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Capecitabine
In Advanced Gastric or Oesophagogastric Cancer

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Contents

Abstract

- The oral fluoropyrimidine capecitabine is metabolised preferentially in tumour tissue to the cytotoxic moiety fluorouracil.
- In a well designed phase III trial in patients with advanced gastric cancer, capecitabine plus cisplatin was noninferior to fluorouracil plus cisplatin in terms of progression-free survival (hazard ratio [HR] 0.81 [95% CI 0.63, 1.04]).
- In another similarly designed phase III trial in patients with oesophagogastric cancer (REAL 2), pooled capecitabine-based regimens were noninferior to pooled fluorouracil-based regimens in terms of overall survival (HR 0.86 [95% CI 0.80, 0.99]).
- These data are supported by randomised and noncomparative phase II trials in treatment-naive or pretreated patients with advanced gastric cancer or oesophagogastric cancer receiving capecitabine either as monotherapy or in combination with other antitumour agents.
- Given the nature of chemotherapy, capecitabine-based regimens were generally well tolerated, with the nature of treatment-related adverse events occurring with capecitabine-based regimens being similar to those of fluorouracil-based regimens.

Features and properties of capecitabine (CAP) [Xeloda®]	
Featured indication	
Advanced gastric or oesophagogastric cancer	
Mechanism of action	
Antineoplastic agent	A fluoropyrimidine that is metabolised, via a 3-step enzymatic process, to the cytotoxic moiety fluorouracil (FLU)
Dosage and administration (phase III clinical trials)	
Dose	1000 mg/m^2 twice daily on days 1–14, or 625 mg/m^2 twice daily taken continuously, in combination with other cytotoxic agent(s) over a 3-week cycle
Route of administration	Oral
Pharmacokinetic profile (1250 and 2000 mg/m^2 single oral doses in patients with cancer)	
Geometric mean peak plasma concentration (C_{max})	CAP: 3.5 and 4.0 μg/mL FLU: 0.29 and 0.23 μg/mL
Median time to C_{max}	CAP and FLU: both dosages 2h
Geometric mean area under the plasma concentration-time curve from time zero to infinity	CAP: 5.5 and 5.6 μg • h/mL FLU: 0.62 and 0.46 μg • h/mL
Mean elimination half-life	CAP: 0.55 and 0.58h
Most frequent treatment-related adverse events occurring during CAP-based treatment (≥grade 3 or 4 in severity; incidence ≥10%)	
Neutropenia, lethargy, leukopenia, thromboembolism, anaemia, hand-foot syndrome, nausea/vomiting, diarrhoea and infection	

Gastric and oesophagogastric cancers are significant health problems, accounting for a substantial proportion of the worldwide cancer burden.[1] According to a 2005 analysis of the worldwide incidence of and mortality from cancer, ≈934 000 new cases of gastric cancer and ≈462 000 new cases of oesophageal cancer were reported in 2002, ranking them as the fourth and eighth most common cancers in terms of incidence; in terms of mortality, they were ranked second and sixth.[2]

The only potentially curative treatment for gastric cancer is surgical resection.[3] However, it is more common to detect gastric cancer when it is locally advanced or metastatic[3] and <30% of these patients are cured by gastrectomy.[4] Moreover, ≈60% of patients who undergo curative resection after early-stage detection of the disease eventually relapse, either locally or with distant metastases.[5] Chemotherapy is the main treatment option for patients with advanced gastric cancer.[3] Studies have shown a survival advantage in patients receiving chemotherapy over those receiving supportive care in terms of median survival time, which improved from 3–5 to 8–12 months.[3]

Although there are no international standard regimens for the treatment of advanced gastric or oesophagogastric cancer, fluorouracil-based combination chemotherapy regimens are most widely used.[3] Fluorouracil- and cisplatin-based combinations appear to be the most active and may be considered as reference standards,[3] with a regimen of epirubicin plus fluorouracil and cisplatin being widely used in the UK, much of Europe and Australia.[6,7] Fluorouracil plus cisplatin is the other current standard of care for gastric cancer.[8]

Capecitabine (Xeloda®)[1] is an oral fluoropyrimidine that is metabolised via an enzymatic process to fluorouracil.[9] Compared with intravenously administered fluorouracil, capecitabine is more convenient for the patient, both in terms of the ease of administration as well as reduced time at the hospital.[6,8] Moreover, metabolism of capecitabine occurs preferentially in tumour tissue, thereby reducing exposure of normal tissues to the drug.[9] The antiumour efficacy of capecitabine is established in colorectal cancer and breast cancer, and it is approved for use in these patients in the US and Europe.[10,11] This review focuses on the use of oral capecitabine in patients with advanced gastric or oesophagogastric cancer.

1. Pharmacodynamic Profile

The pharmacodynamic properties of capecitabine are well established and have been discussed in detail elsewhere.[9,12] This section provides a brief overview of the pharmacodynamic properties of capecitabine and recent information relevant to the use of the drug in patients with gastric cancer.

- Oral capecitabine, a fluoropyrimidine, is absorbed through the gastrointestinal mucosa as an intact molecule and is metabolised, via a three-step enzymatic cascade, into cytotoxic fluorouracil and its metabolites.[9,12] In the first step, capecitabine is metabolised to 5′-deoxyfluorocytidine (5′-dFCR) by the enzyme carboxyl esterase, which is found almost exclusively in the liver and hepatoma cells.[12,13] 5′-dFCR is then converted to 5′-deoxyfluorouridine (5′-dFUR) by cytidine deaminase, and finally 5′-dFUR is converted to fluorouracil by thymidine phosphorylase.[9,12,13]
- Although both cytidine deaminase and thymidine phosphorylase are found in many tissues, it has been shown that both enzymes have increased activity in tumour tissue versus that in adjacent healthy tissue of the same patient, which would account for the preferential activation of capecitabine to fluorouracil in tumour tissue.[9,12,13] In human gastric cancer tissue, the activities of cytidine deaminase and thymidine phosphorylase have been shown to be ≈2- and ≈3-fold higher (both $p < 0.05$) than in adjacent normal tissue.[13]
- Fluorouracil, in turn, is metabolised to fluorodeoxyuridine monophosphate and fluorouridine triphosphate (FUTP), which mediate their antitumour activity by inhibiting thymidylate synthase, the rate-limiting step in *de novo* thymidine synthe-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

sis, and by interfering with RNA synthesis and function via incorporation of FUTP as a false nucleotide.[9,12]

- The antineoplastic activity of capecitabine has been demonstrated in numerous human cancer xenograft models including those for gastric, colon and breast cancer.[9,13,14] Capecitabine and its intermediate metabolite 5′-dFUR effectively inhibited tumour growth (defined as >50% inhibition) in 75% and 63% of xenograft models.[14] By contrast, tegafur and uracil combination therapy and fluorouracil therapy were effective in 21% and 4% of models.[14]

- In human cancer xenograft models, tumour susceptibility to capecitabine correlated well with the activity of thymidine phosphorylase ($p < 0.05$).[14] There was also a significant ($p < 0.05$) correlation between the susceptibility of the xenograft to capecitabine and the ratio of thymidine phosphorylase to dihydropyrimidine dehydrogenase, which catabolises fluorouracil to inactive metabolites.[14]

- The antitumour activity of oral capecitabine and docetaxel combination therapy for 4 weeks in mice bearing MKN45 or MKN28 gastric cancer xenografts was shown to be greater than with either agent alone.[15] It was suggested that this additive or synergistic effect may have resulted, at least in part, from the up-regulation of thymidine phosphorylase, since docetaxel was separately shown to produce a 5-fold increase in the enzyme in mice bearing the MKN45 gastric cancer. Mice bearing xenografts were treated with oral capecitabine 269 mg/kg/day five times a week for 4 weeks, intravenous docetaxel 15 mg/kg on days 8 and 22 or with a combination of the two agents.[15]

- However, docetaxel did not up-regulate thymidine phosphorylase in mice with the MKN28 xenograft, yet the combination of capecitabine plus docetaxel resulted in complete regression of the xenograft, suggesting that factors other than thymidine phosphorylase activity are (also) involved in the synergistic effect. [15]

2. Pharmacokinetic Profile

This section provides an overview of the pharmacokinetic properties of oral capecitabine, which have been reviewed in detail elsewhere.[9,12,16] Additional information is available from the manufacturer's prescribing information.[10,11] The data focus on capecitabine single doses of 1250 and 2000 mg/m^2/day, which were equivalent to the daily doses administered in phase III trials in patients with advanced gastric or oesophagogastric cancer (section 3).

- Capecitabine is rapidly and extensively absorbed, as an intact molecule, through the gastrointestinal mucosa,[9] with its bioavailability estimated to be nearly 100%.[16] Geometric mean maximum plasma concentrations (C_{max}) of 3.5 and 4.0 μg/mL were reached a median 2 hours after single oral doses of capecitabine 1250 and 2000 mg/m^2 were administered to patients with cancer (n = 12 and 25).[16]

- Geometric mean area under the plasma concentration-time curves from zero to infinity (AUC_∞) for single oral doses of capecitabine 1250 and 2000 mg/m^2 were 5.5 and 5.6 μg • h/mL.[16] The rate and extent of the absorption of capecitabine are reduced by food intake, resulting in a 60% and 35% decrease in the values for mean C_{max} and AUC_∞.[10] Protein binding of capecitabine is 54% and it is bound largely to albumin (35%).[16]

- As noted in section 1, there is preferential activation of capecitabine to fluorouracil in tumour tissue.[13,16] Geometric mean C_{max} values for the capecitabine metabolites 5′-dFCR, 5′-dFUR and fluorouracil of 2.8, 7.4 and 0.29 μg/mL after a single oral dose of capecitabine 1250 mg/m^2, and 4.7, 5.7 and 0.23 μg/mL after a single oral dose of capecitabine 2000 mg/m^2, were all reached after a median of 2 hours.[16]

- Geometric mean AUC_∞ values for 5′-dFCR, 5′-dFUR and fluorouracil were 6.5, 16.0 and 0.62 μg • h/mL after a single oral dose of capecitabine 1250 mg/m^2, and 10.1, 12.1 and 0.46 μg • h/mL after a single oral dose of 2000 mg/m^2.[16] Plasma protein binding values for 5′-dFCR, 5′-dFUR and fluorouracil were 10%, 60% and 10%.[16]

• Capecitabine and its metabolites are excreted primarily via the kidneys, with 95.5% of the administered dose recovered in urine; faecal excretion is only 2.6%.[10,11] The major metabolite excreted in urine is the inactive moiety α-fluoro-β-alanine, which accounts for 57% of the administered dosage; ≈3% of the drug is excreted unchanged in urine.[10,11]

• Capecitabine, 5′-dFCR, 5′-dFUR and fluorouracil have short mean elimination half-lives of 0.55, 0.77, 0.67 and 1.15 hours after a single oral dose of capecitabine 1250 mg/m^2, and 0.58, 0.81, 0.69 and 0.75 hours after a single oral dose of 2000 mg/m^2.[16]

• In patients with mild to moderate hepatic impairment and concurrent liver metastases, there was no clinically significant alteration in the pharmacokinetic properties of capecitabine or its metabolites.[16] However, the bioavailability and exposure to fluorouracil may increase and caution is advised when administering capecitabine to these patients.[11] No pharmacokinetic data are available for patients with severe hepatic impairment; in Europe, capecitabine is contraindicated in these patients.[11]

• In cancer patients with moderate (creatinine clearance 1.8–3.0 L/h [30–50 mL/min]) or severe (creatinine clearance <1.8 L/h [<30 mL/min]) renal impairment receiving capecitabine therapy, there was increased exposure to the drug and its metabolites (α-fluoro-β-alanine and 5′-dFUR) relative to that in patients with normal renal function.[10] Caution is advised in patients with mild or moderate renal impairment and dosage adjustment is recommended in patients with moderate renal impairment; the drug is contraindicated in patients with severe renal impairment.[10,11]

• Although *in vitro* studies have suggested that capecitabine does not inhibit cytochrome P450 (CYP) isoenzymes 1A2, 2A6, 3A4, 2C9, 2C19, 2D6 and 2E1, caution is advised when administering the drug concomitantly with CYP2C9 substrates.[10,11] Postmarketing reports have indicated toxicity associated with elevated phenytoin concentrations in patients receiving capecitabine and phenytoin, which may be due to the inhibition of CYP2C9.[10,11]

• The pharmacokinetics of warfarin are altered to a clinically relevant degree when the drug is coadministered with capecitabine. The mean AUC of (S)-warfarin showed a 57% increase, and its clearance a 37% decrease, in four patients administered a single dose of warfarin 20mg, while receiving long-term treatment with oral capecitabine 1250 mg/m^2 twice daily.[10,11] The baseline-corrected area under the International Normalised Ratio (INR)-time profile increased 2.8-fold and the maximum observed mean INR increased by 91%.[10,11] In postmarketing studies, clinically significant increases in prothrombin time and INR were observed in patients who were stabilised on anticoagulants when capecitabine therapy was initiated.[10]

• There were no clinically relevant pharmacokinetic interactions between capecitabine and paclitaxel[11] or docetaxel.[10,11,17] Concomitant leucovorin increased the concentration and potentially the toxicity of fluorouracil.[10] Since both irinotecan and capecitabine are metabolised by carboxyl esterase, concomitant administration of the two drugs may result in competitive inhibition of the enzyme.[18] The pharmacokinetics of capecitabine and its metabolites are not affected in patients with recurrent or primary oesophagogastric cancer, or previous resection, receiving concomitant cisplatin plus epirubicin.[19]

3. Therapeutic Efficacy

The efficacy of capecitabine has been evaluated in several clinical trials. This section focuses on data from randomised phase II or III trials in chemotherapy-naive patients with advanced gastric or oesophagogastric cancer.[20-23] Where data are limited, noncomparative phase II trials in >50 treatment-naive patients with advanced gastric or oesophagogastric cancer are included.[24-26] A small study (n = 32) examining the efficacy of capecitabine plus cisplatin in patients with recurrent gastric cancer after fluoropyrimidine-based adjuvant therapy is also discussed.[27] All trials were nonblind[20-27] and, where reported, multicentre.[20,21,24-26] Apart from two fully published trials,[26,27] data were available only as abstracts, posters and/or oral presentations.

Two reports[21,24] were updates on fully published trials,[28,29] whereas two other reports are interim analyses of ongoing trials.[22,23]

In most studies, eligible patients (aged 18–80 years) had advanced gastric (including locally advanced nonresectable tumours and/or metastatic disease) or oesophagogastric (including oesophagus, oesophagogastric junction or stomach) cancer.[20-24,26] Other studies included patients (aged 18–75 years) with advanced, non-resectable gastric cancer or recurrent disease[25] or patients with gastric cancer after previous fluoropyrimidine-based adjuvant chemotherapy.[27]

Patients enrolled in the trials had a Karnofsky performance status of ≥60%[22] or ≥70%,[20] Eastern Cooperative Oncology Group performance status of 0–2,[21,23-27,29] at least one measurable (as per Response Evaluation Criteria In Solid Tumours [RECIST]) lesion[22] of ≥2cm in diameter[27] or ≥1.5 × 1.5 cm^2,[29] expected survival time of ≥3 months[24,26] and adequate organ functions.[22-24,27] The inclusion criterion for patients with proximal lesions was cardia cancer.[29] All treatment cycles were 3-weekly cycles, unless stated otherwise.

Primary efficacy endpoints included: noninferiority of capecitabine plus cisplatin versus fluorouracil plus cisplatin regimens in terms of progression-free survival (PFS), where noninferiority was defined as upper limit of 95% confidence interval for the hazard ratio (HR) of <1.4 (primary test) and <1.25 (secondary test);[20] noninferiority of capecitabine-based regimens versus the fluorouracil-based regimens and the noninferiority of oxaliplatin versus cisplatin regimens in terms of overall survival (OS), where noninferiority was defined as an upper 95% CI limit for the HR of <1.23;[21] between-group differences in OS;[21] and overall response/remission rate (ORR)[22-27,29] [as determined by WHO response[26] or RECIST criteria and classified as complete and partial responses[23,25,27,29]]. Where reported, secondary endpoints included ORR (as per RECIST criteria),[20,21] time to response,[20] tumour control rate (defined as complete and partial remission plus stable disease),[22] PFS,[21,22,24,25] OS,[20,22,24-27] duration of response,[20,26,27] time to progression[26,27] and quality of life (QOL) measured using the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).[21] The analyses were based on the intent-to-treat (ITT)[20,21,24,26,27] and/or per-protocol analysis.[20-23,25]

In Advanced Gastric Cancer

In a pivotal phase III trial[20] comparing the efficacy of a capecitabine-based regimen with a fluorouracil-based regimen, patients received oral capecitabine 1000 mg/m^2 twice daily on days 1–14 plus intravenous cisplatin 80 mg/m^2 on day 1 (n = 139 evaluable), or continuous infusion fluorouracil 800 mg/m^2/day on days 1–5 plus intravenous cisplatin 80 mg/m^2 on day 1 (n = 137 evaluable). The median number of treatment cycles was five for each group and the median follow-up period was 22.1 months.[20]

Patients in two noncomparative phase II trials[24,25] received oral capecitabine 1000 mg/m^2 twice daily on days 1–14 plus intravenous oxaliplatin 130 mg/m^2 over 2 hours on day 1, with treatment continued for a maximum of 8 cycles,[24] or oral capecitabine 1000 mg/m^2 twice daily on days 1–14 plus intravenous etoposide 120 mg/m^2/day for 3 days.[25] In two other noncomparative trials,[26,27] patients received oral capecitabine 1250 mg/m^2 twice daily on days 1–14 plus intravenous cisplatin 60 mg/m^2 over 1 hour on day 1,[27] or monotherapy with oral capecitabine 828 mg/m^2 twice daily from days 1–21.[26] Treatment was given in 4-week cycles for a minimum of 2 treatment cycles (median 4 cycles)[26] or therapy was continued until disease progression, the onset of adverse events or withdrawal of patients.[27]

- In the pivotal phase III trial in patients with advanced gastric cancer,[20] capecitabine plus cisplatin treatment was noninferior, in terms of PFS (primary endpoint), to fluorouracil plus cisplatin (current standard therapy) [figure 1; per-protocol analysis]. The upper limit of the 95% CI for the HR (0.81 [95% CI 0.63, 1.04]) was below the predefined noninferiority value of 1.25.[20]

• Secondary endpoints also showed that the capecitabine plus cisplatin regimen was at least as effective as the fluorouracil plus cisplatin regimen. The median duration of OS in capecitabine plus cisplatin recipients was noninferior to that in fluorouracil plus cisplatin recipients (10.5 vs 9.3 months; per-protocol analysis), with an HR of 0.85 (95% CI 0.64, 1.13).[20] Moreover, in the ITT analysis, the ORR (41% vs 29%) was significantly superior ($p = 0.03$) in capecitabine plus cisplatin (n = 160) than fluorouracil plus cisplatin recipients (n = 156), with the time to response also significantly ($p < 0.01$) favouring recipients of the capecitabine-based regimen.[20]

• In a noncomparative phase II trial,[24] capecitabine plus oxaliplatin (n = 54) was effective as first-line therapy in patients with advanced gastric cancer. The ORR was 63%, with a complete response in 3 and a partial response in 31 patients. After a median follow-up of 13 months, the median duration of PFS was 5.8 months and the median OS 11.9 months.[24]

• In patients with advanced nonresectable gastric cancer or recurrent disease (i.e. patients with a poor prognosis), capecitabine plus etoposide was effective as first-line therapy in a noncomparative phase II trial.[25] After a median of five cycles (range 1–14), the ORR for capecitabine plus etoposide

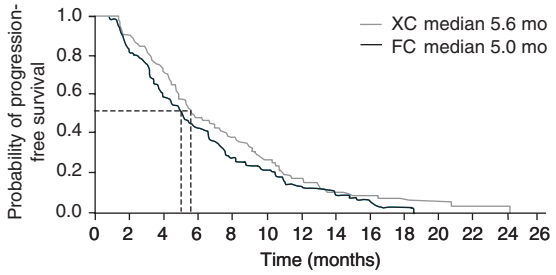

Fig. 1. Efficacy of capecitabine-based chemotherapy in patients with advanced gastric cancer. Kaplan-Meier estimate of the median duration of progression-free survival in patients receiving 3-week treatment cycles of oral capecitabine 1000 mg/m^2 twice daily on days 1–14 plus intravenous cisplatin 80 mg/m^2 on day 1 (XC) [n = 139], or continuous infusion fluorouracil 800 mg/m^2/day on days 1–5 plus intravenous cisplatin 80 mg/m^2 on day 1 (FC) [n = 137] in a randomised, nonblind, multicentre, phase III trial (per-protocol analyses).[20] The median follow-up period was 22.1 months. Adapted from a slide presentation by Kang et al.,[20] with permission from the author.

recipients (n = 53 evaluable) was 38%, with 11% of the patients achieving a complete and 26% a partial response.[25] The median duration of PFS was 5.6 months, with a median duration of OS of 8.8 months; one patient died as a result of tumour progression.[25]

• Capecitabine plus cisplatin was effective as first-line therapy in patients with recurrent gastric cancer after fluoropyrimidine-based adjuvant therapy (ITT population n = 32), with an ORR of 28%.[27] After a median follow-up of 19.4 months (range 9.2–39.8 months), the median time to progression was 5.8 months, the median duration of OS was 11.2 months and the 1-year survival rate was 49%.[27]

• First-line capecitabine monotherapy was efficacious in patients (n = 55 evaluable) with advanced or recurrent gastric cancer.[26] The ORR was 26%, with 7% of patients showing complete response; 29% of patients had stable disease. The median time to tumour progression was 3.4 months. In patients showing a complete or partial response, the median duration of response was 8.8 months (range 2.7–29.6 months).[26]

In Oesophagogastric Cancer

In the pivotal REAL 2 phase III trial,[21] patients with oesophagogastric cancer were randomised, in a 2×2 design, to receive eight cycles of one of four treatments: (i) epirubicin, cisplatin and capecitabine (ECX) [n = 241]; (ii) epirubicin, oxaliplatin and capecitabine (EOX) [n = 239]; (iii) epirubicin, cisplatin and fluorouracil (ECF) [n = 249]; or (iv) epirubicin, oxaliplatin and fluorouracil (EOF) [n = 235]. Oral capecitabine 625 mg/m^2 was given twice daily throughout each cycle. Epirubicin 50 mg/m^2, cisplatin 60 mg/m^2 and oxaliplatin 130 mg/m^2 were administered intravenously once every 3 weeks, whereas fluorouracil 200 mg/m^2 was administered daily as a continuous infusion. The median follow-up period was 17.1 months, with a median of six cycles/group.[21]

In randomised phase II trials, patients in one study (n = 59 evaluable) received oral capecitabine 1000 mg/m^2 twice daily on days 1–14 plus either intravenous irinotecan 250 mg/m^2 or cisplatin 80

mg/m^2 on day 1, with each regimen given once every 3 weeks and treatment continued until disease progression.[22] In another trial, patients (n = 68 evaluable) received either intravenous docetaxel 30 mg/m^2 on days 1 and 8 plus capecitabine 800 mg/m^2 twice daily on days 1–14, or docetaxel 30 mg/m^2 on days 1 and 8, cisplatin 60 mg/m^2 on day 1 plus daily fluorouracil 200 mg/m^2 as a continuous infusion.[23]

- In a per-protocol analysis of the REAL 2 trial, the pooled capecitabine-based (ECX + EOX; n = 480) regimens were noninferior to the pooled fluorouracil-based (ECF + EOF; n = 484) regimens in terms of median OS (10.9 vs 9.6 months; HR 0.86 [95% CI 0.80, 0.99]; primary endpoint), with the upper limit of the 95% CI for the HR being below the predefined value of 1.23.[21] Moreover, the 1-year OS rate for the pooled capecitabine-based regimens was 44.6% versus 39.4% for the pooled fluorouracil-based regimens.[21]

- After a median follow-up duration of 17.1 months, during which 850 events had occurred, the response rates for the ECX, EOX, ECF and EOF treatment groups were 46%, 48%, 41% and 42%, respectively.[21] The duration of OS in the ECX, EOX, ECF and EOF treatment groups was 9.9, 11.2, 9.9 and 9.3 months (ITT population n = 250, 244, 263 and 245), with the median duration of OS being significantly ($p < 0.02$) longer in EOX than in ECF recipients (HR 0.80 [95% CI 0.66, 0.97]).[21] There were also no significant between-group differences in QOL scores from baseline after 12 weeks' treatment.

- Capecitabine plus irinotecan was as effective as capecitabine plus cisplatin in patients with advanced cancer of the stomach or oesophageal junction in an ongoing phase II trial.[22] The respective ORR values (primary endpoint) for the two regimens were 39% and 42% in 59 evaluable patients, with tumour control rates of 64% and 74%.[22] There were also no significant between-group differences in terms of the duration of PFS (5.3 vs 5.1 months) or OS (9.0 vs 9.6 months) in patients receiving the capecitabine plus irinotecan (n = 28) regimen compared with those receiving the capecitabine plus cisplatin (n = 31) regimen.[22]

- In another ongoing phase II trial, capecitabine plus docetaxel was compared with a triple regimen of capecitabine, cisplatin plus docetaxel in patients with metastatic oesophagogastric cancer.[23] The respective ORR values were 20% and 44%, and the median duration of PFS was 3.7 and 5.5 months [n = 34/group in this interim analysis].[23] Further follow-up is needed before any firm conclusions can be drawn from this trial.

4. Tolerability

The tolerability profile of oral capecitabine in patients with colon, colorectal and breast cancer is well established and has been described in previous reviews.[9,12] According to the manufacturer's US[10] and EU[11] prescribing information, the most common (incidence ≥15%) nonhaematological treatment-related adverse events are gastrointestinal in nature, including diarrhoea (47%[11] and 55%[10]), nausea (35%[11] and 43%[10]), vomiting (18%[11] and 27%[10]), abdominal pain (35%[10]) and stomatitis (23%[11] and 25%[10]). Hand-foot syndrome (54%[10] and 57%[11]), fatigue/weakness (16%[11] and 42%[10]), dermatitis (27%[10]), decrease in appetite (26%[10]) and anaemia (80%[10]) are other common treatment-related adverse events (incidence ≥20%).[10,11] This section focuses on data from phase III trials discussed in section 3 in patients with advanced gastric or oesophagogastric cancer (see section 3 for study design and details), with treatment-related adverse events generally being typical of those associated with chemotherapy.

- In patients with advanced gastric cancer, capecitabine plus cisplatin was as well tolerated as a current standard treatment, fluorouracil plus cisplatin.[20] The most common treatment-related grade 3 or 4 adverse events in patients (n = 311) receiving capecitabine plus cisplatin compared with fluorouracil plus cisplatin were neutropenia (16% vs 19%), vomiting (7% vs 9%), diarrhoea (5% vs 5%), anaemia (5% vs 3%) and stomatitis (2% vs 7%); the incidence of all-grade hand-foot syndrome was 22% versus 4%.[20]

- Similarly, in patients with advanced oesophagogastric cancer, capecitabine-based combination reg-

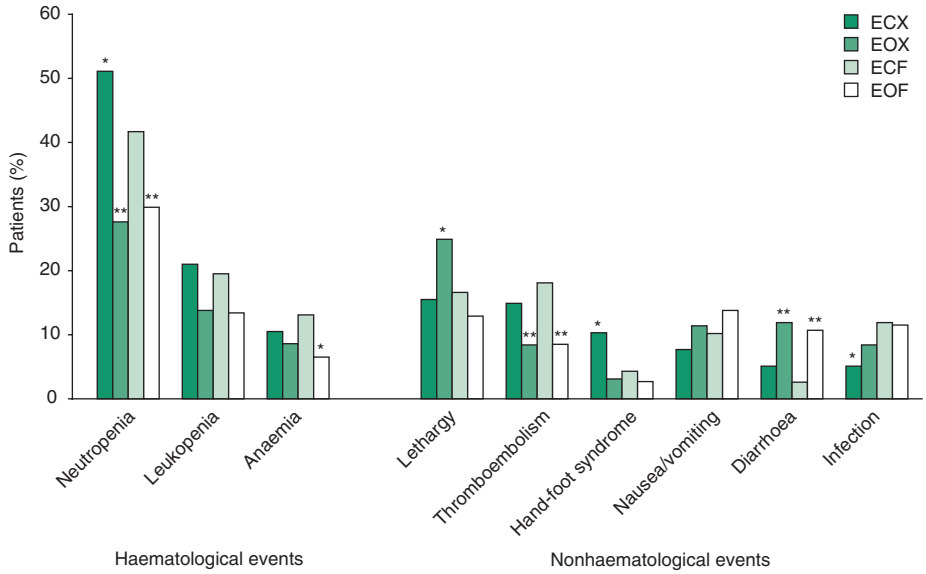

Fig. 2. Tolerability of capecitabine in patients with advanced oesophagogastric cancer. The most common treatment-related adverse events (i.e. incidence ≥10% in any treatment group) of grade 3 or 4 severity in patients receiving capecitabine-based combination therapy in a randomised, phase III trial (REAL 2).[21] Patients received 3-week treatment cycles of 1 of 4 regimens: (i) epirubicin, cisplatin and capecitabine (ECX) [n = 229 for haematological and 234 for nonhaematological events]; (ii) epirubicin, oxaliplatin and capecitabine (EOX) [n = 232 and 227]; (iii) epirubicin, cisplatin and fluorouracil (ECF) [n = 236 and 234]; (iv) epirubicin, oxaliplatin and fluorouracil (EOF) [n = 231 and 225]. Oral capecitabine 625 mg/m^2 was given twice daily continuously, epirubicin 50 mg/m^2, cisplatin 60 mg/m^2 and oxaliplatin 130 mg/m^2 were administered intravenously once every 3 weeks, whereas fluorouracil 200 mg/m^2 was administered daily as a continuous infusion.[21] The median follow-up period was 17.1 months. The analysis was based on per-protocol populations. * $p < 0.05$, ** $p < 0.01$ vs ECF regimen.

imens were generally as well tolerated as fluorouracil-based combination regimens.[21] There were no significant differences in the overall incidence of grade 3 or 4 nonhaematological adverse events in the ECX, EOX, ECF (current standard regimen) or EOF regimens (33%, 45%, 36% and 42%, respectively).[21]

- The most common (i.e. with an incidence of ≥10% in any treatment group) grade 3 or 4 haematological or nonhaematological adverse events in patients receiving ECX, EOX, ECF and EOF regimens are summarised in figure 2.[21] Peripheral neuropathy was significantly ($p < 0.01$ vs ECF) higher in EOF (8.4%) and EOX (4.4%) recipients than in those receiving ECF (0.4%); the incidence in the ECX recipients was 1.7%. On the other hand, the incidence of grade 2 alopecia was significantly ($p < 0.01$ vs ECF) lower in the EOF (27.7%) and EOX (28.8%) recipients than in those receiving ECF (44.2%); the incidence in ECX recipients was 47.4%. There were no between-group differences in the incidence of treatment-related grade 3 or 4 febrile neutropenia (range 6.7–9.3%), thrombocytopenia (4.3–5.2%) or fever (2.6–4.4%).[21]
- Given the nature of chemotherapy, capecitabine was also generally well tolerated when used in combination with other drugs in patients with advanced or metastatic gastric or oesophagogastric cancer, or recurrent gastric cancer, in phase II trials.[22-24] The nature of treatment-related adverse events in these trials was similar to that observed in phase III trials.

5. Dosage and Administration

Currently, there are no formal dosage recommendations for capecitabine in the management of patients with advanced gastric or oesophagogastric cancer. In phase III trials in these patient populations, the dosages of oral capecitabine used were 1000 mg/m^2 twice daily on days 1–14, or 625 mg/

m^2 twice daily taken continuously, during a 3-week cycle in combination with other cytotoxic agents. It should be taken with water within 30 minutes after a meal.[10,11] Caution is advised in patients with mild or moderate renal impairment and dosage adjustment is recommended in patients with moderate renal impairment; the drug is contraindicated in those with severe renal impairment (see section 2).[10,11] As a result of an increased risk of bleeding complications when capecitabine is coadministered with coumarin derivatives such as warfarin (see section 2), the US FDA issued a black-box warning to the labelling of capecitabine.[10] Patients receiving these agents concurrently should be monitored frequently for anticoagulant response, and the anticoagulant dosage should be adjusted accordingly.[10,11]

6. Capecitabine: Current Status in Advanced Gastric or Oesophagogastric Cancer

Capecitabine is in phase III clinical trials in patients with advanced gastric or oesophagogastric cancer. In two large, well designed, phase III trials in treatment-naive patients, capecitabine-based regimens were shown to be noninferior to current standard fluorouracil-based regimens in terms of the duration of PFS in patients with advanced gastric cancer, and in terms of OS in those with oesophagogastric cancer. Furthermore, capecitabine treatment was effective, either as monotherapy or in combination with other antitumour agents, in treatment-naive patients with advanced or metastatic gastric or oesophagogastric cancer, or in pretreated patients with recurrent gastric cancer. Given the nature of chemotherapy, capecitabine-based regimens were generally well tolerated, with the nature of treatment-related adverse events occurring with capecitabine-based regimens being similar to those occurring with fluorouracil-based regimens.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

References

1. Khamly K, Jefford M, Michael M, et al. Recent developments in the systemic therapy of advanced gastroesophageal malignancies. Expert Opin Invest Drugs 2006; 15 (2): 131-53
2. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55 (2): 74-108
3. Leong T. Chemotherapy and radiotherapy in the management of gastric cancer. Curr Opin Gastroenterol 2005; 21 (6): 673-8
4. Macdonald JS. Gastric cancer: new therapeutic options. N Engl J Med 2006; 355 (1): 76-7
5. Ajani JA. Evolving chemotherapy for advanced gastric cancer. Oncologist 2005; 10 Suppl. 3: 49-58
6. Chong G, Cunningham D. Can cisplatin and infused 5-fluorouracil be replaced by oxaliplatin and capecitabine in the treatment of advanced oesophagogastric cancer? The REAL 2 trial. Clin Oncol (R Coll Radiol) 2005; 17 (2): 79-80
7. Roche. New Xeloda combination allows patients with stomach cancer to live significantly longer [online]. Available from URL: http://www.prnewswire.co.uk [Accessed 2006 Jun 7]
8. Roche. Xeloda plus cisplatin combination effective in patients with advanced gastric cancer [online]. Available from URL: http://www.rocheusa.com [Accessed 2006 Aug 8]
9. McGavin JK, Goa KL. Capecitabine: a review of its use in the treatment of advanced or metastatic colorectal cancer. Drugs 2001; 61 (15): 2309-26
10. Roche. Xeloda (capecitabine) tablets: US prescribing information [online]. Available from URL: http://www.fda.gov [Accessed 2006 Jun 7]
11. Roche. Xeloda (tablets): summary of product characteristics [online]. Available from URL: http://emc.medicines.org.uk [Accessed 2006 Jun 7]
12. Robins GW, Keating GM. Capecitabine as adjuvant therapy in stage III colon cancer. Am J Cancer 2005; 4 (5): 315-23
13. Miwa M, Ura M, Nishida M, et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 1998; 34 (8): 1274-81
14. Ishikawa T, Sekiguchi F, Fukase Y, et al. Positive correlation between the efficacy of capecitabine and doxifluridine and the ratio of thymidine phosphorylase to dihydropyrimidine dehydrogenase activities in tumors in human cancer xenografts. Cancer Res 1998; 58 (4): 685-90
15. Kodera Y, Fujiwara M, Yokoyama H, et al. Combination of oral fluoropyrimidine and docetaxel: reappraisal of synergistic effect against gastric carcinoma xenografts. In Vivo 2005; 19 (5): 861-6
16. Reigner B, Blesch K, Weidekamm E. Clinical pharmacokinetics of capecitabine. Clin Pharmacokinet 2001; 40 (2): 85-104
17. Ramanathan RK, Ramalingam S, Egorin MJ, et al. Phase I study of weekly (day 1 and 8) docetaxel in combination with capecitabine in patients with advanced solid malignancies. Cancer Chemother Pharmacol 2005; 55 (4): 354-60
18. Gollamudi R, Baker SD, Desai KK, et al. Pharmacokinetic (pk) and safety study of irinotecan (Ir) and capecitabine (Cp) administered on a weekly schedule [abstract no. 2061]. J Clin Oncol 2006; 24 Suppl. 18: 94
19. Evans TRJ, Pentheroudakis G, Paul J, et al. A phase I and pharmacokinetic study of capecitabine in combination with epirubicin and cisplatin in patients with inoperable oesophagogastric adenocarcinoma. Ann Oncol 2002; 13: 1469-78

20. Kang YK, Kang WK, Shin DB, et al. Randomized phase III trial of capecitabine/cisplatin vs. continuous infusion of 5-FU/cisplatin as first-line therapy in patients with advanced gastric cancer: efficacy and safety results [abstract no. LBA4018]. J Clin Oncol 2006; 24 Suppl. 18: 934. Plus oral presentation at the 42nd Annual Meeting of the American Society of Clinical Oncology; 2006 Jun 2-6; Atlanta (GA)
21. Cunningham D, Rao S, Starling N, et al. Randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer: the REAL 2 trial [abstract no. LBA4017]. J Clin Oncol 2006; 24 Suppl. 18: 934. Plus oral presentation at the 42nd Annual Meeting of the American Society of Clinical Oncology; 2006 Jun 2-6; Atlanta (GA)
22. Moehler M, Kanzler S, Geissler M, et al. Irinotecan/capecitabine versus cisplatin/capecitabine in advanced adenocarcinoma of the stomach or gastroesophageal junction: interim analysis of a randomized German AIO phase II study [abstract no 4032]. J Clin Oncol 2006; 24 Suppl. 18: 186. Plus poster presented at the 42nd Annual Meeting of the American Society of Clinical Oncology; 2006 Jun 2-6; Atlanta (GA)
23. Tebbutt N, Gebski V, Strickland A, et al. Randomised phase II study evaluating weekly docetaxel in combination with cisplatin and 5FU or capecitabine in metastatic oesophago-gastric cancer [abstract no. 4067]. J Clin Oncol 2006; 24 Suppl. 18: 194. Plus poster presented at the 42nd Annual Meeting of the American Society of Clinical Oncology; 2006 Jun 2-6; Atlanta (GA)
24. Park Y, Lee J, Ryoo B, et al. A phase II study of capecitabine plus oxaliplatin (XELOX) as first-line therapy for patients with advanced gastric cancer [abstract no. 4079]. J Clin Oncol 2006; 24 Suppl. 18: 197. Plus poster presented at the 42nd Annual Meeting of the American Society of Clinical Oncology; 2006 Jun 2-6; Atlanta (GA)
25. Reyes S, Tellez E, Fernando A. Capecitabine and etoposide for patients with locally advanced or advanced gastric cancer: a Mexican Oncology Study Group phase II trial [abstract no. 1099P]. Ann Oncol 2006; 17 Suppl. 9: ix315. Plus poster presented at the 31st European Society of Medical Oncology Congress: 2006 Sep 29-30 Oct; Istanbul
26. Sakamoto J, Chin K, Kondo K, et al. Phase II study of a 4-week capecitabine regimen in advanced or recurrent gastric cancer. Anticancer Drugs 2006; 17 (2): 231-6
27. Kang HJ, Chang HM, Kim TW, et al. Phase II study of capecitabine and cisplatin as first-line combination therapy in patients with gastric cancer recurrent after fluoropyrimidine-based adjuvant chemotherapy. Br J Cancer 2005; 92 (2): 246-51
28. Sumpter K, Harper-Wynne C, Cunningham D, et al. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. Br J Cancer 2005; 92 (11): 1976-83
29. Park YH, Kim BS, Ryoo BY, et al. A phase II study of capecitabine plus 3-weekly oxaliplatin as first-line therapy for patients with advanced gastric cancer. Br J Cancer 2006; 94 (7): 959-63

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