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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