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A phase I study of lapatinib in combination with carboplatin in women with platinum sensitive recurrent ovarian carcinoma

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Abstract

Objectives. To determine the maximum tolerated dose (MTD), spectrum of toxicities, clinical activity, and pharmacokinetics of carboplatin given in combination with lapatinib in women with a first recurrence of platinum sensitive epithelial ovarian carcinoma.

Methods. Patients with measurable, platinum sensitive recurrent epithelial ovarian carcinoma were eligible. Cohorts of 3–6 patients were to receive up to 6 cycles of intravenous carboplatin AUC of 6 every 21 days in combination with escalating dosages of oral lapatinib (starting at a dose of 750 mg daily). Toxicity was assessed using NCI CTC for Adverse Events. Clinical response was monitored using RECIST criteria. Pharmacokinetic (PK) analysis was performed for the second cohort of patients.

Results. Twelve patients were enrolled. No dose limiting toxicity was noted. Two of 6 patients in the first cohort had unanticipated excessive delays in treatment due to non-dose limiting G3 neutropenia. Therefore, the study was modified to reduce the carboplatin dose in the second cohort. The median number of courses administered to the 11 evaluable patients in these two cohorts was 2.8 (range 1–6). Drug-related grade 3 or 4 toxicities included non-dose limiting G4 thrombocytopenia ($n=1$), and non-dose limiting G3 neutropenia ($n=3$). Of the 11 patients who received ≥ 1 course of therapy, 3 (27%) had a partial response, and 3 (27%) had stable disease. The pharmacokinetics of carboplatin were not significantly altered by concomitant administration of lapatinib.

Conclusions. This regimen of lapatinib and carboplatin was associated with unacceptable non-dose limiting toxicities, excessive treatment delays and limited clinical responses.

Keywords: Ovarian cancer; Lapatinib; EGFR inhibitor; HER2 inhibitor

Introduction

Despite advances in therapy for ovarian cancer, most patients with this disease continue to have poor long term outcomes and new therapies are needed. Enhanced understanding of the molecular processes associated with carcinogenesis has led to efforts to develop targeted therapeutics for cancer. For example, therapies such as gefitinib and cetuximab that specifically target epidermal growth factor receptor (EGFR), also known as erbB-1, have been demonstrated to be effective in certain lung and colon cancer populations [1–4]. EGFR expression is also common in ovarian tumor cells and is associated with aggressive tumor growth, poor response to therapy, and poor overall outcome [5–7]. However, EGFR inhibitors have, as of yet, not been demonstrated to be highly effective as a potential therapeutic approach for ovarian cancer [8–10]. Even when combined with carboplatin in patients with proven EGFR-positive ovarian tumors, cetuximab produced only modest results [11].

ErbB-2, more commonly known as HER 2/neu, is part of the same family of transmembrane receptor tyrosine kinases as EGFR. The HER 2/neu targeted monoclonal antibody, trastuzumab, has been demonstrated to be highly effective in Her 2/neu expressing breast cancer [12] but, HER 2 is

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expressed in less than 15% of ovarian tumors [13]. Even in Her 2/neu over-expressing ovarian cancer patients, the response rate to trastuzumab has been poor [13]. HER 2/neu, however, is a common heterodimer partner for other ErbB receptors and can promote tumor growth and survival when dimerized with EGFR [14]. Thus, therapeutic strategies for ovarian carcinoma that offer simultaneous inhibition of EGFR and HER 2/neu may be appealing as a means to overcome the limitations noted when utilizing agents that selectively inhibit these growth factor receptors independently.

Lapatinib (TYKERB, GlaxoSmithKline, Research Triangle Park, NC) is an orally active and selective dual inhibitor of both EGFR and Her 2/neu tyrosine kinase activity. Lapatinib has been demonstrated to be both safe and effective in a variety of solid tumor clinical trials that included patients with head and neck, lung, breast, and colorectal carcinomas [15,16]. Clinical activity noted in these trials eventually lead to FDA approval of lapatinib in combination with capecitabine for patients with metastatic breast cancer who failed trastuzumab based combination therapy [17]. Several ovarian cancer patients were included in these initial clinical trials and in some of these patients, stabilization of disease was noted [15,16]. Promising results in these few ovarian cancer patients along with activity noted in other solid tumors led us to evaluate the potential utility of lapatinib in combination with chemotherapy in the context of ovarian cancer. Thus, the purpose of this study was to determine the maximum tolerated dose (MTD), spectrum of toxicities, clinical anti-tumor activity, and pharmacokinetics of oral lapatinib given in combination with carboplatin to women with a first recurrence of platinum sensitive epithelial ovarian carcinoma.

Materials and methods

Eligibility criteria

Patients with a measurable platinum sensitive (defined as recurrence $\geq$6 months from completing primary therapy) first recurrence of epithelial ovarian cancer or primary peritoneal cancer were eligible for the study. Patients had to be $\geq$18 years of age; have adequate organ function including a normal left ventricular ejection fraction; normal hematopoietic reserve, including white blood cell count >3000/uL, a platelet count >100,000/uL, serum creatinine <2.0, total bilirubin <1.5× institutional upper limit of normal, and AST, ALT, and alkaline phosphatase <2.5× the institutional upper limits of normal; GOG performance status of $\leq$2; life expectancy >12 weeks; and have provided informed consent. Patients were excluded if they had known brain metastases, were pregnant, had known HIV infection, or were unable to effectively utilize oral medications or used medications known to interfere with the metabolism of lapatinib.

Prior to enrollment, all potential study patients underwent medical evaluation including complete history and physical, toxicity and performance status assessment. Laboratory evaluation included hematology, serum chemistries, and pregnancy test, as indicated. Other pre-treatment evaluations included an electrocardiogram and an echocardiogram or multigated radionucleotide angiography (MUGA) scan, and clinical and radiographic assessment of disease status by CT or MRI.

General study design

A Phase I trial study design utilizing oral lapatinib in combination with intravenous carboplatin was employed. Cohorts of 3–6 patients were to receive up to six cycles of intravenous carboplatin at an AUC of 6 every 21 days in combination with a daily dose of oral lapatinib. For calculating the Carboplatin dose, the creatinine clearance was estimated using the method of Jelliffe. The dose of lapatinib ranged from 750 mg daily to 1500 mg daily in the various treatment cohorts and was escalated between dosing cohorts in 250 mg increments. The study was approved by the Institutional Review Boards of the University of Alabama at Birmingham and Indiana University.

Assessment of toxicity and dose modification

Clinical toxicity was monitored by history and physical examination prior to each carboplatin infusion, and 3 weeks after completion of therapy. Blood counts and serum chemistries were performed prior to each cycle to assess for acute laboratory toxicities. Echocardiogram or MUGA was repeated every 8 weeks to assess for cardiac toxicity.

Toxicity was assessed using version 3.0 of the NCI Common Terminology Criteria for Adverse Events. Dose limiting toxicity (DLT) was defined as a Grade 3 or 4 prolonged (>21 days) skin rash or diarrhea, Grade 3/4 non-hematologic/non-constitutional toxicity, febrile neutropenia, or any graded 4 neutropenia or thrombocytopenia lasting longer than 7 days. Dose adjustments were made as necessary according to the most significant toxicity. For hematologic or non-hematologic toxicities leading to treatment delays >7 days, the carboplatin AUC was decreased to an AUC of 5 in subsequent cycles. In the event of DLT in the first cohort, a de-escalated carboplatin dose was to be utilized for the remainder of the trial. For grade 3 or higher non-hematologic/non-constitutional toxicities, lapatinib was held up to 21 days until toxicity had resolved to grade 1 or less. The lapatinib dose was lowered one level upon restart. If toxicity was not resolved in 21 days, the patient was taken off study.

Assessment of clinical response

All patients were assessed for clinical response by physical examination and CA-125 prior to each cycle and 3 weeks post-therapy. Radiographic tumor assessment was performed pre-therapy, after the 3rd and 6th doses and post-therapy. Response was determined using Response Evaluation Criteria in Solid Tumors (RECIST) criteria [18].

Pharmacokinetic analyses

To measure and compare carboplatin levels in the presence and absence of lapatinib, blood samples were obtained during