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A randomised phase II trial of weekly high-dose 5-fluorouracil with and without folinic acid and cisplatin in patients with advanced biliary tract carcinoma: results of the 40955 EORTC trial

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Abstract

Previous small phase II trials have demonstrated that the combination of 5-fluorouracil (5FU) and cisplatin(CDDP) could have clinical activity in metastatic biliary tract cancer. This randomised phase II trial was designed to assess the activity and safety of a high-dose infusional weekly 5FU alone (HDFU) and the combination of 5FU, folinic acid (FA) and CDDP. Patients were included if they had histologically proven locally advanced or metastatic biliary tract carcinoma, World Health Organisation (WHO) performance status $\leqslant 2$, bilirubin $<2 \times$ upper normal limit, adequate haematological and renal functions and had not received prior chemotherapy, even in the adjuvant setting. Treatments: Arm A (HDFU) consisted of cycles of 5FU 3 g/m^2 intravenously (i.v.), 24 h infusion, weekly, for 6 weeks, followed by 1 week rest, every 7 weeks; Arm B (5FU + FA + CDDP) consisted of cycles of 5FU 2.0 g/m^2 i.v. with folinic acid 500 mg/m^2, 2 h-infusion, weekly, for 6 weeks, followed by 1 week rest plus cisplatin 50 mg/m^2, once every two weeks, for 6 weeks, followed by 1 week rest, every 7 weeks. From February 1997 to June 1999, 58 patients were randomised (29 in each arm). Patients had a median age of 58 years in Arm A and 62 years in Arm B, locally advanced disease was present in 21% of the patients in Arm A and 11% in Arm B. WHO performance status of 0/1/2 was noted in 48%/45%/7% of the patients in Arm A and 54%/43%/4% in Arm B. In both arms, the most common metastatic sites were the liver and peritoneum. Twenty-eight patients were eligible in each arm and one patient did not start the allocated therapy in Arm B. The median number of cycles was 2 [range 1–12] in Arm A and 2 [range 1–6] in Arm B. Responses for the eligible patients who started their allocated therapy were as follows: Complete Response (CR) 0% in Arm A, 4% in Arm B, Partial Response (PR) 7% in Arm A, 15% in Arm B resulting in an overall response rate [95% CI] of 7.1% in Arm A [0.9–23.5%] and 19% [6.3–38.1%] in Arm B. Disease stabilisation was observed in 46% in Arm A and 44% in Arm B. National Cancer Institute of Canada (NCIC) grade 3–4 adverse events (% of patients in Arm A/Arm B) were neutropenia 4%/26%, thrombopenia 0%/7%, stomatitis 0%/4%, vomiting 7%/14%, diarrhoea 0%/11% and neurotoxicity 4%/0%. There was one early toxic death in Arm B. The median overall survival (OS) [95% CI] was in Arm A/Arm B: 5.0 [4.0–7.4] months/8.0 [5.8–11.8] months and the median progression-free survival (PFS) was 3.3 [1.7–4.7] months/3.3 [2.3–6.7] months. Cisplatin in combination with 5FU + FA showed a higher activity than HDFU, but was more toxic. These results are not sufficient to start a phase III

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trial. However, our group is planning a phase III trial comparing 5FU + folinic acid versus the same schedule + oxaliplatin a platinum analogue.

Keywords: Biliary tract carcinoma; Survival; Toxicity; Phase II; 5-Fluorouracil; Cisplatin

1. Introduction

Carcinoma of the biliary tract is a rare disease, accounting for less than 1% of cancer deaths in Western countries every year. Because of the lack of early symptoms, most patients present with metastases or invasion of the tumour directly into the adjacent liver or the hepatic artery and thus are not candidates for surgical resection. The prognosis of these patients is extremely poor, and the impact of existing chemotherapy is virtually negligible. There have been only a few well-designed chemotherapeutic trials conducted in a sufficient number of patients with advanced biliary tract cancer. A few responses have been reported with 5-fluorouracil (5FU) and mitomycin C (MMC) [1]. However, a previous phase II trial conducted by our group has reported only three objective responses in 30 evaluable patients treated with MMC alone [2]. A randomised 3-arm phase II study including less than 40 patients in each arm has concluded that combination chemotherapy with 5FU + steptozotocin or 5FU + methyl-CCNU was not superior to 5FU alone [3]. However, due to the small number of patients, the negative results of this trial cannot be considered conclusive. Another randomised trial has compared 5FU alone and the FAM regimen (5FU + doxorubicin + MMC); it concluded that combination chemotherapy was feasible, but cannot be recommended [4]. Thus, for patients with advanced gallbladder or bile duct cancer, no chemotherapy regimen seems to be of sufficient value to justify its use in clinical practice. Therefore, there is a need for new, effective chemotherapeutic regimens in the management of biliary tract cancer.

Cisplatin (CDDP) has not shown any activity in metastatic biliary tract cancer [5]. However, we have reported a 30% response rate in such patients when using the combination of continuous infusion 5FU and CDDP [6]. Recently, less toxic schedules of 5FU plus CDDP have been described. Among them, 5FU plus folinic acid (FA) plus CDDP seems to be the most promising [7]. This therapy has already been tested in a randomised phase III study by the European Organisation for the Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Cooperative Group in advanced gastric cancer. By contrast, weekly 5FU has shown good results in colorectal and gastric cancers, without major toxicity [8]. This new schedule seems to optimise the administration of 5FU in terms of dose/intensity and should logically be used for the second arm. The aim of this randomised phase II clinical study was to investigate the therapeutic activity of a combination of weekly high-dose 5FU plus folinic acid plus biweekly CDDP and the activity of weekly high-dose 5FU alone.

2. Patients and methods

2.1. Patients

Patient selection criteria were: histologically proven locally advanced or metastatic biliary tract cancer (gallbladder cancer, cancer of the extra-hepatic bile duct, intra-hepatic cholangiocarcinoma and ampullary carcinoma), the presence of at least one bidimensionally measurable target lesion according to the criteria described in the section on response evaluation, World Health Organisation (WHO) performance status (PS) 0–2, bilirubin $<2\times$ upper limit of normal (in case of jaundice, a satisfactory biliary drainage had to be done before the inclusion of the patient), no cardiac or pulmonary insufficiency, no prior chemotherapy even in adjuvant setting, no prior radiotherapy to the tumour site chosen for evaluation, absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule. Informed consent was obtained and documented according to national and local regulatory requirements and the local rules followed in the institution. Other exclusion criteria were: pre-treatment granulocyte count $<2\times10^9$/l and pre-treatment platelet count $<100\times10^9$/l, Central Nervous System (CNS) metastases, renal insufficiency (serum creatinine >120 μmol/l or creatinine clearance <1 ml/s), pregnancy, active infection, history of other malignant disease <10 years ago except Carcinoma *in situ* (CIS) of the cervix or non-melanoma skin cancer.

2.2. Protocol treatment

Eligible patients were randomised to receive 5FU alone (HDFU) or in combination with cisplatin and folinic acid (5FU + FA + CDDP). In the HDFU arm, patients received cycles of 7 weeks of weekly 24-h infusion of 3.0 g/m^2 of 5FU for 6 weeks (days 1, 8, 15, 22, 29, 36) followed by a weeks rest. In the other arm, they received cycles of 7 weeks of weekly infusion of 500 mg/m^2 of folinic acid followed by a 24-h infusion of 2.0 g/m^2 of 5FU for 6 weeks (days 1, 8, 15, 22, 29, 36) followed by a weeks rest plus cisplatin 50 mg/m^2 every 2 weeks (day

1, 15, 29) for 6 weeks, followed by a weeks rest. Evaluation was done every 7 weeks until documented progression, and the treatment side-effects were assessed separately for each cycle of therapy.

2.3. Statistics

The two-stage Simon Design was used in each arm separately. In the first step, 15 patients per arm (i.e. total of 30 patients) were needed to assure with 95% power and a type I error of 10% that if the true response rate is less than 10%, the investigations were stopped at this stage. In each arm, if at least two responses were observed then 9 more patients (i.e. a total of 18 patients) were registered. With the same power, the same type I error and the assumption of a true response rate of 35%, to observe five responses out of 24 patients should prompt the recommendation to further investigate the regimen in the phase III setting.

The toxicity of the protocol treatment was evaluated using the National Cancer Institute of Canada (NCIC)-Common Toxicity Criteria. At the end of every cycle, the anti-tumour activity of the treatments was assessed using WHO response criteria. The response rate and its associated 95% Confidence Intervals (95% CI) was calculated by pooling the Complete (CR) and Partial (PR) Responders. Progression-free survival (PFS) was defined as the time interval between the date of randomisation and the date of progression or death, whatever occurs first. If neither progression nor death were observed then the patient was censored at the date last seen alive. Overall survival (OS) was measured until the date of death or last follow-up. Duration of response was measured for the CRs and PRs from the date of observation of the response until the first sign of radiological progression of disease or last follow-up. OS and PFS were estimated by the Kaplan–Meier method. All analyses were restricted to patients who started the allocated treatment. Efficacy analyses were further restricted to eligible patients only.

3. Results

3.1. Patients characteristics

Fifty-eight patients with biliary tract carcinoma from 10 institutions were treated in this randomised phase II trial. Two patients were ineligible. One had a too small target lesion at entry and the other one a too high bilirubin value. A patient randomised in the combination arm did not receive the folinic acid and cisplatin drugs. He was reported separately and excluded from all tables and analyses to avoid selection bias. He progressed during the administration of the first cycle with 5FU alone and died from progression of the disease and/or toxicity (general malaise, no appetite, fatigue). The main patient's characteristics at study entry are listed in Table 1. Median age was 58 and 62 years in the HDFU and 5FU + FA + CDDP arms, respectively. The PS distributions 0/1/2 were 48%/45%/7% in the HDFU arm and 54%/43%/4% in the combination arm. Metastatic disease was present in 79% and 89% of the patients in the HDFU and combination groups, respectively. In the HDFU and the 5FU/FA/CDDP arms, 48% and 54%, respec-

Table 1
Patient demographics and disease characteristics

	HDFU	5FU + FA + CDDP
	$n = 29$	$n = 28$
Median age	58	62
Gender (M/F)	52%/48%	57%/43%
General status WHO 0/1/2	48%/45%/7%	54%/43%/4%
Extension of disease		
Locally advanced	21%	11%
Metastatic disease	79%	89%
Sites of metastases (not exclusive categories)		
Liver	69%	75%
Peritoneum	24%	21%
Differentiation grade		
Well differentiated	14%	14%
Moderately differentiated	28%	18%
Poorly differentiated	24%	21%
Undifferentiated	3%	0%
Unknown	31%	46%
Main presenting symptoms (not exclusive categories)	($n = 26$)	($n = 22$)
Icterus	35%	14%
Pain	42%	55%
Weight loss	10%	0%
Anorexia	0%	11%

M, male; F, female; WHO, World Health Organisation; HDFU, high-dose 5-fluorouracil; 5-FU + FA + CDDP, 5-fluorouracil + fluoricacid + cisplatin.

Table 2
Patients with grade 3 and 4 adverse reactions related to treatment

G 3–4 toxicity	HDFU (%) $n = 29$	5FU + FA + CDDP (%) $n = 28$
Anaemia	0	11
Neutropenia	4	26[a]
Thrombopenia	0	7
Nausea	10	4
Diarrhoea	0	11
Vomiting	7	14
Mucositis	0	4
Toxic deaths[b]	0	7

[a] Grade 3 neutropenia: 22%, only one patient had grade 4 neutropenia.

[b] A patient randomised in the combination arm did not receive FA + CDDP. He was reported separately and excluded from all of the Tables and analyses to avoid selection bias. He progressed during the administration of the first cycle of HDFU and died from progression of the disease and/or toxicity (general malaise, no appetite, fatigue).

Table 3
Response and survival rates

	HDFU $n = 28$	5FU + FA + CDDP $n = 27$
Complete response	0%	4%
Partial response	7%	15%
Objective response rate [95% CI]	7.1 [0.9–23.5]	18.5 [6.3–38.1]
Overall median survival [95% CI]	5.0 [4.0–7.4]	8.0 [5.8–11.8]
Median Progression-free survival [95% CI]	3.3 [1.7–4.7]	3.3 [2.3–6.7]

95% CI, 95% Confidence Interval.

tively, underwent a prior surgical procedure, 45% and 25% had a prior endoscopic drainage, and 7% and 4% received prior radiotherapy.

3.2. Treatment

The median number of cycles [range] was 2 [1–12] in the HDFU arm and 2 [1–6] in the 5FU + FA + CDDP arm. Thirty nine percent of the patients received only 1 cycle in the combination arm and 48% in the HDFU arm in which two patients received more than 6 cycles. Thirty one per cent of the patients in the HDFU arm and 25% in the combination arm received less than 70% of the theoretical dose. In the 5FU + FA + CDDP arm, all drugs in the same administration were reduced or delayed. Globally, one patient in two had a dose reduction in at least one cycle. This was mainly due to toxicity in 43% of cases in the HDFU arm and 79% in the combination arm. For the same reason, delays occurred in 45% of the patients in the HDFU arm and 68% in the combination arm.

The main toxicity was severe leucopenia which was observed in 4% and 10% of the patients in HDFU and 5FU + FA + CDDP arms, respectively. As shown in Table 2, the 5FU + FA + CDDP arm resulted in slightly more toxicities, mainly in terms of neutropenia, thrombopenia, anaemia, diarrhoea and vomiting. Grade 2 neurosensory toxicity was observed in 11% of the patients treated with cisplatin and for 3% in the other arm. Similarly, 29% in the combination arm had other grade 2–3 neurological toxicities and this was observed for 3% in the HDFU arm. Surprisingly, the rate of grade 2–3 alopecia was 14% in the HDFU arm and 7% in the 5FU + FA + CDDP group. One patient in the HDFU arm had cardiovascular ischaemia during the first cycle which prevented any further administration of HDFU.

The major reason for protocol discontinuation was progression of the disease, determined either radiologically or clinically. Six patients had to stop treatment due to toxicity, including one toxic death in the 5FU + FA + CDDP group. Among these six patients, five received the combined treatment, the other patient in the HDFU arm had cardiac ischaemia during the first cycle of treatment.

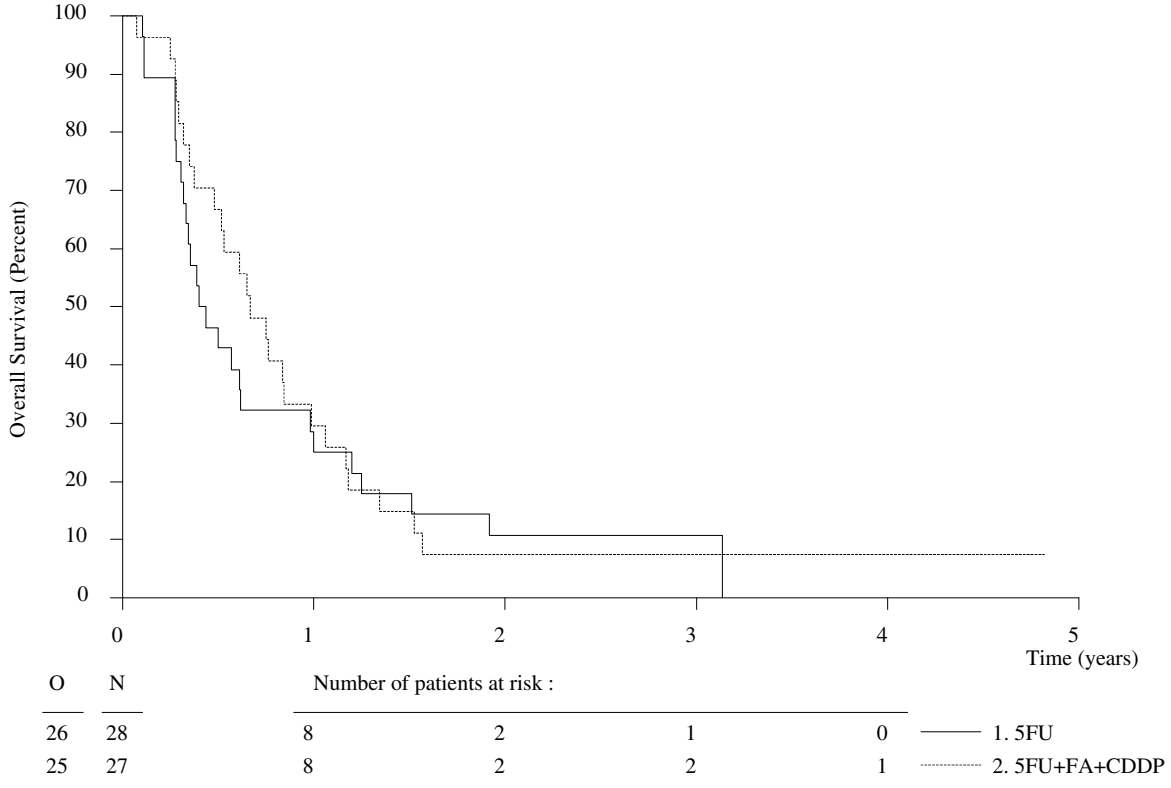

Fig. 1. Overall survival: O, observed; N, number; 5Fu, 5-Fluorouracil; FA, folinic acid; CDDP, cisplatin.

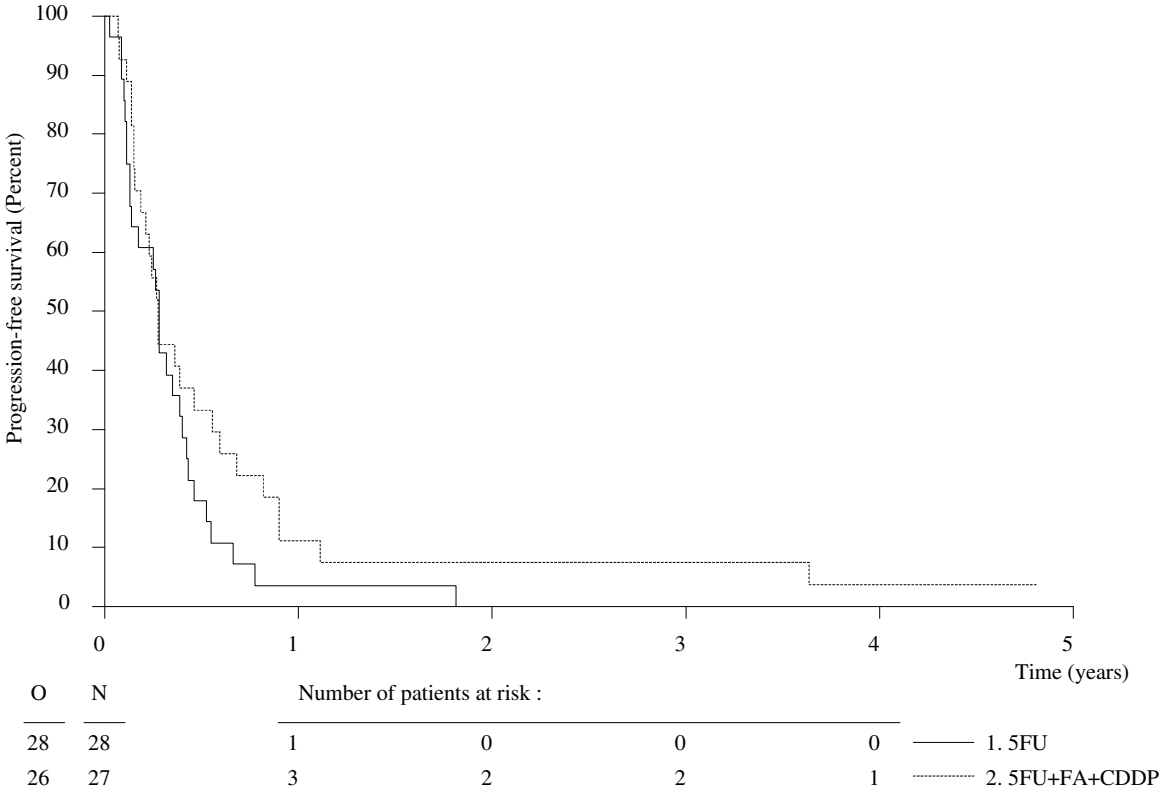

Fig. 2. Progression-free survival.

3.3. Response

As given in Table 3, one CR was observed in 5FU + FA + CDDP arm and none in the HDFU group. PRs were observed in two and four patients in the HDFU and 5FU + FA + CDDP groups, respectively. The objective response rates [95% CI] were 7.1 [0.9–23.5]% in the HDFU arm and 18.5 [6.3–38.1]% in the 5FU + FA + CDDP arm.

3.4. Survival

The overall median survival [95% CI] was 5.0 [4.0–7.4] months in the HDFU arm and 8.0 [5.8–11.8] months in the 5FU + FA + CDDP arm (Fig. 1). Progression-free survival [95% CI] was 3.3 [1.7–4.7] months in the HDFU arm and 3.3 [2.3–6.7] months in the 5FU + FA + CDDP arm (Fig. 2). The main cause of death was disease progression.

4. Discussion

This trial is the first randomised study evaluating a combination chemotherapy with platinum analogues for treatment of biliary tract cancer. In this study, the combination chemotherapy gave results in the same range (18% objective response rate) as those previously reported in one arm phase II trials (24–34%) [6,9]. As shown in numerous phase III trials, including those with colorectal cancer patients, weekly infusional schedules give similar results to biweekly regimens [10,11].

However, the benefit observed in terms of response rate in the 5FU and cisplatin arm seems to be partially hampered by its associated higher toxicity. Very similar results have been reported with the use of combined chemotherapy in pancreatic carcinoma. In fact, a randomised phase III trial including 204 patients with pancreatic carcinoma failed to show a clear benefit in favour of the combination of 5FU and cisplatin versus 5FU alone [12]. This problem of toxicity with cisplatin treatment seems very difficult to solve since in this trial we used an infusional schedule of 5FU and fractionated administration of cisplatin (50 mg/m^2 every two weeks) which seems to be one of the least toxic ways to administer this combination [7].

Only a few new drugs have been tested in biliary tract carcinoma and this cancer could be considered as an "orphan" disease. The first drug tested was paclitaxel and gave very disappointing results, with no objective responses being observed in a phase II study including 15 patients [13]. One of the most promising agents tested is gemcitabine, with 17–36% objective response rates being reported in different phase II trials including more than 20 patients [14,15]. Despite encouraging results in a phase II study with a 53% objective response rate in 30 patients with biliary tract carcinoma [16], the combina-

tion of gemcitabine and cisplatin gave disappointing results in a recent phase III trial involving pancreatic carcinoma patients [17] and seems not to have been considered in this disease. Oxaliplatin, a new platinum analogue, which plays a part in the treatment of colorectal cancer, seems to be active in this disease. However, no data evaluating the efficacy of this agent given alone in the first-line setting are available. It has been reported that the combination of gemcitabine and oxaliplatin resulted in a 29% objective response rate in 31 patients [18].

Even when considering the favourable results of gemcitabine in this disease and the fact that it has been considered to be superior to 5FU in monotherapy for pancreatic carcinoma [19], 5FU nevertheless is likely to remain a key drug in the treatment of biliary tract cancer. The first reason for this is that a comparison of gemcitabine and 5FU in pancreatic carcinoma has been made using a toxic and less active bolus schedule of 5FU than those that are currently used in the treatment of colorectal metastatic carcinoma. The second reason is that the modulation of infusional 5FU with folinic acid has been shown to increase the activity of the schedule and this type of treatment has never been clearly compared with gemcitabine in patients with carcinoma of the pancreas and/or biliary tract. Furthermore, the combination of folinic acid plus 5FU remains a 'standard of care' in metastatic biliary tract cancer, since it has been shown to increase the survival of patients when compared with best supportive care [20]. The advantage, in terms of survival, was non-significant, but was similar to that observed in the whole group of mixed pancreatic and biliary tract carcinomas.

In conclusion, 5FU plus cisplatin gave interesting results in this randomised phase II trial, but also increased the occurrence of severe side-effects in patients with a poor life-expectancy. Thus, we do not propose a further evaluation of this combination in a randomised phase III trial, but suggest new combination drugs, such as 5FU plus oxaliplatin should be evaluated in this disease.

Conflict of interest statement

None declared.

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