Background: Gallbladder cancers and cholangiocarcinomas make up a heterogeneous group of tumors with a poor prognosis in advanced stages. On the basis of evidence of dysregulation of the epidermal growth factor receptor, vascular endothelial growth factor, and mitogen-activated protein kinase pathways in biliary cancers, we performed a phase 2 trial of sorafenib and erlotinib in patients with advanced biliary cancers.

Methods: Eligible patients were previously untreated in the advanced setting with adequate hepatic and bone marrow function. Sorafenib and erlotinib were administered continuously at 400 mg BID and 100 mg daily, respectively.

Results: Thirty-four eligible patients were recruited. The study was terminated after the first stage of accrual owing to failure to meet the predetermined number of patients who were alive and progression free at 4 months. There were two unconfirmed partial responses (6%, 95% CI: 1–20%), with a median progression-free survival of 2 months (95% CI: 2–3), and median overall survival of 6 months (95% CI: 3–8 months). Grade 3 and 4 adverse events included hypertension, AST/ALT increase, bilirubin increase, diarrhea, hypokalaemia, hypophosphatemia, and rash.

Conclusions: Despite compelling preclinical rationale, the combination of sorafenib and erlotinib does not have promising clinical activity in an unselected population of patients with biliary cancers. Improved patient selection based on tumor biology and molecular markers is critical for future evaluation of targeted therapies in this disease.

Biliary tract cancers represent a heterogeneous group of neoplasms including intrahepatic and extrahepatic bile duct cancers (cholangiocarcinomas) and gallbladder cancers. The American Cancer Society estimates that 10,310 new cases of gallbladder and bile duct cancers (excluding bile ducts within the liver) will be diagnosed in 2013 in the United States. Similarly, there are predicted to be 30,640 new cases of liver and intrahepatic biliary cancers in 2013, about 15% of which are intrahepatic cholangiocarcinomas (IHCC; Siegel et al., 2013).

Advances in the treatment of unresectable and metastatic biliary cancers have been limited by several factors including the heterogeneity of the disease and incomplete understanding of biliary molecular carcinogenesis. Furthermore, most cytotoxic and targeted drugs had been evaluated for efficacy in the setting of phase 2 studies until the report by Valle et al. (2010) established the superiority of gemcitabine and cisplatin over gemcitabine alone, with increases in both progression-free survival (PFS; 8.0 vs 5 months, \( P < 0.001 \)) and overall survival.
The initiation of study therapy.

It was important and ethical to explore the efficacy of novel agents as all the stakeholders, including patient advocates, believed that it was important and ethical to explore the efficacy of novel agents for the treatment of patients with biliary cancers. In a phase 2 study of 42 patients with unresectable or metastatic biliary cancer who were treated with erlotinib as a single agent, Philip et al (2003) reported the results of a phase 2 study of sorafenib in patients with advanced biliary cancers and noted a median PFS of 3 months and a median OS of 9 months (95% CI: 4–12 months), which was comparable to the survival reported with cytotoxic chemotherapy regimens (El-Khoueiry et al, 2012).

Both sorafenib and erlotinib have been evaluated as single agents for the treatment of patients with biliary cancers. In a phase 2 study of 42 patients with unresectable or metastatic biliary cancer who were treated with erlotinib as a single agent, Philip et al (2006) reported three partial responses and a stable disease rate of 43%. The median time to progression was 2.6 months and the median OS was 7.5 months. We previously reported the results of a phase 2 study of sorafenib in patients with advanced biliary cancers and noted a median PFS of 3 months and a median OS of 9 months (95% CI: 4–12 months), which was comparable to the survival reported with cytotoxic chemotherapy regimens (El-Khoueiry et al, 2012).

Given these data, we designed and conducted a phase 2 study evaluating the combination of sorafenib and erlotinib based on the modest clinical activity of each agent alone and the extensive molecular cross-talk between the EGFR and VEGF pathways (Ciardiello et al, 2006). A phase 1 study of the combination of sorafenib and erlotinib had been reported by Duran and colleagues (Quintela-Fandino et al, 2010) and determined the maximum tolerated dose to be sorafenib 400 mg PO twice daily and erlotinib 150 mg once daily. At this dose level, six out of seven patients needed a dose delay and five out of seven required a dose reduction at cycle 2 or higher. The toxicities and subsequent dose reductions represented a potential concern for our population, which may be even more susceptible to gastrointestinal toxicities and anorexia.

For this reason, we proceeded with sorafenib at 400 mg twice daily and erlotinib at 100 mg daily. Our study was conceived and planned before the initial presentation of the ABC-02 trial results in June of 2009, which established the combination of gemcitabine and cisplatin as a new standard of care for patients with advanced biliary cancers. The study proceeded to activation in April of 2010 as all the stakeholders, including patient advocates, believed that it was important and ethical to explore the efficacy of novel combinations in first-line treatment of biliary cancers as long as they were supported by strong scientific rational. Furthermore, there was agreement that the combination of gemcitabine and cisplatin could be utilised as second-line treatment upon progression that could be determined as early as 8 weeks from the initiation of study therapy.

SWOG study of sorafenib and erlotinib were supplied by the division of Cancer Treatment and Diagnosis, National Cancer Institute (Bethesda, MD, USA). Patients were treated with sorafenib 400 mg orally twice daily and erlotinib 100 mg orally once daily on a continuous basis. One treatment cycle was of 28 days. Patients were seen and evaluated on a weekly basis during cycle 1, and every 2 weeks in cycle 2 and beyond. Toxicities were graded as per the National Cancer Institute Common Terminology Criteria for adverse events version 4.0. The worst grade of toxicity per patient was recorded in each cycle. Specific dose modification and treatment interruption criteria for sorafenib and erlotinib were applied. If one of the two study drugs was temporarily held due to a specific toxicity that was determined by the treating physician to be exclusively related to that drug, the other drug could be continued per protocol. Treatment with both drugs was held for grade 3 or 4 toxicity, including bilirubin elevation, AST/ALT elevation, diarrhoea, neutropaenia and thrombocytopaenia. In the case of hypertension, sorafenib was held for grade 2 symptomatic or grade 3 hypertension and subsequently restarted with one dose level reduction once diastolic BP was ≤100 mm Hg and symptoms had resolved. Sorafenib was held in the case of a second or higher recurrence of grade 2 palmar–plantar erythrodysesthesia syndrome, or at the first occurrence of a grade 3 or higher toxicity. Symptomatic management for maculopapular or acneiform rash was instituted at first occurrence, and treatment with both drugs was held for intolerable rash of any grade. Both drugs were dose reduced in the event of a recurrence of an intolerable rash.

Two dose reductions were allowed for each drug; for sorafenib, dose level −1 was 200 mg twice daily, and dose level −2 was 200 mg once daily; for erlotinib, dose level −1 was 75 mg once daily and dose level −2 was 50 mg once daily. Patients requiring treatment interruption for more than 4 weeks or requiring more than two dose reductions were removed from protocol treatment.

Disease assessment. Patient response was assessed every 8 weeks using the Response Evaluation Criteria in Solid Tumors classification 1.1. Measurable disease was defined as at least one lesion for which the longest diameter could be accurately measured as ≥1 cm using spiral computed tomography or magnetic resonance imaging. Measurable lymph nodes had to have a short-axis measurement of 1.5 cm. All other lesions, including ascites and...
pleural effusions, were considered non-measurable. Patients who met stable disease criteria at least once after study entry at a minimum interval of 6 weeks were considered to have achieved disease stabilisation. Progression-free survival was calculated from the date of registration to the date of first observation of progressive disease, death due to any cause or symptomatic deterioration. Patients known to be alive and progression free were censored at last date of contact.

**Statistical considerations.** The primary end point of the trial was PFS in patients with advanced gallbladder cancer or cholangiocarcinoma treated with sorafenib and erlotinib. The secondary end points included response probability, OS and toxicity. We assumed that the combination of sorafenib and erlotinib would be of interest for further study if the true median PFS was 8 months or more, and of no further interest if it were 4 months or less. A two-stage design was planned to evaluate PFS. If after the first 25 patients were accrued, we observed 13 or more patients to be alive and without progression at 4 months, the study would accrue an additional 25 patients to the second stage.

**RESULTS**

A total of 40 patients were registered between April of 2010 and March of 2011. Six were ineligible because of elevated blood pressure or baseline laboratory abnormalities. The median age of eligible patients was 63 (range 49–82). Thirteen patients (38%) were male and 28 (82%) were white. Fifty-six percent of patients had a Zubrod performance status of 0. Twenty patients had cholangiocarcinoma (59%) and 14 (41%) had gallbladder cancer. Only one patient had received prior adjuvant chemotherapy and no patients had received radiation therapy. Twenty-eight (82%) patients had metastatic disease and six (18%) had locally advanced disease (Table 1).

**Administration of sorafenib and erlotinib.** The median number of cycles administered was 2 (range 1–14). Reasons for treatment discontinuation included adverse events in 7 patients (21%), progression in 24 (71%) and death in 2 (6%). Dose reduction or interruption secondary to adverse events occurred in 17 out of 34 patients (50%) in cycle 1 and 14 out of 26 patients (54%) in cycle 2. The median dose of sorafenib and erlotinib delivered in cycle 1 was 77% and 98% of the planned dose, respectively. When combining cycles 1 and 2, the median dose of sorafenib and erlotinib delivered over the first two cycles was 52% and 75%, respectively. It is important to note that the dose intensity was not only affected by dose reduction and interruption for adverse events but also by discontinuation due to disease progression or patient refusal in 8 out of 34 patients (24%).

**Toxicity.** Thirty-four patients were evaluated for adverse events. One patient died on protocol therapy after being admitted for abdominal pain. The most common grade 3 and 4 toxicities that were at least possibly related to study drugs and occurred in two or more patients were hypertension (15%), ALT increase (12%), alkaline phosphatase increase (9%), diarrhoea (9%), hypophosphatemia (9%), AST increase (9%), bilirubin increase (6%), hand-foot skin reaction (6%), hepatic infection (6%), hypokalaemia (6%) and rash (6%; Table 2).

**Efficacy.** The study was terminated after the first stage of accrual because of failure to meet the requirement of 13 patients being alive and without progression at 4 months. Thirty-four patients were evaluable for response. Two patients (6%) achieved an unconfirmed partial response. Ten (29%) patients had stable disease. Eighteen (53%) patients had progressive disease, one patient had symptomatic deterioration leading to treatment interruption secondary to adverse events occurred in 17 out of 34 patients (50%) in cycle 1 and 14 out of 26 patients (54%) in cycle 2. The median dose of sorafenib and erlotinib delivered in cycle 1 was 77% and 98% of the planned dose, respectively. When combining cycles 1 and 2, the median dose of sorafenib and erlotinib delivered over the first two cycles was 52% and 75%, respectively. It is important to note that the dose intensity was not only affected by dose reduction and interruption for adverse events but also by discontinuation due to disease progression or patient refusal in 8 out of 34 patients (24%).
In this phase 2 trial, we explored the efficacy of the combination of erlotinib and sorafenib in patients with unresectable or metastatic gallbladder cancer and cholangiocarcinoma. The study was closed after the first stage of accrual owing to failure to meet predetermined criteria for efficacy. The median PFS was 2 months (95% CI: 2–3 months) and 4 month PFS was 29% (95% CI: 13–45%; Figure 1). Median OS was 6 months (95% CI: 3–8 months; Figure 2). Information about subsequent therapy was available for 32 patients; 13 patients (41%) received systemic treatment after progression on study. The second-line treatments were gemcitabine and a platinum combination in eight patients, gemcitabine and capcitabine combination in two patients, erlotinib in one patient and docetaxel in one patient. Only two patients received third-line treatment.

**DISCUSSION**

In this phase 2 trial, we explored the efficacy of the combination of erlotinib and sorafenib in patients with unresectable or metastatic gallbladder cancer and cholangiocarcinoma. The study was closed after the first stage of accrual owing to failure to meet predetermined criteria for efficacy. The median PFS was 2 months (95% CI: 2–3 months) and 4 month PFS was 29% (95% CI: 13–45%; Figure 1). Median OS was 6 months (95% CI: 3–8 months; Figure 2). Information about subsequent therapy was available for 32 patients; 13 patients (41%) received systemic treatment after progression on study. The second-line treatments were gemcitabine and a platinum combination in eight patients, gemcitabine and capcitabine combination in two patients, erlotinib in one patient and docetaxel in one patient. Only two patients received third-line treatment.
origin (intrahepatic vs extrahepatic vs gallbladder carcinoma; Jarnagin et al, 2006) or to the fact that most studies that have examined the frequency of genetic alterations such as KRAS or BRAF have been plagued by small sample sizes and yielded inconsistent results (Kipp et al, 2010; Robertson et al, 2013; Voss et al, 2013). Nonetheless, there are emerging and promising therapeutic targets in cholangiocarcinoma that are under active investigation. For example, two small studies using MEK inhibitors have shown single-agent objective responses and promising survival (Bekaii-Saab et al, 2011; Finn et al, 2012). On the basis of this, a clinical trial evaluating the single-agent MEK inhibitor trametinib in comparison with 5-fluorouracil or capcetibamine in patients with biliary cancers after progression on gemcitabine and cisplatin is planned by the Southwest Oncology Group. A comprehensive translational medicine plan is included in this trial with the aim of identifying predictive markers of activity. Similarly, a randomised study comparing gemcitabine and cisplatin vs gemcetibine and cisplatin in combination with selumitinib is planned in the United Kingdom. This is an important approach as it is currently unknown whether single-agent targeted therapies will achieve sufficient therapeutic benefit in biliary cancers in the absence of an established ‘driver’ target. Another promising target in biliary cancers is the MET oncogene (Miyamoto et al, 2011; Andersen et al, 2012). Evaluation of MET targeting agents in cholangiocarcinoma would be warranted, especially given the promising activity of MET inhibitors in hepatocellular carcinoma where MET expression appears to be associated with the likelihood of benefit (Santoro et al, 2013). In conclusion, the combination of sorafenib and erlotinib does not have promising clinical activity in an unselected population of patients with biliary cancers. Improved patient selection based on tumour location, tumour biology and molecular markers will be critical for future evaluation of targeted therapies in this heterogeneous disease.

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