A phase II trial of gemcitabine, irinotecan and panitumumab in advanced cholangiocarcinoma

tonio, M. Carberry, P. Wissel, M. Jacobs-Small, P. J. O'Dwyer, A. Sepulveda & W. Sun*

Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA

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Background: Current data suggest that chemotherapy combinations may be superior to single agents in biliary tract cancer. The epidermal growth factor receptor (EGFR) pathway appears to be associated with tumor stage, prognosis and response to therapy. This trial was designed to evaluate the tolerability and efficacy of the combination of panitumumab, a monoclonal anti-EGFR antibody, with gemcitabine and irinotecan.

Patients and methods: Patients with advanced (unresectable or metastatic) cholangiocarcinoma, ECOG PS 0–2, and adequate organ function were treated with panitumumab (9 mg/kg) on day 1, and gemcitabine (1000 mg/m²) and irinotecan (100 mg/m²) on days 1 and 8 of a 21-day cycle. The primary objective was to evaluate the 5-month progression-free survival (PFS). Secondary objectives included overall response rate (ORR) and overall survival (OS).

Mutational analyses of EGFR, KRAS and BRAF were carried out when feasible.

Results: Thirty-five patients received a median of 7 (0–30) cycles. The most common grade 3/4 toxic effects were neutropenia (10 patients, 29%), thrombocytopenia (10 patients, 29%), skin rash (13 patients, 37%) and dehydration (9 patients, 26%). Two patients had CR, 9 had partial response (PR), and 15 had SD for a disease-control rate of 74% (by RECIST) in 28 assessable patients. Two patients went on to have surgical resection. The 5-month PFS was 69%. The median PFS was 9.7 months and the median OS was 12.9 months. In 17 testable samples, no EGFR or BRAF mutations were identified; there were 7 KRAS mutations, with no difference in OS by KRAS status.

Conclusions: This study showed encouraging efficacy of this regimen with good tolerability. Further study in this area is warranted.

Clinical Trials Number: The trial was registered with the National Cancer Institute (www.clinicaltrials.gov identifier NCT00948935).

Key words: biliary tract cancer, cholangiocarcinoma, epidermal growth factor receptor EGFR, gemcitabine, irinotecan, panitumumab

introduction

Biliary tract cancer (BTC), commonly referred to as cholangiocarcinoma, and defined as a neoplasm originating from the biliary epithelium, including intrahepatic and extrahepatic bile ducts, and the gallbladder, is an uncommon malignancy but remains highly lethal. While reliable statistics are difficult to obtain since intrahepatic cholangiocarcinoma is often combined with liver cancer into one category, over 10 000 people develop this disease every year in the United States [1]. More importantly, clinical outcomes in this disease remain very poor—median overall survival (OS) for advanced BTC is around 9–10 months [2–4]. Focusing on this group is important because there are no screening tests for BTC and most patients present at an advanced stage, making surgical resection—the only curative treatment—impossible. For these patients, 5-year survival remains around 5%, making advanced BTC one of the deadliest human malignancies [5].

Many cytotoxic chemotherapy agents (fluoropyrimidines, platinum agents, gemcitabine, taxanes and irinotecan) have been studied and have shown some activity in the treatment of this disease, either as single agents or in combinations; however, the overall benefits are limited, including with the combination of gemcitabine and cisplatin that has been recently accepted as a standard treatment regimen, based on a phase III randomized study (ABC-02) [6].

Preclinical work had shown a role for the epidermal growth factor receptor (EGFR) pathway in BTC. EGFR expression and activation were seen in cell lines [7, 8], and EGFR inhibitors showed preclinical activity, along with an association with KRAS mutation status [7, 9]. In the clinical arena, a study with a series of 236 cholangiocarcinoma cases showed that EGFR
overexpression was seen in 27% of the cases and was associated with aggressive tumor features and disease progression [10]. KRAS and BRAF mutations have also been analyzed in this disease, with reports revealing KRAS mutations in 45% and BRAF mutations in 22%; as in colorectal cancer, these were mutually exclusive [11–13]. Therefore, the combination of an EGFR inhibitor with cytotoxic chemotherapy may improve outcomes in BTC. Earlier, we have evaluated the combination of gemcitabine and irinotecan in patients with advanced pancreaticobiliary cancers and demonstrated a response rate of 23% and a disease control rate of 76%, with acceptable toxic effects [14]. In this phase II trial, we evaluated the toxicity and efficacy of the combination of panitumumab, an antibody against EGFR, with gemcitabine and irinotecan.

patients and methods

study design and patients

This single arm, open-label, phase II clinical trial evaluated the combination of gemcitabine, irinotecan and panitumumab in advanced BTC. To be enrolled, patients had to have a histologically confirmed diagnosis of unresectable or metastatic BTC, and measurable disease at baseline, defined as at least one lesion accurately measurable in at least one dimension as ≥20 mm. Patients had to be ≥18 years, with ECOG performance scores of 0–2, with no prior chemotherapy, biologic therapy or radiation therapy for BTC, and with adequate bone marrow, renal and hepatic function. Exclusions were made for serious coexisting illnesses, pregnancy, lactation, treatment for other cancers within prior 5 years and major surgery within prior 3 weeks. The protocol was approved by the Institutional Review Board at the University of Pennsylvania, and all patients provided written informed consent at the time of enrollment. The trial was registered with the National Cancer Institute (www.clinicaltrials.gov identifier NCT00948935).

treatment

Patients were treated with gemcitabine (1000 mg/m²) and irinotecan (100 mg/m²) on days 1 and 8 of a 21-day cycle, with panitumumab (9 mg/kg) administered on day 1 of each cycle. All doses were based on the actual body weight. All agents were administered as intravenous infusions. Gemcitabine was administered at a fixed dose rate of 10 mg/m²/min (100 min), irinotecan was administered over 60 min and panitumumab was administered over 1 h (±15 min). Prophylactic anti-emetics were routinely administered. Dose modification criteria and protocols were established a priori. For panitumumab, a dose-modification algorithm was used, wherein the dose was modified or withheld for skin or non-skin toxic effects; modified dose levels were 7.5 and 6 mg/kg. For gemcitabine and irinotecan, doses were modified for hematologic toxic effects, diarrhea and other grade 3 or higher toxic effects. For panitumumab-induced rash, topical emollients, topical and/or oral steroids and pyridoxine were allowed. For hematologic toxicity, the use of granulocyte colony-stimulating factor was allowed.

data evaluation and analyses

Treatment toxic effects were evaluated at each visit, using Common Terminology Criteria for Adverse Events (CTCAE 3.0). For efficacy, imaging using a contrast-enhanced CT scan or MRI scan was obtained at baseline, within 4 weeks before start of treatment. Subsequently, the same imaging test was repeated every two cycles for response assessment. Response on imaging was determined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1). For response evaluation, patients had to have a scan at least 42 days after treatment initiation. The primary efficacy outcome of the study was progression-free survival (PFS), defined as time in months from enrollment on study to first documentation of progression of disease, or death, whichever came earlier. A total sample size of 40 patients was prespecified. The null hypothesis was that the 5-month PFS is ≤65%. A 5-month PFS of ≥65% was to be taken as evidence of activity in this patient population. A two-stage design was utilized in this study. During stage 1, 20 eligible patients would be accrued. If there were eight or fewer patients observed to be progression-free at 5 months, we would stop the study. Otherwise, we would continue to the second stage of accrual. If there were ≥24 patients who were progression-free at 5 months, the specified treatment would be considered promising (90% two-stage CI for 23 patients progression-free at 5 months: [42%, 69%]). This test had 80% power under the alternative hypothesis if the true 5-month PFS was 65%. Secondary outcomes included OS, defined as time in months from enrollment on study to death, and response rates. All survival analyses were carried out using the Kaplan–Meier method. Statistical analyses were carried out using SAS 9.3. Correlative molecular analyses were conducted on specimens with adequate tumor tissue for evaluation. DNA sample preparation from microdissected tumor areas of tissue sections from formalin-fixed paraffin-embedded (FFPE) tissues was followed by DNA extraction using DNeasy Blood & Tissue Kits (Qiagen, Inc). Detection and quantitation of mutations in codons 12, 13 and 61 of K-RAS, and detection of the hotspot transversion mutation T1799A that causes the amino acid substitution V600E in BRAF were carried out by pyrosequencing analyses using the PyroMark Q24 (Qiagen, Inc). PCR and sequencing methods were used for detection of the E19del and L858R mutations in the EGFR gene.

results

treatment and toxicity

Between March 2009 and July 2012, a total of 35 patients were enrolled in this study. Data are presented for all patients, updated till March 2013. Baseline characteristics are presented in Table 1. Of note, more than half (54%) of the patients had intrahepatic cholangiocarcinoma, and a quarter (26%) of the study population had biliary stents. A median of 7 (range 0–30) treatment cycles were administered. Treatment-related toxic effects experienced are listed in Table 2, with 30 (86%) patients experiencing grade III or higher toxic effects during their treatment on the study. Prominent toxic effects were hematologic, with 6 (17%) patients developing neutropenic

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**Table 1.** Baseline characteristics of patients enrolled (n = 35)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (range)</td>
<td>62 (26–82)</td>
</tr>
<tr>
<td>Males</td>
<td>18 (51%)</td>
</tr>
<tr>
<td>Whites</td>
<td>33 (94%)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Intrahepatic</td>
<td>19 (54%)</td>
</tr>
<tr>
<td>Perihilar (Klatskin)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Extrahepatic</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>CEA, median (range)</td>
<td>10 (Undetectable-12817)</td>
</tr>
<tr>
<td>CA19.9, median (range)</td>
<td>40 (Undetectable-8812)</td>
</tr>
<tr>
<td>Biliary stent</td>
<td>9 (26%)</td>
</tr>
</tbody>
</table>

*Unless otherwise specified.
fever; dermatologic, with 13 (37%) developing a grade III/IV rash; and abnormal liver function tests.  

**efficacy**

Two (6%) patients had complete response (CR) and went on to have surgical resection; nine (26%) patients had partial response (PR). Stable disease (SD) was seen in 15 (42%) patients, progressive disease (PD) in 2 (6%) patients and 7 (20%) were not assessable (NE) for response due to treatment cessation before first imaging evaluation. The overall response rate (ORR, CR + PR) was 31%, and the disease control rate (CR + PR + SD) was 74%. There were no statistically significant differences in outcomes by site of primary tumor (intrahepatic, extrahepatic, gallbladder). The median follow-up time for all patients, estimated by the reverse Kaplan–Meier method, was 21.7 months [15]. The 5-month PFS, the primary efficacy outcome, was 69% (95% CI 51% to 82%). The median PFS was 9.7 months (95% CI 5.1–12.9 months). The median OS was 12.9 months (95% CI 9.5–27.8 months). Estimates of 1-year progression-free and overall survival were 44% (95% CI 26% to 61%) and 59% (95% CI 40% to 73%), respectively. Survival curves are shown in Figure 1.

**correlative analyses**

We were able to carry out mutational analyses on 17 samples with adequate tissue available for evaluation. No EGFR or BRAF mutations were detected. There were seven samples (41% of those tested) with KRAS mutations; three G12D, two G12V and two G13D. An exploratory analysis of OS by KRAS mutation status (wild-type versus mutated) for 17 patients showed no association; this curve is shown in Figure 2.

**discussion**

We employed combination chemotherapy and an EGFR antibody to study tolerability and efficacy of this regimen in advanced BTC. Our earlier phase I study had shown a feasible combination of gemcitabine and irinotecan [14], to which we added panitumumab, based on similar combinations and data from ongoing studies at the time [16]. The study demonstrated that the regimen was well-tolerated. As expected, major grade III and IV toxic effects were limited to hematologic, dermatologic (panitumumab-induced rash), and liver function abnormalities (attributable to a combination of disease and therapy). There were no major unexpected toxic effects and no treatment-related deaths.

The publication of the ABC-02 study, a randomized, controlled trial of a combination of gemcitabine and cisplatin...
compared with gemcitabine alone, has shown improved antitumor efficacy with the combination, making it a standard regimen in the treatment of advanced BTC [6]. In that study, the combination improved median OS (the primary outcome) to 11.7 months (vs. 8.1 months, HR = 0.64, P < 0.001) and median PFS to 8.0 months (versus 5.0 months, HR = 0.63, P < 0.001). The response rate was 24% and the tumor control rate was 81% [6]. Results from this combination of cytotoxic agents and a biologic agent compare favorably with these outcomes, with suggestion of an advantage of adding an anti-EGFR antibody to a cytotoxic chemotherapy backbone. While understanding the limitations of cross-trial comparisons, it is conceivable that the addition of an EGFR antibody to a doublet of chemotherapeutic agents might confer a clinical benefit. Initial clinical studies of EGFR inhibitors in BTC showed promising results, including moderate activity of erlotinib as a single agent [17, 18]. A recently published randomized phase III trial of erlotinib, an EGFR tyrosine kinase inhibitor, in combination with gemcitabine and oxaliplatin, when compared with the chemotherapy doublet, did not show an obvious improvement in clinical outcomes [3]. Although the median PFS may suggest some potential benefit, there was no statistically significant difference (5.8 versus 4.2 months, HR = 0.80, P = 0.09). The median OS was unchanged (9.5 months in each arm). It is unclear whether EGFR monoclonal antibodies such as cetuximab and panitumumab behave differently from the EGFR tyrosine kinase inhibitors such as erlotinib and gefitinib in BTC. Indeed, most solid tumor malignancies appear to respond differently to the two classes of EGFR-directed therapies [19]. Therefore, it is conceivable that EGFR antibodies may have clinical efficacy in biliary tract cancers. One phase II study tested cetuximab, another anti-EGFR monoclonal antibody, in combination with gemcitabine and oxaliplatin in advanced unresectable or metastatic biliary tract cancer [20]. The study showed objective response in 19 patients (63%; 95% CI 56.2–69.8), of whom 3 (10%) achieved CR. Nine patients underwent potentially curative secondary resection after major response to therapy. Grade 3 adverse events were recorded in 13 patients: skin rash (n = 4), peripheral neuropathy (n = 4), thrombocytopenia (n = 3), nausea (n = 1), diarrhea (n = 1) and neutropenia (n = 1); no grade 4 adverse events were recorded. The other study with a similar design, of gemcitabine, oxaliplatin and panitumumab (instead of cetuximab) in cholangiocarcinoma with wild-type KRAS reported median OS of 10.0 months and median PFS of 8.3 months [21]. On the other hand, a randomized phase II study did not show any obvious difference by adding cetuximab to the combination of gemcitabine and oxaliplatin in advanced biliary tract cancers [20]. However, there was no extra toxicity either. Further trials with EGFR antibodies in cholangiocarcinoma are ongoing, and the results from these studies will shed further light on this interesting arena [22].

Another aspect is the role of mutations of EGFR pathway genes in response to EGFR-directed therapy. In colorectal cancer, evidence has established that KRAS mutations preclude therapeutic benefit from EGFR antibodies. Interestingly, a similar hypothesis could not be confirmed in other cancers in the gastrointestinal system (esophageal, gastric or pancreatic cancer), or lung cancer [19, 23]. Our exploratory correlative analyses showed no clear relationship between survival outcomes and KRAS mutations. Whether KRAS mutations are not predictive, or the numbers in our cohort were too small to find a difference wherein it exists or KRAS mutational status is moot since panitumumab is not conferring major clinical benefit cannot be ascertained from our data. We did not find any EGFR or BRAF mutation, which is consistent with results from more recent series [24, 25].

Our study has limitations. It was a single-arm study, so the role of panitumumab in addition to the chemotherapy combination cannot be elucidated clearly. Correlative analyses were retrospective, and limited by tissue availability due to several diagnostic specimens being from needle aspirations or bile duct brushings, which yield little cellular material for mutational analyses. The final results of this study are promising, and consistent with data from some of the similar studies. Even though there has been no confirmatory evidence to demonstrate the benefit of adding an anti-EGFR monoclonal antibody to combination chemotherapy, yet, data are encouraging and further investigation is warranted.

**funding**

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**disclosure**

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**references**

An individual patient-data comparison of combined modality therapy and ABVD alone for patients with limited-stage Hodgkin lymphoma

A. E. Hay†, B. Klimm‡, B. E. Chen†, H. Goergen‡, L. E. Shepherd†, M. Fuchs‡, M. K. Gospodarowicz§, P. Borchmann‡, J. M. Connors¶, J. Markova†*, M. Crump‡, A. Lohri‡, J. N. Winter‡, B. Dörken‡, R. G. Pearcey†, V. Diehl‡, S. J. Horning¶, H. T. Eich‡, A. Engert‡, R. M. Meyer‡, & Conducted by the NCIC Clinical Trials Group (Canada) and German Hodgkin Study Group (GHSG)‡

1. NCIC Clinical Trials Group and Queen’s University, Kingston, Ontario, Canada; 2. German Hodgkin Study Group, University Hospital of Cologne, Cologne, Germany; 3. Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada; 4. BC Cancer Agency Centre for Lymphoid Cancer, Vancouver, British Columbia, Canada; 5. University Hospital Královské Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic; 6. Division of Medical Oncology and Hematology, Princess Margaret Hospital, University of Toronto, Ontario, Canada; 7. Medical University Clinic, Liestal, for the Swiss Group for Clinical Cancer Research, Bern, Switzerland; 8. Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA; 9. Campus Virchow Clinic, Charité Hospital of Münster, Münster, Germany; 10. Juravinski Hospital and Cancer Centre, Hamilton, Ontario, Canada

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Background: Treatment options for patients with nonbulky stage IA–IIB Hodgkin lymphoma include combined modality therapy (CMT) using doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) plus involved-field radiation therapy (IFRT), and chemotherapy with ABVD alone. There are no mature randomized data comparing ABVD with CMT using modern radiation techniques.

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