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A phase I study of IV doxorubicin plus intraperitoneal (IP) paclitaxel and IV or IP cisplatin in endometrial cancer patients at high risk for peritoneal failure (GOG 9920): An NRG Oncology/ Gynecologic Oncology Group study

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Abstract

Objective—To determine the maximum tolerated dose (MTD) of a modified paclitaxel/ doxorubicin/cisplatin (TAP) regimen which incorporated intraperitoneal (IP) paclitaxel or IP paclitaxel/cisplatin in advanced endometrial cancer.

Methods—Patients (pts) with FIGO (1998) Stage IIIA/IIIC with positive cytologic washings/ ascites, adnexa, or serosa or Stage IV (intraperitoneal disease spread), histologically confirmed endometrial cancer were eligible. The study was designed as a phase I, 3+3 dose escalation study evaluating 5 dose levels (DL). All pts received cycle 1–2 with IV TAP, and cycles 3–6 with IV/IP therapy, on a 21 day schedule. Adverse events were evaluated on cycles 3–4 for dose limiting toxicity (DLT) and dose escalation decisions.

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Conflicts of Interest

The authors wish to report that there are no relevant conflicts of interests with the exception of Dr. Kathleen Moore who would like to disclose that she has received personal fees for being on the advisory boards of Astra Zeneca, Genentech/Roche, ImmunoGen, Advaxis and Amgen. Additionally, Dr. Premal Thaker reports that he has received personal fees from Incyte as a member of the Data Advisory Board as well as Celsion for his role as a Consultant.

Results—Twenty-one pts were enrolled, of which 17 were evaluable for DLT. Most pts had Stage IV disease (76%) and serous/clear cell histology (59%). The MTD was determined to be DL3 (cycles 3–6 including paclitaxel 90 mg/m² IP, doxorubicin 45 mg/m² IV, cisplatin 50 mg/m²). Three DLT events occurred and were related to grade 3–4 metabolic toxicities. There was one grade 2 sensory neuropathy event and myelosuppression was tolerable without the use of G-CSF. 88% of evaluable pts completed 6 cycles of therapy. With a median follow-up of 22 mo, 46% of patients remain progression-free at 2-yr.

Conclusion—We described an IV/IP based modification of a standard TAP regimen in endometrial cancer. Based on the high rate of completing 6 cycles of therapy, low rates of neuropathy, and promising PFS, further study of IP therapy in endometrial cancer is warranted.

Keywords

doxorubicin plus intraperitoneal; endometrial cancer patients; cisplatin; NRG Oncology

INTRODUCTION

The evolution in management of patients with advanced stage endometrial cancer has been pushed by an understanding of patterns of spread and recurrence. Among patients with clinically apparent Stage I-II disease evaluated in large surgical-pathologic studies, 9% were found to have node positive disease, and 2-6% were found to have intraperitoneal metastases [1–2]. Stage is one of the most important risk factors associated with recurrence and survival, and the extent and distribution of disease defines use of post-operative adjuvant therapies [3]. Clinical trials for patients with advanced stage disease commonly include populations with Stage IIIA-IVB. However, patients with Stage III and IV disease have different clinical behaviors and prognosis. For example, patients with Stage IIIC endometrial cancer and negative cytology, adnexa, and serosa have good outcomes with standard therapies producing 5-yr survival of 72–100% [4–6]. Patterns of failure for these patients occur at a distant site as the most common with isolated abdominal failures being distinctly unusual. Patients with Stage IIIC disease and positive cytology, adnexa, and/or serosa have a much poorer prognosis with 5-yr survival rates of ~30%, [5,7]. Patients with intraperitoneal disease spread have a high-risk of disease recurrence with 5-yr survivals reported from 5–20% [8–11]. Patients with Stage IV endometrial cancer, by virtue of intraperitoneal disease spread, appear to have a clinical behavior similar to those patients with Stage IIIC disease with additional extra nodal disease spread. In a series of 51 patients with Stage IV disease, intraperitoneal failures accounted for 48% of recurrences [8]. Mariani and colleagues evaluated 131 patients with recurrent endometrial cancer and found that of the 37 patients with peritoneal failure, nearly 60% had Stage IV disease. By contrast, only 2% of patients with Stage I-III disease experience intraperitoneal failures [9]. Novel approaches to treat subsets of patients with unique patterns of failure or risk of recurrence are needed.

Chemotherapy in endometrial cancer has been derived from the identification of single agent activity of doxorubicin, paclitaxel, and platinum analogues in recurrent disease. These agents have been evaluated in various combinations in patients with advanced or recurrent disease. The GOG 122 study compared whole abdomen radiation therapy (WART) to doxorubicin and cisplatin chemotherapy in patients with Stage III-IV endometrial cancer

with gross residual disease < 2 cm [12]. Results demonstrated that combination chemotherapy achieved superior progression-free survival (PFS) (5-yr, 50% vs 38%, Hazard ratio [HR] 0.71) and overall survival (OS) (5-yr, 55% vs 42%, HR 0.68) compared to those patients treated with WART. The differential response to chemotherapy was more apparent in the patients with Stage IV disease (HR 0.56, confidence interval [CI] 0.37–0.84) than for patients with Stage III disease (HR 0.82, CI 0.59–1.13). The results of this study pushed chemotherapy into the forefront of management of patients with advanced stage disease. Which chemotherapy regimen is superior has also been the subject of much study in patients with bulky, advanced or recurrent endometrial cancers. Within the GOG, the three drug paclitaxel, doxorubicin, and cisplatin (TAP) regimen produced improved response rates (RR) (57% vs. 34%), PFS (median 8.3 vs. 5.3 mo), and OS (median 15.3 vs. 12.3 mo) compared to doxorubicin and cisplatin resulting in the TAP regimen being considered a new standard of care [13]. Despite improvements in response rate and survival with chemotherapy, the complete response rate is still low (<25% in patients with measurable disease), and ~50% of Stage III patients and 90% of Stage IV patients recur and die of their disease [12,13].

In ovarian cancer, introducing new combinations of cytotoxic agents or the addition of biologic agents have failed to result in improvement in survival in first-line management [14–15]. However, manipulating dose, schedule, and route of administration of standard chemotherapy regimens with intraperitoneal or dose-dense administration have resulted in improved survival and suggest a possible pathway to improve outcomes in patients with endometrial cancer [16–17]. In an effort to develop a regimen with improved intraperitoneal disease control while maintaining adequate systemic coverage, we envisioned that adding intraperitoneal (IP) drug delivery to the TAP regimen would be an effective therapy in advanced endometrial cancer. The IP route might also allow for a reduction in the toxicity noted with the IV TAP regimen. Since IP based regimens in endometrial cancer had not been well-studied the present phase I study with IP-based TAP was conducted [18].

MATERIALS AND METHODS

This phase I study was performed to determine the maximum tolerated dose (MTD) of a modified TAP regimen. Patients were required to have histologically confirmed endometrial cancer and FIGO (1998) Stage IIIA/IIIC with positive cytologic washings/ascites, adnexal spread, or serosal involvement or Stage IV by virtue of intraperitoneal disease spread. Eligible patients had a GOG performance status (PS) of 0-2 and adequate organ function including an absolute neutrophil count (ANC) $1,500/\text{mm}^3$, platelets (PLT) $100,000/\text{mm}^3$, hemoglobin 10 g/dl , creatinine $2 \text{ mg/\%}$ or 24 hour creatinine clearance 50 ml/min , bilirubin $1.5 \times$ upper limit of normal (ULN), SGOT and alkaline phosphatase $2.5 \times$ ULN. Patients were required to have a normal left ventricular ejection fraction at study entry. All patients were enrolled within 8 weeks of initial surgery. The initial surgery included a hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic nodal dissection was encouraged but not required. Intraperitoneal and bulky nodal disease, if present, was to be debulked to 2 cm residual. Patients were not allowed to have received prior radiation or chemotherapy for endometrial cancer. Eligible and enrolled patients were centrally registered and provided signed informed consent consistent with all regulatory requirements.

For all patients, cycles 1–2 were administered with standard IV TAP [12] and cycles 3–6 were administered with modified IV/IP TAP regimen (IP paclitaxel, IV doxorubicin, or IP or IV cisplatin depending on the DL, see Table 1). For DL 1–3, patients received IP paclitaxel and for DL 4–5, patients received IP paclitaxel and cisplatin during cycles 3–6. Once the MTD for IP paclitaxel (given in combination with the fixed doses of intravenous doxorubicin and cisplatin) had been established, two dose levels were proposed administering intravenous doxorubicin with IP cisplatin and IP paclitaxel.

Cycles were to be given every 21 days, and 6 total cycles of therapy were to be administered. Routine anti-emetic regimens and hypersensitivity prophylaxis were used. All patients received prophylactic G-CSF during cycles 1–2, but its use was not permitted with cycles 3–6. Following cycle 2, all patients underwent a CT scan of the abdomen and pelvis to evaluate for progressive disease. Patients with documented disease progression or symptomatic deterioration were removed from study. Patients failing to treat with cycle 3 were replaced.

Adverse events (AEs) were scored (CTCAE v 3.0). Dose limiting toxicity (DLT) for the purposes of dose escalation decisions was defined based on AEs reported on cycles 3 and 4. Criteria defining a DLT included grade 4 thrombocytopenia or grade 3 thrombocytopenia and associated with clinically significant bleeding, grade 4 neutropenia lasting 7 days, treatment related febrile neutropenia, related toxicity of any grade leading to a treatment delay > 2 weeks, any grade 3–4 non-hematologic toxicity (excluding fatigue, hypersensitivity reaction, or nausea and vomiting), or any drug related death. The frequency and severity of adverse events was assessed during cycles 1–6. Toxicity was managed by prescribed dose delays or modifications. Subsequent cycles of therapy did not start until toxicities grade 2 resolved to Grade 1 and until ANC 1500 cells/mm³, PLT 100,000/mm³, and the creatinine 2 mg/%.

The dose escalation phase of the study was conducted in a standard 3+3 cohort design. Three patients were to be evaluated at the first dose level. Depending on the rate of dose limiting toxicity a decision to proceed to the next dose level (and subsequent ones) versus evaluating an additional 3 patients at the DL would be made. Escalation continued with 3 patients evaluated per DL until a DLT event was observed. If only one patient was observed with a DLT event among the first 3 patients accrued to a DL, 3 more patients were accrued to the same dose level. If there were no other observed DLT events in these additional patients, then the dose escalation continued. However, if there were any further DLT events in these additional patients, the current dose was considered to have exceeded the MTD.

RESULTS

From July 2008 to April 2014, 21 eligible patients were enrolled on trial. Of these patients, 4 were inevaluable for assessment of DLT and were replaced. All patients were evaluated for toxicity. Of the 17 evaluable patients, the median age was 65 yrs, 13 (76%) had Stage IV disease, and 10 (59%) had serous or clear cell tumors (Table 2).

In DL1 and 2, three patients each were enrolled and completed six cycles of therapy without a DLT. At DL 3, eight patients were enrolled, and six were evaluable. The two patients that were inevaluable both withdrew from study after the first IV TAP cycle (one patient experienced a grade 3 infection/urosepsis and declined further therapy, and the other because insurance approval for IP therapy was declined). Of the first three evaluable patients, one patient experienced a DLT consisting of grade 3/4 metabolic event (grade 4 hypocalcemia, grade 3 hyponatremia, hypomagnesemia, and hypokalemia). This patient did complete all 6 cycles of therapy. Three additional patients were evaluable and completed cycles 3 and 4 without a DLT. At Dose Level 4, six patients were enrolled, and four were evaluable. Of the inevaluable patients, one received cycles 1 and 2 had an IP port malfunction on cycle 3 and was subsequently treated off study with IV chemotherapy only. The other inevaluable patient received six cycles of therapy but did not have scheduled blood draws on cycle 3 to determine the duration of neutropenia, a necessary study requirement for DLT assessment. Of the first 3 evaluable patients treated at DL4, one patient developed grade 4 hypokalemia and grade 3 hypomagnesemia and hypocalcemia. As a result, the DL was expanded. The next enrolled patient experienced a DLT consisting of grade 4 hyponatremia and grade 3 hypokalemia, mucositis, and syncopal event). Since 2 of the 4 evaluable patients experienced a DLT, DL4 exceeded the MTD, and was closed to further enrollment. However, one patient had been consented and registered during this escalation phase but had only received cycle 1 and 2. Given the DLT data at DL4, the patient was offered study participation at DL 3 and received all 6 cycles of therapy without a DLT event. Enrollment and DLT events are summarized in Table 3.

Of the 21 enrolled patients who received at least 1 cycle of therapy, 40 cycles of IV TAP and 68 cycles of IV/IP chemotherapy were administered. Of the 17 evaluable patients, 15 received all 6 cycles of IV/IP chemotherapy (88%), one patient received 5 cycles (DL3), and one patient following a DLT discontinued treatment after cycle 3 (DL4). A summary of AEs for all dose levels is presented in Table 4. In general, hematologic toxicities were tolerable grade 4 ANC in 18 cycles, grade 3 thrombocytopenia in 1 cycle, and febrile neutropenia (during IV TAP) in 1 cycle. One patient developed a grade 2 sensory neuropathy but no patients developed grade 3–4 sensory neuropathy. There were two patients with IP port malfunctions, one was replaced and the patient completed 6 cycles of therapy, and one discontinued after the first attempt at IP administration. The three reported grade 3 gastrointestinal adverse events (diarrhea, nausea, vomiting) were only observed during cycle 1 with the IV TAP regimen. There were no protocol-related deaths. The 3 DLT defining AEs were all attributed to metabolic toxicities and in one patient, these metabolic toxicities were associated with grade 3 mucositis. All patients who discontinued protocol therapy, except one who discontinued all therapy following cycle 1, were subsequently able to be treated and complete chemotherapy.

Of the 17 evaluable patients, 9 remain alive, 8 have died, and 8 have recurred with a median follow-up time 22 months. Two-year PFS was 46% and the median PFS was 18 months. The 2-year survival rate was 55% with a median overall survival of 30 months for the 17 evaluable patients (Figure 1). As a phase I study, long term disease surveillance with serial CT imaging was not specified by protocol. As such, without uniform long term follow up, we are limited in reporting patterns of failure.

DISCUSSION

At the time of study initiation, the most active chemotherapy regimen for use in patients with advanced or recurrent endometrial cancer identified by the GOG phase III program was the three drug TAP regimen [13]. In a study, comparing the combination of doxorubicin and cisplatin with or without paclitaxel, RR, PFS and OS were improved with the addition of paclitaxel. Previous work by the GOG, demonstrated improved PFS and OS with doxorubicin and cisplatin chemotherapy over WART and lead to a substantial change in treatment philosophy increasing the use of chemotherapy in the first-line management of patients with advanced but potentially curable endometrial cancer [12]. Despite the successes noted in both studies, there were limitations. Both regimens caused neurotoxicity though TAP produced significantly more neurotoxicity with 39% experiencing Grade 2 toxicity, and TAP also required 3 days to administer and use of G-CSF. In addition, despite the improvement in response rates, particularly complete responses, with chemotherapy, the response rate still remained low making the investigation of alternative regimens desirable. Therefore, based on the observed improvements in outcomes in patients treated with intraperitoneal therapy in ovarian cancer, the present study was developed.

The study population was selected to enrich for patients at greatest risk of intraperitoneal failures. The intraperitoneal regimen, cisplatin and paclitaxel, has been developed, and dosing and toxicities are well described [19]. In endometrial cancer, the question of whether platinum and taxane-based chemotherapy could replace the TAP regimen was unknown at the time of study initiation. As such, investigating whether the IV TAP regimen could be modified into an IV/IP based regimen to reduce toxicity and enhance efficacy were clinically relevant hypotheses. The results of this study demonstrate that a maximum tolerated regimen IP therapy using the TAP backbone was at dose level 3 using IV 45 mg/m² doxorubicin D1, IV cisplatin 50 mg/m² D1, and IP paclitaxel 90 mg/m² d1. We were unable to identify a tolerable dosing for combined IP paclitaxel and cisplatin with the dose levels evaluated. IP based therapy in this study was well tolerated with 88% of evaluable patients across all dose levels receiving all 6 cycles of therapy.

Most patients in this study had Stage IV disease (76%). Patients with Stage IV endometrial cancer with intraperitoneal disease spread can be surgically debulked, and it is generally advocated to resect intraperitoneal disease to the smallest residual possible when feasible [10–12]. In an effort to reduce initial bulk of peritoneal disease and improve the therapeutic ratio for IP chemotherapy, patients received two initial cycles of IV chemotherapy prior to initiating IP based therapy. Based on the experience in ovarian cancer, patients receiving a moderately-high dose IV carboplatin for two cycles prior to beginning IV/IP paclitaxel and cisplatin had an improved PFS (28 vs. 22 mo, $p=0.01$) and overall survival (median 63 vs. 52 mo, $p=0.05$) compared to a standard IV paclitaxel/cisplatin regimen [20]. The resulting delay in initiating IP chemotherapy may also benefit those endometrial cancer patients with large volume ascites and the 10–20% aggressively cytoreduced Stage IV patients who undergo bowel resections [21]. Furthermore, the IP route may also allow for a reduction in the toxicity noted with the IV TAP regimen. In this study, we noted that neuropathy and myelo-suppression were tolerable and that prophylactic G-CSF was not required. As seen with other cisplatin based IP regimens, electrolyte abnormalities were the predominant

toxicity in this study and accounted for all 3 DLT events. More aggressive support measures, substitution of carboplatin for cisplatin, or further dose adjustments (as were introduced with ovarian cancer IP studies) may have allowed us to dose escalate further. In this population we were unable to identify a safe or feasible IP/IP paclitaxel/cisplatin dose level.

The assessment of efficacy in a phase I study is difficult. The eligibility criteria were selected to enrich for patients thought to be at greater risk for abdominal failure, and perhaps more likely to benefit from intraperitoneal drug exposure. Our study population was particularly high-risk and included 76% of patients with Stage IV disease and 59% with serous/clear cell histology. There was only one patient included with Stage IIIA disease (adnexal disease and no other factors). Of the 17 evaluable patients, 8 have recurred, and 9 have not. The two year OS rates of 55% compares favorably to those seen with IV chemotherapy or WART in GOG 122 [12].

The preliminary results of GOG 209, a randomized phase III trial comparing TAP to paclitaxel and carboplatin (TC) in patients with advanced endometrial cancer showed the regimens to be clinically equivalent. The PFS (median TC vs TAP, 14 vs 14 months; HR=1.03) and OS (median TC vs TAP, 32 vs 38 months; HR=1.01) were similar demonstrating that TC was not inferior to TAP [22]. Given the more favorable toxicity profile and ease of administration of TC, a decision was made to forgo further development of IV/IP TAP regimen. However, continued work optimizing chemotherapy regimens in endometrial cancer are necessary. In ovarian cancer, modifications of standard chemotherapy regimens by IP or dose dense therapy have produced the only survival advantages since 1996. Therefore, based on the ability to complete 6 cycles of therapy, reductions in neuropathy rates, and favorable PFS rates, further study of IP therapy in endometrial cancer is warranted.

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Research Highlights

- Patterns of failure data in some high risk endometrial cancer populations support the evaluation of intraperitoneal chemotherapy
- A phase Ib trial evaluating a modified TAP (paclitaxel, doxorubicin, cisplatin) regimen including intraperitoneal administration of agents was conducted
- The regimen was tolerable and produced promising PFS rates

Figure 1.
Progression-Free and Survival Estimates for 17 Evaluable Patients

Table 1

Dose Level Evaluations

Dose Level	Doxorubicin (mg/m ² , IV, q 21 day 1)	Cisplatin (mg/m ² , IV, q 21 day 1)	Paclitaxel (IP, mg/m ² , q 21 day 1)
DL (-1)	30	50	50
DL 1 (Start)	45	50	60
DL 2	45	50	75
DL 3	45	50	90
DL 4	45	75 IP (d1)	MTD-1 (d8) (75 mg/m ²)
DL 5	45	75 IP (d1)	MTD (d8)

DL= dose level, IV= intravenous administration, IP intraperitoneal administration, MTD= maximum tolerated dose

Table 2

Patient Characteristics of 17 evaluable patients

Variable	N	
Age	Median	65 year
Weight	Median	64 kg
Stage	IIIA	1
	IIIC	3
	IVB	13
Histology		
Endometrioid	Grade 1	1
	Grade 2	5
	Grade 3	1
	Total	7
Serous		7
Clear cell		2
Mixed		1
Disease Distribution		
(+) cytology		9
(+) uterine serosa		1
(+) adnexa		10
(+) peritoneum		11
(+) omentum		11
Status		
Alive		9
Dead		8
Recurred		8
Not recurred		9

Table 3

Patient Enrollment and Dose Limiting Toxicity per Dose Level

Dose	# Patients	DLT
Level	Enrolled/Evaluable	
DL (-1)	0	0
DL 1 (Start)	3/3	0
DL 2	3/3	0
DL 3	9/7	1
DL 4	6/4	2
DL 5	0	0
Totals	21/7	3

DL= dose level, DLT= dose-limiting toxicity

Table 4

Summary of Adverse Events Related to Study Treatment (N=21)

AE Category	0	1	2	3	4	5
Leukopenia	1	1	3	11	5	0
Thrombocytopenia	8	10	2	1	0	0
Neutropenia	1	0	1	1	18	0
Anemia	0	5	14	2	0	0
Other Hematologic	20	0	0	0	1	0
Allergy/Immunology	19	1	1	0	0	0
Auditory/Ear	15	0	6	0	0	0
Cardiac	14	2	5	0	0	0
Coagulation	21	0	0	0	0	0
Constitutional	0	9	10	2	0	0
Dermatologic	2	4	15	0	0	0
Gastrointestinal	1	7	8	5	0	0
Genitourinary/Renal	20	0	0	1	0	0
Hemorrhage	18	3	0	0	0	0
Infection	13	0	5	3	0	0
Lymphatics	20	1	0	0	0	0
Metabolic	3	8	3	4	3	0
Musculoskeletal	18	3	0	0	0	0
Neuropathy	10	10	1	0	0	0
Other Neurological	6	10	4	1	0	0
Ocular/Visual	14	6	1	0	0	0
Pain	3	10	8	0	0	0
Pulmonary	7	10	4	0	0	0