Outcomes review

Capecitabine: an evidence-based review of its effectiveness in the treatment of carcinoma of the pancreas

David B. Smith[1], John P. Neoptolemos[2]

[1]Clatterbridge Centre for Oncology, Bebington, Wirral, UK; [2]School of Cancer Studies, University of Liverpool, Liverpool, UK

Abstract

Introduction: More than 90% of patients with pancreatic cancer present either with incurable locally advanced or metastatic disease or relapse following surgery. For these patients systemic therapy offers the only prospect of salvage, but pancreatic cancer is one of the most chemoresistant of tumors; current chemotherapy can only delay progression in a limited proportion of patients and survival rates are poor. There is therefore a pressing need for more effective therapy. Capecitabine is a new oral prodrug of fluorouracil, which has shown activity in pancreatic cancer particularly when used in combination with gemcitabine.

Aims: To review the emerging evidence for the clinical effectiveness of capecitabine in the management of carcinoma of the pancreas.

Evidence review: There is evidence from phase II testing that capecitabine is active in pancreatic cancer. The Swiss Group for Clinical Cancer Research/Central European Cooperative Oncology Group (SAKK/CECOG) phase III trial found that the combination of gemcitabine and capecitabine did not improve overall median survival as compared with gemcitabine alone (8.4 vs 7.3 months, respectively; P=0.314) but subgroup analysis in patients with good performance score [Karnofsky Performance Scores (KPS) $\geq$90] revealed a significant survival improvement with the combination arm (10.1 months) compared with single-agent gemcitabine (7.5 months; P=0.033). Preliminary data from the GemCap phase III trial indicated significantly improved response rates and survival for the combination of gemcitabine with capecitabine (7.4 months) compared with gemcitabine alone (6 months; P=0.026) but analysis of the mature data with adequate follow-up awaits reporting.

Clinical potential: The addition of capecitabine to gemcitabine may represent a small step forward in the management of advanced pancreatic cancer but further data are required in order to determine its full impact.

Core Evidence. 2007;2(2):111–119.

Key words: adjuvant, advanced, cancer, capecitabine, chemotherapy, gemcitabine, pancreas, pancreatic

Core evidence outcomes summary for capecitabine in advanced carcinoma of the pancreas

Outcome measure	Evidence	Implications
Patient-oriented evidence		
Statistically significant improvement in survival in combination with gemcitabine	Substantial	Capecitabine can be considered as first-line treatment in combination with gemcitabine to prolong survival by a small but significant margin
Clinical benefit in good PS patients	Moderate	Patients with good PS more likely to benefit from combination chemotherapy
Acceptable toxicity profile	Substantial	The addition of capecitabine is generally well tolerated
Disease-oriented evidence		
Statistically significant response rate improvement in combination with gemcitabine	Substantial	Capecitabine can be administered as first-line treatment in combination with gemcitabine to improve response rates
Economic evidence		
Capecitabine adds only drug-acquisition costs to gemcitabine therapy	Substantial	Minor additional resource implications

PS, performance status.

Scope, aims, and objectives

Capecitabine (Xeloda®, F. Hoffmann-La Roche) is an orally active prodrug of the fluoropyrimidine fluorouracil (Miwa et al. 1998; Tabata et al. 2004). This review seeks to assess the emerging evidence for capecitabine in the management of carcinoma of the pancreas.

Methods

English language literature searches were conducted on September 25, 2006 in the following databases, searching from the beginning of the database to current date unless otherwise stated. The search strategy was "capecitabine AND pancreatic cancer" unless otherwise stated:

- PubMed, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi, 1966 to date. Limits imposed for specificity: "English," "clinical trial," "meta analysis," "randomized controlled trial," "humans"
- EMBASE, http://www.datastarweb.com
- BIOSIS, http://www.datastarweb.com
- Database of Abstracts of Reviews of Effects (DARE), National Health Service (NHS) Economic Evaluations Database (NHSEED), Health Technology Assessment (HTA), http://www.york.ac.uk/inst/crd/crddatabases.htm. All three databases searched together. All fields searched
- NHS HTA, http://www.ncchta.org
- National Guideline Clearinghouse, http://www.guideline.gov
- National Institute for Health and Clinical Excellence (NICE), http://www.nice.org.uk
- Cochrane Database of Systematic Reviews (CDSR), http://www.cochrane.org/index0.htm. Entire site searched
- Clinical Evidence (BMJ), http://www.clinicalevidence.com

Online abstracts from the following congresses were searched using the search term "capecitabine":

- American Society of Clinical Oncology, all conferences from 2000 to 2006, http://www.asco.org
- European Society for Medical Oncology, all conferences from 2003 to 2005, http://www.esmo.org
- European Cancer Conference 2005, http://ex2.excerptamedica.com/ciw-05ecco

Following hand searching and removal of duplicates, nonsystematic reviews, editorials, records of study methodology, and pharmacokinetic studies, a total of nine full papers and 16 abstracts were included in the evidence base.

After peer review of the initial submission there was a further search of the abstracts presented at the joint meeting of the International Association of Pancreatology and the American Association of Pancreatology meeting held in November 2006. This identified a further systematic review and meta analysis (Sultana et al. 2006). An additional phase II trial was identified via PubMed published in March 2007 (Park et al. 2007). Since the literature searches were conducted, the study by Moore and colleagues has been published as a full paper (Moore et al. 2007). A summary of the literature search results is shown in Table 1.

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	10	102
records excluded	1	86
records included	9	16
Additional studies identified	0	1
Total records included	9	17
Level 1 clinical evidence	0	1
Level 2 clinical evidence	1	4
Level ≥3 clinical evidence		
trials other than RCT	8	11
case reports	0	1
Economic evidence	0	0

For definitions of levels of evidence, see Editorial Information on inside back cover.
RCT, randomized controlled trial.

Disease overview

Adenocarcinoma of the pancreas is one of the main causes of cancer-related death in the western world with about 33 000 new cases annually in the USA (Jemal et al. 2007) and 7000 in the UK (Office for National Statistics 2005). Pancreatic cancer is more common in men (male:female ratio 1.3:1) and is unusual before the age of 45 years but the incidence rises sharply thereafter, reaching a peak in the mid to late 70s. The majority of cases have no obvious genetic predisposition but 5–10% of patients have a first-degree relative with the disease, suggesting some form of familial aggregation (McWilliams et al. 2005; McFaul et al. 2006). The risk of developing pancreatic cancer is increased in a number of familial cancer syndromes (Vitone et al. 2006); for example, the lifetime risk in Peutz-Jegher syndrome approaches 36% (Giardiello et al. 2000; Latchford et al. 2006). Patients with hereditary pancreatitis have a 40% chance of developing pancreatic cancer by the age of 70 (Howes et al. 2004) but the risk is lower for sporadic forms of chronic pancreatitis (Howes & Neoptolemos 2002). Several environmental and lifestyle factors have been implicated in the development of pancreatic cancer including smoking, diet, and body mass index (Vimalachandran et al. 2004). Of these the evidence is most conclusive for cigarette smoking with a two-fold increased risk (Coughlin et al. 2000).

The majority of patients present with painless obstructive jaundice, although upper abdominal and/or back pain, anorexia, and weight loss are also common (Alexakis et al. 2004). Initial investigations include routine hematology, biochemistry, computed tomography scanning of the chest and abdomen, and serum carcinoembryonic (CA) 19-9 estimation, a tumor marker

detectable in a high proportion of patients with pancreatic cancer (BSG 2005). Surgical resection remains the only potentially curative treatment; however, the majority of patients have either locally advanced or metastatic disease at presentation and only around 10% of patients are candidates for pancreatectomy (Alexakis et al. 2004). The prognosis for patients with pancreatic cancer is poor with an overall survival of 0.4%, median survival of 8 to 12 months for patients with locally advanced disease, and 3 to 6 months for those who present with metastases (Bramhall et al. 1995). For patients with resectable disease the 5-year survival is around 10% for patients with node-positive disease, and 20–30% for those with node-negative cancers (Alexakis et al. 2004).

Current therapy options

Adenocarcinoma of the pancreas is highly resistant to radiotherapy and chemotherapy (Sultana et al. 2006, 2007; Yip et al. 2006) and although many drugs have been tested in this disease none have consistently demonstrated objective response rates above 10% (Shore et al. 2003). Pancreatic cancer has a highly complex molecular pathology and is uniquely characterized by a high frequency of activating K-ras mutations and loss of function of the p53, p16, and Smad 4 tumor suppresser genes (Bardeesy & DePinho 2002). A number of altered signaling, DNA repair, and apoptotis pathways may contribute to the resistance of pancreatic cancer to conventional therapies, notably block of the p16/pRb cell cycle control system (Plath et al. 2002). The phosphoinositide 3-OH kinase (PI3K)/Akt pathway, which is frequently amplified or activated in pancreatic cancer, may also contribute to resistance in several ways including the inhibition of proapoptotic proteins BAD and caspase 9 (Schlieman et al. 2003), dysregulation of the mammalian target of rapamycin (mTOR)-S6K1 signaling pathway (Asano et al. 2005), and activation of the nuclear factor kappa B (NFκB) transcription factor (Fernandez-Zapico & Urrutia 2004).

The fluoropyrimidine fluorouracil is used extensively in the treatment of a number of gastrointestinal malignancies including esophageal, gastric, and colorectal cancers, and historically —before the introduction of gemcitabine—was considered to be the most effective available treatment for advanced pancreatic cancer (Carter & Comis 1975; Shore et al. 2003). However, more recent trials of fluorouracil with folinic acid (leucovorin) modulation using both infusional and bolus schedules suggest a relatively low response range (0–9%) and a median survival of 10–24 weeks (Crown et al. 1991; Decaprio et al. 1991; Shore et al. 2003; Van Rijswijk et al. 2004). The deoxycytidine analog gemcitabine has now replaced fluorouracil as the treatment of choice for advanced pancreatic cancer (Burris et al. 1997) with slightly improved objective response rates (6–11%) in chemotherapy-naïve patients (Casper et al. 1994; Carmichael et al. 1996) but with superior clinical benefit response (Burris et al. 1997). Clinical benefit response was initially defined in a phase II study of gemcitabine as an improvement in pain (analgesic consumption and pain intensity), Karnofsky Performance Scores (KPS), or weight gain without a deterioration in any other factor even in the absence of an objective response (Rothenberg et al. 1996). In this trial although the objective response rate for patients with measurable disease was only 11%, a clinical benefit was observed in 27%.

In the pivotal trial by Burris et al. (1997) both clinical benefit and survival were used as the primary endpoints, where clinical benefit required a sustained (≥4 weeks) improvement in at least one parameter without worsening in any others. One hundred and twenty-six previously untreated patients with locally advanced or metastatic pancreatic cancer were randomized between fluorouracil (600 mg/m^2 intravenous bolus weekly) or gemcitabine (1000 mg/m^2 intravenous infusion weekly for 7 weeks followed by a week of rest, then weekly for 3 out of every 4 weeks). Of 56 patients in the gemcitabine arm with bidimensionally measurable disease at study entry, three (5.4%) had a partial response and 22 (39%) had stable disease. Among 57 fluorouracil-treated patients with measurable disease, none had a complete or partial response and 11 (19%) had stable disease. The difference in partial response rates was not statistically significant. Despite the fact that there was no difference in objective response rate between the two groups, gemcitabine was associated with significantly better clinical benefit response (24%) compared with fluorouracil (5%; P=0.002). The median survival was 5.7 months for gemcitabine-treated patients and 4.4 months for the fluorouracil-treated patients, with 1-year survival rates of 18% versus 2%, respectively (P=0.0025). Criticisms of this study included failure to use a prospectively validated quality-of-life instrument, not using blind treatment assignment for those assessing clinical benefit responses, and comparison with a control arm which employed what is now considered to be a suboptimal method of delivering fluorouracil. Nevertheless, gemcitabine was approved for first-line therapy of metastatic pancreatic cancer and, given its relatively low toxicity, it is now the drug of choice (Shore et al. 2003).

In the adjuvant setting both fluorouracil/leucovorin and single-agent gemcitabine each have been tested in two separate phase III trials called ESPAC-1 and CONKO-001, respectively (Neoptolemos et al. 2004; Ghaneh et al. 2006; Oettle et al. 2007). Although both regimens produced a similar doubling in 5-year survival rates compared with the control (resection-only) arms, in the case of CONKO-001 the primary endpoint was progression-free survival rather than overall survival as in ESPAC-1 (Neoptolemos et al. 2004; Ghaneh et al. 2006; Oettle et al. 2007).

A number of groups have investigated other, newer drugs in advanced pancreatic cancer both as single agents and in combination. Studies involving anthracyclines, ifosfamide, taxanes, camptothecins, and platinum analogs have all yielded response rates of less than 10% with no demonstrable improvement in overall survival (Shore et al. 2003). Many combinations have also been tested and although a number of phase II trials have suggested improved response rates for combination chemotherapy, up to now there has been little evidence that these are translated into improved survival (Yip et al. 2006). A systematic review and meta analysis has also demonstrated that chemoradiation followed by chemotherapy does not demonstrate any survival advantage over chemotherapy alone (Sultana et al. 2007).

Although a 2006 Cochrane meta analysis concluded that single-agent gemcitabine remained the standard of care (Yip et al. 2006), a more up to date meta analysis indicated that gemcitabine combined with a platinum derivative was indeed superior to gemcitabine alone (Sultana et al. 2006).

Moreover, erlotinib, a small molecule tyrosine kinase inhibitor, has also recently been shown to have limited clinical benefit in combination with gemcitabine in the National Canadian Institute of Cancer-led international, multicenter, placebo-controlled phase III trial (PA.3) (Moore et al. 2005). Approximately 75% of the 569 patients randomized had metastatic disease. The overall survival was significantly better in the erlotinib arm compared with the placebo-controlled arm with a median survival of 6.4 versus 5.9 months [hazard ratio (HR) 0.81; 95% confidence intervals (CI) 0.67, 0.97; *P*=0.025] and a 1-year survival of 24% versus 17%, respectively. Progression-free survival was also significantly improved with medians of 3.8 versus 3.6 months, respectively (HR 0.76; 95% CI 0.63, 0.91; *P*=0.003). The overall response rate, however, was not different between the two arms (8.6% vs 8.0%, respectively). Toxicity from skin rash and diarrhea was increased in the erlotinib arm although there were no significant differences for global quality-of-life scores (Moore et al. 2005).

In July 2006, the Committee for Medicinal Products for Human Use (CHMP) representing the European Medicines Agency (EMEA) rejected registration of erlotinib because the survival benefit of the combination was very limited. It was concluded that the benefit did not outweigh the risk of side effects, and there was neither improvement in the quality of life nor in progression-free survival and objective response rate (EMEA 2006). In December 2006, however, the CHMP recommended the granting of a variation to the marketing authorization for erlotinib for patients with metastatic cancer based on the evidence that there was a 25% improvement in overall survival in this group of patients (but not in patients with locally advanced disease). The Committee also concluded that erlotinib could be prescribed on a patient-by-patient basis, taking into account the chance of survival (EMEA 2006).

Unmet needs

The majority of patients with pancreatic cancer will either present with inoperable or metastatic disease or will relapse following resection leading to an overall 5-year survival of <5% (Alexakis et al. 2004). Despite the progress made with gemcitabine, systemic therapy is of limited value, with only a small percentage of patients experiencing a short-term benefit usually lasting 4 months or less and the 1-year survival in this group is around 18–20% (Burris et al. 1997). Although there may be improved survival with the combinations of gemcitabine with either erlotinib (Moore et al. 2005) or a platinum derivative (Sultana et al. 2006), the absolute improvement in survival is small. The 5-year survival rate following resection alone is about 10%, improving to around 23–29% with adjuvant systemic chemotherapy with either fluorouracil and leucovorin or gemcitabine but most patients relapse soon after (Neoptolemos et al. 2004; Ghaneh et al. 2006; Oettle et al. 2007). There is therefore an urgent need for new effective treatments to use in this disease both in locally advanced disease and as adjuvant therapy following potentially curative resection.

Clinical evidence with capecitabine in advanced carcinoma of the pancreas

Fluorouracil is most active and least toxic when delivered using an infusional schedule (Meta-analysis Group In Cancer 1998) but such treatment either involves a prolonged inpatient stay or the placement of a central line with its attendant risks and inconvenience. Continuous oral dosing can be used to mimic a protracted infusion but this is not possible with fluorouracil because extensive metabolism by dihydropyrimidine dehydrogenase in the mucosa of the gastrointestinal tract and the liver leads to highly variable bioavailability (Schoffski 2004; Tabata et al. 2004).

Capecitabine is a fluorouracil prodrug which was developed in an effort to overcome this problem (Miwa et al. 1998). It is absorbed intact through the intestinal wall unaffected by dihydropyrimidine dehydrogenase and then undergoes conversion to fluorouracil in a sequential three-stage enzymatic process (Miwa et al. 1998). The final requisite enzyme, thymidine phosphorylase, is present at consistently higher levels in tumor compared with normal tissues, thereby suggesting that fluorouracil delivered in this way may benefit from an element of tumor targeting and thus enhanced selectivity and better tolerability (Ishikawa et al. 1998). Clinical evidence to support this comes from a study in patients with colorectal cancer. Capecitabine was administered 7 days before planned resection of the primary cancer and fluorouracil levels assayed in tumor and adjacent tissues. The median ratio of fluorouracil concentration in colorectal tumors to adjacent tissues was 2.9 (range 0.9–8.0) (Schüller et al. 2000). The effectiveness of capecitabine is such that it may replace fluorouracil as the fluoropyrimidine of choice in colorectal (Van Cutsem et al. 2001; Twelves et al. 2005) and perhaps other cancers as well.

Efficacy

An initial phase II trial of 42 patients with locally advanced or metastatic pancreatic cancer who had received no prior chemotherapy, were treated with standard capecitabine monotherapy (1250 mg/m^2 twice daily on days 1–14 of a 3-week cycle) in order to investigate safety and efficacy (Cartwright et al. 2002). The major grade 3/4 adverse events were diarrhea, hand-foot syndrome, and nausea, and overall the safety profile was similar to that of capecitabine in patients with colorectal and breast cancer. Ten (24%) patients achieved a clinical benefit response and 12 (29%) patients had reduced pain intensity. The overall median survival was 6 months with three (7%) partial responses and another 17 (41%) patients with stable disease for a median duration of 2.8 months.

Capecitabine appeared to have definite, albeit limited, activity in advanced pancreatic cancer and it was therefore decided to explore combination treatment with gemcitabine as the next phase of development. This was based on potential synergy

between gemcitabine and capecitabine as a result of gemcitabine inhibiting ribonucleotide reductase thus depleting intracellular pools of deoxyuridine monophosphate and leading to enhanced binding of 5-fluorodeoxyuridine monophosphate, the active metabolite of fluorouracil, to thymidylate synthase (Ren et al. 1998) (Fig. 1).

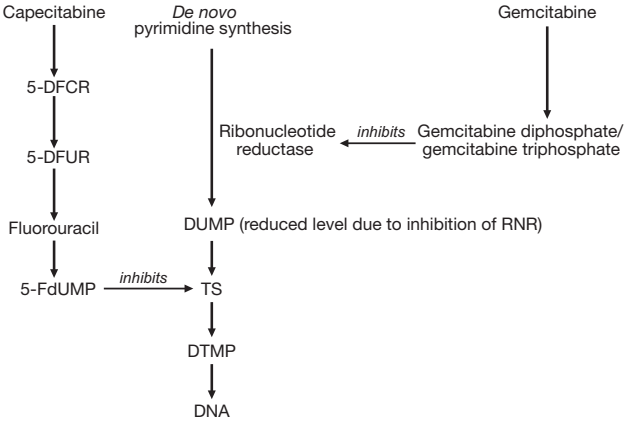

Fig. 1 | Mechanism of action of capecitabine plus gemcitabine. 5-DFCR, 5-deoxyfluorocytidine; 5-DFUR, 5-deoxyfluorouridine; 5-FdUMP, 5-fluorodeoxyuridine monophosphate; DUMP, deoxyuridine monophosphate; DTMP, deoxythymidine monophosphate; RNR, ribonucleotide reductase; TS, thymidylate synthase

Phase I/II dose-finding trials were conducted using both 21- and 28-day cycles. An initial study investigated capecitabine in combination with gemcitabine in 36 patients with previously untreated pancreatic cancer (Hess et al. 2003). Escalating doses of capecitabine were administered keeping gemcitabine at a fixed dose of 1000 mg/m^2 on days 1 and 8. The dose-limiting toxicities were neutropenia and mucositis. A 21-day regimen of capecitabine 650 mg/m^2 twice daily on days 1–14 in combination with gemcitabine 1000 mg/m^2 on days 1 and 8 was found to be the most suitable regimen for phase II testing. There was only one grade 4 adverse event in the 12 patients treated at this dose level and there were no cases of diarrhea, hand-foot syndrome, or alopecia in these patients. In patients with evaluable disease the overall response rate was 15%. A second phase I trial in patients with advanced pancreatic cancer determined that capecitabine 880 mg/m^2 twice daily on days 1–21 of a 28-day cycle with gemcitabine 1000 mg/m^2 on days 1, 8, and 15 was the most appropriate regimen for further investigation (Schilsky et al. 2002).

A subsequent phase II trial using a 21-day schedule of gemcitabine 1000 mg/m^2 on days 1 and 8 plus capecitabine 650 mg/m^2 on days 1–14 involved 53 patients with advanced pancreatic cancer. There were 10 (18%) partial remissions, 22 patients (42%) with stable disease, and 15 (28%) with progressive disease (Stathopoulos et al. 2004). The median time to progression was 6 months, the median survival was 8 months, and 12-month survival was 35%.

Similar results have been reported recently from Korea in a phase II study of 45 patients with advanced pancreatic cancer given gemcitabine combined with dose-escalated 14-day capecitabine as first-line chemotherapy (Park et al. 2007). Gemcitabine 1000 mg/m^2 was given on days 1 and 8 plus capecitabine 1000 mg/m^2 twice daily on days 1–14, in 21-day cycles. The objective response rate was 40% (95% CI 25%, 55%), including one (2%) complete response. The median time to progression was 5.4 months (95% CI 1.8, 9.0) and the median overall survival was 10.4 months (95% CI 6.2, 14.5). Patients with a ≥25% decline of serum CA19-9 had significantly better time to progression and overall survival than those who did not (P<0.03). The most frequent nonhematologic grade 3/4 toxicity was hand-foot syndrome (7%) (Park et al. 2007).

Following on from the earlier phase I/II studies, the combination of gemcitabine with capecitabine has been compared with gemcitabine alone in one randomized phase II (Scheithauer et al. 2003a) and two phase III trials (Cunningham et al. 2005; Herrmann et al. 2005) and also in a randomized phase II trial against gemcitabine plus oxaliplatin (GemOx) and capecitabine plus oxaliplatin (XelOx) (Heinemann et al. 2005).

In the initial randomized phase II study, 83 patients with metastatic pancreatic cancer received either gemcitabine 2200 mg/m^2 intravenously alone on day 1 with or without capecitabine 2500 mg/m^2 per day orally on days 1–7 of a 14-day cycle (Scheithauer et al. 2003a). The objective response rate for single-agent gemcitabine was 14% compared with 17% for the combination with capecitabine, with median survivals of 8.2 and 9.2 months, respectively. The clinical benefit response was 33% for single-agent gemcitabine and 48% for the combination of gemcitabine with capecitabine. Overall these results support phase III investigation of gemcitabine/capecitabine doublet regimens.

The Swiss Group for Clinical Cancer Research (SAKK) jointly performed a phase III trial with the Central European Cooperative Oncology Group (CECOG) in 319 patients with pancreatic cancer, of whom 79% had metastatic disease (Herrmann et al. 2005). In the single-agent arm patients were randomized to gemcitabine 1000 mg/m^2 intravenously on days 1 and 8; patients in the combination arm were randomized to gemcitabine 1000 mg/m^2 intravenously per week for 2 out of every 3 weeks and capecitabine 1300 mg/m^2 per day for the first 14 consecutive days every 3 weeks. The median overall survival was 7.3 months for gemcitabine and 8.4 months for the combination arm (P=0.314) thus failing to reach the primary endpoint. The response rate was 7.9% for single-agent gemcitabine and 10.1% for the combination arm with a median duration of response of 5.9 versus 7.4 months, respectively. The median time to progression was 4 months for single-agent gemcitabine and 4.8 months for the combination arm. There were 232 patients who were at least 4 weeks on study treatment and therefore evaluable for clinical benefit, of whom 111 (73%) had the combination and 121 (82%) had gemcitabine alone. Overall, 27 (18%) patients with gemcitabine and capecitabine and 29 (20%) patients with single-agent gemcitabine had a clinical benefit response

and toxicity was low in both groups (Herrmann et al. 2005). Cox multivariate analysis found that patients with KPS ≥90 had an improved median survival when treated with the combination arm (10.1 months) compared with single-agent gemcitabine (7.5 months; *P*=0.033) (Herrmann et al. 2005).

The second phase III trial (GemCap) was organized by the National Cancer Research Institute and Cancer Research UK, with a total of 533 patients randomized to gemcitabine (n=266) or the combination of gemcitabine and capecitabine (n=267) (Cunningham et al. 2005). Baseline characteristics were well balanced between the gemcitabine and the combination arms (Table 2). Patients randomized to the single-agent arm were scheduled gemcitabine 1000 mg/m^2 weekly for 7 out every 8 weeks, then 1 week's rest and thereafter weekly for the first 3 of every 4 weeks. The schedule for the combination arm was gemcitabine 1000 mg/m^2 weekly for the first 3 of every 4 weeks; capecitabine was given at a dose of 1660 mg/m^2 per day orally for 21 days every 4 weeks followed by 7 days' rest.

Table 2 | National Cancer Research Institute/Cancer Research UK GemCap trial: patient characteristics and preliminary results

	Gemcitabine	Gemcitabine + capecitabine
Patients	266	267
Median age (years)	62	62
Stage		
metastatic (%)	71	70
locally advanced (%)	29	30
Performance status 0–1 (%)	82	81
Response rate (%)	7	14*
Median survival (months)	6.0	7.4
1-year survival (%)	19	26

*P=0.026.

Preliminary results were reported following an interim analysis in May 2005, when 373 (70%) deaths had occurred. Grade 3/4 toxicity episodes in the gemcitabine alone and combination arms were anemia (2% vs 1%), neutropenia (11% vs 17%), thrombocytopenia (2% vs 3%), fever (1% vs 0%), diarrhea (1% in both groups), hand-foot syndrome (0% vs 2%), and vomiting (2% vs 1%). In the preliminary analysis grade 3/4 stomatitis had not been reported in either group of patients. The objective response rates were 7% (0 complete responses, 19 partial responses) for gemcitabine alone and 14% (three complete responses, 35 partial responses) for the combination arm (*P*=0.008). Patients randomized to the combination arm had improved overall survival compared with single-agent gemcitabine (HR 0.80; 95% CI 0.65, 0.98; *P*=0.026). The median survival was 6 months for patients receiving gemcitabine alone compared with 7.4 months in the combination arm with 1-year survival rates of 19% and 26%, respectively. After adjusting for baseline stratification factors (stage of disease and performance status), the survival advantage for the patients in the combination arm remained (HR 0.77; 95%CI 0.63, 0.95; *P*=0.014).

A further randomized, phase II study compared capecitabine plus gemcitabine (n=50) with gemcitabine plus oxaliplatin (n=57) and capecitabine plus oxaliplatin (n=54) (Heinemann et al. 2005). This also showed a trend in favor of the capecitabine-containing arms in terms of response rate and progression-free survival as follows. Patients received 3-week regimens of either capecitabine 2 x 1000 mg/m^2 daily for 2 weeks plus oxaliplatin 130 mg/m^2 intravenously on day 1 (CapOx); or capecitabine 2 x 825 mg/m^2 daily for 2 weeks plus gemcitabine 1000 mg/m^2 intravenously weekly for 2 weeks (CapGem); or gemcitabine 1000 mg/m^2 intravenously per week for 2 weeks plus oxaliplatin 130 mg/m^2 on day 8 (GemOx). Patients in the CapOx, CapGem, and GemOx arms were well balanced with respect to KPS >70% (89% vs 92% vs 90%, respectively) and stage of disease (metastatic disease in 74% vs 76% vs 75%, respectively). The overall median age was 63 years (range 37–75) and patients received a median of four cycles of treatment. Hematologic grade 3/4 toxicity occurred in 6%, 16%, and 19% for the CapOx vs CapGem vs GemOx groups, respectively; grade 3–4 neurosensoric toxicity was observed in 7%, 0%, and 4%, respectively; while grade 2–3 hand-foot syndrome was found in 9%, 6%, and 2%, respectively. In October 2004, 141 patients were evaluable for response. There were no complete remissions; partial responses were obtained in 22%, 16%, and 13% of the CapOx vs CapGem vs GemOx groups, respectively; and stable disease was reported in 33%, 45%, and 30% respectively. The disease control rates were therefore 55%, 61%, and 43% for the CapOx vs CapGem vs GemOx groups, respectively. The median overall survival for CapOx was 243 days, for CapGem was 229 days, and for GemOx was 241 days (*P*=0.6). The median progression-free survival was 127 days, 143 days, and 91 days for the CapOx vs CapGem vs GemOx groups, respectively (Heinemann et al. 2005).

Although the SAKK/CECOG trial did not achieve statistical significance for survival, it used a less dose-intense schedule of the gemcitabine/capecitabine combination compared with the UK GemCap trial and it was also comparatively underpowered. Nevertheless, both trials demonstrated similar trends towards improvements in overall survival and response rates. A recent meta analysis has confirmed that the combination of gemcitabine and capecitabine may be superior to single-agent gemcitabine (Sultana et al. 2006). Overall, therefore, these preliminary data suggest that the addition of capecitabine to gemcitabine results in a small advantage particularly for patients with good performance status.

There are limited data on second-line chemotherapy in pancreatic cancer and none investigating capecitabine alone following gemcitabine failure. However, the combination of capecitabine plus oxaliplatin has been examined in this group of patients. Oxaliplatin 130 mg/m^2 on day 1 plus capecitabine 1000 mg/m^2 twice daily on days 1–14 were administered on a 21-day schedule to 41 patients who had progressed following gemcitabine (Xiong et al. 2006). There was one partial response and eight patients with stable disease, with a median survival of 5.8 months and 12-month survival rate of 22%, suggesting at least some activity in this difficult group of patients.

Capecitabine has also been included in studies of chemoradiotherapy in locally advanced carcinoma of the pancreas as an alternative to intravenous fluorouracil and has been shown to be tolerable with predictable toxicity (Ben-Josef et al. 2004; Crane et al. 2006). This is a somewhat of a controversial area, however, with little evidence to suggest that chemoradiation adds to systemic chemotherapy in this situation and additional trials are required to define its role (Yip et al. 2006; Sultana et al. 2007).

Tolerability

The toxicity of capecitabine itself is relatively noncytotoxic *in vivo* and thus the toxicity profile tends to reflect that of its active metabolite fluorouracil (Van Cutsem et al. 2001, 2004; Scheithauer et al. 2003b; Twelves et al. 2005). The toxicity of fluorouracil is dependent on the schedule used. Whereas bolus fluorouracil causes mainly diarrhea, oral mucositis, myelosuppression, and ocular irritation, infusional fluorouracil schedules tend to cause hand-foot syndrome and mucositis, typically comprising inner lip surface ulcers, whereas significant myelosuppression is unusual. The toxicity profile of capecitabine appears to lie somewhere between that of bolus and infusional fluorouracil (Budman et al. 1998) with up to 50% of patients experiencing diarrhea of varying degrees that occasionally may require hospital admission (Scheithauer et al 2003b; Twelves et al 2005). Hand-foot syndrome may occur in around 60% of patients, fatigue is common, and nausea and/or vomiting affects 30% of patients but is readily controlled with antiemetics. Less common side effects include constipation, headaches, conjunctivitis, anorexia, abdominal pain, hair thinning, ankle swelling, and chest pain due to coronary vasospasm (Van Cutsem et al. 2002). The use of capecitabine in patients with impaired renal function should be cautious, requiring a 25% dose reduction for those with a creatinine clearance of 30–49 mL/min and should be discontinued if the clearance falls significantly during therapy until recovery occurs. Patients may receive the drug safely despite markedly abnormal liver function since capecitabine does not undergo significant hepatic metabolism (Schüll et al. 2003) but administration in such cases should be cautious as such patients are likely to have advanced disease and a poor performance status with little prospect of an effective benefit.

When capecitabine is used in combination, such as with gemcitabine, the dose-limiting toxicity is myelosuppression and thus the dose of capecitabine needs to be attenuated to allow full-dose gemcitabine to be delivered (Schilsky et al. 2002). The result is a reduction in the incidence of diarrhea and hand-foot syndrome in combination schedules such as in the UK GemCap trial where the incidence of grade 3/4 hand-foot syndrome was 2%, grade 3/4 diarrhea was 1%, and serious stomatitis was not a problem (Cunningham et al. 2005).

Economic evidence

There are as yet no studies that include an economic evaluation of capecitabine in pancreatic cancer. However, studies have been undertaken in colorectal cancer comparing oral capecitabine with intravenous fluorouracil delivered using either bolus or infusional schedules (Ward et al. 2003; Cassidy et al. 2006). The data show that while drug acquisition costs are somewhat higher for capecitabine, the costs of managing toxicity are broadly similar and the cost of delivering capecitabine is significantly less than that of fluorouracil due to considerable savings in pharmacy and chemotherapy nursing resources. In addition, the use of capecitabine allows considerable reduction in patient travel costs, and time spent in hospital. Overall, when compared with fluorouracil, capecitabine results in 57% lower chemotherapy-related costs and is therefore a cost-effective option when used as a single agent in colon cancer. In pancreatic cancer the addition of capecitabine to gemcitabine adds little in terms of administration costs, and with reduced capecitabine toxicity in combination regimens, minimal additional resources are needed to manage side effects. The main additional costs therefore relate to drug acquisition, and individual health economies must decide whether or not the modest increase in survival justifies this outlay.

Patient group/population

Performance status is the most important determinant of likelihood of response to chemotherapy in the common solid tumors and pancreatic cancer is no exception. This was highlighted in the SAKK/CECOG study outlined above where a subgroup analysis showed a significantly improved median survival with capecitabine for patients with KPS $\geq$90% (Herrmann et al. 2005). Thus patients with few symptoms and a World Health Organization performance status of 0–1 are more likely to benefit from palliative chemotherapy and to tolerate treatment without undue toxicity. Patients with a performance status of 3 are most unlikely to benefit, and for these patients chemotherapy frequently results in unacceptable toxicity. A performance status of 2 tends to encompass quite a broad spectrum with some patients being reasonably fit and well enough for a trial of chemotherapy while others, closer to a performance status of 3, are best served by best supportive care.

Clinical potential

Capecitabine (Xeloda) is an oral prodrug which is converted to fluorouracil by three sequential enzymatic reactions (Tabata et al. 2004). The final requisite enzyme, thymidine phosphorylase, is present at consistently higher levels in tumors compared with normal tissues (Miwa et al. 1998; Nakayama et al. 2005), thereby suggesting that fluorouracil delivered in this way may benefit from an element of tumor targeting and thus enhanced selectivity and better tolerability (Ishikawa et al. 1998; Schüller et al. 2000). Fluorouracil is known to be most effective when administered as a protracted infusion but such schedules require indwelling catheters and in pancreatic cancer these cause particular problems with venous thromboembolism. Capecitabine may therefore represent an attractive option since continuous daily dosing can mimic a protracted venous infusion and avoids the need for central lines. Capecitabine has been shown to have modest single-agent activity in advanced carcinoma of the pancreas and when used in combination with gemcitabine may

provide a small but significant improvement in response rates and survival compared with gemcitabine alone. These advantages may be most marked in patients with a good performance status and it is in this group where combination treatment including capecitabine is most likely to be of value.

Publication of the final results of both the SAKK/CECOG (Herrmann et al. 2005) and GemCap phase III (Cunningham et al. 2005) trials in advanced pancreatic cancer are needed before more certain conclusions can be drawn as to the role of capecitabine in conjunction with gemcitabine in advanced pancreatic cancer.

Acknowledgements

The authors are grateful for project and program funding from Cancer Research UK.

References

Alexakis N, Halloran C, Raraty M, Ghaneh P, Sutton R, Neoptolemos JP. Current standards of surgery for pancreatic cancer. *Br J Surg.* 2004;91:1410–1427.

Asano T, Yao Y, Zhu J, Li D, Abbruzzese JL, Reddy SA. The rapamycin analog CCI-779 is a potent inhibitor of pancreatic cancer cell proliferation. *Biochem Biophys Res Commun.* 2005;331:295–302.

Bardeesy N, DePinho RA. Pancreatic cancer biology and genetics. *Nat Rev Cancer.* 2002;2:897–909.

Ben-Josef E, Shields AF, Vaishampayan U, et al. Intensity-modulated radiotherapy (IMRT) and concurrent capecitabine for pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2004;59:454–459.

Bramhall SR, Allum WH, Jones AG, Allwood A, Cummins C, Neoptolemos JP. Treatment and survival in 13,560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study. *Br J Surg.* 1995;82:111–115.

BSG (Pancreatic Section, British Society of Gastroenterology); Pancreatic Society of Great Britain and Ireland; Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland; Royal College of Pathologists; Special Interest Group for Gastro-Intestinal Radiology. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. *Gut.* 2005;54(Suppl. V):v1–v16.

Budman DR, Meropol NJ, Reigner B, et al. Preliminary studies of a novel oral fluoropyrimidine carbamate: capecitabine. *J Clin Oncol.* 1998;16:1795–1802.

Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol.* 1997;15:2403–2413.

Carmichael J, Fink U, Russell RC, et al. Phase II study of gemcitabine in patients with advanced pancreatic cancer. *Br J Cancer.* 1996;73:101–105.

Carter SK, Comis RL. The integration of chemotherapy into a combined modality approach for cancer treatment. VI. Pancreatic adenocarcinoma. *Cancer Treat Rev.* 1975;2:193–214.

Cartwright TH, Cohn A, Varkey JA, et al. Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. *J Clin Oncol.* 2002;20:160–164.

Casper ES, Green MR, Kelsen DP, et al. Phase II trial of gemcitabine (2,2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. *Invest New Drugs.* 1994;12:29–34.

Cassidy J, Douillard JY, Twelves C, et al. Pharmacoeconomic analysis of adjuvant oral capecitabine vs intravenous 5-FU/LV in Duke's C colon cancer: the X-ACT trial. *Br J Cancer.* 2006;94:1122–1129.

Coughlin S, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes Control.* 2000;11:915–923.

Crane CH, Ellis LM, Abbruzzese JL, et al. Phase I trial evaluating the safety of bevacizumab with concurrent radiotherapy and capecitabine in locally advanced pancreatic cancer. *J Clin Oncol.* 2006;24:1145–1151.

Crown J, Casper ES, Botet J, Murray P, Kelsen DP. Lack of efficacy of high-dose leucovorin and fluorouracil in patients with advanced pancreatic adenocarcinoma. *J Clin Oncol.* 1991;9:1682–1686.

Cunningham D, Chau I, Stocken D, et al. Phase III randomised comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. *Eur J Cancer Suppl.* 2005;3:4. Abstract PS11.

DeCaprio JA, Mayer RJ, Gonin R, Arbuck SG. Fluorouracil and high-dose leucovorin in previously untreated patients with advanced adenocarcinoma of the pancreas: results of a phase II trial. *J Clin Oncol.* 1991;9:2128–2133.

EMEA (European Medicines Agency). Questions and answers on recommendation for refusal for a change to the marketing authorisation for Tarceva. London: EMEA; July 27, 2006. Document ref: EMEA/284207/2006. Available at: http://www.emea.europa.eu/pdfs/human/opinion/28420706en.pdf (accessed April 2007).

Fernandez-Zapico ME, Urrutia R. Molecular pathogenesis of pancreatic carcinogenesis. *Drug Discovery Today: Disease Mechanisms.* 2004;1:247–252.

Ghaneh P, Sultana A, Shore S, Stocken D, Neoptolemos J. The case for adjuvant chemotherapy in pancreatic cancer. *Best Pract Res Clin Gastroenterol.* 2006;20:383–401.

Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology.* 2000;119:1447–1453.

Heinemann V, Hoehler T, Seipelt G, et al. Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (GemCap) versus gemcitabine plus oxaliplatin (GemOx): a randomised phase II trial in advanced pancreatic cancer. *J Clin Oncol.* 2005;23(Suppl.). Abstract 4030.

Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine (G) plus capecitabine versus G alone in locally advanced or metastatic pancreatic cancer. A randomized phase III study of the Swiss Group for Clinical Cancer Research (SAKK) and the Central European Cooperative Oncology Group (CECOG). *J Clin Oncol.* 2005:23(Suppl.):310s. Abstract 4010.

Hess V, Salzberg M, Borner M, et al. Combining capecitabine and gemcitabine in patients with advanced pancreatic carcinoma: a phase I/II trial. *J Clin Oncol.* 2003;21:66–68.

Howes N, Neoptolemos JP. Risk of pancreatic ductal adenocarcinoma in chronic pancreatitis. *Gut.* 2002;51:765–766.

Howes N, Lerch MM, Greenhalf W, et al; European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC). Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol.* 2004;2:252–261.

Ishikawa T, Utoh M, Sawada N, et al. Tumor selective delivery of 5-fluorouracil by capecitabine, a new oral fluoropyrimidine carbamate, in human cancer xenografts. *Biochem Pharmacol.* 1998;55:1091–1097.

Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin.* 2007;57:43–66.

Latchford A, Greenhalf W, Vitone LJ, Neoptolemos JP, Lancaster GA, Phillips RK. Peutz-Jeghers syndrome and screening for pancreatic cancer. *Br J Surg* 2006;93:1446–1455.

McFaul CD, Greenhalf W, Earl J, et al; European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC); German National Case Collection for Familial Pancreatic Cancer (FaPaCa). Anticipation in familial pancreatic cancer. *Gut.* 2006;55:252–258.

McWilliams RR, Rabe KG, Olswold C, De Andrade M, Petersen GM. Risk of malignancy in first-degree relatives of patients with pancreatic carcinoma. *Cancer.* 2005;104:388–394.

Meta-analysis Group In Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol.* 1998;16:301–308.

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;34:1274–1281.

Moore M, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared to gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group (NCNC-CTG). *J Clin Oncol.* 2007;25:1960–1966.

Nakayama Y, Inoue Y, Nagashima N, et al. Expression levels of thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD) in patients with gastrointestinal cancer. *Anticancer Res.* 2005;25:3755–3761.

Neoptolemos JP, Stocken DD, Friess H, et al; European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med.* 2004;350:1200–1210.

Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA.* 2007;297:267–277.

Office for National Statistics. Cancer statistics registrations. Registrations of cancer diagnosed in 2003, England. Series MB1 no.34. London: Office for National Statistics; 2005. Available at: http://www.statistics.gov.uk/downloads/theme_health/MB1_34/MB1_34.pdf (accessed

Park BB, Park JO, Lee HR, et al. A phase II trial of gemcitabine plus capecitabine for patients with advanced pancreatic adenocarcinoma. *Cancer Chemother Pharmacol.* 2007 Mar 30; (Epub ahead of print).

Plath T, Peters M, Detjen K, et al. Overexpression of pRB in human pancreatic carcinoma cells: function in chemotherapy-induced apoptosis. *J Natl Cancer Inst.* 2002;94:129–142.

Ren Q, Kao V, Grem JL. Cytotoxicity and DNA fragmentation associated with sequential gemcitabine and 5-fluoro 2'-deoxyuridine in HT-29 colon cancer cells. *Clin Cancer Res.* 1998;4:2811–2818.

Rothenberg ML, Moore MJ, Cripps MC, et al. A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. *Ann Oncol.* 1996;7:347–353.

Scheithauer W, Schüll B, Ulrich-Pur H, et al. Biweekly high-dose gemcitabine alone or in combination with capecitabine in patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial. *Ann Oncol.* 2003a;14:97–104.

Scheithauer W, McKendrick J, Begbie S, et al; X-ACT Study Group. Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomized, phase III trial. *Ann Oncol.* 2003b;14:1735–1743.

Schilsky RL, Bertucci D, Vogelzang NJ, Kindler HL, Ratain MJ. Dose-escalating study of capecitabine plus gemcitabine combination therapy in patients with advanced cancer. *J Clin Oncol.* 2002;20:582–587.

Schlieman MG, Fahy BN, Ramsamooj R, Beckett L, Bold RJ. Incidence, mechanism and prognostic value of activated AKT in pancreas cancer. *Br J Cancer.* 2003;89:2110–2115.

Schoffski P. The modulated oral fluoropyrimidine prodrug S-1, and its use in gastrointestinal cancer and other solid tumors. *Anticancer Drugs.* 2004;15:85–106.

Schüll B, Scheithauer W, Kornek GV. Capecitabine as salvage therapy for a breast cancer patient with extensive liver metastases and associated impairment of liver function. *Onkologie.* 2003;26:578–580.

Schüller J, Cassidy J, Dumont E, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. *Cancer Chemother Pharmacol.* 2000;45:291–297.

Shore S, Raraty MG, Ghaneh P, Neoptolemos JP. Chemotherapy for pancreatic cancer. *Aliment Pharmacol Ther.* 2003;18:1049–1069.

Stathopoulos GP, Syrigos K, Polyzos A, et al. Front-line treatment of inoperable or metastatic pancreatic cancer with gemcitabine and capecitabine: an intergroup, multicenter, phase II study. *Ann Oncol.* 2004;15:224–229.

Sultana A, Tudur Smith C, Ghaneh P. Meta-analyses of the management of locally advanced and metastatic pancreatic cancer. *Pancreas.* 2006;33:499. Abstract.

Sultana A, Tudur Smith C, Cunningham D, et al. Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. *Br J Cancer.* 2007;96:1183–1190.

Tabata T, Katoh M, Tokudome S, et al. Bioactivation of capecitabine in human liver: involvement of the cytosolic enzyme on 5'-deoxy-5-fluorocytidine formation. *Drug Metab Dispos.* 2004;32:762–767.

Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med.* 2005;352:2696–2704.

Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol.* 2001;19:4097–4106.

Van Cutsem E, Hoff PM, Blum JL, Abt M, Osterwalder B. Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. *Ann Oncol.* 2002;13:484–485.

Van Cutsem E, Hoff PM, Harper P, et al. Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. *Br J Cancer.* 2004;90:1190–1197.

Van Rijswijk RE, Jeziorski K, Wagener DJ, et al; EORTC GastroIntestinal Tract Cancer Cooperative Group. Weekly high-dose 5-fluorouracil and folinic acid in metastatic pancreatic carcinoma: a phase II study of the EORTC Gastro-Intestinal Tract Cancer Cooperative Group. *Eur J Cancer.* 2004;40:2077–2081.

Vimalachandran D, Ghaneh P, Costello E, Neoptolemos JP. Genetics and prevention of pancreatic cancer. *Cancer Control.* 2004;11:6–14.

Vitone LJ, Greenhalf W, McFaul CD, Ghaneh P, Neoptolemos JP. The inherited genetics of pancreatic cancer and prospects for secondary screening. *Best Pract Res Clin Gastroenterol.* 2006;20:253–283.

Ward S, Kaltenthaler E, Cowan J, Brewer N. Clinical and cost effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation. *Health Technol Assess.* 2003;7:1–93.

Xiong HQ, Wolff RA, Hess KR, Varadhachary R, Blais JC, Abbruzzese JL. A phase II trial of oxaliplatin plus capecitabine (xelox) as second line therapy for patients with advanced pancreatic cancer. *J Clin Oncol.* 2006;24(Suppl.). Abstract 4119.

Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D. Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. *Cochrane Database Syst Rev.* 2006;(3):CD002093.

Correspondence: Dr David B. Smith, Clatterbridge Centre for Oncology, Bebington, Wirral, Merseyside L63 4JY, UK or at david.smith@ccotrust.nhs.uk