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Phase II Trial of Lapatinib and Topotecan (LapTop) in Patients with Platinum-Refractory/Resistant Ovarian and Primary Peritoneal Carcinoma

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Abstract

Objective—Resistance to chemotherapy is a major challenge in the treatment of ovarian/peritoneal cancer. One purported mechanism of topotecan resistance is the breast cancer resistance protein (BCRP) and P-glycoprotein (Pgp). We designed a phase II clinical trial evaluating the efficacy and adverse events profile of concomitant topotecan and lapatinib, a small molecule pan-erbB inhibitor that can block BCRP/Pgp efflux of topotecan.

Methods—Patients with platinum-refractory or resistant epithelial ovarian/peritoneal cancer were treated with topotecan 3.2 mg/m² IV on Day 1, 8 and 15 and lapatinib 1250 mg PO daily, continuously in 28 day cycles. The primary endpoint was response rate. For correlative studies, archived tissue was assessed for expression of EGFR, HER2, HIF-1 α , CD31, and BCRP.

Results—Eighteen patients were enrolled and treated. Four experienced evidence of clinical benefit: one partial response and three with stable disease. Using a two-stage Simon design, the trial was stopped after the first stage due to insufficient activity. Grade 3+ and 4+ adverse events (AE) were experienced in 14 and 4 patients, respectively. The most common grade 3/4 AE were neutropenia (56%), thrombocytopenia (28%), and diarrhea (22%).

Conclusions—The combination of lapatinib plus topotecan for the treatment of platinum refractory/resistant epithelial ovarian cancer lacks sufficient activity to warrant further investigation. In particular, hematologic adverse events were substantial. Expression of correlative study markers did not reveal patterns of predicted benefit or toxicity. Disruption of erbB signaling

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Conflict of Interest Statement

None of the authors have any conflicts of interest to disclose.

and BCRP/Pgp efflux with lapatinib was insufficient for overcoming topotecan resistance, suggesting alternative mechanisms of resistance are involved.

Introduction

In the United States, ovarian cancer affects an estimated 21,880 women annually, making it the second most common gynecologic cancer [1]. Although the 5-yr survival rate for low-grade, early-stage epithelial ovarian cancer (EOC) is about 90%, the majority of patients are diagnosed at later stages, which is associated with a 28% five-year survival [2]. Most patients with advanced disease who initially respond to treatment will eventually relapse, making EOC the most lethal gynecologic malignancy. When compared to other cancers in women, the death-to-incidence ratio of EOC (68 per 100) is more than 3-times that of breast cancer (21 per 100) and equivalent to lung cancer as the most lethal malignancy [1]. This high mortality rate is multi-factorial, due in part to a lack of effective screening strategies and the resultant predominance of late-stage diagnoses, limited chemotherapy options, high relapse rate, and poor response of platinum-resistant tumors to salvage regimens.

Although the standard of care remains a taxane- and platinum-based chemotherapy regimen, more therapeutic options are needed for treating relapses. Topotecan, a topoisomerase I inhibitor, has demonstrated significant activity against ovarian cancer, leading to approval for its use by the US FDA for the treatment of EOC [3–5]. Myelosuppression is the principal toxicity and can be partially ameliorated by weekly, rather than daily, dosing [6].

Dysregulation of the human epidermal growth factor (HER) family of receptors leads to uncontrolled proliferation, angiogenesis, metastasis, and other pro-tumorigenic effects leading to a survival advantage and poor prognosis [7, 8]. The HER family consists of four related membrane tyrosine kinase receptors: epidermal growth factor receptor (EGFR), HER2, HER3, and HER4. Targeting one or more of the HER receptors has demonstrated activity in the three most common malignancies afflicting American women: breast cancer [9], lung cancer [10], and colorectal cancer [11]. While EGFR and HER2 are expressed in a substantial portion of EOC, 6–6% and 5–57% respectively [12], the role of the HER family in ovarian cancer initiation and progression is less known. Clinical trials of single agent HER antagonists in ovarian cancer have thus far been disappointing. For example, a phase II clinical trial of single-agent trastuzumab, a HER2 receptor antibody, in patients with recurrent or persistent ovarian or primary peritoneal carcinoma exhibited a response rate of 7.3% [13]. Although a larger study with single-agent pertuzumab, a HER dimerization inhibitor, demonstrated a similar response rate [14], the phospho-HER2 subgroup exhibited a trend toward improved progression free survival, suggesting further studies are needed in select biochemically-defined subsets of patients.

Many cancer cells express ABC transporter proteins like breast cancer resistance protein (BCRP) and P-glycoprotein (Pgp), which efflux toxins, including chemotherapeutic agents and thus, provide a mechanism for chemoresistance [15, 16]. Some HER inhibitors, such as gefitinib [17], erlotinib [18], and lapatinib [19], target the BCRP and Pgp and can block its activity, leading to decreased efflux of topotecan [20] and enhanced cytotoxic effects [21]. Concomitant lapatinib and topotecan treatment increased intracellular levels of topotecan *in vitro*, enhanced the efficacy of topotecan *in vivo*, and when patients with advanced solid tumors were treated with combination therapy, stable disease was reported in 46% [22].

We hypothesized that lapatinib would improve the antitumor activity of topotecan through two means: (i) by inhibiting the efflux of topotecan by BCRP and (ii) by decreasing the prosurvival signaling of HER receptors. To test this hypothesis, we conducted a phase II trial to evaluate the efficacy of lapatinib and topotecan in women with platinum-resistant

ovarian cancer and primary peritoneal carcinoma. Secondary objectives were to determine overall survival, time to progression, the adverse event profile, and as correlative work, to determine 100 if HER receptor, BCRP, or other selected biomarkers could predict sensitivity or adverse events.

Methods

Patient Population

Patients were eligible for this clinical trial (RC0661) if they had histologically confirmed, platinum-refractory and/or –resistant (defined below), primary or relapsed, surgically debulked, epithelial ovarian cancer or primary peritoneal carcinoma. Participants also had measurable or non-measurable disease as defined below, life expectancy ≥ 12 weeks, an echocardiogram with an ejection fraction $\geq 50\%$, were at least 18 yrs old, and had acceptable baseline labs (ANC ≥ 1500 , PLT $\geq 100,000$, total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), AST $\leq 3 \times$ ULN or AST $\leq 5 \times$ ULN if liver involvement, creatinine $\leq 1.5 \times$ ULN, and hemoglobin ≥ 9.0 g/dL). Platinum-refractory patients were defined as those who failed to achieve a complete response during or at the completion of their primary adjuvant platinum-containing regimen. This would include patients with progressive disease during this primary therapy or patients with evidence of disease at the completion of platinum-based therapy. Platinum resistant patients initially had a complete response following their primary adjuvant platinum-containing regimen and subsequently relapsed within 6 months of the completion of the last cycle of adjuvant therapy or during/within 6 months after retreatment with a platinum-containing regimen. Patient could have received, at most, 2 prior lines of platinum-based chemotherapy. Patients were excluded from this study if they had malignant mixed müllerian ovarian tumors, pure mucinous ovarian tumors, or prior treatment with topotecan. Accrual occurred from February 2, 2007 to May 9, 2008, when a total of 18 patients were enrolled by eight study member sites. All patients were treated with the study regimen and were eligible for the final analysis.

Response Criteria

Measurable disease was defined as at least one lesion whose longest diameter can be accurately measured as ≥ 2.0 cm. Clinical lesions were only considered measurable when they were superficial (e.g., skin nodules, palpable lymph nodes). Lesions on chest x-ray were acceptable as measurable lesions when clearly defined and surrounded by aerated lung. However, CT was preferable. Measurable disease was assessed using the standard RECIST Criteria. All other lesions (or sites of disease), including small lesions (longer diameter < 2.0 cm) were considered non-measurable. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphagitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions were all non-measurable. Patients with non-measurable disease were allowed if they also had CA-125 values greater than 2-times the post-therapy nadir then progressively increased for two separate measurements prior to study enrollment.

Progressive disease (PD) was defined as one or more of the following: i) any new disease and/or clear progression of evaluable disease, ii) in patients with CA125 persistently elevated above ULN: > 2 fold elevation in CA125 from its lowest level (either initial level or nadir, whichever is lowest, since study enrollment) combined with clinical evidence of disease progression and with CA125 elevation confirmed by re-assay, or iii) in patients with CA125 below ULN at entry or at any point since study enrollment, increase in CA125 to $< 2 \times$ ULN combined with clinical evidence of disease progression and with CA125 elevation confirmed 144 med by re-assay.

A complete response (CR) was defined as: i) disappearance of any sign of evaluable disease, and ii) normalization of CA125. A partial response (PR) was defined as: i) decrement in CA125 by >50%, and ii) improvement in any additional evaluable disease (if present) as assessed by the enrolling physician and the MCCRC Study Chair. Stable disease (SD) was defined as a change in tumor size or CA125 insufficient to meet PD, PR, or CR criteria.

Statistical Analysis

Sample size was determined using a two-stage Simon design to test the null hypothesis that the true objective response rate was 18% versus the alternative hypothesis that the objective response rate was 38% with a type I error (α) of 0.10 and 91% power. Targeted accrual was 17 patients in stage I. If 4 or more of these first 17 patients achieved a partial or complete response during the first six 4-week cycles of treatment, an additional 20 patients would be recruited in stage II.

Overall survival and progression free survival were assessed via Kaplan Meier methods. Demographic data are presented with summary statistics. Expression of correlative markers is summarized via summary statistics. Associations of correlative markers with clinical endpoints were assessed via Fisher's Exact tests and Cox regression models.

Immunohistochemistry

Tumor specimens collected from primary debulking surgery were formalin-fixed and paraffin embedded. Five micron sections were deparaffinized and rehydrated prior to antigen retrieval following standard protocols for proteinase k (EGFR) or low-pH citrate buffer (Her2 and CD31). Antibodies against EGFR (PharmDx Kit, #K1494), Her2 (HercepTest Kit, 168 #K5207), and CD31 (#M0823) were purchased from Dako (Carpinteria, CA 93013). Antigen retrieval for HIF1-alpha (Novus Biologicals LLC #NB100-123; Littleton, CO 80120) and topoisomerase I (Abcam #AB58313; Cambridge, MA 02139) was performed using a Borg Decloaker from Biocare Medical (Concord, CA). BCRP staining was performed by Pathway Diagnostics (Malibu, CA 90265). All stained sections were graded by the same pathologist using the following scale: 0 (no staining), 1+ (weak brown granular staining), 2+ (moderate staining), or 3+ (course dark brown granular staining).

Results

Based on the favorable results of a phase I clinical trial [22], the LapTop trial (RC0661) was conducted to explore the efficacy and adverse events profile of lapatinib and topotecan in patients with platinum-resistant ovarian or primary peritoneal cancer. Using a two-stage Simon design, 18 patients were enrolled in stage 1 from February 2, 2007 to May 9, 2008. Baseline characteristics are shown in Table 1. Study participants had prior surgery and systemic chemotherapy without prior radiotherapy for their disease, had a median age of 66, a performance score of ≤ 2 , and were predominantly diagnosed with platinum-refractory ovarian cancer.

Response

Strategies to increase the bioavailability of chemotherapeutic agents have the potential to increase response rates for patients with ovarian cancer. Since lapatinib decreases the efflux of topotecan from tumor cells, we hypothesized that concomitant treatment with lapatinib and topotecan would demonstrate efficacy in patients with ovarian and primary peritoneal cancer. Thus, 18 patients were treated with lapatinib 1250 mg by mouth daily, continuously in 28 day cycles, and intravenous topotecan on Day 1, 8 and 15 at 3.2 mg/m². However, there were no complete responses, one partial response, and three patients with stable

disease (Table 3). Three patients were no longer on treatment at the 8- and 16-week measurement assessments due to adverse events or physician reasons. The treatment response was not sufficient to exceed the defined efficacy requirements, and thus the study was closed to accrual per protocol.

Overall survival and time to progression

To determine the overall survival and progression-free survival rate, patients were followed until death, or for an average of 2.1 years (range 1.8–2.2) in the four patients alive at study end (Table 3). The estimated one-year survival rate was 77.8% (Figure 1) with a median survival of 15.5 months. The median time to progression was 3.5 months (Figure 2) and progression occurred in all 18 patients.

Adverse Events

All patients were evaluated for adverse events as defined by the Common Terminology Criteria for Adverse Events v3.0 (Table 2). Grade 3+ and 4+ adverse events were reported in 14 (78%) and 4 (22%) patients, respectively, with hematologic events reported most commonly: neutropenia (56%) and thrombocytopenia (28%). The most common grade 3+ non-hematologic adverse events (occurring in 10% or more of patients) were diarrhea (22%) and dehydration (11%). A grade 5 adverse event of disease progression was observed in one patient during cycle 1 but this was not considered to be related to study treatment. This patient also experienced grade 1 thrombocytopenia and grade 3 neutropenia, both felt to be possibly related to study treatment. Grade 3+ adverse events were reported for rash, fatigue, vomiting, nausea, and hyponatremia but the incidence was low, 5.6%, for each. Fewer than 11.1% of patients reported grade 2 or less of the following: clostridial infection, constipation, hypophosphatemia, urinary tract infection, abdominal pain, or bladder pain

Expression profile of tumors

Since the efficacy of targeted therapies like lapatinib and the pharmacokinetics of actively effluxed drugs like topotecan can be influenced by the expression of specific targets or mediators, protein expression analysis by immunohistochemistry was performed on all tumors. The most common ovarian cancer histologic subtype was serous (77.8%), followed by clear cell (16.7%) and endometrioid (5.5%) (Table 1). All tumors expressed detectable levels of topoisomerase 1 and BCRP, the intended targets of topotecan and lapatinib, respectively (Table 4). Measurable EGFR and HER2 was 61.1 and 11.1% respectively. Hypoxia-inducible factor-1 alpha (HIF1- α) is a transcription factor with a key role in cell survival under hypoxic conditions and it is upregulated in many tumor types [23]. Although HIF1- α is associated with poor prognosis for women with ovarian cancer [24], there was no statistically significant association with clinical benefit or over-all survival in LapTop patients. Similarly, CD31, a pan-endothelial cell marker used to assess tumor microvascular density, is associated with poor prognosis [25–27]. However, expression of this and all other biomarkers did not correlate with clinical benefit or overall survival (Supplemental Table S1).

Discussion

The treatment of relapsed ovarian cancer, particularly platinum-resistant disease, poses great therapeutic challenges. As such, this phase II clinical trial investigated the efficacy and toxicity of lapatinib plus topotecan in platinum-resistant ovarian/peritoneal carcinoma. The hematologic adverse events were substantial and the response rate was low. The present study did not demonstrate significant clinical benefit of concomitant lapatinib and topotecan treatment in this patient population and the hematologic adverse events were substantial.

LapTop patients exhibited more grade 3 and 4 hematologic toxicity than previously reported by Molina et al. [22], which may be partially attributed to differences in patient baseline characteristics. For instance, patients in the present study were older and entirely female, both of which are known risk factors for hematologic toxicity [28]. When compared to other women with ovarian cancer treated with weekly-bolus topotecan at varying doses (1.5–4 mg/m²), the rate of grade 3/4 neutropenia in LapTop patients (56%) was higher than average, 19.5% (n=241) [29–35]. The higher rate of hematologic toxicity observed presently cannot be entirely explained by a higher weekly dose of topotecan (3.2 mg/m²) since 4 mg/m² was associated with less frequent grade 3/4 neutropenia, 7.7–47.8% of patients [32–35]. Although patients who have been heavily pretreated would be expected to exhibit greater myelosuppression, none of the LapTop patient received more than two prior courses of chemotherapy and most, 77.8%, received only one platinum-based chemotherapy regimen prior to enrollment (Table 1). Though speculative, the greater prevalence of grade 3 or 4 myelosuppression in the present study is possibly due to inhibition of BCRP by lapatinib and subsequently higher intracellular concentrations of topotecan in hematopoietic bone marrow cells. Indeed, hematopoietic stem cells express BCRP [36] and Bcrp1-null mice demonstrate increased sensitivity to the topoisomerase II inhibitor and BCRP substrate mitoxantrone [37].

Although HER inhibition has not demonstrated clinical benefit in ovarian cancer [13, 14], the concomitant administration of lapatinib and topotecan was expected to elevate tumor intracellular levels of topotecan, resulting in enhanced clinical response. However, the response rate reported herein (5.6%) did not approximate historical controls treated with single-agent topotecan, 19.5% (n=241) [29–35]. One possible contribution to the low response rate in LapTop patients may be dose reductions and treatment delays secondary to hematologic toxicity, which occurred in nine (50%) of LapTop patients, resulting in suboptimal dosing despite concomitant lapatinib treatment. Moreover, the majority of LapTop patients (72.2%) had platinum-refractory disease, which is associated with very poor outcomes. For instance, platinum-refractory ovarian cancer is associated with a shorter overall survival when treated with second-line agents like pegylated liposomal doxorubicin, paclitaxel, or topotecan compared with platinum-resistant ovarian cancer [38, 39]. In addition, there may be unintended biological effects of lapatinib which occurs through crosstalk with other signal transduction pathways. For example, *in vitro* studies have shown that OV202 ovarian cancer cells treated with a pan-HER inhibitor, BMS-599626, resulted in reciprocal activation of the stimulatory insulin-like growth factor 1 receptor, which in turn may confer a growth and survival advantage to cancer cells [40].

Expression of tumor markers by immunohistochemistry did not reveal a potential mechanism for the low response rate. All ovarian tumors expressed topoisomerase I and BCRP but only one patient achieved a partial response, suggesting that BCRP-mediated topotecan resistance is multifactorial. In addition, blockade of HER signaling was not sufficient to overcome topotecan resistance.

Recurrent ovarian cancer is associated with a high mortality rate. Since systemic therapies are not curative in this setting, treatment options should improve symptom-free survival and prolong life. These goals were not achieved in this study combining lapatinib and topotecan. Patients with platinum-refractory/resistant tumors represent a significant subset of ovarian cancers with a compelling need for better treatment options. The unexpectedly low response rate reported herein underscores the complexity of ovarian tumor biology and the need for novel therapies and better preclinical models of ovarian cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1. Overall survival (OS) of patients treated with concomitant lapatinib and topotecan. There were 14 (78%) deaths and the estimated 1-year OS was 77.8% (Exact 95% CI: 60.8–99.6%).

Fig. 2.
Time to Progression, occurring in 18 (100%) patients.

Table 1

Patient Characteristics

Characteristic	N	(%)
Median Age in years (range):	66	(27–94)
Gender:		
Female	18	(100.0)
ECOG Performance Score:		
0	4	(22.2)
1	13	(72.2)
2	1	(5.6)
Primary Tumor Site:		
Ovarian	16	(88.9)
Peritoneal	2	(11.1)
Primary Tumor Status:		
Platinum Resistant	5	(27.8)
Platinum Refractory	13	(72.2)
Number of Prior Treatments:		
One	14	(77.8)
Two	4	(22.2)
Histologic Subtype:		
Serous	14	(77.8)
Clear Cell	3	(16.7)
Endometrioid	1	(5.6)
Current Symptoms & Diseases:		
Yes	5	(27.8)
No	13	(72.2)
Median LVEF (%) (range):	65	(50–76)

Table 2

Grade 3 and 4 Adverse Events

Adverse Event	Grade 3+		Grade 4+	
	N	%	N	%
Any Hematologic	13	72.2	3	16.7
Neutropenia	7	38.9	3	16.7
Thrombocytopenia	5	27.8	0	0
Anemia	1	5.6	0	0
Leukopenia	2	11.1	0	0
Any non-Hematologic	6	33.3	1	5.6
Diarrhea	4	22.2	0	0
Nausea	1	5.6	0	0
Vomiting	1	5.6	0	0
Dehydration	2	11.1	0	0
Hyponatremia	1	5.6	0	0
Rash	1	5.6	0	0
Fatigue	1	5.6	0	0

Table 3

Follow Up (FU)

FU Time in Years for Alive Pts.	
Median (Range)	2.1 (1.8–2.2)
Progression Status, No. (%)	
Progressed	18 (100)
Follow-up Status, No. (%)	
Alive	4 (22.2)
Dead	14 (77.8)
Ended Treatment, No. (%)	
Yes	18 (100)
Reason End Treatment, No. (%)	
Disease Progression	15 (83.3)
Adverse Event	2 (11.1)
Died on Study	1 (5.6)
Cycles of Treatment*	
Median (Range)	4(1–13)
Objective Response	
CR	0 (0.0)
PR	1 (5.6)
SD	3 (16.7)
PD	13 (72.2)

* These patients either were no longer on treatment at the 8-week measurement assessment or went off treatment prior to a confirmatory scan (16-week measurement assessment); one patient went off study due to ANC > 14 days, one patient went off study due to physician reasons (CA125 increased), and one patient went off study due to adverse event of diarrhea (2 hold and no resolution).

Table 4

Correlative study markers

	Staining Score, N (%)			
	0	1	2	3
EGFR	7(38.9)	3(16.7)	6(33.3)	2(11.1)
HER2	16(88.9)	1(5.6)	1(5.6)	0
HIF1 alpha	10(55.6)	3(16.7)	5(27.8)	0
CD31	15(83.3)	0	2(11.1)	1(5.6)
Topoisomerase 1	0	0	1(5.6)	17(94.4)
BCRP	0	6(33.3)	11(61.1)	1(5.6)