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Cetuximab, gemcitabine and capecitabine in patients with inoperable biliary tract cancer: A phase 2 study

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Abstract ***Purpose:*** Biliary tract cancer is rare and has dismal prognosis. Chemotherapy has its role in inoperable disease but the role of targeted agents like cetuximab remains to be defined. On the basis of high epidermal growth factor receptor expression of biliary tract cancers this study aims to investigate the efficacy of cetuximab, gemcitabine and capecitabine in an exploratory phase 2 trial.

Patients and methods: Inoperable biliary tract cancer patients were treated with the combination of gemcitabine (1000 mg/m^2 on day 1 and 8), capecitabine (1300 mg/m^2/d on day 1–14) and weekly cetuximab (400 mg/m^2 loading and 250 mg/m^2 maintenance dose) in 21-d cycles until progression or the appearance of intolerable side-effects.

Results: Out of 34 patients (mean age 59.7 years) accrued in this study 16 had intrahepatic, eight extrahepatic cholangiocarcinoma and 10 gall bladder cancer. The best overall response rate was 17.6% (two complete responses and four partial responses) and the clinical benefit rate was 76.5%. After a median of 15.4 months follow-up the median progression free survival was 34.3 weeks and the median overall survival was 62.8 weeks. The performance status and chemotherapy efficacy were independent and significant markers of survival. Only moderate side-effects were registered in this study. *KRAS* mutation was evaluable in 24 tumours, all of these were of wild type.

Conclusion: The efficacy of cetuximab, gemcitabine and capecitabine combination is encouraging and a well tolerated treatment of inoperable biliary tract cancers.

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1. Introduction

Biliary tract cancer is a rare disease with poor prognosis. Its incidence is increasing, accounting for 3% of all gastrointestinal tumours [1], but regional differences are well described [2,3]. The incidence of the disease in Hungary is 13 cases per 100,000 inhabitants. The diagnosis of biliary tract cancer is usually made between ages 50 and 70. The only curative treatment is surgery, although even after complete resection or transplantation the cancer often recurs with the probability of a 5 year survival of about 15% [4,5]. Locoregional approaches, like chemoembolization, show promising results, although in metastatic disease this modality is not feasible [6–8]. In cases where systemic chemotherapy is the only therapeutic choice the expected survival is short (rarely exceeds 12 months) [1,9,10]. The basic compound of palliative chemotherapy is gemcitabine with a response rate of 5–30% when used alone [11]. Its combination with other agents may have a superior effect. On the grounds of the results of two randomised trials comparing gemcitabine versus gemcitabine plus cisplatin the gemcitabine and cisplatin combination is the current standard chemotherapeutic treatment [12,13]. However, the fluoropyrimidines, like capecitebine also have clinical activity, both as monotherapy or combined with gemcitabine [9,14,15], without such severe side-effects such as neuropathy.

Cetuximab is a monoclonal antibody targeting epidermal growth factor receptor (EGFR) with proven clinical efficacy in head and neck and colorectal cancers. Biliary tract cancers are predominantly EGFR positive by immunohistochemistry and dysfunction in the EGFR-RAS-RAF-MEK signal transduction pathway has an important role in carcinogenesis [11]. This makes biliary tract cancer a potential target to cetuximab. In three clinical trials (one of them a randomised phase 2) cetuximab combined with gemcitabine and oxaliplatin proved to have clinical activity in the biliary tract cancer [1,16,17].

On the basis of high EGFR expression in biliary tract cancers we launched an exploratory phase 2 trial in 2009 with cetuximab, gemcitabine and capecitabine. As far as we know there is no published trial with this combination.

2. Patients and methods

In this explorative single centre study 34 patients with histologically confirmed unresectable biliary tract cancer have been recruited from July 2009 to March 2012. The protocol has been approved by the Medical Research Council of the Ethics Committee for Clinical Pharmacology, the National Institute of Pharmacy and the Local Ethics Committee and registered at the European Medicines Agency (EMEA) (EudraCT No. 2006-001694-23). Patients were informed in detail before they gave consent. Patients were eligible if the tumour was inoperable and the loco-regional therapy was not a choice. Previous surgery and chemotherapy other than gemcitabine and capecitabine were allowed, previous cetuximab therapy was an exclusion criterion. All participants had to have measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST) 1.0, preserved performance status (Eastern Clinical Oncology Group (ECOG) 0-2), sufficient cardiac (New York Heart Association (NYHA) Functional Classification 0-1), hepatic (aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leqslant 5\times$ upper limit of normal (ULN)) and renal function (creatinin $\leqslant 2\times$ ULN), ability to swallow and absorb oral medication. Patients must have had adequate bone marrow reserve (Absolute neutrophil count (ANC) $\geqslant$ 1.5 G/l, platelets $\geqslant$ 100 G/l). Stent implantation was allowed before recruitment, but during the treatment phase it was considered as progression. The EGFR positive status was confirmed by immunohistochemistry (Ventana confirm 3C6) before entering the study. *KRAS* mutation status (exon 2, codons 12 and 13) was analysed prospectively only from May 2010 and retrospectively only if suitable paraffin embedded blocks were available. After whole genome amplification and real-time polynerase chain reaction (PCR), melting-point analysis was performed with positive and negative controls. The *KRAS* status of all patients was evaluated with the same method in the same accredited laboratory.

2.1. Study design

This was a phase 2a, open-label, investigator initiated, single-centre trial. We planned first interim analysis after enroling at least 30 patients on the basis of a previous calculation [1].

Patients received gemcitabine 1000 mg/m^2 i.v. on day 1 and 8 over 60–90 min, followed by a 1 week rest. Capecitabine was administered at a dose of 1300 mg/m^2 every day on days 1–14. Capecitabine daily dose had been rounded down to a dose maintained with 500 mg tablets. The capecitabine daily dose was divided into two doses and given in 12-h intervals. Cycle duration was 21 d. Cetuximab was administered every week with a dose of 250 mg/m^2 daily after a loading dose of 400 mg/m^2. Patients were monitored for toxicity weekly by the treating physician and laboratory tests were performed before every chemotherapy administration. In the case of grade 3 or 4 side-effects either dose modification or temporary or permanent discontinuation of drugs was at the treating physician's discretion taking into account related guidelines. It was recommended for physicians that after grade 3 or 4 haematological or grade 3 non-haematological side-effects the dose should be reduced by 25% as the first step and by 50% as the second step. After grade 4