Efficacy of capecitabine versus 5-fluorouracil in colorectal and gastric cancers: a meta-analysis of individual data from 6171 patients

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Background: To compare the effects of oral capecitabine-containing chemotherapy regimens with i.v. 5-fluorouracil (5-FU)-containing chemotherapy regimens on overall survival in patients with gastrointestinal cancers.

Methods: A meta-analysis, based on individual patient data from six randomised non-inferiority trials, was carried out at the request of regulatory authorities to compare the effects of single-agent capecitabine or capecitabine-containing chemotherapy versus matched 5-FU-based regimens in terms of overall survival in patients with stage III colon, metastatic colorectal or advanced gastric cancer.

Results: Data from a total of 6171 patients with stage III colon cancer (n = 1987), metastatic colorectal cancer (n = 3868) or advanced gastric cancer (n = 316) were included. A total of 3097 patients were treated with capecitabine-containing chemotherapy and 3074 patients with 5-FU-containing chemotherapy. The unadjusted hazard ratio for overall survival for capecitabine-containing chemotherapy versus 5-FU-containing chemotherapy was 0.94 (95% confidence interval 0.89–1.00; \(P = 0.0489\)).

Conclusions: Oral capecitabine is at least equivalent to i.v. 5-FU in terms of overall survival in patients with gastrointestinal cancers. Capecitabine and 5-FU can be used interchangeably in these patient populations.

Key words: 5-fluorouracil, capecitabine, colorectal cancer, gastric cancer, meta-analysis, overall survival

Introduction

The efficacy of the oral fluoropyrimidine capecitabine (Xeloda®; F. Hoffmann-La Roche, Basle, Switzerland) in gastrointestinal cancers has been investigated in a series of six phase III non-inferiority trials. In the mid-1990s, capecitabine was compared with 5-fluorouracil/folinic acid (5-FU/FA; Mayo Clinic regimen) in two identical randomised trials in patients with previously untreated metastatic colorectal cancer [1, 2], and later as adjuvant therapy in patients with resected stage III colon cancer [3]. More recently, capecitabine in combination with oxaliplatin (XELOX) was compared with 5-FU/FA plus oxaliplatin (FOLFOX4) as first-line [4] and second-line [5] treatment of patients with metastatic colorectal cancer; the design of the first-line trial was later modified to a \(2 \times 2\) factorial design to further compare the addition of bevacizumab versus placebo to oxaliplatin-based chemotherapy [6]. In patients with advanced gastric cancer, capecitabine–cisplatin was compared with 5-FU-cisplatin as first-line therapy in a randomised phase III non-inferiority trial [7]. In all of these trials, the efficacy of capecitabine-containing chemotherapy was found to be at least equivalent to that of the 5-FU/FA-containing comparator regimen [1–5, 7]. The consistency of these findings suggests that capecitabine may be a suitable alternative for 5-FU/FA in cancers for which standard treatment involves fluoropyrimidine-based chemotherapy.

In all of these studies, a surrogate measure for overall survival was used as the primary efficacy end point. The studies were, therefore, not powered to show non-inferiority for overall survival, the benchmark of efficacy in cancer patients. With this in mind, we conducted a meta-analysis to allow the effects of treatment on overall survival to be estimated with greater statistical power. The present paper describes a post hoc meta-analysis of the six phase III clinical trials described above, which was requested by European regulatory authorities and evaluated the non-inferiority of capecitabine-containing chemotherapy versus 5-FU-containing chemotherapy in terms of overall survival in gastrointestinal cancers.

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patients and methods

selection criteria
Prospective randomised non-inferiority trials from the Roche clinical trials database comparing single-agent capecitabine or capecitabine-containing regimens (i.e. XELOX ± bevacizumab or capecitabine-cisplatin) with 5-FU/FA or 5-FU ± FA-containing regimens (i.e. FOLFOX4 ± bevacizumab or 5-FU–cisplatin) in patients with colorectal or gastric cancer were included. All studies were conducted in an open-label fashion; blinding was not feasible because of the different routes of administration of 5-FU and capecitabine.

individual patient data
Individual patient data were extracted for all studies. The following information was retrieved from the database: patient age, gender, baseline Eastern Cooperative Oncology Group (ECOG) performance status, assigned treatment and duration of survival.

outcome measure
Overall survival was defined as the time from randomisation until death from any cause. Living patients were censored at the time of last available follow-up.

statistical analysis
Analyses were carried out on an intent-to-treat basis, i.e. all randomised patients were included according to their allocated treatment.

Data were pooled according to assigned treatment, such that the capecitabine arm included patients who received single-agent capecitabine, XELOX ± bevacizumab or capecitabine-cisplatin, and the 5-FU arm included patients who received 5-FU/FA, FOLFOX4 ± bevacizumab or 5-FU–cisplatin.

Overall survival was analysed according to Kaplan–Meier estimates. The results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and stratified by trial. Individual study data were presented as forest plots. A multivariate analysis was carried out to test for the effects of prognostic factors (i.e. age, gender and baseline ECOG performance score) on overall survival using Cox’s proportional hazards model and presented as stratified and unstratified analyses.

results

description of studies
Six randomised studies involving a total of 6171 patients with stage III colon cancer (n = 1987), metastatic colorectal cancer (n = 3868) or advanced gastric cancer (n = 316) were included in the meta-analysis. A total of 3097 patients were treated with capecitabine-containing chemotherapy and 3074 patients with 5-FU ± FA-containing chemotherapy.

Details of these studies, including the patient population, treatment regimens and the number of patients, are presented in Table 1.

overall survival
The unadjusted analysis of overall survival for the six trials grouped according to tumour type (i.e. stage III colon cancer, metastatic colorectal cancer or advanced gastric cancer) is presented in Table 2. The respective Kaplan–Meier curves are shown in Figure 1.

In study M66001, which compared single-agent capecitabine versus 5-FU/FA (Mayo Clinic regimen) as adjuvant therapy in patients with resected stage III colon cancer, the HR for overall survival was 0.86 (95% CI 0.74–1.01). For studies SO14695 and SO14796, which compared single-agent capecitabine versus 5-FU/FA (Mayo Clinic regimen) as first-line therapy in patients with metastatic colorectal cancer, the HR for overall survival was 0.95 (95% CI 0.84–1.06). For studies NO16966 and NO16967, which compared XELOX ± bevacizumab versus FOLFOX4 ± bevacizumab as first- or second-line therapy in patients with metastatic colorectal cancer, the HR for overall survival was 0.97 (95% CI 0.89–1.05). And for study ML17032, which compared capecitabine-cisplatin versus 5-FU–cisplatin as first-line therapy in patients with advanced gastric cancer, the HR for overall survival was 0.85 (95% CI 0.65–1.11).

The results of the unadjusted meta-analysis of overall survival for the pooled treatment groups stratified by study are presented in Table 2 and Figure 2. The unadjusted HR for overall survival for capecitabine-containing chemotherapy versus 5-FU-containing chemotherapy was 0.94 (95% CI 0.89–1.00; P = 0.0489).

multivariate analysis
In the planned multivariate analysis, both female gender and a good baseline ECOG performance status (i.e. 0) were significant prognostic factors for an improved overall survival in the unstratified analysis regardless of the treatment assigned (Table 3). ECOG performance status alone was a significant prognostic factor for improved overall survival, regardless of the treatment assigned in the analysis stratified by study (Table 3).

discussion
Capecitabine, either alone or as part of a combination regimen, has been compared with 5-FU-based regimens in a series of phase III non-inferiority trials in patients with gastrointestinal cancers. In each of the studies, recognised surrogate measures of overall survival were selected as the primary study end point, i.e. objective response rate, progression-free survival or disease-free survival [8–13]. However, overall survival remains the most clinically meaningful measure of treatment effect in patients with cancer. The present meta-analysis combined individual data from >6000 patients from each of these trials so that treatment effect, in terms of overall survival, could be evaluated with greater statistical power. The final result shows that capecitabine-containing chemotherapy is at least equivalent to 5-FU-containing chemotherapy in terms of overall survival in the treatment of gastrointestinal cancers. A multivariate analysis supported this result and suggests that the findings are robust.

The patient population included in the present meta-analysis was clearly heterogeneous, i.e. patients with stage III colon cancer, metastatic colorectal cancer and advanced gastric cancer. Therefore, we also analysed overall survival by cancer type and showed that, for each of these patient subsets, capecitabine-containing chemotherapy had similar or slightly better efficacy than 5-FU-containing chemotherapy (HR 0.85–0.97). The consistency of these findings with the overall meta-analysis result suggests that the non-inferiority of
capecitabine- versus 5-FU-containing chemotherapy can be extended to all patient subsets considered within the analysis. Most of the patients included in the meta-analysis had either colon or colorectal cancer (95%). The dataset for patients with advanced gastric cancer was considerably smaller (n = 316). While not included in our analysis, the recent REAL2 study also compared the efficacy of capecitabine versus 5-FU as part of epirubicin/platinum-based triple therapy in patients with advanced oesophagogastric cancer [14]. Pooled data from capecitabine-based triplet regimens (epirubicin, cisplatin, xeloda + epirubicin, oxaliplatin, xeloda; n = 480) showed significant non-inferiority to the pooled 5-FU-based triplets (epirubicin, cisplatin, fluorouracil + epirubicin, oxaliplatin, fluorouracil; n = 484) in terms of median overall survival (10.9 versus 9.6 months; HR 0.86, 95% CI 0.80–0.99; primary end point); the upper limit of the 95% CI for the HR was below the predefined value of 1.23. Data from REAL2 and ML17032 have recently been combined in a separate meta-analysis, which showed that overall survival was superior in patients treated with capecitabine-containing combinations (n = 654) compared with patients treated with 5-FU-containing combinations (n = 664) (HR = 0.87; 95% CI 0.77–0.98, P = 0.02) [15]. The most recent studies involving capecitabine to have been completed are comparisons of capecitabine–oxaliplatin and 5-FU/FA–oxaliplatin regimens in metastatic colorectal cancer. Two of the clinical studies addressing this question, NO16966 and NO16967, were considered in the present analysis. The subset analysis of these two studies suggests that the two regimens have similar efficacy (HR = 0.97). However, many

Table 1. Characteristics of randomised trials (n = 6)

<table>
<thead>
<tr>
<th>Study [reference]</th>
<th>Accrual period</th>
<th>Patient population</th>
<th>Treatment regimens</th>
<th>Patients randomised</th>
</tr>
</thead>
</table>
FA 20 mg/m² then 5-FU 425 mg/m² days 1–5 q4w | 302 |
FA 20 mg/m² then 5-FU 425 mg/m² days 1–5 q4w | 301 |
| M66001 [3]        | 1998–2001     | Resected stage III colon cancer | Capecitabine 1250 mg/m² bid days 1–14 q3w  
FA 20 mg/m² then 5-FU 425 mg/m² days 1–5 q4w | 1004 |
| NO16966 [4, 6]    | 2003–2005     | Metastatic colorectal cancer (first-line) | Capecitabine 1000 mg/m² bid days 1–14 and oxaliplatin  
130 mg/m² d1 ± bevacizumab  
7.5 mg/kg day 1 q3w* | 1017 |
|                   |               |                          | FA 200 mg/m² and oxaliplatin  
85 mg/m²² (day 1 only) then 5-FU 400 mg/m² followed by 22-h infusion 5-FU 600 mg/m²² days 1 and 2 ± bevacizumab  
5 mg/kg day 1 q2w* | 1017 |
130 mg/m²² day 1 q3w  
FA 200 mg/m²² and oxaliplatin  
85 mg/m²² (day 1 only) then 5-FU 400 mg/m²² followed by 22-h infusion 5-FU 600 mg/m²² days 1 and 2 q2w | 313 |
80 mg/m²² day 1 q3w  
5-FU continuous infusion  
800 mg/m²² days 1–5 and cisplatin 80 mg/m²² day 1 q3w | 160 |

*Three hundred and fifty patients received concomitant bevacizumab.  
*Three hundred and forty-nine patients received concomitant bevacizumab.  
5-FU, 5-fluorouracil; FA, folinic acid; q, every; w, weeks.

The most recent studies involving capecitabine to have been completed are comparisons of capecitabine–oxaliplatin and 5-FU/FA–oxaliplatin regimens in metastatic colorectal cancer. Two of the clinical studies addressing this question, NO16966 and NO16967, were considered in the present analysis. The subset analysis of these two studies suggests that the two regimens have similar efficacy (HR = 0.97). However, many
other phase II and III studies comparing capecitabine– and 5-FU/FA–oxaliplatin, which were not included in the present analysis, have been carried out. It is therefore of interest that two other meta-analyses specifically addressing this question are supportive of the present analysis. Cassidy et al. [16] carried out a meta-analysis of seven phase II and III trials (n = 2826) comparing capecitabine–oxaliplatin with 5-FU/FA–oxaliplatin regimens in metastatic colorectal cancer and reported an HR of 1.02 (95% CI 0.95–1.12) for overall survival. Arkenau et al. [17] also reported similar findings in another meta-analysis of six randomised trials with regard to overall survival (n = 3074; HR = 1.04, 95% CI 0.95–1.12).

Strengths of the present analysis are that it was based on individual patient data taken from well-designed, prospective...
In conclusion, oral capecitabine is at least equivalent to i.v. 5-FU in terms of overall survival in patients with colorectal or gastric cancers; clinicians can, therefore, use these agents interchangeably in these patient populations.

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JC, CT and YC are members of the Roche Speakers Bureau. JC, CT, LS, EVC and PH are members of Advisory Boards or consultants for Roche. JPS and FG hold stock and are employees of F. Hoffmann La Roche, the makers of capecitabine. DC has no relevant competing interest to declare.

**References**