HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2015 June 02.

Published in final edited form as:

Gynecol Oncol. 2009 June ; 113(3): 327–330. doi:10.1016/j.ygyno.2009.02.018.

A phase II study of weekly topotecan and docetaxel in heavily treated patients with recurrent uterine and ovarian cancers☆

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Abstract

Objectives—A phase II trial designed to evaluate the safety and efficacy of weekly topotecan and docetaxel in heavily treated patients with recurrent uterine or epithelial ovarian cancers.

Methods—Eligible patients with recurrent epithelial ovarian or uterine cancers were treated with weekly topotecan 3.5 mg/m^2 and docetaxel 30 mg/m^2 for 3 consecutive weeks. Cycles were repeated every 4 weeks for 6 cycles or until evidence of disease progression, unacceptable toxicity, or death. Response was assessed as per RECIST or Rustin's criteria. Time to best response and overall survival were calculated using Kaplan–Meier statistical methods.

Results—Twenty-seven patients registered, of which 24 were evaluable for response. The majority of patients had received 2 prior chemotherapy regimens. Of the total 86 cycles of chemotherapy that were administered, there were three grade 4 (all neutropenia) and ten grade 3 toxicities. Six of the grade 3 non-hematologic toxicities were unrelated to treatment. There were 8 dose delays and 4 dose reductions. The overall response rate was 25% (95% CI: 7.7%–42.3%, 8% CR, 17% PR), and 38% of the patients had clinical benefit (95% CI: 18.1%–56.9%; CR+PR+13% SD). The median duration of response was 8.5 months (range 3–19 months). The median overall survival was 18.5 months (range 1.8–50.7 months).

Conclusion—The combination of weekly topotecan and docetaxel has clinical benefit and is well tolerated in this heavily treated patient population. Patients with platinum-resistant tumors had clinical benefit and should be considered for further study with this regimen.

Keywords

Ovarian cancer; Uterine cancer; Chemotherapy; Topotecan; Docetaxel; Clinical trial

☆Clinicaltrials.gov Unique Identifier #NCT00231855. A portion of this clinical trial data was previously presented at the 2007 Society of Gynecologic Oncologists Annual Meeting San Diego, CA

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Introduction

Patients with recurrent uterine and recurrent epithelial ovarian cancer (EOC) are often heavily treated with different chemotherapy combinations and they may not tolerate additional standard dose chemotherapeutic regimens. One of the goals of treatment at the time of recurrence is to try to stabilize disease without worsening the patient's quality of life.

Recent data has demonstrated efficacy of topotecan and docetaxel in uterine and ovarian cancers. Phase I/II studies have demonstrated that topotecan has activity in advanced and recurrent uterine cancer with overall response rates ranging from 9 to 23% [1-5]. Reported side effects were mainly hematologic, specifically, neutropenia and thrombocytopenia. These were managed effectively with hematopoietic stimulating factors.

Taxanes have also been reported to be effective in the treatment of advanced and recurrent uterine cancer [6-13]. Endometrial cancer cell lines have demonstrated sensitivity to paclitaxel [8]. Response rates of 35%–37% have been reported in two separate phase II trials of paclitaxel in advanced endometrial cancers [6,7,10]. The SCOTROC trial demonstrated equivalence of docetaxel when substituted for paclitaxel in the treatment of primary ovarian cancer with significantly decreased peripheral neuropathy [14]. Phase II studies have demonstrated a 21–31% response rate of docetaxel in advanced or recurrent uterine cancer [9,11]. Gunthert et al. reported no patients with grade 3 or 4 toxicity while Katsumata, et al. reported significant grade 3 or 4 neutropenia as the major toxicity.

Topotecan is a commonly used agent in patients with recurrent ovarian cancer. Response rates of between 14% and 50% have been reported in the literature, including a large Gynecologic Oncology Group (GOG) study [15-17]. In addition, weekly dosing schedules suggest similar activity in ovarian cancer patients with less toxicity, especially myelosuppression [16-18].

Both topotecan and docetaxel are commonly used agents in recurrent ovarian cancer but not always in combination. Docetaxel has been shown to have response rates of 7–30% in platinum-refractory patients [19-22]. Docetaxel has also demonstrated clinical response in patients classified as paclitaxel-refractory, confirming an incomplete cross-resistance between these two agents [23-24].

Because of the broad-spectrum antitumor activity of topotecan and docetaxel that may not be cross-resistant, several phase I trials have been conducted with this combination regimen in various tumor types [25-31]. Docetaxel was administered on day 1 followed by daily intravenous topotecan on days 1–3 versus 1–5. Dose limiting toxicity for each regimen was myelosuppression, consisting of both neutropenia and/or thrombocytopenia requiring prophylactic growth factor support or dose reduction.

Weekly dosing of this combination regimen may preserve the synergy of this combination while decreasing toxicity. Both patients with recurrent uterine and ovarian cancers have response rates less than 30% with current second or third line chemotherapy regimens after front line therapy, and the clinical outcomes are similar [32,33]. The commonly utilized

chemotherapy regimens after failing first line therapy are similar in recurrent uterine and ovarian cancer patients. Therefore, we initiated a single-institution Phase II trial of weekly docetaxel and topotecan in heavily treated patients with recurrent uterine and ovarian cancer to evaluate the safety and efficacy of this doublet regimen.

Materials and methods

This is an open-labeled phase II trial. The primary outcome is response to treatment. The secondary aim is to evaluate the safety and toxicity profile of the regimen in this patient population.

Patients

Eligible patients must have had recurrent uterine, epithelial ovarian, fallopian, or primary peritoneal cancer. Recurrent uterine cancer was defined as measurable disease that was documented by biopsy or surgery. Recurrent ovarian, fallopian, or primary peritoneal cancer was defined as measurable disease by imaging or by Rustin's criteria [34]. In patients who had prior radiation therapy, the disease recurrence could have been inside or outside the radiation field. Patients were required to be able to have the capacity to consent to the trial, have an ECOG performance status of less than or equal to 2 and no more than grade 1 peripheral neuropathy. They received no chemotherapy or radiotherapy within 4 weeks prior to starting the trial.

Patients were excluded if they had impaired hematologic, renal, or hepatic functions including platelet count less than 100,000/mm^3, absolute neutrophil counts (ANC) less than 1500/mm^3, hemoglobin less than 8.0 g/dL, serum creatinine clearance less than or equal to 50 ml/minute, bilirubin less than or equal to the upper limit of normal, and AST, ALT, and alkaline phosphatase less than or equal to 1.5 times the upper limit of normal. Patients could not have chronic or active hepatitis or other uncontrolled medical conditions. Patients with known severe hypersensitivity to either study medication or the formulants were excluded.

Patients were removed from the study if they had disease progression, an unacceptable adverse event, or by an independent decision by the patient or treating gynecologic oncologist. All patients signed written, informed consent prior to initiating therapy. Institutional review board approval for the protocol and the consent were obtained prior to patient enrollment.

Treatment plan

Patients were clinically evaluated prior to each chemotherapy cycle. Serum chemistry, liver function tests, and complete blood count were performed every week. Tumor markers were drawn every 4 weeks. Radiographic assessment with CT scan of the abdomen and pelvis (and chest, when appropriate) was performed before initiation of therapy, after 3 cycles of chemotherapy, and at the end of the treatment to evaluate tumor measurements. Radiologic target lesions for therapeutic evaluation were identified and designated prior to initiating therapy.

Patients were treated with topotecan 3.5 mg/m^2 followed by docetaxel 30 mg/m^2 on day 1 and then weekly. Each cycle consisted of weekly therapy for 3 weeks (d1, 8, and 15) followed by a 1-week rest for a total of 6 cycles, progressive disease, dose-limiting toxicity, or death. Blood transfusions and G-CSF support were given as clinically indicated based on standard NCCN guidelines [35]. Toxicity was graded based on the standard National Cancer Institute Common Toxicity Criteria, version 2.0. Dose delays were permitted for up to 2 weeks for grade 3 or 4 hematologic or gastrointestinal toxicity. Chemotherapy doses were omitted or decreased based on hematologic parameters. Weekly doses were held for an ANC less than 999/mm^3 or platelets less than 50,000/mm^3. Subsequent doses were reduced by 20–30% based on the severity of the neutropenia or thrombocytopenia as deemed necessary by the primary treating physician. Elevations of AST, ALT, or alkaline phosphatase greater than 2.5 times the upper limits of normal resulted in dose omission or delay. Docetaxel was withheld or delayed for bilirubin levels greater than the upper limits of normal, grade 2 or greater stomatitis or peripheral neuropathy. Hypolacrimation was treated with artificial tears and docetaxel was withheld. For other grade 3 or 4 non-hematologic toxicities (excluding grade 3 or 4 nausea, vomiting, or alopecia), both treatment doses were held until resolution of toxicity to grade 2 or less with a subsequent 20% dose reduction.

Response was measured and confirmed using the standard RECIST and modified Rustin's criteria where appropriate [34,36]. Response was categorized as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) by established criteria. The proportion of patients who responded to treatment was computed along with corresponding 95% confidence interval.

Results

The patient characteristics are presented in Table 1 Twenty-nine patients were enrolled in the study from August, 2004 until February, 2007 and 27 were treated per protocol. One patient died before beginning treatment, and one withdrew consent. Of the 27 patients,15 had recurrent EOC, 3 had primary peritoneal cancer, and 9 had recurrent uterine cancer (6 UPSC, 3 endometrioid adenocarcinoma). All 27 patients had prior combination chemotherapy regimens: 9 had 1 prior regimen, 16 had 2 prior, 1 had 3 prior, and 1 had 4 prior regimens. Two patients had received prior radiation therapy in addition to prior chemotherapy.

A total of 86 cycles of chemotherapy were administered. There were three grade 4 toxicities and ten grade 3 toxicities (Table 2). Six patients were admitted for grade 3 non-hematologic toxicity while on protocol: three for abdominal pain (two due to disease progression, one from diverticulitis), two with lower back pain (both with bone metastases), and one patient with unilateral lower leg swelling and pain due to deep venous thrombosis and cellulitis. The three grade 4 toxicities were related to severe neutropenia. A total of 18 patients required additional supportive therapy due to myelosuppression or at the discretion of the investigator. Five patients received blood transfusions and 16 received erythropoietin-containing products for chemotherapy-related anemia. Two patients required G-CSF support for neutropenia. There were 8 dose delays and 4 dose reductions in total. Two dose reductions were due to grade 3 hepatic toxicity (elevated SGPT and LDH in one patient and

elevated bilirubin in another patient). The other two dose reductions were due to grade 3 thrombocytopenia.

Three patients could not be assessed for response because they voluntarily withdrew from the study after receiving one dose of chemotherapy on study. Out of the 24 evaluable patients, 2 patients had a complete response, 4 had a partial response, 3 had stable disease, and 15 had progressive disease. The overall response rate was 25% (95% CI: 7.7%–42.3%, 8%CR, 17% PR) and 38% of the patients had clinical benefit (95% CI: 18.1%–56.9%; an additional 13% SD). The median time to best response was 2.5 months (range 1.1–6 months). The median duration of response was 8.5 months (range 3– 19 months). The median overall survival was 18.5 months (range 1.8–50.7 months, see Fig. 1 for Kaplan–Meier survival curve). There were no treatment related deaths. Two patients who had a PR and one with stable disease were originally platinum-resistant.

Discussion

To our knowledge, this is the first trial to evaluate the weekly combination of docetaxel and topotecan in heavily treated patients with recurrent uterine, epithelial ovarian, and primary peritoneal cancers. Weekly topotecan (3.5 mg/m^2) and docetaxel (30 mg/m^2) was a well-tolerated regimen in this heavily chemotherapy treated patient population. Treatment was delivered on schedule in the majority of treatment cycles. The majority of the grade 3 toxicities were related to disease progression or other medical problems and non chemotherapy-related toxicities. All three of the grade four toxicities were related to neutropenia. Excluding four of the grade 3 or 4 toxicities related to disease progression, nine out of the 86 cycles (10%) resulted in clinically relevant toxicities. In addition, dose reductions or treatment delays were infrequent.

ICON 4 established the superiority of doublet versus monotherapy in appropriate subsets of patients with platinum-sensitive ovarian cancer [37]. Patients who received a paclitaxel and platinum regimen had an improved overall survival (median 5 months) and progression free survival (median 3 months) as compared to patients who received platinum monotherapy. Published response rates for weekly topotecan monotherapy in patients with recurrent ovarian cancer range from13.6 to 47.8% [16,17]. Up to 21% of patient with advanced or recurrent endometrial cancer responded with weekly docetaxel monotherapy [9]. Our study also included more heavily pretreated subjects than most previously-reported studies. In addition, the overall survival we observed with the combination of weekly topotecan and taxotere is higher (18.5 months) when compared to published data in prior phase II studies with similar patient populations [9,16].

Three patients with platinum-resistant ovarian cancer responded to treatment (2 PR, 1 SD). Albeit not statistically relevant, this suggests that the combination of docetaxel and topotecan may deserve further study in platinum-resistant patients, a group of patients where topotecan and docetaxel monotherapy has demonstrated a variable rate of activity [23,38-42].

Both preclinical and phase I studies build the basis for using topotecan and docetaxel combination. They both have a broad spectrum of activity. *In vitro* data has shown this combination may have synergistic effects on tumor death [43,44]. Docetaxel may have the greatest synergistic effects with topotecan when given at the time of highest topotecan-induced G_2-phase cell arrest [45]. Both of these drugs are also metabolized by the CYP 3A4 system, possibly potentiating toxicity. However, such toxicities were not seen in this study.

There are several limitations of this study. We combined patients with recurrent uterine, ovarian, and primary peritoneal cancers in this study since the responses to therapy in this setting are similar. Also, while the underlying biology of these tumor types is likely different, women with these tumors have similar clinical courses, often with advanced upper abdominal, lymphatic, and distant metastases. In addition, the total number of patients recruited to this study was small, limiting multivariate or subset analyses.

The combination of weekly docetaxel and topotecan appears to have activity in recurrent uterine, ovarian, and primary peritoneal cancers. In addition, the safety profile of this regimen is acceptable in a heavily pretreated population where optimal treatment options are challenging secondary to toxicity. The results of our study suggest that further evaluation of this regimen in patients with platinum-resistant ovarian cancer and recurrent high risk uterine cancers is warranted.

Acknowledgments

Conflict of interest statement

This study was funded, in part, by Investigator-Initiated Grants (M.H.E.) from Sanofi-Aventis and GlaxoSmithKline Oncology for research-related costs.

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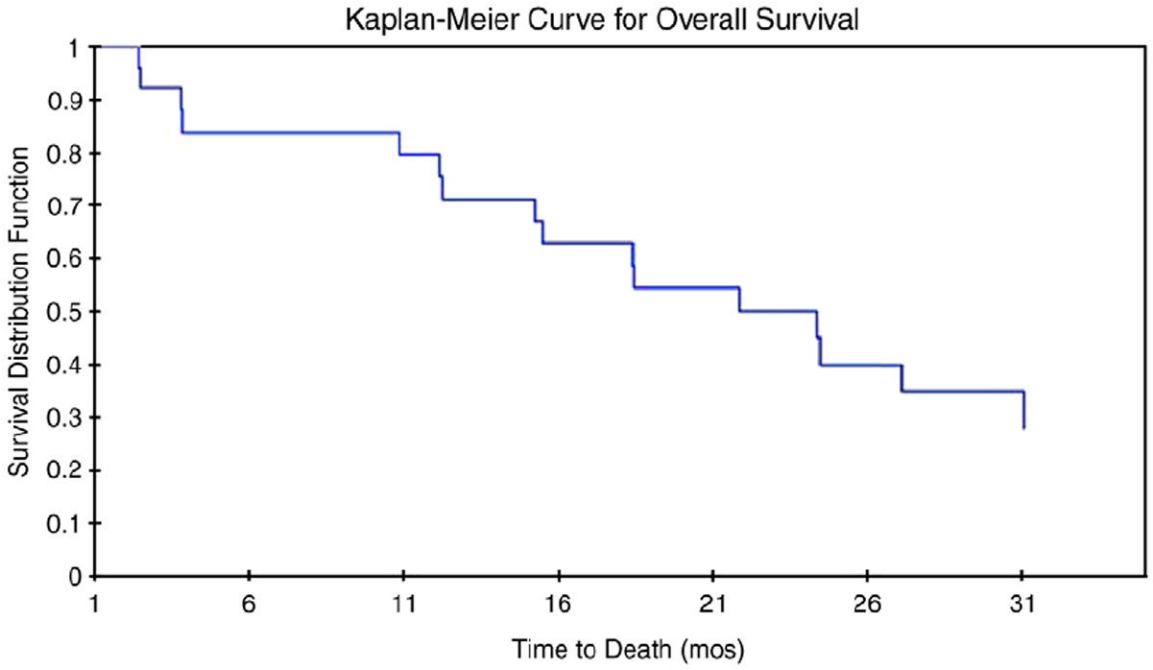

Fig. 1.

Kaplan–Meier curve for overall survival (*N* = 24). Median survival was 18.5 months (range 1.8–50.7 months) for patients treated with weekly topotecan and docetaxel. The median time to best response was 2.5 months (range 1.1–6 months).

Table 1

Patient demographics and baseline disease characteristics, *N*=29.

Median age (years)	63 (47–79)
ECOG performance status	
0	0
1	25
2	4
Primary tumor site	
Ovary	16
Peritoneum	3
Uterine	10
Histology	
Serous	22
Endometrioid	4
Clear cell	2
Carcinosarcoma	1
Stage	
I–II	7
III	17
IV	5
Suboptimal-debulking	3
Platinum resistant	11
Prior # of chemotherapy regimens	
0	2
1	9
2	16
>=3	2
Prior radiation therapy	7

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

Table 2

Dose reduction and delay-related toxicity (out of a total of 86 cycles administered).

Grade	3	4
Gastrointestinal — bloating	1	0
Pain	2	0
Neuro-sensory back/leg pain	2	0
Leg swelling	1	0
LFT elevation	2	0
Thrombocytopenia	2	0
Neutropenia	0	3

Abbreviation: LFT = liver function tests.