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ORIGINAL ARTICLE

A phase II trial evaluating capecitabine and irinotecan as second line treatment in patients with oesophago-gastric cancer who have progressed on, or within 3 months of platinum-based chemotherapy

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Abstract
Rationale There is no standard second line therapy for relapsed oesophago-gastric (O-G) cancer.
Methods We recruited 29 eligible patients with relapsed O-G cancer who had progressed during or within 3 months of prior chemotherapy to assess the efficacy and toxicity of capecitabine [2,000 mg/(m^2 day) on days 1–14] and irinotecan (250 mg/m^2) given every 3 weeks.
Results Five patients (17%) demonstrated objective response, while a further seven patients (24%) achieved disease stabilisation. Median progression-free survival and overall survival were 3.1 months (95% CI = 2.2–4.1 months) and 6.5 months (95%CI = 6–7.1 months), respectively. Among symptomatic patients, palliation of tumour-related symptoms included resolution of reflux (5/12 pts), dysphagia (3/9 pts) and weight loss (4/9 pts), improvements in anorexia (4/10 pts), nausea (3/4 pts), vomiting (4/6 pts) and pain (4/16 pts). Grade 3–4 toxicities were diarrhoea (15%), nausea and vomiting (7%), lethargy (31%), neutropenia (31%), anemia (14%) and thrombocytopenia (7%).
Conclusions Capecitabine and irinotecan has anti-tumour activity as second line treatment for relapsed O-G cancer, and provides an important improvement in disease related symptoms.

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Introduction

Although the incidence of gastric cancer has been on the decline over the last few decades, the incidence of oesophageal cancer has been on the rise, especially due to the increase in oesophageal adenocarcinoma in Western countries. Today, gastric and oesophageal cancers remain the second and sixth leading causes of cancer-related deaths, respectively, with the combination accounting for over 980,000 deaths annually worldwide [1]. Fifty percent of patients with oesophago-gastric (O-G) cancer present with metastatic or unresectable disease at diagnosis and combination chemotherapy with platinum-based regimens are becoming accepted as standard first line treatment with response rates of 35–45% and a median survival of about 9 months [2–4]. But there is no standard second line treatment. Furthermore, an increasing number of patients are receiving chemotherapy in the neoadjuvant and/or adjuvant setting as perioperative chemotherapy has been shown to improve progression-free and overall survival [5, 6]. Unfortunately, a significant number of these will invariably relapse. There is therefore, an increasing need to define effective second line chemotherapy for advanced O-G cancer.

Irinotecan, a topoisomerase I inhibitor has been shown to have activity as a single agent in G-O cancer. Overall response rates of 23% were noted, including a 16% response rate among 45 patients with pretreated gastric cancer [7]. Although, response rates to single agent irinotecan remain modest, studies in colorectal cancer have shown that activity can be enhanced when combination therapy is used. 5 Fluorouracil (5FU) is one of the central drugs in the

treatment of gastrointestinal tumours and a number of studies in metastatic colorectal cancer have shown that 5FU can be safely and effectively combined with irinotecan [8, 9]. These data have provided the rationale for phase II studies evaluating the efficacy of irinotecan in combination with 5FU in O-G cancer. Objective response rates of 22–42% have been demonstrated in chemotherapy-naïve patients with advanced G-O malignancies [10, 11]. We reported the results of a phase II trial exploring the safety and efficacy of the combination of irinotecan and 5FU (De Gramont schedule) as second line treatment for patients with G-O cancer who had progressed on, or within 3 months of platinum-based chemotherapy [12]. Patients received irinotecan (180 mg/m^2), folinic acid (125 mg/m^2) and 5FU (400 mg/m^2) bolus followed by 5FU (1,200 mg/m^2 infusion over 48 h) every 2 weeks (De Gramont schedule). Among 38 assessable patients, objective response rate was 29% with an additional 34% with stable disease. Treatment was associated with significant palliation in tumour-related symptoms including an improvement in dysphagia and pain in 78 and 55% of symptomatic patients, respectively. The regimen was well tolerated with the most common grade 3–4 toxicities consisting of neutropenia (26%), nausea and vomiting (13%), anemia (13%) and febrile neutropenia (5%). Although infused regimens of 5FU, such as the De Gramont schedule used in this study may be better tolerated than the bolus regimens with less diarrhoea, stomatitis and neutropenia [13], the benefit of reduced toxicity comes at the cost of having to use indwelling catheters for drug delivery. These indwelling venous catheters are associated with their own complications and associated morbidity that should be carefully considered when evaluating the benefit of second line palliative chemotherapy. The oral prodrug of 5FU, capecitabine offers an attractive alternative to continuous 5FU, and the combination of capecitabine (1,000 mg/m^2 twice daily, days 1–14 every 21 days) and irinotecan (250 mg/m^2 every 3 weeks) was shown to be safe in patients with metastatic colorectal cancer [14].

We therefore, proposed to investigate the safety and efficacy of capecitabine in combination with irinotecan in patients who had either progressed on, or within 3 months of first line chemotherapy for advanced oesophago-gastric cancer.

Methods

Eligibility

Patients were required to have histologically proven adenocarcinoma or squamous cell carcinoma of the oesophagus, oesophageal junction or stomach not amenable to surgical resection. Locally advanced or metastatic disease had to be measurable by CT scanning and not be included within previously irradiated areas. Patients were required to have received at least one prior chemotherapy regimen, and demonstrated progressive disease during previous treatment or within 3 months of stopping treatment. No prior exposure to irinotecan was allowed. At study entry, patients, were required to have adequate bone marrow function (platelets $>100 \times 10^9$/L, WBC $>3 \times 10^9$/L and neutrophils $>1.5 \times 10^9$/L), renal function (creatinine ≤ 135 μM/L and calculated creatinine clearance >50 ml/min), satisfactory liver function [in the absence of liver metastases: bilirubin $<1.25 \times$ upper limit of normal (ULN), hepatic transaminases $<2.5 \times$ ULN and prothrombin time $<1.5 \times$ ULN;or in the presence of liver metastases: bilirubin $<1.5 \times$ ULN, hepatic transaminases $<5 \times$ ULN and prothrombin time $<1.5 \times$ ULN], an ECOG performance status of 0, 1, or 2, a life expectancy of at least 3 months, no uncontrolled medical condition or history of other malignant disease except for non-melanoma skin cancer or in situ carcinoma of the cervix and agree to take adequate contraceptive precautions. In addition, the following exclusion criteria prohibited study entry: medical or psychiatric illness resulting in an inability to give consent, intracerebral metastases, or meningeal carcinomatosis, unresolved bowel obstruction or ongoing pregnancy or lactation. Written consent was obtained from each participant before entering the study which had been previously approved by the local institutional ethics committee. Serious adverse events were reported to the local scientific/ethics committee and to the pharmaceutical sponsors. The trial was conducted according to the declaration Helsinki (1964, amended 1989) and performed according to the principles of Good Clinical Practice.

Pre-treatment evaluation

Baseline investigations included classification of histology as well, moderately or poorly differentiated adeno- or squamous carcinoma, a full medical history and physical examination, full blood count, clotting screen, urea and electrolytes, creatinine clearance, liver function tests and tumour markers (CEA and CA19-9). All patients had a CT scan of the thorax, abdomen and pelvis with uni- or bidimensional evaluation of measurable disease, an ECG and completed a baseline quality of life form.

Withdrawal criteria

Patients, were withdrawn if they met any of the following criteria: intolerable adverse events judged by the investigator to be physically or psychologically detrimental to the patient, pregnancy, non-compliance, unresolved or recurrent grade 4 haematological toxicity or grade 3 or 4 non-haematological

toxicity, progressive disease, serious allergic reaction to any of the study drugs as manifested by angioedema, bronchospasm or anaphylaxis, or patient decision to discontinue treatment.

Treatment

Irinotecan was administered at 250 mg/m^2 as an intravenous (IV) infusion over 30–90 min every 21 days, and capecitabine prescribed at 1,000 mg/m^2 twice daily days 1–14 of the same 21 day schedule. Chemotherapy was repeated every 3 weeks up to a maximum of 24 weeks. Atropine 0.25 mg was given subcutaneously prior to irinotecan to prevent the cholinergic syndrome associated with irinotecan. Patients were discharged with a prescription for loperamide and ciprofloxacin to be used in the event of diarrhoea. They were advised to use two capsules of loperamide (4 mg) after the first unformed stool, then one capsule every 2 h for at least 12 h, or for 12 h after the last liquid stool, and drink large volumes of water during the diarrhoea episode. If diarrhoea persisted for more than 24 h despite appropriate loperamide therapy, patients were advised to take prophylactic ciprofloxacin 250 mg twice daily. If the diarrhoea was accompanied by fever or vomiting, or persisted for more than 48 h despite appropriate outpatient medical management, patients were admitted to the hospital.

Study endpoints

The primary endpoints were objective response rates (RR) and progression-free survival (PFS). Secondary endpoints included overall survival (OS), quality of life (QOL), symptom response and toxicity.

Response evaluation

Objective tumour response was evaluated by CT scan according to RECIST criteria [15]. Target lesions, were documented at baseline and after four and eight cycles of chemotherapy. Complete response (CR) was defined as complete resolution of all evaluable disease, partial response (PR) as a 30% or greater decrease in the sum of the longest diameter of target lesions and progressive disease as a 20% or greater increase in the sum of the longest diameter of all target lesions. Stable disease (SD) consisted of radiological responses showing neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD. All other sites of disease were defined as non-target lesions and documented at baseline, as well as subsequent radiological assessments. All CT scans, were reviewed by the same radiologist. Overall survival and PFS, were assessed from date of treatment initiation to death, and progression/or death, respectively. Quality of life measures, were assessed using the EORTC QLC C-30 version 3 questionnaire at baseline and after four and eight cycles of chemotherapy. Symptom response was assessed after each cycle and defined as resolution of that particular symptom for at least 3 weeks.

Evaluation of toxicity and dose adjustments

Toxicity was measured and graded using the National Cancer Institute (NCI) common toxicity criteria (CTC) version 2. For patients developing grade 3–4 or recurrent grade 2 mucositis, or grade 3 palmar-plantar erythema (PPE), treatment was to be discontinued until resolution and resume with a 25% dose reduction of capecitabine. For patients who developed grade 3–4 diarrhoea, lethargy or asthenia, or grade 4 neutropenia, grade 3 febrile neutropenia with grade 2–3 fever, or grade 4 thrombocytopenia, treatment was stopped until resolution and restarted with a 25% dose reduction in capecitabine and a dose reduction of irinotecan from 250 to 210 mg/m^2. Resolution of haematological toxicity was defined as neutrophil count >1,500/mm^3 and platelets >100,000/mm^3. The same dose modifications, were applied if patients developed recurrent grade 2 toxicities. In the event of severe toxicities despite dose modifications, irinotecan was further reduced to 180 mg/m^2.

Statistical considerations

This phase II trial was conducted according to a standard 2-stage Simon design aiming to rule out a RR of 5% and detect a 20% RR with 80% power and a one-sided alpha of 0.05. Twenty-nine patients, were required. At interim analysis after the first ten patients, at least one response, were observed. The treatment would be considered worthy of further investigation if four or more responses, were observed in the cohort of 29 patients. Response rates, were expressed as percentages with their 95% confidence intervals. Survival analysis was performed using the Kaplan–Meier method. Progression-free survival was defined as the time from study registration to the date of progression or death. Patient with no progression or death were censored on the date of last follow-up. Overall survival was defined as the time from study registration to the date of death. Patients who did not have a death recorded, were censored on the date of last follow-up.

Results

Patient characteristics

Thirty-three patients with relapsed O-G carcinoma were enrolled at the Sutton and Fulham branches of the Royal

Marsden, London UK between October 2003 and September 2005. Four patients were subsequently found to be ineligible for the study. Three patients were ineligible due to lack of measurable disease, and one had progressed more than 3 months after prior chemotherapy. Twenty-nine eligible patients were therefore enrolled. The demographics of the patients are detailed in Table 1. The majority of patients were male and 86% had a PS of 0 or 1. Ninety-three percent were adenocarcinomas and 86% had metastatic disease. The median age was 59 (range 25–74 years). Sixty-five percent of patients had an elevated tumour marker at baseline (CEA, Ca19-9 or both).

All patients had progressed or relapsed within 3 months of platinum-based chemotherapy except for one patient who previously received capecitabine monotherapy (Table 2). Prior treatments consisted mainly of combination regimens such as ECX (epirubicin, cisplatin, capecitabine, 38%), ECF (epirubicin, cisplatin and 5FU, 17%) and CarboX (carboplatin and capecitabine, 17%), and 31% of patients had received more than one prior chemotherapy regimen. While 24% of patients relapsed within 3 months of completing prior treatment, the majority (76%) had progressed during prior chemotherapy.

Table 1 Demographics

Characteristics of patients randomised ($N = 29$)		
	Number of patients	Percentage
Sex		
Male	22	76
Female	7	24
Performance status		
0	3	10
1	22	76
2	4	14
Site of primary		
Gastric	5	17
Oesophageal	13	45
O-G junction	11	38
Histology		
Adenocarcinoma	27	93
Squamous carcinoma	2	7
Differentiation		
Moderate	7	24
Poor	21	69
Unknown	1	7
Extent of disease		
Locally advanced	4	14
Metastatic	25	86
Sites of disease		
Lymph nodes	12	41
Liver	13	45
Peritoneum	2	7
Lungs	2	7
Tumour markers at baseline		
Normal CEA and Ca19-9A[a]	8	28
High CEA and normal Ca19-9	5	17
High Ca 19-9 and normal CEA	5	17
High CEA and Ca 19-9	9	31
Unknown	2	7

[a] Normal defined as both CEA and Ca19-9 within normal limits, normal CEA <3 μg/L in non-smokers and <5 μg/L in smokers, normal Ca19-9 <37 U/ml

Response rates

Twenty-nine patients were evaluable for response. Objective partial responses, were observed in five patients (PR = 17%) while a further seven patients achieved disease stabilisation (SD = 24%), amounting to a disease control rate of 41%. Two patients died prior to their first radiological assessment. Among the five objective responders, three of the responders had progressed during prior treatment and two had received more than one prior chemotherapy

Table 2 Prior treatment history

	Number of patients	Percentage
Eligibility		
Progression on treatment	22	75
Progression off treatment within 3 months	7	25
Number of prior chemotherapy regimens		
1	20	69
2	9	31
Prior chemotherapy		
ECX	11	38
CarboX	5	17.2
ECF	5	17.2
EEX	2	7
ECarboX	1	3.4
CarboEpi	1	3.4
EEF	1	3.4
Capecitabine	1	3.4
Carbo5FU	1	3.4
CisplatinX	1	3.4

ECX epirubicin, cisplatin and capecitabine; *CarboX* carboplatin and capecitabine; *ECF* epirubicin, cisplatin and 5-fluorouracil; *EEX* epirubicin, oxaliplatin and capecitabine; *ECarboX* epirubicin, carboplatin and capecitabine; *CarboEpi* carboplatin and epirubicin; *EEF* epirubicin, oxaliplatin and 5-fluorouracil; *Carbo5FU* carboplatin and 5-fluorouracil; *CisplatinX* cisplatin and capecitabine

regimen. Among the patients with stable disease, 86% (6/7 pts) had progressed during prior treatment and 14% (1/7 pts) had received more than one prior chemotherapy regimen.

Survival

Kaplan–Meier curves for overall and progression-free survival are shown in Fig. 1. Median PFS for the 29 patients was 3.1 months (95% CI = 2.2–4.0 months) with a 6 month PFS rate of 24% (95% CI = 10.7–40.5%). The median OS was 6.4 months (95% CI = 2.8–10 months) with a 6 month OS rate of 55% (95% CI = 35.6–71%) and a 1 year OS rate of 21% (95% CI = 8.4–36.7%). With a median follow-up of 18 months for surviving patients, one patient who achieved a PR and one with disease stabilisation were still alive at last follow-up over 1 year after enrolment (14 and 17 months, respectively).

Quality of life and symptom response

Patients demonstrated significant improvement in disease related symptoms. Forty-four percent (4/9 pts) patients initially presenting with weight loss demonstrated weight gain or stabilisation. Similarly 42% (5/12 pts) of patients with baseline reflux and 33% (3/9 pts) of patients with dysphagia experienced complete resolution of symptoms, while 25% (4/16 pts) of symptomatic patients reported relief of pain. Other tumour-related symptoms that improved included anorexia 40% (4/10 pts), nausea 75% (3/4 pts), vomiting 67% (4/6 pts) and lethargy 14% (3/22 pts).

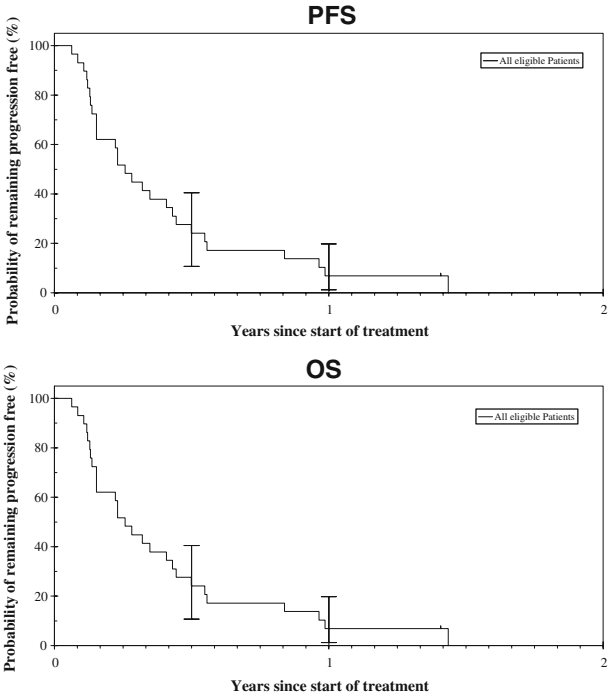

Fig. 1 Progression-free (*PFS*) and overall survival (*OS*) ($N = 29$)

Global quality of life (QOL) was assessed at 12 and 24 weeks using the EORTC QLQ C-30 version 3 questionnaire. Quality of life parameters, were graded by the patient from 0 to 100, with a higher score equating to a higher QOL. Completed questionnaires were available for 21/29 patients at baseline, 13/29 at 12 weeks and 12/29 at 24 weeks (Table 3). There was a non-significant increase in global QOL scores from a median score of 67 at baseline to 83 at 24 weeks. Functional QOL scores (e.g., physical, role, cognitive and social functioning) all showed a trend for improvement, although none reached statistical significance ($P > 0.05$).

Dose intensity and toxicity

Seventy-six percent of prescribed irinotecan and 73% of prescribed capecitabine were delivered, respectively. Seventeen patients (59%) completed four or more cycles of chemotherapy, five patients (17%) completed all eight scheduled courses including one patient who went on to receive a further cycle due to clinical benefit. The majority of patients stopped prematurely due to disease progression (62%) while five patients (17%) stopped treatment due to an adverse event (one small bowel obstruction, one neutropenic sepsis, one pulmonary embolus and one gastrointestinal bleed) and one patient was switched from capecitabine to ralitrexed for chest pain. One further patient was taken off treatment despite stable disease due to declining nutritional status attributed to chemotherapy.

Treatment was well tolerated (Table 4). Mucositis and PPE were rarely reported, maximum toxicity was grade 2 stomatitis in 7% of patients, and grade 2 PPE in 4% of patients. Other expected non-haematological toxicities included grade 3 diarrhoea (15%), grade 3 nausea and vomiting (7%), grade 3 or 4 lethargy (37%). The most significant haematological toxicity was grade 4 neutropenia (21%), however, this was only associated with one grade 3 febrile neutropenia (3%) and two events of grade 4 febrile neutropenia (7%). Other haematological toxicities included

Table 3 Quality of life scores at baseline and at 24 weeks (scored by patients from 0 to 100 using the EORTC QLQ C-30 v.03)

Functional parameter	Score at baseline	Score at 24 weeks	*P* value
Global	67	83	NS
Physical	83	87	NS
Role	83	100	NS
Emotional	92	92	NS
Cognitive	91	100	NS
Social	67	91	NS

Table 4 Toxicity

	Any grade (%) $N = 29$	Grade 3–4 (%) $N = 29$
Diarrhoea	63	15
Stomatitis	18	0
Nausea and vomiting	86	7
Alopecia	81	0
Hand–foot syndrome	18	0
Lethargy	96	31
Febrile neutropenia	10	10
Neutropenia	72	31
Anemia	86	14
Thrombocytopenia	14	7

grade 3 or 4 anemia (14%) and grade 3 thrombocytopenia (7%).

Discussion

There is currently no standard second line chemotherapy for advanced G-O cancer. A number of regimens are therefore, being evaluated in this setting including various combinations of capecitabine, paclitaxel, 5FU, cisplatin and irinotecan [16–18]. We have previously shown encouraging anti-tumour activity with a combination of irinotecan and infused 5FU. However, the discomfort and potential morbidity associated with the indwelling catheter required for delivery of infused 5FU should be carefully considered when weighing the benefit of palliative chemotherapy. Capecitabine is an oral prodrug of 5FU which is metabolised in the liver and tissues to its active form as a pyrimidine antimetabolite. Its cytotoxic activity is mediated via the inhibition of thymidylate synthase, thereby blocking the methylation of deoxyuridylic acid to thymidylic acid and interfering with DNA. The final step in the conversion of capecitabine to 5FU is mediated by thymidine phosphorylase, an enzyme present in higher concentration in tumour than in healthy tissue [19]. As a 5FU analogue with preferential activation in tumour tissue, capecitabine offers an attractive alternative to intravenous 5FU and studies comparing single agent capecitabine (1,250 mg/m^2 twice daily for 14 days followed by 1 week rest) with bolus 5FU according to the Mayo schedule in metastatic colon cancer have shown that the oral agent offers superior response rates with less toxicity [20]. A dose finding study in relapsed gastrointestinal cancer identified capecitabine 1,000 mg/m^2 twice daily days 1–14 and irinotecan 250 mg/m^2 day-1 of a 21 day cycle as the recommended dose for further study [21]. We present the results of the first phase II trial of capecitabine and irinotecan as second line treatment in patients with advanced G-O cancer.

The regimen demonstrated efficacy with a median overall survival of 6.5 months, and objective partial response and stable disease rates of 17 and 24%, respectively. Given the fact that 75% of the patients enrolled in this trial demonstrated active progression on prior treatment, and that 30% were receiving this regimen in the third line setting, a disease control rate of 41% suggests meaningful anti-tumour activity. This is supported by a recent trial of capecitabine and irinotecan as first line treatment for metastatic or relapsed gastric cancer showing an objective response rate (CR + PR) of 46% [22]. Importantly, this treatment was associated with marked improvements in disease related symptoms such as reflux (42%), anorexia (40%), dysphagia (33%) and pain (25%). There was also an improvement in all QOL functional scores as assessed by the EORTC QLQ questionnaire, although none reached statistical significance due to the small numbers of returned questionnaires.

A number of regimens have been tested as second line treatment for relapsed upper GI cancer, including epirubicin plus docetaxel [21], taxol [23], capecitabine plus cisplatin [17], as well as irinotecan in combination with infused 5FU [18], cisplatin [24] or mitomycin-C [25]. These phase II studies demonstrated objective response and overall survival rates comparable to those reported here (RR = 15–30%, OS = 5–8 months). However, many of these trials used weekly or bi-weekly chemotherapy regimens, necessitating more frequent hospital visits. Furthermore, these studies enrolled an unselected patient population. Studies in a number of tumour types, including GO cancer, have shown that progression-free interval after first line chemotherapy correlates with benefit from second line treatment [26]. Therefore, our results demonstrate especially clinically meaningful activity in a poor prognosis patient population selected for fast growing aggressive tumours based on progressive disease during or within 3 months of prior combination chemotherapy.

In our study, the capecitabine–irinotecan regimen was well tolerated with minimal non-haematological toxicities consisting of grade 3 diarrhoea (15%), grade 3 nausea/vomiting (7%) and grade 3 or 4 lethargy (37%). The most significant toxicity was grade 4 neutropenia in 21% of patients, however, there was only one grade 4 neutropenic sepsis event. The treatment doses and schedule selected for this study, were based on safety data from phase II trials in colorectal cancer demonstrating that the most frequent associated grade 3/4 toxicities were diarrhoea in 19% of patients [14, 27]. However, resulting larger phase III studies using a regimen of irinotecan 250 mg/m^2 and capecitabine 2,000 mg/m^2 days 1–14 with or without celecoxib or bevacizumab on a 3-weekly schedule in advanced colorectal

Table 5 Dose, schedule and toxicity reported in published phase II trials of capecitabine (CAP) plus irinotecan (IRI) as first line treatment for advanced upper gastrointestinal carcinoma

Reference	Dose and schedule	Cumulative monthly dose (mg/m^2/months)[c]	Number of patients	Highest grade 3/4 haematological and non-haematological toxicity (%)
Baek et al. [22]	CAP[b] 2,000 mg/m^2 days 1–14 IRI 100 mg/m^2 days 1 and 8 every 3 weeks	CAP: 37.3 × 10^3 IRI: 266	40	Neutropenia:10 Diarrhoea: 15
Burge et al.[a] [32]	CAP[b] 2,000 mg/m^2 days 1–9 IRI 180 mg/m^2 day 1 every 2 weeks	CAP: 36 × 10^3 IRI: 360	30	Neutropenia:10 Diarrhoea: 17
Oh et al. [33]	CAP[b] 3,500 mg/m^2 days 1–7 IRI 130 mg/m^2 days 1 and 15 every 2 weeks	CAP: 49 × 10^3 IRI: 260	55	Neutropenia: 22 Diarrhoea: 7

[a] Included a phase I dose escalation and a phase II at the maximum tolerated dose, only the phase II component is included here

[b] Given in two divided doses

[c] Monthly cumulative dose used in this trial (CAP 2,000 mg/m^2 days 1–14 and IRI 250 mg/m^2 day 1 every 3 weeks): CAP: 37.3 × 10^3 mg/m^2/month, IRI: 333 mg/m^2/month

cancer have reported significantly higher toxicity with grade 3/4 diarrhoea rates of 25–47% [28–30]. Importantly, the EORTC phase III trial was terminated early due to eight toxic deaths including three deaths attributable to treatment related diarrhoea [29]. The investigators recommended a 20% dose reduction and a resulting phase II trial using capecitabine 1,600 mg/m^2 days 1–14 and irinotecan 200 mg/m^2 with bevacizumab in metastatic colorectal cancer reported 15% grade 3/4 diarrhoea [31]. Whether the lower GI toxicity observed in our study is attributable to a patient selection bias (all but one patient had previously received and tolerated a 5FU or capecitabine based regimen), or to differential treatment tolerance in the setting of an intact colon is unclear. In this regard, three phase II trials have been published, investigating the safety and efficacy of capecitabine and irinotecan as first line treatment of advanced G-O carcinoma and reported more favourable toxicity profiles, however, the doses and schedules utilised varied (Table 5) [22, 32, 33].

There is currently no consensus on the optimal management of metastatic or relapsed G-O cancer after first line chemotherapy, and no randomised trials have compared second line therapy to best supportive care. However, response rates reported here, and in similar published phase II trials are comparable to those described in other tumour types that routinely receive second line treatment. These overall response rates combined with the significant improvement in cancer-related symptoms suggest a role for second line chemotherapy in the management of metastatic G-O cancer and provide the rationale for a phase III trial investigating the benefit of second line chemotherapy versus best supportive care.

This trial was designed as a follow-up to our previously reported phase II study of irinotecan and 5FU in refractory or relapsed G-O cancer and has demonstrated comparable efficacy and toxicity profile but without the need for an indwelling catheter for delivery of infused 5FU. The combination of capecitabine and irinotecan was well tolerated and associated with encouraging PFS and OS, and significant palliation of disease related symptoms. These findings confirm that irinotecan-based therapy has activity in the second line or salvage setting for relapsed G-O cancer and provides meaningful improvements in disease related symptoms. However, given the significant GI toxicity observed in colorectal trials, for our own practice we have implemented a dose reduction to 3-weekly capecitabine 1,700 mg/m^2 days 1–14 and irinotecan 200 mg/m^2 day 1.

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