A randomized phase III multicenter trial comparing irinotecan in combination with the Nordic bolus 5-FU and folinic acid schedule or the bolus/infused de Gramont schedule (Lv5FU2) in patients with metastatic colorectal cancer

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Background: To compare irinotecan with the Nordic 5-fluorouracil (5-FU) and folinic acid (FA) bolus schedule [irinotecan 180 mg/m² on day 1, 5-FU 500 mg/m² and FA 60 mg/m² on day 1 and 2 (FLIRI)] or the Lv5FU2 schedule [irinotecan 180 mg/m² on day 1, FA 200 mg/m², 5-FU bolus 400 mg/m² and infused 5-FU 600 mg/m² on day 1 and 2 (Lv5FU2-IRI)] due to uncertainties about how to administrate 5-FU with irinotecan.

Patients and methods: Patients (n = 567) with metastatic colorectal cancer were randomly assigned to receive FLIRI or Lv5FU2-IRI. Primary end point was progression-free survival (PFS).

Results: Patient characteristics were well balanced. PFS did not differ between groups (median 9 months, \( P = 0.22 \)). Overall survival (OS) was also similar (median 19 months, \( P = 0.9 \)). Fewer objective responses were seen in the FLIRI group (35% versus 49%, \( P = 0.001 \)) but the metastatic resection rate did not differ (4% versus 6%, \( P = 0.3 \)). Grade 3/4 neutropenia (11% versus 5%, \( P = 0.01 \)) and grade 2 alopecia (18% versus 9%, \( P = 0.002 \)) were more common in the FLIRI group. The 60-day mortality was 2.4% versus 2.1%.

Conclusions: Irinotecan with the bolus Nordic schedule (FLIRI) is a convenient treatment with PFS and OS comparable to irinotecan with the Lv5FU2 schedule. Neutropenia and alopecia are more prevalent, but both regimens are equally well tolerated.

Key words: chemotherapy, colorectal cancer, irinotecan, randomized trial, 5-fluorouracil

introduction

Several trials have shown that a combination of two drugs has superior antitumor activity with higher response rates, longer time to progression and at least a tendency to improved survival in metastatic colorectal cancer compared with the previously most active compound, 5-fluorouracil (5-FU) with folinic acid (FA) [1–3]. Colorectal cancer went from a one-drug disease to a three-drug disease. Clinical research could focus on improving outcome by optimizing these combinations and adding new drugs than trying to explore yet another way to biochemically modulate the old compound, being around for several decades [4]. It soon became apparent, however, that the way 5-FU was delivered was still of importance for the balance between antitumor efficacy and toxicity [5] and potentially even more important than before since some combinations resulted in pronounced morbidity and unacceptable mortality [5, 6]. It should be mentioned though that the up-front use of combination chemotherapy, rather than a sequential use in many patients, has been challenged recently by two large randomized studies [7, 8].

5-FU can be given in many ways, although they can be categorized into two groups, bolus injection and infusion. Presently, oral administration is increasing in relevance [9]. Even if bolus or infused 5-FU can be given in many ways, it is generally considered that infused 5-FU is more efficacious and less toxic [4, 10, 11]. This, however, has not been generally

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accepted, and one reason for this is the poor tolerability of the most commonly used bolus regimen in the trials, the Mayo Clinic schedule [12].

The Nordic fortnightly bolus 5-FU/FA regimen (Nordic FLv) had an efficacy that appeared similar to other 5-FU/FA schedules, and low toxicity, at least when compared with the Mayo Clinic schedule [13–15]. Nordic FLv was also possible to combine at full doses with irinotecan [16] and oxaliplatin [17] with apparently high activity and low toxicity.

The purpose of this randomized phase III trial was to compare irinotecan with the Nordic bolus FLv schedule [irinotecan 180 mg/m² on day 1, 5-FU 500 mg/m² and FA 60 mg/m² on day 1 and 2 (FLIRI)] or with a widely used infused schedule, the Lv5FU2 schedule [irinotecan 180 mg/m² on day 1, FA 200 mg/m², 5-FU bolus 400 mg/m² and infused 5-FU 600 mg/m² on day 1 and 2 (Lv5FU2-IRI)].

patients and methods

patient selection

The study included, from June 2001 to March 2004, 567 patients with histologically confirmed colorectal adenocarcinoma and nonresectable metastatic disease. No prior chemotherapy other than adjuvant 5-FU-based chemotherapy completed at least 6 months before the study entry was allowed. All patients had measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [18], an age between 19 and 76 years, a World Health Organization performance status of zero to two, a neutrophil count >1.5 × 10⁹/l, platelet count >100 × 10⁹/l, serum creatinine level <1.25 × upper normal limit (UNL), serum bilirubin level <1.25 × UNL (1.5 if liver metastases) and serum aspartate aminotransferase and serum alanine aminotransferase <3 × UNL (5 × UNL if liver metastases). Exclusion criteria were unresolved bowel obstruction, uncontrolled Crohn’s disease/ulcerative colitis, current history of diabetes, infection and central nervous system metastasis. The study was approved by the ethical committees at each site/country and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

 treatment

The patients were randomly assigned to receive irinotecan with the Nordic FLv schedule [13] or the Lv5FU2 schedule [19]. The FLIRI regimen [16] consisted of irinotecan (Campto®, Sanofi-Aventis) 180 mg/m² (initially 210 mg/m², see below) as a 60-min i.v. infusion on day 1, followed immediately by 5-FU 500 mg/m² as a bolus (<5 min) injection, followed 30–40 min later by FA 60 mg/m² i.v. bolus. The 5-FU/FA administrations were repeated on day 2. The Lv5FU2-IRI regimen [2] consisted of irinotecan 180 mg/m² on day 1, followed by FA 200 mg/m² as a 2-h infusion and 5-FU bolus 400 mg/m² followed by 600 mg/m² as a 22-h infusion. The 5-FU/FA administrations were repeated on day 2. All treatments were repeated every 2 weeks until disease progression or unacceptable toxicity. A 20% reduction in dose of irinotecan and 5-FU was made in the case of grades 3–4 hematological and non-hematological toxic effects. A second 20% reduction was also allowed if toxic effects remained.

Concomitant medication included s.c. atropine 0.25 mg, generally administered from the first irinotecan dose or otherwise as a curative treatment for severe cholineric symptoms and then as prophylaxis for subsequent cycles. Oral loperamide, 2 mg every 2 h for at least 12 h was administered as soon as the first liquid stool occurred. If the diarrhea persisted for >48 h, or in case of severe diarrhea or diarrhea associated with vomiting, fever or severe neutropenia, a prophylactic broad spectrum oral antibiotic (ciprofloxacin) was to be administered. Patients with febrile neutropenia were hospitalized to receive i.v. antibiotics.

response and toxicity evaluation

Tumor response was assessed according to RECIST criteria [18] (complete response [CR]: Complete response means complete disappearance of all signs of tumour; partial response [PR]: partial response means at least a 30% decrease in the sum of the largest diameters of the target lesions; stable disease [SD]: Stable disease was less than a 30% reduction and less than a 20% increase in the sum of the largest diameters of the target lesions and the appearance of no new lesions and progressive disease [PD]) every 8 weeks. The overall response rate was the percentage of patients with CR or PR.

Patients who interrupted treatment without having PD were evaluated every second month until PD was seen. The primary end point was progression-free survival (PFS) defined as the time from randomization to the date of any progression or death. No patient was lost to follow-up. Secondary end points were overall survival (OS), objective response rate and toxicity. All PFS was independently evaluated but not all objective responses. The major reasons for treatment interruption were disease progression and toxicity, but for some patients, a break was made because of patient wish or for practical reasons.

Toxicity was evaluated according to National Cancer Institute—Common Toxicity Criteria, version 2 [20]. Grades 3 and 4 toxic effects, serious adverse events and deaths within 60 days were monitored by an independent committee 60 days after every 100 randomized patients. These analyses did not reveal any differences between randomization groups, although numerically slightly more grades 3–4 toxic episodes were seen in the FLIRI group (49 versus 38) for the first 100 patients. This together with the report of excessive toxicity using the bolus Saltz regimen [5], led to a lowering of the irinotecan dose from 210 to 180 mg/m² in the FLIRI arm (136 patients were randomized). Recently randomly allocated patients generally had their irinotecan dose reduced, even if this was not recommended.

statistical analyses

A sample size of 446 patients (378 events) was decided upon to exclude a 25% difference in PFS between the two groups [from median 6.7 months, equivalence was considered if the two median PFS times differed by <2.2 months, hazard ratio (HR) of 0.75] with a significance level of 5% and a power of 80%. When the irinotecan dose was lowered in the FLIRI group, it was decided to increase patient number to 366 so that 446 patients were be randomly allocated to and treated with the same irinotecan dose. Since we could not detect any numerical difference in any end point between the first 68 patients in each group and the remaining patients, all randomized patients are analyzed together.

The duration of survival and PFS were estimated using the Kaplan–Meier method and compared using a two-sided log-rank test. Multivariate Cox regression analyses were carried out to correct for any potential baseline imbalances and for the initially higher irinotecan dose in the FLIRI group. Student’s t-test and χ² tests were used to compare differences in means and proportions, respectively.

results

patient characteristics and treatment

Patient characteristics at baseline were well balanced between groups (Table 1). No patient was ineligible. A flowchart is shown in Figure 1. Virtually, all patients started therapy as scheduled. The mean (and median) number of cycles was 12 in both groups. Dose reductions did not differ between groups. At the fourth cycle, given dose of the drugs was similarly high in both groups (95%–96%). Dose delays were more common in the FLIRI group during the first four cycles, given dose of the drugs was similarly high in both groups (95%–96%). Dose delays were more common in the FLIRI group during the first four cycles, given dose of the drugs was similarly high in both groups (95%–96%). Dose delays were more common in the FLIRI group during the first four cycles, given dose of the drugs was similarly high in both groups (95%–96%).
was given to 152 (54%) patients after FLIRI and to 175 (61%) patients after Lv5FU2-IRI.

**PFS and OS**

Median PFS was 9 months in both groups [9.4 months FLIRI, 9.0 months Lv5FU2-IRI, a difference of 0.4 [95% confidence interval (CI) −1.0 to 1.4] months]. Likewise, OS (72% dead) did not differ between groups [median 19.4 months FLIRI, 19.0 months Lv5FU2-IRI, a difference of 0.4 (95% CI −2.6 to 2.8)] (Figure 2). Excluding the first 100 or 136 randomized patients did not change these figures (data not shown). Similarly, the HRs for PFS, HR = 1.1 (95% CI 0.9–1.3) and OS, HR = 1.0 (95% CI 0.8–1.2) were not changed when adjusting for initially a higher dose in a multivariate Cox regression model. The HRs for PFS and OS were also not changed when adjustments were made for initial dose, primary tumor site, whether the primary tumor was resected or not, performance status, prior adjuvant chemotherapy, number of organs involved and low baseline hemoglobin levels (data not shown).

**tumor response and surgical resectability**

More objective tumor responses (all investigator assessed) were seen in the Lv5FU2-IRI group (Table 2). The difference in the proportion of patients who had CR + PR (35% FLIRI versus 49% Lv5FU2-IRI, P = 0.001) was the same if the first 138 randomized patients were excluded (P = 0.005). Ten (4%) and 16 (6%) (P = 0.3) patients in the FLIRI and Lv5FU2-IRI groups, respectively, could be resected for cure. Liver was the predominant metastatic site. Of the resected patients, three and two patients are recurrence free after a minimum of 3-year follow-up.

**toxicity**

Although the toxicity profiles differed between groups, there was no overall difference with the exception of neutropenia and alopecia which were seen more often with FLIRI (Table 3). The number of febrile neutropenic episodes or thromboembolic events did not differ. Sixty-day mortality was low in both groups [2.4% (seven patients) in the FLIRI group and 2.1% (six patients) in the Lv5FU2-IRI group]. The number of deaths that could potentially be ascribed to another reason than colorectal cancer was low in both groups [10 (4.9%) versus 8 (3.9%)].

**discussion**

This study shows that irinotecan together with a bolus 5-FU/FA regimen is not substantially inferior to or more toxic than irinotecan with an infused 5-FU/FA regimen. A generally held opinion [4, 21–24], although never tested in a randomized trial, is otherwise that infused 5-FU is superior to bolus 5-FU when given in combination with either irinotecan or oxaliplatin. When 5-FU was the only cytotoxic drug with activity in colorectal cancer, two meta-analyses showed that infused 5-FU resulted in more tumor responses, marginally superior OS and less toxicity than bolus 5-FU [10, 11]. The comparatively toxic Mayo Clinic schedule, however, was the predominant bolus schedule [12] in the trials. Otherwise, great heterogeneity existed between both bolus and infusion regimens. Whether the bolus treatment was given as a true i.v. bolus (<5 min) or as a short infusion (5–30 min) also mattered with higher antitumor activity using an i.v. bolus [14]. Different bolus or different infused regimens have otherwise not been directly compared with each other. A generally held impression was that the antitumor activity was similar between regimens, and, for routine purposes, you used the one you were used to. The Nordic bolus Flv schedule [13–15] was judged to have antitumor activities similar to all the others around but less toxic than the Mayo Clinic schedule and more convenient than any of the infused schedules.

When 5-FU was combined with another cytotoxic drug, particularly irinotecan, it appeared as if the different 5-FU schedules again became important [4]. Indirect comparisons between trials and within one trial, comparing irinotecan with a bolus regimen (IFL) and oxaliplatin with an infused regimen

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FLIRI (n = 281)</th>
<th>Lv5FU2-IRI (n = 286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Median</td>
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<td>Range</td>
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<td>29–76</td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>179 (64%)</td>
<td>171 (60%)</td>
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<tr>
<td>WHO performance status</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>149 (53%)</td>
<td>157 (55%)</td>
</tr>
<tr>
<td>1</td>
<td>109</td>
<td>106</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Missing</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>170 (61%)</td>
<td>191 (67%)</td>
</tr>
<tr>
<td>Primary tumor resected</td>
<td>228 (81%)</td>
<td>238 (83%)</td>
</tr>
<tr>
<td>Prior adjuvant chemotherapy</td>
<td>37 (15%)</td>
<td>44 (17%)</td>
</tr>
<tr>
<td>Organ involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>224</td>
<td>233</td>
</tr>
<tr>
<td>Lymph node</td>
<td>73</td>
<td>61</td>
</tr>
<tr>
<td>Lung</td>
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<td>91</td>
</tr>
<tr>
<td>Peritoneum</td>
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<td>4</td>
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<td>Bone</td>
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<td>8</td>
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<tr>
<td>Other</td>
<td>77</td>
<td>69</td>
</tr>
<tr>
<td>No. of organs involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>138 (49%)</td>
<td>140 (50%)</td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>98</td>
</tr>
<tr>
<td>3+</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
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<td></td>
</tr>
<tr>
<td>information</td>
<td>128 (52%)</td>
<td>125 (50%)</td>
</tr>
<tr>
<td>information</td>
<td>35 no information</td>
<td>34 no information</td>
</tr>
<tr>
<td>Low hemoglobin</td>
<td></td>
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</tr>
<tr>
<td>(&lt;130 g/l)</td>
<td>127 (45%)</td>
<td>120 (42%)</td>
</tr>
<tr>
<td>Mean (g/l)</td>
<td>127 (83–174)</td>
<td>128 (96–101)</td>
</tr>
</tbody>
</table>

FLIRI, irinotecan 180 mg/m² on day 1, 5-FU 500 mg/m² and FA 60 mg/m² on day 1 and 2; Lv5FU2-IRI, irinotecan 180 mg/m² on day 1, FA 200 mg/m², 5-FU bolus 400 mg/m² and infused 5-FU 600 mg/m² on day 1 and 2; WHO, World Health Organization.
(FOLFOX-4) [6, 23], again concluded that infused 5-FU appears superior to bolus 5-FU [4, 21–24]. Irinotecan combined with oral capecitabine, an alternative to i.v. 5-FU, has quite some unpredictable toxicity [25, 26], although not seen in a third study [7].

A direct comparison between the Nordic FLv and a commonly used infusion schedule, Lv5FU2, with irinotecan, gained support in the Nordic countries. If the Nordic FLv turned out to be inferior in the primary and most important efficacy end point (PFS), or more toxic, particularly with more toxic deaths and a higher 60-day mortality, a change in routine was prompted. Although no differences were seen in either of these aspects, or in OS, being the ultimate end point in cancer trials, the Lv5FU2-CPT11 schedule resulted in more objective responses. Many may thus state that infused 5-FU has superior antitumor activity to bolus 5-FU, as the meta-analysis 8 years ago revealed [11], even if it then did not show up in PFS or OS. PFS was the primary end point in this trial, it was available in all randomized patients and independently assessed. In contrast, response rates were a secondary end point and only investigator assessed (the group did not have resources to collect all images for an independent evaluation). The distinction between a PR (>30% decrease in the sum of the largest diameters [18]) and SD is clear but clinically arbitrary. Most patients with SD for at least 4 months have some tumor regression, albeit not sufficient for a PR, are improved symptomatically [13] and have their lives prolonged [27]. Disease control (CR + PR + SD) for at least 4 months was seen in ~90% of the patients in both groups. We can otherwise not explain why a significant difference was seen in response rates but not in PFS; there was no difference in the number of resected patients and we could not detect any difference when the treatments were interrupted for other reasons than disease progression. Dose delays were slightly more frequent after FLIRI than after Lv5FU2-IRI, and although tumor evaluations were to be done every 8th week, it is possible that some computed tomography (CT) evaluations were postponed for a few weeks more often in the FLIRI than in the Lv5FU2-IRI group. Median times between baseline and the first three CT evaluations did, however, not differ between groups.

Figure 1. Flowchart showing the number of patients available for different subset analyses and treatments.
Although many infused schedules are available, the Lv5FU2 is the reference schedule to be used in comparative trials. It was used in the trials showing superiority of the addition of irinotecan [2] and oxaliplatin [3]. It is also the base of the FOLFOX-4 schedule used in palliative [6, 23] and adjuvant trials [28]. Many simplifications, omitting the bolus 5-FU dose on day 2, are presently used. They are considered to have similar antitumor efficacy [29, 30], but have never been compared directly in randomized phase III trials. The Lv5FU2 was designed as a ‘hybrid’ regimen, containing both bolus and infusion 5-FU. Actually, this may be one reason for its success [31]. It can, however, be regarded as 80% bolus and 20% infusion, although in milligrams, more 5-FU is given as an infusion (1200 mg/m²) than as a bolus dose (800 mg/m² every other week). This depends upon the much more rapid clearance of an infusion than a rapid bolus dose [14].

A 20% dose reduction of bolus 5-FU (from 500 to 400 mg/m², i.e. the same daily bolus dose as in Lv5FU2) in the Nordic FLv schedule resulted in inferior activity with fewer responses, whereas a 20% increase (to 600 mg/m²) resulted in more toxicity (500 mg/m² of 5-FU i.v. bolus 2 days every fortnight is consequently regarded as 100% bolus) [15].

**conclusions**

Irinotecan with a bolus 5-FU/FA schedule (Nordic FLv) results in the same PFS and OS as when combined with the ‘infused’, Lv5FU2 schedule. More objective responses were, however, seen with the infused Lv5FU2-IRI schedule. Serious toxicity did not differ, although the bolus FLIRI schedule resulted in slightly more neutropenia and more alopecia. A simple and convenient bolus schedule is thus an attractive alternative for routine palliative treatments.

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**appendix**

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references