PERGAMON

European Journal of Cancer 39 (2003) 1121–1128

European Journal of Cancer

www.ejconline.com

A randomised study of protracted venous infusion of 5-fluorouracil (5-FU) with or without bolus mitomycin C (MMC) in patients with carcinoma of unknown primary

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Received 10 December 2002; accepted 13 December 2002

Abstract

No standard regimen has been identified for patients with a carcinoma of unknown primary (CUP). This study compared protracted venous infusion 5-fluorouracil (PVI 5-FU) with or without mitomycin C (MMC) in patients with CUP in a multicentre, prospectively randomised study. 88 patients were randomised to PVI 5-FU (300 mg/m^2/day for a maximum of 24 weeks) ±MMC (7 mg/m^2 6 weekly for four courses). The overall response rate was 11.6% for PVI 5-FU alone compared with 20.0% for PVI 5-FU plus MMC ($P=0.29$). Median failure-free survival (FFS) was 4.1 months for PVI 5-FU and 3.6 months for PVI 5-FU plus MMC ($P=0.78$) with an equivalent overall survival (OS) (6.6 versus 4.7 months, $P=0.60$). Symptomatic benefit was observed in most patients in each arm. PVI 5-FU is a well tolerated outpatient treatment regimen for patients with CUP, although the addition of MMC provides little extra benefit. PVI 5-FU may be a potential reference regimen in randomised trials with newer chemotherapy agents in patients with CUP.

Keywords: Unknown primary; Carcinoma; 5-Fluorouracil; Randomised

1. Introduction

Patients with carcinoma of an unknown primary site (CUP) comprise a heterogenous group that represents up to 5% of all cancer diagnoses. Within this diverse group of patients, several subgroups exist for whom specific treatments are indicated by clinical and/or pathological features. These include women with peritoneal carcinomatosis, women with axillary lymph node involvement only and young men with clinical features of extragonadal germ cell tumour. However, the majority of patients with CUP are not included in these subgroups. They have a particularly poor prognosis with a median survival of only 4–7 months and, although systemic chemotherapy is given to control symptoms and to attempt to prolong survival, no standard regimen has been identified [1]. Studies of the natural history of CUP have identified multiple sites, male gender and hepatic involvement as poor prognostic features with lymph node and peritoneum involvement being good prognostic features [2]. However, as no phase III studies have included a best supportive care (BSC) arm, it is difficult to determine whether or not there is any quality of life (QoL) or survival advantage with the present chemotherapy regimens.

It is difficult to compare studies of different treatment regimens due to the heterogeneity of CUP and the different inclusion criteria of phase II studies. The optimum chemotherapy should have activity in as broad a range of tumour types as possible. Several treatment regimens, often including a platinum or an anthracycline agent, have been employed, producing response

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doi:10.1016/S0959-8049(03)00150-3

rates of 20–30% and a median survival of 4–10 months [1]. Although response rates are slightly superior with platinum-based regimens, survival rates are similar. Therefore, in view of their increased toxicity, platinum-based regimens are not considered to be standard therapy as palliative treatment for patients with CUP.

In addition to activity in upper and lower gastrointestinal and breast malignancies, the fluorinated pyrimidine 5-fluorouracil (5-FU) has a modest toxicity profile. Although there have been few studies with 5-FU as a single agent in CUP, several phase II studies have been performed using 5-FU in combination with a platinum agent or taxane [3–6]. A meta-analysis of six randomised trials has demonstrated that continuous infusion 5-FU is superior to bolus 5-FU with respect to tumour response and survival in metastatic colorectal cancer, with significantly less frequent haematological toxicity in the infused regimens [7,8]. Mitomycin C (MMC) has demonstrated synergistic activity with 5-FU *in vitro* and has a mild, predominantly haematological toxicity profile [9,10]. Therefore, it was postulated that protracted venous infusion (PVI) 5-FU may be an effective and well-tolerated palliative treatment for patients with CUP and that the addition of MMC may improve efficacy without a significant increase in toxicity.

This study was designed to test the hypothesis that a combination of PVI 5-FU and MMC is a superior chemotherapy regimen to PVI 5-FU alone in patients with CUP. It was a component of a stratified study designed to investigate the efficacy of PVI 5-FU plus MMC compared with PVI 5-FU alone in advanced gastrointestinal cancer. We have previously reported the results for patients with oesophagogastric [11], colorectal [12] and pancreatic [13] carcinomas. Here, we report on the combination of PVI 5-FU and MMC compared with PVI 5-FU alone in patients with adenocarcinoma of unknown primary using the endpoints of response rate, toxicity and survival.

2. Patients and methods

2.1. Patient eligibility

Patients were required to have histologically- or cytologically-confirmed CUP. They had to have an adequate bone marrow function (platelets $>100\times10^9$/l, white blood count $>3\times10^9$/l, neutrophils $>1.5\times10^9$/l), renal function (serum creatinine <132 μmol/l, urea <10.7 mmol/l) and hepatic function (bilirubin <30 μmol/l). Patients had to have a good performance status (PS) (Eastern Cooperative Oncology Group (ECOG) PS 0-2) and a life expectancy of more than 3 months. They were excluded if there were intracerebral metastases, history of other malignancy (apart from adequately treated non-melanotic skin cancer or carcinoma *in situ* of the uterine cervix), uncontrolled angina pectoris or clinically significant cardiac dysrhythmias, pregnancy or any psychological condition precluding informed consent. Prior to randomisation, written informed consent was obtained from all of the patients. The study was approved by the Local Research and Ethics Committee at each of the five participating centres. Eligibility criteria were verified by the data manager and patients were randomly assigned to treatment with PVI 5-FU or PVI 5-FU and MMC on a 1:1 basis. The patients were randomised centrally by the Institute of Cancer Research Clinical Trials Office in random permuted blocks and stratified by centre.

2.2. Pretreatment evaluation, assessment during treatment and follow-up

Baseline evaluation included a complete medical history and physical examination, full blood count and film (for red cell fragmentation), serum biochemistry including electrolytes, liver and renal function tests, carcinoembryonic antigen (CEA), CA125, alphafetoprotein (AFP), βHCG (human chorionic gonadotrophin), prostate-specific antigen (PSA) and CA19-9. Computed tomographic (CT) scans of the chest, abdomen and pelvis were performed at baseline. Gastroscopy and colonoscopy were performed if indicated and all women had baseline mammograms and pelvic ultrasound scans. During the study, patients were monitored every 3 weeks whilst on treatment with medical history, physical evaluation, full blood count and serum chemistry. In addition, CT scans were performed at 12 and 24 weeks.

2.3. Intravenous access

A double lumen central venous catheter was inserted under local anaesthesia with antibiotic cover and warfarin (1 mg/day orally) was commenced and administered throughout the treatment to prevent catheter thrombosis [13]. Catheters were removed due to septicaemia secondary to catheter infection, catheter infection worsening in spite of appropriate antibiotic treatment, catheter thrombosis, intolerable shoulder pain and slippage/incorrect placement of the catheter. The catheter was removed under local anaesthesia at the end of treatment.

2.4. Chemotherapy

PVI 5-FU was commenced at a dose of 300 mg/m^2/day, via an ambulatory pump. Patients randomised to receive MMC started this treatment on the same day at a dose of 10 mg/m^2 intravenous (i.v.) bolus every 6 weeks for four courses. Subsequent to 2 patients developing haemolytic uraemic syndrome (HUS) in a study of similar design at this institution, the dose of MMC was reduced to a cumulative dose of 28 mg/m^2 following

ethics committee approval (7 mg/m^2 per course for four courses) [12]. In this study, 7 patients received MMC at 10 mg/m^2, none of whom developed HUS. Patients in both groups continued on therapy for 12 weeks and were then re-assessed by CT scan. If there was no progression of disease, therapy continued for a further 12 weeks, to a maximum of 24 weeks.

2.5. Evaluation of response

Tumour response was assessed by CT scan with response classified according to World Health Organization (WHO) criteria [14]. Disease in the peritoneum and/or omentum was considered as one site of disease. ECOG PS and the presence of symptoms of pain, dysphagia, reflux, anorexia, lethargy, diarrhoea, weight loss, nausea, vomiting and dyspnoea were assessed using a checklist prior to chemotherapy, 6 weekly during chemotherapy and 3 monthly thereafter until death or disease progression. Symptom response was defined as the disappearance of that particular symptom for a minimum of 6 weeks. In the case of weight loss, symptom response was defined as weight stabilisation or weight gain. PS was considered to have improved if there had been at least one grade improvement although patients who were grade zero at baseline were not included in the denominator.

2.6. Toxicity evaluation and dose modification

Toxicity was evaluated on a weekly basis and graded according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) [15]. Dose reductions and supportive treatment were given as previously described in Ref. [13].

2.7. Quality of life

Patients were requested to complete European Organization for Research and Treatment of Cancer Quality of Life questionnaires Core 30 (EORTC QLQ-C30) before starting treatment and every 12 weeks thereafter, as previously described in Ref. [13]. Reliability and validity of this measure have been previously Ref. [16]. At the time of initiation of this study, no validated disease-specific module was available. Scoring of the questionnaire was performed according to guidelines provided by the EORTC quality of life working group with the conversion of all scores to a 0–100 scale using the recommended standardisation algorithm. Scores were interpreted so that increased functional status and decreased symptom status indicated a benefit to patients.

2.8. Statistical methods

This study constitutes part of a stratified study to evaluate PVI 5-FU with or without MMC in patients with inoperable gastrointestinal cancers. This included patients with CUP, colorectal cancer [12], oesophagogastric cancer [11], neuroendocrine tumours and pancreatic cancer [13]. It was intended at the outset that the pancreas and CUP cohorts would be combined. With 266 patients randomised in the two cohorts, a difference in response rate increasing from 10 to 25% could be detected with at least 90% power (alpha 5%, two-sided). However, the pancreas study was expanded to 209 patients so that it could be reported alone [13]. The CUP cohort would, therefore, require 200 patients to be reported separately. However, due to poor recruitment, the study was closed having recruited 88 patients (Fig. 1). In this paper, we report on the CUP patients only.

The primary endpoint was tumour response. Patients with non-evaluable disease were excluded from the response evaluation. Further endpoints were failure-free survival (FFS), overall survival (OS), toxicity and QoL. Tumour response rates and toxicities in the two arms were compared using the chi-squared test with Fisher's Exact test being used where appropriate. Time to progression or death from the time of randomisation (FFS) and time from randomisation to death from any cause (OS) were examined with the Kaplan–Meier product limit method [17], and treatment arms compared with the log-rank test [18]. Continuous variables such as QoL parameter and age were compared using the Mann–Whitney U test. Analyses were performed on an intention-to-treat (ITT) basis.

Multivariate logistic regression was similarly used to determine factors predictive of response. Multivariate Cox regression analysis stratified by treatment centre was used to identify prognostic groups that influenced FFS and OS. Factors included in these analyses were treatment arm, age, gender, site of tumour, the presence of locally advanced or metastatic disease and PS in addition to biochemical factors such as tumour markers, serum albumin, bilirubin, alanine transferase (ALT), alkaline phosphatase, sodium, urea, creatinine and lactate dehydrogenase (LDH) which were

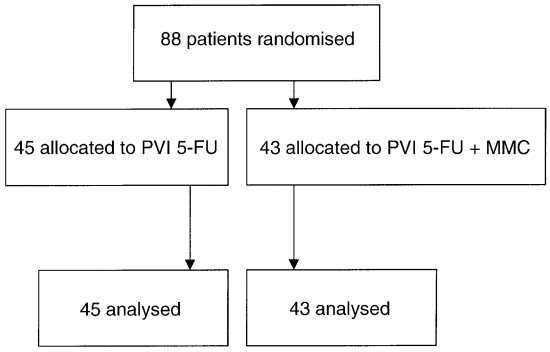

Fig. 1. Trial profile. PV1 5-FU, protracted venous infusion 5-fluorouracil; MMC, mitomycin C.

considered as continuous variables. P values of less than 0.05 were considered statistically significant.

3. Results

88 patients were randomised between September 1994 and September 2000. The treatment groups were well matched for baseline characteristics (Table 1). 69% of patients had a PS of 0 or 1 and 80% of patients had two or less metastatic sites of disease with the majority having hepatic involvement (58%). There were 14 patients with peritoneum/omentum only disease, of whom 10 were men and 4 were women. Retrospectively, on progression of disease, one patient was found to have a pancreatic primary carcinoma (5-FU alone arm) whilst another patient was withdrawn after 17 weeks of treatment due to evidence of a primary lung carcinoma (5-FU and MMC arm). The mean duration of chemotherapy was 13 and 12 weeks for the 5-FU and combination arms, respectively ($P = 0.12$). Median dose intensity of prescribed chemotherapy was 80.0 (range

Table 1
Patient demographics

Characteristic		PVI 5-FU ($n = 45$) n (%)	PVI 5-FU + MMC ($n = 43$) n (%)	P value
Age (years)				
Median (range)		56 (24–83)	59 (27–78)	0.95
Gender				
Male		28 (62)	20 (47)	0.14
Female		17 (38)	23 (53)	
Performance status				
0		2 (4)	8 (19)	0.40
1		31 (69)	20 (47)	
2		12 (27)	15 (35)	
Histology				
Carcinoma		20 (44)	12 (28)	0.74
WDA		1 (2)	0	
MDA		14 (31)	18 (42)	
PDA		9 (20)	12 (28)	
Undifferentiated		1 (2)	1 (2)	
Treatment centre				
Royal Marsden Hospital		34 (76)	32 (74)	0.90
Other		11 (24)	11 (26)	
Number of known metastatic sites				
1		22 (49)	26 (60)	0.60
2		12 (27)	10 (23)	
>2		10 (22)	7 (16)	
Unknown		1 (2)	0	
Sites involved				
Liver		30 (67)	21 (49)	0.09
Lung		10 (22)	6 (14)	0.41
Peritoneum		15 (33)	16 (37)	0.70
Lymph node		10 (22)	13 (30)	0.39
Bone		2 (4)	2 (5)	1.00
Bone marrow		1 (2)	0	1.00
Raised tumour markers				
CEA	Normal	29 (67)	21 (57)	0.33
	Elevated	11 (33)	16 (43)	
CA125	Normal	4 (25)	4 (15)	0.44
	Elevated	12 (75)	23 (85)	
CA19-9	Normal	9 (36)	11 (41)	0.73
	Elevated	16 (64)	16 (59)	
AFP	Normal	22 (92)	24 (92)	1.00
	Elevated	2 (8)	2 (8)	

CEA, carcinoembryonic antigen; AFP, alphafetoprotein; 5-FU, 5-fluorouracil; MMC, mitomycin C; PVI, protracted venous infusion; WDA, well differentiated adenocarcinoma; MDA, moderately differentiated adencarcinoma; PDA, poorly differentiated adenocarcinoma.

18–100) and 85.7% (range 14–100) in patients receiving 5-FU and the combination, respectively ($P=0.45$). Treatment interruptions occurred in 68.9% of patients receiving 5-FU alone compared with 53.5% of patients receiving 5-FU and MMC ($P=0.10$).

3.1. Tumour response

Five patients were non-evaluable for response and were not included in the response analysis. Overall response rate (RR) was 11.6 (95% Confidence Interval (CI) 3.9–25.1%) in the 5-FU alone arm compared with 20.0% (95% CI 9.1–35.6%) in the combination arm ($P=0.294$) (Table 2). On univariate logistic regression analysis, female sex ($P=0.018$) and bilirubin ($P=0.043$) predicted for response, although there was no significant prognostic variable for overall response on multivariate analysis. The treatment arm did not predict for response.

3.2. Failure-free survival

At the time of analysis, 95% of patients had died. 8 patients died within the first 6 weeks of treatment from progressive disease. With a median follow-up of 23 months, median FFS was 126 days (95% CI, 69–182 days) (4.1 months) in the 5-FU treatment arm and 92 days (95% CI, 82–100 days) (3.0 months) in the combination arm (Hazard Ratio (HR) 0.94 (95% CI 0.62–1.43), $P=0.78$) (Fig. 2). One-year FFS was 2.2% (95% CI 0.2–10.1%) for 5-FU and 9.3% (95% CI 3.0–20.1%) for 5-FU and MMC. Univariate Cox regression analysis demonstrated that a PS of $\geqslant 1$, lack of response to treatment, younger age, low albumin and sodium and raised ALT and βHCG predicted for a poor FFS. On multivariate analysis, PS $\geqslant 1$ (HR 2.10 (95% CI 1.22–3.65), $P=0.008$) and younger age (HR 0.98 (95% CI 0.96–1.00), $P=0.5$) predicted for a poor FFS.

Table 2
Response to treatment

Total	PVI 5-FU ($n=45$) *n* (%)	PVI 5-FU + MMC ($n=43$) *n* (%)	*P* value
Response rate (RR)			
Overall response (95% CI)	11.6 (3.9–25.1)	20.0 (9.1–35.6)	0.294
Total evaluable for response	43	40	
CR	0	1 (3)	
PR	5 (12)	7 (18)	
SD	14 (33)	8 (20)	
PD	20 (47)	16 (40)	
Died	1 (2)	6 (15)	
No Follow-up	3 (7)	2 (5)	
NE[a]	2	3	
Response by site-evaluable patients			
Liver			
CR			0.400
PR	3 (10)	4 (22)	
PD	27 (90)		
No disease	15		
Lung			
CR	0	0	–
PR	0	0	
PD	10 (100)		
Non-evaluable	1		
No disease	34		
Lymph node			
CR	0	0	0.999
PR	1 (10)	2 (17)	
PD	9 (90)	10 (83)	
No disease	35	31	
Peritoneum/omentum			
CR	0	2 (15)	0.220
PR	0	1 (8)	
PD	12 (100)	10 (77)	
No disease	33	30	

95% CI, 95% Confidence Interval; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease.
[a] Non-evaluable (NE) patients were not included in RR evaluation.

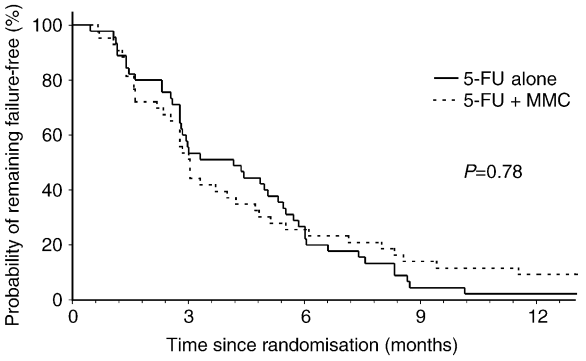

Fig. 2. Failure-free survival.

3.3. Overall survival

Treatment with 5-FU plus MMC resulted in no significant improvement in OS. Median OS was 202 days (95% CI, 86–317) (6.6 months) and 143 days (95% CI, 77–209) (4.7 months) for the combination (HR 1.12 (95%CI 0.73–1.72), $P=0.60$) (Fig. 3). One year survival was 28.0% (95% CI 15.7–41.6%) and 20.9% (95% CI 10.4–34.0%) for 5-FU and 5-FU plus MMC, respectively ($P=0.60$). Univariate Cox regression analysis demonstrated that treatment centre, PS of >1, lack of response to treatment, raised CA19-9, CEA, βHCG, AFP and urea and low albumin and sodium predicted for a poor OS. On multivariate analysis, after stratification for centre, an increase in ALT (HR 1.022 (95% CI 1.01–1.04), $P=0.001$) and bilirubin (HR 1.06 (95% CI 1.00–1.11), $P=0.039$) and decrease in albumin (HR 0.90 (95% CI 0.86–0.94), $P<0.001$) were poor prognostic indicators for OS. Treatment arm did not predict survival on multivariate analysis.

3.4. Symptomatic response

Weight stabilisation and improvements in pain, nausea, vomiting and anorexia were seen in the majority of patients in whom the checklist was completed prior to chemotherapy (Table 3). No improvement in lethargy or PS was seen for most patients. Improvements in PS were not significantly different between the two treatment arms, although 10 patients had a PS of zero at baseline and were therefore not included in the denominator.

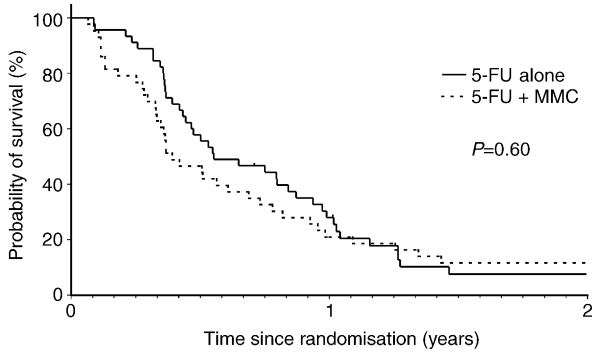

Fig. 3. Overall survival.

3.5. Toxicity

Both chemotherapy regimens were well tolerated for grade 3 and 4 toxicities (Table 4). There was no statistically significant difference between the 5-FU and 5-FU plus MMC arms. In particular, no significant difference was observed for thrombocytopenia (4 versus 7%, $P=0.68$) or anaemia (7 versus 0%, $P=0.24$). The most prevalent non-haematological toxicity was lethargy, but no difference was observed between study arms (22 versus 23% for 5-FU and 5-FU plus MMC, respectively, $P=0.60$). 4 patients developed red blood cell fragmentation in the peripheral blood film, of whom 1 was in the 5-FU arm, but no patients developed HUS in this series. There were no treatment-related deaths.

The incidence of complications from central venous catheters was low and well balanced between the arms. The most frequent complications were superficial infection (15%) and pain (7%). The incidence of serious complications was low, with thrombotic events in 2% and no pneumothoraces. Line replacement as a result of complications was required in 4 of 66 (6%) patients treated at the Royal Marsden Hospital.

Table 3
Symptom response to treatment

	5-FU *n* (%)	5-FU AND MMC *n* (%)	*P* value
Weight loss	25/28 (89)	14/19 (74)	0.241
Pain	20/33 (61)	14/27 (52)	0.496
Nausea	11/14 (79)	6/8 (75)	0.999
Vomiting	6/8 (75)	1/1 (100)	0.999
Anorexia	15/21 (71)	10/15 (67)	0.999
Lethargy	8/29 (28)	10/25 (40)	0.335
Improved PS	6/43 (14)	6/35 (17)	0.700

PS, Performance Status.

Table 4
Grade 3 or 4 toxicities

Toxicity	5-FU ($n=45$) *n* (%)	5-FU + MMC ($n=43$) *n* (%)	*P* value
Anaemia	3 (7)	0 (0)	0.24
Neutropenia	0 (0)	2 (5)	0.22
Thrombocytopenia	2 (4)	3 (7)	0.68
Diarrhoea	1 (2)	1 (2)	1.00
Stomatitis	2 (4)	4 (9)	0.41
Nausea/vomiting	0 (0)	3 (7)	0.10
PPE	1 (2)	3 (7)	0.33
Lethargy	10 (22)	10 (23)	0.60
Infection	2 (4)	1 (2)	1.00

PPE, palmar-plantar erythrodysesthesia.

3.6. Quality of life

Although 60 patients (68%) completed QoL forms at baseline (29 treated with 5-FU alone and 31 in the combination arm), only 23 patients (26%) completed QoL forms at 12 weeks. There was no significant difference between the treatment arms for any of the parameters at baseline or at 12 weeks.

3.7. Second-line therapy and response

27 patients in this series received second-line chemotherapy after progression, 17 in the 5-FU alone arm and 10 in the combination arm. 5 patients in the 5-FU alone arm received third-line chemotherapy. Of the patients initially treated with 5-FU alone, 11 received additional MMC as second-line treatment, 8 received a platinum agent (cisplatin or carboplatin), 2 received 5-FU alone and 1 received an anthracycline. Of the patients initially treated with 5-FU and MMC, 6 received a platinum agent, 2 received 5-FU alone, 1 received irinotecan and 1 received raltitrexed. There was one partial response in each initial treatment arm with second-line chemotherapy. None of the 5 patients who received third-line chemotherapy responded.

4. Discussion

This prospective, randomised trial set out to evaluate the efficacy and toxicity of PVI 5-FU with or without MMC in CUP as a component of a stratified study designed to investigate the combination compared with PVI 5-FU alone in advanced gastrointestinal cancer. In the previously reported studies, the addition of MMC did not result in improvements in OS for oesophagogastric, pancreatic and colorectal carcinomas, although an improvement in RR in the pancreas cohort and RR and FFS was seen in the colorectal cohort [11–13].

In this study in patients with CUP, poor prognostic features such as male gender, hepatic involvement and number of metastatic sites were well balanced between the treatment arms and were similar to those seen in phase II studies [5,19–21]. All patients had CT scans performed in an attempt to identify the primary tumour whilst upper and lower gastrointestinal endoscopies were performed if indicated, as recommended [22].

As a result of poor accrual, our study was closed prematurely and, therefore, the power to detect a difference between the two treatment arms was insufficient. Although response rates were low, PVI 5-FU achieved palliation of symptoms, with the exception of lethargy, in most patients and was associated with a modest toxicity profile. In addition, PVI 5-FU as a single agent had a median OS of 6.7 months. This is similar to results from studies of patients with CUP that employed a platinum or anthracycline agent in a combination regimen [3,23–25].

In view of the poor accrual and the availability of newer chemotherapeutic agents, the premature closure of the study was considered justified, particularly following the introduction of oral fluoropyrimidine agents [26]. Unfortunately, recent phase 2 studies that have evaluated the use of taxanes with cisplatin or carboplatin have demonstrated median survivals of only 8–11 months with grade 3–4 leucopenia in nearly 50% of patients [20,21,27]. Another phase 2 study, in which 77 patients with CUP were treated with carboplatin and paclitaxel along with granulocyte colony-stimulating factor (GCSF) support, demonstrated a median survival of 15 months in women with peritoneal carcinomatosis, 13 months for patients with predominantly nodal/pleural disease and 10 months in patients with visceral or disseminated metastases [19].

In view of the wide biological and clinical heterogeneity of CUP, it is unlikely that a single, optimum cytotoxic regimen will be identified. One study involving patients with CUP determined a therapeutic strategy prospectively according to histological differentiation of the tumour; patients with poorly differentiated carcinoma were treated with cisplatin and etoposide whilst patients with well/moderately differentiated carcinoma received cisplatin, continuous infusion 5-FU and α-interferon, achieving median survivals of 9.4 and 16.1 months, respectively [5]. However, future progress in the treatment of CUP may be made with therapeutic approaches based on translational studies. Recently, cDNA microarray technology has been shown to classify certain malignancies more accurately than histopathological and other molecular techniques [28,29]. In the future, it may be possible to determine the sequence of genetic events that are induced during carcinogenesis which support metastatic, but not local growth, by studying the biology of tumours from patients with CUP.

Until the time that rational treatment strategies can be made for an individual patient according to translational data, it is necessary to continue to evaluate chemotherapy regimens that may improve survival with minimal toxicity in this cohort of patients. This should be performed within the context of randomised clinical trials to assess further promising chemotherapy regimens. To date, no randomised trials have included a BSC arm in the treatment of patients with CUP. As this is unlikely to be acceptable to patients, we suggest that in the future, due to the heterogeneity of CUP, multicentre randomised trials should be performed with the inclusion of a well-tolerated, outpatient-based chemotherapy arm and that QoL and toxicity data are evaluated. We consider that continuous 5-FU may be a suitable reference regimen in randomised trials with newer chemotherapy agents for patients with CUP.

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