HER2/neu May Not Be an Interesting Target in Biliary Cancers: Results of an Early Phase II Study with Lapatinib

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Key Words

Biliary cancer · Lapatinib · Epidermal growth factor receptor · HER2/neu

Abstract

Purpose: Biliary cancers (BCs) respond poorly to chemotherapy. Lapatinib is a dual inhibitor of epidermal growth factor receptor (EGFR) and HER2/neu, both implicated in cholangiocarcinogenesis. This trial was designed to determine the safety and efficacy of lapatinib in BC. **Methods:** A Fleming phase II design with a single stage of 25 patients was used. The dose of lapatinib was 1,500 mg/day administered orally in 28-day cycles. Tumor and blood specimens were analyzed for expression of HER2/neu and EGFR. **Results:** Nine patients with BC enrolled in this study. The study was terminated early because of futility. The most common toxicities were nausea and fatigue (78%) and diarrhea (67%). No responses were observed. Of 8 evaluable patients, 4 (50%) had stable disease. Median progression-free survival was 2.6 months (95% CI 1.6–4.4) and median overall survival was 5.1 months (95% CI 2.0–16.5). No somatic mutations in EGFR (exons 18–21) or HER2/neu were found. We did not find evidence of HER2

overexpression. **Conclusions:** Lapatinib is well tolerated but failed to show activity as a single agent in treating patients with BC. Despite the small patient population, our study is consistent with previous findings, suggesting that targeting HER2/neu does not appear to be an effective therapy for BC.

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Introduction

Bile duct cancers, which include cholangiocarcinoma and gallbladder cancers, have an incidence of >14,000 new cases diagnosed per year in the US [1]. The current standard of care for patients with advanced biliary cancer (BC) consists of the combination of gemcitabine and cisplatin based on a recent study that showed superior outcome over gemcitabine alone [2]. However, the survival for advanced BC rarely exceeds 1 year and the prognosis is universally poor [3]. This has led to a search for molecular targets for therapy.

Potential targets for anticancer therapy in BC included epidermal growth factor receptor (EGFR) and HER2/neu (EGFR2 or ERBB2), both thought to be overexpressed in

BC [4, 5] and directly implicated in cholangiocarcinogenesis [6–9]. The role of EGFR inhibition was considered significant based on a phase II study, suggesting that erlotinib, an oral tyrosine kinase EGFR inhibitor, had interesting activity in BC [5].

Lapatinib is a dual inhibitor of EGFR and HER2/neu and acts by docking to the ATP-binding site of the two receptors [10, 11]. In early clinical studies, lapatinib was well tolerated with preliminary evidence of anti-tumor activity. It is currently approved for the treatment of breast cancer [12].

Given that both EGFR and HER2/neu contribute to the behavior of BC, we hypothesized that a dual inhibitor blocking both targets would have a significant therapeutic advantage over compounds that inhibit one receptor. Given these observations, we conducted and report here a phase II study to evaluate the efficacy and tolerability of single-agent lapatinib in patients with advanced BC.

Methods

Eligible patients were required to have histologically confirmed unresectable advanced BC and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) [13], as well as ≤ 1 prior systemic anticancer therapy. Patients with prior cryotherapy, radiofrequency ablation, ethanol injection, transarterial chemoembolization or photodynamic therapy were eligible provided that >6 weeks since therapy have passed and indicator lesion(s) were outside the area of prior treatment; if the only indicator lesion was inside the prior treatment area, a clear evidence of disease progression was demonstrated. Prior radiation therapy with or without the use of a fluoropyrimidine as a radiosensitizer was allowed in the study if >12 weeks have elapsed since therapy. Additional criteria included a life expectancy ≥ 12 weeks, an Eastern Cooperative Oncology Group performance status <2 and the ability to take and absorb oral medications. Patients were required to have normal organ function. Exclusion criteria included patients with prior treatment with EGFR inhibitors, >450 mg/m² doxorubicin (given the potential with lapatinib for additional cardiotoxicity, a class effect toxicity seen with HER2/neu inhibitors), major surgery occurring within 3 weeks prior to the planned starting date, brain metastases, history of malignancy other than BC within the previous 3 years except for adequately treated basal cell carcinoma, squamous cell cancer, or carcinoma of the cervix, uncontrolled intercurrent illness, pregnancy, HIV infection, and concomitant requirement for medication classified as CYP3A4 inducer or inhibitor.

Study Design

This was a National Cancer Institute (NCI)-sponsored phase II, open-label, multicenter trial led by the Ohio State University with the participation of the University of Michigan, Virginia Commonwealth University, H. Lee Moffitt Cancer Center, and the University of North Carolina. Lapatinib was provided by the

Fig. 1. Kaplan-Meier plots for OS and PFS.

NCI/Cancer Therapy Evaluation Program. The primary endpoint of this trial is the proportion of patients demonstrating objective response [partial response (PR) + complete response (CR)] as defined by the RECIST response criteria. We used a Fleming phase II design resulting in a single stage of 25 patients. If ≥ 5 of the 25 patients demonstrate a PR or a CR, the agent will be recommended for further study in this patient population ($\alpha = 0.10$; $\beta = 0.10$; $p_0 = 0.1$; $p_1 = 0.3$). Tissue and blood samples were required for all patients. Secondary objectives included evaluation of toxicity, overall survival (OS), assessment of mutations of EGFR and HER2/neu genes and measurement of expression of proteins in signaling pathways relevant to lapatinib including HER2/neu.

Lapatinib Administration and Dose Modifications

The starting dose and schedule of lapatinib was 1,500 mg/day orally without interruption in 28-day cycles. There were three levels of dose reductions planned (1,250, 1,000 and 750 mg/day) with patients taken off the study if they needed additional dose reductions.

Assessment of Response and Toxicity

Radiological assessment was done by CT or MRI (as long as the same consistent measure was used serially) every 8 weeks, and responses were measured according to the RECIST criteria. Toxicities were defined by the NCI-CTCAE, version 3.0.

Correlative Studies

Either fresh or paraffin-embedded tissue from tumor blocks and adjacent normal tissue was required from patients before enrolling in this study. One blood sample was obtained before patients enrolled in the study with a goal to examine germline mutations.

Methods for assessment of HER2/neu and enumeration of chromosome 17 (CEP17) by fluorescence in situ hybridization, HER2/neu and EGFR mutation screening were previously published by our group [14, 15].

Table 1. Patient demographics and characteristics

Sex	Male	3
	Female	6
Age, years	Median	61
	Range	31–83
Race/ethnicity	White	9
Prior treatments	X-ray	1
	Surgery	5
	Chemotherapy	3
Sites of metastasis	Lymph nodes	6
	Lungs	3
	Hepatic metastases	3
	Porta hepatis	2
	Long bones	2
	Spine	2
	Abdomen	1
	Ribs	1
	Hepatorenal fossa	1
	Chest wall	1
	Pericardiac region	1
	Adrenal gland	1
CA19-9 at start of treatment	>ULN	6
	<ULN	3

ULN = Upper limit of normal (37 U/ml).

Statistical Methods

The primary endpoint of this study was objective response (PR + CR) as defined by the RECIST response criteria. Descriptive statistics were provided to describe patient demographics and toxicities. Progression-free survival (PFS) was calculated from the date of the start of therapy to disease progression or death, whichever occurred first. OS was determined from the date of the start of therapy to death from any cause. Median time to survival was estimated using the Kaplan-Meier method. 95% confidence interval (95% CI) for survival was calculated by the Brookmeyer-Crowley method.

Results

Patient Characteristics

Out of the planned 25 patients, only 9 patients were accrued between the dates of 22/11/2005 and 1/6/2006. The study was terminated early because of possible futility as described in Discussion. Of the 9 patients enrolled, 1 was considered non-evaluable for response (passed away before restaging). All 9 patients were evaluable for toxicity, PFS and OS analysis (table 1).

Table 2. Toxicities (n = 9)

Toxicity	All toxicities	Grade 1	Grade 2	Grade 3
Diarrhea	11	8	2	1
Fatigue	9	3	6	0
Nausea	9	4	5	0
Abdominal pain	3	0	3	0
Anorexia	4	0	4	0
Dizziness	3	3	0	0
Rash	3	3	0	0
Constipation	2	0	2	0
Hypercalcemia	2	1	1	0
Joint pain	2	2	0	0
Neck pain	2	2	0	0
Agitation	1	1	0	0
ALT	1	1	0	0
AST	1	1	0	0
Bloating	1	1	0	0
Chest pain	1	1	0	0
Dysgeusia	1	1	0	0
Emesis	1	1	0	0
Fracture	1	0	0	1
Generalized pain	1	0	1	0
Headache	1	1	0	0
Hypoalbuminemia	1	1	0	0
Hypokalemia	1	0	1	0
Hyponatremia	1	1	0	0
Partial gastric outlet obstruction	1	0	1	0

There were no grade 4 toxicities. ALT = Alanine aminotransferase; AST = aspartate aminotransferase.

Treatment Toxicity

Only 1 patient (11%) required dose reduction. One patient had to stop the drug secondary to fatigue (grade 2 toxicity). The most common toxicities included nausea and fatigue (both 78%) and diarrhea (67%). Only one grade 3 toxicity (diarrhea) was noted. There were no grade 4 toxicities. All toxicities were reversible (table 2).

Treatment Efficacy

A median of 3.4 cycles was administered (range 1–5) with a median follow-up time of 69 days. There were no objective responses. Out of 8 evaluable patients, only 4 patients (50%) had stable disease and another 4 (50%) had progressive disease as their best response. Three patients (33%) had a >20% decrease in their CA19-9 baseline levels. The mean PFS (mPFS) was 2.6 months (95% CI 1.6–4.4) and the mean OS (mOS) was 5.1 months (95% CI 2.0–16.5) (fig. 1).

Biological Markers

Tissue and blood specimens were available for all patients. No somatic mutations in EGFR (exons 18–21) were found. Additionally, we did not find evidence of HER2/neu somatic mutations. The HER2/neu copy number was neither elevated per fluorescence in situ hybridization nor was HER2/neu protein expression increased per immunohistochemistry.

Discussion

BC represents one of the most challenging cancers. The rationale for this study was based on the demonstration of a role for EGFR and HER2/neu signaling pathways in the carcinogenesis of BC.

Results from our analysis reveal no activity for lapatinib as a single agent in treating patients with advanced BC based on the lack of objective response in the first 9 patients. There was biochemical (CA19-9) evidence of response in 3 patients. The reported mPFS and mOS were short and not clinically meaningful. Despite the small number of patients included in our analysis, our findings are very consistent with those of a similar study with 17 BC patients that was terminated early because of futility [16].

Retrospective studies report HER2/neu overexpression ranging from 5 to 76% in cholangiocarcinoma [4, 16–18], but our prospective correlative analysis reveals no overexpression of HER2/neu. The discrepancy in the reported rates could possibly be attributed to different phe-

notypic subtypes. Of course, this conclusion is limited by the small sample size of our study, although arguably if present, HER2/neu overexpression is unlikely to be significant. Consistent with other reports [15, 16] and our previously published data [14], we also found no evidence of activating mutations in EGFR or HER2/neu.

Despite the initial enthusiasm for targeting HER2/neu in addition to EGFR in BC, two studies with lapatinib (including ours) were terminated early because of lack of activity. As such, HER2/neu inhibition is not worth pursuing further in advanced BC. Lapatinib has likely weak EGFR activity, and EGFR remains an interesting target given encouraging results from a previous study [5]. Understanding the molecular and genetic mechanisms of BC is essential to improve the outcome of patients with this deadly disease. Several targets including MEK [19], EGFR [5] and vascular endothelial growth factor [20] remain interesting to pursue, given evidence of preliminary clinical activity.

Ethical Standards

The trial protocol has been approved by an ethical committee and thus meets the standards of the Declaration of Helsinki in its revised version and its amendments [21].

Disclosure Statement

The authors declare that they have no conflict of interest.

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