



Capecitabine for the treatment of advanced gastric cancer

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Declared competing interests of authors: M Sculpher has a minority shareholding in a consulting company that has undertaken work for Roche during the last 3 years, but not in the clinical area of gastric cancer. He did not participate personally in this consultancy. M Seymour is a co-investigator in a trial ('321GO'), which includes capecitabine as treatment for patients with advanced gastroesophageal cancer. The trial is peer reviewed and funded by Cancer Research UK, but also receives some supplementary financial support from Roche (£50k over 2 years). M Seymour also attended the ASCO Oncology Conference last year as a guest of Roche. D Suh is also a co-investigator on the '321GO' study. Roche have also offered to sponsor his trip to ASCO this year. Stephen Kelly accepted financial support from Roche in 2008 and 2009 to attend the British Oncology Pharmacists Association Annual Symposium on behalf of the Leeds Teaching Hospitals NHS Trust Pharmacy Department.

Abstract

This paper presents a summary of the evidence review group (ERG) report into capecitabine for advanced gastric cancer (aGC). Capecitabine is an oral prodrug of 5-fluorouracil (5-FU). The decision problem addressed was the use of capecitabine (X) compared to 5-FU (F), in combination regimens with platinum agents [cisplatin (C) or oxaliplatin (O)] with or without epirubicin (E), in patients with inoperable aGC. Approximately 7000 new cases of gastric cancer are diagnosed in England and Wales every year. Of these, 80% are candidates for palliative chemotherapy and around 2900 receive such treatment. The standard UK practice for patients with aGC who are considered fit enough has consisted of a triplet regimen comprising intravenous 5-FU in combination with a platinum agent (capecitabine or oxaliplatin) and epirubicin. The manufacturer's submission (MS) focused on direct evidence from two phase III non-inferiority randomised controlled trials (RCTs), REAL-2 (Randomized ECF for Advanced and Locally advanced oesophagogastric cancer-2; $n = 1002$) and ML17032 ($n = 316$). REAL-2 randomised patients to four regimens (ECF, ECX, EOF and EOX) to compare 5-FU with capecitabine and cisplatin with oxaliplatin, whereas ML17032 compared CX with CF. Efficacy outcomes from these trials were

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

pooled in an individual patient data (IPD) meta-analysis. Both RCTs demonstrated statistically significant non-inferiority of capecitabine on the outcome of overall survival (OS) assessed in the per-protocol population; equivalent results were also demonstrated for progression-free survival (PFS). The IPD meta-analysis found a statistically significant benefit in OS for capecitabine compared with 5-FU [unadjusted hazard ratio (HR): 0.87; 95% confidence interval (CI) 0.77 to 0.98, $p = 0.027$]. There was no evidence of a poorer safety profile for capecitabine overall, nor of any difference in quality of life (QoL) between the two fluoropyrimidines. The MS included a de novo economic evaluation based on a cost-minimisation analysis (CMA), where the costs of capecitabine-based regimens were compared with their equivalent 5-FU-based regimens in aGC. A time horizon of 5.5 cycles (each lasting for 21 days) was used in the base-case analysis, representing the duration of treatment. The results of the manufacturer's base-case analysis showed that capecitabine regimens are associated with mean net cost savings of £1620 (ECX vs ECF), £1572 (EOX vs EOF) and £4210 (CX vs CF). The manufacturer failed to comment explicitly on the uncertainty around the estimates of efficacy and on the fact that the IPD meta-analysis suggests that capecitabine may actually be more effective on average. Further analyses exploring additional costs incurred by the UK NHS from extending survival duration showed that these are unlikely to have a material effect on conclusions. A full probabilistic analysis was not performed; however, the evidence explored by the MS and ERG is consistent in suggesting that capecitabine has a lower mean cost than 5-FU-based regimens. The submission was considered to contain convincing evidence of the non-inferiority of capecitabine to 5-FU on survival; this evidence was considered to be applicable to UK practice. Although some uncertainty remains, the ERG deemed CMA to be an appropriate framework with which to analyse this decision problem. Overall cost estimates for the CMA were generated appropriately and were robust to uncertainties regarding assumptions and sources. At the time of writing, the guidance document issued by NICE on 28 July 2010 states that capecitabine in combination with a platinum-based regimen is recommended for the first-line treatment of inoperable advanced gastric cancer.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process¹ is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor (Roche). Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is prepared by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled '*Capecitabine for the treatment of advanced gastric cancer*'.²

Description of the underlying health problem

Gastric cancer is the 10th most commonly diagnosed cancer in the UK, with approximately 7000 new cases diagnosed in England and Wales every year. Of these, some 80% of patients are unsuitable for curative treatment and are candidates for palliative chemotherapy. It is estimated that just over one-half (around 2900) of these patients with advanced gastric cancer (aGC) receive such treatment.

The standard UK practice for patients with aGC, who are considered fit enough, has consisted of a triplet regimen comprising a fluoropyrimidine, intravenous 5-fluorouracil (5-FU) in combination with a platinum agent (cisplatin or oxaliplatin) and an anthracycline (epirubicin).

Scope of the ERG report

The decision problem addressed was the use of capecitabine (Xeloda) in combination with platinum-based chemotherapy regimens (cisplatin or oxaliplatin) with or without epirubicin, compared with 5-FU in combination with such

regimens, in patients with inoperable aGC. Capecitabine is an oral prodrug of 5-FU, and is licensed for the first-line treatment of aGC in combination with a platinum-based regimen. Oral chemotherapies are usually considered to be preferred by patients and may have fewer associated costs and/or adverse events.

The outcome measures considered were overall survival (OS), progression-free survival (PFS), response rates, adverse effects of treatment and health-related quality of life (QoL). These were assessed in direct comparisons by two open-label non-inferiority randomised controlled trials (RCTs), assessing doublet or triplet regimens.^{3,4}

Economic outcomes included cost per life-year gained (LYG) and cost per quality-adjusted life-year (QALY) gained. The manufacturer proposed evaluating the cost-effectiveness of capecitabine-based regimens compared with 5-FU-based regimens by using cost-minimisation analyses (CMAs).

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology, based upon the manufacturer's/sponsor's submission (MS) to NICE as part of the STA process. The ERG checked the literature searches and carried out a search for ongoing trials. The review methodology including inclusion criteria was appraised. The validity assessments of the included RCTs were critiqued and the ERG carried out its own assessment using the CRD guidelines for the critical appraisal of RCTs.

In evaluating the cost effectiveness of capecitabine, the manufacturer used a cost-minimisation approach. The ERG has thus first commented on the appropriateness of using such methodology, within this specific decision problem, taking into consideration NICE's reference case methods.⁵ Next, the ERG assessed the manufacturer's de novo economic evaluation using Drummond *et al.*'s checklist.⁶ In response to the ERG's points of clarification regarding the initial submission, the manufacturer provided additional evidence on the costs of adverse events, drug acquisition inputs and costs of additional survival. The ERG considered this evidence throughout. Based on the identified limitations in the MS, the ERG revisited the base case according to drug use, unit costs of treatments and pharmacy drug preparation costs. The ERG

also undertook additional sensitivity analyses based on the revised base case, and conducted a threshold analysis, evaluating the maximum costs that the NHS would be willing to pay for the extension of survival time implied by prespecified cost-effectiveness thresholds.

Results

Summary of submitted clinical evidence

The MS focused on direct evidence from two phase III non-inferiority RCTs.^{3,4}

Efficacy outcomes from these trials were pooled in an individual patient data (IPD) meta-analysis.⁷ REAL-2 (Randomized ECF for Advanced and Locally advanced oesophagogastric cancer-2) was a 2×2 factorial trial that compared 5-FU with capecitabine and cisplatin with oxaliplatin.³ The following regimens were used: epirubicin + cisplatin + 5-FU (ECF); epirubicin + cisplatin + capecitabine (ECX); epirubicin + oxaliplatin + 5-FU (EOF); and epirubicin + oxaliplatin + capecitabine (EOX). A second trial, ML17032, compared cisplatin + capecitabine (CX) with cisplatin + 5-FU (CF).⁴

REAL-2 found statistically significant non-inferiority of capecitabine on the primary outcome of OS assessed in the per-protocol population adjusted [hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.77 to 1.02]. ML17032 found statistically significant non-inferiority of capecitabine on the primary outcome of PFS in the per-protocol population (adjusted HR 0.85, 95% CI 0.65 to 1.11). Statistically significant non-inferiority on OS (unadjusted HR 0.85, 95% CI 0.64 to 1.13) was also demonstrated.

The IPD meta-analysis of the intention-to-treat (ITT) populations of the REAL-2 and ML17032 trials found a statistically significant benefit in OS for capecitabine compared with 5-FU (unadjusted HR 0.87, 95% CI 0.77 to 0.98, $p = 0.027$).⁷

There was minimal QoL data reported in the MS. The REAL-2 trial was reported as assessing QoL using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-30), version 3,⁸ administered at baseline, and after 3, 6, 9 and 12 months. The manufacturer subsequently provided the levels of compliance, data on the baseline scores for all

subscales, and changes from baseline at 12 weeks and 24 weeks for the REAL-2 trial. These showed few statistically significant differences between the individual trial arms.

Safety analyses showed some significant differences in adverse events profiles between capecitabine and 5-FU regimens. However, in the REAL-2 trial, all statistical analyses were pairwise comparisons with the ECF arm, which the trial was not powered to assess. Of particular note was grade 3 or 4 neutropenia, which occurred significantly more often in the ECX arm ($p < 0.05$) and significantly less often in the EOX and EOF arms ($p < 0.01$) compared with the ECF arm; grade 3 or 4 diarrhoea, which occurred significantly more often in the EOX and EOF arms compared with the ECF arm ($p < 0.05$); and grade 3 or 4 hand-foot syndrome, which occurred significantly more often in the ECX arm compared with the ECF arm ($p < 0.05$). In the ML17032 trial, stomatitis occurred more often, and with greater severity, in the CF arm, while hand-foot syndrome was more common in the CX arm.

Summary of submitted cost-effectiveness evidence

The manufacturer's literature search identified one economic evaluation relevant to this decision problem. This was Roche's 2007 submission to the Scottish Medicines Consortium for capecitabine in this indication. The methods and results reported are consistent with the current submission.

The MS included a de novo economic evaluation based on a CMA, where the costs of capecitabine-based regimens were compared with their equivalent 5-FU-based regimens (ECX vs ECF, EOX vs EOF, CX vs CF) in the treatment of advanced gastric cancer. A time horizon of 5.5 cycles (each lasting for 21 days) was used in the base-case analysis, representing the duration of treatment of the alternative regimens.

The cost-minimisation approach was based on evidence from two clinical trials – REAL-2 and ML17032 – reporting that capecitabine is at least as effective as intravenous 5-FU (see above). The calculations considered costs relating to drug acquisition and to drug administration. The drug administration costs comprised the costs of

TABLE 1 Drug administration activities costed for each cycle of a treatment regimen and the days in each cycle (of 21 days) during which the activity takes place

Activity/component	Activity cost (£)	ECF and EOF	ECX and EOX	CF	CX
Line insertion	445.77	Day 1 ^a		Day 1 ^a	
Drug delivery, 1st attendance; outpatient/day case	281.45	Day 1	Day 1	Day 1 ^b	Day 1
Drug delivery, subsequent attendances; nurse cost to flush central line a change pump	36.83	Days 7, 14			
Drug delivery, subsequent attendances; outpatient/day case	198.72			Days 2–4 ^b	
Drug delivery; inpatient stay 5 days	1435.64			Days 1–5 ^c	
Pump cost	38.50	Days 1, 7, 14			
Transport cost (20% of patients)	28.43	Days 1, 7, 14	Day 1	Days 1–5	
Pharmacy preparation	'Complex' (intravenous): 41.87 'Simple' (oral): 25.34	Days 7, 14 'Complex'	Day 1 'Simple'	Days 1–5 'Complex'	Day 1 'Simple'

CF, cisplatin + 5-FU; CX, cisplatin + capecitabine; ECF, epirubicin + cisplatin + 5-FU; ECX, epirubicin + cisplatin + capecitabine; EOF, epirubicin + oxaliplatin + 5-FU; EOX, epirubicin + oxaliplatin + capecitabine; 5-FU, 5-fluorouracil.
a Line insertion was only considered at the start of the first cycle.
b Base-case activity.
c Activity in scenario analysis, which replaces the outpatient/day case drug-delivery activities.
Shaded cells indicate that the activity was not costed for the regimen.

hospital visits (central line insertion, delivery of chemotherapy, and subsequent care by a nurse to flush central line and change the pump), pharmacy drug preparation costs, ambulatory pump costs and NHS transport costs (*Table 1*). The manufacturer assumed that there were no significant economically important differences in the incidence or severity of adverse events between capecitabine and 5-FU-based regimens, and therefore the costs of treatment-related adverse events were not included in the analysis. After a request for clarifications, the manufacturer presented the expected costs associated with the relevant adverse events.

The results of the manufacturer's base-case analysis showed that capecitabine regimens are cost saving compared with their equivalent 5-FU-based regimens. The total net cost savings for capecitabine-based regimens were £1620 (ECX vs ECF), £1572 (EOX vs EOF), and £4210 (CX vs CF). Capecitabine remained cost saving in the manufacturer's one-way sensitivity analysis, scenario analysis and worst-case analysis. The manufacturer did not conduct probabilistic sensitivity analysis or subgroup analysis. The submission also included a threshold analysis that explored the additional effectiveness (in terms of QALYs) needed for 5-FU to be considered cost-effective.

Commentary on the robustness of submitted evidence

The MS appears to include all relevant evidence from completed RCTs with respect to the question of efficacy; the ERG's search revealed no additional completed RCTs, although one additional ongoing trial was located.

The ERG identified a number of issues and errors in the review process, which had the potential to exclude relevant studies. However, it did not appear that this had impacted on the results of the review.

Two RCTs that directly addressed the comparison between capecitabine and 5-FU in combination with platinum in the licensed population were included.

The REAL-2 trial was large ($n = 1002$), adequately powered, and closely reflective of UK standard practice. The patient population was also representative of those UK patients who were considered fit enough for standard chemotherapy,

although these patients are significantly younger than the UK aGC patient population as a whole. The trial included a majority of patients who are outside the licensed indication, having advanced inoperable cancer of the oesophagus or gastroesophageal junction. The ERG's clinical experts confirmed that treatment for each of these cancers would follow the same course as that for advanced inoperable gastric cancer. There was also no evidence of a statistically significant difference in prognosis based on primary tumour location.⁹

The ML17032 ($n = 316$) trial assessed doublet therapy, which the ERG's clinical advisors indicated would be used in patients who were considered unable to tolerate triplet therapy. However, such doublets would be given at a lower dose than was used in the trial. The trial population was also unrepresentative of UK patients, being younger and having a different ethnic composition. When the non-inferiority analyses of efficacy outcomes were performed using a margin of 1.25 relative to the efficacy of 5-FU, rather than 1.40 as the protocol had specified, the trial had only 50% power to detect statistically significant non-inferiority.

Both trials were necessarily open-label, and REAL-2 was unblinded for all outcomes, whereas for ML1703 the MS reported blinded outcome assessment only for the primary outcome of PFS. The ERG requested these independently assessed data for the outcomes of tumour response and adverse events. The manufacturer subsequently supplied these data for response rates and, although differences in the data sets were present, there was no indication of systematic bias.

The primary weakness of the initial MS was the limited QoL data. This is of particular importance where the decision problem centres on an issue of clinical non-inferiority and patient preference.

With respect to economic evaluation, the ERG deems CMA to be an appropriate framework with which to analyse the decision problem. However, it should be noted that the appropriateness of using such an approach is dependent not only on clinical evidence from the REAL-2 and ML17032 trials, but also on evidence relating to QoL and adverse events. The weaknesses identified above regarding the evidence presented by the manufacturer are therefore relevant. The manufacturer has also failed fully to consider uncertainty when justifying the use of CMA.

TABLE 2 Estimated overall NHS incremental costs reported in the manufacturer's (MS) base-case and worst-case scenario analysis, and results from the ERG's additional analysis

	Cost (£)		
	ECX vs ECF	EOX vs EOF	CX vs CF
Base case			
MS	-1620	-1572	-4210
ERG	-1585	-1538	-4060
Worst-case scenario			
MS	-74	-41	-1175
ERG	-213	-180	-965

CF, cisplatin + 5-FU; CX, cisplatin + capecitabine; ECF, epirubicin + cisplatin + 5-FU; ECX, epirubicin + cisplatin + capecitabine; EOF, epirubicin + oxaliplatin + 5-FU; EOX, epirubicin + oxaliplatin + capecitabine; ERG, evidence review group; MS, manufacturer's submission.

Overall, cost estimates for the CMA were generated appropriately. The ERG identified a number of shortcomings and potential uncertainties related to resource utilisation, unit costs, utilities and sensitivity analysis in the MS. However, these were considered minor, and additional analysis provided by the manufacturer, and further evaluations by the ERG, showed no impact on the overall conclusions. Results from the MS and ERG's additional analysis are compared in *Table 2*.

A full probabilistic analysis was not performed, so the probabilities that capecitabine is less and more costly than its comparators have not been formally quantified. However, the mean estimates, sensitivity analyses and worst-case scenario are consistent in suggesting that capecitabine has a lower mean cost than 5-FU-based regimens. Further analyses exploring the additional costs incurred by the NHS resulting from extending survival duration show that these are unlikely to have a material effect on decision-making regarding capecitabine.

Conclusions

The submission was considered to contain convincing evidence of the non-inferiority of capecitabine to 5-FU on the outcomes of OS and PFS; this evidence was considered to be applicable to UK practice. There was evidence of some differences in adverse event profiles, but there was no evidence of a poorer safety

profile for capecitabine overall. There was also no evidence of any difference in QoL between the two fluoropyrimidines.

Although some uncertainty remains over the issues identified above, the ERG deems CMA to be an appropriate framework with which to analyse the current decision problem. Overall, cost estimates for the CMA were generated appropriately and were robust to uncertainties regarding assumptions and sources.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance document issued by NICE on 28 July 2010 states that:

Capecitabine in combination with a platinum-based regimen is recommended for the first-line treatment of inoperable advanced gastric cancer.

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