and/or persistence of grade 1 or 2 gastrointestinal toxic effects (diarrhoea, mucitis), the cycle was to be delayed until complete recovery. In case of grade 3 or 4 haematological or gastrointestinal toxic effects, the cycle was to be delayed until recovery and the doses to be reduced by 20% for the subsequent cycles. No support of growth factors in case of neutropenia was allowed. In case of chest angina or myocardial infarction, treatment had to be stopped. If the same toxicity persisted after dose reduction, the treatment had to be interrupted. In case of nonrecovery after 3 weeks, the treatment had to be definitely stopped. Doses which were reduced due to toxicity were not to be increased.

assessment

At inclusion and before each cycle, clinical examination, blood counts, hepatic and renal function tests were carried out. Chest X-ray, abdominal ultrasound or computer tomography (CT) scan was carried out within 5 weeks before enrolment. Maximum toxicity grades for each 2-week cycle were reported according to the National Cancer Institute Common Toxicity Criteria (v2).

Follow-up consisted of a required clinical examination every 3 months from surgery during the first 2 years and every 6 months during the following 3 years, an abdominal ultrasound every 3–6 months the first 3 years and every year during the following 2 years, a chest X-ray every year during 5 years and a coloscopy at 3 years and every 5 years if normal, otherwise every year if abnormal. Carcinoembryonic antigen plasma levels and CT scan were optional according to institutional procedures.

randomisation

Centralised 1 : 1 randomisation was carried out by the FFCD data centre in Dijon using a minimisation technique, balancing patients by type of detection (N2 alone versus N1/N2 detected by occlusion or perforation), expected time from surgery to start of chemotherapy (≤28 versus >28 days), age (<65 versus ≥65 years) and centre.

statistical considerations

The sample size of 400 patients (186 events) was required from an expected increase in 3-year DFS from 45% to 60% for LV5FU2 and LV5FU2 + IRI, respectively (hazard ratio of 0.64) for 85% statistical power and 5% two-sided type I error (alpha). Survival rates were estimated from the date of randomisation until the date of the event of interest using the Kaplan–Meier method. Median survival and HRs are presented with 95% CIs. For DFS, events were local recurrence, metastasis, second cancer or death whatever the cause. For OS, the event was death whatever the cause. Patients lost to follow-up were censored at the last documented visit. The differences in survival times were evaluated using a log-rank test and a proportional hazards regression model was used to adjust the treatment comparison for significant prognostic covariates. Backward stepwise analyses were undertaken using Cox proportional hazards model to identify prognostic factors. Differences in grade 3 or 4 toxicity grades between groups were evaluated with the chi-squared test. Median follow-up was estimated with the inverse Kaplan–Meier method. Survival data were updated in January 2007. Statistical analyses were carried out with Stata at the Biostatistics Unit in the Regional Val d'Aurelle Cancer Centre in Montpellier, France.

results

patients

From November 1998 to September 2002, 400 patients were randomised in 75 French centres, 200 in each arm. Ten patients were considered ineligible. Reasons for ineligibility included nonocclusive N1 (five patients), metastatic disease (two patients) and N0 (three patients). Among them, two did not receive treatment. One other patient was lost to follow-up before starting treatment (without data). A total of 397 patients contributed to intent-to-treat analysis (Figure 1). Median age was 60 (range 26–75) and one-third of patients were >65 years. Ten per cent of patients started chemotherapy >42 days after surgery (range (11–77 days). The median number of positive nodes was 5 (range 1–58). Seven per cent of patients had less than eight sampled nodes and 27% of patients had <12 sampled nodes.

Baseline characteristics for all randomised patients were similar in the treatment groups, except for stage and number of involved lymph nodes (Table 1). Patients in arm B had more often T4 tumours (34% versus 20%, $P = 0.002$) and >15 positives nodes (9% versus 2%, $P = 0.007$).

exposure to study treatment

After randomisation, one patient in arm B refused to receive irinotecan and received only LV5FU2 (arm A). This patient was considered for analysis in the arm to which he was randomised.

Cycle delays of >3 days were more frequent in arm B (15% versus 7%, $P < 0.0001$).

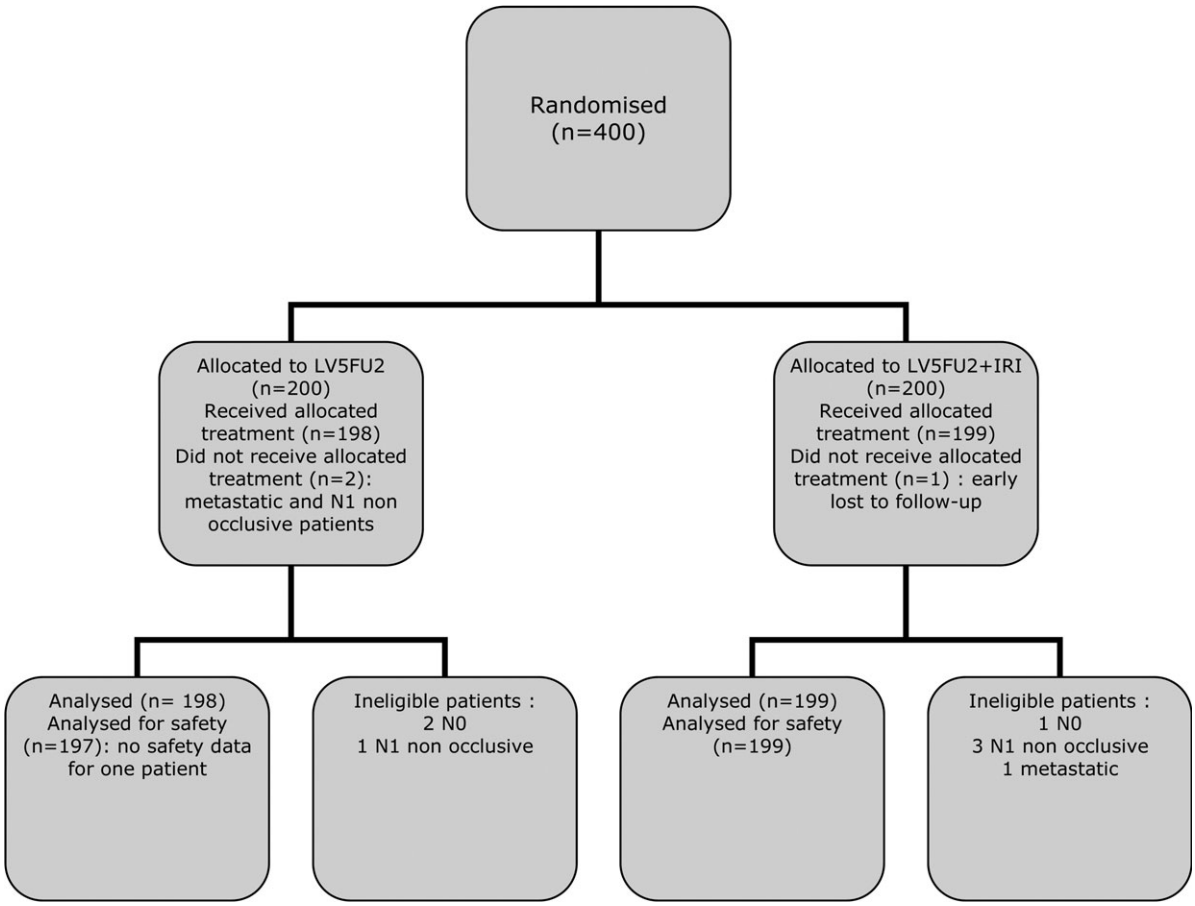


Figure 1. CONSORT flowchart.

There were significantly more dose reductions of 5-FU in the LV5FU2 + IRI arm [relative dose intensity (RDI) 98% versus 94%, $P < 0.0001$]. Also, more patients in arm A received the full 12 cycles of planned treatment (87% versus 79%, $P = 0.035$). This is reflected by the total number of cycles: 2228 and 2164, respectively.

5-FU RDI was >0.80 for 94% and 77% patients and >0.90 for 84% and 60% patients in arms A and B, respectively ($P < 0.001$). The RDI for irinotecan was >0.80 for 70% patients and >0.90 for 56% of patients.

safety

Overall, there were more grades 3–4 adverse events in the experimental arm as compared with the control arm. Grades 3–4 neutropenia (28% versus 4%), febrile neutropenia (3% versus 0%), nausea (13% versus 2%), vomiting (9% versus 1%), diarrhoea (12% versus 6%) and alopecia (10% versus 1%) were more frequent in arm B than in arm A (Table 2). Seven patients experienced grade 4 diarrhoea, four and three patients in arms A and B, respectively. Hand–foot syndrome was observed for 14 patients (7%) (eight patients with grade 1, five patients with grade 2 and one patient with grade 3) in arm A and seven patients (4%) with grade 1 in arm B ($P = 0.11$). There was one toxic death after two cycles in arm B due to cardiac arrest, medullar aplasia and a subocclusive state. Overall, there were three deaths within 60 days from last infusion in the experimental arm (1.5%) as compared with none in the control arm.

disease-free survival

The database was locked on 31 March 2005 for DFS when 84% of the required number of events was reached after a median follow-up of 36 months. Following Independant Data Monitoring Committee (IDMC) recommendations in July 2004, the results were presented at the ASCO meeting in 2005 [9]. At the cut-off date for analysis, 191 events were recorded. The 3-year DFS rates were 60% [95% confidence interval (CI) 53% to 66%] in arm A and 51% (95% CI 44% to 58%) in arm B. No significant difference was observed between the treatment arms [unadjusted hazard ratio (HR) = 1.19, 95% CI 0.90–1.59, $P = 0.22$].

The database was updated in January 2007 with a median follow-up of 63 months and a total of 203 first event failures were recorded. There were 177 confirmed relapses: locoregional (A/B: 5 and 12), distant (63 and 68) and local and distant (15 and 14). Median survival after relapse was 19.0, 20.4 and 16.8 months in arms A and B, respectively, corresponding to 2-year OS rates of 41% and 36% which were not statistically significant ($P = 0.56$). Surgery was used for treatment of relapse in 36% of patients, 37% and 34% in arms A and B, respectively.

Table 1. Baseline patient characteristics

	LV5FU2 (n = 198)		LV5FU2 + IRI (n = 199)	
	No. of patients	%	No. of patients	%
Stratification factors: all randomised patients				
Age, years				
<65	131	66.2	131	65.8
≥65	67	33.8	68	34.2
Type of detection				
Occlusion/perforation	76	38.4	76	38.2
N2 alone	122	61.6	123	61.8
Planned time since surgery, days				
≤28	46	23.2	40	20.1
>28	152	76.8	159	79.9
Characteristics: all treated patients				
Gender				
Male	111	56.1	117	58.8
Female	87	43.9	82	41.2
Age, years				
<65	132	66.7	131	65.8
≥65	66	33.3	68	34.2
Type of detection				
Occlusion/perforation	76	38.4	76	38.2
N2 alone	122	61.6	123	61.8
Actual time since surgery, days				
≤28	45	22.7	32	16.1
>28	130	65.7	148	74.4
>42	23	11.6	19	9.5
Performance status				
0	103	52.8	132	67.0
1	82	42.1	63	32.0
2	10	5.1	2	1.0
Missing	3		2	
Primary site				
Right colon	60	30.3	62	31.2
Transverse colon	16	8.1	22	11.1
Left colon	73	36.9	73	36.7
Colorectal junction	44	22.2	35	17.6
Rectum	5	2.5	7	3.5
T stage				
T1	5	2.5	2	1.0
T2	8	4.0	2	1.0
T3	145	73.2	127	63.8
T4	40	20.2	68	34.2
N stage				
N0	2	1.0	1	0.5
N1	45	22.7	38	19.1
N2	151	76.3	160	80.4
No. of sampled nodes				
4–7	15	7.6	11	5.6
<12	33	16.7	46	23.2
≥12	150	75.8	141	71.2
Missing	0		1	
No. of positive nodes				
1–3	42	21.4	38	19.2
4–8	121	61.7	123	62.1
9–14	30	15.3	20	10.1
≥15	3	1.5	17	8.6
Missing	2		1	

FU, fluorouracil; LV, leucovorin; IRI, irinotecan.

Table 2. Maximum NCI-CTC (v2) toxicity grade per patient, % of grade ≥3

Toxicity	LV5FU2 (n = 198, %)		LV5FU2 + IRI (n = 199, %)		P[a]
	Grade 3	Grade 4	Grade 3	Grade 4	
Neutropenia	4	–	19	10	<0.001
Febrile neutropenia	–	–	1	2	0.03
Thrombocytopenia	–	–	–	<1	NS
Anaemia	<1	–	3	–	NS
Nausea	2	–	12	1	<0.001
Vomiting	1	–	7	2	0.001
Diarrhoea	4	2	10	2	0.053
Cutaneous	3	–	1	–	NS
Hand–foot syndrome	<1	–	–	–	NS
Alopecia	1	–	10	–	<0.001
Thromboembolic accident	2	–	1	<1	NS
Maximum toxicity[b]	12	2	35	13	<0.001

[a]Grade 3/4 versus 0/1/2, P >0.05.

[b]Maximum toxicity calculated among all described toxic effects above.

NCI-CTC, National Cancer Institute—Common Toxicity Criteria; NS, nonsignificant if P >0.05 FU, fluorouracil; LV, leucovorin; IRI, irinotecan.

Other first events (A/B) included 10 second cancers (six/four) and 16 deaths (eight/eight). The second cancers included colorectal (two in each arm), three lung and one breast in arm A and one bladder and one melanoma in arm B. Causes of deaths as first events were as following: carcinopharyngioma, epilepsy, suicide, cerebral haemorrhage and cerebral vascular accident in arm A and toxic death, cardiac failure, sudden death and probable pulmonary embolism in arm B and seven unknown reasons (four and three in arms A and B, respectively).

The HR on the updated analysis for treatment effect changed slightly but remained nonsignificant (unadjusted HR = 1.12, 95% CI 0.85–1.47, P = 0.42) (Table 3, Figure 2A). T4 stage and the number of lymph nodes were identified as independent prognostic factors for DFS. The HR for treatment, adjusted for these two variables were nonsignificant (adjusted HR = 0.98, 95% CI 0.74–1.31, P = 0.92) (Table 3, Figure 2B). Results are similar in a multivariate Cox model when adjusted on other important risk factors.

overall survival

Median survival on the updated database was not reached. A total of 147 deaths was observed: 68 and 79 deaths in arms A and B, respectively.

The 5-year survival rates were 67% (95% CI 59% to 73%) in arm A and 61% (95% CI 53% to 67%) in arm B (unadjusted HR = 1.20, 95% CI 0.87–1.67, P = 0.26) (Table 3, Figure 3A). The treatment comparison when adjusted for T4 stage and number of lymph nodes was not significant (adjusted HR = 1.00, 95% CI 0.71–1.40, P = 0.99) (Table 3, Figure 3B).

discussion

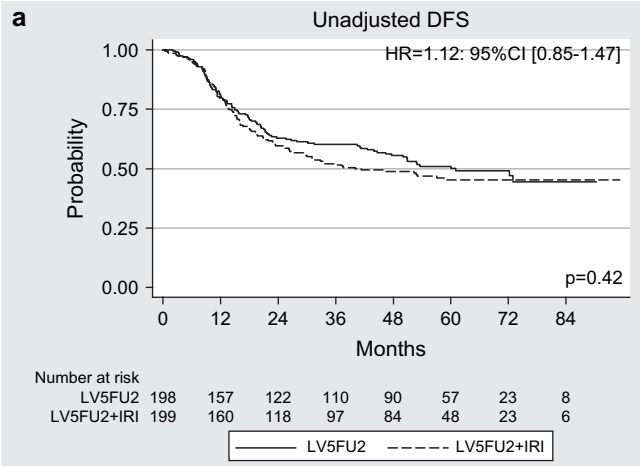
This is the second published trial which showed no significant difference in terms of DFS and OS with the addition of IRI to

Table 3. Updated univariate and multivariate analysis on disease-free and overall survival

	Disease-free survival			Overall survival		
	HR	95% CI	P^a	HR	95% CI	P^a
Univariate analysis						
Treatment arm			0.42			0.26
LV5FU2	1			1		
LV5FU2 + IRI	1.12	0.85–1.47		1.20	0.87–1.67	
Multivariate analysis						
Treatment arm			0.92			0.99
LV5FU2	1			1		
LV5FU2 + IRI	0.98	0.74–1.31		1.00	0.71–1.40	
T stage						
T4 versus T1–T3	1.67	1.24–2.26	0.001	1.75	1.23–2.48	0.002
Positive nodes						
≥15 versus <15	1.78	1.03–3.08	0.039	2.74	1.54–4.87	0.001

[a]Likelihood ratio test adjusted on significant variables in multivariate analysis.

HR, hazard ratio; CI, confidence interval; FU, fluorouracil; LV, leucovorin; IRI, irinotecan.



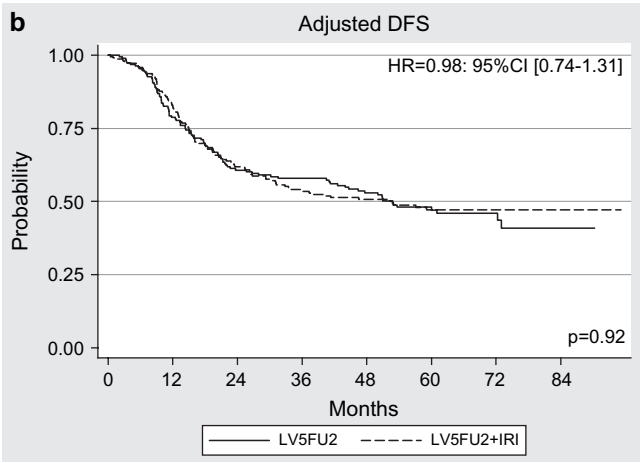
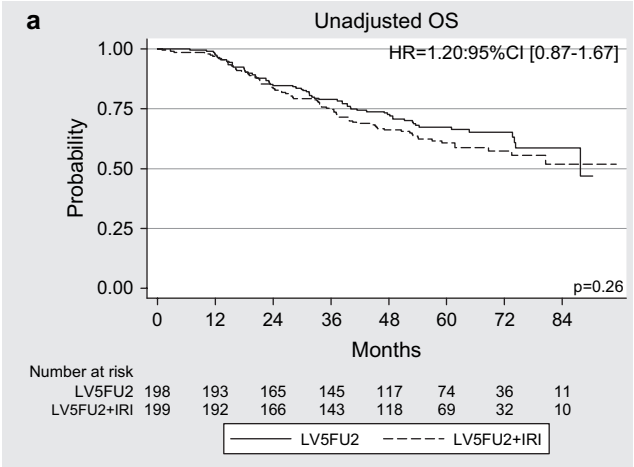


Figure 2. Disease-free survival according to treatment, unadjusted (a) and adjusted (b) for T4 stage and number of involved nodes ≥15.
———LV5FU2, fluorouracil and leucovorin bimonthly;
———————LV5FU2 + IRI, addition of irinotecan.



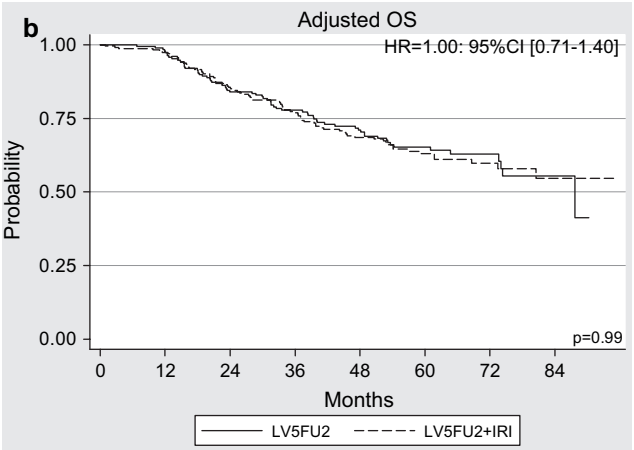


Figure 3. Overall survival according to treatment, unadjusted (a) and adjusted (b) for T4 stage and number of involved nodes ≥15.
———LV5FU2, fluorouracil and leucovorin bimonthly; ——————— LV5FU2 + IRI, addition of irinotecan.

5-FU in the adjuvant setting for patients with colon cancer. The CALGB89803 trial used the bolus FU + LV Roswell Park regimen as the control arm [10] as opposed to LV5FU2 in our trial. LV5FU2 + IRI (FOLFIRI) as compared with IFL is currently recognised as standard treatment in the metastatic setting following better results observed in terms of efficacy and safety [11]. The patient population in our trial was selected according to a higher risk of relapse including N2 patients or N1 detected by perforation or occlusion. Nevertheless, we did not observe improved results with the combination treatment. Compared with the standard bolus FU plus LV regimen used in the CALGB89803 trial, our control arm is better tolerated, with no deaths within 60 days as compared with a 6.7% 60-day all-cause mortality rate reported in the CALGB89803 trial. [10].

In spite of randomisation, the two arms were unbalanced unfavourably in the experimental arm for two important prognostic factors: T stage (T4) and number of positive lymph nodes (>15). The HR for DFS, adjusted for T4 stage and lymph nodes decreased from 1.12 to 1.01 for DFS (Figures 2A and B) and from 1.20 to 1.04 for OS (Figures 3A and B).

The observed 60% 3-year DFS rate in the control arm was unexpectedly better than the estimated 45% rate used at the

design stage of this trial, which was based on the results extrapolated from previous studies. However, at the time of the trial design, no results were available for the LV5FU2 control arm in this selected patient population considered at high risk of relapse. Since the start of this trial, the only published results comparing LV5FU2 to monthly FU leucovorin (FUFOL) in the adjuvant setting presented results for stage III patients with more than four involved lymph nodes, for which a 42% 3-year DFS rate was observed [5]. In our LV5FU2 control arm, for the 112 patients with more than four involved lymph nodes, the 3-year DFS rate was 55% (95% CI 45% to 64%). We have no clear explanation for the unusually favourable results observed in the control arm in this population at a high risk of relapse which exhibited a 3-year DFS rate of 60%.

Adjuvant LV5FU2 + IRI as compared with LV5FU2 alone is associated with more grades 3–4 neutropenia, resulting in a lower dose intensity of 5-FU, with only 77% of patients with a RDI of 5-FU >0.80 in the combination arm as compared with 94% in the control arm. In the experimental arm, 70% of patients had a RDI >0.80. If granulocyte colony-stimulating factor support had been allowed in case of neutropenia, then there may have been less dose reductions and fewer cycle delays.

No difference was observed between the two treatment arms in an unadjusted or adjusted analysis, in spite of the imbalance in important prognostic factors between the two arms. Low RDI of 5-FU and IRI in the combination arm with more dose reductions and cycle delays due to neutropenia, without the use of growth factors, could partially explain the results.

The PETACC-3 trial, which compared the same two treatment arms, presented results in abstract form and showed nonsignificant results in the subgroup of stage III patients on the primary DFS end point (3-year DFS 60.3% versus 63.3%, HR = 0.89) [12]. In this trial, DFS was defined as relapse, second cancer or death. However, a significant difference was observed on the secondary end point RFS, which excluded second cancer types other than colon cancer from DFS. The 3-year RFS rates were 62.2% versus 66.0% (HR = 0.86). Final results are awaited for OS.

The MOSAIC trial which compared LV5FU2 to FOLFOX showed a significant result in the subgroup of stage III patients with a 3-year DFS rate of 65.3% versus 72.2% (HR = 0.76) [13]. In this trial, DFS was defined as relapse, death or second colon cancer. Recently, an attempt has been made to standardise definitions of end points in the adjuvant setting for colon cancer to enable cross comparability among different studies [14].

Is there still room for the LV5FU2 + IRI treatment combination in the adjuvant setting? Perhaps using a better selection of patients both for toxicity and efficacy. In our trial, DNA was extracted from 184 patients and genotyped to detect nucleotide polymorphisms. Results show that the identification of UGT1A1 promoter polymorphisms before LV5FU2 + IRI treatment can be used to predict early haematologic toxicity [15]. In a study of the identification of molecular signatures for response to FOLFIRI, 14 predictor genes have been identified in metastatic patients [16]. A validation study is undergoing. Once the results of this study are completed, these predictor genes could benefit patients in the adjuvant setting.

Another approach including targeted therapy in combination with cytotoxic agents may individualise even more future treatment strategies.

In conclusion, this study failed to demonstrate an improvement of DFS and OS with the addition of IRI to LV5FU2 in a population of colon cancer patients at high risk of recurrence.

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