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A randomised phase III trial of adjuvant radio-chemotherapy comparing Irinotecan, 5FU and Leucovorin to 5FU and Leucovorin in patients with rectal cancer: A Hellenic Cooperative Oncology Group Study ☆

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ABSTRACT

The primary objective was to compare the 3-year survival of rectal cancer patients randomised postoperatively to irinotecan (IRI), Leucovorin (LV) and bolus 5-fluorouracil (5FU) or LV-bolus 5FU with radiotherapy. Secondary objectives included disease-free survival, local relapse and toxicity.

The study included 321 eligible patients. The treatment consisted of weekly administration of IRI 80 mg/m^2 intravenously (IV), LV 200 mg/m^2 and 5FU 450 mg/m^2 bolus (arm A) versus LV 200 mg/m^2 and 5FU 450 mg/m^2 IV bolus (arm B). One cycle included four infusions and treatment was continued for a total of six cycles. The first cycle was followed by pelvic irradiation plus 5FU.

There were no differences between the arms in 3-year overall, disease-free and local relapse-free survival. Grades 3 and 4 toxicity was similar in both the arms with the exception of leucopaenia, neutropaenia and alopecia, which were higher in the IRI arm.

IRI added to adjuvant radiochemotherapy with LV and bolus 5FU was not shown to improve survival, whereas the incidence of severe leucopaenia was significantly higher in the IRI arm.

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1. Introduction

Adjuvant chemoradiotherapy following or preceding resection of high-risk rectal cancer improves overall survival (OS) and local recurrence as compared to surgery alone or surgery plus irradiation. Postoperative adjuvant 5FU-based chemotherapy plus radiotherapy has been established in prospective, randomised trials demonstrating the efficacy of combined treatment for stages II (T3/4) and III (N 1/2) rectal cancer.[1,2] The National Cancer Institute Consensus Conference concluded in 1990 that the use of adjuvant combined modality therapy was the standard postoperative management for patients with stages II and III rectal cancer.[3] However, after the results of the randomised trial performed by the German Rectal Cancer Study Group, preoperative 5FU-based chemoradiotherapy administered in the conventional way over 5 weeks is more effective in local control than when the same treatment is given postoperatively.[4] Furthermore, the incidence of acute and long-term toxicities, also favours the group of patients with preoperative treatment but no differences in distant metastases or OS were observed. Therefore, preoperative chemoradiotherapy with its better tolerability and improved local control may be considered as the new standard treatment of rectal cancer.

A number of relatively new effective antineoplastic agents are available for the management of patients with colorectal cancer. Combinations of drugs such as IRI or oxaliplatin with 5FU or oral capecitabine, with the addition of bevacizumab or cetuximab are sequentially used in the treatment of patients with advanced disease. IRI, a topoisomerase I inhibitor, has shown consistent efficacy in both chemotherapy-naïve and 5FU-pretreated patients with metastatic colorectal cancer.[5–7] Additionally, IRI with 5FU or capecitabine and radiation have also shown consistent efficacy in local control and disease-free survival (DFS) of patients with locally advanced rectal cancer.[8–10] However, adjuvant randomised studies in colon cancer have failed to show a benefit of adding IRI to bolus or continuous infusion LV-modulated–5FU in improving the disease-free survival.[7] Additionally, these results have illustrated the importance of not extrapolating efficacy data in advanced colorectal cancer into the adjuvant colon and rectal setting without randomised confirmatory data.[7]

Toxicity profile of postoperatively administered IRI plus LV-modulated bolus 5FU and radiotherapy has been studied by our group in patients with rectal cancer,[11] and that of IRI plus LV-modulated bolus 5FU has been dealt with in another two studies in patients with advanced colorectal cancer[12,13] based on previous dose finding study. Toxicity was acceptable and this phase III study was performed to investigate the impact of the addition of IRI to conventional postoperative adjuvant treatment with LV-modulated bolus 5FU and radiotherapy. The primary end-point of this study was to compare the 3-year OS, and the secondary objective was to compare disease-free survival, local relapse and toxicity profiles of the two regimens. Three-year OS is a meaningful end-point since pooled analysis of 18 randomised trials with 5FU-based regimens in the setting of adjuvant colorectal cancer demonstrated that highly significant differences assessed after 3 years were highly likely to be present in OS after 5 years of follow-up.[7,14]

2. Patients and methods

Patients were recruited into the study between October 1999 and December 2004. All eligible patients had histologically confirmed rectal adenocarcinoma beginning within 12 cm of the anal verge, as determined by endoscopy. All patients underwent complete surgery for stages B_2 and C rectal adenocarcinoma with neither gross nor microscopic evidence of residual disease. The recommended standard surgical procedure across all the centres was rectal surgery with total mesorectal excision. Although total mesorectal excision was recommended for all the patients, it was not required. The patients entered the study 3–6 weeks after surgery and had not received any prior radiotherapy or chemotherapy. The patients were aged at least 18 years, with a WHO performance status $\leqslant 2$, and should have no history of other malignancies except of adequately treated carcinoma in situ of the cervix uteri or curatively treated non-melanomatous skin cancer or serious illness that would preclude protocol chemoradiotherapy. Exclusion criteria included metastatic disease, pregnant or lactating women, the presence of current history of chronic diarrhoea and other serious illness. Laboratory criteria in the initial evaluation included: neutrophil count $\geqslant 1500/mm^3$, platelets $\geqslant 100{,}000/mm^3$, serum creatinine <1.5 mg/dl, SGOT/SGPT $<3\times$ normal value and ALP $<3\times$ normal value.

The clinical protocol and collateral translational studies were approved by the Hellenic Cooperative Oncology Group (HeCOG) Protocol Review Committee, and the Bioethics Committee of Aristotle University of Thessaloniki School of Medicine. Before randomisation all the patients gave written inform consent according to institutional guidelines, and eligibility was confirmed by a protocol-specific checklist.

Before starting chemotherapy, all eligible patients were required to provide a complete medical history and to undergo a physical examination that included assessment of weight and height. Staging studies included chest-X-ray, abdominal-pelvis computed tomography scan, colonoscopy and magnetic resonance imaging or endorectal ultrasound as well as blood cell count, biochemistry profile, tumour serum markers CEA and Ca 19-9, and cardiological evaluation with ECG. During treatment, clinical evaluation and complete blood count were performed every week. Furthermore, biochemistry laboratory evaluations were performed every 2 weeks until the end of the treatment, and then every 3 months thereafter. Abdominal–pelvic CT scan and chest-X-ray were performed at the end of the study, and then every 6 months thereafter. However, CT scans were repeated earlier whenever clinically indicated depending on the discretion of the investigator. Endoscopy was performed annually.

2.1. *Treatment schedule*

Patients were treated with one cycle of chemotherapy which consisted of four weekly courses followed by pelvic radiotherapy with concomitant 5FU as a rapid intravenous administration (30 min before radiotherapy) at a dose of 400 mg/m^2 on the first 3 and the last 3 d of radiotherapy, and 5 more cycles of the same chemotherapy schedule. Chemotherapy was resumed 2–4 weeks after the completion of radiotherapy.

Patients in group A received chemotherapy, which consisted of four weekly courses with IRI, 80 mg/m^2 in 250 ml normal saline as a 90-min i.v. infusion followed by LV, 200 mg/m^2 in 500 ml normal saline as a 2-h i.v. infusion and 5FU, 450 mg/m^2 as intravenous (i.v.) rapid administration at the end of LV infusion followed by a 2-week rest period. Doses selected were based on the previous studies by our Group.[11–13] Patients in group B received chemotherapy, which consisted of LV, 200 mg/m^2 in 500 ml normal saline as a 2-h i.v. infusion and 5FU, 450 mg/m^2 as i.v. rapid administration at the end of LV infusion followed by a 2-week rest period. Chemotherapy in both the groups was continued for six cycles, or until consent withdrawal or occurrence of non-tolerable toxicity.

2.2. *Radiation therapy*

Radiation was delivered with linear accelerators (energy range 6–18 MV), at 1.8–2.0 Gy per day, 5 d per week. The whole pelvis was treated with a three- or four-field technique. The patients were treated in a prone position with a distented bladder. Customised blocks were used to exclude normal tissues from the treatment field. The postoperative clinical target volume included the tumour bed, 5 cm below the anastomosis or the pelvic floor down to the level of the ischiac tuberosity (after an abdominoperineal excision), the pre-sacral and internal iliac nodes and the dorsal wall of the pelvic organs. The upper limit of the field was the top of the sacrum. Patients received 45 Gy to the whole pelvis and a boost of 5 Gy to the tumour bed.

2.3. *Dose modification*

Toxicities were graded using the WHO common criteria. Dose adjustments of the drugs or treatment delays were decided according to the worst toxicity grade at preceding cycle. The dose modification was determined according to the body system showing the greatest toxicity. Chemotherapy and radiotherapy were interrupted if grade more than 2 toxicity was encountered. Chemotherapy and radiotherapy were restarted when toxicity had resolved to $\leqslant$grade 1. In case of diarrhoea, the patients underwent supportive care as also intensive treatment with loperamide and were hospitalised if necessary. The doses of IRI and 5FU were reduced by 20% or 30% in the case of grades 2 and 3 diarrhoea, respectively. In the presence of grades 2, 3 and 4 haematological toxicity, treatment was delayed until haematological recovery and IRI as well as the 5FU dose was reduced by 20%, 30% and 40%, respectively, in all the subsequent courses. There was no re-escalation for patients experiencing bone marrow or gastrointestinal toxicity requiring dose modification. In case of hand–foot syndrome (grades 3 and 4), only the dose of 5FU was to be reduced by 20%. In case of angina or myocardial infarction the treatment would be ceased. Furthermore, for grade 3 mucositis, there was a possibility for restarting the treatment after one week delay, if toxicity had resolved to $\leqslant$grade 1 and the dose of 5FU was to be reduced by 25%. In the presence of any grade 4 toxicity except for gastrointestinal or haematological toxicity, the patients were withdrawn from the study.

Antiemetic drugs were chosen in accordance with the conventional antiemetic protocol of each centre. No prophylactic treatment was permitted for diarrhoea. Specific guidelines for curative treatment of delayed diarrhoea were provided, which recommended loperamide one capsule (2 mg) every 2 h for 12 h after the last loose stool, for a maximum of 48 consecutive hours. If diarrhoea was not controlled after 48 h of non-stop loperamide intake, or if the patient was dehydrated, loperamide was stopped and the patient was hospitalised for intravenous fluids. If blood or mucus was in the stools at any time during diarrhoea, loperamide was stopped and the patient was hospitalised.

3. Statistical analysis

This was an open-label, randomised, parallel-group study. The clinical trial was designed to detect a difference in the 3-year survival rate with an 80% power, assuming a 15% difference in the 3-year OS rate to a baseline 3-year survival rate of 70%. For an α error of 0.05, with an accrual rate of 70 patients per year, 327 patients were required. Taking into account a 5% withdrawal rate, 344 patients were needed to observe 57 events with a corresponding maximum study duration of 4.7 years. Patients were stratified by stage (Dukes' B2, C1 and C2) and performance status (PS: 0 versus 1 versus 2).

The Fisher's exact test was used to compare patient characteristics and toxicity. As a measure of the amount of drug delivered per unit of time the Dose intensity (DI) is presented, calculated as the total amount of drug delivered per m^2, over the duration of treatment in weeks for each patient (mg/m^2/wk). Relative dose intensity (RDI) was calculated dividing the DI of the administered regimen by the planned DI of the drug. Survival time was calculated from the date of randomization to the date of death or last follow-up. Disease-free survival was calculated from the date of randomization to the date of relapse, death or last follow-up. The Kaplan–Meier method was used to estimate overall and disease-free survival distributions, whereas the log-rank test was used to compare them. Prognostic factor analyses were performed with Cox proportional hazards model. Variables included in the initial model were grade (I or II versus III or undifferentiated), age, WHO performance status (0 versus 1 and 2), Duke's stage (B2 versus C1 versus C2), presence of involved lymph nodes, and randomization arm (A versus B).

The backwards selection procedure with the Likelihood ratio test was used to conclude on the variables that have a significant effect on OS or DFS. All statistical tests were performed on $\alpha = 0.05$ level of significance. The analysis was performed based on the modified intent-to-treat principle, which means excluding ineligible patients.

4. Results

4.1. *Patient characteristics*

From October 1999 until December 2004, a total of 347 patients entered the study. Twenty-six patients were ineligible, 11 in arm A and 15 in arm B and therefore excluded from the analysis. Eleven patients had advanced disease (3 in group A and 8 in group B), nine patients had colon cancer (5 in group

A and 4 in group B), five were staged B_1 (2 in group A and 3 in group B) and one patient from group A had microscopic involvement of surgical margins. Only the 321 eligible patients were included in the analysis.

The outline of the study is shown in Fig. 1. For 13 patients medical records were incomplete at the time of the analysis (nine from arm A and four from arm B). Furthermore, three patients in arm B never started on chemotherapy; these patients were included in the efficacy analysis according to the intent-to-treat method, but were excluded from the toxicity and treatment characteristics analyses. Four patients randomised to arm A received arm B treatment. There were 201 men and 120 women. A summary of baseline patient characteristics is presented in Table 1. Demographics and clinical characteristics were balanced between the two arms.

4.2. *Treatment characteristics*

Out of the 321 eligible patients, 81 were discontinued from the study, 52 (32%) and 29 (18%) in arms A and B, respectively ($p = 0.007$). The most common reason for treatment discontinuation was voluntary withdrawal (18 patients in arm A and 16 patients in arm B). Additional reasons for treatment discontinuation were toxicity (13 patients in arm A and 2 patients in arm B, $p = 0.006$), disease progression (3 versus 4), death (1 versus 1), radiotherapy complication (4 versus 1), physician's decision (5 versus 2) and others (5 versus 2). In all, 100 (61%) patients randomised in arm A and 122 (77%) in arm B completed treatment. In group A, chemotherapy was delayed by more than 7 d in 90 patients (60%), and in group B in 94 patients (61%), $p = 0.908$. In group A, dose was reduced at least 10% of the planned dose on 53 patients (35%), and in group B on 23 patients (15%), $p < 0.001$. In the majority of cases, both dose reductions and delays were due to diarrhoea or haematological toxicity. Additionally, two patients originally allocated to arm A, received complete treatment in arm B. Selected treatment characteristics, for the 305 treated patients are presented in Table 2. In this table, patients are included in the arm they were actually treated.

The median relative dose intensity for 5FU was 0.83 (range 0.20–1.07) in arm A and 0.85 (0.28–1.17) in arm B. The relative dose intensity for IRI in arm A was 0.82 (range 0.20–1.00). The median numbers of treatment cycles were 6 (range 1–6) in arm A and 6 (1–6) in arm B (Table 2).

4.3. *Efficacy*

The median follow-up time was 52 months (range, 0.1–90). There were no significant differences between arms A and B in OS, disease-free survival or disease recurrence. Overall survival at 3 years was 81% in arm A and 86% in arm B ($p = 0.129$) (Fig. 2). The hazard ratio for death in arm A, as compared with the arm B, was 0.73 (95% CI, 0.46–1.15). Three-year DFS was 66% in arm A and 72% in arm B ($p = 0.557$) (Fig. 3), and the

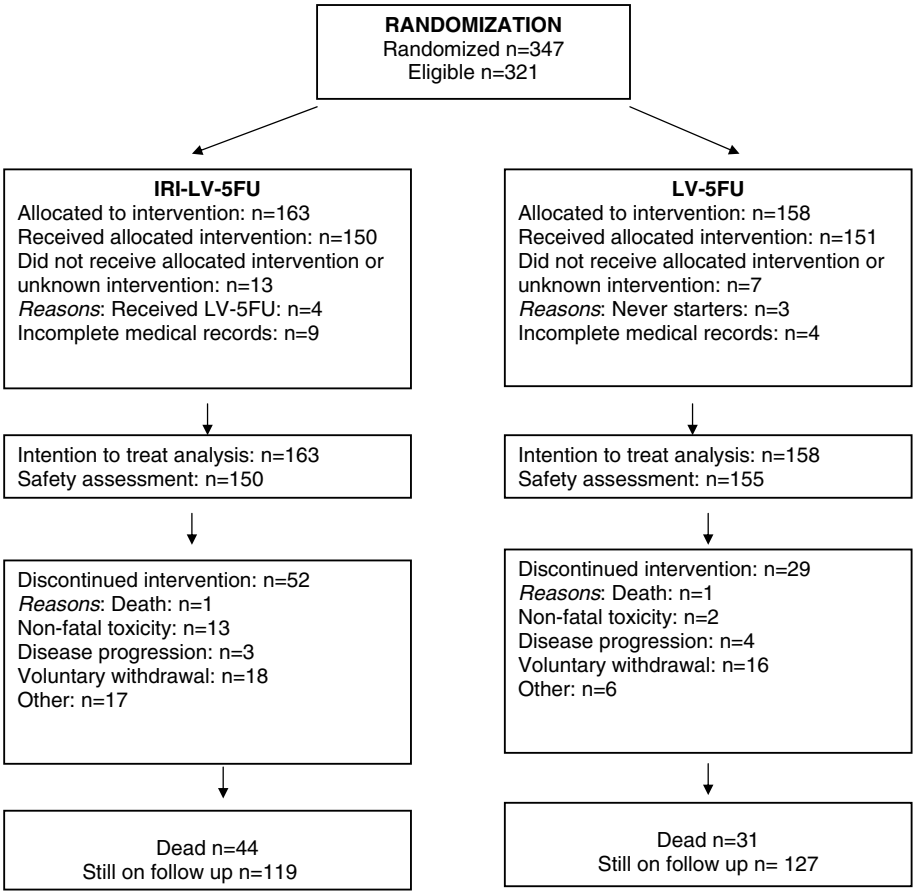

Fig. 1 – Outline of the study.

Table 1 – Patient characteristics

	Group A, N = 163	Group B, N = 158
Age (years)		
Median	63	63
Range	35–78	32–78
	N (%)	N (%)
Sex		
Female	69 (42)	51 (32)
Male	94 (58)	107 (68)
Performance status		
0	139 (85)	137 (87)
1 or 2	15 (9)	17 (11)
Unknown	9 (6)	4 (3)
Initial stage at diagnosis		
Dukes B_2	69 (42)	69 (44)
Dukes C_1	23 (14)	24 (15)
Dukes C_2	70 (43)	63 (40)
Unknown	1 (1)	2 (1)
Grade		
I	11 (7)	12 (8)
II	118 (72)	116 (73)
III	29 (18)	25 (16)
IV	0	1 (1)
Unknown	5 (3)	4 (2)
Number of lymph nodes examined		
Median	13	12
Range	0–82	0–64
Number of lymph nodes involved		
Median	1	1
Range	0–17	0–24
Perforation	8 (5)	7 (4)
Obstruction	4 (3)	5 (3)
Metastatic nodules	9 (6)	10 (6)

hazard ratio for DFS in the arm B, as compared with arm A, was 0.92 (95% CI, 0.63–1.34). The 3-year local relapse-free rate was 94% in both arms ($p = 0.837$). Furthermore, the 3-year distant metastasis-free rate was 72% in arm A and 78% in arm B ($p = 0.583$). In the presence of treatment arm, stage (C1 versus B2 HR: 2.95; 95% CI 1.55–5.64; $p = 0.001$ and C2 versus B2 HR: 2.11; 95% CI 1.21–3.67, $p = 0.009$) and grade (poor or undifferentiated versus good or moderate HR: 2.06; 95% CI 1.24–3.44, $p = 0.005$) were identified as independent prognostic factors for OS. Similarly, stage (C1 versus B2 HR: 3.43; 95% CI 1.99–5.91; $p < 0.001$ and C2 versus B2 HR: 2.61; 95% CI 1.65–4.13, $p < 0.001$) and grade (poor or undifferentiated versus good or moderate HR: 1.58; 95% CI 1.02–2.47, $p = 0.042$) were found to be significantly associated with poorer DFS.

4.4. *Safety*

Serious adverse events associated with each treatment regimen are listed in Table 3. Regarding toxicity, patients were analysed according to the treatment patients actually received. With the exception of leucopaenia, neutropaenia and alopecia, which was higher in patients in arm A ($p = 0.005$ and $p = 0.026$ and $p = 0.006$, respectively), there were no significant differences in toxicities between the two regimens. The most frequently recorded grade 3/4 toxicity was

Table 2 – Selected treatment characteristics (treatment as administered)

N	Group A, N = 150		Group B, N = 155	
Number of cycles per patient	N	%	N	%
1	17	11	13	8
2	4	3	1	1
3	9	6	8	5
4	7	5	3	2
5	13	9	6	4
6	100	67	124	80
Total number of cycles delivered	745 (83%)		825 (89%)	
Median (range)	6 (1–6)		6 (1–6)	
Delays (at least 7 d)[a]	90 (60%)		94 (61%)	
Reason for delay				
Diarrhoea	54 (36%)		43 (28%)	
Haematologic toxicity	28 (19%)		37 (24%)	
Infection	0 (0%)		3 (2%)	
Neuropathy	2 (1%)		0 (0%)	
Other toxicity	6 (4%)		11 (7%)	
Dose reductions (>10%)[b]				
LV	17 (11)		11 (7)	
Median (range)	20% (10–50%)		20% (10–80%)	
5FU	43 (29)		20 (13)	
Median (range)	20% (10–40%)		20% (10–30%)	
IRI	48 (32)		–	
Median (range)	20% (10–45%)		–	
At least one dose reduced	53 (35%)		23 (15%)	
Reason for the reduction				
Diarrhoea	35 (23%)		16 (10%)	
Haematologic toxicity	15 (10%)		5 (3%)	
Other toxicity	3 (2%)		1 (1%)	
DI of 5FU (mg/m^2/week)				
Median (range)	281 (64–360)		318 (104–440)	
Relative DI of 5FU				
Median (range)	0.83 (0.20–1.07)		0.85 (0.28–1.17)	
DI of LV (mg/m^2/week)				
Median (range)	126 (28–160)		132 (30–290)	
Relative DI of LV				
Median (range)	0.84 (0.20–1.07)		0.88 (0.20–1.93)	
DI of IRI (mg/m^2/week)				
Median (range)	49 (11–60)		–	
Relative DI of IRI				
Median (range)	0.82 (0.20–1.00)		–	

a $p = 0.908$ for the delays.
b $p < 0.001$ for the dose reduction of any drug.

leucopaenia in both treatment arms, followed by diarrhoea. In arm A, a total of 13 discontinued treatment, two due to grade 4 febrile neutropaenia, one due to grade 4 neutropaenia, two due to grade 4 leucopaenia, four due to grade 3 diarrhoea, one due to grade 3 anaemia and another three patients for unknown serious adverse events. In arm B, 2 patients discontinued treatment, one because of grade 4 leucopaenia and neutropaenia, and one because of grade 4 diarrhoea. However, of the 75 deaths that occurred during follow-up, 67 (89%) were due to rectal cancer, 2 due to toxicity of the treatment and 6 due to other causes such as cardiac events

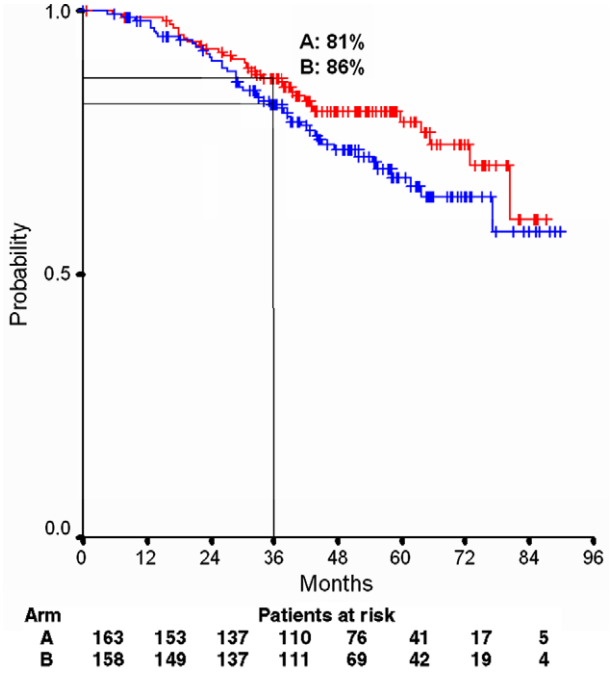

Fig. 2 – Kaplan–Meier curves for the OS in the two groups (blue line corresponds to group A, whilst red line corresponds to group B).

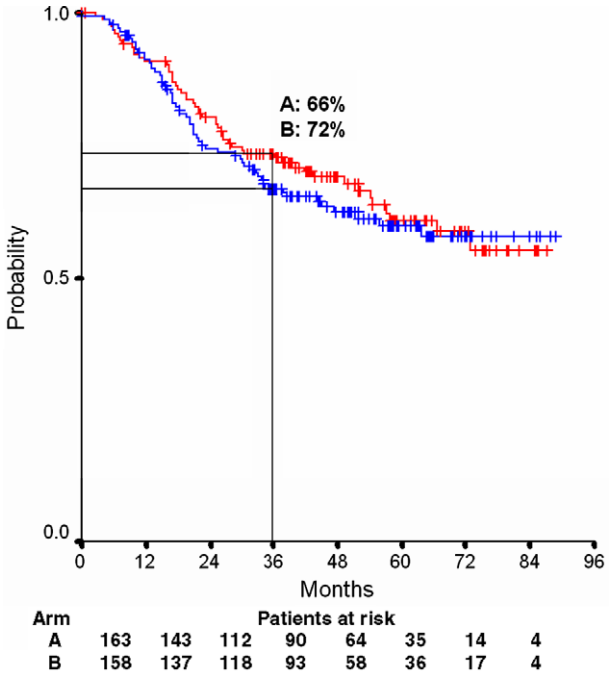

Fig. 3 – Kaplan–Meier curves for the DFS in the two groups (blue line corresponds to group A, whilst red line corresponds to group B).

(3 patients), CVS (2 patients) and ileus (1 patient). Deaths due to treatment toxicity occurred in two patients only, one in each arm. The unscheduled hospital admissions of patients due to treatment grades 3 and 4 toxicity were 15 in arm A and 11 in arm B. G-CSF because of leucopaenia and febrile neutropaenia was administered in 67 patients, 45 in arm A and 22 in arm B ($p = 0.001$).

Table 3 – Incidence n (%) of grades 3–4 toxicities (treatment as administered)

	Group A ($N = 150$)		Group B ($N = 155$)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	2 (1)	–	–	–
Leucopaenia	17 (11)	4 (3)	6 (4)	1 (1)
Neutropaenia	12 (7)	7 (5)[a]	7 (5)	1 (1)
Thrombocytopaenia	1 (1)	–	–	–
Nausea/Vomiting	3 (2)	–	–	–
Diarrhoea	14 (9)	–	8 (5)	1 (1)
Alopecia	7 (5)	–	–	–
Constipation	1 (1)	–	2 (1)	–
Fever	1 (1)	–	–	–
Infection	1 (1)	–	–	–

a Three of these patients developed febrile neutropaenia. Percentages are rounded.

5. Discussion

This study was designed to assess the impact of the addition of IRI to conventional adjuvant treatment with LV-modulated bolus 5FU and radiotherapy on the 3-year survival. The rationale for comparing these regimens was based on the previous studies demonstrating improved outcome of patients with the addition of IRI in LV-modulated 5FU-based chemotherapy in advanced colorectal cancer.[5,6,15]

To date, limited clinical data are available about the use of IRI-based chemoradiotherapy in the rectal cancer adjuvant setting.[8,10,11,15,16] Our study did not demonstrate a statistically significant difference in the 3-year OS between the study arms, and the secondary end-points of DFS and local relapse were also not statistically different. In accordance with multivariate analysis, stage and differentiation grade had an impact on survival. In contrast, number of involved lymph nodes, performance status and age did not have an effect. However, these findings should be interpreted with caution because of the size of the study. In agreement with our study, all large prospective randomised trials evaluating the addition of IRI to bolus or continuous infusion 5FU and LV had failed to show a survival benefit in colon cancer adjuvant setting[17–19] even though IRI-5FU-based chemotherapy has shown to double the response rate in metastatic disease,[6] and in locally advanced rectal cancer IRI-5FU with radiotherapy as preoperative treatment reported high pCR rates.[8,10,20] However, adjuvant studies performed with IRI-based chemotherapy were not adequately designed and the value of IRI is still to be proved.[7]

Regarding safety and treatment tolerance in our study, no unexpected adverse events were observed and two toxic deaths one in each arm had been recorded. Treatment related grade 3/4 toxicities were acceptable and corresponded to the known toxicities of IRI-5FU adjuvant chemoradiotherapy, as recorded in the previous studies.[10,11] The incidence of severe (grade 3/4) toxicity was similar in both the arms except alopecia, leucopaenia and neutropaenia which were higher in the

IRI based regimen. Higher rate of discontinuation and dose reduction of study treatment was observed in those patients allocated in the IRI-based chemotherapy, 32% versus 18%, ($p = 0.007$) and 35% versus 15% ($p < 0.001$), respectively. Because of the higher incidence of leucopaenia, more G-CSF was administered in patients who were allocated to IRI-based chemoradiotherapy arm.

Concerns have also been raised relating to the use of bolus regimen of 5FU-LV plus weekly IRI such as the IFL regimen[6] instead of IRI plus continuously administered 5FU-LV or capecitabine. A higher incidence of treatment-related deaths has been reported with IFL regimen compared to LV-5FU[21] in patients enrolled in the Intergroup trial CALGB C89903 where no difference in disease-free survival and OS was observed.[19] However, in this study this increased incidence was not observed with the IRI-LV and bolus 5FU regimen, possibly due to the dose level of IRI.[11] An approach to further optimise 5FU-based therapy and overcome the drawbacks of continuous i.v. infusion has been the development of oral fluoropyrimidine derivatives designed to generate 5FU predominately within tumour cells.[22,23] Oral administration of capecitabine avoids the technical barriers of infusional administration, thus allowing significant flexibility. Capecitabine plus IRI and radiotherapy have been evaluated preoperatively in a number of phase I/II studies[9,24,25] and could be an important alternative in the management of patients with rectal cancer.[26]

The actual outcomes of combined treatments with IRI plus LV-modulated bolus 5FU and radiotherapy in this study and others with different doses and schedules indicate that the IRI could be combined with LV plus 5FU and radiotherapy. However, IRI added to adjuvant chemoradiotherapy with LV and bolus-administered 5FU was not shown to improve OS of patients, disease-free survival or local relapse, whereas the incidence of severe toxicity was substantially higher. IRI-based chemoradiotherapy should not be routinely used in postoperative adjuvant setting in rectal cancer. There is a need for new studies to integrate new effective agents such as monoclonal antibodies raised against EGFR and VEGF in adjuvant 5-FU-based chemoradiotherapy, keeping in mind the superior convenience of oral fluoropyrimidines with similar efficacy and toxicity profiles.

Conflict of interest statement

None declared.

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