Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer

A. F. C. Okines, A. R. Norman, P. McCloud, Y.-K. Kang & D. Cunningham

1The Royal Marsden Hospital NHS Foundation Trust, Sutton, Surrey, UK; 2Roche Products Pty Ltd, Dee Why, Australia and 3Division of Oncology, Department of Internal Medicine, Asan Medical Centre, University of Ulsan College of Medicine, Songpa Gu, Seoul, South Korea

Received 2 January 2009; accepted 3 February 2009

Background: The REAL-2 and ML17032 trials demonstrated that the oral fluoropyrimidine, capecitabine, is noninferior to 5-fluorouracil (5-FU) for overall survival (OS) and progression-free survival (PFS), respectively, in advanced oesophago-gastric cancer.

Methods: Individual patient data were collected on all patients randomised within the trials (n = 1318). Kaplan–Meier survival curves were generated and the log-rank test was used to compare OS and PFS between patients receiving 5-FU combinations and capecitabine combinations. Stepwise multivariate Cox regression analysis was used to calculate corrected hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and PFS. Logistic regression was used for objective response rate. Forest plots with tests of heterogeneity were generated.

Results: OS was superior in the 654 patients treated with capecitabine combinations compared with the 664 patients treated with 5-FU combinations; HR 0.87 (95% CI 0.77–0.98, \(P = 0.02\)). Poor performance status, age <60 and metastatic disease were independent predictors of poor survival. There was no significant difference in PFS between treatment groups on multivariate analysis. Assessable patients treated with capecitabine combinations were significantly more likely to have an objective response to treatment than those treated with 5-FU combinations; odds ratio 1.38 (95% CI 1.10–1.73, \(P = 0.006\)).

Conclusion: OS is superior in patients treated with capecitabine combinations compared with 5-FU combinations in advanced oesophago-gastric cancer.

Key words: capecitabine, fluoropyrimidine, 5-fluorouracil, oesophago-gastric cancer, overall survival

introduction

A recent meta-analysis demonstrated that chemotherapy improves survival for patients with advanced gastric cancer compared with best supportive care alone [hazard ratio (HR) 0.39, 95% confidence interval (CI) 0.28–0.52] and that combination chemotherapy is superior to monotherapy [HR 0.83, 95% CI 0.74–0.93] [1]. The same meta-analysis supported the addition of an anthracycline to the cisplatin and 5-fluorouracil (5-FU) doublet (HR 0.83, 95% CI 0.76–0.91); however, this remains controversial as it has not been confirmed in a phase III randomised trial.

Capecitabine is an oral fluoropyrimidine carbamate designed to deliver 5-FU selectively to tumour cells via metabolism by thymidine phosphorylase, an enzyme found in higher concentrations in tumours than normal tissues [2–4]. Phase I [5–7] and II [8–12] clinical trials have demonstrated that capecitabine is both safe and active in advanced gastric cancer both as monotherapy and within a variety of combination chemotherapy regimens.

Capecitabine was demonstrated to be noninferior to 5-FU in the treatment of advanced oesophago-gastric cancer in two large phase III trials [13, 14]. REAL-2 [13] comprised 1002 patients with untreated advanced oesophago-gastric cancer, randomised in a two-by-two design to receive epirubicin and cisplatin plus capecitabine (ECX) or 5-fluorouracil (ECF) or epirubicin and oxaliplatin plus capecitabine (EOX) or 5-fluorouracil (EOF). The trial was designed to demonstrate noninferiority of the capecitabine-containing triplets compared...
with the 5-FU-containing triplets and the oxaliplatin-containing triplets compared with the cisplatin-containing triplets for overall survival (OS) and met both primary end points: The unadjusted HR for death in the capcitabine group relative to the 5-FU group was 0.86, with a 95% CI of 0.80–0.99; well below the predefined margin for noninferiority of 1.23. Similarly, the unadjusted HR for death in the oxaliplatin group relative to the cisplatin group was 0.92 (95% CI 0.80–1.10). In ML17032, 316 patients with untreated advanced gastric cancer were randomised to receive cisplatin plus 5-fluorouracil (CF) or cisplatin plus capecitabine (CX). Again, the primary end point was noninferiority, but for progression-free survival (PFS) rather than OS. The investigators reported a PFS of 5.6 months in the CX arm and 5 months in the CF arm, with a HR of 0.81 (95% CI 0.63–1.04), which was again below the predefined margin for noninferiority of <1.40 for the first test and <1.25 for the second test. Median OS was comparable for the two arms at 10.5 and 9.3 months, respectively (P = 0.27). Superiority of capcitabine over 5-FU was demonstrated for response rate (RR: 41% versus 29%, P = 0.03). Both trials also demonstrated that the toxicity profile of capcitabine is similar to that of 5-FU within doublet and triplet chemotherapy regimens, respectively [13, 14].

This analysis was conducted to determine whether capcitabine is superior to 5-FU for survival in the treatment of advanced oesophago-gastric cancer.

methods

hypothesis
Capcitabine is superior to 5-FU within doublet and triplet combination chemotherapy for patients with advanced oesophago-gastric cancer.

Primary and secondary end points are OS and PFS and RR, respectively.

patients
Individual patient data were collected on the 1002 patients randomised within REAL-2 and 316 patients randomised within ML17032 on patient study number, gender, age and performance status (PS) at randomisation [Eastern Cooperative Oncology Group (ECOG) PS for REAL-2, Karnofsky PS for ML17032], dates of disease progression, death and last follow-up, histopathology (adenocarcinoma/squamous/undifferentiated), site of primary tumour (oesophagus/oesophago-gastric junction/stomach), extent of disease (locally advanced/metastatic) and chemotherapy arm randomised (CF/CX for ML17032 or EOX/EOF/ECX/ECF for REAL-2).

statistical methods
All calculations used a two-sided P value and a threshold of 0.05 to indicate statistical significance. Statistical analyses were carried out using SPSS.

analysis population
OS and PFS were analysed strictly on an intention-to-treat (ITT) basis; the ITT population being defined as all patients randomised in the REAL-2 and ML17032 studies (total n = 1318). RR was analysed in patients with measurable disease only (n = 1264).

primary end point
OS was calculated from the date of randomisation to the date of death from any cause. Patients lost to follow-up or those with no date of death recorded were censored on the date of last follow-up. Kaplan–Meier survival curves [15] were generated and median OS calculated for the ITT population with 95% CI. Comparison between patients treated with 5-FU combinations and those treated with capcitabine combinations were made using the log-rank test [16] and the HR and its 95% CI were calculated for the comparison. Stepwise multivariate Cox regression analysis was used to calculate the corrected HR and 95% CI, incorporating the factors: age (<60 versus ≥60), PS (ECOG PS 0–1 or Karnofsky PS ≥20 versus ECOG PS ≥2 or Karnofsky < 80% which have been validated as equivalent [17]), histology (adenocarcinoma versus squamous cell versus undifferentiated), extent of disease (locally advanced versus metastatic) and gender. Forest plots with tests of heterogeneity were created to show the treatment effects in each group.

secondary end points
PFS was calculated from the date of randomisation to the date of disease progression or death from any cause. Patients without a date of progression recorded were censored on the date of last follow-up. As per the analysis of OS, Kaplan–Meier survival curves [15] were generated and median PFS calculated for the ITT population with 95% CI. Comparison between patients treated with 5-FU combinations and those treated with capcitabine combinations was again made using the log-rank test [16] and HR and 95% CIs calculated. Stepwise multivariate Cox regression analysis was used to calculate the corrected RR and 95% CI, incorporating factors as previously described.

RR, defined as best response evaluated by RECIST criteria [18], was calculated for all patients with measurable disease at randomisation (n = 1264). As additional confirmatory scans were not required the REAL-2 trial, the unconfirmed RR and its 95% CI was calculated. Comparison was made using the chi-squared test and multivariate logistic regression analysis used to control for demographic factors on patients with complete data (n = 1231).

results
The baseline characteristics of the patients in the REAL-2 and ML17032 trials are summarised in Table 1.

overall survival
A total of 1318 patients were randomised within REAL-2 (n = 1002) and ML17032 (n = 316) and were therefore eligible for analysis. OS was compared for the 664 patients treated with 5-FU combinations with the 654 treated with capcitabine combinations. The median OS was 285 days (95% CI 265–305 days) for patients treated with 5-FU and 322 days (95% CI 300–343 days) for patients treated with capcitabine, giving an unadjusted HR of 0.87 (95% CI 0.77–0.98) in favour of capcitabine (P = 0.027) (Figure 1).

There was no evidence of any significant heterogeneity of treatment effect according to the baseline characteristics of the patients (Figure 2).

Superiority of capcitabine over 5-FU was maintained on multivariate analysis; adjusted HR 0.87 (95% CI 0.77–0.98, P = 0.02). PS of two, age <60 and the presence of metastatic disease were statistically significant predictors of poor prognosis. Gender and histopathological subtype were shown to influence the analysis due to lack of effect (Table 2).

progression-free survival
There was no significant difference in PFS in the two treatment groups (unadjusted HR 0.91, 95% CI 0.81–1.02, P = 0.093). The median PFS was 182 days in the 5-FU group (95% CI 167–197) and 199 days in the capcitabine group (95% CI 180–217 days).
On multivariate analysis, PS of two, age < 60, metastatic disease and squamous histology were independent predictors of poor PFS. Treatment with 5-FU or capecitabine was thrown out of the model for lack of statistically significant effect on PFS ($P = 0.052$) (Table 2).

Logistic regression analysis demonstrated a statistically significant higher objective RR in patients treated with capcitabine compared with those treated with 5-FU [odds ratio 1.38 (95% CI 1.10–1.73), $P = 0.006$]. This was confirmed on multivariate analysis, which also showed that in the 1231 patients with complete data; male patients, those of good PS and age $\geq 60$ were also significantly more likely to respond to chemotherapy. Extent of disease and histopathological subtype were thrown out of the analysis for lack of effect (Table 3).

**discussion**

The combined data from REAL-2 and ML17032, which individually demonstrated that capcitabine is noninferior to 5-FU, have shown a modest, but statistically significant benefit in OS in favour of the oral fluoropyrimidine, which was maintained on multivariate analysis. It is recognised that cross comparisons of OS between different clinical trials is of limited benefit because of the heterogeneity of patient populations and confounding variables including patient age, PS and stage of disease. Nevertheless, within these two trials, the best survival was seen with the EOX triplet regimen (median 11.2 months).

The median survival of patients treated within the control arms (9.9 months with ECF in REAL-2, 9.5 months with CF in ML17032) were comparable to the 8.9 months median survival seen in the ECF arm of the REAL trial [19] and 7.2–8.6 months with CF in three phase III trials [20–22]; therefore, the difference seen cannot be explained by poor outcomes in

**Table 1.** Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>REAL-2</th>
<th></th>
<th>ML17032</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECF ($n = 249$)</td>
<td>ECX ($n = 241$)</td>
<td>EOF ($n = 235$)</td>
<td>EOX ($n = 239$)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>65</td>
<td>64</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>81.1</td>
<td>80.5</td>
<td>81.3</td>
<td>82.8</td>
</tr>
<tr>
<td>Female</td>
<td>18.9</td>
<td>19.5</td>
<td>18.7</td>
<td>17.2</td>
</tr>
<tr>
<td>PS (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 0–1 (or KPS $\geq 80%$)</td>
<td>88.4</td>
<td>87.6</td>
<td>91.5</td>
<td>90.0</td>
</tr>
<tr>
<td>ECOG 2 (or KPS $&lt; 80%$)</td>
<td>11.6</td>
<td>12.4</td>
<td>8.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Site of primary tumour (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td>34.9</td>
<td>29.5</td>
<td>39.6</td>
<td>34.3</td>
</tr>
<tr>
<td>OGI</td>
<td>28.9</td>
<td>28.2</td>
<td>23.4</td>
<td>22.2</td>
</tr>
<tr>
<td>Stomach</td>
<td>36.1</td>
<td>42.3</td>
<td>37.0</td>
<td>43.5</td>
</tr>
<tr>
<td>Number of metastatic sites (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>63.5</td>
<td>59.3</td>
<td>60.9</td>
<td>64.4</td>
</tr>
<tr>
<td>&gt;1</td>
<td>36.5</td>
<td>40.7</td>
<td>39.1</td>
<td>35.6</td>
</tr>
<tr>
<td>Histopathology (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>90.0</td>
<td>89.6</td>
<td>86.0</td>
<td>87.4</td>
</tr>
<tr>
<td>SCC</td>
<td>7.6</td>
<td>9.5</td>
<td>12.8</td>
<td>12.1</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>2.4</td>
<td>0.8</td>
<td>1.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

ECF, epirubicin and cisplatin plus 5-fluorouracil; ECX, epirubicin and cisplatin plus capcitabine; EOF, epirubicin and oxaliplatin plus 5-fluorouracil; EOX, epirubicin and oxaliplatin plus capcitabine; CX, cisplatin plus capcitabine; CF, cisplatin plus 5-fluorouracil; PS, performance status; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; OGI, oesophago-gastric junction; SCC, squamous cell carcinoma.

*Figure 1.* Kaplan–Meier estimate for overall survival in patients treated with capcitabine-based chemotherapy and 5-fluorouracil (5-FU)-based chemotherapy.

On multivariate analysis, PS of two, age <60, metastatic disease and squamous histology were independent predictors of poor PFS. Treatment with 5-FU or capcitabine was thrown out of the model for lack of statistically significant effect on PFS ($P = 0.052$) (Table 2).

**response rate**

Overall RR was 45.6% in the 631 patients treated with capcitabine combinations compared with 38.4% in the 633 patients treated with infused 5-FU combinations.
the control arms. The median survival of patients treated with the three-weekly CF regimen used in ML17032 is not only comparable to that achieved with the ECF regimen within REAL-2 but also markedly longer than seen previously with a CF doublet regimen, especially when compared with the 4-weekly cisplatin and infused 5-FU regimens used in the European Organisation for Research and Treatment of Cancer [20] and JCOG9205 studies [21]. This encouraging median survival has not been achieved in a Western trial with this doublet; possibly a reflection of both the regimen used and the patient population treated.

Patients treated with capecitabine combinations were also significantly more likely to have an objective response than those treated with 5-FU combinations in this analysis ($P = 0.006$). Of note, ~5% of patients within REAL-2 did not have measurable disease and were therefore excluded from this analysis. RR correlated well with survival which was significantly better in the capecitabine-treated patients than the 5-FU-treated group. The improvement in response has potential implications for use in the neoadjuvant setting. In a phase II trial of docetaxel, cisplatin and capecitabine, a RR of 67.5% was reported and of interest, 10 of the 40 patients with...
advanced gastric cancer treated with the regimen were rendered operable by four to nine cycles of chemotherapy [23]. While this is a small series of selected patients, new, capecitabine-based regimens may define a new population of potentially resectable disease in whom surgical resection can be attempted if down-staging is achieved.

It was an unexpected finding that the difference in PFS was not statistically significant since PFS is often used as a surrogate marker of survival in clinical trials. It is likely that as the difference in survival between the two treatments is modest, any difference in the PFS curves is lost due to the shorter time period within which the majority of progression events occur compared with survival events. Additionally, PFS events are only measured at a limited number of time points. In the larger REAL-2 trial, computed tomography scan (CT) evaluations were undertaken at 12 and 24 weeks (the mid- and end points of treatment) whereas in the ML17032 trial patients were treated until disease progression with CT evaluations undertaken every 6 weeks. It is therefore likely that many progression events, especially within the REAL-2 trial, could have been captured many weeks later than they actually occurred, making PFS a less useful marker of the regimens’ efficacy.

We did not evaluate the relative toxic effects of capecitabine and 5-FU in this meta-analysis as this was addressed comprehensively in the presentation and publication of ML17032 [14] and REAL-2 [13], respectively. It is well established that the safety profiles of the two drugs are similar.

Additional advantages of capecitabine over continuous infused 5-FU within these doublet and triplet regimens include the convenience of oral chemotherapy, which is generally more acceptable to patients [24–27], avoiding the potential morbidity associated with central venous access and the opportunity to make simple dose adjustments to the oral agent during the treatment cycle, to manage toxicity.

The substitution of capecitabine for 5-FU may also be applied to other regimens used in the treatment of advanced oesophago-gastric cancer. Docetaxel is widely used in the first- and second-line treatment within doublet and triplet regimens such as TCF (docetaxel, cisplatin plus 5-FU) [22], although the latter regimen has received some criticism for its significant haematological toxicity. Data from the phase II ATTAX trial [28] of weekly TCF or weekly TX (docetaxel plus capecitabine) which demonstrated that docetaxel can be delivered safely without unacceptable toxicity were particularly encouraging. That capecitabine can be substituted for 5-FU has also been demonstrated in colorectal cancer, in both the advanced disease [29] and adjuvant [30] settings.

OS is likely to be influenced by prognostic factors at baseline, including the patients’ age, PS and extent of disease and the use of second-line chemotherapy. Only 14% of patients in REAL-2 and 24% of patients in ML17032 were treated with second-line chemotherapy; therefore, OS can be considered a good representation of the efficacy of the first-line regimen in each trial. In this analysis, PS of two, age <60 and metastatic disease were independent predictors of poor PFS and OS. Squamous histology was a statistically significant predictor of poor PFS (HR 1.24, 95% CI 1.0–1.54, \( P = 0.047 \)) but the effect was modest. The forest plots demonstrated no significant heterogeneity of treatment effect on OS according to gender, age, extent of disease, PS or histopathological subtype; therefore, capecitabine can replace infused 5-FU in the treatment of advanced oesophageal or gastric cancer.

**Conclusion**

OS was superior in patients with advanced oesophago-gastric cancer treated with capecitabine doublets or triplets compared with those treated with 5-FU doublets or triplets within the combined populations from the ML17032 and REAL-2 trials.

**Funding**

NHS funding to the NIHR Biomedical Research Centre.

**Acknowledgements**

Conflicts of interest: AFCO received an honorarium for a presentation from Roche. ARN has no conflicts of interest to declare. PM is an employee of Roche Products. Y-KK received honoraria from Roche and worked as a consultant (advisory board) for Roche. In the past, DC has received honoraria for attending advisory boards and giving presentations. He has also received research funding from Roche.

**References**


