Published in final edited form as:

Gynecol Oncol. 2008 June ; 109(3): 323–328. doi:10.1016/j.ygyno.2008.02.024.

Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study

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Abstract

Objective—Doxorubicin-based treatment is standard therapy for metastatic uterine leiomyosarcoma. There is no standard second-line therapy. We determined activity of fixed-dose rate gemcitabine plus docetaxel as second-line treatment for metastatic uterine leiomyosarcoma.

Methods—Eligible women with unresectable uterine leiomyosarcoma progressing after prior cytotoxic therapy were treated with gemcitabine 900 mg/m² days one and eight over 90 minutes, plus docetaxel 100 mg/m² on day 8 of a 21-day cycle with granulocyte growth factor. Patients with prior pelvic radiation received lower doses. Response Evaluation Criteria in Solid Tumors (RECIST) response was assessed by computed tomography (CT).

Results—Forty-eight of 51 women were evaluable for response (one wrong histology, two never treated). Prior therapy was doxorubicin-based in 90%, and ifosfamide-based in 6%. The overall objective response rate is 27%, with complete response in 6.3% (3/48), and partial response in 20.8% (10/48). An additional 50% (24/48) had stable disease (median duration 5.4 months). The median number of cycles per patient was 5.5 (range 1–22); 73% of patients remained progression-free at 12 weeks and 52% at 24 weeks. The predominant toxicity was uncomplicated myelosuppression: thrombocytopenia grade 3 (29%), grade 4 (10.4%); neutropenia grade 3 (12.5%), grade 4 (8.3%) anemia grade 3 (20.8%), grade 4 (4.2%). While pulmonary toxicity was reported, no patient had drug-related pneumonitis/hypoxia-type toxicity. Median progression-free survival (PFS) was 5.6+

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CONFLICT OF INTEREST STATEMENT: Dr. Peter Rose has received honoraria from Lilly Pharmaceuticals. All other authors have no conflict of interest to disclose.

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months (range 0.7 – 27+ months). The median duration of objective response was 9+ months (range 3.9 – 24.5+ months).

Conclusion—Fixed-dose rate gemcitabine plus docetaxel is active second-line therapy for uterine leiomyosarcoma.

Keywords

uterine leiomyosarcoma; gemcitabine; docetaxel

INTRODUCTION

Uterine leiomyosarcoma accounts for approximately 1% of all uterine malignancies and thus is diagnosed in only a few thousand women each year [1]. Women who present with advanced disease, and women whose disease recurs after initial surgical resection have a poor prognosis; and, except for rare, highly-selected cases with resectable, isolated pulmonary metastases, are not curable [2]. Median survival among women with advanced disease is less than one year.

Current treatment options for recurrent or advanced uterine leiomyosarcoma are limited. Negligible activity was observed in phase II trials testing the following drugs as single agents: cisplatin, mitoxantrone, amonifide, oral etoposide, diazoquone (AZQ), intravenous etoposide, topotecan, paclitaxel, thalidomide, and trimetrexate [3–14]. Single agents that show moderate activity in leiomyosarcoma include ifosfamide (response rate 17.2%), doxorubicin (response rate 25%), and gemcitabine (bolus infusion achieved a 20% response rate among women with uterine leiomyosarcoma who had received 0–1 prior cytotoxic regimen) [15–17]. Trabectedin achieved a response rate of 8% among patients with prior treatment, and 17% as first-line therapy, in patients with soft tissue sarcoma [18–19].

Combination chemotherapy regimens with activity in previously untreated patients include hydroxyurea, dacarbazine and etoposide (overall response rate 18.4%) and doxorubicin plus ifosfamide (response rate 30.3%) [20,21]. Doxorubicin with or without ifosfamide is frequently employed as first line therapy for women with advanced or recurrent leiomyosarcoma. Standard second-line therapy for uterine leiomyosarcoma has not been established.

In a single-institution study, the combination of fixed-dose-rate gemcitabine plus docetaxel achieved objective response rates of 53% among patients with unresectable leiomyosarcoma who had received up to two prior cytotoxic regimens. Nearly all patients had uterine-primary leiomyosarcoma [22]. This high response rate was observed even among the subgroup of patients previously treated with doxorubicin-based chemotherapy. The rationale for using the fixed-dose rate infusion of gemcitabine was based on pre-clinical data which showed that a gemcitabine concentration of 20 $\mu\text{mol/liter}$ was optimal for the formation of the active gemcitabine metabolite, and for its subsequent incorporation of into deoxyribonucleic acid (DNA). Delivering gemcitabine at a rate of 10 $\text{mg/m}^2/\text{minute}$ was determined to be the best rate for maintaining the gemcitabine concentration at 20 $\mu\text{mol/liter}$, and thus optimizing *in vivo* cell kill [23,24]. Pharmacokinetic analyses in the single institution phase II study [22] showed that fixed-dose rate gemcitabine at 10 $\text{mg/m}^2/\text{minute}$ increased the duration of time that the gemcitabine metabolite remained above the threshold for incorporation into deoxyribonucleic acid (DNA) compared with bolus gemcitabine infusion in patients. Furthermore, in a randomized phase II trial in pancreatic cancer, fixed-dose-rate gemcitabine (1500 mg/m^2 over 150 minutes) achieved longer time-to-treatment-failure and longer median survival than bolus gemcitabine therapy at a higher dose (2200 mg/m^2 over 30 minutes) [25].

The Gynecologic Oncology Group (GOG) conducted this phase II trial of fixed-dose-rate gemcitabine plus docetaxel to determine the activity of this regimen as second-line therapy among women with advanced or recurrent uterine leiomyosarcoma.

MATERIALS AND METHODS

Patients

Women with advanced or recurrent uterine leiomyosarcoma who had progressed after treatment with one prior cytotoxic regimen, and who had measurable disease that was not considered resectable, were eligible. Histologic confirmation was accomplished by central review of the GOG Pathology Committee. Prior therapy with gemcitabine or docetaxel was not permitted. Patients were permitted to have had prior pelvic radiotherapy. Patients were required to have GOG performance status of 0–2, and adequate bone marrow function (absolute neutrophil count (ANC) greater than or equal to 1,500/microliter, and platelets greater than or equal to 100,000/microliter); renal function (creatinine less than or equal to $1.5 \times$ institutional upper limit of normal); hepatic function (bilirubin less than or equal to $1.5 \times$ institutional upper limit of normal, and SGOT and alkaline phosphatase less than or equal to $2.5 \times$ institutional upper limit of normal); and neurologic function (baseline neuropathy (sensory and motor) less than or equal to Common Toxicity Criteria grade 1).

All patients signed written, informed consent. The protocol and consent were reviewed and approved annually by participating institutions' Institutional Review Boards.

Treatment plan

All participants had baseline imaging (CT scan of chest, abdomen, and pelvis) within four weeks of starting therapy, which was repeated following every other cycle of treatment to assess response. History and physical examination, and assessment of toxicities were done each cycle. Complete blood counts were monitored weekly and comprehensive metabolic panels on day one of each cycle.

Participants without a history of pelvic radiation received gemcitabine 900 mg/m² on days one and eight intravenously over 90 minutes, followed by docetaxel 100 mg/m² on day eight intravenously over one hour. Granulocyte-colony-stimulating factor (G-CSF) 150 micrograms/m² was given subcutaneously on days 9–15, or pegfilgrastim 6 mg was given subcutaneously on day nine or 10. Participants with a history of prior pelvic radiation received gemcitabine 675 mg/m² on days one and eight intravenously over 90 minutes, followed by docetaxel 75 mg/m² on day eight intravenously over one hour, with the same granulocyte growth factor support as above. Treatment cycles were repeated approximately every three weeks.

Recommended pre-medication for the docetaxel was dexamethasone 8 mg orally twice a day starting the day prior to docetaxel and continuing for three days. Early intervention with diuretics was encouraged for signs of docetaxel-related fluid retention. Treatment continued until time of objective progression of disease, or unacceptable toxicity.

Patients received day one treatment of each cycle provided the ANC was greater than or equal to 1500/microliter and platelet count greater than or equal to 100,000/microliter. Patients received full-dose day eight treatment provided the ANC was greater than or equal to 1000/microliter and platelet count greater than or equal to 100,000/microliter. Seventy-five percent of the planned day eight dose was given if the ANC was between 500 and 1000/microliter or the platelet count was between 50,000 and 100,000/microliter, and provided the bilirubin from day one or after was within institutional normal limits. Day eight treatment with docetaxel was omitted if the bilirubin was still above normal on day eight. Day eight gemcitabine and

docetaxel were both omitted if the day eight ANC was under 500/microliter or the platelet count was less than 50,000/microliter.

Doses of both docetaxel and gemcitabine were reduced by 25% in subsequent cycles if a patient experienced grade 3 elevations in SGOT, SGPT, or alkaline phosphatase; and treatment was not resumed until such grade 3 elevations had resolved to grade 1 or less.

Patients who experience grade 2 or worse neurotoxicity had treatment held for a maximum of two weeks, and could resume treatment at 75% of the prior docetaxel dose if the neuropathy had improved. Other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) required 25% dose reduction and delay in subsequent therapy for a maximum of two weeks until recovered to grade 1, or pre-therapy baseline.

Toxicities were graded according to National Cancer Institution Common Toxicity Criteria version 3.0 (CTC 3.0).

Response was assessed by RECIST. Complete response (CR) is disappearance of all target and non-target lesions and no evidence of new lesions documented by two disease assessments at least four weeks apart. Partial response (PR) is at least a 30% decrease in the sum of longest dimensions (LD) of all target measurable lesions taking as reference the baseline sum of LD. There can be no unequivocal progression of non-target lesions and no new lesions.

Documentation by two disease assessments at least four weeks apart is required. In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% decrease in the LD is required. Progression of disease requires at least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD or the appearance of new lesions or death due to disease or global deterioration due to disease. Stable disease (SD) is any condition not meeting the above criteria.

Statistical design

The study employed a two-stage accrual design with an early stopping rule in the event that the treatment demonstrated insufficient activity [26]. During the first stage of accrual, 19–26 patients were to be entered and evaluated. If at least three responses were observed among the first 19–25 patients, or at least four responses out of 26 patients, a second phase of accrual was to be initiated which would increase accrual to 44–51 patients. The regimen would be considered active if at least seven responses were observed among 44–45 patients, or at least eight responses were observed among 46–51 patients. If the true response rate is 10%, the average probability of designing the treatment as designating the treatment as active is limited to 10%. Conversely, if the true response rate was 25%, then the probability of correctly classifying the treatment as active was 90%.

RESULTS

Patient characteristics

Fifty-one women were enrolled on study through 26 participating GOG institutions. The first stage of accrual (23 patients) was achieved over two years, and the second stage (28 patients) was achieved in one year. Forty-eight women were evaluable for response (one patient ineligible due to inadequate pathology to confirm diagnosis, and two patients never treated). The median age was 50 years (range 30–72). All but one patient had a GOG performance status of 0–1. Seventy-nine percent were white; 14.5% black; 6% Asian or Hispanic. Seventeen of 48 patients (35%) had received prior pelvic radiation. All patients had received one prior cytotoxic regimen, and in the majority, the prior therapy had been doxorubicin-based (90%) or ifosfamide-based (6%) (Table 1).

Response to treatment and survival

Confirmed CR was observed in 6.3% (3/48), and PR observed in 20.8% (10/48) of patients treated for an overall objective response rate of 27% (95% confidence interval 15.3%–41.8%). An additional 50% (24/48) had stable disease on therapy, for a clinical benefit rate of 77%. Best response was progression of disease in 16.6% (8/48) of patients.

Fifty percent (24/48) of patients received six or more cycles of therapy. The median number of cycles per patient was 5.5 (range 1–22). Median PFS for all 48 patients was 6.7+ months (range 0.7–27+ months) (Figure 1). Among the 13 patients with objective response, the median duration of response was nine plus months (range 3.9–24.5+ months). One patient had sustained response for over two years, and two others had response durations of over one year (13.3 months and 20.5 months). The median PFS for patients whose best response was stable disease was 5.4 months. The percent of patients remaining free from progression at 12 weeks is 73% (95% confidence interval 58.2%–84.7%) and the percent progression-free at 24 weeks is 52% (95% confidence interval 37.2%–66.7%). Median overall survival (OS) is 14.7 months (.8–50.9+).

Adverse events

A summary of all adverse events of all grades is provided in Table 3. The predominant toxicity was myelosuppression: leukopenia grade 3 (14.5%), grade 4 (8.3%); thrombocytopenia grade 3 (29%), grade 4 (10.4%); neutropenia grade 3 (12.5%), grade 4 (8.3%) anemia grade 3 (20.8%), grade 4 (4.2%). Complications of myelosuppression were uncommon: one patient with hemorrhage grade 3 (2%); two patients with neutropenic fever grade 3 (4.2%). Fluid retention syndrome is a known toxicity of docetaxel and was grade 3 in nine patients (19%). Grade 3 constitutional symptoms were reported in five patients (10%), while grade 3 fatigue was reported in only one (2%). Half of the patients received at least one red blood cell transfusion, and six (12.5%) received at least one platelet transfusion. Patients with a history of prior pelvic radiation were more likely to require red blood cell transfusion but not platelet transfusion: 12 of the 17 patients with prior pelvic radiation received red blood cell transfusion (71%), and one of 17 received platelets (6%); whereas 12 of the 31 patients with no history of pelvic radiation received red blood cells (39%), and five of 31 received platelets (16%).

Pulmonary toxicity has been reported with gemcitabine, docetaxel, and the combination. In this study pulmonary toxicity was reported as grade two in four patients (8.3%), grade 3 in three patients (6.2%), and grade 4 in one patient (2%). Details of these pulmonary events suggest that none were typical drug-related pneumonitis-hypoxia type pulmonary toxicities. The reported grade 3 events are: one patient had pneumonia without neutropenia or hypoxia during cycle 6, requiring a three-day hospitalization for intravenous antibiotics; one patient had grade 3 dyspnea without significant hypoxia due to new bilateral effusions, cytology was negative for malignancy; one patients had acute dyspnea and hypoxia during gemcitabine infusion on cycle 6 day one with work-up negative for pulmonary embolism, cardiac event, or disease progression. She improved clinically and received her day eight treatment but came off study approximately two weeks later for evidence of disease progression on CT scan. The grade 4 event was bilateral pneumonia without neutropenia in a 71-year-old woman with lung metastases, which occurred after cycle 3 of study treatment. The CT scan after cycle two had shown stable disease. The pneumonia was associated with hypoxia requiring intubation. This grade 4 pulmonary toxicity was attributed to both disease and treatment. There were no grade 3 or 4 neurotoxicity events.

DISCUSSION

For decades doxorubicin, with or without ifosfamide, has been the mainstay of treatment for unresectable leiomyosarcoma, with no established second-line therapy. This large phase II trial demonstrates that fixed-dose rate gemcitabine plus docetaxel achieves high objective response rates, including complete responses, as second-line therapy for advanced uterine leiomyosarcoma. Objective responses were sustained in duration (median duration of response was greater than nine months) with some patients having responses that lasted more than two years.

Compared with other agents that have been tested in the second-line metastatic sarcoma setting, the fixed-dose rate gemcitabine plus docetaxel response rate is encouraging. Gemcitabine as bolus infusion, single-agent therapy for patients with 0–1 prior cytotoxic regimen (17% had had no prior therapy) achieved response in 20% of patients; however, the median duration of response was only 4.9 months, and the clinical benefit rate (CR, PR, or stable disease) was 36% [27]. Trabectedin achieved objective response in 8% of patients as second-line therapy [19]. In a phase II study of sorafenib for patients with soft tissue sarcoma who had had 0–1 prior therapies, sorafenib achieved response in two of 37 (5%) patients with leiomyosarcoma [28].

Fixed-dose rate gemcitabine plus docetaxel has been prospectively evaluated in other sarcoma treatment settings. The objective response rate of 53% in the single-institution phase II study is somewhat higher than the objective response in this cooperative group study, a finding that is typical for single-institution versus cooperative group studies [22]. In the randomized trial of fixed-dose rate gemcitabine v. fixed dose-rate gemcitabine plus docetaxel for patients with soft tissue sarcoma who had received zero to three prior regimens, response rate, PFS, and OS were all superior for the gemcitabine-docetaxel arm [29]. The objective response rate across all sarcoma histologic types was 16% with gemcitabine-docetaxel. This lower response rate, compared with the 27% observed in this GOG phase II study, is likely due to the varied-histology sarcoma patient population treated on the randomized trial, and the eligibility criteria permitting up to three prior regimens [22].

The side effect profile for fixed-dose rate gemcitabine plus docetaxel is acceptable. Myelosuppression is common but is only rarely complicated by neutropenic fever. Although 50% of patients received at least one red blood cell transfusion, only 20% of patients had grade 3 anemia (hemoglobin < 8 gm/dl), suggesting that the threshold for recommending red cell transfusion was low among treating physicians. Pulmonary toxicity, described as interstitial lung toxicity with dyspnea and hypoxia that may be severe, has been reported with gemcitabine, docetaxel, and with combinations of gemcitabine plus taxanes [30–34]. Although grade 3 pulmonary toxicity was reported in three patients, and grade 4 in one, none of these four patients appears to have had the typical chemotherapy-related interstitial lung toxicity described with gemcitabine plus taxane therapy. The patient with grade 4 pulmonary toxicity had bilateral pneumonia on CT scan with hypoxia requiring intubation. The event was attributed to both disease and treatment, and it seems likely that there was a component of treatment-related interstitial lung toxicity. The PFS rate at 12 weeks and 24 weeks has been suggested as an endpoint for phase II trials in soft tissue sarcoma [35]. Among patients with prior therapy, chemotherapy agents considered to be active were associated with progression-free rates of 39% at 12 weeks and 14% at 24 weeks. By this measure, fixed dose-rate gemcitabine plus docetaxel meets criteria to be considered active by achieving progression-free rates of 73% at 12 weeks, and 52% at 24 weeks, respectively.

Fixed-dose rate gemcitabine plus docetaxel achieves the highest objective response rates as second line therapy for metastatic uterine leiomyosarcoma of any regimen studied to date. The

duration of objective response exceeded nine months, and OS for the whole cohort was 14.7 months in this second-line treatment population. Participating sites enrolled an average of two patients per site, yet toxicity was limited and response rates high, suggesting that this relatively intense treatment regimen can be easily delivered in clinical practice. A separate GOG trial has recently been completed evaluating the efficacy of this regimen as first-line therapy. Fixed dose-rate gemcitabine plus docetaxel regimen should be considered as a treatment option for second-line therapy for women with uterine leiomyosarcoma.

Acknowledgments

This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical and Data Center (CA 37517). The following Gynecologic Oncology Group member institutions participated in this study: University of Alabama at Birmingham, Duke University Medical Center, Abington Memorial Hospital, University of Mississippi Medical Center, University of Washington, Milton S. Hershey Medical Center, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center at Dallas, Indiana University School of Medicine, Wake Forest University School of Medicine, Tufts-New England Medical Center, SUNY Downstate Medical Center, University of Kentucky, The Cleveland Clinic Foundation, State University of New York at Stony Brook, Memorial Sloan-Kettering Cancer Center, Cooper Hospital/University Medical Center, Columbus Cancer Council, Women's Cancer Center, University of Oklahoma, University of Virginia Health Sciences Center, Tacoma General Hospital, Gynecologic Oncology Network, Yale University, and Community Clinical Oncology Program.

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Progression – free Survival

Figure 1.
Progression-free survival, n=48 patients with advanced uterine leiomyosarcoma

Table 1

Patient Characteristics (n=48)

Characteristic	Number of Patients
Age	
<40	6
40–49	18
50–59	17
60–69	4
≥70	3
Performance Status	
0	34
1	13
2	1
Race	
White	38
Black	7
Asian	2
Hispanic	1
Prior Chemotherapy	48
Doxorubicin-based	43
Ifosfamide-based	3
Other (paclitaxel-cisplatin, temozolomide)	2
Prior Radiotherapy	17
Number of cycles received on study	
1	5
2	7
3	3
4	7
5	2
6	5
7	5
>7	14

Table 2

RECIST-defined responses to treatment

Response Category	Number of Patients	%
Complete Response	3	6.3
Partial Response	10	20.8
Stable Response	24	50.0
Increasing Disease	8	16.6
Inevaluable	<u>3</u>	<u>6.3</u>
Total	48	100.0

Table 3
Adverse events, all grades, by number of patients experiencing the event.

Adverse Event	Grade					Total
	0	1	2	3	4	
Leukopenia	15	9	13	7	4	48
Thrombocytopenia	8	11	10	14	5	48
Neutropenia	19	9	10	6	4	48
Anemia	4	6	26	10	2	48
Hemorrhage	44	3	0	1	0	48
Coagulation	46	0	0	2	0	48
RBC transfusion	24	0	0	24	0	48
Platelet transfusion	42	0	0	6	0	48
Nausea/vomiting	29	12	6	0	1	48
Gastrointestinal	18	15	12	2	1	48
Genitourinary	45	2	1	0	0	48
Alkaline phosphatase	39	9	0	0	0	48
SGOT	41	7	0	0	0	48
Alopecia	21	1	26	0	0	48
Dermatologic	27	9	10	2	0	48
Neurotoxicity	26	15	7	0	0	48
Renal	45	3	0	0	0	48
Infection	41	0	4	2	1	48
Fatigue	40	2	5	1	0	48
Pain	22	14	11	1	0	48
Hepatic	38	6	3	1	0	48
Cardiovascular/Edema	24	10	5	9	0	48
Metabolic	29	11	7	1	0	48
Lymphocytopenia	46	0	0	2	0	48
Fever	43	2	1	2	0	48
Musculoskeletal	46	1	0	1	0	48
Pulmonary	36	4	4	3	1	48
Ocular	44	3	1	0	0	48
Dyspnea	47	0	1	0	0	48
Endocrine	45	3	0	0	0	48

Adverse Event	Grade					Total
	0	1	2	3	4	
Allergy	46	0	2	0	0	48
Constitutional	14	13	16	5	0	48
DVT	47	0	0	1	0	48

The median WBC nadir for those 33 patients experiencing leukopenia was 2200 (range: 200–3750).