High-Dose FOLFIRI plus Bevacizumab in the Treatment of Metastatic Colorectal Cancer Patients with Two Different UGT1A1 Genotypes: FFCD 0504 Study

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Abstract

High-dose FOLFIRI has an acceptable safety profile and promising efficacy. UDP-glucuronosyltransferase-1A1 (UGT1A1) polymorphism may be predictive of toxicity and efficacy of irinotecan. This phase II study aimed to evaluate the combination of high-dose FOLFIRI plus bevacizumab in patients with previously untreated metastatic colorectal cancer (MCRC) based on their UGT1A1 genotype. Patients with the UGT1A1 *1/*1 (group 1) or *1/*28 (group 2) genotype received bevacizumab plus high-dose FOLFIRI every 2 weeks. Using the Bryant and Day design with objective response rate as the primary endpoints, 54 patients in each group were required with a planned interim analysis after inclusion of 17 patients per group. We planned to stop the trial at the interim analysis if ≤7 patients exhibited an objective response (OR) and/or ≥3 patients exhibited severe toxicity. At the interim analysis, ORs were higher than the number expected: 52.9% (group 1) and 58.8% (group 2). More than three toxic events occurred in both groups and, according to the interim analysis rule, the trial was closed due to unacceptable toxicity. Recruitment was stopped when 86 patients were included and an analysis on overall population was done for overall survival (OS) and progression-free survival (PFS). The median OS was 10.7 months (group 1) and 10.4 months (group 2). The median OS was 25.5 months (group 1) and 23.9 months (group 2). This trial does not support the use of the intensive treatment with HD-FOLFIRI plus bevacizumab combination for MCRC in patients with the UGT1A1 *1/*1 or UGT1A1 *1/*28 genotype. Mol Cancer Ther; 14(12): 2782-8. ©2015 AACR.

Introduction

Irinotecan is a camptothecin analogue with antitumor activity mediated through the inhibition of topoisomerase I. Irinotecan is metabolized by carboxylesterase to form active SN-38, which is further conjugated and detoxified by UDP-glucuronosyltransferase (UGT; ref. 1). Multiple factors determine SN-38 levels, among them UGT ability to inactivate SN-38 by glucuronidation seems to be of importance. Several polymorphisms in UGT, especially the UGT1A1 isoform, have been shown to influence conjugation and, consequently, the pharmacokinetics and toxicity of irinotecan. Different UGT1A1 genotypes have been described. Some of these genotypes are associated with the decreased activity of the corresponding enzyme isoform, leading to constitutional unconjugated jaundice, Crigler-Najjar or Gilbert’s syndrome (2), or decreased SN-38 glucuronidation activity (3, 4). Accumulation of the active metabolite SN-38 would increase toxicity of irinotecan.

The most common (wild-type) UGT1A1 allele is believed to be UGT1A1*1. The UGT1A1*1 allele is associated with a 2-base pair (bp) insertion (TA) in the TATA box in the promoter, resulting in the sequence (TA)_{8-10}TAA (the most common sequence is (TA)_{8-10}TAA). This nucleotide change in the promoter region is associated with the reduced expression of the protein and, therefore, with the decreased activity of SN-38 glucuronidation (a 50% decrease in UGT1A1*28/UGT1A1*1 patients and a 25% decrease...
in UGT1A1*1/UGT1A1*28 patients compared with UGT1A1*1/
UGT1A1*1 patients; ref. 4).

Taking into account both toxicity and compliance, a clinical
dose-finding study established the recommended dose of iri-
notecan combined with the biweekly LV5FU2 regimen to be
180 mg/m² every 2 weeks, although MTD criteria were not met
at doses up to 260 mg/m² (5).

Results from a genotype-driven phase I study suggested, how-
ever, that this recommended dose is considerably lower than the
dose that can be tolerated by patients with normal SN-38 glucur-
onidation (6). Therefore, because there is a dose linearity of
irinotecan pharmacokinetics with proportional increases in the
AUC of both irinotecan and SN-38 with higher doses of irinotecan
(7), dose intensification may be a way to optimize the efficacy of
treatments in selected patients (6). The combination of high-dose
irinotecan (260 mg/m²) with the simplified LV5FU2 regimen
(HD-FOLFIRI regimen) was shown to be feasible with an ac-
setable safety profile and promising efficacy data (8).

The combination of 5-fluorouracil, irinotecan, and bevacizum-
ob is a standard treatment for metastatic colorectal cancer
(MCRC; ref. 9). Adding bevacizumab to this optimized chemother-
apy regimen may be of interest.

The aim of this phase II study was to evaluate the tolerance
and efficacy of the HD-FOLFIRI regimen in combination with
bevacizumab (B) in patients with the UGT1A1*1/1 and 1/28
genotypes.

Patients and Methods

Participants

This study was an open-label, nonrandomized, phase II trial.
Patients 18 to 74 years old with a World Health Organization
(WHO) performance status (PS) of less than 2 and nonresectable
MCRC who had not previously been treated were eligible for
inclusion if they exhibited the UGT1A1*1/1 or UGT1A1*1/28
genotype. We excluded patients with UGT1A1*28/28 genotypes
because this genotype is present in only 9.8% to 11% of the
population (10) and would increase dramatically the number of
patients to screen and to include and the time length of the study.
Previous adjuvant chemotherapy without irinotecan was allowed
in UGT1A1*1 patients; ref. 4). Prophylactic G-CSF administra-
tion was not allowed as a primary prevention. G-CSF use was recom-
ended in the case of infection with concomitant grade 3
neutropenia for more than 7 days, febrile neutropenia,
and 5FU 2,400 mg/m² 46-hour infusion D1-2 every 2 weeks.

Treatment

Patients were treated with bevacizumab 5 mg/kg D1, irinotecan
260 mg/m² D1, LV 400 mg/m² D1, 5FU 400 mg/m² IV bolus D1,
and 5FU 2,400 mg/m² 46-hour infusion D1-2 every 2 weeks.
Treatment was started within 2 weeks after inclusion in the study.

Prophylactic G-CSF administration was not allowed as a pri-
mary prevention. G-CSF use was recommended in the case of
grade 4 neutropenia for more than 7 days, febrile neutropenia,
infection with concomitant grade 3–4 neutropenia, or nonrecov-
ery of neutrophil cell counts ≥1,500/mm³ after 1 week.

Genotyping

UGT1A1 genotyping was performed on blood samples (10-mL
EDTA tubes) after obtaining written consent from the patient.
DNA was extracted using the QiAmp blood DNA extraction kit
(Qiagen) in the Laboratory of Biochemistry at the "Hospital
Européen Georges Pompidou" in Paris. After quantification, DNA
was stored at −20°C until genotyping was performed. The
UGT1A1*2 allele of the gene was detected by fragment analysis.
All alleles were characterized after the amplification of the DNA
fragment using PCR by capillary electrophoresis for polymorph-
sisms (9700 sequencing, Applied Biosystems). Genotyping results
were sent within 10 days to the investigator.

Statistical considerations and trial design

The goal of adding targeted therapy to chemotherapy is gen-
erally to increase efficacy without increasing unacceptable toxicity.
We have considered, after literature analysis, that a reasonable
expected objective response rate (ORR) rate must be at least 60%
(ORR for FOLFIRI Bevacizumab combination is around 58%
(11)) and 37 more patients per group
after 6 months of follow-up; if 7 patients or less had no objective
response or/and 3 or more patients had unacceptable toxicity,
the study would be stopped for futility, if 8 or more patients had an
objective response or/and 2 or less patients had unacceptable
grade 3–4 toxicity, 37 more patients per group were required for a
total of 108 patients, 54 in each group, (α 5% and power 80%).

The secondary endpoints included progression-free survival
(PFS) and overall survival (OS). PFS was calculated as the interval
from the date of inclusion in the study to the first report of disease
progression or death from any cause or cutoff date. OS was calcu-
lated as the interval from the date of inclusion until death from any
cause or until the date of the last follow-up or cutoff date. The
Kaplan–Meier method was used to estimate the OS and PFS curves.

The cutoff date for the final analysis was January 01, 2011. All
analyses were based on the intent to treat principle. All tests were
two sided, and P values less than 0.05 were regarded as significant.
Data were analyzed using the STATA statistical software (version
10.0). In the absence of very serious adverse events, the study was
planned not to stop enrollment during the interim analysis and
finally 86 patients were included, we present here the results of the
interim analysis and in parallel of the overall population
included.

High-Dose FOLFIRI plus Bevacizumab in the Treatment of MCRC
Drug dose reductions and delays in the case of hematologic or nonhematologic toxicities were detailed in the protocol. The treatment was stopped in the event of patient withdrawal, disease progression, or unacceptable toxic effects (nonhematologic grade 4 toxicity, nonrecovery from grade 3 toxicity after two dose adjustments, or nonrecovery after a 2-week treatment delay). Any dose reduction was permanent.

The tumor response was assessed every four cycles with CT or MRI according to the RECIST criteria. An objective response had to be confirmed by CT or MRI after 4 weeks. An external radiologic review was performed. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0) until 4 weeks after the end of study treatments. At every visit, patients underwent history taking, physical examination, hematologic tests, and biochemical tests. An independent data monitoring committee reviewed the safety data on a regular basis.

Results

Patients were recruited between January 29, 2007, and January 30, 2008, for the first 34 patients analyzed in the interim analysis, December 11, 2008, for the final 86 included patients, at 20 centers in France. Thirty-four patients were analyzed in the interim analysis (IA; 17 in each group). As study inclusion was not stopped before the availability of the IA results, a total of 86 patients were included (40 patients in group 1 and 46 patients in group 2). One patient in group 2 was never treated because brain metastases were discovered after the patient’s inclusion.

**Overall population.** The median population age was 59 and 61 years for group 1 and group 2. The WHO PS was 0–1, respectively, for 92.5% and 91.3% of the patients. The primary tumor location was the colon for 70.0% in the group 1 and 73.9% in the group 2. Liver metastasis rates were, respectively, 72.5% and 84.8% for group 1 and 2, 35.0% and 26.1% for lung metastasis.

**Treatment administration**

**Interim analysis.** The median duration of treatment was 14 months (range: 1–28 months) in group 1 and 6.5 months (range: 0–25 months) in group 2 (Table 2). The median dose per cycle for cycles 1 to 4 was similar in both groups, but the patients in group 2 received a median of 12 treatment cycles (range: 0–30 cycles), compared with 22 cycles (range: 4–38 cycles) for the patients in group 1.

**Overall population.** The median duration of treatment was similar in the two groups: 7.0 months. The median dose per cycles 1 to 4 was similar in the both groups, and the patients received the same median number of cycles: 14.5 for group 1 and 13.5 for group 2.

**Primary endpoint results**

**Interim analysis.** In both groups, the confirmed ORR, as estimated by the independent central review, was higher than the number (>7) required by the stopping rule [9 (52.9%) and 10 (58.8%) objective responses in group 1 and group 2, respectively].

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**Results**

**Patient characteristics**

**Interim analysis.** The baseline characteristics of the patients analyzed in the interim analysis are presented in Table 1. The median patient age was 59 years (range: 52–75 years) in group 1 and 57 years (range: 44–72 years) in group 2. The WHO PS was 0–1 for 94.1% of the patients in both groups, but only 29.4% of the patients had a PS equal to 0 in group 1, compared with 52.9% in group 2. The primary tumor location was the colon and rectum in, respectively, 58.8% and 11.8% of the patients in group 1 and group 2. Patients of group 2 had more frequently liver metastasis than patients of group 1, respectively, 88.2% and 52.9%, lung metastasis was more frequent in group 1 than in group 2: 58.8% and 11.8%.
Three or more toxic events occurred in both groups (group 1: 7 events; group 2: 3 events), and the interim analysis stopping rules required less than 3 events to continue the trial (Table 3). The trial was therefore closed to inclusion after the results of the interim analysis.

Overall population. However, during the interim analysis and the availability of the results, recruitment was ongoing and finally a total of 86 patients were included (40 patients in group 1 and 46 patients in group 2). ORR was 45.0% in group 1 and 56.5% in group 2. ORR was equally frequent in the two groups.

Tolerance

Interim analysis. Toxicities by group are presented in Table 4. There was no death due to toxicity. All the patients experienced at least one adverse event, and 94.1% and 81.2% of the patients in group 1 and group 2, respectively, exhibited at least grade 3 toxicity.

Severe diarrhea occurred in 23.5% of the patients in group 1 and in 12.5% of the patients in group 2, whereas severe neutropenia was more frequent in group 2 (37.5% vs. 29.4%). Bevacizumab-related adverse events did not differ between the groups [except for grade 3–4 venous thromboembolic events (VTE), which occurred in 23.6% of patients in group 1 vs. 6.2% in group 2]. Arterial hypertension was observed in 23.5% of the patients in group 1 compared with 6.2% in group 2. Only one patient in each group exhibited grade 3 arterial hypertension. Approximately half of the patients exhibited epistaxis (mainly grade 1–2) in each group. Cerebral ischemia occurred in one patient in group 1.

Overall population. About 75.0% and 82.2% of patients of groups 1 and 2 exhibited at least one grade 3–4 toxicity. Severe diarrhea and VTE were more frequent in group 1 than in group 2, whereas severe neutropenia was more frequent in group 2 than in group 1. Arterial hypertension rate was similar in the both group. Epistaxis was equally frequent in the two groups.

PFS and OS on the overall population (Table 5)

The median PFS was 10.7 months (95% confidence intervals; CI, 8.5–13.1) in group 1 and 10.4 months (95% CI, 8.8–12.3) in group 2 (nonsignificant: NS). The median OS was 25.5 months.
Table 3. Results of primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Interim population</th>
<th>Overall population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td></td>
<td>n = 17</td>
<td>n = 17</td>
</tr>
<tr>
<td>Confirmed ORR n (%)</td>
<td>9 (52.9)</td>
<td>11 (58.8)</td>
</tr>
<tr>
<td>(interim analysis stopping rules required &gt;7 events)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Considered toxic events total number of patients (interim analysis stopping rules required &lt;3 events)</td>
<td>2a 0 3b</td>
<td>2</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 2c 4b</td>
<td>2</td>
</tr>
<tr>
<td>Grade 3 diarrhea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4 diarrhea</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: Group 1: UGT1A1*/UGT1A1*; Group 2: UGT1A1*/UGT1A1*/28.

*(a) patient in group 2 was never treated because brain metastases were discovered after the patient's inclusion.

*(b) patient with grade 4 neutropenia and grade 3 diarrhea.

*(c) patient with febrile neutropenia and grade 3 diarrhea.

*(d) patient with grade 4 neutropenia and febrile neutropenia.

(95% CI, 21.7–36.6) in group 1 and 23.9 months (95% CI, 18–37.1) in group 2 (NS).

Discussion

Optimization of medical treatment to improve efficacy with better tolerance is an important goal in the management of MCRC patients. According to irinotecan metabolism, the standard dose of 180 mg/m² every 2 weeks may not be the optimal dose for patients with the UGT1A1*/1 or *1*/28 genotype (13). Previous studies demonstrated the feasibility and interest of higher doses of irinotecan in patients as monotherapy (7, 14) or in combination with 5FU: FOLFIRI regimen (8). The important interpatient variability for irinotecan pharmacokinetic can be, at least partly, explained by the UGT1A1*28 polymorphism (15).

The link between the UGT1A1*28 allele and the increase in SN38 and the occurrence of diarrhea and leukopenia during irinotecan therapy suggested by retrospective studies (16–18) was prospectively reported by Innocenti and colleagues (19). In this study, the UGT1A1 genotype and haplotype were correlated with SN38 pharmacology and the incidence of severe neutropenia. The rate of grade 4 neutropenia was 50% among *28/*28 patients and 12.5% among *1*/28 patients, and there was no grade 4 neutropenia among *1*/1 patients. The prevalence of grade 3 diarrhea was 5% (1 *28/*28 and 2 *1*/28 patients, no grade 4 diarrhea). In the PETACC-3 trial, the risk of severe hematologic toxicity was increased among patients with homozygous UGT1A1*28 genotype (20). A recent meta-analysis reported that although the toxicity relationships were much stronger with the UGT1A1*28 homozygous variant, associations were also found with the UGT1A1*28 heterozygous variant (21). At least three prospective randomized phase III trials (22–24), however, did not confirm these initial results, suggesting that the influence of the UGT1A1*28 allele on the toxicity of irinotecan is modest and that its assessment should not be mandatory in routine clinical practice (23).

In a phase II study, 35 unselected patients were treated with the HD-FOLFIRI regimen as the first-line treatment of MCRC.

Table 4. Adverse events (all cycles)

<table>
<thead>
<tr>
<th></th>
<th>Interim population</th>
<th>Overall population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td></td>
<td>n = 17</td>
<td>n = 17</td>
</tr>
<tr>
<td>All</td>
<td>17 (100)</td>
<td>16 (94.1)</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (70.6)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (76.5)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (52.9)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>9 (52.9)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Mucoitis</td>
<td>8 (47.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (23.5)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>6 (35.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>VTE</td>
<td>7 (41.2)</td>
<td>4 (23.6)</td>
</tr>
<tr>
<td>ATE</td>
<td>1 (5.9)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Hematologic Neutropenia</td>
<td>15 (76.5)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 (11.8)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (94.1)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Thrombocytemia</td>
<td>15 (71.7)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

NOTE: Group 1: UGT1A1*/UGT1A1*; Group 2: UGT1A1*/UGT1A1*/28.

Abbreviations: VTE, venous thromboembolic event; ATE, arterial thromboembolic event.

*(a) patient in group 2 was never treated because brain metastases were discovered after the patient's inclusion.
The treatment administration was eventually delayed in 74% of the cases, and the dose was reduced in 43% of the cases. A granulocyte colony-stimulating factor G-CSF secondary prophylaxis to maintain cycle intervals and dose intensities was used in 37% of patients. There was one toxic death, and the main severe toxicities included neutropenia (74% of the patients), febrile neutropenia (11%), diarrhea (14%), and fatigue (17%; ref. 8). A recent meta-analysis (25) reported that UGT1A1*28 allele (homozygous, heterozygous, or wild-type) does not impact the survival in patient receiving irinotecan. In the present study, using the same chemotherapy regimen in combination with bevacizumab in selected patients with “favorable” UGT1A1 genotypes, the occurrence of severe neutropenia was much lower (29.7% in the ‘1’/‘1’ and 37.5% in the ‘1’/‘28 genotype patient groups, respectively), whereas the occurrence of severe diarrhea was very similar in ‘1’/‘28 patients and, interestingly, 2-fold higher in ‘1’/‘1’ patients.

A Bryant and Day design was used with a composite primary endpoint combining the ORR and toxicity. Toxicities associated with this primary endpoint included grade 4 neutropenia, febrile neutropenia, and grade 3–4 diarrhea. Expected ORRs were reached in the two groups, but the trial was stopped at the interim analysis in both groups because the number of unacceptable toxicity was higher than the number of expected ORRs. A posteriori, and from a clinical point of view, it can be judged that the stopping rules of the trial based on the defined toxic events (that led to an early stop) were too stringent and not adapted to daily clinic.

There was, however, no clear benefit of the HD-FOLFIRI/bevacizumab combination with respect to efficacy. The observed ORRs (approximately 53%–59%) do not seem to be superior to those observed with the FOLFIRI regimen alone (49% in the trial by Douillard and colleagues (12) and 47.2% in the BICC-C trial (11)) or in combination with bevacizumab (58% in the BICC-C trial). The addition of bevacizumab to the FOLFIRI HD regimen, compared with the trial by Ducreux and colleagues, in which a 54% ORR was reported, is also questionable (8).

In conclusion, this trial does not provide a convincing argument to support the adoption of the intensive treatment with HD-FOLFIRI plus bevacizumab combination for MCRC in patients with the UGT1A1*1/UGT1A1*1 or UGT1A1*1/UGT1A1*28 genotype. The overall response rate reached in our study is not superior to standard treatments.

Disclosure of Potential Conflicts of Interest

O. Bouché has received speakers bureau honoraria from Lilly. No potential conflicts of interest were disclosed by the other authors.

References


Table 5. PFS and OS (overall population)

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<th>Group 2</th>
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<tr>
<td><strong>n</strong></td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>10.7</td>
<td>10.4</td>
</tr>
<tr>
<td>IC (95%)</td>
<td>(8.5–13.1)</td>
<td>(8.8–12.3)</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>25.5</td>
<td>23.9</td>
</tr>
<tr>
<td>IC (95%)</td>
<td>(21.7–36.6)</td>
<td>(18.0–37.1)</td>
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Grant Support

All the authors received grants from La Ligue Nationale Contre le Cancer, Chugai, and Pfizer. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 21, 2015; revised August 5, 2015; accepted August 21, 2015; published OnlineFirst October 22, 2015.

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Mol Cancer Ther 2015;14:2782-2788. Published OnlineFirst October 22, 2015.

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