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Combination of gemcitabine and cetuximab in patients with advanced cholangiocarcinoma: a phase II study of the Belgian Group of Digestive Oncology

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Background: Cholangiocarcinomas are uncommon tumours with a poor prognosis, that frequently present epidermal growth factor receptor overexpression.

Methods: In a multi-centre phase II trial, patients with unresectable cholangiocarcinoma, naïve to chemotherapy, received Cetuximab (400 mg/m^2 at week 1, then 250 mg/m^2/week) and Gemcitabine (1 g/m^2 on day 1, 8 and 15 every 4 weeks). Primary end point was progression-free survival (PFS) rate at 6 months, using a Simon 2-stage design. Moreover, we assessed the impact of KRAS status and skin toxic effect on efficacy.

Results: Forty-four patients (41% locally advanced/59% metastatic) were enrolled. Median age was 61.5 years; ECOG PS was 0 (68%) or 1. Six months PFS reached 47%. Median OS was 13.5 months [95% confidence interval (CI) 9.8–31.8 months]. Nine patients (20.4%) had PR and disease-control rate was 79.5%. Grade 3/4–related toxic effects were haematological (52.2%), skin rash (13.6%) and fatigue (11.4%). KRAS mutations were found in 7 of 27 patients and had no influence on PFS. Skin toxic effect ≥grade 2 was associated with increased PFS ($P = 0.05$).

Conclusion(s): Our study met its primary end point, suggesting that Gemcitabine-Cetuximab has activity in cholangiocarcinoma. KRAS status was not associated with PFS, unlike skin toxic effect, which could be used as a surrogate marker for efficacy.

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Key words: cholangiocarcinoma, chemotherapy, gemcitabine, cetuximab, KRAS

introduction

Cholangiocarcinomas (CCK) are uncommon tumours arising as a result of neoplastic transformation of bile duct epithelial cells [1]. They can be divided into intra-hepatic tumours, hilar (klatskin) and common bile duct tumours [2]. CCK remains the second most common hepatobiliary cancer (≈5000 new cases annually in the United States) [3] and its detection rate is increasing due to a better knowledge of the disease and improved diagnosis [4]. Hilar tumour still represents the most commonn form of CCK but the intra-hepatic form is steadily increasing in incidence since the seventies [3].The only curative treatment of CCK is surgery, feasible in only 30% of patients. Furthermore, patients who undergo curative surgery experience a high recurrence rate [5]. Chemoradiation followed by liver transplantation is an option for selected patients [6]. Until recently, there was no recognized standard treatment of advanced CCK, due to a lack of consideration of this rare disease for large phase III randomized, controlled trials (RCT). The nucleoside analogue gemcitabine (Gem) has shown activity, either in monotherapy or in combination with other cytostatic drugs [7]. Recently, a phase III RCT (ABC-02) has shown that the combination cisplatin-Gem led to significant improvements in overall survival (OS) (median 11.7 versus 8.1 months, $P < 0.001$) and in progression-free survival (PFS) (median 8.0 versus 5.0 months, $P < 0.001$) versus Gem [8]. The epidermal growth factor receptor (EGFR) expression and activation is involved in many epithelial tumours' growth. EGFR is frequently overexpressed [9] and/or mutated [10] in CCKs. Mutations of KRAS and BRAF, effectors of the EGFR pathway, have also been reported [9]. Therefore, targeting EGFR is an

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attractive therapeutic approach. Cetuximab (Ctx) is a chimerized IgG1 monoclonal antibody which blocks binding of EGF and TGFα to the EGFR. A phase II trial investigating Ctx in combination with Gem and oxaliplatin (GEMOX) in CCK showed an objective response rate of 63% [11]. Recently, the randomized phase 2 BINGO trial failed to show a significant improvement of adding Ctx to the GEMOX regimen [12]. Other targeted therapies have been explored in phase II trials: the VEGF-targeting antibody bevacizumab, combined with GEMOX, led to a 7.0 months median PFS [13]; a phase III RCT failed to demonstrate the efficacy of GEMOX +/− erlotinib, an EGFR tyrosine kinase inhibitor, in CCK and gallbladder adenocarcinoma. However, a sub-analysis showed that CCK patients experienced a prolonged median PFS: 5.9 versus 3.0 months, $P = 0.049$ [14]. At the time we designed this phase II study combining Ctx and Gem in first-line treatment of advanced CCK, the ABC-02 study results were unknown; therefore, we did not assess the combination of Gem-platinum to Ctx. The primary objective of this trial was the PFS rate at 6 months; secondary objectives included OS, response rate and safety. Exploratory objectives were to assess relationship between KRAS mutational status and skin toxic effect with PFS and OS outcomes.

patients and methods

patient eligibility

All patients had a histologically or cytologically confirmed CCK, excluding gallbladder cancer, that was either unresectable or metastatic. Eligibility criteria were measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), ECOG performance status (PS) 0 or 1; estimated life expectancy ≥12 weeks; adequate liver (total bilirubin ≤2× the upper limit of normal (ULN) range); renal (serum creatinin <1.5× ULN range) and haematopoietic (Hb >9 g/dl, absolute neutrophil count >1.500/mm^3 and platelets >100 000/mm^3) functions. All patients with jaundice underwent an adequate bile duct drainage. Exclusion criteria were previous radiation therapy, therapies targeting the EGF pathway or any other systemic treatment of CCK; history of malignancy within the previous 5 years (except for adequately treated basal cell skin cancer and *in situ* cervix cancer); HIV; infectious or uncontrolled concurrent CNS diseases; cardiac diseases. Informed Consent document were signed after appropriate explanations of the study and alternate treatments.

treatment plan

The trial regimen consisted on the administration of Ctx (Erbitux®, Merck, Darmstadt), at the initial dose of 400 mg/m^2 in a 120-min i.v. infusion and further injections of 250 mg/m^2 in a 60 min i.v. infusion every 7 days followed after 1-hour rest by Gem (Gemzar®, Eli-Lilly, IN), 1000 mg/m^2, administrated in a 30-min i.v. infusion on days 1, 8 and 15 every 4 weeks, i.e., one cycle. Pre-treatment with anti-histaminic drugs and corticosteroids was required before each Ctx injection to prevent allergic reactions. Reasons for discontinuation included disease progression, unacceptable toxic effect and patient or clinician choice. Ctx was provided by Merck and Gem was provided by Eli-Lilly.

pre-treatment evaluation

Pre-treatment examinations were carried out within 5 weeks before starting treatment and included performance status (PS), physical examination, concomitant medications, biological evaluation of liver, renal and haematopoietic functions, CA 19.9 and CEA dosages, pregnancy test for women with a childbearing potential, ECG and thoraco-abdominal computerized tomography (CT)-scan [or magnetic resonance imaging (MRI)] for tumour assessment. Data regarding tumour diagnosis were also collected: date, histology and staging.

safety assessment and dose adjustments

Patients were carefully evaluated for treatment-related toxic effects according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0. The worst grade of toxic effect per patient was recorded. Patients were examined before each treatment administration for PS assessment, blood analysis and monitoring of side-effects. In cases of non-haematologic toxic effects >2, Gem was held until toxic effect ≤2 and led to a subsequent dose reduction of 75% (grade 3) or 50% (grade 4) of the initial dose. For haematologic toxic effects, Gem was held, then reduced to 75% (grade 3 neutropenia, grade 2 thrombocytopenia) and to 50% (grade 4 neutropenia, grades 3–4 thrombocytopenia). Ctx dose was held if grade 3 skin toxic effect occurred, then reduced to 200 mg/m^2 after the second occurrence and to 150 mg/m^2 after the third occurrence. If >2 consecutive infusions were withheld, or a fourth occurrence of grade 3 skin toxic effect occurred despite dose reduction, or in case of a grade 3 or 4 allergic/hypersensitivity reaction, Ctx was permanently discontinued.

disease assessment

During the study, tumour imaging (CT/MRI) was carried out every 2 months. Disease response was evaluated by RECIST (version 1.1). PFS was defined as the time from the first day of treatment to the date of objective tumour/clinical progression or death, whichever occurs first. PFS for subjects without progression at the time of analysis was censored at the date of last tumour assessment. Patients were considered to have achieved disease stabilization if at least one stable disease (SD) assessment >6 weeks after start of treatment was met. Duration of SD was calculated from first day of treatment until the criteria for disease progression is met. Disease control rate (DCR) was defined as the proportion of patients with a best overall response of CR or PR or SD achieved during treatment. Duration of response was calculated from the date of the first documented response (CR or PR) to the date of progression. OS was defined as the time from the first day of treatment to death. OS of subjects alive at the time of analysis was censored at the last date known to be alive.

KRAS mutational status assessment

Mutations in codons 12 and 13 of the KRAS gene were detected by pyrosequencing of polymerase chain reaction (PCR) products that were amplified from tumour DNA extracted from representative tumour tissue. Tumour tissue, on formalin-fixed paraffin-embedded slides, came from either fine-needle aspiration or core biopsy and resected surgical specimens.

statistical analysis

The primary end point of the trial was the proportion of patients who were progression free at 24 weeks. The number of patients required for the trial was determined according to a two-stage Simon design. Assuming an increase of PFS rate at 24 weeks, from 20% with Gem, based on available data, up to 40% with combination (type I error of 0.05 and type II error of 0.2), three patients without disease progression at 24 weeks had to be observed in the first 13 patients to allow the completion of the study, including 43 patients.

Secondary end points included OS response rate and safety profile. Median time to event end points were estimated using the Kaplan–Meier methodology. The 95% confidence interval (CI) of the median time was also estimated. For the exploratory analyses, the comparison of PFS and OS

according to skin toxic effect and KRAS mutational status groups was carried out using the log-rank test.

results

patient characteristics

A total of 44 patients from nine Belgian institutions affiliated to the Belgian Group of Digestive Oncology were enrolled over 18 months (September 2008 to January 2010). Patients (59.1% male) were age 40–86 years old (mean 61.3 years). Baseline ECOG PS was 0 (30 patients, 68.2%) and 1 (14 patients, 31.8%). Nineteen patients (43.2%) underwent prior surgery and 26 (59.1%) were metastatic at study entry. Sixty-one percent of the patients had intrahepatic CCK (Table 1).

gemcitabine and cetuximab administrations

Patients received a total of 310 cycles of treatment (mean: 7, range: 1–34 cycles per patient). Sixty-one percent of patients received between two and six cycles of study treatment. The mean treatment duration was 22.1 weeks (range: 2–149.4 weeks). For 15 patients (34.1%), Gem dose remained unchanged, while it was reduced for three patients (6.8%) and both reduced and delayed for 11 patients (25.0%). Fourteen patients (31.8%) had a Gem dose reduction and 26 patients a dose temporary interruption, both mostly due to haematological toxic effect. Ctx treatment was delayed in 7 patients (15.9%), both reduced and delayed in 3 (6.8%) and interrupted in 10 (22.7%), mainly due to dermatologic events.

toxic effect

At the time of analysis (30 June 2012), all patients had discontinued from study treatment. Reasons for discontinuation were disease progression for 34 patients (77.3%), toxic effect for 6 (13.6%), patient's request for 2 (4.5%) and investigator's decision for 2 (4.5%). All patients were assessable for toxic effect. Table 2 summarizes all adverse reactions during the trial, split by toxic effect grading. All patients reported at least one grade 1–2 adverse event (AE), while 26 patients (59.1%) had at least one grade 3–4 AE. Most frequent grades 3–4 AEs were haematologic abnormalities (52.2%), biliary tract infections (15.9%, considered to be related to study disease), skin toxic effect (13.6%) and fatigue (11.4%). There were no treatment-related deaths. Six patients (13.6%) discontinued study treatment because of toxic effect: two patients for prolonged grade 3 skin toxic effect, one for grade 4 skin toxic effect, two for haemolytic uraemic syndrome (HUS) and one for nephrotic syndrome.

Table 1. Demographic and baseline characteristics of the patients ($n = 44$)

Age (years)	
Mean (range)	61.3 (40–86)
Gender, *n* (%)	
Male	26 (59.1)
Female	18 (40.9)
ECOG performance status, *n* (%)	
0	30 (68.2)
1	14 (31.8)
Site of primary disease, *n* (%)	
Intra-hepatic bile duct	27 (61.4)
Distal bile duct	5 (11.4)
Hilar bile duct	12 (27.3)
Extent of disease, *n* (%)	
Locoregional	18 (40.9)
Metastatic	26 (59.1)
Prior surgery, *n* (%)	
Yes	19 (43.2)
No	25 (56.8)

ECOG, Eastern Cooperative Oncology Group.

efficacy and patient's outcome

Forty-three patients had a response assessment (S1, supplementary Table S1, available at *Annals of Oncology* online). Nearly 47% of the patients were progression-free at 6 months. The median PFS time was 5.8 months (95% CI 3.6–8.5 months). (Figure 1A). The median OS time (Figure 1B) was 13.5 months (95% CI 9.8–31.8 months) with 53.7% of patients alive at 1 year. At the time of analysis, eight patients (18.2%) were still alive. Nine patients achieved PR (20.4%) with a median duration of 8 months (95% CI 2–31.0 months). Among these responders, five and three patients experienced a grade 2 and 3 skin toxic effect patients, respectively. Twenty-six patients (59.1%) achieved SD with a median duration of 6.0 months

Table 2. Adverse events during treatment ($n = 44$)

	Grades 1–2, *n* (%)	Grades 3–4, *n* (%)	Any grade, *n* (%)
Any AE	44 (100.0)	26 (59.1)	44 (100.0)
Haematologic			
Anaemia	34 (77.3)	5 (11.3)	39 (88.6)
Thrombocytopenia	29 (65.9)	6 (13.6)	35 (79.5)
Neutropenia	13 (29.5)	12 (27.3)	25 (56.8)
Non-haematologic			
Skin toxic effect	31 (70.5)	6 (13.6)	37 (84.1)
Fatigue	25 (56.8)	5 (11.4)	30 (68.2)
Nausea	16 (36.4)	2 (4.5)	18 (40.9)
Vomiting	13 (29.5)	1 (2.3)	14 (31.8)
Diarrhoea	13 (29.5)	0	13 (29.5)
Anorexia	6 (13.6)	1 (2.3)	7 (15.9)
Infection			
Biliary	0	7 (15.9)	7 (15.9)
Other	2 (4.5)	1 (2.3)	3 (6.8)
Oedema	3 (6.8)	0	3 (6.8)
Stomatitis	2 (4.5)	0	2 (4.5)
Liver dysfunction	0	2 (4.5)	2 (4.5)
Allergic reaction	2 (4.5)	0	2 (4.5)
Deep venous thrombosis	1 (2.3)	1 (2.3)	2 (4.5)
Haemolytic uraemic syndrome	0	2 (4.5)	2 (4.5)
Nephrotic syndrome	0	1 (2.3)	1 (2.3)
Other	9 (20.5)	3 (6.8)	12 (27.3)

Results are expressed as the worst toxic effect per patient, using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0.

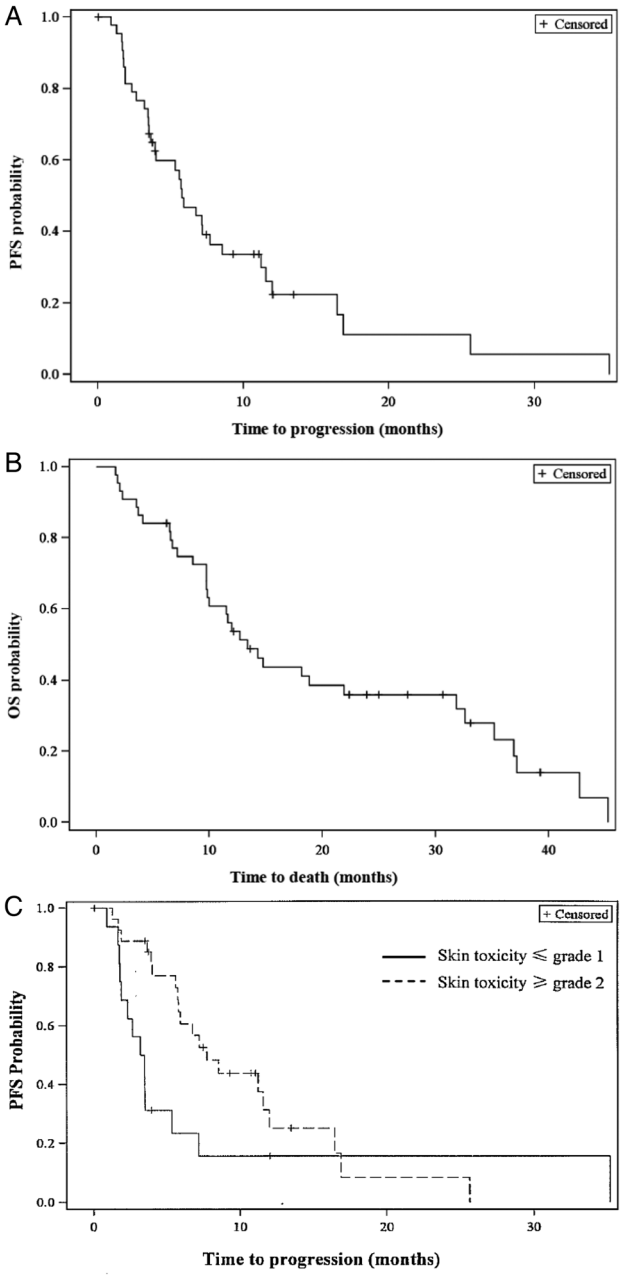

Figure 1. (**A**) Kaplan–Meier analysis for progression-free survival in the whole population. Among 44 patients, the median PFS was 5.8 months [95% confidence interval (CI) 3.6–8.5 months]. (**B**) Kaplan–Meier analysis for overall survival in the whole population. Among 44 patients, the median OS was 13.5 months (95% CI 9.8–31.8 months). (**C**) Kaplan–Meier analysis for progression-free survival according to skin toxic effect. The median PFS time was 7.7 months (95% CI 5.7–12.0 months) in patients with a skin toxic effect ≥grade 2 and 3.3 months (95% CI 1.8–5.3 months) in patients with a skin toxic effect ≤grade 1 ($P = 0.05$).

(95% CI 5.0–12.0 months). The estimated DCR was 79.5%, for a median time of 7 months (95% CI 4.0–12.0 months). PFS and OS were not statistically different between patients with extra-hepatic CCK (5.7 and 12.0 months, respectively) and intra-hepatic CCK (7.1 and 14.3 months) (log-rank test; $P = 0.773$ and $P = 0.555$, respectively).

skin toxic effect and response

Of the 44 patients, 7 (15.9%) had no skin toxic effect, 9 (20.5%) had grade 1 and 28 (63.3%) ≤grade 2 toxic effect. The median PFS time was 7.7 months (95% CI 5.7–12.0 months) in patients with a skin toxic effect ≥grade 2 and 3.3 months (95% CI 1.8–5.3 months) in patients with a skin toxic effect ≤grade 1 (log-rank test; $P = 0.05$), as shown in Figure 1C. The median OS time was also longer in patients with a skin toxic effect ≥grade 2 compared with patients with a skin toxic effect ≤grade 1: 18.2 months (95% CI 9.7–36.9 months) versus 9.9 months (95% CI 3.6–18.4 months): log-rank test; $P = 0.104$.

KRAS mutational status and response

Twenty-seven patients (61.4%) had sufficient tissue for KRAS mutational status determination. Twenty patients (74.1%) had KRAS-wild-type tumours and 7 (25.9%) harboured exclusively codon 12 mutations (S2, supplementary Table S2, available at *Annals of Oncology* online). Of these seven, three had extra-hepatic CCK and four intra-hepatic CCK. Five of seven had SD as best response, the two others showed progression under treatment. PFS and OS were not statistically different between wild-type (6.7 and 14.8 months, respectively) and mutated subjects (7.1 and 18.8 months): log-rank test; $P = 0.616$ and $P = 0.611$, respectively.

discussion

Clinical trials have been impacted by the rarity of CCK. Despite this, important advances have been accomplished over these last years. Two phase III trials showed that Gem plus platinum salts were superior compared with BSC or Gem [8, 15]. Furthermore, two phase II trials exploring addition of monoclonal antibodies to the doublet GEMOX also showed promising results. The choice of EGFR as a therapeutic target in this study was based on its known involvement, when activated, in oncogenesis and tumour progression of CCK [9, 10]. Based on the available data at time of our study design, we set the threshold for additional benefit of the gem-Ctx combination to a 40% PFS rate at 24 weeks. This objective was clearly met with 47% of our patients being free from progression at 6 months. These results compare favourably to the gem arm of the ABC-02 trial but not the combination arm [8]. Median PFS obtained was also less than it was found in the phase II trial combining Ctx with GEMOX [11]. However, direct comparison of our results cannot be made due to differences in eligibility criteria and study design. Indeed, no patients with gallbladder adenocarcinoma were included in our study. These might be clinically and biologically different due to their different sensitivities to chemotherapy [14].

We assessed response according to skin toxic effect, as such correlation was observed in colorectal cancer patients receiving Ctx [16]. The majority of patients developed Ctx-related skin toxic effect. Median PFS was more than doubled in patients who experienced a skin toxic effect ≥grade 2; a finding already reported, although with much less patients [11].

Similar to the findings of the BINGO trial [12], we did not observe a statistically significant correlation between KRAS status and treatment efficacy. KRAS mutations were detected in 25.9% of our patients, a result similar to that obtained in a

cohort of resected CCK patients [17]. In the Gruenberger et al. trial [11], KRAS mutations were recorded in 3 of 27 patients, Other trials report great variation in the prevalence of KRAS mutations in biliary tract cancers, mostly due to small sample size and detection methodology. Some published reports suggest that the proportion of KRAS mutations is dependent on CCK location [17, 18], which is difficult to assess in our study due to the small sample size. This should be further explored in studies with larger cohorts.

The trial regimen was well tolerated with only six patients (13.6%) withdrawing treatment due to toxic effect and without any treatment-related deaths. However, we experienced a higher than expected rate of serious renal toxic effect, with 2 HUS and one patient with nephrotic syndrome; all three events evolved favourably, requiring no renal support. HUS is a rare but well recognized serious side-effect of gem, not reported in other trials in CCK [19]. Its incidence is 0.25%–0.4% with gem and it has not been reported with Ctx. The physiopathology of HUS does no support an addictive effect of Ctx to Gem in this regard, but we must acknowledge this has never been specifically studied. This unexpected high toxic effect rate remains unexplained.

In summary, the combination of gem-Ctx met our hypothesis for efficacy. However, as recent RCT failed to show a superiority of platin-gem doublets with Ctx, it is uncertain if further investigations in a prospective phase III RCT will be conducted. Furthermore, a higher than expected renal toxic effect was observed, warranting caution in future trials. Finally, as for other types of cancer, establishing molecular (KRAS, hENT1) [20] surrogate markers in a homogenous CCK population is needed to better define those patients that will benefit the most from this combination therapy.

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disclosure

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